UNIVERSIDADE D
COIMBRA

Susana Isabel Simão Mouga

Testing A Specific Link Between Executive Functions And Social Cognition In Autism Spectrum Disorders

Tese no âmbito do Programa de Doutoramento em Ciências da Saúde, ramo de Ciências Biomédicas orientada pela Professora Doutora Guiomar Gonçalves de Oliveira e pelo Professor Doutor Miguel de Sá e Sousa Castelo Branco e apresentada à Faculdade de Medicina da Universidade de Coimbra

Dezembro de 2020

Universidade de Coimbra

Faculdade de Medicina

Testing a specific link between executive functions and social cognition in Autism Spectrum Disorders

Thesis to obtain a Ph.D. degree in Biomedical Sciences at the Doctoral Program in Health Sciences, supervised by Professor Guiomar Gonçalves de Oliveira and Professor Miguel de Sá e Sousa Castelo Branco, presented at the Faculty of Medicine of the University of Coimbra.

Tese no âmbito do Programa de Doutoramento em Ciências da Saúde, ramo de Ciências Biomédicas, orientada pela Professora Doutora Guiomar Gonçalves de Oliveira e pelo Professor Doutor Miguel de Sá e Sousa Castelo Branco e apresentada à Faculdade de Medicina.

Susana Isabel Simão Mouga

December 2020

Supervised by: Guiomar Gonçalves de Oliveira, M.D., Ph.D.
Co-Supervised by: Miguel de Sá e Sousa Castelo Branco, Ph.D.

The studies presented in this thesis were carried out at the CNC.IBILI / CIBIT-ICNAS / UNDA-CDC-HP-CHUC and CIFC-HP-CHUC (Center for Neuroscience and Cell Biology | Institute for Biomedical Imaging and Life Sciences, Faculty of Medicine / Coimbra Institute for Biomedical Imaging and Translational Research - Institute of Nuclear Sciences Applied to Health / Unidade de Neurodesenvolvimento e Autismo, Centro de Desenvolvimento da Criança, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra / Centro de Investigação e Formação Clínica, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra), University of Coimbra, Portugal, and were supported by an individual fellowship from the Portuguese Foundation for Science and Technology (SFRH/BD/102779/2014), grants from the Portuguese Foundation for Science and Technology (Grant numbers SAICTPAC/0010/2015; UID/4950/2020) and the national projects AAC N°13 SI/2011/Hometech/QREN – Compete, cofunded by FEDER and BIGDATIMAGE CENTRO-01-0145-FEDER-000016 (Portugal2020, Centro2020, UE).

Para a Maria Leonor e para a Célia, as minhas maiores motivações

Para a Benvinda e para o Armando, as minhas maiores inspirações

"*Now this is not the end.*

It is not even the beginning of the end.

But it is, perhaps, the end of the beginning."

Winston Churchill

Agradecimentos

As viagens que nos ficam marcadas para sempre na memória são as que nos abrem novos horizontes, que nos fazem ver o que ainda não tínhamos sequer imaginado, que nos desafiam e confundem, que nos fazem distanciar do que somos para nos fazer procurar ver melhor, ser melhor. Este percurso, chamado doutoramento, que culmina nestas páginas aqui escritas, foi das viagens mais desafiantes da minha vida, mas tive a sorte de ter sempre comigo pessoas que me estenderam o mapa quando estava perdida, que foram farol, que caminharam ao meu lado tantas vezes e outras tantas me fizeram caminhar sozinha, porque também faz parte. É aos meus "companheiros de viagem" que aqui agradeço.

Começo por agradecer à Professora Doutora Guiomar Oliveira, que me acompanhou desde os primeiros dias no caminho para o conhecimento da Perturbação do Espectro do Autismo, quando um doutoramento ainda não estava no horizonte, que sempre me incentivou a ir mais longe, ser diferente, ser melhor e cujo contributo clínico, científico e espírito crítico foi determinante no desenvolvimento deste trabalho, assim como no meu crescimento profissional e pessoal. Agradeço todas as partilhas, os ensinamentos, o apoio e confiança.

Dirijo igualmente ao Professor Doutor Miguel Castelo-Branco, um sentido agradecimento à forma entusiasta como me acolheu sua equipa, por me ter integrado nos mais variados projetos e por me ter permitido iniciar uma viagem de descoberta científica, mas também profissional e pessoal, sem nunca me ter feito fechar as portas que conduziam a outros caminhos. Agradeço as horas de apaixonada discussão científica, a genialidade, o delinear de planos, os ensinamentos, a disponibilidade, a motivação, a confiança e o apoio.

O privilégio de percorrer um caminho na ciência sem nunca ter deixado o contacto com os pacientes e o ambiente clínico é um privilégio de poucos e só possível quando se têm orientadores que têm horizontes largos, sonham mais alto e assim me permitiram sentir mais completa ao longo destes anos. Muito obrigada Professora Guiomar e Professor Miguel por possibilitarem este "estar com um pé na clínica e outro no laboratório" tão gratificante!

Um agradecimento muito especial a todos os "meus" meninos com Perturbação do Espectro do Autismo e às suas famílias. Não apenas aos que integraram este trabalho, mas a todos os que conheci ao longo dos anos e me fizeram apaixonar desde logo por esta patologia e querer estudá-la durante toda a minha vida profissional. Foi amor à primeira vista e sei que será um amor para a vida. Obrigada pela colaboração incansável e pela disponibilidade infindável, pelo carinho com que sempre me trataram e pela vontade de ajudar no desenvolvimento do conhecimento científico. É importante continuar a estudar esta

patologia, conhecer-lhe os mecanismos, tentar melhorar as intervenções, mas é acima de tudo importante respeitar as suas particularidades e deixar de tentar normalizar quem é tão especial precisamente por ser diferente.

Agradeço igualmente a todas as crianças, adolescentes e jovens e suas famílias que integraram os outros grupos deste trabalho, pela sua colaboração e disponibilidade.

Um agradecimento sentido e importante a todas as pessoas que tiveram uma participação fundamental no desenvolvimento destes trabalhos. Agradeço em particular ao João Castelhano, à Catarina Duarte e à Bárbara Regadas Correia, pela partilha de conhecimentos, pela paciência, pelas discussões produtivas, pelas correções certeiras e também pela amizade. Agradeço ao Dr. Frederico Duque pelos anos de trabalho clínico lado-a-lado, à Cátia Café por estar sempre presente, disponível e, por muitas vezes, trazer organização ao caos, à Daniela Sousa por me ensinar todas as dimensões do que é ser orientador de alguém e me mostrar que na partilha ganhamos todos, à Joana Almeida, companheira dos primeiros trabalhos nesta área e de tantos outros momentos, e a todas as outras pessoas que integram ou integraram a Unidade de Neurodesenvolvimento e Autismo do CDC/HP/CHUC. Agradeço igualmente à Sónia Afonso e Tânia Lopes, pela disponibilidade, profissionalismo e paciência comigo e com "os meus meninos" na ressonância. Agradeço também ao Professor Doutor Mário Simões pelo seu contagiante entusiasmo pela avaliação neuropsicológica e pela disponibilização de materiais de avaliação.

Agradeço profundamente a todos os meus colegas do IBILI/CIBIT/ICNAS por me mostrarem que colegas de trabalho também podem ser amigos, que a resolução da nossa dificuldade pode estar à distância de uns passos num corredor, um email ou de uma janela zoom, por me darem segurança para continuar sempre a viagem. Agradeço à Inês, por ser a melhor companheira de gabinete, pela amizade, por tantas vezes ter sido farol, bússola e por estar (literal e figurativamente) ao meu lado em todos os momentos, mas em especial quando houve turbulência. Agradeço aos que serão "Sala de Cálculo Forever", por todas as horas (infinitas) boas e más que partilhámos e que me fizeram seguir em frente com sorriso no rosto (em especial ao Marco, Carlos, Raquel, Ana, Joãozinho, Andrade, Raquelita, Pereira, Andreia, Filipa, Alexandre, Miguel). Agradeço ao Hugo pelas horas de conversa, histórias mirabolantes e exames a estes olhos cansados. Agradeço ao Marco, por me ensinar que vale sempre a pena levantar a cabeça e olhar o horizonte. Ao Bruno, pela ajuda (com o Matlab, SNOMED e tantas outras coisas) e por me ter mostrado que músicas de 12 minutos podem ser terapêuticas. À Catarina Pereira pelo entusiasmo e força que me transmite. Ao Hélio não só pela ajuda com imagens, mas por ter sempre tudo o que precisamos à mão (ou no gabinete

do lado). À Filipa pelas palavras certas no momento certo. À Inês A pelo cuidado (e também pela paciência). Ao Carlos pela motivação, sempre!

Agradeço às "Cachopas do PhD" por terem transformado o espírito de sacrifício de horas de estudo, apresentações e trabalhos de grupo, em amizade para a vida!

Aos amigos "não de sempre, mas para sempre": Inês, Alex, Zé, Hugo, Cláudia, Ricardo, Miguel, Quim, Ana, por estarem sempre a torcer por mim, por serem colete salva-vidas na tempestade e me lembrarem que a viagem é tão importante como o destino, e é tão bom viajar convosco!

Aos amigos "de sempre e para sempre": Daniela, Nuno, Xana, Ana, Ângela, Tiago, Phill, por fazerem parecer que a distância não existe, por me incentivarem e ficarem orgulhosos mesmo que não percebam bem o que faço, e pelos abraços apertados a cada encontro.

Agradeço à minha família: à que me construiu, à que construí e a ambas por me edificarem. Aos meus pais, Benvinda e Armando, por serem e me darem amor, por me transmitirem esperança, por serem um modelo a seguir e por estarem sempre ao meu lado, a motivarem-me para nunca desistir. À minha irmã Célia por me mostrar que ser diferente é apenas ser muito especial, por ser ternura, mimo e festa! Ao Gonçalo, por ser o meu melhor amigo e companheiro desde sempre e para sempre, e um elemento crucial nesta viagem. Por todo o amor, apoio incondicional, compreensão inesgotável e paciência ao longo destes anos. À minha filha, Maria Leonor, por ter vindo ao meu mundo colocar tudo no seu devido lugar, por me mostrar o que é realmente importante e ser a principal razão pela qual quero ser melhor todos os dias.

Susana Mouga, Dezembro de 2020

"A viagem não acaba nunca. (…) Quando o viajante se sentou na areia da praia e disse: "Não há mais que ver", sabia que não era assim. O fim de uma viagem é apenas o começo de outra. É preciso ver o que não foi visto, ver outra vez o que se viu já, (…). É preciso voltar aos passos que foram dados, para os repetir, e para traçar caminhos novos no lado deles. É preciso recomeçar a viagem. Sempre."

(José Saramago, Viagem a Portugal)

Abstract

Autism spectrum disorder (ASD) is an early-onset, life-long severe neurodevelopmental disorder with a high worldwide prevalence. ASD is marked by the specificity of significant impairments in social interaction and communication, restricted interests, and the presence of repetitive and stereotyped behaviours. These individuals also show difficulties across multiple domains, including neurodevelopmental, intellectual functioning and adaptive behaviour, negatively affecting multiple areas from personal autonomy to coping skills. In addition, executive functioning (EF) impairments are common in ASD, having a cascading-effect on daily-life demands involving complex functions such as social cognition (SC), a central core symptom. Several cognitive models have been proposed to explain characteristics and difficulties that ASD individuals exhibit. In fact, ASD is one of the most studied neurodevelopmental disorders and at the same time, intriguingly, one of which we have less certainties about. The nature of these impairments can potentially be dissected by neuroimaging which bears an enormous potential for unveiling the neural mechanisms mediating the affected EF and SC. Furthermore, by unravelling the role of both EF and SC, the cognitive and functional deficits observed in ASD can potentially be explained.

The main focus of this thesis is the comprehensive investigation and characterization of the functional, intellectual and neurodevelopmental profile of ASD and definite establishment of the specific link between two of the main dysfunctional areas in this condition, namely EF and SC.

In the first study of this thesis, the functional profile in ASD was comprehensively investigated by exploring the adaptive behaviour profile and the impact of intelligence quotient (IQ) in these abilities. For this, we recruited participants with other neurodevelopmental disorders (OND), such as intellectual disability (ID) or learning disabilities, as a comparison model of putative deficits in adaptive behaviour. We highlighted that the main impairment in adaptive behaviour is within the domain of socialization skills, representing a distinctive factor of ASD versus OND, independently of ID. We also proved that co-occurring ID results in further debilitating effects on overall functioning, especially in ASD. Additionally, our study showed a disappointing and intriguing result that chronological age is negatively associated with measures of adaptive behaviour.

We further characterized the ASD phenotype, by studying the intellectual profile of ASD individuals, as compared to OND. We found that ASD have lower scores in the verbal intelligence quotient (IQ) than performance IQ. The core distinctive score between groups, in intellectual profile, was the Processing Speed Index, which has an impact in EF, is lower

in ASD. Surprisingly, this study demonstrated that the strengths and deficits are not the same in ASD with and without ID, and that the intellectual profile is associated with adaptive behaviour and not with core ASD symptoms.

The neurodevelopmental profile of ASD was also characterized. Specifically, we questioned if there was any marker in the neurodevelopmental profile and, particularly in early milestones that could predict later acquisition of expressive language, determinant in communication skills which directly impacts the functional profile and SC. Our findings suggest that core abilities (global and nonverbal intelligence) at early age, have great and important information about the potential development of language later in children with ASD.

After the characterization of our clinical sample, we directly assessed SC and executive functioning. We explored social attention that integrates SC, in ASD by using an experimental paradigm based on an assessment tool that we used in the diagnostic process of these individuals. Our results suggest that social attention allocation is task dependent, raising the question whether spontaneous attention deficits can be rescued by guiding goal-directed actions.

Finally, we explicitly explored the link between EF and SC in ASD by investigating the behavioural performance, visual patterns and neural underpinnings using a new ecological goal-oriented task. This task is based on a daily living chore: shopping in a supermarket, which draws heavily on EF, and SC. Our findings show that attentional deficits can be rescued by guiding goal-directed actions using explicit cues and stresses the importance of the structured or not structured context of the task and the cognitive load that implies. Taken together, our results point to the very relevant fact that attentional allocation in ASD population is context and task dependent.

We also went further in the understanding of the neural correlates of these impairments by demonstrating a hyperactivation of three simultaneous brain networks (executive, saliency and social cognition networks) in the same ecological task in our ASD sample.

In sum, we provided novel clues to the current understanding of the neurocognitive and functional profile of ASD, namely in which concerns EF and SC. By using different approaches and methodologies and studying different ASD samples, we added to current knowledge by characterizing, for the first time, the adaptive, neurodevelopmental and intellectual profiles of Portuguese ASD population and clearly corroborating the link between EF and SC using an ecological approach.

Resumo

A perturbação do espectro do autismo (PEA) é uma perturbação crónica do neurodesenvolvimento, com uma elevada prevalência na população mundial que se manifesta na infância. Caracteriza-se por défices na interação e comunicação social, acompanhados pela presença de interesses restritivos assim como comportamentos repetitivos e estereotipados. Estes indivíduos manifestam ainda alterações noutros domínios relevantes como o desenvolvimento psicomotor, o funcionamento intelectual e o comportamento adaptativo, afetando negativamente a aprendizagem de competências de autonomia e a capacidade para resolver situações do dia-a-dia. Défices ao nível do funcionamento executivo são também comuns nesta patologia, tendo um impacto significativo na execução de tarefas quotidianas que envolvem competências mais complexas como a cognição social, que constitui um dos sintomas centrais na PEA. Vêm sendo propostos vários modelos cognitivos na tentativa de explicar este conjunto de sintomas e dificuldades característicos dos indivíduos com PEA. Na verdade, esta é uma das patologias mais estudadas e, no entanto, uma das que desperta mais dúvidas e incertezas na comunidade científica. A constelação de défices frequentemente observados nestes doentes constitui uma excelente oportunidade para explorar, usando a neuroimagem, os mecanismos neuronais que estão na base de alterações do funcionamento executivo e da cognição social. Outro ponto importante prende-se com o facto de que melhor conhecimento do funcionamento executivo e da cognição social, pode constituir um valioso contributo para compreender as dificuldades cognitivas e funcionais encontradas nestes indivíduos.

O foco desta tese prende-se, primeiramente, com a investigação do perfil funcional, intelectual e de neurodesenvolvimento desta população, pretendendo-se ainda esclarecer de forma inequívoca a ligação entre o funcionamento executivo e a cognição social, duas das áreas substancialmente afetadas nesta doença.

O primeiro estudo que compõe esta tese incidiu sobre a investigação funcional, tendo sido especificamente investigado o perfil de comportamento adaptativo destes doentes assim como a importância do quociente de inteligência para explicar estas competências. Para isso, foram recrutados participantes com outras perturbações do neurodesenvolvimento (ODN), nomeadamente perturbação do desenvolvimento intelectual (PDI) e dificuldades de aprendizagem, que constituíram um importante modelo de comparação. Neste estudo demonstrámos que, na PEA, a área do comportamento adaptativo que apresenta maior comprometimento prende-se com a socialização, o que constitui um fator distintivo da amostra com ODN, independentemente da PDI. Foi também possível verificar que a

comorbilidade com PDI tem um impacto negativo sobre o funcionamento geral, especialmente na PEA. Por outro lado, o nosso estudo revelou de forma surpreendente que a idade cronológica tem uma associação negativa com medidas do comportamento adaptativo.

A tentativa de obter uma caracterização aprofundada do fenótipo da PEA foi o foco do segundo trabalho experimental, através do estudo do perfil intelectual destes doentes quando comparados com indivíduos com ODN. Foram reunidas evidências de que indivíduos com PEA apresentam resultados inferiores no quociente de inteligência verbal quando comparado com o quociente de inteligência de realização. Adicionalmente a medida que melhor distingue os grupos experimentais é o Índice de Velocidade de Processamento, que tem um impacto significativo no funcionamento executivo. Surpreendentemente, este estudo revelou que o perfil de competências e défices encontrado em doentes com PEA com e sem PDI é distinto e que o perfil intelectual está associado ao comportamento adaptativo, contudo, a mesma associação não se verifica para os sintomas nucleares da PEA.

O perfil de neurodesenvolvimento na PEA foi igualmente abordado. Foi investigada a existência de marcadores precoces do perfil de neurodesenvolvimento suscetíveis de predizer mais tarde a aquisição ou não da linguagem expressiva, a qual influencia fortemente o perfil funcional e a cognição social destes indivíduos. Os nossos resultados revelaram que capacidades centrais (inteligência global e não-verbal) em idades precoces, são relevantes como, preditores do desenvolvimento da linguagem em crianças com PEA.

De seguida o foco deste trabalho centrou-se no estudo da cognição social e do funcionamento executivo.

Primeiramente, investigámos a capacidade de atenção social, que integra a cognição social, na PEA, através do uso de um paradigma experimental construído para o efeito, tendo por base um instrumento de avaliação amplamente usado no processo de diagnóstico. Reunimos evidência de que a alocação da atenção social depende do tipo de tarefa apresentada, sugerindo que os défices de atenção podem ser minimizados através da implementação de estratégias de ação orientadas para objetivos.

Pretendemos também investigar a associação entre funcionamento executivo e cognição social através do estudo do desempenho comportamental, do padrão de movimentos oculares e dos correlatos neuronais numa tarefa com validade ecológica e orientada para objetivos. Esta tarefa requeria que o participante fizesse uma compra no supermercado, uma atividade do dia-a-dia que implica o recrutamento de funções executivas e cognição social. Verificámos que os défices de atenção podem ser minimizados através do

uso de estratégias de ação focadas em objetivos com o recurso a pistas orientadoras destacando, assim, a importância do contexto, mais ou menos estruturado, e do esforço cognitivo exigido em cada tarefa no desempenho obtido. No seu conjunto, os nossos dados evidenciam que o contexto e o tipo de tarefa a executar têm reflexo na alocação da atenção na PEA.

Por fim, conseguimos compreender durante a execução de uma compra no supermercado (tarefa experimental com validade ecológica) os correlatos neuronais encontrados na PEA, onde foi demonstrado um aumento da atividade neuronal em áreas pertencentes a três redes neuronais (executiva, saliência e cognição social).

Em suma, o trabalho aqui apresentado contribui com novas pistas que permitem melhorar a compreensão do perfil neurocognitivo e funcional nos indivíduos que sofrem de PEA, particularmente no que respeita ao funcionamento executivo e à cognição social. Aplicando diferentes abordagens metodológicas e fazendo uso de diversas técnicas para o estudo de grupos com PEA, caracterizámos, pela primeira vez, os perfis adaptativo, de neurodesenvolvimento e intelectual em amostras da população portuguesa com PEA e estabelecemos, de forma inequívoca, a associação entre o funcionamento executivo e a cognição social através do uso de uma experiência ecológica do ponto de vista neurocomportamental.

Contents

List of Abbreviations

3D	Three-Dimensional
A	Anterior
ABC	Adaptive Behaviour Composite
ACC	Anterior Cingulate Cortex
ACID	Arithmetic, Coding, Information and Digit Span
ACK	Acquired Knowledge
ADDM	Autism and Developmental Disabilities Monitoring
ADHD	Attention Deficit Hyperactivity Disorder
ADI	Autism Diagnostic Interview
ADI-R	Autism Diagnostic Interview – Revised
ADI-R L/C	ADI – R Language/Communication
ADI-R RB/I	ADI-R Repetitive Behaviours/Interests
ADI-R RSI	ADI-R Reciprocal Social Interactions
ADOS	Autism Diagnostic Observation Schedule
ADOS COM	ADOS Communication
ADOS SI	ADOS Social Interaction
AFD	Average Fixation Duration
AOI	Area of Interest
APSP	Assessment in the Preschool Period
ASD	Autism Spectrum Disorder
ASD_ID	ASD with Intellectual Disability
ASD_NID	ASD with no Intellectual Disability
ASD_NV	Non-Verbal Autism Spectrum Disorder
ASD_V	Verbal Autism Spectrum Disorder
BA	Brodmann Area

BANC	Coimbra Neuropsychological Assessment Battery
BOLD	Blood-Oxygen-Level-Dependent Contrast
BSID-II	Bayley Scales of Infant Development
CA	Chronological Age
CDC	Centers for Disease Control and Prevention
CEN	Central Executive Network
COM	Communication
COR	Coronal Plane
DLPFC	Dorsolateral Prefrontal Cortex
DLS	Daily Living Skills
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5
DT%	Dwell Time Percentage
ED	Executive Dysfunction
EF	Executive Functioning
EPI	Echo-Planar Imaging
ET	Entry Time
F	Female
FDI	Freedom from Distractibility Index
FFD	First Fixation Duration
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
FSIQ	Full-Scale Intelligence Quotient
FT%	Fixation Time Percentage
GLM	General Linear Model
GMDS	Griffiths Mental Development Scales
ID	Intellectual Disability
IPL	Inferior Parietal Lobule

IQ	Intelligence Quotient
IQR	Interquartile Range
L	Left
LCD	Liquid Crystal Display
LH	Left Hemisphere
M	Male
MANOVA	Multivariate analysis of variance
Mdn	Median
MFG	Middle Frontal Gyrus
MNI	Montreal Neurological Institute
MPFC	Medial Prefrontal Cortex
MPRAGE	Magnetization-Prepared Rapid Acquisition Gradient Echo
MRI	Magnetic Resonance Imaging
NDT%	Net Dwell Percentage
NormD	Normalized Dwell
OCD	Obsessive–Compulsive Disorder
OFC	Orbitofrontal Cortex
OND	Other Neurodevelopmental Disorders/Outras patologias do Neurodesenvolvimento
OND_ID	OND with Intellectual Disability
OND_NID	OND with no Intellectual Disability
P	Posterior
PDI	Perturbação do Desenvolvimento Intelectual
PEA	Perturbação do Espectro do Autismo
pgACC	Pregenual Anterior Cingulate Cortex
PCC	Posterior Cingulate Cortex
PFC	Prefrontal Cortex

PHG	Parahippocampal Gyrus
PIQ	Performance Intelligence Quotient
POI	Perceptual Organization Index
PSI	Processing Speed Index
R	Right
RH	Right Hemisphere
RSP	Reassessment in the School Period
SAG	Sagittal Plane
SC	Social Cognition
SCAD	Symbol Search, Coding, Arithmetic and Digit Span
SD	Standard Deviation
SE	Standard Error
SMA	Supplementary Motor Area
SOC	Socialization
SPA	Spatial Ability
SPL	Superior Parietal Lobule
SPSS	Statistical Package for Social Sciences
SQA	Sequencing Ability
SS	Standard Scores
STS	Superior Temporal Sulcus
TD	Typical Neurodevelopment
TE	Echo Time
ToM	Theory of Mind
TPJ	Temporo-Parietal Junction
TR	Repetition Time
TRA	Transversal Plane
USA	United States of America

VABS	Vineland Adaptive Behaviour Scales
VCA	Verbal Conceptualizing Ability
VCI	Verbal Comprehension Index
VIQ	Verbal Intelligence Quotient
vlPFC	Ventrolateral Prefrontal Cortex
vmPFC	Ventromedial Prefrontal Cortex
WAIS-III	Wechsler Adult Intelligence Scale – Third Edition
WASI	Wechsler Abbreviated Scale of Intelligence
WCC	Weak Central Coherence
WISC	Wechsler Intelligence Scale for Children
WISC-R	Wechsler Intelligence Scale for Children-Revised
WISC-III	Wechsler Intelligence Scale for Children – Third Edition
WISC-IV	Wechsler Intelligence Scale for Children – Fourth Edition

List of Figures

List of Tables

INTRODUCTION

CHAPTER 1

CHAPTER 1

1.1. General Introduction of the thesis

"I think prime numbers are like life. They are very logical, but you could never work out the rules, even if you spent all your time thinking about them"
(Christopher Boone, ASD
In Mark Haddon, The Curious Incident of the Dog in the Night-Time)

In this introductory chapter, the central clinical and neurocognitive characteristics of Autism Spectrum Disorder (ASD) will be described as well as the current knowledge regarding the nature of neuroanatomical functioning in this disorder and the most prominent hypotheses for its causes. Since the main focus of the current work was to investigate the link between executive functions and social cognition, particular emphasis will be given to those specific cognitive theories on the explanation of ASD clinical phenotype and to evidence of the relationship between cognitive and social impairments.

The final part of this chapter will present the general outline of this thesis and elucidate its core objectives.

Historical overview

The term autism derives from the Greek word *autos*, "of itself", and the nominal suffix *-ism* that translates to an orientation or state. In a literal sense, autism is defined as a condition or state of someone who appears to be unusually self-absorbed or a tendency to view life in terms of one's own needs and desires.

Defining the concept of autism, beyond etymology, seems to be a complex task. Many authors have focused on the subject, carrying out various investigations and reformulating the term in an attempt to find a universally accepted definition and enlightening characterization of this disorder.

Eugene Bleuler was the first author in 1911 to use the term autism to designate the subject's symbolic "inner life" which was not readily accessible to observers and integrates a category of the thought that is present in schizophrenia, a designation also introduced by this author (Bleuler, 1911, 1950).

In 1943, Leo Kanner, a pedopsychiatrist at John Hopkins University, briefly described eleven children whose characteristics did not correspond to any previously described syndrome. His description was based on a change in the children's neurodevelopment, in which there was an inability to establish relationships with others, delay and alterations in language acquisition and use, an obsessive desire for immutability in the environment, and a tendency toward repetitive and ritualized activities (Kanner, 1943). With the publication of the article *Autistic disorders of affective contact*, Kanner (1943) intended to give to this disorder a differentiating identity from the *infantile psychosis* that had been described so far. The finding that the clinical symptoms of this syndrome manifested itself very early and that isolation was

apparent from the earliest months of life led Kanner (1943) to assume the innate and biologically determined origin of this condition.

This disorder was described almost simultaneously by Hans Asperger a paediatrician in Vienna in 1944. This author, with the publication of an article entitled *Die Autistischen pshychopathen im kindesalter*, described the same type of disturbance in children with better verbal ability and fine motor difficulties, using the denomination of autistic psychopathy (Asperger, 1944). However, this publication was only known to the general scientific community when Uta Frith, in 1991, published Asperger's translated and annotated article (Asperger, 1991).

According to Frith (1989) the difference between the two descriptions does not appear to have a clearly sustainable basis, but Asperger's definition was, however, broader than Kanner's, since it was used to describe subjects with autism with intelligence close to normal standards and with verbal skills.

In the 1950s and 1960s, despite the aforementioned publications, autism continued to be ignored as a distinct condition and misunderstood with schizophrenia. Thus, in the first two editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM and DMS-II) of the American Psychiatric Association's, autism was considered a psychosis and was classified as a "schizophrenic reaction or childhood-type schizophrenia" (American Psychiatric Association, 1952, 1968). The dominant causal theory was strictly behavioural and psychogenic. In 1967, Bettelheim considered that autistic behaviour was the result of an early maladjusted affective relationship between parents and child (Bettelheim, 1967).

In the ensuing decade, in an attempt to differentiate childhood-onset mental disorders, such as autism, from those that began later, such as schizophrenia, a number of researchers have developed work that has proved important in changing their conception. In the 1970's, Rutter (1978), Ritvo and Ortiz (1976) also redefined the autism diagnostic criteria. Recognition of these works by the American Psychiatric Association resulted in the inclusion of autism, for the first time, in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) (American Psychiatric Association, 1980) in a new class of disorders, Global Developmental Disorders, differentiating autism from schizophrenia.

In the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders, text revision* (DSM-IV-TR) (American Psychiatric Association, 2000), autism encompassed autistic disorder (typical autism), Asperger's disorder and global developmental disorder without another specification (atypical autism).

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (American Psychiatric Association, 2013), which is the current standard reference for the

diagnosis of mental and behavioural disorders, defines autism as a clinical spectrum, using the term *autism spectrum disorder* (ASD) to define a complex chronic neurodevelopmental disorder that is characterized by impairments in social interaction and communication, as well as by repetitive and limited patterns of behaviour and interests. In the DSM-5, the individuals are also differentiated using additional clinical specifiers and modifiers, acknowledging the substantial clinical heterogeneity in ASD and recognizing multiple aetiologies for this unique disorder (Catherine Lord & Bishop, 2015).

Since 1943, when Kanner made his paradigmatic communication, great advances have been made in understanding the disturbances of the ASD, including its biological basis (Ozonoff & Rogers, 2003). Epidemiological studies and research on the behavioural, cognitive and neurodevelopmental phenotype have increased considerably in recent decades, which has allowed us to deepen our knowledge regarding this complex disorder. This led to better diagnostic practices and improved educational and therapeutic interventions, as well. Thus, in the last decades, the conception of this disorder, as well as the clinical practice, underwent valuable changes and were shaped by empirical research.

ASD is currently considered an organic, highly heritable and heterogeneous neurodevelopmental disorder. This medical condition results from early brain lesion with chronic neurological sequelae, clinically manifesting as neurodevelopmental and behavioural abnormalities, with underlying specific cognitive features. Commonly co-occurs with other neurological and biological conditions (Lord et al., 2020).

Epidemiology

Prevalence

The prevalence rate of ASD has been steadily increasing in the past decades (Hansen et al., 2015).

According to the DSM-5 (American Psychiatric Association, 2013), epidemiological studies indicated that prevalence of ASD in the United States of America (USA) has reached 1% of the population, with similar estimates in children and adults. It is not yet clear whether higher rates reflect expansion of the DSM-IV-TR diagnostic criteria to include subliminal cases, improved detection and growing awareness, differences in study's methodology or real increase in the occurrence of the disorder (Hansen et al., 2015).

In the last decades, in the USA, the Autism and Developmental Disabilities Monitoring (ADDM) Network from the Centers for Disease Control and Prevention (CDC)

has conducted systematic studies (Baio et al., 2018; Maenner et al., 2020). The last one, in 2016, in eleven ADDM Network sites from the USA, found the overall ASD prevalence estimate of 18.5 per 1.000 children (one in 54) aged 8 years, which is higher than previous estimates from the same ADDM Network. In addition, they found that ASD prevalence estimates also varied by sex and race/ethnicity, as well as gender, with males being four times more likely than females to have this diagnosis (Maenner et al., 2020).

A national epidemiological study carried out in Portugal (Oliveira, 2005) points to a prevalence of ASD of one case in every thousand school age subjects (1:1.000), with a predominance of males with a ratio of 3/1. In this study, a uniform distribution was also reported with regard to socio-economic level.

The variation of the estimates of the prevalence of ASD in various populations and settings may be attributed to the method of ascertainment used in the study, including definition of the diagnosis, sampling and the type of assessment: independent population case in contrast to administratively based sources.

The causes of the growth of estimates in prevalence over the last few years has been associated to several factors: improvement on diagnostic techniques, increase of the general awareness on autism, younger age of diagnosis and a high rate of false positive cases in screening instruments (Baio et al., 2018; Carbone et al., 2020; Lai et al., 2014; Lord et al., 2020; Maenner et al., 2020). Some studies have tried to quantify the impact of the changes in reporting practices and found that it can account for most (60%) of the increase in the observed prevalence of ASD in children (Hansen et al., 2015). Hence, despite this major contribution, other effects, like environmental factors, cannot be discarded (Lord et al., 2020).

Risk and protective factors

Epidemiological studies have identified various risk factors for ASD but none has proven to be necessary or sufficient alone for this disorder to develop, which stresses the importance of the research and understanding of gene–environment interplay (Corrales & Herbert, 2013).

Genetic studies have shown that recurrence risk of developing ASD in siblings of an affected individual is approximately 7–19% (Grønborg et al., 2013; Sally Ozonoff et al., 2011; Sandin et al., 2014) and estimates of heritability are high not only in twin (64−91%) (Tick et al., 2016) but also in whole genome genotyping studies (31−71%) (Gaugler et al., 2014). In the last decade, rare and *de novo* structural and sequence variation analysis in ASD identified genes and related aspects of the biology underpinning autism, notwithstanding with direct

relevance to only a small proportion of cases (Pinto et al., 2010; The Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium, 2017).

Evidence from the latest studies suggest that several environmental factors including vaccination, maternal smoking, thimerosal exposure, and assisted reproductive technologies are unrelated to risk of ASD (Modabbernia et al., 2017). In contrast, advanced parental age is being associated with higher risk of ASD (Wu et al., 2017). Gestational and birth complications that could affect neurodevelopment and are associated with trauma or ischemia and hypoxia have also shown strong links to ASD, whereas other pregnancy-related factors such as maternal obesity, gestational diabetes mellitus, valproate use during pregnancy, and caesarean section have shown a less strong (however significant) association with increased risk of ASD. Conversely, folic acid supplements before conception and during early pregnancy seem to be protective (Lord et al., 2020; Modabbernia et al., 2017). Evidence is emerging that prematurity and being of low birth weight are risk factors for later development of ASD (C. Wang et al., 2017). These factors are not considered causal, but could be reactive, independent or contributory for ASD (Lord et al., 2020).

Thus, although environmental factors cannot be discarded in the aetiology of ASD, its heritability is widely accepted, and it is therefore currently broadly accepted that there is a genetic component to many cases of ASD.

Clinical features and symptomatology

ASD is commonly described as complex chronic neurodevelopmental disorder characterized by impairments in social interaction and communication, repetitive and limited patterns of behaviour and interests, sensory anomalies and varying levels of intellectual disability (ID) (American Psychiatric Association, 2013; Lord et al., 2020).

Diagnosis

The ASD diagnosis is based exclusively on clinical criteria, a symptom-based definition since there are no specific diagnostic biomarkers available for the disorder (Mandy et al., 2015).

The diagnosis process of ASD is usually carried out through clinical observation along with the use of some well-established standardized assessment instruments. In the clinical observation, carried out by experienced clinicians, not all difficulties experienced by the child may become evident, which is why the report of the parents (or caregivers) is fundamental.

However, parents or caregivers do not have the expertise or experience of professionals to recognize all difficulties and interpret them, and for this reason information and tests by well-informed specialists in a controlled environment are also essential (Sally Ozonoff et al., 2005).

In sum, a diagnosis of autism is reached after obtaining a detailed neurodevelopmental history from the caregivers, often from the parents, and observation of the patient interacting with parents or other individuals (Risi et al., 2006). Children with ASD are now being identified at significantly younger ages, due probably to the raising awareness regarding this disorder (Bhat et al., 2014; Luyster et al., 2008).

The gold standard instruments to diagnose ASD are Autism Diagnostic Interview–Revised, ADI-R (Le Couteur et al., 2003; Catherine Lord et al., 1994), a parental or caregiver interview and Autism Diagnostic Observation Schedule, ADOS (Lord & Rutter, 1999; Catherine Lord et al., 1989), a direct structured proband assessment. These instruments should be complemented by a clinical examination performed by experienced clinicians, ideally in a multidisciplinary team, based on the current diagnostic criteria for ASD according to the DSM-5 (American Psychiatric Association, 2013), the current standard reference for the diagnosis of mental and behavioural disorders.

The DSM-5 (American Psychiatric Association, 2013), defines two main axis of symptoms found in ASD (A. Deficits in social communication and social interaction, and B. Restricted, repetitive patterns of behaviour, interests, or activities) and provides some examples. For the social interaction and communication deficits, the provided list of illustrative (not exhaustive) examples states:

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

A similar list of illustrative cases is provided for the restricted, repetitive patterns of behaviours, interests or activities, with the diagnosis in this axis to refer the need for

identifying at least two of those items, currently manifesting or that have manifested previously during the development of the child:

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behaviour (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat the same type of food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

The other axis specifies obligation of the presence of the symptoms in the early developmental stage (despite the possibility of becoming fully manifest when social demands exceed limited capacities or may be masked by learned strategies in later life), the impact that these symptoms have in social, occupational, or other important areas of current functioning and the exclusion of a better explanation for the disturbances (comorbid diagnosis).

Accompanied with these axes, a level of severity must be defined along with the diagnosis, in accordance with the following table:

Table 1.1.1. Severity level in ASD		
Severity Level	**Social Communication**	**Restricted, Repetitive Behaviours**
Level 3 "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. For example, a person with few words of intelligible speech who rarely initiates interaction and, when it occurs is only unusual approaches to meet needs. Responds to very direct social approaches.	Inflexibility of behaviour, extreme difficulty coping with change, or other restricted/ repetitive behaviours markedly interfere with functioning in all spheres. Great distress/ difficulty changing focus or action.
Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. For example, a person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communication.	Inflexibility of behaviour, difficulty coping with change, or other restricted/ repetitive behaviours appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/ or difficulty changing focus or action.
Level 1 "Requiring support"	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions. For example, a person who is able to speak in full sentences and engages in communication but whose conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful.	Inflexibility of behaviour causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.

NOTE. Adapted from DSM-5 (American Psychiatric Association, 2013)

Co-occurring conditions

In addition to the core features of ASD, already mentioned, there are co-occurring conditions, extensively recognized in research (Havdahl & Bishop, 2019; Lai et al., 2019). About 70% of the ASD individuals show at least one concurrent medical condition and 50% show two or more of these comorbidities (Lai et al., 2014).

These co-occurring conditions differ with age and neurodevelopmental stage. In preschool age, the most frequently observed in children with ASD are language delays, motor problems, epilepsy, difficulties with sleep and eating, and high levels of activity (Mannion et al., 2013). In turn, intellectual disability (ID), academic challenges, irritability, disruptive behaviours, as well as attention deficit hyperactivity disorder (ADHD), anxiety and obsessive–compulsive disorder (OCD), are the most common manifestations in the school-aged children with ASD, (Mannion et al., 2013; Maskey et al., 2013). Some of these often issues continue to be present in adolescence and adulthood, and symptoms of depression become more prevalent (Pezzimenti et al., 2019).

There is growing evidence, based on administrative case-finding data, that individuals with ASD have premature mortality, increased risk of self-harm and possibly suicide (Hirvikoski et al., 2016). Immune conditions, sleep disorders and obesity are also more prevalent in ASD adults than in the general population at same age (Croen et al., 2015).

This high incidence of co-occurring conditions could be an effect of growing up with ASD, a result of shared pathophysiology, shared symptom domains and associated mechanisms. Generally, the more co-occurring conditions, the greater the ASD severity and the individual's disability, with a substantial impact in the autonomy and well-being at each age (K. A. Havdahl et al., 2016; Mattila et al., 2010; Nicolaidis et al., 2013). Since ASD traits and characteristics often overlap with symptoms of these other disorders, the differential diagnosis is often hardened (Bauman, 2010). This has important implications for the clinical practice and the need of clinical research that provide appropriate group comparisons, including other neurodevelopment disorders, is highlighted by this issue. In the work developed in this thesis, this was carefully considered in order to capture ASD specificities that may contribute to better differential diagnostic strategies.

Functional and Cognitive Phenotype of Autism Spectrum Disorder

To develop a deeper understanding of how individuals with ASD experience the world, their attributes, abilities, and difficulties, we must characterize their functional and cognitive profile.

ASD core symptoms have an early presentation, typically during the first two years of age. Previous studies have enhanced the relevance of careful clinical records, specially, regarding the age of onset of psychomotor developmental milestones (Baghdadli et al., 2003; Chawarska et al., 2007; De Giacomo & Fombonne, 1998; Ferreira & Oliveira, 2016). These neurodevelopmental milestones are crucial elements for characterizing the clinical history of ASD, since they are linked with the specific clinical presentation of this disorder (for instance, the more severe presentations have earlier onset), as well as with cognitive skills and adaptive functioning (Ferreira & Oliveira, 2016).

Functional profile of Autism Spectrum Disorder: Adaptive behaviour

Since ASD diagnosis is based on behavioural presentation and neurodevelopmental deficits, one of the first difficulties to be noted, along with the ones related to core symptoms, is adaptive behaviour impairment. Adaptive behaviour refers to any behaviour that allows an individual to adjust to each situation appropriately and effectively. In other words, it is the capacity to attain to conceptual, social and practical demands on our daily life or the extent to which an individual is capable of being self-sufficient in real-life situations (American Association on Mental Retardation, 2002; American Psychiatric Association, 2013; S Sparrow et al., 1984). In ASD population, adaptive behaviour impairments are a primary impediment to an autonomous life, they appear early in life and, without appropriate, intensive, and effective intervention, persist throughout life (Matson et al., 2009; Paul et al., 2014; Ventola et al., 2014). They affect a wide range of tasks that go from basic personal and domestic autonomy (such as hygiene, dressing, making meals) to self-sufficiency (such as having a competitive employment or managing your money) (Dawson et al., 1998). Therefore, this life-long incapacity is one of the more important in the prognosis of ASD individuals and as a consequence, has a great repercussion in society and economy, with large cost to the society (Knapp et al., 2009).

Adaptive behaviour is an age-related construct, which means that as children grow older, adaptive behaviour becomes more complex and demanding (Sparrow et al., 2005). As a consequence, the gap between cognitive and adaptive skills in ASD becomes more evident (Fenton et al., 2003; Kanne et al., 2011; Klin et al., 2007; Szatmari et al., 2003; Sparrow et al.,

2005). In fact, good adaptive skills are assumed as better predictors of positive outcome in adulthood, than cognitive variables (Farley et al., 2009).

A specific profile of adaptive behaviour has been associated to ASD individuals, mostly based on assessments with the Vineland Adaptive Behaviour Scales (VABS) (Sparrow et al., 1984), which is the most studied measure of adaptive behaviour in ASD. This profile shows relative strengths in daily living skills, intermediate deficits in communication domains, and significant impairments in socialization (Bölte & Poustka, 2002; Carter et al., 1998; Gillham et al., 2000; Liss et al., 2001). Additionally, ASD individuals showed greater adaptive impairments when compared to chronological and mental-age matched individuals without ASD, but with ID or learning disabilities (Carpentieri & Morgan, 1996; Loveland & Kelley, 1991; Perry et al., 2009; VanMeter et al., 1997; Volkmar et al., 1987). Even ASD individuals without ID present a discrepancy between the levels of cognitive functioning and the ability to apply these skills to a real-world context (A Klin et al., 2007).

However, the precise relevance of intelligence to the symptomatic expression of ASD and direct involvement in the subject's adaptive behaviour remains unclear. This specific question will be further explored and the first and broader characterization of the adaptive behaviour in a large Portuguese sample will be further detailed in chapter 2.1 of this thesis.

Neurodevelopmental and intellectual profile of Autism Spectrum Disorder

A cognitive profile represents an individual's pattern of abilities, where relative strengths and difficulties across several cognitive domains are identified (Groth-Marnat, 2003). Several assessment instruments have been used in numerous studies about the cognitive profile of ASD. Nonetheless, present literature has failed to provide a proper cognitive profile in ASD, first, because most studies on cognitive aspects tend focus only in one particular characteristic, and second, most research into ASD cognition study phenomena that exists at a group level. In sum, this means that even the most widely accepted cognitive characteristics of ASD are not universal, nor specific to ASD (Mandy et al., 2015).

Despite the fact that an individual having ASD is not synonymous of having global neurodevelopmental delay or ID, and although it may occur simultaneously, the neurodevelopmental and intellectual profile of individuals with ASD differs from the individuals with other neurodevelopmental disabilities. The assessment of the neurodevelopmental and intellectual profile in individuals with ASD is of utmost importance, not only for the characterization of diagnosis (for instance, the DSM-5 norms requires the specification whether ASD is associated with an intellectual disability), for differential

diagnosis, for comorbidity definition, but also for intervention planning (American Psychiatric Association, 2013).

In the last years, although ASD comorbidity with ID has been decreasing, it remains common, being that about one third to half of ASD subjects have co-occurring ID (American Psychiatric Association, 2013; Centers for Disease Control and Prevention, 2009, 2012, 2014). This has a serious social and economic impact, because individuals with ASD with comorbid neurodevelopmental delay or ID, generally have lower social adaptation abilities, require further support and early intensive intervention to promote their learning progress, which may influence the outcome (Gardner et al., 2018; Hinnebusch et al., 2017; Miller et al., 2019).

The psychomotor developmental profile of ASD is usually characterized by "developmental dissociation", with a substantial difference in the level of neurodevelopment across various skill areas. The visual and non-verbal skills are usually of disproportionate strength compared to verbal skills (Akshoomoff, 2006; Tony Charman, Drew, et al., 2003; Robert M. Joseph et al., 2002; Paul et al., 2008; Thurm et al., 2007). General measures of cognition have been associated with language outcome in children with ASD by early studies (Mundy et al., 1990), which were later emphasized in studies that established non-verbal cognitive ability as a strong predictor of both receptive and expressive language skills (Anderson et al., 2007; Tony Charman et al., 2005; Tony Charman, Baron-Cohen, et al., 2003; Luyster et al., 2008; Paul et al., 2008; Thurm et al., 2007; Wodka et al., 2013).

Given that one of the major concerns for parents, families and professionals in general is related to the acquisition of verbal language in ASD children, the investigation of differences in the early neurodevelopmental profile and the assessment of what and when may determine that acquisition is of great importance (these implications will be further detailed and explored in Chapter 2.3. of this thesis).

In what concerns to the intellectual profile, the Wechsler Intelligence Scales are the most frequently used intelligence tests in the world and one of the most commonly used tools for measuring intelligence in ASD individuals (Goldstein, Naglieri, J. A., & Ozonoff, S., 2008; R M Joseph, 2011; L Mottron, 2004; Rabiee et al., 2019; Zwick, 2017). Despite the large number of studies of the intellectual profiles of ASD using the Weschler scales, there is no conclusive data regarding the relationship between verbal and non-verbal intelligence quotients (IQ). A number of studies reported that ASD profile is characterized by higher scores on Performance IQ (PIQ) than on Verbal IQ (VIQ) (Allen et al., 1991; Asarnow et al., 1987; Freeman et al., 1985; Lincoln et al., 1988; Narita & Koga, 1987; Ohta, 1987;

Schneider & Asarnow, 1987; Siegel et al., 1996; Venter et al., 1992), while others have documented the inverse: higher VIQ than PIQ (Minshew et al., 1992; Szatmari et al., 1990). There are also studies that found no differences between the level of verbal and non-verbal intelligence (Ghaziuddin & Mountain-Kimchi, 2004; Goldstein et al., 2008).

Besides neurodevelopmental and intellectual global level, specific cognitive deficits are linked to ASD, so, it could be expected that individuals with ASD would show other cognitive weaknesses and strengths. The most recent meta-analysis on cognitive profile, included 75 studies with ASD adults with an IQ within a normal range (without ID), combined samples of 3361 individuals with ASD and 5344 matched neurotypical adults, and showed consistent impairments in individuals with ASD across all cognitive domains: reasoning and problem solving, processing speed, attention and vigilance, working memory, visual learning and memory, verbal learning and memory, verbal comprehension, and verbal fluency (Velikonja et al., 2019). They found a cognitive profile with major impairments in processing speed, followed by verbal learning and memory, as well as reasoning and problem solving. On the other hand, the least altered domains were attention, vigilance, and working memory. However, they found a significant heterogeneity in studies for verbal learning and memory.

Notwithstanding the fact that much progress has been made in determining the cognitive profile of strengths and weaknesses of subjects with ASD, a number of outstanding questions remain to be answered, namely: i) if the strengths and deficits are the same in high and low-functioning ASD; ii) whether cognitive subgroups exist; iii) and how cognition is associated with core ASD features and adaptive behaviour, as well as associated psychopathology. Small sample sizes, a focus on single domains of cognition and the absence of comprehensive behavioural phenotypic information are methodological factors that have contributed to these limitations in the scientific knowledge (Charman et al., 2011). These questions will be further described and explored in Chapter 2.2.

Cognitive theories of Autism Spectrum Disorder

The impairments and characteristics of ASD have been the subject of countless studies, which have led to the formulation of several theories, in an attempt to explain both its aetiology and the diversity of symptoms. Various cognitive theories have tried to describe and characterize the ASD phenotype, some focused on the core features of the diagnosis, and others having a broader approach. The cognitive theories overlap and are not mutually

exclusive, but each of them has a valuable contribution to the understanding of ASD individuals.

The three most prominent theories that have dominated research and have been especially influential in shaping current ideas about the cognitive characteristics of ASD are: Theory of Mind (ToM) (Baron-Cohen et al., 1985), Weak Central Coherence (WCC) (Frith & Happé, 1994) and Executive Dysfunction (ED) (Pennington & Ozonoff, 1996).

Theory of Mind

The ToM account focuses in one of the core features of ASD by suggesting that these individuals have an impairment in the development of social cognition, having an inability to mentalise, or failure to infer others' mental states (beliefs, desires, intentions, imagination, emotions) that cause action (Baron-cohen, 2001).

One of the most widely used tasks for the study of ToM is the false-belief task, developed by Wimmer and Perner (1983) where the participant watches a sequence of events, usually enacted by dolls, where one doll has a belief about the location of an object that is incongruent with its real location. The participant then is asked where he thinks the doll will look, and in order to give the correct answer the participant must infer the mental state of the doll ["*I think the doll thinks* (the object is in that location)"]. Baron-Cohen et al. (1985) in the seminal work about ToM in ASD with this false-belief task, found that 80 percent (16/20) of children with ASD failed to infer the mental state of the doll and therefore, presented a deficit in their theory of mind.

However, some weaknesses of this theory as an explanation of the core symptoms of ASD, in particular the issue of universality, were pointed out (Happé, 1994). This led to an open debate and a reformulation of the ToM by Baron-Cohen in which the ASD individuals have a delay on ToM, rather than a deficit. This was proved in a study where they used a second-order false belief task ("*I think he thinks she thinks*") and found that none of the children with ASD could respond correctly, while 90 percent of individuals with typical neurodevelopment (TD) and 60 percent of children with Down Syndrome had a correct answer (Baron-Cohen, 1989). Nevertheless, subsequent studies questioned these new conceptualization of ToM, having contradictory results (Bowler, 1992; Ozonoff, Pennington, et al., 1991; Ozonoff, Rogers, et al., 1991). Some researchers, then, moved into a different territory of language and face processing in the study of ToM in ASD, developing specific advanced tests for that purpose that included: the Eyes Test (Baron-Cohen et al., 1997; Baron-Cohen, Wheelwright, Hill, et al., 2001; Baron-Cohen, Wheelwright, Spong, et al.,

2001), the Recognition of Faux Pas Test (Baron-Cohen et al., 1999), and the Strange Stories test (Happé, 1994; Jolliffe & Baron-Cohen, 1999). Some researchers considered ToM as a social problem-solving (Peterson & Bowler, 2000) and other theories have arisen as a reconceptualization, which is the case of the Enactive Mind hypothesis (Klin et al., 2003). This hypothesis stated that ASD individuals, contrary to TD, were unprepared to interpret social meaning, and overextend this capacity to find social meaning even in non-living entities (this last hypothesis will be further discussed in chapter 2.5).

Weak Central Coherence Account

The WCC theory has been proposed to addressed cognitive weaknesses and strengths in ASD and stated these individuals have a tendency to show a local bias, a detailed-focused or piece-meal way of processing incoming information, while TD individuals process information by extracting overall meaning or gist, searching for global coherence (Frith, 2003; Frith & Happé, 1994; Happé, 1999).

This account explained cognitive phenotype of ASD in terms of dissociation between local and global information processing and redirected and strengthened research into the perceptual abilities of individuals with ASD (for a review on this theory, please see [Happé & Frith, 2006; Happé, 1999]). An extensive range of experimental paradigms were used to measure WCC, namely the block design subtest (Caron et al., 2006; Shah & Frith, 1993), the embedded-figure test (Frith & Shah, 1983; Mottron et al., 2003), the copying impossible-figure (Mottron et al., 1999), visual illusion tasks (Happé, 1996; Ropar & Mitchell, 1999) and hierarchical figures, such as Navon stimuli (Mottron et al., 2003; Navon, 1977; Plaisted et al., 1999; Rondan & Deruelle, 2007). Despite the great interest that this theory has generated in the cognitive research of ASD, the body of evidence includes many contradictory results. One of this conflicting results is our previous work (Bernardino et al., 2012), using the Navon hierarchical figures, to study coherent visual processing. We found that ASD participants only showed the expected pattern of coherence loss in task conditions favouring local analysis, but this trend actually tended to disappear when matching for ID, what led us to conclude that abnormal central coherence does not provide a comprehensive explanation of ASD deficits.

Executive Dysfunction Theory

The ED theory (Pennington & Ozonoff, 1996) offers a distinct conceptualization of cognition in ASD, compared to the other two theories previously presented, for not focusing on one domain-specific deficit. Contrasting with ToM, ED was conceived in the premise that some ASD symptoms, like need for sameness, a difficulty on switching attention, a tendency to perseverate and a lack of impulse control, were similar to those associated with frontal lobe injury, also known as Dysexecutive Syndrome (Baddeley & Wilson, 1988).

Executive functions are a theorized collection of mental functions which coordinate and manage other cognitive processes such as planning, working memory, impulse control, inhibition and mental flexibility, as well as for the initiation and self-monitoring required for the execution of purposeful, effective, non-routine actions (Stuss & Knight, 2009). Ozzonoff et al. (1991) gave a more complete definition:

"Executive function is defined as the ability to maintain an appropriate problem-solving set for attainment of a future goal; it includes behaviours such as planning, impulse control, inhibition of prepotent but irrelevant responses, set maintenance, organized search, and flexibility of thought and action."(p.1083)

Gillberg and Coleman (Coleman & Cillberg, 1994) added one central characteristic to the previously established definition of executive functions which was the concept of motivation. Thus, these authors defined executive functions as the abilities needed to work in a motivated manner, towards a goal that may not be reached immediately.

Executive functions have also been divided as core or high-order executive functions (Goldstein & Naglieri, 2014b), being referred to as "cool" executive functions (Zelazo & Mller, 2005), while the cognitive processes, which represent goal-oriented behaviours, mediated by affective and motivational demands are called "hot" executive functions (Zelazo & Carlson, 2012; Zimmerman et al., 2016).

There has been a large number of studies investigating this dichotomy, since the introduction of the ED hypothesis in ASD. The studies on "cool" executive functions have been synthesized in a number of meta-analyses (Demetriou et al., 2018; Lai et al., 2017) and focus manly in set shifting (ability to shift mindset to new ideas), response inhibition (capability to impede a dominant response), and working memory (maintaining and updating information in short-term memory). The first studies focused on set shifting and its connection to stereotypic and repetitive behaviours, concluding that there is a link between

cognitive rigidity and the perseverance to routines and stereotypies observed in ASD (Boyd et al., 2009; Hill, 2004a; Lopez et al., 2005; Sally Ozonoff & Jensen, 1999; South et al., 2007).

The "hot" executive functions are now being increasingly investigated, in part because of the thought influence on social cognition (Jones, Simonoff, Baird, Pickles, Marsden, Tregay, Happé, et al., 2018; Kouklari et al., 2017; Kouklari et al., 2018; Zelazo & Carlson, 2012), but also in lifelong functioning outcomes, such aging in ASD (Wallace et al., 2016).

ASD individuals present impairments in executive functions from early ages, which is thought to have a significant impact in their social cognition and adaptive behaviour contributing to everyday deficits, disability and absence of autonomy (Demetriou et al., 2018; Geurts, van den Bergh, et al., 2014; Lai et al., 2017; Leung & Zakzanis, 2014). Executive functioning is also associated with socialization and communication in ASD (Dichter et al., 2009; Gilotty et al., 2002; Kenworthy et al., 2009; Leung et al., 2016; McEvoy et al., 1993; Pellicano et al., 2006). Some studies found that impaired executive functioning (EF) may have a negative impact on the development of the ToM (Jones, Simonoff, Baird, Pickles, Marsden, Tregay, Happe, et al., 2018; Russell et al., 1999), or joint attention (McEvoy et al., 1993). Faja and Dawson (2014) found that an individual's flexibility to communicate with and respond to others, adjust social behaviours within interactional contexts, and to multi-task between processing dynamic social information and formulating an appropriate response, may be influenced by difficulties in set shifting or working memory. On the other hand, Ozonoff and colleagues (2004) found no significant associations between performance-based executive functions and social skills, but found that planning was associated with adaptive communication skills. On the contrary, Kenworthy and colleagues (2009) found performance-based measures of divided attention and verbal fluency were related to fewer social symptoms. Other studies failed to find significant connections between EF and the social domain of impairment in ASD (Cantio et al., 2016; Robert M. Joseph & Tager-Flusberg, 2004; Landa & Goldberg, 2005)

Overall, findings on EF in ASD suggest a broad impairment (Demetriou et al., 2018; Lai et al., 2017) that is characterized by marked heterogeneity (Geurts, Sinzig, et al., 2014). Investigation has predominantly focused upon understanding the putative causal relationship between difficulties in executive functions and ASD symptoms. However, executive functions are thought to have a role in the real-life outcomes of individuals with ASD, such as social competence, adaptive behaviour, and academic achievement. It is crucial to definitely establish this link in order to better understand the extent of ED in ASD and allow

for suitable interventional strategies with impact in patients' quality of life. These questions will be further examined and investigated in Chapters 2.5 and 2.6.

Assessment of executive function: need for ecological validity

Assessment of executive functions has classically focused on neuropsychological measures sensitive to frontal lobe damage (Delis, Kaplan and Kramer, 2001; Lezak et al., 2012), using tools such as the Stroop Colour (Stroop, 1935) and Wisconsin Card Sorting Tests (Lezak, 2004), experimental tasks measuring discrete executive functions (Miyake et al., 2000), and behavioural rating scales (Goldstein & Naglieri, 2014a; Roth et al., 2005). These last were aimed to provide more ecologically valid assessments of executive functions focusing on executive regulation of everyday behaviours (Burgess et al., 2006; Kenworthy et al., 2008). However, most of the times, these behavioural rating scales are based on information given by parents or caregivers, which can lead to biased conclusions.

Ecologically valid measures of executive functions can also include tasks that attempt to replicate real-world scenarios and experiences. For that purpose, these tasks have to produce logically sound data representing individuals' interactions with their surroundings (Wallisch et al., 2018). Ecological validity is the degree to which results obtained through tasks and assessments are related to those obtained in authentic contexts (Chaytor & Schmitter-Edgecombe, 2003). These tasks should be representative (the extent to which an assessment corresponds to situations outside the laboratory or clinic spaces) and generalizable (the degree to which worries on the assessment are concerns in everyday life) (Burgess et al., 2006).

Ecological validity is increasingly appraised in research, particularly in respect to measures of executive functions. The use of brain imaging and other sophisticated research techniques, as eye-tracking has shifted neuropsychology's role from diagnosis and lesion location to the definition of functional capacities at everyday-life: at home, work, and school, and elevated the importance of ecologically valid measures of neuropsychological constructs (Chaytor & Schmitter-Edgecombe, 2003; Manchester et al., 2004). The development of ecologically valid executive functions tasks designed to simulate real life problem-solving is of utmost importance, taking also in account the social and language demands when striving for verisimilitude (Kenworthy et al., 2008).

Unravelling impairments of executive functions of everyday life and understand its connections with deficits in social cognition is one of the major questions that remains to be answered. This question will be further addressed in the Chapters 2.5 and 2.6.

Social cognition in Autism Spectrum disorder

Social deficits in ASD are a core feature of the disorder and are present not only in communication and in interaction, but also in social cognition. This cognitive function is a complex capability that depends on a range of competences, including social attention, social orienting, social motivation, emotion recognition, learning from others, empathy and verbal abilities (Happé et al., 2017). ASD individuals show deficits in other domains, including deviations in basic attentional processes; diminished attentional allocation to social stimuli across a number of contexts; impairments in attention to faces or social stimuli across the lifespan, as well as attention during social exchanges (Chita-Tegmark, 2016a; Guillon et al., 2014).

The capacity to direct the attention to social stimuli, namely, people, faces and body motion is present and evident in TD children from early infancy (Gliga & Csibra, 2007; Goren et al., 1975; Vuilleumier, 2002). The attention to faces provides critical information for social, cognitive, and communicative development and functioning (Feldman et al., 1999; Grelotti et al., 2002; Johnson, 2005; Schultz, 2005; Trevarthen & Aitken, 2001; Tronick, 1989). It has been hypothesized that deficits in social attention present in ASD, such as reduced attention to social stimuli as a whole or atypical allocation of attention to social stimuli is the cause of a compromised social functioning. The fact that ASD subjects do not attend to these types of stimuli reduces social processing, which leads to a loss of relevant information necessary for the development of adaptive social functioning, reflecting a cascading effect of reduced social attention (Chevallier et al., 2012; G. Dawson et al., 2005). Additionally, these deficits may also conduct to difficulties in the interpretation of emotional information which is also critical in the daily life (Pelphrey et al., 2002; Wagner et al., 2013).

Eye-tracking studies in ASD have found that reduced attention to social stimuli or increased attention to non-social stimuli is correlated with behavioural measures of ASD (Bird et al., 2011; Chawarska et al., 2012; Ami Klin et al., 2002; Shic et al., 2011). Klin and colleagues (Ami Klin et al., 2002) showed, in one of the first eye-tracking studies in this topic, that adolescents with ASD spent significantly less time attending to people when watching a segment of a movie and more time attending to the objects and the background of the scene. Deficits in social attention were then replicated in other studies: i.) when looking at pictures of social scenes, participants with ASD spent less time attending to faces (Riby & Hancock, 2009a); ii.) ASD children showed no difference in the time looking at people or objects, while TD children looked at people for longer periods (Wilson et al., 2010); iii.) TD toddlers paid

more attention to people's activities, while the ones with ASD attended less to the activities of others and focused more on the background objects (Shic et al., 2011).

Empirical evidence from eye-tracking studies also demonstrated atypical attention to faces in ASD, as early as six months of age. Those studies focused on selective social attention to faces that used dynamic free-viewing paradigms, in which infants explore video scenes freely, showed a limited ability in 6-month-old infants with ASD to selectively attend to faces of interactive partners (Chawarska et al., 2013), especially when the person is speaking (Shic et al., 2014). These and other characteristics, as limited selective attention and other atypical processing of facial stimuli at 6 months, may constitute specific early-infancy neurodevelopmental markers of ASD that are present before more obvious clinically-observed symptoms (Macari et al., 2020).

The presence of an atypical imbalance in the attention for social versus non-social stimuli in ASD was reported in a large-cohort study (Pierce et al., 2016). This study concluded that enhanced preference for visual stimuli displaying geometric repetition as compared to social stimuli (e.g., videos of playing children) may be an early neurodevelopmental biomarker of an ASD subtype with more severe symptoms. In a recent meta-analysis on gaze patterns, Frazier and colleagues (Frazier et al., 2017) concluded that individuals with ASD present a reliable pattern of gaze abnormalities, which suggests a basic problem selecting socially relevant versus irrelevant information, when compared with TD controls.

Nonetheless, there are other studies that do not confirm this hypothesis of deficits in social attention in ASD suggesting that ASD and TD children did not differ in the attention toward faces (similar fixation times) even when opposed to objects (Kemner et al., 2007) (Parish-Morris et al., 2013). In a different investigation, focused on magic, the authors (Kuhn et al., 2010) found that ASD individuals were more susceptible to magic tricks than TD controls, contrary to what they hypothesized, since these tricks rely on sensitivity to social cues. They also found that there were no differences between the groups in the fixation time on the magician's face and eyes. These studies additionally suggest that the type of context may be relevant to disclose differences in attentional allocation, which also conditionate the social interaction.

Several research with infants suggest that innate or early-emerging attentional biases for faces may be intact within the first few months of life in infants who later were diagnosed with ASD (Di Giorgio et al., 2016; Elsabbagh et al., 2013; W. Jones & Klin, 2013) as well as the ability of attending to complex social scenes (Elsabbagh et al., 2013). These last works

are in line with negative results from the behavioural studies in early infancy (Macari et al., 2020).

Some meta-analyses have also suggested that ASD subjects have increased gaze to regions of the stimulus with less relevance, such as non-social regions, including extraneous objects and non-core face regions (as hair and ears) (Chita-Tegmark, 2016a, 2016b), and small-to-medium decreases in looking to socially relevant regions, namely, eye and whole-face regions (Papagiannopoulou et al., 2014).

Taken all together, these results suggest that eye-tracking methods are promising for studying social attention in ASD population. There are a large number of works showing significantly diminished attention to social information in ASD compared to TD controls (Kirchner et al., 2011; Ami Klin et al., 2002; Riby et al., 2013; Riby & Hancock, 2009b, 2009a; Rice et al., 2012; Shi et al., 2015; Shic et al., 2011), while another considerable number of studies show no differences (Birmingham et al., 2011; M. Freeth et al., 2010; Megan Freeth et al., 2011; Kemner et al., 2007; Kuhn et al., 2010; Marsh et al., 2014; Nadig et al., 2010; Parish-Morris et al., 2013; Van Der Geest et al., 2002). Given these diverse results, the variety of stimuli used in these investigations, and the different experimental procedures, it is important to understand whether there is an overall difference in social attention between individuals with ASD and TD and to provide additional insights into why differences are found across studies.

Considering the knowledge of these deficits, it is of great importance the identification and development of feasible, valid, and reliable measures and tools that are sensitive to assess the core phenotypic features of ASD, namely their social attention profile. These questions will be further examined and investigated in Chapters 2.4, 2.5 and 2.6.

Brain imaging contributions to understand executive functioning and social cognition in ASD

Brain imaging, specifically magnetic resonance imaging (MRI), enables the understanding of how the brain structurally and functionally develops differently and how altered neural circuits relate to clinical symptoms in individuals with ASD, as compared to individuals with TD. MRI has proven to be a useful tool to investigate neural correlates of various cognitive functions, given its excellent contrast properties and spatial resolution (Dichter, 2012).

Hence, these approaches may constitute crucial tools to improve the knowledge of neurofunctional accounts of ASD, while at the same time, may provide new diagnostic biomarkers, as well as targets for novel intervention approaches.

In this thesis, we focused on the functional neuroimaging studies that could inform us about the neural correlates of EF and social cognition.

Functional magnetic resonance imaging (fMRI) is a non-invasive imaging technique that enables the measurement and localization of specific functions of the human brain (Bandettini et al., 1992; Kwong et al., 1992). fMRI measures brain activity by detecting alterations associated with blood flow (Logothetis et al., 2001). This technique relies on the fact that cerebral blood flow and neuronal activation are coupled. This neurovascular coupling can be exploited as a neuroimaging technique. The information processing activity of neurons consumes energy, which means that when an area of the brain is in use, blood flow to that region increases, to supply the required glucose and oxygen. Nevertheless, the total delivery of oxygen exceeds consumption demands and, therefore, a surplus of oxygenated blood surrounds the active areas of the brain some seconds after its activation. This causes change in oxy and deoxyhaemoglobin status with increasing concentration of oxyhaemoglobin and decreasing concentration of deoxyhaemoglobin (hemodynamic response). Given that oxygenated and deoxygenated blood have different magnetic properties, they cause a different impact in the magnetic resonance signal. Oxyhaemoglobin (present in oxygenated blood) has diamagnetic properties (weak, negative susceptibility to magnetic fields) and therefore does not distort the surrounding magnetic field. In turn, deoxyhaemoglobin (present in deoxygenated blood) is paramagnetic (positive susceptibility to magnetic field, which leads to magnetic field distortions and signal loss). This differential effect represents the basis of the blood-oxygen level dependent (BOLD) contrast used in fMRI (S. Ogawa et al., 1990, 1993). The BOLD contrast, was discovered in 1990 by Seiji Ogawa and is the primary form of fMRI (S. Ogawa et al., 1990; Seiji Ogawa & Lee, 1990). BOLD fMRI consists of an indirect measure of brain activity and the debate into the neural mechanisms underlying BOLD signal still remains. However, BOLD constitutes the most common functional imaging method applied in neuroscience. The major goal in fMRI is to assess and anatomically locate regions or networks involved in sensory, motor and cognitive functions. To this end, careful paradigm choice and experimental design is crucial. This is an important point, particularly in ASD research in which MRI results are far from being clarifying and definitive, since the disturbances of the neural structure and function described in ASD are currently ambiguous (Lord et al., 2020).

Functional neuroimaging studies of executive functioning and social cognition in ASD

Taking into consideration the core symptoms that characterize ASD, neuroimaging studies have tried to identify mechanisms of disease in the core social cognition network as well as in other networks that are linked with ASD phenotype, especially the Central Executive Network (CEN) and the Saliency Network.

The brain areas that are most frequently involved in social cognition processes have been identified by previous neuroimaging studies, likewise the network connected to these focal brain areas (Arioli & Canessa, 2019; Park et al., 2018). The "social brain" (see Figure 1.1.1), is the brain network that supports social cognitive skills, and is formed by the prefrontal cortex (PFC), the amygdala, the thalamus, the anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC), the superior temporal sulcus (STS), temporo-parietal junction (TPJ) and inferior parietal lobule (IPL) (Arioli & Canessa, 2019; Fernández et al., 2018; Kennedy & Adolphs, 2012; Müller & Fishman, 2018; Schurz et al., 2014; Y. Wang & Olson, 2018; Wolf et al., 2010).

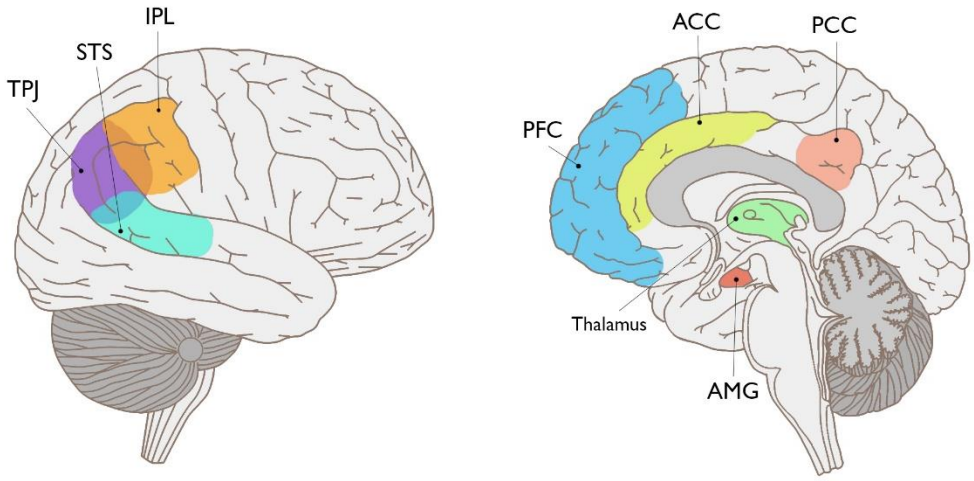

Figure 1.1.1. The 'social brain'. Schematic representation of the brain structures traditionally associated with social cognitive processes as inferred from original lesion studies and/or highly activated when people perform tasks involving social cognition processes in an fMRI study. Abbreviations: ACC, anterior cingulate cortex; AMG, amygdala; IPL, inferior parietal lobule; PCC, posterior cingulate cortex; PFC, prefrontal cortex; STS, superior temporal sulcus; TPJ, temporo-parietal junction.(Adapted from Fernández et al., 2018 and Wang & Olson, 2018).

Studies that used tasks operationalizing social cognition have reported differences between individuals with ASD and TD. Some of these studies reported distinct activation of these regions in ASD (Kana et al., 2014; Kim et al., 2016; Patriquin et al., 2016; White et al., 2014), combined with structural differences of some of these areas, including the STS, insula, fusiform face area and inferior frontal gyrus (Patriquin et al., 2016). There is growing consensus that the impairments in ASD are usually not due to abnormalities in a specific unique area, but instead to particular brain networks (Chen et al., 2017; Eack et al., 2017; Müller & Fishman, 2018; Park et al., 2018).

Functional network–level investigations of ASD pathophysiology have focused also in alterations in the relative perceptual salience of social and non-social stimuli, as well as differences in EF (Chita-Tegmark, 2016; Lai et al., 2017; Lai et al., 2014; Ruta et al., 2017).

The wider brain network that is responsible for the processes involved in EF, as active maintenance and manipulation of information in working memory, judgment and decision making in the context of goal directed behaviour, is the CEN (Sridharan et al., 2008). The CEN is interrelated with the salience network, which is a collection of regions of the brain, including primarily the anterior cingulate and ventral anterior insular cortices, which is thought to play a role in detecting and coordinating a response to salient interoceptive and exteroceptive stimuli. Thus, is responsible for selecting which stimuli are deserving of our attention, playing a role in switching between internally (for example, the default mode network) and externally focused networks (for example, the central executive network) (Menon & Uddin, 2010; Seeley, 2019; Seeley et al., 2007; Sridharan et al., 2008). The default mode network is a set of connections comprising the medial PFC, PCC, precuneus and bilateral IPL, which is activated when there is no engagement in any specific task and deactivated in the context of effortful cognitive tasks and social cognitive tasks (Buckner et al., 2008; Corbetta et al., 2008; Nair et al., 2020). The relations and functions of these three major networks are summarized in Figure 1.1.2. In this thesis, we only focused on CEN and salience network, given the fact that we used a task-based fMRI approach.

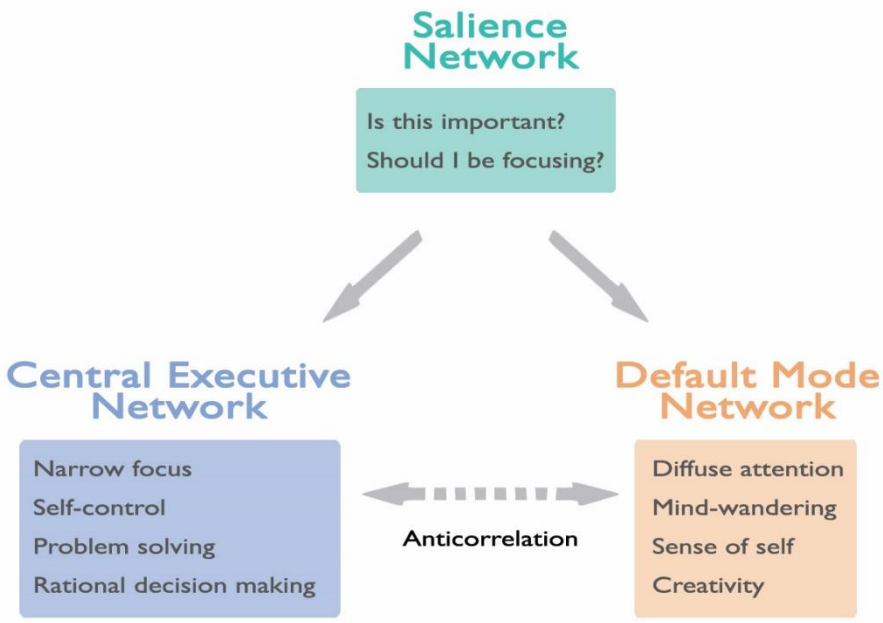

Figure 1.1.2. Schematic figure of the triple network model consisting of the central executive network (CEN), salience network and default mode network (DMN). (Adapted from Menon & Uddin, 2010 and Nekovarova et al., 2014)

Executive functioning has been studied in ASD in functional neuroimaging studies that indicated reduced activation of some brain areas, namely, the dorsolateral prefrontal cortex (DLPFC) (Dichter & Belger, 2008; Luna et al., 2002; Shafritz et al., 2008), superior and inferior parietal lobules (Just et al., 2007; Schmitz et al., 2006; Shafritz et al., 2008; Solomon et al., 2009, 2014), anterior frontal (Solomon et al., 2009). Other activations were found depending on the cognitive context and emotional reaction (Schmitz et al., 2006). Despite these results, there is no consensus in the literature about the neural correlates of EF difficulties in ASD, which can be attributed to the type of task used, contextual demands, group heterogeneity and ASD comorbidity (Gilbert & Burgess, 2008; Nancy J. Minshew & Keller, 2010). A recent meta-analysis that analysed data from sixteen fMRI studies with executive functions tasks, including 739 participants (356 ASD, 383 TD individuals) aged from 7 to 52 years, revealed that both TD and ASD participants had significant activity in PFC regions, although ASD presented greater activation, comparing to TD participants, in left ACC and left cingulate gyrus, and lesser activation in the bilateral IPL, left middle frontal gyrus (MFG), right precuneus, left putamen, left thalamus, left medial prefrontal cortex

(MPFC), and right superior parietal lobule (SPL) (May & Kana, 2020). These authors concluded that executive functions impairments present in ASD subjects are due to dysfunction in a wider executive network, instead of the unique PFC recruitment, that they concluded that is similar in both ASD and TD groups.

Resting-state functional connectivity has been the most widely used fMRI technique in the study of salience network in ASD, showing inconsistent results (Chen et al., 2017; Elton et al., 2016; Uddin, 2015; von dem Hagen et al., 2013). One study proposed that ASD and TD participants can be discriminated based on hyperconnectivity within the salience network (Uddin et al., 2013). However, little is known about how this altered resting-state connectivity relates to brain activity during information processing (Green et al., 2016). Task-based experimental designs are therefore needed in the study of these networks, especially the ecological ones similar to the real world.

Although fMRI research has revealed similarities or differences in individuals with ASD in comparison to TD groups, it has been constrained by averaging data across many individuals, which can mask heterogeneity and differences across age groups. In addition, the studies have been limited by small sample sizes and difficulties with replication probably caused by the many challenges with MRI data collection in individuals with ASD, such as differences in data processing, inter-subject variability and data quality (Lord et al., 2020).

The neural correlates underpinning abnormal social cognition and EF in those with ASD have been largely studied, but mainly in separate approaches and with experimental tasks that lack ecological validity. Therefore, how these networks interact in ASD remains an intriguing question that need to be clarified and will be addressed in chapter 2.6.

References

Akshoomoff, N. (2006). Use of the Mullen Scales of Early Learning for the assessment of young children with Autism Spectrum Disorders. *Child Neuropsychology*. https://doi.org/10.1080/09297040500473714

Allen, M. H., Lincoln, A. J., & Kaufman, A. S. (1991). Sequential and simultaneous processing abilities of high-functioning autistic and language-impaired children. *J Autism Dev Disord*, *21*(4), 483–502.

American Association on Mental Retardation. (2002). *Mental retardation: definition, classification, and systems of supports*. .

American Psychiatric Association. (1952). *Diagnostic statistical manual of mental disorders* (2nd ed.). American Psychiatric Publishing.

American Psychiatric Association. (1968). *Diagnostic statistical manual of mental disorders* (2nd ed.). American Psychiatric Publishing.

American Psychiatric Association. (1980). *Diagnostic statistical manual of mental disorders* (3rd ed.). American Psychiatric Publishing, Inc.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.-T). American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). American Psychiatric Publishing.

Anderson, D. K., Lord, C., Risi, S., DiLavore, P., Shulman, C., Thurm, A., Welch, K., & Pickles, A. (2007). Patterns of growth in verbal abilities among children with autism spectrum disorder. *Journal of Consulting and Clinical Psychology*, *75*(4), 594–604. https://doi.org/10.1037/0022-006X.75.4.594

Arioli, M., & Canessa, N. (2019). Neural processing of social interaction: Coordinate-based meta-analytic evidence from human neuroimaging studies. *Human Brain Mapping*, *40*(13), 3712–3737. https://doi.org/10.1002/hbm.24627

Asarnow, R. F., Tanguay, P. E., Bott, L., & Freeman, B. J. (1987). Patterns of intellectual functioning in non-retarded autistic and schizophrenic children. *J Child Psychol Psychiatry*, *28*(2), 273–280.

Asperger, H. (1944). Die "Autistischen Psychopathen" im Kindesalter. *Archiv Für Psychiatrie Und Nervenkrankheiten*. https://doi.org/10.1007/BF01837709

Asperger, H. (1991). Autistic psychopathy in childhood (translated by Frith, Uta). In *Autism and Asperger syndrome*.

Baddeley, A., & Wilson, B. (1988). Frontal amnesia and the dysexecutive syndrome. *Brain and Cognition*. https://doi.org/10.1016/0278-2626(88)90031-0

Baghdadli, A., Picot, M. C., Pascal, C., Pry, R., & Aussilloux, C. (2003). Relationship between age of recognition of first disturbances and severity in young children with autism. *European Child and Adolescent Psychiatry*. https://doi.org/10.1007/s00787-003-0314-6

Baio, J., Wiggins, L., Christensen, D. L., Maenner, M. J., Daniels, J., Warren, Z., Kurzius-Spencer, M., Zahorodny, W., Rosenberg, C. R., White, T., Durkin, M. S., Imm, P., Nikolaou, L., Yeargin-Allsopp, M., Lee, L. C., Harrington, R., Lopez, M., Fitzgerald, R. T., Hewitt, A., … Dowling, N. F. (2018). Prevalence of autism spectrum disorder among children aged 8 Years - Autism and developmental disabilities monitoring network, 11 Sites, United States, 2014. *MMWR Surveillance Summaries*, *67*(6). https://doi.org/10.15585/mmwr.ss6706a1

Bandettini, P. A., Wong, E. C., Hinks, R. S., Tikofsky, R. S., & Hyde, J. S. (1992). Time course

EPI of human brain function during task activation. *Magnetic Resonance in Medicine*. https://doi.org/10.1002/mrm.1910250220

Baron-cohen, S. (2001). Theory of mind and autism : a review. *Russell The Journal Of The Bertrand Russell Archives*, *23*(169), 169–184. http://linkinghub.elsevier.com/retrieve/pii/S0074775000800105

Baron-Cohen, S., Jolliffe, T., Mortimore, C., & Robertson, M. (1997). Another Advanced Test of Theory of Mind: Evidence from Very High Functioning Adults with Autism or Asperger Syndrome. *Journal of Child Psychology and Psychiatry*, *38*(7), 813–822. https://doi.org/10.1111/j.1469-7610.1997.tb01599.x

Baron-Cohen, S., Leslie, A. M., & Frith, U. (1985). Does the autistic child have a "theory of mind" ? *Cognition*. https://doi.org/10.1016/0010-0277(85)90022-8

Baron-Cohen, S., O'Riordan, M., Stone, V., Jones, R., & Plaisted, K. (1999). Recognition of faux pas by normally developing children and children with asperger syndrome or high-functioning autism. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1023/A:1023035012436

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" Test Revised Version: A Study with Normal Adults, and Adults with Asperger Syndrome or High-functioning Autism. *Journal of Child Psychology and Psychiatry*, *42*(2), S0021963001006643. https://doi.org/10.1017/S0021963001006643

Baron-Cohen, S., Wheelwright, S., Spong, A., Scahill, V., & Lawson, J. (2001). Are intuitive physics and intuitive psychology independent ? A test with children with Asperger Syndrome. *Learning*.

Baron-Cohen, S. (1989). The Autistic Child's Theory of Mind: a Case of Specific Developmental Delay. *Journal of Child Psychology and Psychiatry*. https://doi.org/10.1111/j.1469-7610.1989.tb00241.x

Bauman, M. L. (2010). Medical comorbidities in autism: Challenges to diagnosis and treatment. *Neurotherapeutics*. https://doi.org/10.1016/j.nurt.2010.06.001

Bernardino, I., Mouga, S., Almeida, J., Van Asselen, M., Oliveira, G., & Castelo-Branco, M. (2012). A Direct Comparison of Local-Global Integration in Autism and other Developmental Disorders: Implications for the Central Coherence Hypothesis. *PLoS ONE*, *7*(6), e39351. https://doi.org/10.1371/journal.pone.0039351

Bettelheim, B. (1967). The autistic anlage. In *The empty fortress : infantile autism and the birth of the self*.

Bhat, S., Acharya, U. R., Adeli, H., Bairy, G. M., & Adeli, A. (2014). Autism: Cause factors, early diagnosis and therapies. *Reviews in the Neurosciences*, *25*(6), 841–850. https://doi.org/10.1515/revneuro-2014-0056

Bird, G., Press, C., & Richardson, D. C. (2011). The role of alexithymia in reduced eye-fixation in autism spectrum conditions. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-011-1183-3

Birmingham, E., Cerf, M., & Adolphs, R. (2011). Comparing social attention in autism and amygdala lesions: Effects of stimulus and task condition. *Social Neuroscience*, *6*(5–6), 420–435. https://doi.org/10.1080/17470919.2011.561547

Bleuler, E. (1911). Dementia Praecox oder Gruppe der Schizophrenien. In *GermanyDeuticke*.

Bleuler, E. (1950). Dementia Praecox or the Group of Schizophrenias (translated by Joseph Zinkin). In *International Universities Press*. https://doi.org/10.1126/science.113.2935.368-a

Bölte, S., & Poustka, F. (2002). The relation between general cognitive level and adaptive

behavior domains in individuals with autism with and without co-morbid mental retardation. *Child Psychiatry and Human Development*. https://doi.org/10.1023/A:1020734325815

Bowler, D. M. (1992). "Theory of mind" in Asperger's syndrome. *J Child Psychol Psychiatry*, *33*(5), 877–893.

Boyd, B. A., McBee, M., Holtzclaw, T., Baranek, G. T., & Bodfish, J. W. (2009). Relationships among repetitive behaviors, sensory features, and executive functions in high functioning autism. *Research in Autism Spectrum Disorders*, *3*(4), 959–966. https://doi.org/10.1016/j.rasd.2009.05.003

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The Brain's Default Network. *Annals of the New York Academy of Sciences*, *1124*(1), 1–38. https://doi.org/10.1196/annals.1440.011

Burgess, P. W., Alderman, N., Forbes, C., Costello, A., Coates, L. M. A., Dawson, D. R., Anderson, N. D., Gilbert, S. J., Dumontheil, I., & Channon, S. (2006). The case for the development and use of "ecologically valid" measures of executive function in experimental and clinical neuropsychology. *Journal of the International Neuropsychological Society*. https://doi.org/10.1017/S1355617706060310

Cantio, C., Jepsen, J. R. M., Madsen, G. F., Bilenberg, N., & White, S. J. (2016). Exploring 'The autisms' at a cognitive level. *Autism Research*, *9*(12), 1328–1339. https://doi.org/10.1002/aur.1630

Carbone, P. S., Campbell, K., Wilkes, J., Stoddard, G. J., Huynh, K., Young, P. C., & Gabrielsen, T. P. (2020). Primary Care Autism Screening and Later Autism Diagnosis. *Pediatrics*, *146*(2), e20192314. https://doi.org/10.1542/peds.2019-2314

Caron, M. J., Mottron, L., Berthiaume, C., & Dawson, M. (2006). Cognitive mechanisms, specificity and neural underpinnings of visuospatial peaks in autism. *Brain*. https://doi.org/10.1093/brain/awl072

Carpentieri, S., & Morgan, S. B. (1996). Adaptive and intellectual functioning in autistic and nonautistic retarded children. *J Autism Dev Disord*, *26*(6), 611–620.

Carter, A. S., Volkmar, F. R., Sparrow, S. S., Wang, J. J., Lord, C., Dawson, G., Fombonne, E., Loveland, K., Mesibov, G., & Schopler, E. (1998). The Vineland Adaptive Behavior Scales: supplementary norms for individuals with autism. *J Autism Dev Disord*, *28*(4), 287–302.

Centers for Disease Control and Prevention. (2009). Prevalence of autism spectrum disorders - Autism and Developmental Disabilities Monitoring Network, United States, 2006. *MMWR Surveill Summ*, *58*(10), 1–20. https://doi.org/ss5810a1 [pii]

Centers for Disease Control and Prevention. (2012). Prevalence of autism spectrum disorders -- autism and developmental disabilities monitoring network, 14 sites, United States, 2008. Morbidity and mortality weekly report. Surveillance summaries. *Centers for Disease Control and Prevention*, *61*(3), 1–19.

Centers for Disease Control and Prevention. (2014). Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *MMWR Surveill Summ*, *63*(2), 1–21. https://doi.org/ss6302a1 [pii]

Charman, T., Jones, C. R. G., Pickles, A., Simonoff, E., Baird, G., Happé, F., Happe, F., & Happé, F. (2011). Defining the cognitive phenotype of autism. *Brain Research*, *1380*(1943), 10–21. https://doi.org/10.1016/j.brainres.2010.10.075

Charman, Tony, Baron-Cohen, S., Swettenham, J., Baird, G., Drew, A., & Cox, A. (2003). Predicting language outcome in infants with autism and pervasive developmental

disorder. *International Journal of Language & Communication Disorders / Royal College of Speech & Language Therapists*, *38*(3), 265–285. https://doi.org/10.1080/136820310000104830

Charman, Tony, Drew, A., Baird, C., & Baird, G. (2003). Measuring early language development in preschool children with autism spectrum disorder using the MacArthur communicative development inventory (Infant Form). *Journal of Child Language*. https://doi.org/10.1017/S0305000902005482

Charman, Tony, Taylor, E., Drew, A., Cockerill, H., Brown, J. A., & Baird, G. (2005). Outcome at 7 years of children diagnosed with autism at age 2: Predictive validity of assessments conducted at 2 and 3 years of age and pattern of symptom change over time. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *46*(5), 500–513. https://doi.org/10.1111/j.1469-7610.2004.00377.x

Chawarska, K., Macari, S., & Shic, F. (2013). Decreased spontaneous attention to social scenes in 6-month-old infants later diagnosed with autism spectrum disorders. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2012.11.022

Chawarska, K., MacAri, S., & Shic, F. (2012). Context modulates attention to social scenes in toddlers with autism. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *53*(8), 903–913. https://doi.org/10.1111/j.1469-7610.2012.02538.x

Chawarska, K., Paul, R., Klin, A., Hannigen, S., Dichtel, L. E., & Volkmar, F. (2007). Parental recognition of developmental problems in toddlers with autism spectrum disorders. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-006-0330-8

Chaytor, N., & Schmitter-Edgecombe, M. (2003). The ecological validity of neuropsychological tests: A review of the literature on everyday cognitive skills. In *Neuropsychology Review*. https://doi.org/10.1023/B:NERV.0000009483.91468.fb

Chen, H. H., Uddin, L. Q., Duan, X., Zheng, J., Long, Z., Zhang, Y. Y., Guo, X., Zhang, Y. Y., Zhao, J., & Chen, H. H. (2017). Shared atypical default mode and salience network functional connectivity between autism and schizophrenia. *Autism Research*. https://doi.org/10.1002/aur.1834

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2012.02.007

Chita-Tegmark, M. (2016a). Social attention in ASD: A review and meta-analysis of eye-tracking studies. *Research in Developmental Disabilities*, *48*, 79–93. https://doi.org/10.1016/j.ridd.2015.10.011

Chita-Tegmark, M. (2016b). Attention Allocation in ASD: a Review and Meta-analysis of Eye-Tracking Studies. *Review Journal of Autism and Developmental Disorders*, *3*(3), 209–223. https://doi.org/10.1007/s40489-016-0077-x

Coleman, M., & Cillberg, C. (1994). Biology of the Autistic Syndromes. *Pediatric Physical Therapy*. https://doi.org/10.1097/00001577-199400610-00026

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The Reorienting System of the Human Brain: From Environment to Theory of Mind. *Neuron*, *58*(3), 306–324. https://doi.org/10.1016/j.neuron.2008.04.017

Corrales, M. A., & Herbert, M. R. (2013). Autism and Environmental Genomics: Synergistic Systems Approaches to Autism Complexity. In *Autism Spectrum Disorders* (Issue May 2018). https://doi.org/10.1093/med/9780195371826.003.0056

Croen, L. A., Zerbo, O., Qian, Y., Massolo, M. L., Rich, S., Sidney, S., & Kripke, C. (2015). The health status of adults on the autism spectrum. *Autism*. https://doi.org/10.1177/1362361315577517

Dawson, G., Webb, S. J., & McPartland, J. (2005). Understanding the nature of face processing impairment in autism: Insights from behavioral and electrophysiological studies. In *Developmental Neuropsychology*. https://doi.org/10.1207/s15326942dn2703_6

Dawson, J. E., Matson, J. L., & Cherry, K. E. (1998). An analysis of maladaptive behaviors in persons with autism, PDD-NOS, and mental retardation11This article was based on a master's thesis submitted by the first author to the Graduate School, Louisiana State University, in partial fulfillment of the requi. *Research in Developmental Disabilities*, *19*(5), 439–448. https://doi.org/10.1016/S0891-4222(98)00016-X

De Giacomo, A., & Fombonne, E. (1998). Parental recognition of developmental abnormalities in autism. *European Child and Adolescent Psychiatry*. https://doi.org/10.1007/s007870050058

Delis, DC., Kaplan, E., Kramer, J. (2001). Examiner's Manual for the Delis-Kaplan Executive Function System. In *Child Neuropsychology*.

Demetriou, E. A., Lampit, A., Quintana, D. S., Naismith, S. L., Song, Y. J. C., Pye, J. E., Hickie, I., & Guastella, A. J. (2018). Autism spectrum disorders: a meta-analysis of executive function. *Molecular Psychiatry*, *23*(5), 1198–1204. https://doi.org/10.1038/mp.2017.75

Di Giorgio, E., Frasnelli, E., Rosa Salva, O., Maria Luisa, S., Puopolo, M., Tosoni, D., Simion, F., Vallortigara, G., Apicella, F., Gagliano, A., Guzzetta, A., Molteni, M., Persico, A., Pioggia, G., Valeri, G., & Vicari, S. (2016). Difference in Visual Social Predispositions between Newborns at Low-and High-risk for Autism. *Scientific Reports*. https://doi.org/10.1038/srep26395

Dichter, G. S. (2012). Functional magnetic resonance imaging of autism spectrum disorders. *Dialogues in Clinical Neuroscience*, *14*(3), 319–351. https://doi.org/10.31887/dcns.2012.14.3/gdichter

Dichter, G. S., & Belger, A. (2008). Atypical modulation of cognitive control by arousal in autism. *Psychiatry Research: Neuroimaging*, *164*(3), 185–197. https://doi.org/10.1016/j.pscychresns.2007.12.005

Dichter, G. S., Lam, K. S. L., Turner-Brown, L. M., Holtzclaw, T. N., & Bodfish, J. W. (2009). Generativity abilities predict communication deficits but not repetitive behaviors in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *39*(9), 1298–1304. https://doi.org/10.1007/s10803-009-0742-3

Eack, S. M., Wojtalik, J. A., Keshavan, M. S., & Minshew, N. J. (2017). Social-cognitive brain function and connectivity during visual perspective-taking in autism and schizophrenia. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2017.03.009

Elsabbagh, M., Gliga, T., Pickles, A., Hudry, K., Charman, T., & Johnson, M. H. (2013). The development of face orienting mechanisms in infants at-risk for autism. *Behavioural Brain Research*. https://doi.org/10.1016/j.bbr.2012.07.030

Elton, A., Di Martino, A., Hazlett, H. C., & Gao, W. (2016). Neural Connectivity Evidence for a Categorical-Dimensional Hybrid Model of Autism Spectrum Disorder. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2015.10.020

Faja, S., & Dawson, G. (2014). Performance on the dimensional change card sort and backward digit span by young children with autism without intellectual disability. *Child Neuropsychology*, *20*(6), 692–699. https://doi.org/10.1080/09297049.2013.856395

Farley, M. A., McMahon, W. M., Fombonne, E., Jenson, W. R., Miller, J., Gardner, M., Block, H., Pingree, C. B., Ritvo, E. R., Ritvo, R. A., & Coon, H. (2009). Twenty-year outcome for individuals with autism and average or near-average cognitive abilities. *Autism Res*, *2*(2), 109–118. https://doi.org/10.1002/aur.69

Feldman, R., Greenbaum, C. W., & Yirmiya, N. (1999). Mother-infant affect synchrony as an antecedent of the emergence of self-control. *Developmental Psychology*. https://doi.org/10.1037/0012-1649.35.1.223

Fenton, G., D'Ardia, C., Valente, D., Del Vecchio, I., Fabrizi, A., & Bernabei, P. (2003). Vineland adaptive behavior profiles in children with autism and moderate to severe developmental delay. *Autism*, *7*(3), 269–287.

Fernández, M., Mollinedo-Gajate, I., & Peñagarikano, O. (2018). Neural Circuits for Social Cognition: Implications for Autism. *Neuroscience*, *370*, 148–162. https://doi.org/10.1016/j.neuroscience.2017.07.013

Ferreira, X., & Oliveira, G. (2016). Autism and Early Neurodevelopmental Milestones. *Acta Medica Portuguesa*, *29*(3), 168–175. https://doi.org/10.20344/amp.6790

Frazier, T. W., Strauss, M., Klingemier, E. W., Zetzer, E. E., Hardan, A. Y., Eng, C., & Youngstrom, E. A. (2017). A Meta-Analysis of Gaze Differences to Social and Nonsocial Information Between Individuals With and Without Autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(7), 546–555. https://doi.org/10.1016/j.jaac.2017.05.005

Freeman, B. J., Lucas, J. C., Fomess, S. R., & Ritvo, E. R. (1985). Cognitive processing of high-functioning autistic children: Comparing the K-ABC and the WlSC-R. *J. Psychoeduc. Assess*, *4*, 357–362.

Freeth, M., Ropar, D., Chapman, P., & Mitchell, P. (2010). The eye gaze direction of an observed person can bias perception, memory, and attention in adolescents with and without autism spectrum disorder. *Journal of Experimental Child Psychology*. https://doi.org/10.1016/j.jecp.2009.10.001

Freeth, Megan, Ropar, D., Mitchell, P., Chapman, P., & Loher, S. (2011). Brief report: How adolescents with ASD process social information in complex scenes. Combining evidence from eye movements and verbal descriptions. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-010-1053-4

Frith, U. (1989). The Background Facts. In *Autism: Explaining the enigma* (pp. 51–67). Blackwell.

Frith, U. (2003). Autism: Explaining the Enigma (2nd edition). In *Blackwell; Oxford*.

Frith, U., & Happé, F. (1994). Autism: beyond "theory of mind." *Cognition*. https://doi.org/10.1016/0010-0277(94)90024-8

Frith, U., & Shah, A. (1983). An Islet of Ability in Autistic Children: A Research Note. *Journal of Child Psychology and Psychiatry*.

Gardner, L. M., Campbell, J. M., Keisling, B., & Murphy, L. (2018). Correlates of DSM-5 Autism Spectrum Disorder Levels of Support Ratings in a Clinical Sample. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-018-3620-z

Gaugler, T., Klei, L., Sanders, S. J., Bodea, C. A., Goldberg, A. P., Lee, A. B., Mahajan, M., Manaa, D., Pawitan, Y., Reichert, J., Ripke, S., Sandin, S., Sklar, P., Svantesson, O., Reichenberg, A., Hultman, C. M., Devlin, B., Roeder, K., & Buxbaum, J. D. (2014). Most genetic risk for autism resides with common variation. *Nature Genetics*, *46*(8), 881–885. https://doi.org/10.1038/ng.3039

Geurts, H. M., Sinzig, J., Booth, R., & Happé, F. (2014). Neuropsychological heterogeneity in executive functioning in autism spectrum disorders. *International Journal of Developmental Disabilities*. https://doi.org/10.1179/2047387714Y.0000000047

Geurts, H. M., van den Bergh, S. F. W. M., & Ruzzano, L. (2014). Prepotent response inhibition and interference control in autism spectrum disorders: Two Meta-Analyses. *Autism Research*, *7*(4), 407–420. https://doi.org/10.1002/aur.1369

Ghaziuddin, M., & Mountain-Kimchi, K. (2004). Defining the intellectual profile of Asperger Syndrome: comparison with high-functioning autism. *J Autism Dev Disord*, *34*(3), 279–284.

Gilbert, S. J., & Burgess, P. W. (2008). Executive function. *Current Biology*, *18*(3), R110–R114. https://doi.org/10.1016/j.cub.2007.12.014

Gillham, J. E., Carter, A. S., Volkmar, F. R., & Sparrow, S. S. (2000). Toward a developmental operational definition of autism. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1023/A:1005571115268

Gilotty, L., Kenworthy, L., Sirian, L., Black, D. O., & Wagner, A. E. (2002). Adaptive Skills and Executive Function in Autism Spectrum Disorders. *Child Neuropsychology*, *8*(4), 241–248. https://doi.org/10.1076/chin.8.4.241.13504

Gliga, T., & Csibra, G. (2007). Seeing the face through the eyes: a developmental perspective on face expertise. In *Progress in Brain Research*. https://doi.org/10.1016/S0079-6123(07)64018-7

Goldstein Naglieri, J. A., & Ozonoff, S., S. (2008). *Assessment of autism spectrum disorders*. Guilford Press.

Goldstein, G., Allen, D. N., Minshew, N. J., Williams, D. L., Volkmar, F., Klin, A., & Schultz, R. T. (2008). The structure of intelligence in children and adults with high functioning autism. *Neuropsychology*, *22*(3), 301–312. https://doi.org/2008-05020-003 [pii]10.1037/0894-4105.22.3.301

Goldstein, S., & Naglieri, J. A. (2014a). Handbook of executive functioning. *Handbook of Executive Functioning*, 1–567. https://doi.org/10.1007/978-1-4614-8106-5

Goldstein, S., & Naglieri, J. A. (2014b). Introduction: A History of Executive Functioning as a Theoretical and Clinical Construct. In S. Goldstein & J. A. Naglieri (Eds.), *Handbook of Executive Functioning* (pp. 1–567). Springer New York. https://doi.org/10.1007/978-1-4614-8106-5

Goren, C. C., Sarty, M., & Wu, P. Y. (1975). Visual following and pattern discrimination of face-like stimuli by newborn infants. *Pediatrics*, *56*(4), 544–549. https://doi.org/10.1016/j.ridd.2015.10.011

Green, S. A., Hernandez, L., Bookheimer, S. Y., & Dapretto, M. (2016). Salience Network Connectivity in Autism Is Related to Brain and Behavioral Markers of Sensory Overresponsivity. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(7), 618-626.e1. https://doi.org/10.1016/j.jaac.2016.04.013

Grelotti, D. J., Gauthier, I., & Schultz, R. T. (2002). Social interest and the development of cortical face specialization: What autism teaches us about face processing. *Developmental Psychobiology*. https://doi.org/10.1002/dev.10028

Grønborg, T. K., Schendel, D. E., & Parner, E. T. (2013). Recurrence of autism spectrum disorders in full- and half-siblings and trends over time: A population-based cohort study. *JAMA Pediatrics*, *167*(10), 947–953. https://doi.org/10.1001/jamapediatrics.2013.2259

Groth-Marnat, G. (2003). Handbook of psychological assessment. In *International Journal of Clinical Neuropsychology*.

Guillon, Q., Hadjikhani, N., Baduel, S., & Rogé, B. (2014). Visual social attention in autism spectrum disorder: Insights from eye tracking studies. *Neuroscience and Biobehavioral Reviews*, *42*, 279–297. https://doi.org/10.1016/j.neubiorev.2014.03.013

Hansen, S. N., Schendel, D. E., & Parner, E. T. (2015). Explaining the increase in the prevalence of autism spectrum disorders: The proportion attributable to changes in reporting practices. *JAMA Pediatrics*, *169*(1), 56–62.

https://doi.org/10.1001/jamapediatrics.2014.1893

Happé, F. G. E. (1994). An advanced test of theory of mind: Understanding of story characters' thoughts and feelings by able autistic, mentally handicapped, and normal children and adults. *Journal of Autism and Developmental Disorders*, *24*(2), 129–154. https://doi.org/10.1007/BF02172093

Happé, F. G. E. (1996). Studying weak central coherence at low levels: Children with autism do not succumb to visual illusions. A research note. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1111/j.1469-7610.1996.tb01483.x

Happé, F, & Frith, U. (2006). The Weak Coherence Account: Detail-focused Cognitive Style in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *36*(1), 5{\textendash}25.

Happé, Francesca. (1999). Autism: cognitive deficit or cognitive style? *Trends in Cognitive Sciences*, *3*(6), 216–222. https://doi.org/10.1016/S1364-6613(99)01318-2

Happé, Francesca, Cook, J. L., & Bird, G. (2017). The Structure of Social Cognition: In(ter)dependence of Sociocognitive Processes. *Annual Review of Psychology*, *68*(September 2016), 243–267. https://doi.org/10.1146/annurev-psych-010416-044046

Havdahl, A., & Bishop, S. (2019). Heterogeneity in prevalence of co-occurring psychiatric conditions in autism. In *The Lancet Psychiatry*. https://doi.org/10.1016/S2215-0366(19)30326-8

Havdahl, K. A., Hus Bal, V., Huerta, M., Pickles, A., Øyen, A.-S., Stoltenberg, C., Lord, C., & Bishop, S. L. (2016). Multidimensional Influences on Autism Symptom Measures: Implications for Use in Etiological Research. *Journal of the American Academy of Child & Adolescent Psychiatry*, *55*(12), 1054-1063.e3. https://doi.org/10.1016/j.jaac.2016.09.490

Hinnebusch, A. J., Miller, L. E., & Fein, D. A. (2017). Autism Spectrum Disorders and Low Mental Age: Diagnostic Stability and Developmental Outcomes in Early Childhood. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-017-3278-y

Hirvikoski, T., Mittendorfer-Rutz, E., Boman, M., Larsson, H., Lichtenstein, P., & Bölte, S. (2016). Premature mortality in autism spectrum disorder. *British Journal of Psychiatry*. https://doi.org/10.1192/bjp.bp.114.160192

Johnson, M. H. (2005). Subcortical face processing. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn1766

Jolliffe, T., & Baron-Cohen, S. (1999). The strange stories test: A replication with high-functioning adults with autism or Asperger syndrome. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1023/A:1023082928366

Jones, C. R. G., Simonoff, E., Baird, G., Pickles, A., Marsden, A. J. S., Tregay, J., Happe, F., & Charman, T. (2018). The association between theory of mind, executive function, and the symptoms of autism spectrum disorder. *Autism Research : Official Journal of the International Society for Autism Research*, *11*(1), 95–109. https://doi.org/10.1002/aur.1873

Jones, C. R. G., Simonoff, E., Baird, G., Pickles, A., Marsden, A. J. S., Tregay, J., Happé, F., & Charman, T. (2018). The association between theory of mind, executive function, and the symptoms of autism spectrum disorder. *Autism Research*. https://doi.org/10.1002/aur.1873

Jones, W., & Klin, A. (2013). Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. *Nature*. https://doi.org/10.1038/nature12715

Joseph, R M. (2011). The significiance of IQ and differential cognitive abilities. In D. A. Fein (Ed.), *The neuropsychology of autism*. Oxford University Press.

Joseph, Robert M., & Tager-Flusberg, H. (2004). The relationship of theory of mind and executive functions to symptom type and severity in children with autism. *Development and Psychopathology*, *16*(1), 137–155. https://doi.org/10.1017/S095457940404444X

Joseph, Robert M., Tager-Flusberg, H., & Lord, C. (2002). Cognitive profiles and social-communicative functioning in children with autism spectrum disorder. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1111/1469-7610.00092

Just, M. A., Cherkassky, V. L., Keller, T. A., Kana, R. K., & Minshew, N. J. (2007). Functional and Anatomical Cortical Underconnectivity in Autism: Evidence from an fMRI Study of an Executive Function Task and Corpus Callosum Morphometry. *Cerebral Cortex*, *17*(4), 951–961. https://doi.org/10.1093/cercor/bhl006

Kana, R. K., Libero, L. E., Hu, C. P., Deshpande, H. D., & Colburn, J. S. (2014). Functional brain networks and white matter underlying theory-of-mind in autism. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nss106

Kanne, S. M., Gerber, A. J., Quirmbach, L. M., Sparrow, S. S., Cicchetti, D. V, & Saulnier, C. A. (2011). The role of adaptive behavior in autism spectrum disorders: implications for functional outcome. *J Autism Dev Disord*, *41*(8), 1007–1018. https://doi.org/10.1007/s10803-010-1126-4

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child*, *2*, 217–250. http://www.autismtruths.org/pdf/Autistic Disturbances of Affective Contact - Leo Kanner.pdf

Kemner, C., van der Geest, J. N., Verbaten, M. N., & van Engeland, H. (2007). Effects of object complexity and type on the gaze behavior of children with pervasive developmental disorder. *Brain and Cognition*. https://doi.org/10.1016/j.bandc.2006.05.006

Kennedy, D. P., & Adolphs, R. (2012). The social brain in psychiatric and neurological disorders. *Trends in Cognitive Sciences*, *16*(11), 559–572. https://doi.org/10.1016/j.tics.2012.09.006

Kenworthy, L., Black, D. O., Harrison, B., Della Rosa, A., & Wallace, G. L. (2009). Are executive control functions related to autism symptoms in high-functioning children? *Child Neuropsychology*, *15*(5), 425–440. https://doi.org/10.1080/09297040802646983

Kenworthy, L., Yerys, B. E., Anthony, L. G., & Wallace, G. L. (2008). Understanding Executive Control in Autism Spectrum Disorders in the Lab and in the Real World. *Neuropsychology Review*, *18*(4), 320–338. https://doi.org/10.1007/s11065-008-9077-7

Kim, E., Kyeong, S., Cheon, K. A., Park, B., Oh, M. K., Chun, J. W., Park, H. J., Kim, J. J., & Song, D. H. (2016). Neural responses to affective and cognitive theory of mind in children and adolescents with autism spectrum disorder. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2016.04.026

Kirchner, J. C., Hatri, A., Heekeren, H. R., & Dziobek, I. (2011). Autistic symptomatology, face processing abilities, and eye fixation patterns. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-010-1032-9

Klin, A, Saulnier, C. A., Sparrow, S. S., Cicchetti, D. V, Volkmar, F. R., & Lord, C. (2007). Social and communication abilities and disabilities in higher functioning individuals with autism spectrum disorders: the Vineland and the ADOS. *J Autism Dev Disord*, *37*(4), 748–759. https://doi.org/10.1007/s10803-006-0229-4

Klin, Ami, Jones, W., Schultz, R., & Volkmar, F. (2003). The enactive mind, or from actions to cognition: lessons from autism. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *358*(1430), 345–360. https://doi.org/10.1098/rstb.2002.1202

Klin, Ami, Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual Fixation Patterns

During Viewing of Naturalistic Social Situations as Predictors of Social Competence in Individuals With Autism. *Archives of General Psychiatry*, *59*(9), 809. https://doi.org/10.1001/archpsyc.59.9.809

Knapp, M., Romeo, R., & Beecham, J. (2009). Economic cost of autism in the UK. *Autism*. https://doi.org/10.1177/1362361309104246

Kouklari, E.-C., Thompson, T., Monks, C. P., & Tsermentseli, S. (2017). Hot and Cool Executive Function and its Relation to Theory of Mind in Children with and without Autism Spectrum Disorder. *Journal of Cognition and Development*, *18*(4), 399–418. https://doi.org/10.1080/15248372.2017.1339708

Kouklari, E. C., Tsermentseli, S., & Auyeung, B. (2018). Executive function predicts theory of mind but not social verbal communication in school-aged children with autism spectrum disorder. *Research in Developmental Disabilities*, *76*(March 2017), 12–24. https://doi.org/10.1016/j.ridd.2018.02.015

Kuhn, G., Kourkoulou, A., & Leekam, S. R. (2010). How Magic Changes Our Expectations About Autism. *Psychological Science*. https://doi.org/10.1177/0956797610383435

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., Kennedy, D. N., Hoppel, B. E., Cohen, M. S., Turner, R., Cheng -, H. M., Brady, T. J., & Rosen, B. R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.89.12.5675

Lai, C. L. E., Lau, Z., Lui, S. S. Y., Lok, E., Tam, V., Chan, Q., Cheng, K. M., Lam, S. M., & Cheung, E. F. C. (2017). Meta-analysis of neuropsychological measures of executive functioning in children and adolescents with high-functioning autism spectrum disorder. *Autism Research*, *10*(5), 911–939. https://doi.org/10.1002/aur.1723

Lai, M.-C. C., Lombardo, M. V., & Baron-Cohen, S. (2014). Autism. *The Lancet*, *383*(9920), 896–910. https://doi.org/10.1016/S0140-6736(13)61539-1

Lai, M.-C., Kassee, C., Besney, R., Bonato, S., Hull, L., Mandy, W., Szatmari, P., & Ameis, S. H. (2019). Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *The Lancet Psychiatry*, *6*(10), 819–829. https://doi.org/10.1016/S2215-0366(19)30289-5

Lai, M.-C., Lombardo, M. V., & Baron-Cohen, S. (2014). Autism. *The Lancet*, *383*(9920), 896–910. https://doi.org/10.1016/S0140-6736(13)61539-1

Landa, R. J., & Goldberg, M. C. (2005). Language, social, and executive functions in high functioning autism: A continuum of performance. *Journal of Autism and Developmental Disorders*, *35*(5), 557–573. https://doi.org/10.1007/s10803-005-0001-1

Le Couteur, A., Lord, C., & Rutter, M. (2003). The Autism Diagnostic Interview-Revised (ADI-R). In *Los Angeles CA Western Psychological Services*. Western Psychological Services.

Leung, R. C., Vogan, V. M., Powell, T. L., Anagnostou, E., & Taylor, M. J. (2016). The role of executive functions in social impairment in Autism Spectrum Disorder. *Child Neuropsychology*, *22*(3), 336–344. https://doi.org/10.1080/09297049.2015.1005066

Leung, R. C., & Zakzanis, K. K. (2014). Brief report: Cognitive flexibility in autism spectrum disorders: A quantitative review. *Journal of Autism and Developmental Disorders*, *44*(10), 2628–2645. https://doi.org/10.1007/s10803-014-2136-4

Lezak, M. D. (2004). The Wisconsin Card Sorting Test. In *Neuropsychological assessment*.

Lezak, M., Howieso, D., Bigle, E., & Tranel, D. (2012). *Neuropsychological assessment*. (5th editio). Oxford University Press.

Lincoln, A. J., Courchesne, E., Kilman, B. A., Elmasian, R., & Allen, M. (1988). A study of intellectual abilities in high-functioning people with autism. *J Autism Dev Disord*, *18*(4),

505–524.

Liss, M., Harel, B., Fein, D., Allen, D., Dunn, M., Feinstein, C., Morris, R., Waterhouse, L., & Rapin, I. (2001). Predictors and Correlates of Adaptive Functioning in Children with Developmental Disorders. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1023/A:1010707417274

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*. https://doi.org/10.1038/35084005

Lord, C, Brugha, T. S., Charman, T., Cusack, J., Dumas, G., Frazier, T., Jones, E. J. H., Jones, R. M., Pickles, A., State, M. W., Taylor, J. L., & Veenstra-VanderWeele, J. (2020). Autism spectrum disorder. *Nature Reviews. Disease Primers*, *6*(1), 5. https://doi.org/10.1038/s41572-019-0138-4

Lord, C, & Rutter, M. (1999). Autism diagnostic observation schedule-WPS (ADOS-WPS). *Los Angeles CA Western Psychological*.

Lord, Catherine, & Bishop, S. L. (2015). Recent Advances in Autism Research as Reflected in DSM-5 Criteria for Autism Spectrum Disorder. *Annual Review of Clinical Psychology*, *11*(1), 53–70. https://doi.org/10.1146/annurev-clinpsy-032814-112745

Lord, Catherine, Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., & Schopler, E. (1989). Austism diagnostic observation schedule: A standardized observation of communicative and social behavior. *Journal of Autism and Developmental Disorders*, *19*(2), 185–212. https://doi.org/10.1007/BF02211841

Lord, Catherine, Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/BF02172145

Loveland, K. A., & Kelley, M. L. (1991). Development of adaptive behavior in preschoolers with autism or Down syndrome. *Am J Ment Retard*, *96*(1), 13–20.

Luna, B., Minshew, N. J., Garver, K. E., Lazar, N. A., Thulborn, K. R., Eddy, W. F., & Sweeney, J. A. (2002). Neocortical system abnormalities in autism: An fMRI study of spatial working memory. *Neurology*, *59*(6), 834–840. https://doi.org/10.1212/WNL.59.6.834

Luyster, R. J., Kadlec, M. B., Carter, A., & Tager-Flusberg, H. (2008). Language assessment and development in toddlers with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *38*(8), 1426–1438. https://doi.org/10.1007/s10803-007-0510-1

Macari, S., Milgramm, A., Reed, J., Shic, F., Powell, K. K., Macris, D., & Chawarska, K. (2020). Context-Specific Dyadic Attention Vulnerabilities During the First Year in Infants Later Developing Autism Spectrum Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2019.12.012

Maenner, M. J., Shaw, K. A., Baio, J., Washington, A., Patrick, M., DiRienzo, M., Christensen, D. L., Wiggins, L. D., Pettygrove, S., Andrews, J. G., Lopez, M., Hudson, A., Baroud, T., Schwenk, Y., White, T., Rosenberg, C. R., Lee, L.-C., Harrington, R. A., Huston, M., … Dietz, P. M. (2020). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. *MMWR. Surveillance Summaries*, *69*(4), 1–12. https://doi.org/10.15585/mmwr.ss6904a1

Manchester, D., Priestley, N., & Jackson, H. (2004). The assessment of executive functions: Coming out of the office. In *Brain Injury*. https://doi.org/10.1080/02699050410001672387

Mandy, W., Murin, M., & Skuse, D. (2015). The cognitive profile in autism spectrum disorders. *Key Issues in Mental Health*, *180*, 34–45. https://doi.org/10.1159/000363565

Mannion, A., Leader, G., & Healy, O. (2013). An investigation of comorbid psychological disorders, sleep problems, gastrointestinal symptoms and epilepsy in children and adolescents with Autism Spectrum Disorder. *Research in Autism Spectrum Disorders*. https://doi.org/10.1016/j.rasd.2012.05.002

Marsh, L. E., Pearson, A., Ropar, D., & Hamilton, A. F. C. (2014). Predictive Gaze During Observation of Irrational Actions in Adults with Autism Spectrum Conditions. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-014-2215-6

Maskey, M., Warnell, F., Parr, J. R., Le Couteur, A., & McConachie, H. (2013). Emotional and behavioural problems in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-012-1622-9

Matson, J. L., Rivet, T. T., Fodstad, J. C., Dempsey, T., & Boisjoli, J. A. (2009). Examination of adaptive behavior differences in adults with autism spectrum disorders and intellectual disability. *Research in Developmental Disabilities*. https://doi.org/10.1016/j.ridd.2009.05.008

Mattila, M. L., Hurtig, T., Haapsamo, H., Jussila, K., Kuusikko-Gauffin, S., Kielinen, M., Linna, S. L., Ebeling, H., Bloigu, R., Joskitt, L., Pauls, D. L., & Moilanen, I. (2010). Comorbid psychiatric disorders associated with asperger syndrome/high-functioning autism: A community- and clinic-based study. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-010-0958-2

May, K. E., & Kana, R. K. (2020). Frontoparietal Network in Executive Functioning in Autism Spectrum Disorder. *Autism Research*, *13*(10), 1762–1777. https://doi.org/10.1002/aur.2403

McEvoy, R. E., Rogers, S. J., & Pennington, B. F. (1993). Executive Function and Social Communication Deficits in Young Autistic Children. *Journal of Child Psychology and Psychiatry*, *34*(4), 563–578. https://doi.org/10.1111/j.1469-7610.1993.tb01036.x

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, *214*(5–6), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Miller, L. E., Burke, J. D., Robins, D. L., & Fein, D. A. (2019). Diagnosing Autism Spectrum Disorder in Children with Low Mental Age. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-018-3810-8

Minshew, N J, Goldstein, G., Muenz, L. R., & Payton, J. B. (1992). Neuropsychological functioning in nonmentally retarded autistic individuals. *J Clin Exp Neuropsychol*, *14*(5), 749–761. https://doi.org/10.1080/01688639208402860

Minshew, Nancy J., & Keller, T. A. (2010). The nature of brain dysfunction in autism: Functional brain imaging studies. *Current Opinion in Neurology*, *23*(2), 124–130. https://doi.org/10.1097/WCO.0b013e32833782d4

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. *Cognitive Psychology*. https://doi.org/10.1006/cogp.1999.0734

Modabbernia, A., Velthorst, E., & Reichenberg, A. (2017). Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. *Molecular Autism*, *8*(1), 1–16. https://doi.org/10.1186/s13229-017-0121-4

Mottron, L. (2004). Matching strategies in cognitive research with individuals with high-functioning autism: current practices, instrument biases, and recommendations. *J*

Autism Dev Disord, *34*(1), 19–27.

Mottron, Laurent, Belleville, S., & Ménard, E. (1999). Local bias in autistic subjects as evidenced by graphic tasks: Perceptual hierarchization or working memory deficit? *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1017/S0021963098003795

Mottron, Laurent, Burack, J. A., Iarocci, G., Belleville, S., & Enns, J. T. (2003). Locally oriented perception with intact global processing among adolescents with high-functioning autism: Evidence from multiple paradigms. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1111/1469-7610.00174

Müller, R. A., & Fishman, I. (2018). Brain Connectivity and Neuroimaging of Social Networks in Autism. *Trends in Cognitive Sciences*, *22*(12), 1103–1116. https://doi.org/10.1016/j.tics.2018.09.008

Mundy, P., Sigman, M., & Kasari, C. (1990). A longitudinal study of joint attention and language development in autistic children. *Journal of Autism and Developmental Disorders*, *20*(1), 115–128. https://doi.org/10.1007/bf02206861

Nadig, A., Lee, I., Singh, L., Bosshart, K., & Ozonoff, S. (2010). How does the topic of conversation affect verbal exchange and eye gaze? A comparison between typical development and high-functioning autism. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2010.05.020

Nair, A., Jolliffe, M., Lograsso, Y. S. S., & Bearden, C. E. (2020). A Review of Default Mode Network Connectivity and Its Association With Social Cognition in Adolescents With Autism Spectrum Disorder and Early-Onset Psychosis. *Frontiers in Psychiatry*, *11*. https://doi.org/10.3389/fpsyt.2020.00614

Narita, T., & Koga, Y. (1987). Neuropsychological assessment of childhood autism. *Adv. Biol. Psychiatr.*, *16*, 156–170.

Navon, D. (1977). Forest before trees: The precedence of global features in visual perception. *Cognitive Psychology*. https://doi.org/10.1016/0010-0285(77)90012-3

Nekovarova, T., Fajnerova, I., Horacek, J., & Spaniel, F. (2014). Bridging disparate symptoms of schizophrenia: a triple network dysfunction theory. *Frontiers in Behavioral Neuroscience*, *8*(MAY), 1–10. https://doi.org/10.3389/fnbeh.2014.00171

Nicolaidis, C., Raymaker, D., McDonald, K., Dern, S., Boisclair, W. C., Ashkenazy, E., & Baggs, A. (2013). Comparison of healthcare experiences in autistic and non-autistic adults: A cross-sectional online survey facilitated by an academic-community partnership. *Journal of General Internal Medicine*. https://doi.org/10.1007/s11606-012-2262-7

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.87.24.9868

Ogawa, S., Menon, R. S., Tank, D. W., Kim, S. G., Merkle, H., Ellermann, J. M., & Ugurbil, K. (1993). Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. *Biophysical Journal*. https://doi.org/10.1016/S0006-3495(93)81441-3

Ogawa, Seiji, & Lee, T. -M. (1990). Magnetic resonance imaging of blood vessels at high fields: In vivo and in vitro measurements and image simulation. *Magnetic Resonance in Medicine*. https://doi.org/10.1002/mrm.1910160103

Ohta, M. (1987). Cognitive disorders of infantile autism: a study employing the WISC, spatial relationship conceptualization, and gesture imitations. *J Autism Dev Disord*, *17*(1), 45–62.

Oliveira, G. G. (2005). Epidemiologia do autismo em Portugal : um estudo de prevalência da perturbação do espectro do autismo e de caracterização de uma amostra populacional de idade escolar. *Coimbra: Universidade de Coimbra*.

Ozonoff, S., & Rogers, S. J. (2003). From Kanner to the millennium: Scientific advances that have shaped clinical practice. In S. Ozonoff, S. J. Rogers, & R. L. Hendren (Eds.), *Autism spectrum disorders: A research review for practitioners* (pp. 3–33). American Psychiatric Publishing, Inc.

Ozonoff, Sally, Cook, I., Coon, H., Dawson, G., Joseph, R. M., Klin, A., McMahon, W. M., Minshew, N., Munson, J. A., Pennington, B. F., Rogers, S. J., Spence, M. A., Tager-Flusberg, H., Volkmar, F. R., & Wrathall, D. (2004). Performance on Cambridge neuropsychological test automated battery subtests sensitive to frontal lobe function in people with autistic disorder: Evidence from the Collaborative Programs of Excellence in Autism network. *Journal of Autism and Developmental Disorders*, *34*(2), 139–150. https://doi.org/10.1023/B:JADD.0000022605.81989.cc

Ozonoff, Sally, Goodlin-Jones, B. L., & Solomon, M. (2005). Evidence-based assessment of autism spectrum disorders in children and adolescents. In *Journal of Clinical Child and Adolescent Psychology*. https://doi.org/10.1207/s15374424jccp3403_8

Ozonoff, Sally, & Jensen, J. (1999). Specific executive function profiles in three neurodevelopmental disorders. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1023/A:1023052913110

Ozonoff, Sally, Pennington, B. F., & Rogers, S. J. (1991). Executive Function Deficits in High-Functioning Autistic Individuals: Relationship to Theory of Mind. *Journal of Child Psychology and Psychiatry*. https://doi.org/10.1111/j.1469-7610.1991.tb00351.x

Ozonoff, Sally, Rogers, S. J., & Pennington, B. F. (1991). Asperger's Syndrome: Evidence of an Empirical Distinction from High-Functioning Autism. *Journal of Child Psychology and Psychiatry*. https://doi.org/10.1111/j.1469-7610.1991.tb00352.x

Ozonoff, Sally, Young, G. S., Carter, A., Messinger, D., Yirmiya, N., Zwaigenbaum, L., Bryson, S., Carver, L. J., Constantino, J. N., Dobkins, K., Hutman, T., Iverson, J. M., Landa, R., Rogers, S. J., Sigman, M., & Stone, W. L. (2011). Recurrence risk for autism spectrum disorders: A baby siblings research consortium study. *Pediatrics*, *128*(3). https://doi.org/10.1542/peds.2010-2825

Papagiannopoulou, E. A., Chitty, K. M., Hermens, D. F., Hickie, I. B., & Lagopoulos, J. (2014). A systematic review and meta-analysis of eye-tracking studies in children with autism spectrum disorders. *Social Neuroscience*. https://doi.org/10.1080/17470919.2014.934966

Parish-Morris, J., Chevallier, C., Tonge, N., Letzen, J., Pandey, J., & Schultz, R. T. (2013). Visual attention to dynamic faces and objects is linked to face processing skills: A combined study of children with autism and controls. *Frontiers in Psychology*, *4*(APR), 1–7. https://doi.org/10.3389/fpsyg.2013.00185

Park, M. T. M., Raznahan, A., Shaw, P., Gogtay, N., Lerch, J. P., & Mallar Chakravarty, M. (2018). Neuroanatomical phenotypes in mental illness: Identifying convergent and divergent cortical phenotypes across autism, ADHD and schizophrenia. *Journal of Psychiatry and Neuroscience*. https://doi.org/10.1503/jpn.170094

Patriquin, M. A., DeRamus, T., Libero, L. E., Laird, A., & Kana, R. K. (2016). Neuroanatomical and neurofunctional markers of social cognition in autism spectrum disorder. *Human Brain Mapping*. https://doi.org/10.1002/hbm.23288

Paul, R., Chawarska, K., Cicchetti, D., & Volkmar, F. (2008). Language outcomes of toddlers

with autism spectrum disorders: A two year follow-up. *Autism Research*, *1*(2), 97–107. https://doi.org/10.1002/aur.12

Paul, R., Loomis, R., & Chawarska, K. (2014). Adaptive behavior in toddlers under two with autism spectrum disorders. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-011-1279-9

Pellicano, E., Murray, M., Durkin, K., & Maley, A. (2006). Multiple cognitive capabilities/deficits in children with an autism spectrum disorder: "Weak" central coherence and its relationship to theory of mind and executive control. *Development and Psychopathology*, *18*(1), 77–98. https://doi.org/10.1017/S0954579406060056

Pelphrey, K. A., Sasson, N. J., Reznick, J. S., Paul, G., Goldman, B. D., & Piven, J. (2002). Visual Scanning of Faces in Autism. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1023/A:1016374617369

Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. In *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1111/j.1469-7610.1996.tb01380.x

Perry, A., Flanagan, H. E., Dunn Geier, J., & Freeman, N. L. (2009). Brief report: the Vineland Adaptive Behavior Scales in young children with autism spectrum disorders at different cognitive levels. *J Autism Dev Disord*, *39*(7), 1066–1078. https://doi.org/10.1007/s10803-009-0704-9

Peterson, D. M., & Bowler, D. M. (2000). Counterfactual reasoning and false belief understanding in children with autism. *Autism*. https://doi.org/10.1177/1362361300004004005

Pezzimenti, F., Han, G. T., Vasa, R. A., & Gotham, K. (2019). Depression in Youth with Autism Spectrum Disorder. *Child and Adolescent Psychiatric Clinics of North America*, *28*(3), 397–409. https://doi.org/10.1016/j.chc.2019.02.009

Pierce, K., Marinero, S., Hazin, R., McKenna, B., Barnes, C. C., & Malige, A. (2016). Eye Tracking Reveals Abnormal Visual Preference for Geometric Images as an Early Biomarker of an Autism Spectrum Disorder Subtype Associated With Increased Symptom Severity. *Biological Psychiatry*, *79*(8), 657–666. https://doi.org/10.1016/j.biopsych.2015.03.032

Pinto, D., Pagnamenta, A. T., Klei, L., Anney, R., Merico, D., Regan, R., Conroy, J., Magalhaes, T. R., Correia, C., Abrahams, B. S., Almeida, J., Bacchelli, E., Bader, G. D., Bailey, A. J., Baird, G., Battaglia, A., Berney, T., Bolshakova, N., Bölte, S., … Betancur, C. (2010). Functional impact of global rare copy number variation in autism spectrum disorders. *Nature*, *466*(7304), 368–372. https://doi.org/10.1038/nature09146

Plaisted, K., Swettenham, J., & Rees, L. (1999). Children with autism show local precedence in a divided attention task and global precedence in a selective attention task. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1017/S0021963099004102

Rabiee, A., Samadi, S. A., Vasaghi-Gharamaleki, B., Hosseini, S., Seyedin, S., Keyhani, M., Mahmoodizadeh, A., & Kermani, F. R. (2019). The cognitive profile of people with high-functioning autism spectrum disorders. *Behavioral Sciences*, *9*(2). https://doi.org/10.3390/bs9020020

Riby, D. M., & Hancock, P. J. B. (2009a). Do faces capture the attention of individuals with Williams syndrome or autism? Evidence from tracking eye movements. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-008-0641-z

Riby, D. M., & Hancock, P. J. B. (2009b). Looking at movies and cartoons: Eye-tracking evidence from Williams syndrome and autism. *Journal of Intellectual Disability Research*.

https://doi.org/10.1111/j.1365-2788.2008.01142.x

Riby, D. M., Hancock, P. J., Jones, N., & Hanley, M. (2013). Spontaneous and cued gaze-following in autism and Williams syndrome. *Journal of Neurodevelopmental Disorders*, *5*(1), 13. https://doi.org/10.1186/1866-1955-5-13

Rice, K., Moriuchi, J. M., Jones, W., & Klin, A. (2012). Parsing heterogeneity in autism spectrum disorders: Visual scanning of dynamic social scenes in school-aged children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(3), 238–248. https://doi.org/10.1016/j.jaac.2011.12.017

Risi, S., Lord, C., Gotham, K., Corsello, C., Chrysler, C., Szatmari, P., Cook, E. H., Leventhal, B. L., & Pickles, A. (2006). Combining information from multiple sources in the diagnosis of autism spectrum disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, *45*(9), 1094–1103. https://doi.org/10.1097/01.chi.0000227880.42780.0e

Ritvo, E. R., & Ornitz, E. M. (1976). *Autism: diagnosis, current research and management*. Spectrum.

Rondan, C., & Deruelle, C. (2007). Global and configural visual processing in adults with autism and Asperger syndrome. *Research in Developmental Disabilities*. https://doi.org/10.1016/j.ridd.2006.02.007

Ropar, D., & Mitchell, P. (1999). Are individuals with autism and Asperger's syndrome susceptible to visual illusions? *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1017/S0021963099004667

Roth, R. M., Isquith, P. K., & Gioia, G. A. (2005). Behavior rating inventory of executive function -- adult version: Professional manual. *Lutz, FL: Psychological Assessment Resources, Inc.*

Russell, J., Jarrold, C., & Hood, B. (1999). Two intact executive capacities in children with autism: Implications for the core executive dysfunctions in the disorder. *Journal of Autism and Developmental Disorders*, *29*(2), 103–112. https://doi.org/10.1023/A:1023084425406

Ruta, L., Famà, F. I., Bernava, G. M., Leonardi, E., Tartarisco, G., Falzone, A., Pioggia, G., & Chakrabarti, B. (2017). Reduced preference for social rewards in a novel tablet based task in young children with Autism Spectrum Disorders. *Scientific Reports*. https://doi.org/10.1038/s41598-017-03615-x

Rutter, M. (1978). Diagnosis and definition of childhood autism. *Journal of Autism and Childhood Schizophrenia*. https://doi.org/10.1007/BF01537863

Sandin, S., Lichtenstein, P., Kuja-Halkola, R., Larsson, H., Hultman, C. M., & Reichenberg, A. (2014). The familial risk of autism. *JAMA - Journal of the American Medical Association*, *311*(17), 1770–1777. https://doi.org/10.1001/jama.2014.4144

Schmitz, N., Rubia, K., Daly, E., Smith, A., Williams, S., & Murphy, D. G. M. (2006). Neural correlates of executive function in autistic spectrum disorders. *Biological Psychiatry*, *59*(1), 7–16. https://doi.org/10.1016/j.biopsych.2005.06.007

Schneider, S. G., & Asarnow, R. F. (1987). A comparison of cognitive/neuropsychological impairments of nonretarded autistic and schizophrenic children. *J Abnorm Child Psychol*, *15*(1), 29–45.

Schultz, R. T. (2005). Developmental deficits in social perception in autism: The role of the amygdala and fusiform face area. *International Journal of Developmental Neuroscience*. https://doi.org/10.1016/j.ijdevneu.2004.12.012

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., & Perner, J. (2014). Fractionating theory of mind: A meta-analysis of functional brain imaging studies. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2014.01.009

Seeley, W. W. (2019). The Salience Network: A Neural System for Perceiving and

Responding to Homeostatic Demands. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *39*(50), 9878–9882. https://doi.org/10.1523/JNEUROSCI.1138-17.2019

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Shafritz, K. M., Dichter, G. S., Baranek, G. T., & Belger, A. (2008). The Neural Circuitry Mediating Shifts in Behavioral Response and Cognitive Set in Autism. *Biological Psychiatry*, *63*(10), 974–980. https://doi.org/10.1016/j.biopsych.2007.06.028

Shah, A., & Frith, U. (1993). Why do autistic individuals show superior performance on the block design task? *J Child Psychol Psychiatry*, *34*(8), 1351–1364.

Shi, L., Zhou, Y., Ou, J., Gong, J., Wang, S., Cui, X., Lyu, H., Zhao, J., & Luo, X. (2015). Different Visual Preference Patterns in Response to Simple and Complex Dynamic Social Stimuli in Preschool-Aged Children with Autism Spectrum Disorders. *PLOS ONE*, *10*(3), e0122280. https://doi.org/10.1371/journal.pone.0122280

Shic, F., Bradshaw, J., Klin, A., Scassellati, B., & Chawarska, K. (2011). Limited activity monitoring in toddlers with autism spectrum disorder. *Brain Research*. https://doi.org/10.1016/j.brainres.2010.11.074

Shic, F., Macari, S., & Chawarska, K. (2014). Speech disturbs face scanning in 6-month-old infants who develop autism spectrum disorder. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2013.07.009

Siegel, D. J., Minshew, N. J., & Goldstein, G. (1996). Wechsler IQ profiles in diagnosis of high-functioning autism. *J Autism Dev Disord*, *26*(4), 389–406.

Solomon, M., Ozonoff, S. J., Ursu, S., Ravizza, S., Cummings, N., Ly, S., & Carter, C. S. (2009). The neural substrates of cognitive control deficits in autism spectrum disorders. *Neuropsychologia*, *47*(12), 2515–2526. https://doi.org/10.1016/j.neuropsychologia.2009.04.019

Solomon, M., Yoon, J. H., Ragland, J. D., Niendam, T. A., Lesh, T. A., Fairbrother, W., & Carter, C. S. (2014). The development of the neural substrates of cognitive control in adolescents with autism spectrum disorders. *Biological Psychiatry*, *76*(5), 412–421. https://doi.org/10.1016/j.biopsych.2013.08.036

South, M., Ozonoff, S., & Mcmahon, W. M. (2007). The relationship between executive functioning, central coherence, and repetitive behaviors in the high-functioning autism spectrum. *Autism*, *11*(5), 437–451. https://doi.org/10.1177/1362361307079606

Sparrow, S, Balla, D. A., & Cicchetti, D. V. (1984). *Vineland Adaptative Behaviour Scales: Interview edition, Survey form*. American Guidance Service.

Sparrow, SS, Cicchetti, D., & Balla, D. (2005). *Vineland Adaptive Behavior Scales – Second Edition: Manual*. NCS Pearson.

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences*, *105*(34), 12569–12574. https://doi.org/10.1073/pnas.0800005105

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*. https://doi.org/10.1037/h0054651

Stuss, D. T., & Knight, R. T. (2009). Principles of Frontal Lobe Function. In *Principles of Frontal Lobe Function*. https://doi.org/10.1093/acprof:oso/9780195134971.001.0001

Szatmari, P., Bryson, S. E., Boyle, M. H., Streiner, D. L., & Duku, E. (2003). Predictors of

outcome among high functioning children with autism and Asperger syndrome. *J Child Psychol Psychiatry*, *44*(4), 520–528.

Szatmari, P., Tuff, L., Finlayson, M. A., & Bartolucci, G. (1990). Asperger's syndrome and autism: neurocognitive aspects. *J Am Acad Child Adolesc Psychiatry*, *29*(1), 130–136.

The Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium. (2017). Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. *Molecular Autism*, *8*, 21. https://doi.org/10.1186/s13229-017-0137-9

Thurm, A., Lord, C., Lee, L.-C., & Newschaffer, C. (2007). Predictors of Language Acquisition in Preschool Children with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *37*(9), 1721–1734. https://doi.org/10.1007/s10803-006-0300-1

Tick, B., Bolton, P., Happé, F., Rutter, M., & Rijsdijk, F. (2016). Heritability of autism spectrum disorders: A meta-analysis of twin studies. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *57*(5), 585–595. https://doi.org/10.1111/jcpp.12499

Trevarthen, C., & Aitken, K. J. (2001). Infant intersubjectivity: Research, theory, and clinical applications. In *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1017/S0021963001006552

Tronick, E. Z. (1989). Emotions and Emotional Communication in Infants. *American Psychologist*. https://doi.org/10.1037/0003-066X.44.2.112

Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn3857

Uddin, L. Q., Supekar, K., Lynch, C. J., Khouzam, A., Phillips, J., Feinstein, C., Ryali, S., & Menon, V. (2013). Salience network-based classification and prediction of symptom severity in children with autism. *JAMA Psychiatry*, *70*(8), 869–879. https://doi.org/10.1001/jamapsychiatry.2013.104

Van Der Geest, J. N., Kemner, C., Camfferman, G., Verbaten, M. N., & Van Engeland, H. (2002). Looking at Images with Human Figures: Comparison between Autistic and Normal Children. *Journal of Autism and Developmental Disorders*, *32*(2), 69–75. https://doi.org/10.1023/A:1014832420206

VanMeter, L., Fein, D., Morris, R., Waterhouse, L., & Allen, D. (1997). Delay versus deviance in autistic social behavior. *J Autism Dev Disord*, *27*(5), 557–569.

Velikonja, T., Fett, A.-K. K., & Velthorst, E. (2019). Patterns of Nonsocial and Social Cognitive Functioning in Adults with Autism Spectrum Disorder: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *76*(2), 135–151. https://doi.org/10.1001/jamapsychiatry.2018.3645

Venter, A., Lord, C., & Schopler, E. (1992). A follow-up study of high-functioning autistic children. *J Child Psychol Psychiatry*, *33*(3), 489–507.

Ventola, P., Saulnier, C. A., Steinberg, E., Chawarska, K., & Klin, A. (2014). Early-emerging social adaptive skills in toddlers with autism spectrum disorders: An item analysis. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-011-1278-x

Volkmar, F. R., Sparrow, S. S., Goudreau, D., Cicchetti, D. V, Paul, R., & Cohen, D. J. (1987). Social deficits in autism: an operational approach using the Vineland Adaptive Behavior Scales. *J Am Acad Child Adolesc Psychiatry*, *26*(2), 156–161. https://doi.org/S0890-8567(09)65643-4 [pii]10.1097/00004583-198703000-00005

von dem Hagen, E. A. H., Stoyanova, R. S., Baron-Cohen, S., & Calder, A. J. (2013). Reduced functional connectivity within and between "social" resting state networks in autism

spectrum conditions. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nss053

Vuilleumier, P. (2002). Facial expression and selective attention. In *Current Opinion in Psychiatry*. https://doi.org/10.1097/00001504-200205000-00011

Wagner, J. B., Hirsch, S. B., Vogel-Farley, V. K., Redcay, E., & Nelson, C. A. (2013). Eye-tracking, autonomic, and electrophysiological correlates of emotional face processing in adolescents with autism spectrum disorder. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-012-1565-1

Wallace, G. L., Budgett, J., & Charlton, R. A. (2016). Aging and autism spectrum disorder: Evidence from the broad autism phenotype. *Autism Research*. https://doi.org/10.1002/aur.1620

Wallisch, A., Little, L. M., Dean, E., & Dunn, W. (2018). Executive Function Measures for Children: A Scoping Review of Ecological Validity. *OTJR Occupation, Participation and Health*, *38*(1), 6–14. https://doi.org/10.1177/1539449217727118

Wang, C., Geng, H., Liu, W., & Zhang, G. (2017). Prenatal, perinatal, and postnatal factors associated with autism. *Medicine*, *96*(18), e6696. https://doi.org/10.1097/MD.0000000000006696

Wang, Y., & Olson, I. R. (2018). The Original Social Network: White Matter and Social Cognition. *Trends in Cognitive Sciences*, *22*(6), 504–516. https://doi.org/10.1016/j.tics.2018.03.005

White, S. J., Frith, U., Rellecke, J., Al-Noor, Z., & Gilbert, S. J. (2014). Autistic adolescents show atypical activation of the brain's mentalizing system even without a prior history of mentalizing problems. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2013.12.013

Wilson, C. E., Brock, J., & Palermo, R. (2010). Attention to social stimuli and facial identity recognition skills in autism spectrum disorder. *Journal of Intellectual Disability Research*, *54*(12), 1104–1115. https://doi.org/10.1111/j.1365-2788.2010.01340.x

Wimmer, H., & Perner, J. (1983). Beliefs about beliefs: Representation and constraining function of wrong beliefs in young children's understanding of deception. *Cognition*. https://doi.org/10.1016/0010-0277(83)90004-5

Wodka, E. L., Mathy, P., & Kalb, L. (2013). Predictors of Phrase and Fluent Speech in Children With Autism and Severe Language Delay. *Pediatrics*, *131*(4), e1128–e1134. https://doi.org/10.1542/peds.2012-2221

Wolf, I., Dziobek, I., & Heekeren, H. R. (2010). Neural correlates of social cognition in naturalistic settings: A model-free analysis approach. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2009.08.060

Wu, S., Wu, F., Ding, Y., Hou, J., Bi, J., & Zhang, Z. (2017). Advanced parental age and autism risk in children: a systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, *135*(1), 29–41. https://doi.org/10.1111/acps.12666

Zelazo, P. D., & Carlson, S. M. (2012). Hot and Cool Executive Function in Childhood and Adolescence: Development and Plasticity. *Child Development Perspectives*, *6*(4), 354–360. https://doi.org/10.1111/j.1750-8606.2012.00246.x

Zelazo, P. D., & Mller, U. (2005). Executive Function in Typical and Atypical Development. In *Blackwell Handbook of Childhood Cognitive Development* (Vol. 3, Issue 1, pp. 445–469). Blackwell Publishers Ltd. https://doi.org/10.1002/9780470996652.ch20

Zimmerman, D. L., Ownsworth, T., O'Donovan, A., Roberts, J., & Gullo, M. J. (2016). Independence of Hot and Cold Executive Function Deficits in High-Functioning Adults with Autism Spectrum Disorder. *Frontiers in Human Neuroscience*, *10*, 24.

https://doi.org/10.3389/fnhum.2016.00024
Zwick, G. P. (2017). Neuropsychological assessment in autism spectrum disorder and related conditions. *Dialogues in Clinical Neuroscience*, *19*(4), 373–379. https://doi.org/10.1016/S0140-6736(00)57467-4

1.2. General aims and outline of the thesis

General aims and outline of the thesis

Autism spectrum disorder (ASD) is one of the most studied neurodevelopmental disorders and at the same time, intriguingly, one of we have less certainties about. The ASD is characterized by deficits in social cognition, observable in the impairments in social communication and interaction, but also characterized by deficits in executive functioning (EF) with cascading effects in adaptive behaviour skills. The nature of these impairments bears an enormous potential for unveiling the neural mechanisms mediating the affected EF and social cognition. Furthermore, by unravelling the role of both EF and social cognition, the cognitive and functional deficits observed in ASD can be explained. The present thesis is thus aimed at comprehensively investigate and characterize the functional, intellectual and neurodevelopmental profile of ASD and to definitely establish the specific link between two of the main dysfunctional areas in this condition, namely EF and social cognition.

Chapter 1 presents the current knowledge on the diagnosis, neurocognitive theories and neurofunctional imaging in ASD, specially focused on EF and social cognition. Moreover, the functional and cognitive phenotypes are described in order to understand the disorder.

Chapters 2 (*2.1, 2.2, 2.3, 2.4, 2.5* and *2.6*) present the body of research obtained from the experimental testing conducted to fully characterize ASD functional, intellectual and neurodevelopmental profiles and to deepen our knowledge regarding ASD main symptoms by investigating the specific link between EF and social cognition in this condition.

Limitations present in the daily life of ASD individuals and frequent concerns in the outpatient clinic are firstly addressed, by performing a broad and comprehensive phenotypic characterization of a Portuguese clinical sample: from what we can see and assess (adaptive behaviour), to what we can infer from our evaluations (intellectual and neurodevelopmental profile).

In the *Chapter 2.1.,* we investigated the functional profile in ASD by exploring the adaptive behaviour profile, focusing on communication, daily living skills and socialization, and on the impact of intelligence quotient (IQ) in these abilities and using participants with other neurodevelopmental disorders (OND), such as intellectual disability (ID) or learning disabilities, as comparison model of putative deficits in adaptive behaviour. This framework for the study of adaptive behaviour provides a new insight into the influence of the primary diagnosis of ASD and the relevance of the IQ on adaptive behaviour and its functional profile.

Although previous studies have suggested impaired adaptive functioning in ASD, the exact relevance of IQ (are the adaptive difficulties the same or proportional in ASD

individuals with or without ID?) to the symptomatic expression of ASD and direct involvement in the subject's personal and social autonomy and self-sufficiency remains unclear.

Chapter 2.2 explores the intellectual profile of ASD individuals, as compared to OND, focusing on the characterization of the strengths and deficits of ASD, definition of cognitive subgroups (again, are the cognitive difficulties the same or proportional in ASD individuals with or without ID?) and how cognition is associated with core ASD features and adaptive behaviour. We expect the corroboration of our previous study.

Chapter 2.3 characterizes the neurodevelopmental profile of ASD to understand how it evolved from the preschool to the school age and if there was any marker in the neurodevelopmental profile and early neurodevelopmental milestones that could predict later acquisition of expressive language, determinant in communication skills that directly impacts the functional profile and social cognition.

The previous chapters were based on assessment tests that are used massively in our clinical practice to characterize this population, therefore these studies may bring new insights in the interpretation of the results with implications, for instance, in the definition of the intervention.

After the characterization of our clinical sample, we start to directly assess social cognition and EF.

In the *Chapter 2.4.,* we explore social attention that integrates social cognition, in ASD by using an experimental paradigm based on an assessment tool that we used in the diagnostic process of these individuals. Previous studies do not reach a consensus on whether social attention is fundamentally reduced or absent in individuals with ASD and we hypothesize that the role of type of stimuli and task are critical in the putative social attention deficits.

Chapters 2.5 and *2.6* explicitly explore the link between EF and social cognition in ASD by investigating the behavioural performance, visual patterns and neural underpinnings in a new ecological goal-oriented task, based on a daily living chore: shopping in a supermarket, that draws heavily on EF, and social cognition. The need for ecological tasks has been taking growing importance in the study of EF, particularly in ASD, since classical task do not seem to really capture the nature and the extent of ASD impairments in EF and social cognition. *Chapter 2.5* focuses on the assessment of EF with the integration of attentional social vs. non-social cues, in ASD and matched controls with typical neurodevelopment (TD), involving explicit manipulations of levels of cognitive load and attentional saliency of the social and

non-social cues that could help in task solving. *Chapter 2.6* examines the neural correlates associated with the performance of a goal-oriented ecologic task with social and non-social conditions in ASD and matched TD individuals. This chapter also provides the first examination of the brain activity of ASD and TD subjects while performing a task that requires social cognition, EF, and cue saliency processing, at the same time, in the context of an ecological social situation.

As a final point, the overall results are discussed in *Chapter 3* in order to provide an integrative view of the main findings of the present work and their integration in the current body of knowledge on ASD phenotype and the specific link between executive function and social cognition. In this chapter, the main conclusions and directions to future studies are also presented.

RESEARCH WORKS

CHAPTER 2

CHAPTER 2

2.1. Adaptive profiles in autism and other neurodevelopmental disorders

This chapter consists in the paper: **Mouga S,** Almeida J, Café C, Duque F, Oliveira G. Adaptive profiles in autism and other neurodevelopmental disorders. *J Autism Dev Disord*. 2015 Apr; 45(4):1001-12. doi: 10.1007/s10803-014-2256-x. PubMed PMID: 25241010.

Abstract

We investigated the influence of specific autism spectrum disorder (ASD) deficits in learning adaptive behaviour, besides Intelligence Quotient (IQ).

Participated 217 school-aged: ASD (N=115), and Other Neurodevelopmental Disorders (OND) groups (N=102) matched by Full-Scale IQ. We compared standard scores of Vineland Adaptive Behaviour Scale (VABS) in communication, daily living skills, socialization and adaptive behaviour composite. Pearson-correlation analysis was performed between each domain of VABS and Full-Scale, Verbal and Performance IQ, and chronological age (CA).

Results indicated that impairment in adaptive behaviour within the domain of socialization skills remains a distinctive factor of ASD versus OND, independently of intellectual disability (ID). Co-occurring ID results in further debilitating effects on overall functioning, especially in ASD. CA is negatively associated with VABS scores.

Introduction

Autism spectrum disorder (ASD) is a severe, early-onset and life-long neurodevelopmental disorder with a high worldwide prevalence and a distribution of four males (M) to one female (F) (Centers for Disease Control and Prevention 2009; Oliveira et al. 2007; Fombonne 2003). ASD is characterized by deficits in social interaction and communication as well as by a repetitive pattern of behaviour and interests (American Psychiatric Association 2013). Even though comorbidity with intellectual disability (ID) is showing a decrease in recent studies it remains very common, being that about one third to half of ASD subjects have co-occurring ID (Centers for Disease Control and Prevention 2012, 2014, 2009).

The ASD core symptoms typically are apparent before the age of three years and, in addition with ID, compromise functioning across multiple domains, including cognitive functioning and adaptive behaviour, affecting multiple areas of a person's life (Ventola et al. 2014; American Psychiatric Association 2013; Paul et al. 2014).

Adaptive behaviour refers to the capacity to accomplish conceptual, social and practical demands on a daily basis (American Association on Mental Retardation 2002), that is, the effectiveness with which individuals can achieve personal independence and social responsibility as it is expected for their chronological age (CA) and cultural set. To be successful in those demands and therefore support personal, domestic and social self-

sufficiency, individuals have to perform daily activities that require adaptive skills (Tasse et al. 2012; Sparrow et al. 1984). These skills integrate the definition of ID and are preponderant to a person's overall functioning and adjustment to the surrounding environment (Tasse et al. 2012; Goldberg et al. 2009). Consequently, independent living is highly reliant in adaptive abilities (Soenen et al. 2009). Deficits in this area are a primary barrier to a wide range of tasks that go from basic personal and domestic autonomy (such as hygiene, dressing, making meals) to self-sufficiency (such as having a competitive employment or money management) (Dawson et al. 1998). Difficulties in adaptive behaviour appear early in life (Ventola et al. 2014; Paul et al. 2014) and, without appropriate, intensive, and effective intervention, persist throughout life (Matson et al. 2009). Hence, this life-long disability is one of the most important in the prognosis of the people with ASD and consequently has social and economic repercussion with large cost to the society (Knapp et al. 2009).

The Vineland Adaptive Behaviour Scale (VABS) (Sparrow et al. 1984) is the most studied measure of adaptive behaviour. It is a semi-structured interview performed to the subject's parents or caregivers and constitutes a measure of personal and social self-sufficiency (for a detailed description, see Materials in Methods Section). This scale has been particularly used in the area of ASD research (Klin et al. 1992; Volkmar et al. 1987; Volkmar et al. 1993) and can be employed in several domains, serving diverse purposes: from documenting delays in adaptive behaviour development in individuals with ASD (Gillham et al. 2000; Griffith et al. 2010; Jacobson and Ackerman 1990; Liss et al. 2001; Loveland and Kelley 1991; Rodrigue et al. 1991; Schatz and Hamdan-Allen 1995; Perry et al. 2009), to discriminate ASD from individuals with other neurodevelopmental disorders (OND). VABS also provides proper supplementary norms for ASD population (Carter et al. 1998).

There is a host of research on adaptive behaviour well documenting that in ASD individuals (in studies from children to young adults) there is usually a meaningful inconsistency between general cognitive ability and adaptive functioning favouring intelligence quotient (IQ) over real adaptive life skills (Bolte and Poustka 2002; Carter et al. 1998; Freeman et al. 1999; Liss et al. 2001; Volkmar et al. 1987). Therefore, individuals with ASD at all age ranges from childhood to adulthood, tend to be more impaired in adaptive functioning than their cognitive skills would predict, leastwise for individuals with ASD with normal or above normal intellectual abilities (Bolte and Poustka 2002; Freeman et al. 1991; Freeman et al. 1988; Klin et al. 2007; Fenton et al. 2003; Gabriels et al. 2007; Tomanik et al. 2007). However, when we only focus on ASD individuals with lower cognitive levels, adaptive skills are matched with their IQ (Perry et al. 2009; Kanne et al. 2011). When these individuals are compared with age

and IQ matched peers without ASD, they tend to have lower overall adaptive performance (Gabriels et al. 2007). Given the fact that impairments in adaptive functioning are part of the required criteria for the diagnosis of ID (Bramer 1988; American Association on Mental Retardation 2002), several studies have investigated the nature of adaptive impairments in individuals with ID with and without ASD. In the individuals with ASD co-occurring with ID, the results in adaptive behaviour are lower than in individuals with ID plus schizophrenia, personality disorders, mood disorders, attention deficit hyperactivity disorder or epilepsy (Di Nuovo and Buono 2007).

When we analyse in detail the pattern of adaptive functioning in ASD, findings have shown a distinctive and specific profile of adaptive behaviour including intermediate impairment in Communication , relative strengths in daily living skills (DLS) and significant deficits in Socialization (Bolte and Poustka 2002; Carter et al. 1998). Similarly, studies, ranging in age from 22 months up to 20 years old, have also found that individuals with ASD present inferior Socialization and Communication scores when compared to chronological and mental-age matched non ASD individuals with ID or learning disabilities (Carpentieri and Morgan 1996; Loveland and Kelley 1991; Perry et al. 2009; VanMeter et al. 1997; Volkmar et al. 1987). A review (Kraijer 2000) on adaptive behaviour in individuals with ASD and ID when compared with matched non autistic individuals using the VABS, showed that the performance of the ones with ASD and ID is found to be predominantly poor in the Socialization domain and at to some extent less poor in the Communication domain. In the other domains: DLS and Motor Skills the performance of the two groups did not differ. Despite the fact that both altered communication and socialization are characteristic of the disorder, individuals with ASD tend to evidence greater impairment in Socialization relative to both Communication and DLS (Carter et al. 1996).

The effect of age on the gap between cognitive skills and adaptive performance in ASD has also been considered. Studies report that this gap seems to extend with age (Klin et al. 2007; Szatmari et al. 2003; Kanne et al. 2011) and a recent longitudinal study (Farley et al. 2009) found that good adaptive skills are better predictors of positive outcome in adulthood, contrary to cognitive variables.

Despite the extended research on adaptive behaviour, the exact relevance of IQ to the symptomatic expression of ASD and direct involvement in the subject's personal and social autonomy and self-sufficiency remains unclear. Therefore, the longitudinal assessment of adaptive skills is an important factor to diagnostic evaluation, treatment planning and progress monitoring. Additionally, the need of efficient intervention to improve personal and social

autonomy in the prognosis of subjects with ASD in adulthood is a major concern of clinicians and parents. These questions are specific to ASD, which led us to analyse their adaptive profile compared with non ASD population, matched for IQ.

The present study involves participants with the principal diagnosis of ASD with and with no ID (ASD_ID/ASD_NID) and participants with other neurodevelopmental disorders (OND), such as intellectual disability or learning disabilities, with and with no ID (OND_ID/OND_NID). It is important to know the degree of influence of IQ in the different domains of adaptive behaviour because treatment and educational programming decisions are often made based on the needs of the patient, as determined by his or her strengths and weaknesses. Therefore, our aim is to study the influence of the primary diagnosis of ASD versus OND, matched for IQ, on adaptive behaviour and its profile.

Methods

Participants

Participants included 217 school-aged children and adolescents, ranging in age from 6 to 18 years. They were divided in two clinical main groups: ASD (N=115; mean age = 150 ± 34 months, 106 M/9 F) versus OND (N=102; mean age = 144 ± 38 months, 69 M/33 F). Participants were seen as part of an outpatient clinic, between 2007 and 2013. The characteristics of these two clinical groups are summarized in Table 2.1.1.

To be included in this study all participants had to be given an individually administered IQ test (Portuguese version of Wechsler Intelligence Scale for Children – Third Edition [WISC-III] (Wechsler 2003)) and the participants' primary caregiver had been administered the VABS-Survey form (Sparrow et al. 1984). They must have between 6-18 years old at the moment of evaluation. ASD diagnosis was assigned on the basis of the gold standard instruments: parental or caregiver interview (Autism Diagnostic Interview– Revised, ADI-R (Lord et al. 1994)), direct structured proband assessment (Autism Diagnostic Observation Schedule, ADOS (Lord et al. 1989), and clinical examination performed by an experienced neurodevelopmental Paediatrician. The current diagnostic criteria for autism were revised according to the Diagnostic and Statistical Manual of Mental Disorders 5, DSM-5 (American Psychiatric Association 2013). All ASD patients had positive results in the ADI-R and ADOS for autism or ASD and met the criteria for ASD from the DSM-5. A comprehensive medical observation excluded associated medical condition such as epilepsy, neurocutaneous or other genetic syndromes, or other usual comorbidity in ASD samples.

In the OND group were included subjects diagnosed and followed in our clinic with ID (full-scale IQ – FSIQ<70) or learning disabilities (FSIQ>70). The parents of participants included in OND group completed the Social Communication Questionnaire to exclude co-morbidity with ASD (Rutter et al. 2003). Associated medical conditions were excluded as in the ASD group.

Table 2.1.1. Characterization of the two main clinical groups (ASD *versus* OND)

Groups (N)	CA (months)		Gender (M/F)	FSIQ (WISC-III)		VIQ (WISC-III)		PIQ (WISC-III)	
	Mean (SD)	Range		Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
ASD (115)	150 (34)	82-227	106/9	80.3 (20.2)	47-137	80.2 (21.3)	46-131	85.9 (20.6)	50-146
OND (102)	144 (38)	73-225	69/33	75.2 (17.7)	47-135	76.4 (17.2)	48-129	80.3 (18.2)	46-130

NOTE. ASD = Autism Spectrum Disorder; OND = Other Neurodevelopmental Disorder; CA = Chronological Age; FSIQ = Full-Scale Intelligence Quotient; F = Female; M = Male; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; WISC-III = Wechsler Intelligence Scale for Children – Third Edition.

Measures

All measures (even the ones referred in the previous point for clinical characterization) were administered by experienced psychologists and neurodevelopmental paediatricians, for diagnostic or treatment planning, during routine clinical multidisciplinary assessments in a neurodevelopmental Unity that it is a National reference for ASD and other neurodevelopmental disorders in a Tertiary Paediatric Hospital. All population in this study is routinely followed by this team in a clinical set at least two times per year.

Vineland Adaptive Behaviour Scale – Survey Form

The VABS (Sparrow et al. 1984) is a recognized, semi-structured interview designed to assess global adaptive functioning from birth through adulthood.

For that propose three main domains are available for assessment: Communication DLS and Socialization. Each of one contains several subdomains that can be classified in five adaptive levels: Low, Moderately Low, Adequate, Moderately High, and High. The subdomains for the Communication competence are Receptive (that is, the verbal and non-

verbal communication a person understands), Expressive (that is, what a person says), and Written (that is, what a person reads and writes). The subdomains for DLS are as follows: Personal (that is, how a person eats, dresses, and practices personal hygiene), Domestic (that is, what household tasks is the person able to complete independently), and Community (that is, appropriate use of time, money, the telephone, and job skills). The subdomains for the Socialization are Interpersonal Relationships (that is, how a person interacts with others), Play and Leisure (that is, how a person plays and uses his/her leisure time), and Coping Skills (that is, how a person is able to be responsible and sensitive to others). Within subdomains, the VABS is divided into clusters of items that probe a specific developmental and functional area. The VABS main domains raw scores are calculated summing the raw scores from each subdomain.

The VABS has also a total score, the Adaptive Behaviour Composite (ABC) that is calculated via summing the raw scores from the VABS main domains used.

All raw scores of the main domains are then transformed in standard scores (SS) (mean = 100; standard deviation = 15).

For the purposes of this study, we analysed the Communication, DLS, and Socialization domains. In addition, comparisons were made using each participant's overall measure, the ABC, which represents the real individual's global adaptive functioning. To further comprehend these comparisons, we also analysed VABS subdomains.

Procedure

Data were collected from a database according to the National policy on archival research of the Paediatric Hospital. The group of participants included in this study represents a subset of patient information usually collected for clinical and research characterization of the outpatient clinics. A total of 217 records meeting the inclusion criteria were included in this study.

The two clinical main groups: ASD and OND were each further subdivided into two, totalizing four subgroups, taking into account the FSIQ. The classification of ID of the International Classification of Diseases, 10th Revision (Bramer 1988) was applied. According to this classification, a subject has ID when the FSIQ is below 70. The four subgroups were: [ASD with no ID (ASD_NID, N=72); ASD with ID (ASD_ID; N=43); OND with no ID (OND_NID; N=54); OND with ID (OND_ID; N=48])]. They were matched by CA and

FSIQ score (*t*-test, p>.05). The characteristics of the four subgroups are summarized in Table 2.1.2.

Table 2.1.2. Characterization of the four clinical subgroups divided by FSIQ

Subgroups (N)	CA (months)		Gender (M/F)	FSIQ (WISC-III)		VIQ (WISC-III)		PIQ (WISC-III)	
	Mean (SD)	Range		Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
ASD_ID (43)	166 (36)	104-227	40/3	60.1 (6.7)	47-69	58.8 (8.2)	46-78	69.7 (12.0)	50-98
ASD_NID (72)	140 (29)	82-216	66/6	92.4 (15.2)	71-137	93.1 (15.7)	57-131	95.5 (18.5)	64-146
OND_ID (48)	161 (35)	89-225	27/21	61.0 (6.4)	47-68	64.0 (8.3)	48-84	66.0 (9.5)	46-79
OND_NID (54)	129 (33)	73-208	42/12	87.8 (14.6)	72-135	87.4 (15.4)	62-129	92.9 (14.2)	69-130

NOTE. ASD_ID = ASD with intellectual disability (ID); ASD_NID = ASD with No ID; OND_ID = OND with ID; OND_NID = OND with No ID; CA = Chronological Age; M = Male; F= Female; FSIQ = Full-Scale Intelligence Quotient, VIQ= Verbal Intelligence Quotient; PIQ= Performance Intelligence Quotient, WISC-III= Wechsler Intelligence Scale for Children – Third Edition.

In the two main groups and in the four clinical subgroups we compared the functional profile of VABS analysing the standard scores (SS) by ID, namely in the Communication, DLS, Socialization and the ABC.

Statistical analysis

Statistical analysis was performed by the version for Microsoft Windows® of the Statistical Package for Social Sciences software (SPSS ®, Chicago, IL, USA).

The verification of the assumptions of normality for the application of parametric tests on the variables of interest (SS of the domains and composite of VABS: Communication; DLS; Socialization; ABC) was done resorting to the Kolmogorov-Smirnov test with Lilliefors correction.

To assess the significance of the differences between groups and subgroups we used *T*-tests for independent samples and variables with normal distribution.

Additionally, we performed Pearson-correlation analysis to determine the linear correlation between the VABS SS of each domain and FSIQ, Verbal IQ (VIQ) and Performance IQ (PIQ), as well as CA in the two main groups.

We used Mann-Whitney tests to assess the significance of the differences between groups and subgroups within VABS subdomains.

We considered the significance level (α) = 0.05 (p <.05).

Ethics Statement

This study and all the procedures were reviewed and approved by the Ethics Commission of our Paediatric Hospital and was conducted in accordance with the declaration of Helsinki. Informed consent was obtained from the parents/guardians of all younger participants. Children and adolescents also gave oral informed consent.

Results

Initial analyses were conducted to ensure that participants were matched with respect to CA and FSIQ in both two main clinical groups and four subgroups (*t*-test, p>.05).

To determine differences between two main clinical groups and the four subgroups with respect to adaptive behaviour skills, the SS of VABS domains above mentioned were analysed.

The average SS from VABS evaluation in two main clinical groups and four subgroups, as well as group comparisons, significance levels and effect sizes are reported in Table 2.1.3.

When we analyse the two main groups (ASD versus OND) not taking in account the level of IQ, both show no significant statistical differences in Communication domain and in the ABC (*t*-test, p>0.05, see Table 2.1.3. for details on exact *p*-values, specific comparisons, and effect sizes). However, in the other domains (Socialization, DLS) *t*-test showed significant differences. There was a significant effect for diagnosis, with ASD group having lower scores than OND group for Socialization [t (215) = -2,105, p = .036] and DLS [t (215) = -2,323, p = .021] (Table 2.1.3).

Table 2.1.3. SS from VABS domains in the two clinical groups and the four subgroups considering the classification of ID: means, significance levels and effect-sizes

	VABS Domains Mean (SD)											
Groups and Subgroups (N)	**COM**			**DLS**			**SOC**			**ABC**		
	Mean (SD)	*p*	*d*	Mean (SD)	*p*	*d*	Mean (SD)	*p*	*d*	Mean (SD)	*p*	*d*
ASD (N = 115)	77.43 (17.05)	0.253	0.16	70.10 (14.21)	0.021*	-0.32	74.22 (13.93)	0.036*	-0.29	69.13 (13.59)	0.376	-0.12
OND (N = 102)	74.73 (17.66)			74.67 (14.64)			78.03 (12.58)			70.78 (13.84)		
ASD_ID (N = 43)	63.95 (17.03)	0.292	-0.22	62.37 (15.78)	0.011*	-0.54	66.33 (13.56)	0.040*	-0.43	59.53 (13.57)	0.047*	-0.42
ASD_NID (N = 72)	67.77 (17.29)			70.75 (15.12)			71.71 (11.06)			65.04 (12.46)		
OND_ID (N = 48)	85.47 (10.93)	0.071	0.34	74.72 (10.91)	0.118	-0.28	78.93 (11.94)	0.026*	-0.41	74.86 (9.93)	0.630	-0.09
OND_NID (N = 54)	80.91 (15.70)			78.15 (13.50)			83.65 (11.17)			75.89 (13.07)		

NOTE. ASD = Autism Spectrum Disorder; OND = Other Neurodevelopmental Disorders; ASD_ID = ASD with intellectual disability (ID); ASD_NID = ASD with no ID; OND_ID = OND with ID; OND_NID = OND with no ID; COM = communication; DLS = daily living skills; SOC = socialization; ABC = adaptive behaviour composite; SD= standard deviation [Normal values of the scale: mean = 100; standard deviation = 15]. *T*-tests; * $p<0.05$. All comparisons signalled with * are significant and related to inferior results in the groups with ASD diagnosis. Effect sizes were computed using Cohen's *d*.

Although ASD group had globally lower scores on VABS, the exception was for the Communication domain, where ASD showed higher results than OND (still with no statistical significance). Concerning the subdomains, Mann-Whitney tests indicated that the two main groups differ in Receptive Communication, Personal and Domestic DLS and in Interpersonal Relationships and Coping Skills of Socialization domain (see Table 2.1.4 for details on exact *p*-values and specific comparisons). In fact, the OND population had better results in all subdomains with exception for receptive communication (Figure 2.1.1).

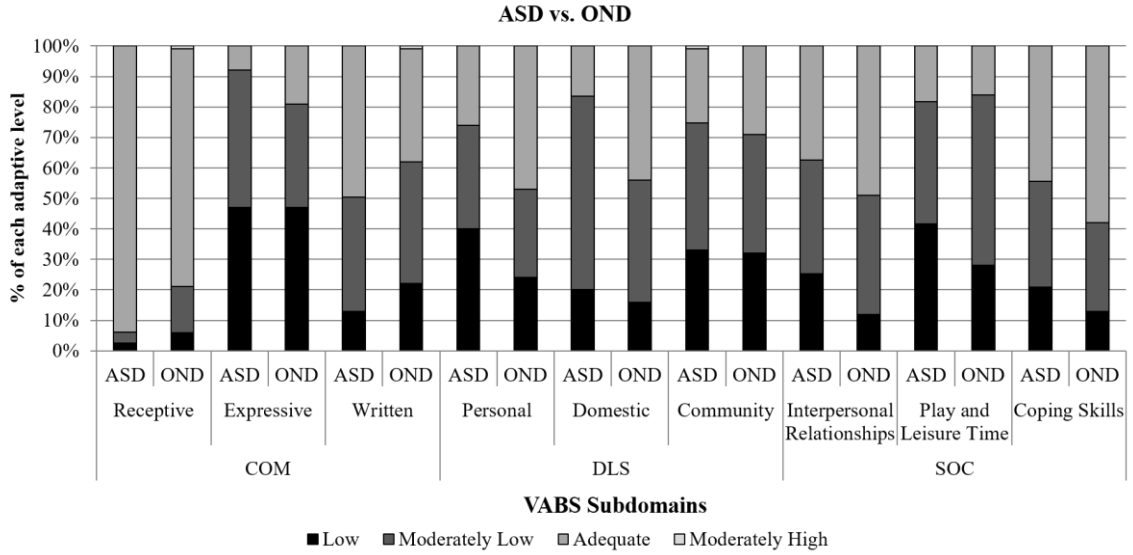

Fig. 2.1.1 VABS adaptive levels in the different subdomains for ASD and OND groups

NOTE. ASD = Autism Spectrum Disorder; OND = Other Neurodevelopmental Disorders; COM = communication; DLS = daily living skills; SOC = socialization; VABS = Vineland Adaptive Behaviour Scales.

Regarding the subgroups with ID (ASD_ID and OND_ID), there was also a significant effect for diagnosis, with ASD_ID subgroup having lower scores for Socialization [t (89) = -2,083, p = .040], DLS [t (89) = -2,585, p = .011], and ABC [t (89) = -2,018, p = .047] (Figure 2.1.2). However, no significant differences were found in the domain Communication, despite the average lower score of ASD_ID subgroup (*t*-test, p>0.05). In what concerns to subdomains, Mann-Whitney tests indicated that these subgroups differ in Personal DLS, Interpersonal Relationships and Coping Skills in the Socialization domain (see Table 2.1.4 for details on exact *p*-values and specific comparisons). In all subdomains where the groups differ, the OND_ID had better results (Figure 2.1.2).

Table 2.1.4. Groups and subgroups comparison analyses for VABS subdomains. All comparisons signalled with */ are significant**

	VABS Subdomains								
	Receptive	**Expressive**	**Written**	**Personal**	**Domestic**	**Community**	**Interpersonal Relationships**	**Play and Leisure Time**	**Coping Skills**
	p (*r*)	*p* (*r*)	*p* (*r*)	*p* (*r*)	*p* (*r*)	*p* (*r*)	*p* (*r*)	*p* (*r*)	*p* (*r*)
ASD vs. OND	*p* = .003** *r* =-0.20	*p* = .414 *r* =-0.06	*p* = .054 *r* =-0.13	*p* = .001** *r* =-0.22	*p* < .001** *r* =-0.24	*p* = .680 *r* =-0.03	*p* = .021* *r* =-0.16	*p* = .173 *r* =-0.09	*p* = .035* *r* =-0.14
ASD_ID vs. OND_ID	*p* = .219 *r* =-0.13	*p* = .880 *r* =-0.02	*p* = .517 *r* =-0.07	*p* < .001** *r* =-0.38	*p* = .060 *r* =-0.20	*p* = .119 *r* =-0.17	*p* = .018* *r* =-0.25	*p* = .515 *r* =-0.07	*p* = .041* *r* =-0.22
ASD_NID vs. OND_NID	*p* = .005 *r* =-0.25	*p* = .061 *r* =-0.17	*p* = .010* *r* =-0.23	*p* = .088 *r* =-0.15	*p* < .001** *r* =-0.31	*p* = .918 *r* =-0.01	*p* = .039* *r* =-0.18	*p* = .082 *r* =-0.16	*p* = .039* *r* =-0.01

NOTE. Man-Witney U; * p<0.05;** p<0.005. VABS = Vineland Adaptive Behaviour Scales, ASD = Autism Spectrum Disorder; OND = Other Neurodevelopmental Disorder; ASD_ID = ASD group with intellectual disability (ID); ASD_NID = ASD with no ID; OND_ID = OND group with ID; OND_NID = OND with no ID. Effect sizes are represented by r.

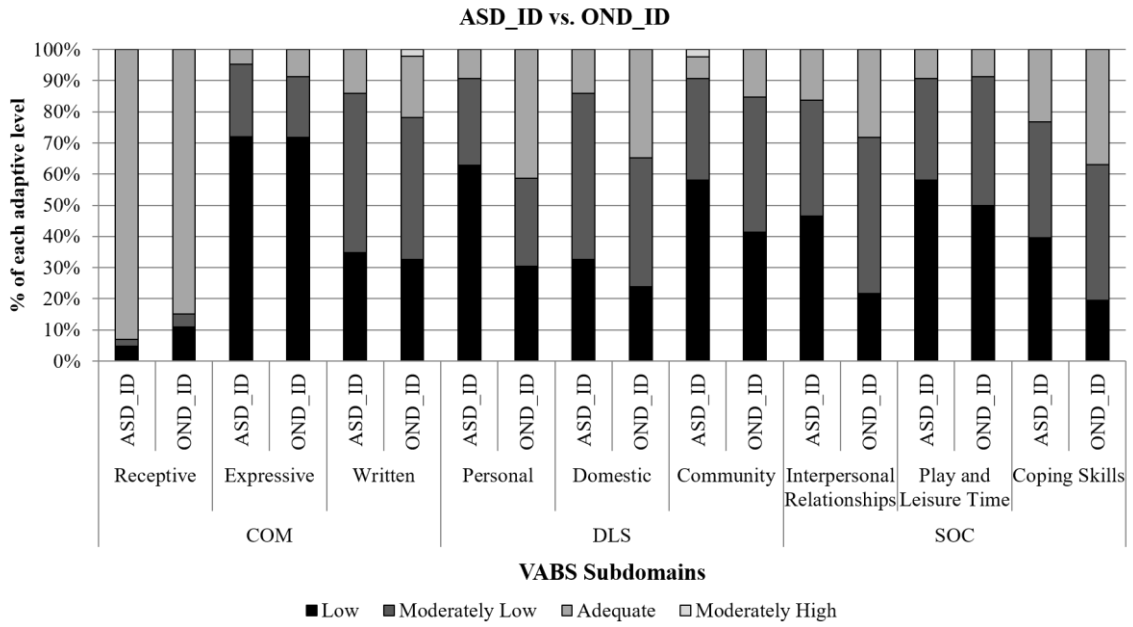

Fig. 2.1.2 VABS adaptive levels in the different subdomains for ASD_ID and OND_ID subgroups

NOTE. ASD_ID = autism spectrum disorder group with intellectual disability (ID); OND_ID = other neurodevelopmental disorders group with ID; COM = communication; DLS = daily living skills; SOC = socialization; VABS = Vineland Adaptive Behaviour Scales.

When comparing the subgroups with no ID (ASD_NID and OND_NID), *t*-test showed significant differences only in Socialization domain. There was a significant effect for diagnosis, with ASD_NID having lower scores [t (124) = -2,255, p = .026] (Figure 2.1.3). In the remaining domains ASD_NID subgroup had lower scores in DLS and ABC, and higher in Communication, still with no statistical significance. Mann-Whitney tests indicated that relatively to VABS subdomains, these two NID subgroups differ in Receptive and Written Communication, Domestic DLS and in Socialization domain: Interpersonal Relationships and Coping Skills (see Table 2.1.4 for details on exact p-values and specific comparisons). The ASD_NID subgroup had greater percentage of adequate receptive and written communication than the OND_NID. In all other subdomains where the subgroups differ, the OND_NID had better results (Figure 2.1.3).

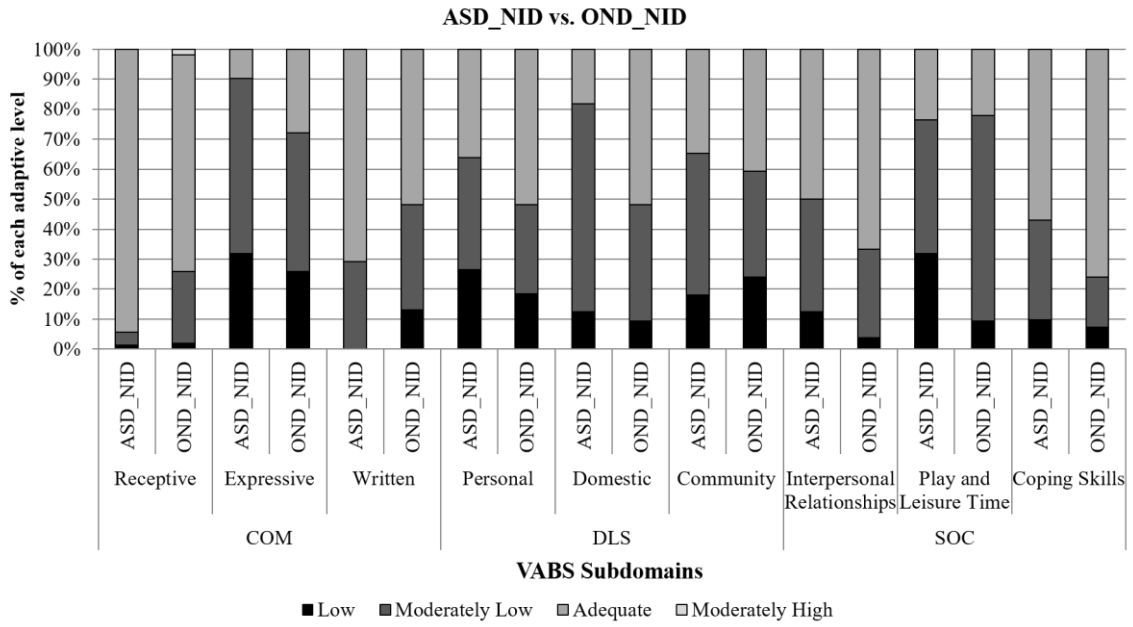

Fig. 2.1.3 VABS adaptive levels in the different subdomains for ASD_NID and OND_NID subgroups

NOTE. ASD_NID = autism spectrum disorder group with no intellectual disability (ID); OND_ID = other neurodevelopmental disorders group with no ID; COM = communication; DLS = daily living skills; SOC = socialization; VABS = Vineland Adaptive Behaviour Scales.

We performed Pearson correlation analysis between the SS of each domain (Communication, Socialization, DLS and ABC) from VABS and FSIQ, VIQ and PIQ, as well as CA at the two main groups of diagnosis: ASD versus OND (see Table 2.1.5 for details on exact *p*-values and specific correlations).

Indeed, we observed that in the ASD group the FSIQ, the VIQ and the PIQ were all statistically significant ($p < .05$) positively correlated with all VABS SS domains, being the strongest association between the VIQ and Communication ($r = 0.652$) and the VIQ and ABC ($r = 0.601$). The FSIQ and Communication were moderately correlated ($r = 0.516$). Positive correlations between PIQ and VABS SS were statistically significant ($p < .05$) but all weak ($r < 0.302$).

Similarly, in the OND group the FSIQ, the VIQ and the PIQ were all statistically significant ($p < .05$) positively correlated with all VABS SS domains, however, the strongest correlations were between the FSIQ and Communication ($r = 0.515$), PIQ and Socialization ($r = 0.544$) and PIQ and ABC ($r = 0.531$). Correlations between the FSIQ and Socialization ($r = 0.497$), FSIQ and ABC ($r = 0.498$), VIQ and Communication ($r = 0.498$), PIQ and Communication ($r = 0.479$) were moderated. Correlations between the DLS, Socialization,

and ABC and the VIQ, as well as the DLS and FSIQ or PIQ were statistically significant ($p < .05$) and positive but all weak ($r = 0.395$).

In what concerns to CA, the only VABS SS domains that were statistically significant ($p < .05$) but negatively correlated were: Communication, Socialization and ABC in the ASD group and the Socialization in the OND group. In the ASD group, the association between CA and Socialization was moderated ($r = -0.477$), being the rest weak correlations ($r = -0.363$). In the OND group, the association between CA and Socialization was weak ($r = -0.282$).

Table 2.1.5. Pearson correlation analysis between the FSIQ, VIQ, PIQ and CA and VABS SS of each domain at the different groups and subgroups: ASD and OND. All comparisons signalled with*/ are significant.**

	COM		DLS		SOC		ABC	
	ASD	**OND**	**ASD**	**OND**	**ASD**	**OND**	**ASD**	**OND**
FSIQ	0.516**	0.515**	0.406**	0.344**	0.435**	0.497**	0.494**	0.489**
VIQ	0.652**	0.498**	0.456**	0.247*	0.490**	0.395**	0.601**	0.392**
PIQ	0.283*	0.479**	0.255*	0.389**	0.302*	0.544**	0.285*	0.531**
CA	-0.346**	-0.154	-0.135	0.120	-0.477**	-0.282**	-0.363**	-0.111

NOTE. Pearson correlations; * $p<0.05$; ** $p<0.001$. ASD = Autism Spectrum Disorder; OND = Other Neurodevelopmental Disorder; COM = communication; DLS = daily living skills; SOC = socialization; ABC = adaptive behaviour composite. F= Female; FSIQ = Full-Scale Intelligence Quotient, VIQ= Verbal Intelligence Quotient; PIQ= Performance Intelligence Quotient, CA=chronological age.

Discussion

In the current work, we have studied the influence of the primary diagnosis of ASD on adaptive behaviour besides IQ. For that we compare the adaptive behaviour measured by the most studied tool for this, VABS, between two samples with neurodevelopmental disorders, one with ASD and other without ASD (other neurodevelopmental disorders) controlled by intellectual level.

We can conclude that our ASD patients exhibit more deficits in their adaptive skills. ASD population was characterized by significantly lower scores in the DLS and Socialization domains than Communication level, particularly in the Personal and Domestic DLS and in Interpersonal Relationships and Coping Skills subdomains. These results corroborate in part the typical profile of individuals with ASD (Fenton et al. 2003; Tomanik et al. 2007; Paul et al. 2004; Bolte and Poustka 2002; Carter et al. 1998; Volkmar et al. 1987). As previous studies,

we also found marked delays in socialization and lesser delays in adaptive communication. However, other studies report relative strengths in DLS in autistic samples, and we did not found differences between groups. A surprising result has to do with the fact that albeit ASD group had globally lower scores (in Socialization, DLS and ABC), for the Communication domain, ASD showed higher results than OND, however, with no statistical significance. When we look into the subdomains, we can perceive that the greater percentage of adequate receptive communication in the ASD population, can be contributing to this higher result.

When we take into account the presence or absence of ID, the results differ. Actually, when comparing both subgroups with ID the autistic subgroup showed lower scores for all domains of VABS including Communication. In what concerns to subdomains, Personal DLS, Interpersonal Relationships and Coping Skills remain as a core distinctive factor from subjects without ASD.

These results corroborate previous findings that reported that individuals with ASD tend to have lower overall adaptive skills when compared with age and IQ matched peers without ASD (Gabriels et al. 2007; Di Nuovo and Buono 2007; Kraijer 2000). However, we did not find lower Communication scores or preserved DLS in the ASD group without ID when compared to age and mental-age matched individuals without intellectual disabilities as shown by other authors (Carpentieri and Morgan 1996; Loveland and Kelley 1991; Perry et al. 2009; VanMeter et al. 1997; Volkmar et al. 1987; Kraijer 2000). Our results concerning better Communication scores in the main ASD group and ASD sample without ID compared with the population without ASD, regardless of being not statically significant, may be explained by the fact that we have studied school-age children, which can have better results in written domain. Actually, when we take into account the results in VABS subdomains in patients without ID we see that the ASD high functioning population had greater percentage of adequate Receptive and Written Communication, results only in part highlighted by previous studies (Klin et al. 2007; Saulnier and Klin 2007). In addition, we can speculate the hyperlexic profile in autistic population with normal or above normal IQ (Newman et al. 2007) may explain this expertise in written communication as evaluated by the VABS. We can still argue that a structured teaching approach usually implemented in schools in Portugal focused on autistic children's needs may improve these specific skills.

On the other hand, Socialization, in the autistic subsample without ID had lower scores, especially in subdomains of Interpersonal Relationships and Coping Skills. This is in line with part of the findings that have shown a distinctive pattern of adaptive behaviour stressing the significant deficits in adaptive socialization skills. Importantly, these results

demonstrated that the socialization deficits found in the autistic population cannot be explain only by the ID and constitute the core domain in which ASD group is distinctive as assessed by the VABS.

Previous studies reported intermediate deficits in Communication, and relative strengths in DLS when controlling for ID (Bolte and Poustka 2002; Carter et al. 1998), which we do not replicate in our study.

Our study showed that co-occurring intellectual deficit conditions result in further debilitating effects on overall functioning and adjustment in real life, especially in autistic patients which is line with previous studies (Gabriels et al. 2007; Perry et al. 2009; Di Nuovo and Buono 2007).

In fact, the associations between VABS domains and intelligence show that IQ was positively correlated with adaptive functioning, especially in Communication domain, which corroborates previous findings (Perry et al. 2009). The Communication domain relates not only with the ability to use the spoken language but also with learning capabilities, especially in that age range, therefore, it is expected that the cognitive ability in some way modulates this domain. However, these associations seem to differ in particular aspects. In ASD sample, the strongest associations were between verbal intellectual ability, Communication, and global level of adaptive behaviour, whereas in OND patients only moderate correlations were verified between FSIQ and Communication, non-verbal intelligence and Socialization and global level of adaptive behaviour. In fact, the verbal abilities seem to determine the adaptive functioning in the school aged ASD individuals, highlighting the importance of the development of functional language skills for later outcome and supporting recent findings (Howlin et al. 2014). In the other hand, in our OND sample, the adaptive functioning, especially in Communication and Socialization domains, as well as in the ABC, seems to be defined by the performance, verbal and global capabilities, not having the verbal abilities a determining value in the adaptive behaviour, as occurs in the autism subjects.

Chronological age tended to be negatively associated with VABS scores, which have been reported in previous studies (Klin et al. 2007; Perry et al. 2009). In our study, Communication, Socialization and global adaptive ability in the autistic population and the Socialization in the OND group were negatively correlated with CA. These disturbing findings may suggest that ASD subjects, compared to OND peers, may fall behind with respect to adaptive functioning as they grow older, enhancing the gap between cognitive skills and adaptive behaviour that seems to extend with age (Klin et al. 2007; Szatmari et al. 2003; Kanne et al. 2011). These results may anticipate the difficulties present in these patients in social

adaptation that are present from the first years of life (Paul et al. 2014; Ventola et al. 2014) and that extend to adulthood, as it is reviewed recently (Magiati et al. 2014). Therefore, this information has a prognostic value, which should be used not only to inform parents, caregivers, and therapists, but more importantly to target the areas of intervention.

In our study through VABS evaluation, the socialization impairment in the functional skills remains a distinctive factor between autism and other neurodevelopmental disorders independently of cognitive ability. These data may contribute to help differential diagnosis in a clinical set. In accordance with our finding, Ventola et al. (2011) and collaborators had already stressed that the socialization deficits in ASD impact foundational social skills in their study with toddlers. These authors suggest that examination of the specific social adaptive behaviours contribute not only for differential diagnosis but should also be targeted for intervention. Our study enhances these specific social adaptive deficits in a broader age group of school-aged children to adolescents. This can raise a set of important questions related not only to the intervention that is being given to school-aged children and adolescents with ASD, but also to the future integration of ASD young adults in a society that is highly competitive and requires so many social abilities.

We can conclude that with VABS evaluation the adaptive behaviour in domain of socialization skills impairment remains a distinctive factor of the primary diagnosis of ASD versus OND peers, independently of IQ. However, co-occurring ID conditions result in further debilitating effects on overall functioning and adjustment, especially in autism.

It is possible to presume that the specific cognitive social deficits in ASD in the application of knowledge is a factor that limits adaptive competence for daily living skills, especially the ones related to interpersonal relationships, and coping strategies, as well as on a daily basis problem solving skills, indispensable capacity to acquire full social inclusion.
Additionally, notwithstanding of a superior, average, or borderline IQ, subjects with ASD experience substantial difficulties in everyday life. This can lead to an overvaluation of intelligence and a misleading as good outcome without adequate consideration of functional social skills.

These results have significant clinical and educational implications, enhancing the relevance to focus the intervention on teaching the daily live activities as early and intensively as possible to the autistic population, reinforcing the need to teach skills with impact in social adaptation and survival in a current society based essentially in higher level social rules.

The use of the VABS as a clinical diagnostic tool was also reinforced by our study, since this scale seems to accurately differentiate ASD subjects from individuals with OND, in what concerns to socialization skills.

Our findings are also very meaningful since they show high consistency between samples in Portugal – a European country vs. samples from the United States of America. The implications of this study, should, however, be taken in account considering that although the sample of study is large and well-characterized, there may be biases associated with the range of age used (only school-aged children), that may limit the generalization of results. Extending these particular findings to toddlers, young children and adults will be an important following step in future studies. The level of communication skills of our subjects is also a limitation of our study. For a richer understanding of the whole autism spectrum in what concerns to adaptive behaviour, studies similar to ours should be replicated in samples with nonverbal individuals.

References

American Association on Mental Retardation (2002). *Mental retardation: definition, classification, and systems of supports.* . Washington, DC, USA.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th edition ed.). Arlington, US: American Psychiatric Publishing.

Bolte, S., & Poustka, F. (2002). The relation between general cognitive level and adaptive behavior domains in individuals with autism with and without co-morbid mental retardation. *Child Psychiatry Hum Dev, 33*(2), 165-172.

Bramer, G. R. (1988). International statistical classification of diseases and related health problems. Tenth revision. *World Health Stat Q, 41*(1), 32-36.

Carpentieri, S., & Morgan, S. B. (1996). Adaptive and intellectual functioning in autistic and nonautistic retarded children. *J Autism Dev Disord, 26*(6), 611-620.

Carter, A. S., Gillham, J. E., Sparrow, S. S., & Volkmar, F. R. (1996). Adaptive behavior in autism. *Child and Adolescent Psychiatric Clinics of North America, 5*(4), 945-&.

Carter, A. S., Volkmar, F. R., Sparrow, S. S., Wang, J. J., Lord, C., Dawson, G., et al. (1998). The Vineland Adaptive Behavior Scales: supplementary norms for individuals with autism. *J Autism Dev Disord, 28*(4), 287-302.

Centers for Disease Control and Prevention (2009). Prevalence of autism spectrum disorders - Autism and Developmental Disabilities Monitoring Network, United States, 2006. *MMWR Surveill Summ, 58*(10), 1-20, doi:ss5810a1 [pii].

Centers for Disease Control and Prevention (2012). Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. *MMWR Surveill Summ, 61*(3), 1-19, doi:ss6103a1 [pii].

Centers for Disease Control and Prevention (2014). Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *MMWR Surveill Summ, 63*(2), 1-21, doi:ss6302a1 [pii].

Dawson, J. E., Matson, J. L., & Cherry, K. E. (1998). An analysis of maladaptive behaviors in persons with autism, PDD-NOS, and mental retardation. *Res Dev Disabil, 19*(5), 439-448, doi:S0891-4222(98)00016-X [pii].

Di Nuovo, S. F., & Buono, S. (2007). Psychiatric syndromes comorbid with mental retardation: differences in cognitive and adaptive skills. *J Psychiatr Res, 41*(9), 795-800, doi:S0022-3956(06)00055-0 [pii]
10.1016/j.jpsychires.2006.02.011.

Farley, M. A., McMahon, W. M., Fombonne, E., Jenson, W. R., Miller, J., Gardner, M., et al. (2009). Twenty-year outcome for individuals with autism and average or near-average cognitive abilities. *Autism Res, 2*(2), 109-118, doi:10.1002/aur.69.

Fenton, G., D'Ardia, C., Valente, D., Del Vecchio, I., Fabrizi, A., & Bernabei, P. (2003). Vineland adaptive behavior profiles in children with autism and moderate to severe developmental delay. *Autism, 7*(3), 269-287.

Fombonne, E. (2003). Epidemiological surveys of autism and other pervasive developmental disorders: an update. *J Autism Dev Disord, 33*(4), 365-382.

Freeman, B. J., Del'Homme, M., Guthrie, D., & Zhang, F. (1999). Vineland Adaptive Behavior Scale scores as a function of age and initial IQ in 210 autistic children. *J Autism Dev Disord, 29*(5), 379-384.

Freeman, B. J., Rahbar, B., Ritvo, E. R., Bice, T. L., Yokota, A., & Ritvo, R. (1991). The Stability of Cognitive and Behavioral Parameters in Autism - a 12-Year Prospective-Study. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*(3), 479-482, doi:Doi 10.1097/00004583-199105000-00020.

Freeman, B. J., Ritvo, E. R., Yokota, A., Childs, J., & Pollard, J. (1988). Wisc-R and Vineland Adaptive-Behavior Scale Scores in Autistic-Children. *Journal of the American Academy of Child and Adolescent Psychiatry, 27*(4), 428-429, doi:Doi 10.1097/00004583-198807000-00008.

Gabriels, R. L., Ivers, B. J., Hill, D. E., Agnew, J. A., & McNeill, J. (2007). Stability of adaptive behaviors in middle-school children with autism spectrum disorders. *Research in Autism Spectrum Disorders, 1*(4), 291-303, doi:DOI 10.1016/j.rasd.2006.11.004.

Gillham, J. E., Carter, A. S., Volkmar, F. R., & Sparrow, S. S. (2000). Toward a developmental operational definition of autism. *J Autism Dev Disord, 30*(4), 269-278.

Goldberg, M. R., Dill, C. A., Shin, J. Y., & Nguyen, V. N. (2009). Reliability and validity of the Vietnamese Vineland Adaptive Behavior Scales with preschool-age children. *Res Dev Disabil, 30*(3), 592-602, doi:S0891-4222(08)00114-5 [pii] 10.1016/j.ridd.2008.09.001.

Griffith, G. M., Hastings, R. P., Nash, S., & Hill, C. (2010). Using matched groups to explore child behavior problems and maternal well-being in children with Down syndrome and autism. *J Autism Dev Disord, 40*(5), 610-619, doi:10.1007/s10803-009-0906-1.

Howlin, P., Savage, S., Moss, P., Tempier, A., & Rutter, M. (2014). Cognitive and language skills in adults with autism: a 40-year follow-up. *J Child Psychol Psychiatry, 55*(1), 49-58, doi:10.1111/jcpp.12115.

Jacobson, J. W., & Ackerman, L. J. (1990). Differences in adaptive functioning among people with autism or mental retardation. *J Autism Dev Disord, 20*(2), 205-219.

Kanne, S. M., Gerber, A. J., Quirmbach, L. M., Sparrow, S. S., Cicchetti, D. V., & Saulnier, C. A. (2011). The role of adaptive behavior in autism spectrum disorders: implications for functional outcome. *J Autism Dev Disord, 41*(8), 1007-1018, doi:10.1007/s10803-010-1126-4.

Klin, A., Saulnier, C. A., Sparrow, S. S., Cicchetti, D. V., Volkmar, F. R., & Lord, C. (2007). Social and communication abilities and disabilities in higher functioning individuals with autism spectrum disorders: the Vineland and the ADOS. *J Autism Dev Disord, 37*(4), 748-759, doi:10.1007/s10803-006-0229-4.

Klin, A., Volkmar, F. R., & Sparrow, S. S. (1992). Autistic social dysfunction: some limitations of the theory of mind hypothesis. *J Child Psychol Psychiatry, 33*(5), 861-876.

Knapp, M., Romeo, R., & Beecham, J. (2009). Economic cost of autism in the UK. *Autism, 13*(3), 317-336, doi:13/3/317 [pii] 10.1177/1362361309104246.

Kraijer, D. (2000). Review of adaptive behavior studies in mentally retarded persons with autism/pervasive developmental disorder. *J Autism Dev Disord, 30*(1), 39-47.

Liss, M., Harel, B., Fein, D., Allen, D., Dunn, M., Feinstein, C., et al. (2001). Predictors and correlates of adaptive functioning in children with developmental disorders. *J Autism Dev Disord, 31*(2), 219-230.

Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., et al. (1989). Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *J Autism Dev Disord, 19*(2), 185-212.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord, 24*(5), 659-685.

Loveland, K. A., & Kelley, M. L. (1991). Development of adaptive behavior in preschoolers with autism or Down syndrome. *Am J Ment Retard, 96*(1), 13-20.

Magiati, I., Tay, X. W., & Howlin, P. (2014). Cognitive, language, social and behavioural outcomes in adults with autism spectrum disorders: A systematic review of longitudinal follow-up studies in adulthood. *Clin Psychol Rev, 34*(1), 73-86, doi:S0272-7358(13)00157-8 [pii]
10.1016/j.cpr.2013.11.002.

Matson, J. L., Rivet, T. T., Fodstad, J. C., Dempsey, T., & Boisjoli, J. A. (2009). Examination of adaptive behavior differences in adults with autism spectrum disorders and intellectual disability. *Res Dev Disabil, 30*(6), 1317-1325, doi:S0891-4222(09)00091-2 [pii]
10.1016/j.ridd.2009.05.008.

Newman, T. M., Macomber, D., Naples, A. J., Babitz, T., Volkmar, F., & Grigorenko, E. L. (2007). Hyperlexia in children with autism spectrum disorders. *J Autism Dev Disord, 37*(4), 760-774, doi:10.1007/s10803-006-0206-y.

Oliveira, G., Ataide, A., Marques, C., Miguel, T. S., Coutinho, A. M., Mota-Vieira, L., et al. (2007). Epidemiology of autism spectrum disorder in Portugal: prevalence, clinical characterization, and medical conditions. *Dev Med Child Neurol, 49*(10), 726-733, doi:DMCN726 [pii]
10.1111/j.1469-8749.2007.00726.x.

Paul, R., Loomis, R., & Chawarska, K. (2014). Adaptive behavior in toddlers under two with autism spectrum disorders. *J Autism Dev Disord, 44*(2), 264-270, doi:10.1007/s10803-011-1279-9.

Paul, R., Miles, S., Cicchetti, D., Sparrow, S., Klin, A., Volkmar, F., et al. (2004). Adaptive behavior in autism and Pervasive Developmental Disorder-Not Otherwise Specified: microanalysis of scores on the Vineland Adaptive Behavior Scales. *J Autism Dev Disord, 34*(2), 223-228.

Perry, A., Flanagan, H. E., Dunn Geier, J., & Freeman, N. L. (2009). Brief report: the Vineland Adaptive Behavior Scales in young children with autism spectrum disorders at different cognitive levels. *J Autism Dev Disord, 39*(7), 1066-1078, doi:10.1007/s10803-009-0704-9.

Rodrigue, J. R., Morgan, S. B., & Geffken, G. R. (1991). A comparative evaluation of adaptive behavior in children and adolescents with autism, Down syndrome, and normal development. *J Autism Dev Disord, 21*(2), 187-196.

Rutter, M., Bailey, A., & Lord, C. (2003). *Social Communication Questionnaire*. Los Angeles: Western Psychological Services.

Saulnier, C. A., & Klin, A. (2007). Brief report: social and communication abilities and disabilities in higher functioning individuals with autism and Asperger syndrome. *J Autism Dev Disord, 37*(4), 788-793, doi:10.1007/s10803-006-0288-6.

Schatz, J., & Hamdan-Allen, G. (1995). Effects of age and IQ on adaptive behavior domains for children with autism. *J Autism Dev Disord, 25*(1), 51-60.

Soenen, S., Van Berckelaer-Onnes, I., & Scholte, E. (2009). Patterns of intellectual, adaptive and behavioral functioning in individuals with mild mental retardation. *Res Dev Disabil, 30*(3), 433-444, doi:S0891-4222(08)00044-9 [pii]
10.1016/j.ridd.2008.04.003.

Sparrow, S., Balla, D., & Cicchetti, D. (1984). *Vineland Adaptative Behaviour Scales: Interview edition, Survey form*. Circle Pines, MN: American Guidance Service.

Szatmari, P., Bryson, S. E., Boyle, M. H., Streiner, D. L., & Duku, E. (2003). Predictors of outcome among high functioning children with autism and Asperger syndrome. *J Child Psychol Psychiatry, 44*(4), 520-528.

Tasse, M. J., Schalock, R. L., Balboni, G., Bersani, H., Jr., Borthwick-Duffy, S. A., Spreat, S., et al. (2012). The construct of adaptive behavior: its conceptualization, measurement, and use in the field of intellectual disability. *Am J Intellect Dev Disabil, 117*(4), 291-303, doi:10.1352/1944-7558-117.4.291.

Tomanik, S. S., Pearson, D. A., Loveland, K. A., Lane, D. M., & Bryant Shaw, J. (2007). Improving the reliability of autism diagnoses: examining the utility of adaptive behavior. *J Autism Dev Disord, 37*(5), 921-928, doi:10.1007/s10803-006-0227-6.

VanMeter, L., Fein, D., Morris, R., Waterhouse, L., & Allen, D. (1997). Delay versus deviance in autistic social behavior. *J Autism Dev Disord, 27*(5), 557-569.

Ventola, P., Saulnier, C. A., Steinberg, E., Chawarska, K., & Klin, A. (2011). Early-Emerging Social Adaptive Skills in Toddlers with Autism Spectrum Disorders: An Item Analysis. *J Autism Dev Disord*, doi:10.1007/s10803-011-1278-x.

Ventola, P., Saulnier, C. A., Steinberg, E., Chawarska, K., & Klin, A. (2014). Early-emerging social adaptive skills in toddlers with autism spectrum disorders: an item analysis. *J Autism Dev Disord, 44*(2), 283-293, doi:10.1007/s10803-011-1278-x.

Volkmar, F. R., Carter, A., Sparrow, S. S., & Cicchetti, D. V. (1993). Quantifying social development in autism. *J Am Acad Child Adolesc Psychiatry, 32*(3), 627-632, doi:S0890-8567(09)65274-6 [pii]
10.1097/00004583-199305000-00020.

Volkmar, F. R., Sparrow, S. S., Goudreau, D., Cicchetti, D. V., Paul, R., & Cohen, D. J. (1987). Social deficits in autism: an operational approach using the Vineland Adaptive Behavior Scales. *J Am Acad Child Adolesc Psychiatry, 26*(2), 156-161, doi:S0890-8567(09)65643-4 [pii]
10.1097/00004583-198703000-00005.

Wechsler, D. (2003). *Manual for intelligence scale for children*. Lisbon: CegocTea.

2.2. Intellectual profiles in the autism spectrum and other neurodevelopmental disorders

This chapter consists in the paper: **Mouga S**, Café C, Almeida J, Marques C, Duque F, Oliveira G. Intellectual Profiles in the Autism Spectrum and Other Neurodevelopmental Disorders. *J Autism Dev Disord*. 2016 Sep;46(9):2940-55. doi: 10.1007/s10803-016-2838-x. PubMed PMID: 27312715.

Abstract

The influence of specific autism spectrum disorder (ASD) deficits in Intelligence Quotients (IQ), Indexes and subtests from the Wechsler Intelligence Scale for Children-III was investigated in 445 school-aged children: ASD (N=224) and other neurodevelopmental disorders (OND) (N=221), matched by Full-Scale IQ and chronological age.

ASD have lower scores in the verbal IQ than performance IQ. The core distinctive scores between groups are Processing Speed Index and "Comprehension" and "Coding" subtests with lower results in ASD. ASD group with normal/high IQ showed highest score on "Similarities" subtest whereas the lower IQ group performed better on "Object Assembly".

The results replicated our previous work on adaptive behaviour, showing that adaptive functioning is positively correlated with intellectual profile, especially with the Communication domain in ASD.

Introduction

Autism spectrum disorder (ASD) is an early-onset, life-long severe neurodevelopmental disorder with a high worldwide prevalence and a distribution of four males (M) to one female (F) (Centers for Disease Control and Prevention 2009; Oliveira et al. 2007; Fombonne 2003). Deficits in social interaction and communication, as well as repetitive patterns of behaviour and interests, are the core characteristics of ASD (American Psychiatric Association 2013).

Although comorbidity with intellectual disability (ID) is decreasing, as it is shown in recent studies, it remains very common, being that about one third to half of ASD subjects have co-occurring ID (Centers for Disease Control and Prevention 2009, 2012, 2014). However, ID as measured by Intelligence Quotient (IQ) scores can vary, depending on the test used. Many children with ASD are described as having low intelligence quotients, which is partially due to the use of various editions of the Wechsler Intelligence Scale for Children (WISC) (Wechsler 1949). WISC is undoubtedly the most widely used test to estimate intelligence among ASD subjects (Joseph 2011; Mottron 2004; S. Goldstein, Naglieri, J. A., & Ozonoff, S. 2008). An important issue is whether the tasks included in the Wechsler scales are sensitive to unique characteristics of children with ASD, which might affect test performance (Carothers and Taylor 2013) and differ in gender (Ryland et al. 2014; Rivet and Matson 2011). Even though non-verbal children garner low scores on verbal IQ tests, they can, at times,

obtain scores appropriate to their age level on tests of spatial intelligence, for example. The Wechsler Intelligence Scale for Children- third edition (WISC-III) (Wechsler 1991) overcomes this difficulty by separately scoring both verbal and non-verbal, performance, IQ, which can then be further broken down into more discrete categories such as Indexes.

WISC-III (Wechsler 1991, 2003b), the most recently normed measure for our country's population, is an individually administered intelligence test intended for children that can be completed without reading or writing and was designed to measure human intelligence as reflected in both verbal and nonverbal (performance) abilities. WISC-III (Wechsler 1991, 2003b) include questions of general knowledge, traditional arithmetic problems, vocabulary, completion of mazes, and arrangement of blocks and pictures (for a detailed description, see Materials in Methods Section).

There is a host of research on intellectual functioning among patients with ASD. Although IQ measures are not used as diagnostic tool for ASD, one primary use of it in this population is the differentiation between high- and low-functioning individuals. The knowledge of intellectual profiles allows technicians to assist parents of children with neurodevelopmental disorders in making decisions and academic curricula adaptations to further stages of education (Oliveras-Rentas et al. 2012), as well as to predict future achievements of their offspring. The monitoring of progresses in the therapeutic process (Koegel et al. 1997) and the acquisition of additional information required for the purposes of differential diagnosis and outcome prediction are also motivations to continue to use Wechsler scales (Koyama et al. 2006; Mayes and Calhoun 2008).

Most of the studies focusing on the intellectual functioning of individuals with ASD, in which Wechsler scales were used, concluded that when examining subtest performance at the group level, subjects with ASD obtain the lowest scores in "Comprehension" (Siegel et al. 1996; Freeman et al. 1985; Asarnow et al. 1987; Narita and Koga 1987; Ohta 1987; Rumsey and Hamburger 1988; Lincoln et al. 1988; Allen et al. 1991; Venter et al. 1992; F. G. Happe 1994; Bailey et al. 1996; Dennis et al. 1999; Koyama et al. 2007; Mayes and Calhoun 2003), and the highest in "Digit span" (Allen et al. 1991; Lincoln et al. 1988; Narita and Koga 1987; Ohta 1987; Rumsey and Hamburger 1988; Siegel et al. 1996; Bailey et al. 1996; Szatmari et al. 1990; Dennis et al. 1999) among verbal scales. On the other hand, in the performance scales, the lowest scores are obtained in "Picture arrangement"(Allen et al. 1991; Lincoln et al. 1988; Ohta 1987; Rumsey and Hamburger 1988; Venter et al. 1992; Szatmari et al. 1990; Shah and Frith 1993) and "Coding"(Asarnow et al. 1987; Freeman et al. 1985) and the highest scores in "Block design" (Allen et al. 1991; Asarnow et al. 1987; Freeman et al. 1985; F. G. Happe 1994;

Lincoln et al. 1988; Rumsey and Hamburger 1988; Siegel et al. 1996; Venter et al. 1992; Bailey et al. 1996; Shah and Frith 1993; Szatmari et al. 1990; Lockyer and Rutter 1970; Bowler 1992; Dennis et al. 1999; Koyama et al. 2007; Mayes and Calhoun 2003).

Despite the differences in individual studies, all of them point to two common elements in intellectual profile of autistic population: "Block design" is the subtest with highest results and "Comprehension" the one with the lowest. In contrast, there is no conclusive data regarding the relationship between verbal and non-verbal intelligence quotients. A number of studies also reported that individuals with ASD are characterized by higher scores on Performance IQ (PIQ), rather than on Verbal IQ (VIQ) (Asarnow et al. 1987; Freeman et al. 1985; Narita and Koga 1987; Ohta 1987; Siegel et al. 1996; Allen et al. 1991; Lincoln et al. 1988; Venter et al. 1992; Schneider and Asarnow 1987). Contrarily, others have documented higher scores on verbal scales than on PIQ (Minshew et al. 1992; Szatmari et al. 1990). More recent studies using WISC-III (Wechsler 1991) found no differences between the level of verbal and non-verbal intelligence (Ghaziuddin and Mountain-Kimchi 2004; G. Goldstein et al. 2008).

A specific Wechsler profile, commonly reported among school age children with ASD when taking into consideration the factor analysis, includes higher scores on Verbal Comprehension Index (VCI) and on the Perceptual Organization Index (POI), when compared to the Freedom from Distractibility Index (FDI) and the Processing Speed Index (PSI) (Mayes and Calhoun 2003, 2008; Nyden et al. 2001; Wechsler 2003a). Mayes and Calhoun (2004) were able to identify children with high-functioning autism, with 73% accuracy, that had obtained lower results in FDI and PSI indexes, and Comprehension subtest scores on the WISC-III. This profile has been consistently found across various age groups and functioning levels, but it is not used as a diagnostic tool (Siegel et al. 1996).

The pursuit of a result that can be a tool with diagnostic utility for autism versus other neurodevelopmental problems led to more empirically oriented classification systems for WISC-III results, such as Bannatyne's categories (Bannatyne 1974) and Kaufman's factors (Kaufman 1975, 1994). Bannatyne (1974) proposed four categories that were composed of a group of subtests: Spatial Ability (includes Picture Completion, Block Design, Object Assembly), Verbal Conceptualisation Ability (Comprehension, Similarities, Vocabulary), Sequencing Ability (Digit Span, Arithmetic, Coding), and Acquired Knowledge (Information, Arithmetic, Vocabulary). These had a more interpretative meaning of the subjects' capabilities than the Verbal and Performance Scales. Kaufman (1975, 1994) factor analysed the Wechsler Intelligence Scale for Children-Revised (WISC-R) standardisation data and proposed various

factors, namely: Arithmetic, Coding, Information and Digit Span subtests - ACID; Symbol Search, Coding, Arithmetic and Digit Span subtests – SCAD and Freedom from Distractibility Index (Arithmetic, Digit Span subtests) - FDI. Ottem (1999) argued that the Bannatyne's categories and Kaufman's factors did not explained the differences in the profiles of two populations: ASD and reading impaired subjects. In fact, more studies with different approaches to Wechsler scales are needed, as well as intellectual profile comparisons with groups with other neurodevelopmental disorders.

Besides global intellectual level, specific cognitive deficits are linked to ASD, so it should be expected that children with ASD would show weaknesses in some subtests of the Wechsler scales and different patterns in VIQ or PIQ (Baron-Cohen 2001; F. Happe and Frith 2006; Pennington and Ozonoff 1996; Pisula 2010). For instance, discrepancies between verbal and nonverbal IQ are frequently found in ASD children (Kaufman and Lichtenberger 2000) and have been related to ASD features. Black and colleagues (2009) showed that both discrepantly higher PIQ than VIQ, as measured by the WISC-III (Wechsler 1991), WISC-IV (Wechsler 2003a) or Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999), were associated with higher (i.e. more abnormal) social symptoms scores as assessed by the Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 1989) and the Autism Diagnostic Interview (ADI) (Le Couteur et al. 1989) in a sample of 78 high-functioning children with autism aged six to seventeen years. However, two studies report otherwise. One of the studies including 156 children aged ten to fourteen years with ASD could not establish any relation between such a discrepant score and symptom presentation of ASD (Charman et al. 2011b). The other study, including 325 children, found that VIQ-PIQ discrepancies were, to some extent, unrelated to ASD symptoms (Ryland et al. 2014).

Despite the fact that much progress has been made in determining the cognitive profile of strengths and weaknesses of subjects with ASD, a number of outstanding questions remain to be answered: i) if the strengths and deficits are the same in high and low-functioning ASD; ii) whether cognitive subgroups exist; iii) and how cognition is associated with core ASD features and adaptive behaviour, as well as associated psychopathology. Small sample sizes, a focus on single domains of cognition and the absence of comprehensive behavioural phenotypic information are methodological factors that have contributed to these limitations in the scientific knowledge (Charman et al. 2011a).

The present study involves participants with the principal diagnosis of ASD with and with no ID (ASD_ID/ASD_NID) and participants with other neurodevelopmental disorders (OND), such as intellectual disability or learning disabilities, with and with no ID

(OND_ID/OND_NID). It is important to know whether the performance on a standard cognitive test can be used to clearly separate ASD from OND, aiding in the diagnosis of ASD but also in the interpretation of its pathogenicity. Therefore, the purpose of this study is to examine the influence of the primary diagnosis of ASD versus OND, matched for IQ and chronological-age (CA), on cognitive ability; its intellectual profile; and study whether performance on a standard cognitive test can be used to clearly separate or as clinical aid, in order to discriminate ASD from OND.

Methods

Participants

Participants included 445 school-aged children and adolescents, ranging in age from 6 years to 16 years and 11 months. They were divided into two clinical main groups: ASD (N=224; mean age = 117 ± 21 months, 202 Male / 22 Female) versus OND (N=221; mean age = 113 ± 26 months, 147 Male / 74 Female). Participants were seen as part of an outpatient clinic between 2004 and 2015.

To be included in this study, all participants had to be given an individually administered IQ test (Portuguese version of WISC-III (Wechsler 2003b)) and the participants' primary caregiver had been administered the Vineland Adaptive Behaviour Scale (VABS)-Survey form (Sparrow et al. 1984). Another requirement was to have between 6-16 years old at the moment of evaluation. ASD diagnosis was assigned on the basis of the gold standard instruments: parental or caregiver interview (ADI-R (Lord et al. 1994)), direct structured proband assessment (ADOS (Lord et al. 1989)), and clinical examination performed by an experienced neurodevelopmental Paediatrician. The current diagnostic criteria for autism were revised according to the Diagnostic and Statistical Manual of Mental Disorders 5, DSM-5 (American Psychiatric Association 2013). All ASD patients had positive results in the ADI-R and ADOS for autism or ASD and met the criteria for ASD from the DSM-5. A comprehensive medical observation excluded associated medical condition such as epilepsy, neurocutaneous or other genetic syndromes, or other usual comorbidity in ASD samples. All population in this study is routinely followed by this team in a clinical set at least two times per year.

The gold standard diagnostic assessment scales ADI-R (Lord et al. 1994) and ADOS (Lord et al. 1989) are also used to characterize the ASD symptomatology and to correlate with

the WISC-III results. ADI-R (Lord et al. 1994) is a structured interview used for diagnosing autism, planning treatment, and distinguishing autism from other developmental disorders. It can be used for diagnostic purposes for anyone with a mental age of at least 18 months and gives us quantitative measures of behaviour in the areas of i) reciprocal social interactions, ii) language and communication, and iii) repetitive behaviours/interests. ADOS (Lord et al. 1989) is used for assessing and diagnosing autism and pervasive developmental disorder across ages, developmental levels, and language skills. It consists of a series of structured and semi-structured tasks that involve social interaction between the examiner and the subject. The examiner observes and identifies segments of the subject's behaviour and assigns these to predetermined observational categories, which are combined to a score. The score is assessed through cut-offs in i) reciprocal social interaction and ii) communication and language that identify the potential diagnosis of autism spectrum disorder.

In the OND group were included subjects diagnosed and followed in our clinic with ID (full-scale IQ – FSIQ≤70) or learning disabilities (FSIQ>70). The parents of participants included in OND group completed the Social Communication Questionnaire (Rutter et al. 2003) to exclude co-morbidity with ASD. Associated medical conditions were excluded as in the ASD group.

Measures

All measures (even the ones referred to in the previous point for clinical characterization) were administered by experienced psychologists and neurodevelopmental paediatricians, for diagnostic or treatment planning, during routine clinical multidisciplinary assessments in a neurodevelopmental Unity that it is a National reference for ASD and other neurodevelopmental disorders in a Tertiary Paediatric Hospital.

Wechsler Intelligence Scale for Children- Third Edition (WISC-III)

The WISC-III (Wechsler 1991) is an individually administered cognitive assessment tool used to evaluate the intelligence of subjects aged between six to sixteen years and eleven months. It has been adapted and standardized for the Portuguese population by Simões and colleagues in 2003 (Wechsler 2003b).

The WISC-III is a reference in the assessment of intelligence and is used to establish a pattern of intra and inter-comparison, which identifies a global level of cognitive ability (or an estimate of intellectual potential). Its analysis also allows for the verification of the

performance in a specific subtest and whether it suggests the presence of a specific cognitive deficit or, on the contrary, is widespread evidence of global intellectual deficit (Hynd et al. 1988).

This scale assumes that intelligence has a composite nature, that is, that the intellectual capacity of the subject is based on a potential arising from the integration and balancing of diverse skills and cognitive functions (Wechsler 1991). It thus explores the intellectual functioning in its varied aspects through both the division into diverse subtests and the plurality of tasks that individuals have the possibility of evidencing their abilities in (Wechsler 2003b).

This evaluation instrument consists of thirteen subtests (M = 10; SD = 3) spread over two subscales: Verbal and Performance, each one evaluating a different aspect of intelligence (Wechsler 2003b). The performance of the subjects in the various subtests is clustered in three composite results: a general intelligence measure (FSIQ) and two ratios divided by the nature of its subtests: the VIQ, measurement of verbal intelligence, and the PIQ, a nonverbal intelligence measure (Wechsler 2003b).

The subtests that compose the WISC-III enable a first distinction between skills or psychological functions, providing a reference point for the examination of higher cortical functions (Kaufman 1994).

The WISC-III yields three composite IQs scores (M = 100; SD = 15): VIQ, PIQ and FSIQ, and four index scores: VCI, POI, PSI and FDI resulting from groupings of the subtests (Wechsler, 1991, 2003).

The various composite scores correspond to different levels of interpretation (Wechsler 1991). The first level of interpretation is the FSIQ, determined by the sum of the standardized results of subtests of the subscales Verbal and Performance. The analysis of VIQ and PIQ defined, respectively, by the sums of standardized results in verbal and performance subtests, refers to the second level of interpretation. In this level, the comparison of results between VIQ and PIQ is valued. The interpretation of the difference between VIQ and PIQ must be carried out carefully considering a number of factors, like the presence of language, hearing or motor problems, motivational questions, or cultural and language differences. Thus, even though the VIQ-PIQ discrepancy could be the basis for formulating hypotheses, their presence or absence cannot be regarded as conclusive evidence of an inability (Hynd et al. 1988). The VIQ-PIQ dichotomy is useful to know if the child has a deficit that only harms the language skills (VIQ) or the perceptual space capabilities (PIQ) too. Through the dominance of the analysis concerning these skills, it can be known if the weak areas of the

child's intellectual capacity match their language skills (VIQ<PIQ) or the perceptual spatial skills (PIQ<VIQ) (Hynd et al. 1988). The third level of interpretation concerns to the indexes identified by factor analysis, providing more detail in the search for strong and weak areas of the cognitive function of the subject. Thus, the VCI is composed of four verbal subtests (Information, Similarities, Vocabulary and Comprehension), the POI of four subtests (Picture Completion, Picture Arrangement, Block Design and Object Assembly), and the PSI of two subtests (Code and Symbol Search).

The fourth level of interpretation is the analysis of each subtest: Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span, Picture Completion, Coding, Picture Arrangement, Block Design, Object Assembly, Symbol Search and Mazes (Hynd et al. 1988). Further information about each subtest is in the discussion section, when considered necessary.

The factor structure of the Portuguese version of WISC-III yields a three-factor model (VCI, POI and PSI), however in this study, the FDI was analysed as a profile (sum of the scaled scores of Arithmetic and Digit Span) rather than as an index score. The Mazes subtest was not administered.

All participants were tested with the Portuguese version of WISC-III (Wechsler 2003b).

Procedure

Data was collected from a database according to the National policy on archival research of the Paediatric Hospital. The group of participants included in this study represents a subset of patients, which information is usually collected for clinical and research characterization of the outpatient clinic. A total of 445 records meeting the inclusion criteria were included in this study.

The two clinical main groups: ASD and OND were each further subdivided into two, totalizing four subgroups, taking into account the FSIQ. The classification of ID of the International Classification of Diseases, 10th Revision (Bramer 1988) was applied. According to this classification, a subject has ID when the FSIQ is equal to or below 70 and has no ID when the FSIQ is above 70. The four subgroups were: [ASD with no ID (ASD_NID, N=166); ASD with ID (ASD_ID; N=58); OND with no ID (OND_NID; N=166); OND with ID (OND_ID; N=55])]. They were matched by CA and FSIQ score (*t*-test, p>.05).

In the two main groups and in the four clinical subgroups we compared the intellectual profile of WISC-III analysing the standard scores (SS) of IQs, index scores, subscales, Kaufman's factors (Kaufman 1975, 1994; Reynolds and Kaufman 1990) and Bannatyne's categories (Bannatyne 1968, 1974).

Data analysis

Data was analysed using the version for Microsoft Windows® of the Statistical Package for Social Sciences software (SPSS ®, Chicago, IL, USA).

Paired samples *t*-tests were calculated to investigate the significance of differences between quantitative variables VIQ and PIQ, in the different groups and subgroups. Independent samples *t*-tests with Bonferroni correction were calculated to investigate the significance of differences in WISC-III IQs, index scores, subtests, Kaufman's factors and Bannatyne's categories between groups. Cohen's d was additionally calculated to determine the effect sizes of these differences.

Additionally, we performed Pearson-correlation analysis with Bonferroni correction to determine the linear correlation between each result of WISC-III and VABS scores, and CA in the two main groups and ASD symptomatology (Language/Communication, Reciprocal Social Interactions, and Repetitive Behaviours/Interests results from ADI-R and ADOS), in the ASD group.

We considered the significance level (α) = 0.05 (p <.05).

Ethics Statement

This study and all the procedures were reviewed and approved by the Ethics Commission of our Paediatric Hospital and was conducted in accordance with the declaration of Helsinki. Informed consent was obtained from the parents/guardians of all younger participants. Children and adolescents also gave oral informed consent.

Results

Initial analysis was conducted to ensure that participants were matched with respect to CA and FSIQ in both two main clinical groups and four subgroups (*t*-test, p>.05).

The average SS of IQs, index scores, subtests from WISC-III evaluation, Kaufman's factors and Bannatyne's categories in the two main clinical groups and four subgroups, as well as group comparisons, significance levels and effect sizes are reported in Tables 2.2.1, 2.2.2 and 2.2.3.

IQs and Index Scores

VIQ-PIQ differences

A paired sample *t*-test showed a statistically significant difference between VIQ and PIQ for both clinical main groups: ASD t (223) = -2.615, p = .010, d = -0,16 and OND t (220) = -2.302, p = .022, d = -0,12 with PIQ > VIQ in both ASD and OND. For the subgroups there was a pattern related with ID. In the subgroups with ID, there was a significant difference between with PIQ > VIQ in both, although it was higher in ASD: ASD_ID t (57) = -4.192, p < .001, d = -0,11 and OND_ID t (54) = -2.280, p = .027, d = -0,40. In the subgroups with no ID there was no significant difference: ASD_NID t (165) = -1.113, p = .267, d = -0,78 and OND_NID t (165) = -1.593, p = .113, d = -0,12.

ASD vs. OND

When we analyse the two main groups (ASD versus OND), not taking into account the level of IQ, there are no significant statistical differences in FSIQ, VIQ, PIQ (*t*-test, p > .05, see Table 2.2.1 for details on exact p-values, specific comparisons and effect sizes).

Relative to the WISC-III index scores, statistically significant differences (Table 2.2.2) were found between children with ASD and OND for PSI (p < .001), with the ASD group having lower results than the OND group in PSI. For VCI and POI, no significant difference was found.

Table 2.2.1. WISC-III standard scores in the two clinical groups (ASD *versus* OND): means, standard-errors; standard deviations, range, significance levels and effect-sizes

	ASD (n = 224)				OND (n = 221)						
	M	**(SE)**	**SD**	**Range**	**M**	**(SE)**	**SD**	**Range**	***t*(443)**	***p***	**d**
IQs											
FSIQ	87.28	1.41	21.06	40-142	85.66	1.29	19.21	47-145	.845	1	0.08
VIQ	87.60	1.44	21.49	46-139	86.97	1.26	18.69	50-150	.332	1	0.03
PIQ	91.06	1.40	20.98	46-146	89.18	1.24	18.36	48-130	1.008	.942	0.10
Index Scores											
VCI	88.38	1.41	21.08	48-136	89.10	1.21	18.00	53-145	-.390	1	-0.04
POI	95.06	1.43	21.46	50-145	91.13	1.26	18.68	50-134	2.060	.12	0.20
PSI	82.84	1.26	18.80	50-147	89.53	1.12	16.61	53-131	-3.979	.000**	-0.38
Subtests											
Information	8.66	0.29	4.40	1-19	8.09	0.22	3.31	1-18	1.533	1	0.15
Similarities	10.01	0.25	3.80	1-19	9.30	0.23	3.49	1-19	2.051	.492	0.19
Arithmetic	8.10	0.28	4.14	1-19	7.52	0.23	3.39	1-19	1.624	1	0.15
Vocabulary	8.04	0.26	3.88	1-19	8.21	0.22	3.30	1-17	-.492	1	-0.05
Comprehension	6.43	0.24	3.63	1-17	7.86	0.21	3.12	1-17	-4.444	.000**	-0.42
Digit Span	7.78	0.29	3.55	1-19	7.89	0.24	3.04	1-15	-.276	1	-0.03
Picture Completion	9.50	0.27	4.09	1-19	9.12	0.24	3.61	1-18	1.046	1	0.10
Coding	6.49	0.22	3.24	1-19	7.79	0.22	3.33	1-19	-4.173	.000**	-0.40
Picture Arrangement	8.50	0.29	4.41	1-19	8.29	0.25	3.72	1-19	.521	1	0.05
Block Design	10.11	0.27	3.98	1-19	8.52	0.23	3.36	1-19	4.549	.000**	0.43
Object Assembly	9.19	0.25	3.69	1-19	8.89	0.24	3.59	1-19	.871	.384	0.08
Symbol Search	7.65	0.25	3.75	1-19	8.58	0.22	3.33	1-17	-2.785	.072	-0.26
Kaufman's factors											
ACID	30.12	0.98	11.87	4-64	30.90	0.80	10.05	9-58	-.620	1	-0.07
SCAD	28.74	0.89	10.70	4-59	31.27	0.77	9.69	8-53	-2.158	.096	-0.25
FDI	15.58	0.57	6.83	2-38	15.23	0.44	5.51	4-30	.493	1	0.06
Bannatyne's categories											
VCA	24.49	0.67	10.10	3-50	25.37	0.59	8.73	6-53	-.989	1	-0.09
SPA	28.80	0.67	10.02	3-50	26.53	0.60	8.85	3-49	2.531	.048*	0.24
SQA	21.60	0.70	8.49	3-45	22.87	0.60	7.47	7-40	-1.385	.668	-0.16
ACK	24.80	0.73	10.94	3-52	23.82	0.59	8.79	4-54	1.043	1	0.10

NOTE. WISC-III = Wechsler Intelligence Scale for Children – Third Edition; ASD = Autism Spectrum Disorder; OND = Other Neurodevelopmental Disorder; IQ = Intelligence Quotient; FSIQ = Full-Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; VCI = Verbal Comprehension Index; POI = Perceptual Organization Index; PSI = Processing Speed Index; ACID = Arithmetic, Coding, Information and Digit Span subtest; SCAD = Symbol Search, Coding, Arithmetic and Digit Span subtest; FDI = Freedom from Distractibility Index (Arithmetic, Digit Span); VCA = Verbal Conceptualizing Ability; SPA = Spatial Ability; SQA = Sequencing Ability; ACK = Acquired Knowledge; M = mean; SE = standard error; SD = standard deviation. *T*-tests; * p<.05; ** p<.001 Bonferroni corrected. All comparisons signalled with */** are significant and related to inferior results in the groups with ASD diagnosis. Effect sizes were computed using Cohen's *d*.

ASD_ID vs. OND_ID

Regarding the subgroups with ID (ASD_ID and OND_ID), there was also a significant effect for diagnosis, with the ASD_ID subgroup having lower scores for VIQ [t (111) = -2,895, p = .015]. However, no significant differences were found in the FSIQ and PIQ (t-test, p > .05). In what concerns the WISC-III index scores, t-tests indicated that these subgroups differ in VCI [t (111) = -4,227, p = .006] and PSI [t (111) = -3,157, p < .001]. In the indexes where the groups differ, the OND_ID had better results (see Table 2.2.2 for details on exact p-values and specific comparisons).

ASD_NID vs. OND_NID

When comparing the subgroups with no ID (ASD_NID and OND_NID), t-test did not show significant differences in IQ's. In respect to Index scores, there was a significant effect for diagnosis, with ASD_NID having higher scores in POI [t (330) = 2,520, p = .036] and lower scores in PSI [t (330) = -2.973, p = .009] (Table 2.2.3).

Subtests Scores

ASD vs. OND

As shown in Table 2.2.1, the two main clinical groups, ASD and OND, differ in three subtests scores: Comprehension [t (443) = -4,444, p < .001], Coding [t (443) = -4,173, p < .001] and Block Design [t (443) = 4,549, p = .001]. The ASD group had higher results in Block Design, while the OND group had higher results in Comprehension and Coding. The highest score for the ASD group was in Block Design (M = 10.11) and the lowest was on Comprehension (M = 6.43). In the OND group the subtests with highest and lowest scores were Similarities (M = 9.30) and Arithmetic (M = 7.52), respectively. ASD showed a more heterogeneous profile than the OND, which is homogeneous, as it is shown in Figure 2.2.1.

Table 2.2.2. WISC-III standard scores in the two clinical groups (ASD_ID versus OND_ID): means, standard-errors; standard deviations, range, significance levels and effect-sizes

	ASD_ID (*n* = 58)				OND_ID (*n* = 55)						
	M	**(SE)**	**SD**	**Range**	**M**	**(SE)**	**SD**	**Range**	***t*(111)**	***p***	**d**
IQs											
FSIQ	60.93	0.86	6.52	40-69	62.87	0.65	4.85	47-69	-1.802	.222	-0.34
VIQ	61.19	1.15	8.78	46-80	65.55	0.97	7.17	50-84	-2.895	.015*	-0.54
PIQ	69.34	1.56	11.89	46-98	68.67	1.12	8.29	48-89	.350	1	0.07
Index Scores											
VCI	62.84	1.21	9.22	48-82	68.18	1.18	8.73	53-84	-3.157	.006*	-0.59
POI	73.12	1.76	13.39	50-101	70.31	1.28	9.46	50-94	1.294	.594	0.24
PSI	65.67	1.70	12.96	50-95	75.87	1.71	12.68	53-103	-4.227	.000**	-0.80
Subtests											
Information	3.81	0.32	2.45	1-10	4.62	0.29	2.16	1-9	-1.856	.792	-0.35
Similarities	5.91	0.33	2.54	1-11	6.18	0.36	2.67	1-13	-.547	1	-0.10
Arithmetic	3.98	0.32	2.42	1-10	4.38	0.26	1.93	1-9	-.967	1	-0.18
Vocabulary	3.72	0.27	2.08	1-8	4.91	0.30	2.20	1-9	-2.943	.048*	-0.56
Comprehension	3.10	0.27	2.02	1-8	4.85	0.25	1.83	1-8	-4.816	.000**	-0.91
Digit Span	5.65	0.45	2.97	1-14	5.65	0.38	2.57	1-11	-.002	1	0.00
Picture Completion	5.97	0.45	3.42	1-15	5.67	0.42	3.12	1-15	.475	1	0.09
Coding	3.93	0.29	2.21	1-10	5.47	0.35	2.61	1-13	-3.397	.012*	-0.64
Picture Arrangement	4.22	0.37	2.82	1-11	4.84	0.35	2.59	1-11	-1.200	1	-0.23
Block Design	6.33	0.44	3.36	1-16	5.33	0.30	2.23	1-10	1.875	.768	0.35
Object Assembly	6.74	0.49	3.71	1-15	5.85	0.36	2.63	1-12	1.472	1	0.28
Symbol Search	4.45	0.35	2.66	1-10	6.09	0.32	2.37	1-11	-3.454	.012*	-0.65
Kaufman's factors											
ACID	17.53	1.00	6.56	4-35	20.00	0.76	5.19	9-31	-1.974	.156	-0.42
SCAD	18.05	1.05	6.91	4-38	21.76	0.78	5.27	8-36	-2.864	.015*	-0.60
FDI	9.81	0.66	4.35	2-22	9.91	0.52	3.52	4-18	-.118	1	-0.03
Bannatyne's categories											
VCA	12.74	0.72	5.48	3-24	15.95	0.67	4.96	6-23	-3.252	.008*	-0.61
SPA	19.03	1.06	8.05	3-35	16.85	0.77	5.70	3-29	1.669	.392	0.31
SQA	13.65	0.82	5.36	3-29	15.46	0.63	4.29	7-26	-1.761	.328	-0.37
ACK	11.52	0.72	5.47	3-23	13.91	0.56	4.14	4-23	-2.628	.040*	-0.49

NOTE. WISC-III = Wechsler Intelligence Scale for Children – Third Edition; ASD_ID = ASD with intellectual disability (ID); OND_ID = OND with ID; IQ = Intelligence Quotient; FSIQ = Full-Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; VCI = Verbal Comprehension Index; POI = Perceptual Organization Index; PSI = Processing Speed Index; ACID = Arithmetic, Coding, Information and Digit Span subtest; SCAD = Symbol Search, Coding, Arithmetic and Digit Span subtest; FDI = Freedom from Distractibility Index (Arithmetic, Digit Span); VCA = Verbal Conceptualizing Ability; SPA = Spatial Ability; SQA = Sequencing Ability; ACK = Acquired Knowledge; M = mean; SE = standard error; SD = standard deviation. *T*-tests; * $p<.05$; ** $p<.001$ Bonferroni corrected. All comparisons signalled with */** are significant and related to inferior results in the groups with ASD diagnosis. Effect sizes were computed using Cohen's *d*.

Table 2.2.3. WISC-III standard scores in the two clinical groups (ASD_NID *versus* OND_NID): means, standard-errors; standard deviations, range, significance levels and effect-sizes

	ASD_NID (*n* = 166)				OND_NID (*n* = 166)						
	M	**(SE)**	**SD**	**Range**	**M**	**(SE)**	**SD**	**Range**	***t*(330)**	***p***	**d**
IQs											
FSIQ	96.48	1.24	15.98	71-142	93.21	1.24	15.93	71-145	1.868	.189	0.20
VIQ	96.83	1.27	16.33	65-139	94.07	1.22	15.67	62-150	1.574	.348	0.17
PIQ	98.65	1.39	17.96	64-146	95.97	1.20	15.51	63-130	1.455	.441	0.16
Index Scores											
VCI	97.30	1.26	16.19	61-136	96.04	1.13	14.59	63-145	.748	1	0.08
POI	102.72	1.41	18.22	64-145	98.03	1.21	15.61	64-134	2.520	.036*	0.28
PSI	88.84	1.30	16.73	54-147	94.06	1.18	15.25	59-131	-2.973	.009*	-0.33
Subtests											
Information	10.35	0.28	3.61	2-19	9.24	0.22	2.78	3-18	3.137	.024*	0.34
Similarities	11.44	0.24	3.06	3-19	10.33	0.24	3.10	2-19	3.278	.012*	0.36
Arithmetic	9.54	0.28	3.62	2-19	8.56	0.24	3.12	1-19	2.647	.108	0.29
Vocabulary	9.55	0.25	3.17	2-19	9.31	0.22	2.84	2-17	.748	1	0.08
Comprehension	7.60	0.26	3.34	1-17	8.86	0.22	2.81	3-17	-3.715	.000**	-0.41
Digit Span	8.67	0.33	3.40	3-19	8.81	0.26	2.73	1-15	-.336	1	-0.05
Picture Completion	10.74	0.28	3.55	2-19	10.27	0.23	2.99	4-18	1.321	1	0.14
Coding	7.38	0.24	3.07	1-19	8.55	0.25	3.19	2-19	-3.416	.012*	-0.37
Picture Arrangement	9.99	0.30	3.86	1-19	9.44	0.26	3.31	1-19	1.389	1	0.15
Block Design	11.43	0.25	3.27	3-19	9.58	0.23	2.98	3-19	5.386	.000**	0.59
Object Assembly	10.04	0.26	3.29	2-19	9.89	0.26	3.29	1-19	.417	1	0.05
Symbol Search	8.77	0.27	3.41	1-19	9.41	0.25	3.19	1-17	-1.776	.924	-0.19
Kaufman's factors											
ACID	35.37	0.92	9.38	15-64	35.41	0.75	7.87	17-58	-.039	1	0.00
SCAD	33.20	0.85	8.65	16-59	35.21	0.78	8.26	11-53	-1.733	.255	-0.24
FDI	17.99	0.61	6.22	5-38	17.43	0.44	4.61	4-30	.740	1	0.10
Bannatyne's categories											
VCA	28.59	0.61	7.88	9-50	28.49	0.57	7.36	14-53	.115	1	0.01
SPA	32.22	0.64	8.24	13-50	29.74	0.56	7.23	15-49	2.909	.016*	0.32
SQA	24.92	0.72	7.26	10-45	25.95	0.59	6.24	10-40	-1.108	1	-0.15
ACK	29.45	0.64	8.22	12-52	27.11	0.57	7.33	10-54	2.734	.028*	0.30

NOTE. WISC-III = Wechsler Intelligence Scale for Children – Third Edition; ASD_NID = ASD with No ID; OND_NID = OND with No ID; IQ = Intelligence Quotient; FSIQ = Full-Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; VCI = Verbal Comprehension Index; POI = Perceptual Organization Index; PSI = Processing Speed Index; ACID = Arithmetic, Coding, Information and Digit Span subtest; SCAD = Symbol Search, Coding, Arithmetic and Digit Span subtest; FDI = Freedom from Distractibility Index (Arithmetic, Digit Span); VCA = Verbal Conceptualizing Ability; SPA = Spatial Ability; SQA = Sequencing Ability; ACK = Acquired Knowledge; M = mean; SE = standard error; SD = standard deviation. *T*-tests; * $p<.05$; ** $p<.001$ Bonferroni corrected. All comparisons signalled with */** are significant and related to inferior results in the groups with ASD diagnosis. Effect sizes were computed using Cohen's *d*.

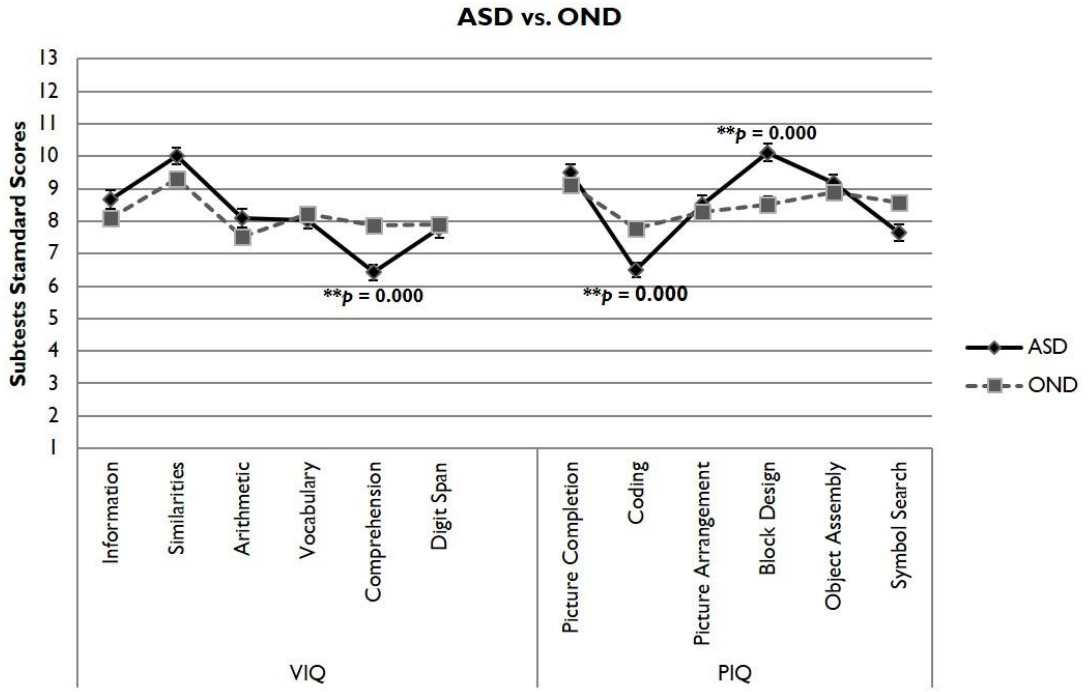

Figure 2.2.1. WISC-III subtests SS profile for ASD and OND groups.

NOTE. ASD = Autism Spectrum Disorders; OND = Other Neurodevelopmental Disorders; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; ** p<.001 Bonferroni corrected

ASD_ID vs. OND_ID

When we analyse the subgroups with ID, statistically significant differences were found between the ASD_ID and OND_ID subgroups in four subtests: Vocabulary [t (111) = -2,943, p = .048], Comprehension [t (111) = -4,816, p < .001], Coding [t (111) = -3,397, p = .012] and Symbol Search [t (111) = -3,454, p = .012], with the OND_ID subgroup having higher scores (Table 2.2.2). The highest score for ASD_ID subgroup was in Object Assembly (M = 6.74) and the lowest was on Comprehension (M = 3.10). In the OND_ID subgroup, the subtests with highest and lowest scores were Similarities (M = 6.18) and Arithmetic (M = 4.38), respectively. ASD_ID showed a more heterogeneous profile than the OND_ID, as shown in Figure 2.2.2.

ASD_NID vs. OND_NID

The two subgroups with no ID, ASD_NID and OND_NID, differ in five subtests scores: Information [t (330) = 3,137, p = .024], Similarities [t (330) = 3,278, p = .012], Comprehension [t (330) = --3,715, p < .001], Coding [t (330) = -3,416, p = .012] and Block Design [t (330) =

5,386, $p < .001$]. ASD_NID subgroup had higher results in Information, Similarities and Block Design, while the OND_NID subgroup had higher results in Comprehension and Coding. The highest score for both groups was in Similarities (ASD_NID: M = 11.44; OND_NID; M = 10.33) and the lowest was on Coding (ASD_NID: M = 7.38; OND_NID; M = 7.52). ASD showed a more heterogeneous profile than the OND, as it is shown in Figure 2.2.3.

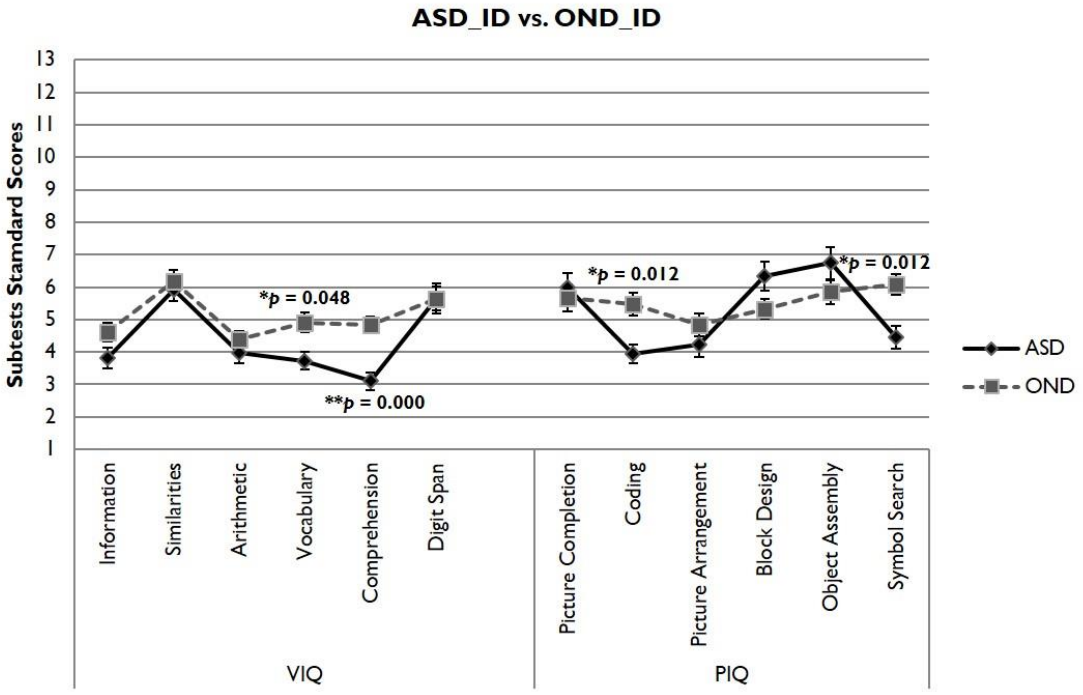

Figure 2.2.2. WISC-III subtests SS profile for ASD_ID and OND_ID subgroups.

NOTE. ASD_ID = ASD with intellectual disability (ID); OND_ID = OND with ID; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; * $p<.05$; ** $p<.001$ Bonferroni corrected.

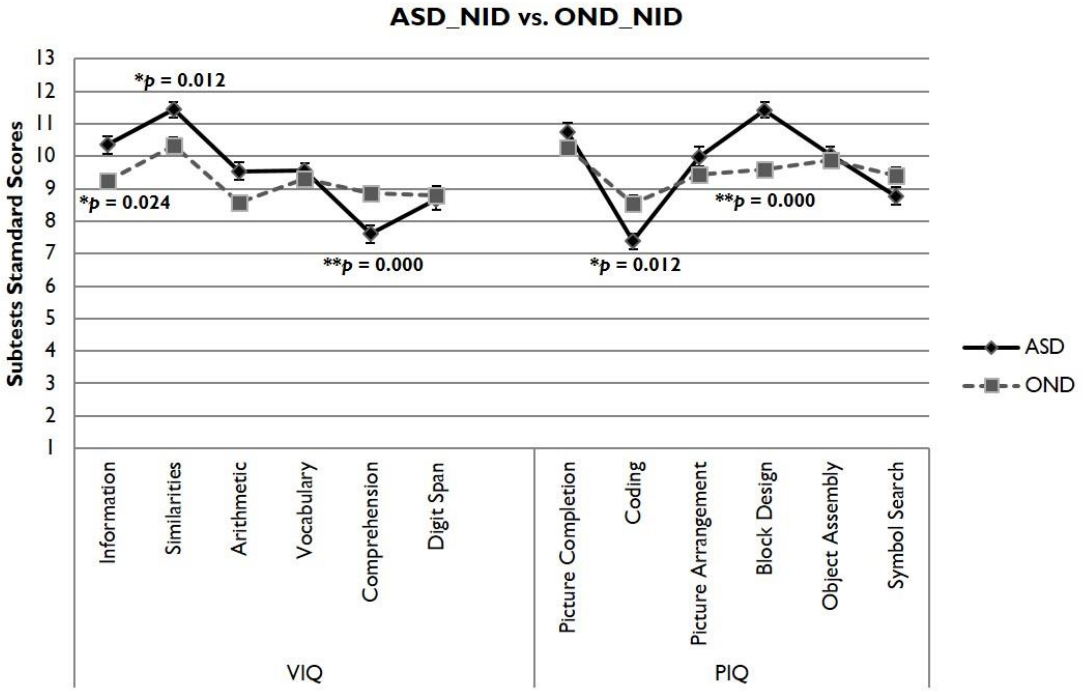

Figure 2.2.3. WISC-III subtests SS profile for ASD_NID and OND_NID subgroups.

NOTE. ASD_NID = ASD with No ID; OND_NID = OND with No ID; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; * p<.05; ** p<.001 Bonferroni corrected.

Profiles Scores

ASD vs. OND

Statistically significant differences between the ASD and OND groups were found in one of the seven analysed WISC-III profiles (SPA [t (443) = 2,531, p = .048]) (Table 2.2.1). In the Bannatyne's spatial abilities, ASD group scored higher than the OND.

ASD_ID vs. OND_ID

T-tests showed statistically significant differences between the ASD_ID and OND_ID subgroups in SCAD [t (111) = -2,864, p = .015], VCA [t (111) = -3,252, p = .008] and ACK [t (111) = -2,628, p = .040], with OND obtaining higher scores (Table 2.2.2).

ASD_NID vs. OND_NID

In the subgroups without ID, the ASD_NID subgroup had higher scores than the OND_NID in the profiles where statistically significant differences were found: SPA [t (330) = 2,909, p = .016] and ACK [t (330) = 2,734, p = .028] (Table 2.2.3).

Correlations

We performed Pearson correlation analysis between the SS of WISC-III (IQ's, Indexes and Subtests), Kaufman's factors, Bannatyne's categories and the domains from VABS, as well as CA at the two main groups of diagnosis: ASD versus OND (see Tables 3.2.4 and 3.2.5 for details on exact p-values and specific correlations).

The VABS (Sparrow et al. 1984) is a recognized, semi-structured interview designed to assess global adaptive functioning in three main domains: Communication (COM), Daily Living Skills (DLS), and Socialization (SOC), attributing a total score, the Adaptive Behaviour Composite (ABC). In previous work (Mouga et al. 2015), was found that there was a significant effect for diagnosis, with ASD, ASD_NID and ASD_ID groups having lower scores than OND, ASD_NID , OND_ID groups in most areas of adaptive behaviour, and with the domain of socialization skills remaining as a distinctive factor of ASD versus OND. In this study, we replicated these results, with ASD and ASD_NID having lower results in DLS and SOC ($p < .05$) than the OND and ASD_NID group and subgroup, respectively. In the subgroups with ID, the ASD_ID had lower results in DLS, SOC and ABC ($p < .05$).

We observed that, in the ASD group, the SS of WISC-III (IQ's, Indexes and Subtests), Kaufman's factors and Bannatyne's categories were all statistically significant ($p < .05$) and positively correlated with all VABS SS domains, being the strongest association between the VABS Communication and FSIQ ($r = .512$), VIQ ($r = .627$), VCI ($r = .605$), ACID ($r = .669$), SCAD ($r = .552$), FDI ($r = .585$), VCA ($r = .555$), SQA ($r = .580$), ACK ($r = .650$), Information ($r = .650$), Similarities ($r = .522$), Arithmetic ($r = .520$), Vocabulary ($r = .536$).

In the OND group, most of the SS of WISC-III (IQ's, Indexes and Subtests), Kaufman's factors and Bannatyne's categories were statistically significant ($p < .05$) positively correlated with all VABS SS domains, being the strongest association the one between the VABS Communication and FSIQ ($r = .610$), VIQ ($r = .604$), VCI ($r = .593$), ACID ($r = .630$), SCAD ($r = .570$), FDI ($r = .522$), VCA ($r = .564$), SQA ($r = .576$), ACK ($r = .611$), Information ($r = .574$), Arithmetic ($r = .514$), Vocabulary ($r = .562$); and between the ABC and PIQ ($r = .564$), VSI ($r = .505$), POI ($r = .529$) and SPA ($r = .507$).

In what concerns CA, the only WISC-III SS that were statistically significant ($p < .05$) and moderately (r between $\pm.300$ and $\pm.390$) correlated were: VCA ($r = -.344$), Similarities ($r = -.361$) and Comprehension ($r = -.302$), in the ASD group, and the Comprehension ($r = -.310$) and VCA ($r = -.320$), in the OND group. In both groups these associations between CA and WISC-III SS were negative.

Concerning ASD symptomatology, the WISC-III SS were not correlated with the data from Language/Communication, Reciprocal Social Interactions, and Repetitive Behaviours/Interests from ADI-R and ADOS ($p > .05$).

Table 2.2.4. Pearson correlation analysis between the FSIQ, VIQ, PIQ, VCI, POI, PSI, ACID, SCAD, FDI, VCA, SPA, SQA and ACK, CA and VABS SS of each domain at the different groups: ASD and OND. All comparisons signalled with*/ are significant**

	COM		DLS		SOC		ABC		CA	
	ASD	**OND**	**ASD**	**OND**	**ASD**	**OND**	**ASD**	**OND**	**ASD**	**OND**
FSIQ	.512**	.610**	.416**	.360**	.374**	.488**	.383**	.552**	-.261**	-.232*
VIQ	.627**	.604**	.434**	.263*	.425**	.427**	.395**	.474**	-.276**	-.237**
PIQ	.285**	.533**	.313**	.406**	.248**	.500**	.290**	.564**	-.207*	-.185*
VCI	.605**	.593**	.405**	.232*	.410**	.406**	.372**	.453**	-.290**	-.246**
POI	.265**	.499**	.286**	.376**	.219*	.498**	.271**	.529**	-.191*	-.161
PSI	.323**	.463**	.353**	.382**	.310**	.442**	.331**	.505**	-.248**	-.233**
ACID	.669**	.630**	.504**	.343*	.411**	.456**	.618**	.545**	-.169	-.118
SCAD	.552**	.570**	.470**	.412**	.347**	.467**	.521**	.556**	-.227*	-.149
FDI	.585**	.522**	.410**	.288*	.353**	.395**	.524**	.459**	-.097	-.051
VCA	.555**	.564**	.384**	.236*	.397**	.396**	.360**	.445**	-.344**	-.320**
SPA	.238**	.486**	.291**	.349**	.201**	.466**	.257**	.507**	-.234**	-.192*
SQA	.580**	.576**	.466**	.370**	.365**	.452**	.543**	.537**	-.157	-.119
ACK	.650**	.611**	.442**	.275*	.426**	.445**	.401**	.480**	-.216*	-.164*

NOTE. Pearson correlations; * p<.05; ** p<.001 Bonferroni corrected. ASD = Autism Spectrum Disorder; OND = Other Neurodevelopmental Disorder; FSIQ = Full-Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; VCI = Verbal Comprehension Index; POI = Perceptual Organization Index; PSI = Processing Speed Index; ACID = Arithmetic, Coding, Information and Digit Span subtest; SCAD = Symbol Search, Coding, Arithmetic and Digit Span subtest; FDI = Freedom from Distractibility Index (Arithmetic, Digit Span); VCA = Verbal Conceptualizing Ability; SPA = Spatial Ability; SQA = Sequencing Ability; ACK = Acquired Knowledge; CA = Chronological Age; COM = communication; DLS = daily living skills; SOC = socialization; ABC = adaptive behaviour composite

Table 2.2.5. Pearson correlation analysis between the WISC-III subtests SS, CA and VABS SS of each domain at the different groups: ASD and OND. All comparisons signalled with*/ are significant**

	COM		DLS		SOC		ABC		CA	
	ASD	**OND**	**ASD**	**OND**	**ASD**	**OND**	**ASD**	**OND**	**ASD**	**OND**
Information	.650**	.574**	.423**	.193	.412**	.345**	.379**	.393**	-.139	-.099
Similarities	.522**	.466**	.363**	.163	.331**	.346**	.319**	.365**	-.361**	-.281**
Arithmetic	.520**	.514**	.395**	.293*	.354**	.461**	.361**	.454**	-.179	-.079
Vocabulary	.536**	.562**	.341**	.260	.355**	.401**	.314**	.451**	-.259**	-.256**
Comprehension	.420**	.487**	.319**	.211	.375**	.317*	.330**	.379**	-.302**	-.310**
Digit Span	.489**	.359*	.337**	.192	.309**	.205	.436**	.272	-.043	-.051
Picture Completion	.253**	.423**	.276**	.308*	.219*	.391**	.255**	.440**	-.217*	-.081
Coding	.315**	.410**	.322**	.326**	.293**	.387**	.298**	.456**	-.200*	-.204*
Picture Arrangement	.330**	.378**	.292**	.331**	.281**	.447**	.289**	.423**	-.120	-.039
Block Design	.240**	.459**	.253**	.279*	.179	.427**	.255**	.441**	-.186*	-.195*
Object Assembly	.108	.380**	.211*	.313*	.111	.391**	.139	.431**	-.195*	-.210*
Symbol Search	.299**	.413**	.358**	.375**	.313**	.390**	.335**	.447**	-.265**	-.207*

NOTE. Pearson correlations; * $p<.05$; ** $p<.001$ Bonferroni corrected; ASD = Autism Spectrum Disorder; OND = Other Neurodevelopmental Disorder; WISC-III = Wechsler Intelligence Scale for Children – Third Edition; SS = Standard Scores; CA = Chronological Age; VABS = Vineland Adaptive Behaviour Scale; COM = communication; DLS = daily living skills; SOC = socialization; ABC = adaptive behaviour composite

Discussion

In the current work, we have studied the influence of specific neurodevelopmental ASD deficits on intellectual profiles of children. For that purpose, we compared the cognitive profile measured by one of the most studied tools for this, WISC-III, between two groups, one with ASD and another without ASD (OND), controlled for CA and global intellectual level.

The population with neurodevelopmental disorders, including the ones with ASD, was characterized by significantly lower scores in the VIQ than PIQ, which became even more evident whenever ID was present. These results corroborate, in part, the typical VIQ-PIQ discrepancies of individuals with ASD (Charman et al. 2011b; Ryland et al. 2014; Minshew et al. 1992; Szatmari et al. 1990), although in our study they were not correlated with ASD symptomatology from the scores from ADI-R and ADOS, as in many of the previous studies (Kaufman and Lichtenberger 2000; Black et al. 2009). Possibly the lack of subgrouping in our study may explain the absence of correlation between the ASD symptomatology and the intellectual measures.

The distinctive profile of ASD, when compared to a sample with neurodevelopmental disorders without autism was more evident when the WISC-III results were analysed in a further complex view of their indexes and subtests. In fact, FSIQ, VIQ and PIQ were unable to discriminate accurately the ASD subjects when we looked at the main groups and at individuals with no ID. Nevertheless, the verbal abilities of ID groups were significantly lower in the ASD sample, and it was possible to conclude that this phenotypic marker will help signalize autism.

Regarding the WISC-III index scores, a commonly reported Wechsler profile among school age children with ASD includes higher scores on VCI and the POI, when compared with the PSI (Mayes and Calhoun 2003, 2008; Nyden et al. 2001; Wechsler 2003a), which was partially corroborated in the present study, with the exception of the ASD_ID subgroup, that had lower VCI. The index scores were also able to differentiate between ASD and OND in what concerns the processing speed capabilities, where ASD presented more difficulties, which was consistent with previous work (Mayes and Calhoun 2004). When we took into account the presence or absence of ID, the results differed. Actually, when comparing both subgroups with ID, the ASD individuals showed lower scores for VCI and PSI and similar results to OND in POI. In the subgroups with no ID, the results from the main groups were replicated. In fact, the core distinctive index from subjects with autism or without ASD was

the ability to focus attention and quickly scan, discriminate between, and sequentially order visual information, which was assessed by PSI. This index requires persistence and planning ability, is sensitive to motivation, to difficulty working under a time pressure, and motor coordination, all deficits that are usually present in the ASD symptomatology. These abilities are related to reading performance and working memory: increased processing speed can decrease the load placed on working memory, while decreased processing speed can impair the effectiveness of working memory (Wechsler 2003a).

Our results corroborate previous findings that reported that individuals with ASD tend to have "Block design" as the subtest with highest results (Allen et al. 1991; Asarnow et al. 1987; Freeman et al. 1985; F. G. Happe 1994; Lincoln et al. 1988; Rumsey and Hamburger 1988; Siegel et al. 1996; Venter et al. 1992; Bailey et al. 1996; Shah and Frith 1993; Szatmari et al. 1990; Lockyer and Rutter 1970; Bowler 1992; Dennis et al. 1999; Koyama et al. 2007; Mayes and Calhoun 2003) and the lowest results in "Comprehension" (Siegel et al. 1996; Freeman et al. 1985; Asarnow et al. 1987; Narita and Koga 1987; Ohta 1987; Rumsey and Hamburger 1988; Lincoln et al. 1988; Allen et al. 1991; Venter et al. 1992; F. G. Happe 1994; Bailey et al. 1996; Dennis et al. 1999; Koyama et al. 2007; Mayes and Calhoun 2003). This is evident when comparing the main groups (ASD vs. OND), and also when analysing the ASD profile. Despite that fact, in the subgroups, the results were different. We did not find the lowest result in "Comprehension" or the highest result on "Block design" on the ASD group without ID, although they differ in these subtests when compared to age and IQ matched individuals without ASD. In this subgroup (ASD_NID), the highest score was on "Similarities" and the lowest in "Coding". This means that the ASD subjects with no ID show good abstract, logical thinking, and reasoning, and have difficulties in visual-motor dexterity, associative nonverbal learning, and nonverbal short-term memory. In the subgroup with ID, ASD showed the lowest results in "Comprehension" and the highest in "Object Assembly", which denoted better capacity to visualize component parts of a concrete object and reassemble these parts into the whole (making "puzzles"), as well as difficulties in social knowledge, practical judgment in social situations and moral conscience, a core feature of ASD.

Previous studies reported deficits in the ability to interpret action as depicted by pictures, in recognizing their sequence in a story, and in arranging these in sequential order to tell a story ("Picture Arrangement" subtest) (Allen et al. 1991; Lincoln et al. 1988; Ohta 1987; Rumsey and Hamburger 1988; Venter et al. 1992; Szatmari et al. 1990; Shah and Frith 1993), and strengths in the subtest "Digit Span", which is a measure of short-term verbal memory and attention (Allen et al. 1991; Lincoln et al. 1988; Narita and Koga 1987; Ohta 1987; Rumsey

and Hamburger 1988; Siegel et al. 1996; Bailey et al. 1996; Szatmari et al. 1990; Dennis et al. 1999), which we did not replicate in our study.

In sum, we can conclude that the WISC-III subtests that better discriminate between ASD and OND are "Comprehension" and "Coding", which were significantly lower in all ASD individuals. Although some previous studies tried to differentiate the ASD subjects by their strengths, these difficulties were the ones which could separate ASD from the other neurodevelopmental disorders in our large sample. We can also conclude that our ASD patients exhibit a more heterogeneous intellectual profile than other neurodevelopmental disorders.

In what concerns the empirically oriented classification systems, such as Bannatyne's (1974) categories and Kaufman's factors (Kaufman 1975, 1994), our study showed that the SCAD (Symbol Search, Coding, Arithmetic and Digit Span subtests) can differentiate ASD subjects when referring to groups with intellectual disability. Bannatyne's Spatial Ability showed strengths in the ASD group and in the ASD subgroup with no ID (as well as Acquired Knowledge), while in the subgroup with ID, the ASD showed difficulties in Verbal Conceptualisation Ability and Acquired Knowledge.

In our study, we replicated the results from previous work on adaptive behaviour (Mouga et al. 2015). In fact, the associations between WISC SS, Kaufman's Factors and Bannatyne's categories with VABS domains show that adaptive functioning is positively correlated with intellectual profile, especially in the Communication domain. The Communication domain relates not only to the ability to use the spoken language, but also to learning capabilities, especially in school-aged children. Therefore, it was expected that the cognitive ability, in some way, would modulate this domain - communication learning (Mouga et al. 2015). However, these associations seem to differ in particular aspects. In the ASD sample, the strongest associations were between VABS Communication and global and verbal intellectual ability, verbal comprehension, Kaufman's factors (ACID, SCAD, and FDI), verbal conceptualisation and sequencing ability, acquired knowledge and verbal subtests, such as Information, Similarities, Arithmetic and Vocabulary. Whereas in OND patients, there were also associations between global adaptive behaviour (ABC) and performance IQ, verbal comprehension and perceptual organization, and spatial abilities. In fact, as shown in previous work (Mouga et al. 2015), verbal abilities seem to determine the adaptive functioning in school aged ASD individuals, highlighting the importance of the development of functional language skills for later outcome, and supporting recent findings (Howlin et al. 2014). Conversely, in

OND sample, the verbal abilities did not have a determining value in the adaptive behaviour, it only occurs in the autism subjects.

We can conclude that WISC-III is recommended as a reliable IQ measure for children with autism spectrum or other neurodevelopmental disorders, albeit additional characterisation with factors and categories, such as Kaufman's factors and Bannatyne's categories, may add significant information.

An accurate evaluation of the intellectual profile of ASD children is important for many reasons, namely the fact that intelligence has proven to be a good predictor of outcome in terms of academic progress (Gillberg and Steffenburg 1987), which cannot be mistaken for an adequate adaptive behaviour, that is, an ability to cope in the everyday life, that is usually considerably impaired, even for the most high functioning individual (Charman et al. 2011b). The assessment of the IQ is also very important to the selection of the intervention type, school adaptations and curriculum, but also to adopt realistic perspectives for the future. On the contrary, an underestimation of intelligence may further increase the stigma that some individuals with ASD experience and may negatively affect opportunities in everyday life, for instance the opportunity of having an employment.

Wechsler scales, although they are not a diagnostic measure for ASD, are used as a criterion to match ASD individuals in research studies and affect how their potential and progress are assessed and predicted in the clinical practice (Nader et al. 2014).

Our study, with a large and well characterized sample, was able to answer some questions: the strengths and deficits are not the same in high and low-functioning ASD and that intellectual profile is associated with adaptive behaviour and not with core ASD features, as measured by ADI-R and ADOS.

In conclusion, enhanced knowledge of the cognitive phenotype, a frequent comorbidity of ASD, may contribute to our understanding of the complex links between genes, brain, and neurodevelopment, as well as to inform approaches to therapeutics.

References

Allen, M. H., Lincoln, A. J., & Kaufman, A. S. (1991). Sequential and simultaneous processing abilities of high-functioning autistic and language-impaired children. *J Autism Dev Disord, 21*(4), 483-502.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th edition ed.). Arlington, US: American Psychiatric Publishing.

Asarnow, R. F., Tanguay, P. E., Bott, L., & Freeman, B. J. (1987). Patterns of intellectual functioning in non-retarded autistic and schizophrenic children. *J Child Psychol Psychiatry, 28*(2), 273-280.

Bailey, A., Phillips, W., & Rutter, M. (1996). Autism: towards an integration of clinical, genetic, neuropsychological, and neurobiological perspectives. *J Child Psychol Psychiatry, 37*(1), 89-126.

Bannatyne, A. (1968). Diagnosing Learning Disabilities and Writing Remedial Prescriptions. *Journal of Learning Disabilities, 1*(4), 242-249.

Bannatyne, A. (1974). Diagnosis: A note on recategorization of the WISC scaled scores. *Journal of Learning Disabilities, 7*(2).

Baron-Cohen, S. (2001). Theory of mind and autism: A review. *International Review of Research in Mental Retardation, Vol 23, 23*, 169-184.

Black, D. O., Wallace, G. L., Sokoloff, J. L., & Kenworthy, L. (2009). Brief report: IQ split predicts social symptoms and communication abilities in high-functioning children with autism spectrum disorders. *J Autism Dev Disord, 39*(11), 1613-1619, doi:10.1007/s10803-009-0795-3.

Bowler, D. M. (1992). "Theory of mind" in Asperger's syndrome. *J Child Psychol Psychiatry, 33*(5), 877-893.

Bramer, G. R. (1988). International statistical classification of diseases and related health problems. Tenth revision. *World Health Stat Q, 41*(1), 32-36.

Carothers, D. E., & Taylor, R. L. (2013). Differential Effect of Features of Autism on IQs Reported Using Wechsler Scales. *Focus on Autism and Other Developmental Disabilities, 28*(1), 54-59, doi:10.1177/1088357612457988.

Centers for Disease Control and Prevention (2009). Prevalence of autism spectrum disorders - Autism and Developmental Disabilities Monitoring Network, United States, 2006. *MMWR Surveill Summ, 58*(10), 1-20, doi:ss5810a1 [pii].

Centers for Disease Control and Prevention (2012). Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. *MMWR Surveill Summ, 61*(3), 1-19, doi:ss6103a1 [pii].

Centers for Disease Control and Prevention (2014). Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *MMWR Surveill Summ, 63*(2), 1-21, doi:ss6302a1.

Charman, T., Jones, C. R., Pickles, A., Simonoff, E., Baird, G., & Happe, F. (2011a). Defining the cognitive phenotype of autism. *Brain Res, 1380*, 10-21, doi:S0006-8993(10)02344-9 [pii]

10.1016/j.brainres.2010.10.075.

Charman, T., Pickles, A., Simonoff, E., Chandler, S., Loucas, T., & Baird, G. (2011b). IQ in children with autism spectrum disorders: data from the Special Needs and Autism Project (SNAP). *Psychol Med, 41*(3), 619-627, doi:S0033291710000991 [pii]10.1017/S0033291710000991.

Dennis, M., Lockyer, L., Lazenby, A. L., Donnelly, R. E., Wilkinson, M., & Schoonheyt, W. (1999). Intelligence patterns among children with high-functioning autism, phenylketonuria, and childhood head injury. *J Autism Dev Disord, 29*(1), 5-17.

Fombonne, E. (2003). Epidemiological surveys of autism and other pervasive developmental disorders: an update. *J Autism Dev Disord, 33*(4), 365-382.

Freeman, B., Lucas, J., Fomess, S., & Ritvo, E. (1985). Cognitive processing of high-functioning autistic children: Comparing the K-ABC and the WlSC-R. *J. Psychoeduc. Assess, 4*, 357-362.

Ghaziuddin, M., & Mountain-Kimchi, K. (2004). Defining the intellectual profile of Asperger Syndrome: comparison with high-functioning autism. *J Autism Dev Disord, 34*(3), 279-284.

Gillberg, C., & Steffenburg, S. (1987). Outcome and prognostic factors in infantile autism and similar conditions: a population-based study of 46 cases followed through puberty. *J Autism Dev Disord, 17*(2), 273-287.

Goldstein, G., Allen, D. N., Minshew, N. J., Williams, D. L., Volkmar, F., Klin, A., et al. (2008). The structure of intelligence in children and adults with high functioning autism. *Neuropsychology, 22*(3), 301-312, doi:2008-05020-003 [pii]
10.1037/0894-4105.22.3.301.

Goldstein, S., Naglieri, J. A., & Ozonoff, S. (2008). *Assessment of autism spectrum disorders*. New York: Guilford Press.

Happe, F., & Frith, U. (2006). The weak coherence account: Detail-focused cognitive style in autism spectrum disorders. *Journal of Autism and Developmental Disorders, 36*(1), 5-25, doi:10.1007/s10803-005-0039-0.

Happe, F. G. (1994). Wechsler IQ profile and theory of mind in autism: a research note. *J Child Psychol Psychiatry, 35*(8), 1461-1471.

Howlin, P., Savage, S., Moss, P., Tempier, A., & Rutter, M. (2014). Cognitive and language skills in adults with autism: a 40-year follow-up. *J Child Psychol Psychiatry, 55*(1), 49-58, doi:10.1111/jcpp.12115.

Hynd, G. W., Cohen, M. J., Riccio, C. A., & Arceneaux, J. M. (1988). Neuropsychological basis of intelligence and the WISC-III. In D. H. S. Prifitera (Ed.), *WISC-III clinical use and interpretation: scientist - practitioner perspectives* (pp. 203-226). San Diego, CA: Academic Press.

Joseph, R. M. (2011). The significiance of IQ and differential cognitive abilities. In D. A. Fein (Ed.), *The neuropsychology of autism*. Oxford: Oxford University Press.

Kaufman, A. S. (1975). Factor-Analysis of Wisc-R at 11 Age Levels between 6-1/2 and 16-1/2 Years. *Journal of Consulting and Clinical Psychology, 43*(2), 135-147, doi:Doi 10.1037/H0076502.

Kaufman, A. S. (1994). *Intelligent testing with the WISC-III*. New York: John Wiley.

Kaufman, A. S., & Lichtenberger, E. O. (2000). *Essentials of WISC-III and WPPSI-R Assessment*. New York: Wiley.

Koegel, L. K., Koegel, R. L., & Smith, A. (1997). Variables related to differences in standardized test outcomes for children with autism. *J Autism Dev Disord, 27*(3), 233-243.

Koyama, T., Tachimori, H., Osada, H., & Kurita, H. (2006). Cognitive and symptom profiles in high-functioning pervasive developmental disorder not otherwise specified and attention-deficit/hyperactivity disorder. *J Autism Dev Disord, 36*(3), 373-380, doi:10.1007/s10803-006-0075-4.

Koyama, T., Tachimori, H., Osada, H., Takeda, T., & Kurita, H. (2007). Cognitive and symptom profiles in Asperger's syndrome and high-functioning autism. *Psychiatry Clin Neurosci, 61*(1), 99-104, doi:PCN1617 [pii]

10.1111/j.1440-1819.2007.01617.x.

Le Couteur, A., Rutter, M., Lord, C., Rios, P., Robertson, S., Holdgrafe, M., et al. (1989). Autism Diagnostic Interview: A semi-structured interview for parents and caregivers of autistic persons. *Journal of Autism and Developmental Disorders, 19*, 363-387.

Lincoln, A. J., Courchesne, E., Kilman, B. A., Elmasian, R., & Allen, M. (1988). A study of intellectual abilities in high-functioning people with autism. *J Autism Dev Disord, 18*(4), 505-524.

Lockyer, L., & Rutter, M. (1970). A five- to fifteen-year follow-up study of infantile psychosis. IV. Patterns of cognitive ability. *Br J Soc Clin Psychol, 9*(2), 152-163.

Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., et al. (1989). Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *J Autism Dev Disord, 19*(2), 185-212.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord, 24*(5), 659-685.

Mayes, S. D., & Calhoun, S. L. (2003). Analysis of WISC-III, Stanford-Binet:IV, and academic achievement test scores in children with autism. *J Autism Dev Disord, 33*(3), 329-341.

Mayes, S. D., & Calhoun, S. L. (2004). Similarities and differences in Wechsler Intelligence Scale for Children--Third Edition (WISC-III) profiles: support for subtest analysis in clinical referrals. *Clin Neuropsychol, 18*(4), 559-572, doi:10.1080/13854040490888530.

Mayes, S. D., & Calhoun, S. L. (2008). WISC-IV and WIAT-II profiles in children with high-functioning autism. *J Autism Dev Disord, 38*(3), 428-439, doi:10.1007/s10803-007-0410-4.

Minshew, N. J., Goldstein, G., Muenz, L. R., & Payton, J. B. (1992). Neuropsychological functioning in nonmentally retarded autistic individuals. *J Clin Exp Neuropsychol, 14*(5), 749-761, doi:10.1080/01688639208402860.

Mottron, L. (2004). Matching strategies in cognitive research with individuals with high-functioning autism: current practices, instrument biases, and recommendations. *J Autism Dev Disord, 34*(1), 19-27.

Mouga, S., Almeida, J., Cafe, C., Duque, F., & Oliveira, G. (2015). Adaptive profiles in autism and other neurodevelopmental disorders. *J Autism Dev Disord, 45*(4), 1001-1012, doi:10.1007/s10803-014-2256-x.

Nader, A. M., Courchesne, V., Dawson, M., & Soulieres, I. (2014). Does WISC-IV Underestimate the Intelligence of Autistic Children? *J Autism Dev Disord*, doi:10.1007/s10803-014-2270-z.

Narita, T., & Koga, Y. (1987). Neuropsychological assessment of childhood autism. *Adv. Biol. Psychiatr., 16*, 156-170.

Nyden, A., Billstedt, E., Hjelmquist, E., & Gillberg, C. (2001). Neurocognitive stability in Asperger syndrome, ADHD, and reading and writing disorder: a pilot study. *Dev Med Child Neurol, 43*(3), 165-171.

Ohta, M. (1987). Cognitive disorders of infantile autism: a study employing the WISC, spatial relationship conceptualization, and gesture imitations. *J Autism Dev Disord, 17*(1), 45-62.

Oliveira, G., Ataide, A., Marques, C., Miguel, T. S., Coutinho, A. M., Mota-Vieira, L., et al. (2007). Epidemiology of autism spectrum disorder in Portugal: prevalence, clinical characterization, and medical conditions. *Dev Med Child Neurol, 49*(10), 726-733, doi:DMCN726 [pii] 10.1111/j.1469-8749.2007.00726.x.

Oliveras-Rentas, R. E., Kenworthy, L., Roberson, R. B., 3rd, Martin, A., & Wallace, G. L. (2012). WISC-IV profile in high-functioning autism spectrum disorders: impaired processing speed is associated with increased autism communication symptoms and decreased adaptive communication abilities. *J Autism Dev Disord, 42*(5), 655-664, doi:10.1007/s10803-011-1289-7.

Ottem, E. (1999). The structures of the WISC-R subtests: a comparison of the IQ-profiles of reading impaired and autistic subjects. *Scand J Psychol, 40*(1), 1-9.

Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry, 37*(1), 51-87, doi:DOI 10.1111/j.1469-7610.1996.tb01380.x.

Pisula, E. (2010). The autistic mind in the light of neuropsychological studies. *Acta Neurobiologiae Experimentalis, 70*(2), 119-130.

Reynolds, C. R., & Kaufman, A. S. (1990). Assessment of children ' s intelligence with the Wechsler Intelligence Scale for Children – Revised (WISC-R). In C. R. Reynolds, & R. W. Kamphaus (Eds.), *Handbook of psychological and educational assessment of children: Intelligence and achievement.* (pp. 127-165). New York: Guilford.

Rivet, T. T., & Matson, J. L. (2011). Review of gender differences in core symptomatology in autism spectrum disorders. *Research in Autism Spectrum Disorders, 5*(3), 957-976.

Rumsey, J. M., & Hamburger, S. D. (1988). Neuropsychological findings in high-functioning men with infantile autism, residual state. *J Clin Exp Neuropsychol, 10*(2), 201-221, doi:10.1080/01688638808408236.

Rutter, M., Bailey, A., & Lord, C. (2003). *Social Communication Questionnaire*. Los Angeles: Western Psychological Services.

Ryland, H. K., Hysing, M., Posserud, M., Gillberg, C., & Lundervold, A. J. (2014). Autistic features in school age children: IQ and gender effects in a population-based cohort. *Research in Autism Spectrum Disorders, 8*(3), 266-274, doi:http://dx.doi.org/10.1016/j.rasd.2013.12.001.

Schneider, S. G., & Asarnow, R. F. (1987). A comparison of cognitive/neuropsychological impairments of nonretarded autistic and schizophrenic children. *J Abnorm Child Psychol, 15*(1), 29-45.

Shah, A., & Frith, U. (1993). Why do autistic individuals show superior performance on the block design task? *J Child Psychol Psychiatry, 34*(8), 1351-1364.

Siegel, D. J., Minshew, N. J., & Goldstein, G. (1996). Wechsler IQ profiles in diagnosis of high-functioning autism. *J Autism Dev Disord, 26*(4), 389-406.

Sparrow, S., Balla, D., & Cicchetti, D. (1984). *Vineland Adaptative Behaviour Scales: Interview edition, Survey form*. Circle Pines, MN: American Guidance Service.

Szatmari, P., Tuff, L., Finlayson, M. A., & Bartolucci, G. (1990). Asperger's syndrome and autism: neurocognitive aspects. *J Am Acad Child Adolesc Psychiatry, 29*(1), 130-136.

Venter, A., Lord, C., & Schopler, E. (1992). A follow-up study of high-functioning autistic children. *J Child Psychol Psychiatry, 33*(3), 489-507.

Wechsler, D. (1949). *Wechsler intelligence scale for children*. New York: The Psychological Corporation.

Wechsler, D. (1991). *Wechsler Intelligence Scale for Children–Third Edition (WISC-III)*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence (WASI)*. San Antonio, TX: Psychological Corporation.

Wechsler, D. (2003a). *Wechsler Intelligence Scale for Children–Fourth Edition*. San Antonio,TX: The Psychological Corporation.

Wechsler, D. (2003b). *Wechsler Intelligence Scale for Children–Third Edition (WISC-III) - Portuguese Version (M. R. Simões, A. M. Rocha, and C. Ferreira)*. Lisbon: Cegoc-Tea.

2.3. Language Predictors in Autism Spectrum Disorder: Insights from Neurodevelopmental Profile in a Longitudinal Perspective

This chapter consists of the paper: **Mouga S,** Correia BR, Café C, Duque F, Oliveira G. Language Predictors in Autism Spectrum Disorder: Insights from Neurodevelopmental Profile in a Longitudinal Perspective. *J Abnorm Child Psychol*. 2020 Jan;48(1):149-161. doi: 10.1007/s10802-019-00578-7. PubMed PMID: 31410701.

Abstract

Language outcome in individuals with autism spectrum disorder (ASD) has been associated with early neurodevelopmental milestones and cognitive abilities. The acquisition of expressive language is a relevant clinical milestone by school age, since its early presentation is associated with better long-term life outcomes and to lower core clinical severity of ASD. Focusing on early predictors of language in ASD children, a number of outstanding questions remain to be answered, namely, whether there are differences in the early key neurodevelopmental abilities and whether those differences in a specific life period might predict verbal development and acquisition of expressive language. The use of a practical and global assessment of neurodevelopmental profile, instead of more extended evaluation, to give more information to the families and caregivers to guide the intervention programs targeting this population can be of great importance.

We aimed to understand how the neurodevelopmental profile of ASD children evolved from the preschool to the school age and if and which subarea of neurodevelopment could better predict acquisition of expressive language.

Children with ASD (n=205) were evaluated with a structured assessment of neurodevelopment in two different age periods: 1) preschool period (mean age four years) and 2) reassessment in the school period (mean age seven years).

Our findings demonstrate that in nonverbal preschool children with ASD normal or near normal Performance Developmental Quotient (superior to 73.5) and Global Developmental Quotient (superior to 62.5) evaluated with Griffiths Mental Development Scales at preschool age is a good predictor of later language development in ASD.

Introduction

Autism spectrum disorder (ASD) is a complex chronic neurodevelopmental disorder that is characterized by impairments in social interaction and communication, as well as by repetitive and limited patterns of behaviour and interests (American Psychiatric Association 2013). ASD is a multifactorial brain dysfunction which cause is undetermined in approximately 80% of cases (Carter and Scherer 2013), with a high worldwide prevalence and a distribution of four males to one female (Centers for Disease Control and Prevention 2009; Fombonne 2003; Oliveira et al. 2007).

The ASD diagnosis is based exclusively on clinical criteria, since there are no specific biomarkers available, however children with ASD are now being identified at significantly younger ages (American Psychiatric Association 2013; Bhat et al. 2014; Luyster et al. 2008). The identification of predictive factors based on neurodevelopmental assessment that is used as routine in every outpatient clinic in the first years of life has a relevant clinical role since it will permit early identification of the needs of the child, the adaptation of the planning of intervention and the adjustment of future expectations for each ASD patient and respective families, allowing for an estimated prognosis (Ellis Weismer and Kover 2015; Ferreira and Oliveira 2016; Kover et al. 2016; Sutera et al. 2007).

One of the most important and limitative features of ASD is an individual's communication deficits, namely the degree of language delay and/or impairment, which explains why the language delay is among the most frequent reasons reported by caregivers for referral for young children with ASD (Chakrabarti and Fombonne 2001, 2005). Prior research has consistently found that early language skills in this population are heterogeneous, since they can vary from highly fluent with large vocabularies and complex grammar, to no meaningful production of words and minimal language comprehension (Luyster et al. 2008; Thurm et al. 2007; Yoder et al. 2015). The proportion of individuals with ASD who remain non-verbal vary widely according to the specificities of these population studies, but is estimated that around one quarter will fail to develop flexible, spontaneous, communicative expressive language abilities over the course of their lifetime (Anderson et al. 2007; Sigman and McGovern 2005; Tager-Flusberg and Kasari 2013). A longitudinal study (Anderson et al. 2007) on speech development which monitored children with ASD with ages between two and nine years old, found that 24% of participants with ASD obtained fluent speech and 30% were nonverbal by nine years of age. Pickett, Pullara, O'Grady, and Gordon (2009), in a comprehensive review of the literature about the age of speech onset and subject characteristics of nonverbal children with ASD, found that children began to speak between five and seven years, and most gained only the ability to produce single words. However, around 30% achieved phrase speech. A global intelligence quotient equal or superior to 50 and participation in behavioural intervention were the characteristics of individuals who began to speak after age of five (Pickett et al. 2009). In a more recent study, acquisition of phrase and/or fluent speech was achieved by the majority (70%) of participants by the age of eight years, with almost half of the sample achieving fluent speech (Wodka et al. 2013).

Language outcome in ASD is known to be affected essentially by early language acquisition and other cognitive abilities (Szatmari et al. 2003). The development and

acquisition of expressive language (particularly the onset of the first phrases), by preschool age, is a relevant early clinical milestone in children diagnosed with ASD, since its early presentation is associated to best intellectual skills, better long-term life outcomes, adaptive functioning and to lower specific clinical severity of autism (Billstedt et al. 2007; Ferreira and Oliveira 2016; Gillberg and Steffenburg 1987; Howlin et al. 2000; Venter et al. 1992). However, complex questions remain to be answered: a) how these predictive relationships change over the course of neurodevelopment; b) why a large number of children with ASD do not develop meaningful language during their preschool years.

Previous studies emphasised the use of general measures of cognition, and other specific behaviours as predictors of language outcome in children with ASD (Mundy et al. 1990). This was later highlighted in studies that recognized non-verbal cognitive ability as a strong predictor of both receptive and expressive language skills (Anderson et al. 2007; Charman et al. 2003, 2005; Paul et al. 2008). Thurm and colleagues (2007) found that non-verbal cognitive ability and earlier communication skills were consistently strong predictors of later language acquisition, emphasising that at age two, direct assessment of non-verbal cognitive ability, provided critical predictive information about language skills at age five. These results were also corroborated by Luyster and colleagues (2008) who found that the most significant predictors for expressive language, were non-verbal cognitive ability, gestures, and imitation skills. Wodka, Mathy and Kalb (2013), in a multivariate study, concluded that higher non-verbal intelligence quotient and social ability were independently associated with the acquisition of phrases and fluent speech.

Despite the fact that much progress has been made in determining the predictors of language in children with ASD, a number of outstanding questions remain to be answered, namely, whether there are differences in the results of early neurodevelopmental assessment of children with ASD and whether those differences in a specific period of time might predict verbal development and acquisition of expressive language later in life. These questions also emerged from our daily clinical experience and are the main focus of concern of many parents, families, and professionals.

Our current study involved participants with ASD diagnosis, assessed longitudinally in two different periods of age: first assessment in the preschool period (APSP) and a reassessment in the school period (RSP). The aim was to understand how the neurodevelopmental profile of these children evolved with regard to stability and change from the preschool to the school period and if there was any marker in the neurodevelopmental profile and early neurodevelopmental milestones that could predict later acquisition of

expressive language (evaluated at school age). We hypothesized that non-verbal skills (performance developmental quotient [DQ]) were determinant in the prediction of the acquisition of expressive language.

It is of great importance in the clinical practice to know whether the early abilities on a standard global neurodevelopmental test can be used as predictor of a later specific neurodevelopmental milestone acquisition (language in ASD patients). In addition, it can aid in the understanding of the natural history of the ASD, the early information given to the family, the planning of intervention and to predict the outcome in the language skills.

Methods

Participants

Participants included 205 children (86.8% male) with the diagnosis of ASD, from a convenience sampling, who were seen as part of an outpatient clinic, between 2000 and 2017. ASD diagnosis was assigned on gold standard instruments: parental or caregiver interview (Autism Diagnostic Interview– Revised, ADI-R (Le Couteur et al. 2003; Lord et al. 1994)), direct structured proband assessment (Autism Diagnostic Observation Schedule, ADOS (Le Couteur et al. 2003; Lord et al. 1989; Lord and Rutter 1999)), and clinical examination performed by experienced neurodevelopmental Paediatricians in a multidisciplinary team. The current diagnostic criteria for autism were revised according to the Diagnostic and Statistical Manual of Mental Disorders 5, DSM-5 (American Psychiatric Association 2013). All ASD patients had positive results in the ADI-R and/or ADOS for autism or ASD and met the criteria for ASD from the DSM-5. A comprehensive medical observation excluded associated medical condition such as epilepsy or other usual comorbidity in ASD samples. Neurocutaneous or other genetic syndromes are part of this sample (n=31).

To be included, all participants had to be given an individually administered global neurodevelopmental test [Griffiths Mental Development Scales (GMDS, Associação Portuguesa de Paralisia Cerebral, n.d.; Griffiths, 1984)] in two different periods. The first assessment was performed in the preschool period (APSP – Assessment in the Preschool period) (aged until 5 years and 11 months) and the reassessment was performed in the school period (RSP – Reassessment in the School Period) (aged from 6 years until 8 years and 11 months, the age limit of the neurodevelopmental test).

The main group (*n*=205) was divided in two subgroups taking in account their expressive language in the first assessment - APSP: i) nonverbal children (non-verbal subgroup at APSP - ASD_NV, *n*=100) - who did not have phrase speech (did not speak with sentences composed of two or more words, one word being a verb, routinely used); and ii) verbal children (verbal subgroup at APSP - ASD_V, *n*=105), the ones that already had acquired phrase speech.

In the RSP: 31 children remained nonverbal, while 174 children were verbal. From these 174 children, 105 were verbal since preschool period (verbal subgroup) and 69 acquired verbal language until school age ("became-verbal" subgroup). So, the verbal evolution in the time of RSP of the subgroup of non-verbal children at preschool age (APSP-ASD_NV, *n*=100) was categorized in two: children who remained nonverbal - "never-verbal" subgroup (*n*=31) and children who, meanwhile, acquired verbal language - "became-verbal" subgroup (*n*=69) (see Figure 2.3.1).

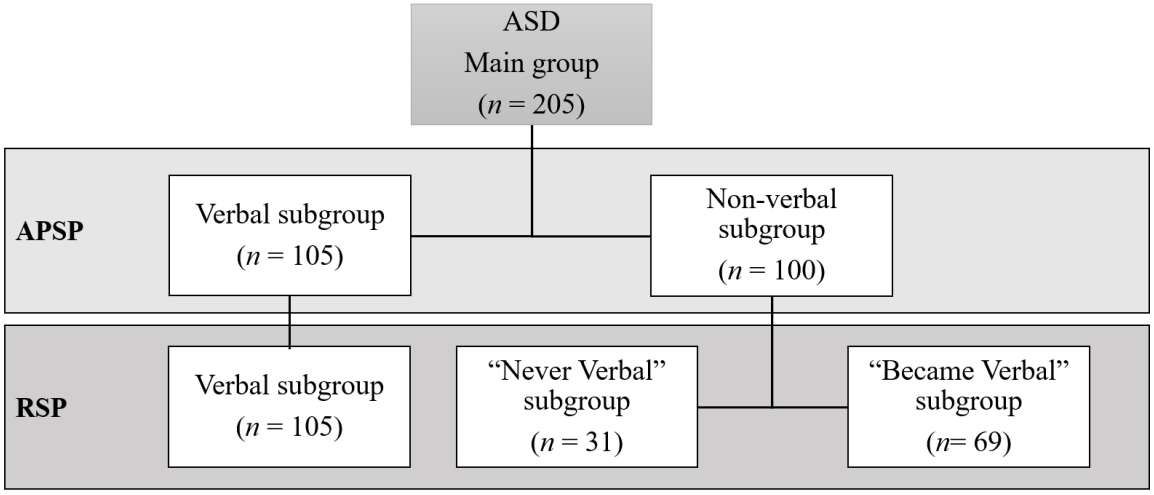

Figure 2.3.1. Flowchart of the study sample.

NOTE. ASD = Autism Spectrum Disorder; APSP = Assessment in the Preschool Period; RSP = Reassessment in the School Period

The chronological age in APSP and RSP, the early neurodevelopmental milestones (age for onset of independent walking, age for onset of first words and age for onset of first phrases) of the main clinical group and the different subgroups are reported in Table 2.3.1.

Table 2.3.1. Clinical characteristics of the main clinical group of subjects with ASD and the subgroups

Group and Subgroups	CA_APSP (months)		CA_RSP (months)		Gender (Male /Female)	Age for onset of walking (months)		Age for onset of first words (months)		Age for onset of first phrases (months)	
	n	Mean (SD)	*n*	Mean (SD)		*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
ASD (main group)	205	49.6 (10.4)	205	89.5 (9.5)	178/27	204	15.2 (4.2)	201	27.0 (14.5)	179	47.8 (16.8)
Verbal subgroup	105	54.51 (9.05)	105	91.6 (9.04)	91/14	105	14.66 (3.23)	105	21.40 (8.81)	105	38.62 (9.21)
"Never-verbal" subgroup	31	49.4 (9.3)	31	86.8 (8.3)	27/4	31	16.8 (6.8)	27	38.3 (22.2)	-	-
"Became-verbal" subgroup	69	42.3 (8.3)	69	88.3 (10.3)	60/9	68	15.2 (3.7)	69	31.0 (13.8)	69	58.7 (14.7)

NOTE. ASD = Autism Spectrum Disorder; CA = Chronological Age; APSP = Assessment in the Preschool Period; RSP = Reassessment in the School Period; SD = Standard Deviation

Measures

All measures were administered, during routine clinical multidisciplinary assessments in a neurodevelopmental unit that is a national reference for ASD and other neurodevelopmental disorders in a Tertiary University Paediatric Hospital, by experienced psychologists and neurodevelopmental paediatricians, for diagnostic or treatment planning. All population in this study is routinely followed by this team, in a clinical set, at least two times per year.

Assessment of early neurodevelopmental milestones

The early neurodevelopmental milestones assessed in our study were: age for onset of independent walking, age for onset of first words and age for onset of first phrases. We considered the definitions of these milestones as described in the ADI-R (Le Couteur et al. 2003). Age for onset of independent walking was defined as the age (in months) at which the child takes unaided gait. Age for onset of first words was defined as the age (in months) at which the child first produced single words, other than "mama" and "dada," in a consistent and meaningful way for the purposes of communication. Age for onset of first phrases was defined as the age (in months) at which the child first produced sentences composed of two or more words, one word being a verb, routinely used.

Neurodevelopmental Assessment with Griffiths Mental Development Scales

The Griffiths Mental Development Scales (GMDS, Associação Portuguesa de Paralisia Cerebral, n.d.; Griffiths, 1984) was used for neurodevelopmental assessment of children. These scales are widely used by European paediatricians and psychologists to measure the rate of neurodevelopment of infants and young children from birth to 8 years specially in samples with neurodevelopmental disorders (Muglia et al. 2018). The GMDS evaluates a child's abilities in six areas, allowing a global assessment of children's mental development, with similar results to Bayley Scales of Infant Development (BSID-II) (Cirelli et al. 2015). The six sub-scales of development measured by GMDS include: A- Locomotor (assesses gross motor skills, including the ability to balance and to co-ordinate and control movements); B- Personal Social (measures proficiency in the activities of daily living, level of independence and interaction with other children); C- Hearing and Language (assesses hearing, expressive language and receptive language); D- Eye and Hand Coordination (assesses fine motor skills, manual dexterity and visual monitoring skills); E- Performance (assesses the developing ability to reason through visuospatial skills including speed of working and precision); and F-

Practical Reasoning (measures the ability of a child (2 to 8 years) to solve practical problems, understanding of basic maths concepts and understanding of moral issues). The global DQ and sub-quotients are calculated using a simple ratio transformation, dividing the mental age by chronological age, as described in the manual (GMDS, Associação Portuguesa de Paralisia Cerebral, n.d.; Griffiths, 1984). The mental age is the result of the sum of the items that the children can perform with success. The DQ has a mean of 100 and a standard deviation of 15. Administration time is generally around one and a half hours. Given the fact that the version of the scale used in this study was only translated and adapted to Portuguese and normative data of the GMDS were not available in our country, we here referred to the 1984 United Kingdom norms (Griffiths 1984).

Procedure

We performed a follow-up study of a cohort of children with ASD. Data was collected from a database according to the National policy on archival research of our Paediatric Hospital. The group of participants included in this study represents a subset of patients of the outpatient clinic, whose information is usually collected for clinical and research documentation. A total of 205 records were included meeting the inclusion criteria: 1. ASD diagnosis; 2. an individually administered global neurodevelopmental test (GMDS, Associação Portuguesa de Paralisia Cerebral, n.d.; Griffiths, 1984) in two different periods.

These children were assessed, in two different periods: one assessment (first time) in the preschool period (APSP) and reassessment (second time) in the school period (RSP), which was on average, at four and seven years of life, respectively, using GMDS. We compared the developmental profile of GMDS analysing the Global DQ, and DQs of the different subscales in these two different periods. We also analysed the impact of the early neurodevelopmental milestones (age for onset of independent walking and age for onset of first words), as predictors of expressive language at school age. The age of onset of first phrases was not used as predictor since it was part of the definition of "verbal children". Children were considered "verbal" when they speak with phrases - sentences composed of two or more words, one word being a verb, routinely used, assessed by the application of ADI-R (Le Couteur et al. 2003), by a trained professional.

Data analysis

Initially we conducted an Exploratory Data-Analysis using graphical techniques and quantitative analysis in order to characterize the sample, detect possible extreme outliers and measurement error. In the RSP: 31 children remained nonverbal ("never-verbal" subgroup, n=31), while 174 children were verbal. From these 174 children, 105 were verbal since preschool period (verbal subgroup) and 69 acquired verbal language until school age ("became-verbal" subgroup).

The evolution of the DQ's in the GMDS assessments in the three subgroups - verbal; "became-verbal"; and "never-verbal" - during the two moments of evaluation (assessment at preschool period – APSP, and reassessment at school period - RSP) was evaluated with mixed Analysis of Variance (ANOVA) with repeated measures (diagnostic age as covariate). The assumptions of the method, namely, the normal distribution and the sphericity of the variance-covariance matrix were evaluated, respectively, using the Kolmogorov-Smirnov test and the Box M test.

Given the high multicollinearity between the independent variables (Locomotor DQ; Personal Social DQ; Hearing and Language DQ; Eye and Hand Coordination DQ; Performance DQ; and Practical Reasoning DQ) (Tolerance < 0.1, VIF >10), we performed the hierarchical clusters analysis (variable cluster) to resize the number of variables (cluster method – between-groups linkage; measure – interval: Pearson correlation). Next, we performed a two-step cluster analysis (standardization of continuous variables; distance measure – log-likelihood) to classify the subgroups "never-verbal" and "became verbal" and to identify power of predictors.

Finally, we used logistic regression to determine the probability of a non-verbal child at the time of the first assessment to belong to the "Became verbal". In models with adequate adjustment, the quality was compared of the adjustment based on the Nagelkerke R Square and area under the receiver operating characteristic curve (ROC). We calculated the cut-off (Youden's index) for AUC greater than 0.7.

All statistical analysis was realized with the support of the version for Microsoft Windows® of the Statistical Package for Social Sciences, version 19 (SPSS ®, Chicago, IL, USA). A significance level of 0.05 was adopted.

Ethics Statement

All the procedures in this study were reviewed in accordance with the ethical standards and approved by the Health Ethics Commission of our Hospital (Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra) and were conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The clinicians obtained informed consent from the parents/guardians of all younger participants. Children, when competent to do so, also gave oral informed consent. The database is approved by the Portuguese Data Protection Authority.

Results

Trend of neurodevelopmental profile

Initially we verified the trend of neurodevelopment over the follow-up period. To determine differences between the APSP and RSP the DQs of GMDS were analysed (to see the exact mean and standard-deviation (SD) values, please see Table 2.3.2).

The mean value of the age of diagnosis was significantly different between the subgroups "never-verbal" subgroup, "became-verbal" subgroup and verbal subgroup ($F(2,204) = 23.284$, $p < .001$). There were significant differences between verbal subgroup and the other subgroups ($p<0.001$ - post hoc multiple comparisons for observed means – Equal variances assumed (Bonferroni)).

Among the subgroups there were no significant differences regarding the academic qualifications of the mother ($X2(2) = 2.680$, $p = .262$) and the gender of the child ($X2(2) = 0.005$, $p = .997$).

Concerning the Global DQ, the mean value was significantly different between the three subgroups "never-verbal" subgroup, "became-verbal" subgroup and verbal subgroup ($F(2,201) = 84.698$, $p < .001$, $\eta2 = 0.457$, power = 1.00), having significant differences between any two subgroups (adjustment for multiple comparisons with Bonferroni correction, $p < .001$). The mean value of the Global DQ throughout the assessment moments was significantly different: "Preschool" and "School" ($F(1,201) = 7.006$, $p = .009$, $\eta2 = 0.034$, power = 0.750). However, only the "never-verbal" subgroup presented significant differences between the two moments of evaluation (decreasing from APSP to RSP) ($F(1,29) = 19.117$, $p < .001$, $\eta2 = 0.397$, power = 0.988).

Table 2.3.2. Descriptive Statistics for the subgroups: verbal; "never-verbal" and "became-verbal"

	Verbal subgroup			"Never-verbal" subgroup			"Became-verbal" subgroup		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Global DQ APSP	105	90.7	16.5	31	56.0	13.8	69	70.4	15.2
Global DQ RSP		87.0	15.3		45.7	15.0		73.5	19.4
Locomotor DQ APSP	105	101.4	14.7	31	81.0	20.6	69	91.2	19.5
Locomotor DQ RSP		89.2	14.3		66.7	19.1		83.4	18.1
Personal Social DQ APSP	105	87.0	16.0	31	52.7	13.4	69	65.0	17.5
Personal Social DQ RSP		81.3	16.0		45.6	16.6		69.0	18.5
Hearing and Language DQ APSP	105	88.3	26.1	31	32.5	8.7	69	47.1	18.2
Hearing and Language DQ RSP		86.0	18.9		26.7	11.8		66.7	24.6
Eye and Hand Coordination DQ APSP	105	89.4	23.8	31	55.5	20.2	69	67.3	16.8
Eye and Hand Coordination DQ RSP		89.1	17.0		47.5	22.4		78.0	22.1
Performance DQ APSP	105	100.2	20.7	31	67.4	23.5	69	85.7	23.5
Performance DQ RSP		92.1	17.1		56.1	22.1		80.2	22.4
Practical Reasoning DQ APSP	103	78.4	19.7	20	45.1	8.8	35	61.2	16.5
Practical Reasoning DQ RSP		84.9	19.9		30.9	11.2		65.0	24.2

NOTE. DQ = Developmental Quotient; APSP = Assessment in the Preschool Period; RSP = Reassessment in the School Period; SD = Standard Deviation

In what concerns to the Locomotor DQ, there were significant differences between any (adjustment for multiple comparisons with Bonferroni correction, $p < .001$) of the subgroups "never-verbal", "became-verbal" and verbal ($F(2,201) = 30.526$, $p < .001$, $\eta 2 = 0.233$; power = 1.000). There were also significant changes in the Locomotor DQ throughout the assessment moments decreasing from "Preschool" to "School" ($F(1,201) = 8.003$, $p < .001$, $\eta 2 = 0.129$, power = 1.000). The "never-verbal" subgroup presented significant differences between the two moments of evaluation ($F(1,29) = 19.249$, $p < .001$, $\eta 2 = 0.399$, power = 0.989) as well as the subgroup "became-verbal" ($F(1,67) = 11.086$, $p = .001$, $\eta 2 = 0.158$, power = 0.999).

In the Personal Social DQ there were significantly differences between the subgroups "never-verbal", "became-verbal" subgroup and verbal subgroup ($F(1,201) = 74.194$, $p < .001$, $\eta 2 = 0.425$; power = 1.000). These differences were significant between any two subgroups (adjustment for multiple comparisons with Bonferroni correction, $p < .001$). There was no significant difference in the mean value of the Personal Social DQ between the two assessment moments: "Preschool" and "School" ($F(1,201) = 3.350$, $p = .069$, $\eta 2 = 0.016$, power = 0.445).

This was also true for the Hearing and Language DQ, which was significantly different in the subgroups "never-verbal", "became-verbal" and verbal subgroup ($F(2,201) = 136.9$, $p < .001$, $\eta 2 = 0.577$, power = 1.000). These differences were present between any two subgroups (adjustment for multiple comparisons with Bonferroni correction, $p < .001$). There was no significant difference in the mean value of the Hearing and Language DQ between the assessment moments: "Preschool" and "School" ($F(1,201) = 0.441$, $p = .507$, $\eta 2 = 0.002$, power = 0.101).

The mean value of the Eye and Hand Coordination DQ was significantly different between any (adjustment for multiple comparisons with Bonferroni correction, $p < .001$) of the subgroups "never-verbal", "became-verbal" and verbal ($F(1,201) = 50.801$, $p < .001$, $\eta 2 = 0.330$; power = 1.000). There was no significant difference in the mean value of the Eye and Hand Coordination DQ between the two assessment moments: "Preschool" and "School" ($F(1,201) = 0.430$, $p = .510$, $\eta 2 = 0.002$, power = 0.101).

Concerning the Performance DQ there were significant differences between the subgroups "never-verbal", "became-verbal" and Verbal ($F(1,201) = 42.71$, $p < .001$, $\eta 2 = 0.298$; power = 1.000). There were significant differences between any two subgroups (adjustment for multiple comparisons with Bonferroni correction, $p < .001$). There were

significant changes in the mean value of the Performance DQ throughout the two assessment moments (decreasing): "Preschool" and "School" ($F(1,201) = 9.814$, $p = .002$, $\eta 2 = 0.047$, power = 0.877). However, only the "never-verbal" subgroup presents significant differences between the two moments of evaluation (decreasing from APSP to RSP) ($F(1,29) = 7.605$, $p = .010$, $\eta 2 = 0.208$, power = 0.761).

The mean value of Practical Reasoning DQ was significantly different between the subgroups "never-verbal", "became-verbal" and Verbal ($F(1,154) = 62.997$, $p < .001$, $\eta 2 = 0.450$, power = 1.000). There were significant differences between any two subgroups (adjustment for multiple comparisons with Bonferroni correction, $p < .001$). There was no significant difference in the mean value of the Practical Reasoning DQ between the two assessment moments: "Preschool" and "School" ($F(1,154) = 0.210$, $p = .647$, $\eta 2 = 0.001$, power = 0.074).

Predictors of language

Given the high multi-linearity between the subscales, a hierarchical cluster analysis was performed to reduce the number of variables. Based on the dendrogram (see Figure 2.3.2), the coefficients (Agglomeration Schedule, see Table 2.3.3) and given the fact that some of the areas evaluated by the GMDS are overlapping in some aspects, it was considered acceptable to use only the variables: Hearing and Language DQ, Performance DQ and Locomotor DQ for the analysis of language predictors.

After a cluster analysis, the silhouette (measure of cohesion and separation) value of 0.5 was obtained, so the quality of the classification between "never-verbal" and "became verbal" is fair to good, with 65% correct. It was also verified that the most important predictor is the Performance DQ (see Table 2.3.4).

Finally, two logistic regressions were performed. One considering as independent variable the Global DQ and another the Performance DQ.

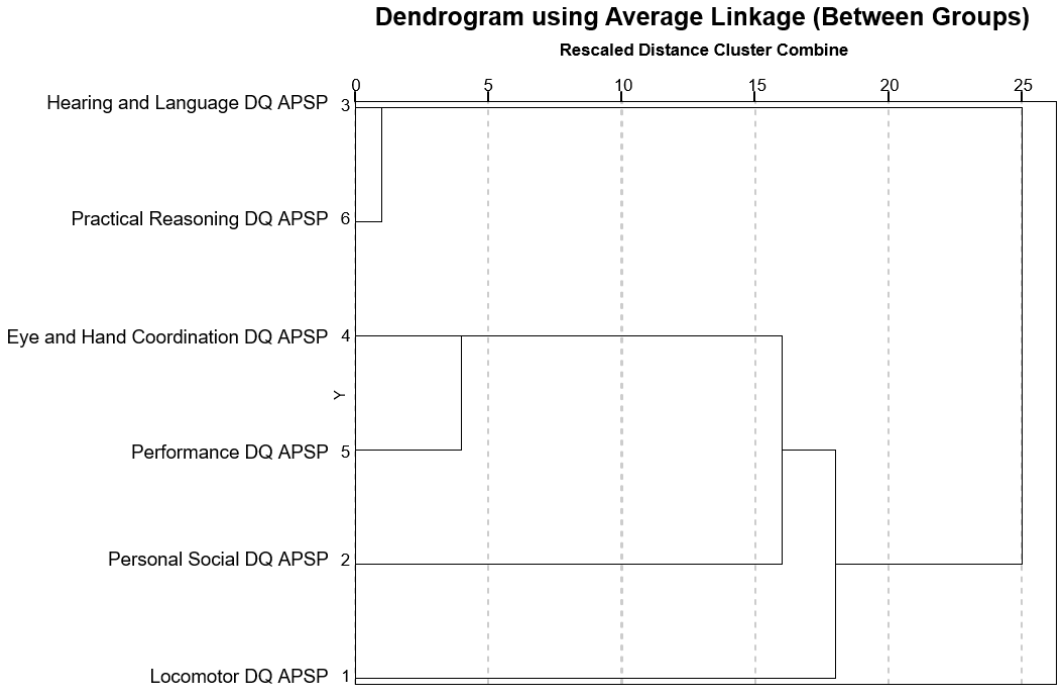

Figure 2.3.2. Dendrogram using Average Linkage (Between Groups) (measure – Interval: Pearson Correlation). NOTE. DQ = Developmental Quotient; APSP = Assessment in the Preschool Period.

Table 2.3.3. Hierarchical cluster analysis - Agglomeration Schedule

Stage	Cluster Combined		Coefficients	Stage Cluster First Appears		Next Stage
	Cluster 1	Cluster 2		Cluster 1	Cluster 2	
1	3	6	0.900	0	0	5
2	4	5	0.862	0	0	3
3	2	4	0.727	0	2	4
4	1	2	0.706	0	3	5
5	1	3	0.623	4	1	0

Table 2.3.4. Two-Step cluster Analysis (distance measure – log-likelihood)

Predictor	Predictor Importance
Locomotor DQ APSP	0.4712
Hearing and Language DQ APSP	0.7325
Performance DQ APSP	1

NOTE. DQ = Developmental Quotient; APSP = Assessment in the Preschool Period.

Global DQ

The model was statistically significant with the variable Global DQ (X2Wald(1) = 13.976, p < .001, OR = 1.068), the probability function of "becoming verbal" for spoken language/phrase speech (see Figure 2.3.3) was given by π̂=1/(1+e^(-[-3.365+0.066 Global DQ])).

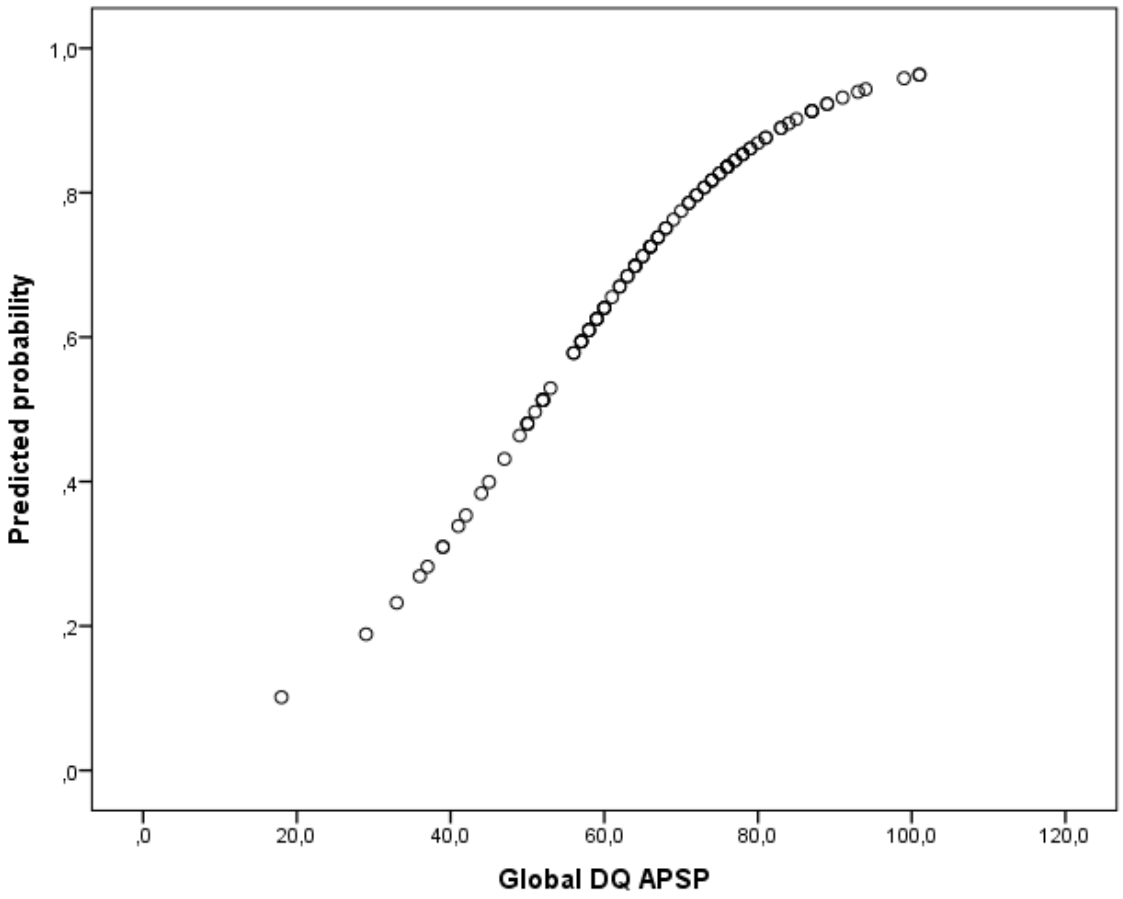

Figure 2.3.3. Probability of "became-verbal" as a function of Global DQ.

NOTE. DQ = Developmental Quotient; APSP = Assessment in the Preschool Period.

The probability of "becoming verbal" increases exponentially with Global DQ (the ratio of chances of "becoming verbal" relative to "never becoming verbal", increases 7% for each Global DQ unit).

A correct classification percentage of 68% (superior to the proportional percentage of correct ratings by chance) and an acceptable discriminant capacity was observed (AUC = 0.767, std. Error = 0.049, p < .001) (see Figure 2.3.4). The cut-off value is 62.5 (sensitivity = 77% and specificity = 77%).

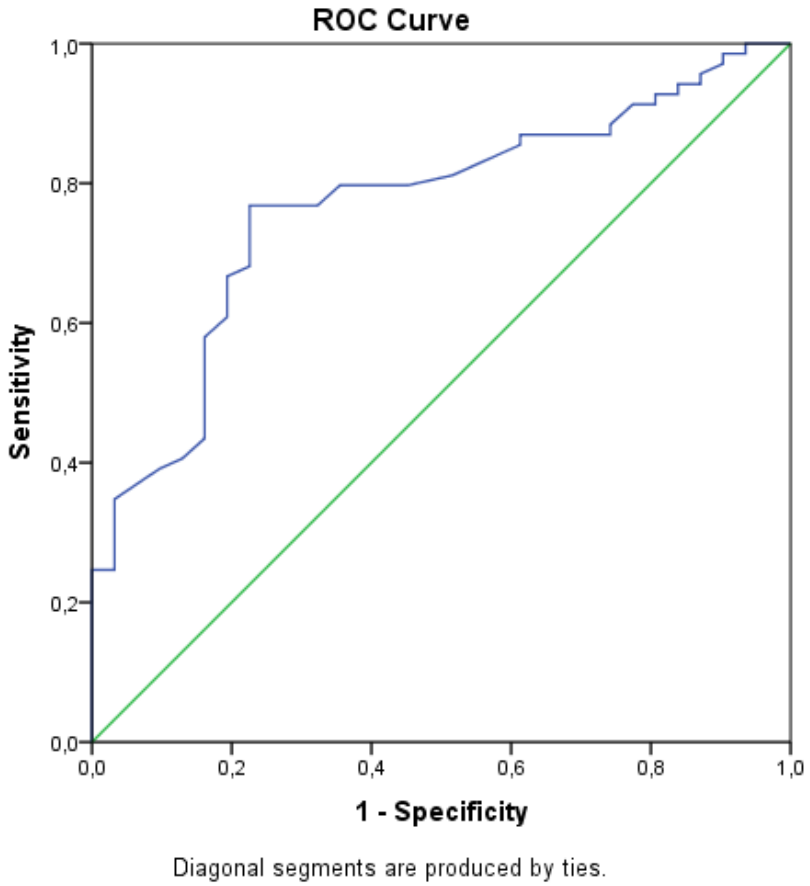

Figure 2.3.4. Diagnostic accuracy of "became-verbal". Receiver operator characteristic curve for diagnosis of "became-verbal" to expressive language based on Global DQ.

NOTE. DQ = Developmental Quotient; ROC = receiver operating characteristic curve

Performance DQ

The model was statistically significant with the variable Performance DQ (X2Wald (1) =10.420, p = .001, OR =1.033), the probability function of "becoming verbal" for spoken language/phrase speech (see Figure 2.3.5) was given by

π^=1/(1+e^(-[-1.681+0.031 Performance DQ])).

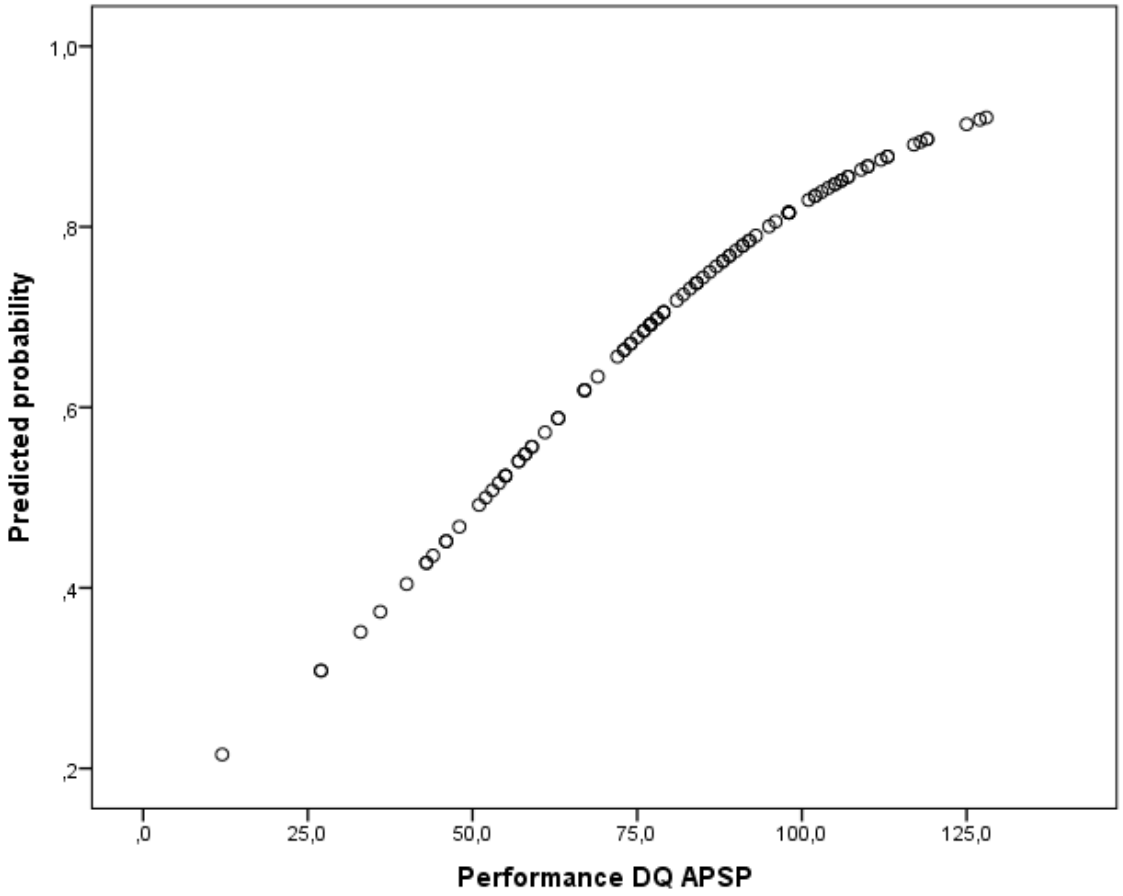

Figure 2.3.5. Probability of "became-verbal" as a function of Performance DQ.

NOTE. DQ = Developmental Quotient; APSP = Assessment in the Preschool Period.

The probability of "becoming verbal" increases exponentially with Performance DQ (the ratio of chances of having "becoming verbal" relative to "never becoming verbal", increases 3% for each Performance DQ unit).

A correct classification percentage of 63% (superior to the proportional percentage of correct ratings by chance). An acceptable discriminant capacity was observed (AUC = 0.716, std. Error = 0.054, $p < .001$) (see Figure 2.3.6). The cut-off value was 73.5 (sensitivity = 77% and specificity = 61%).

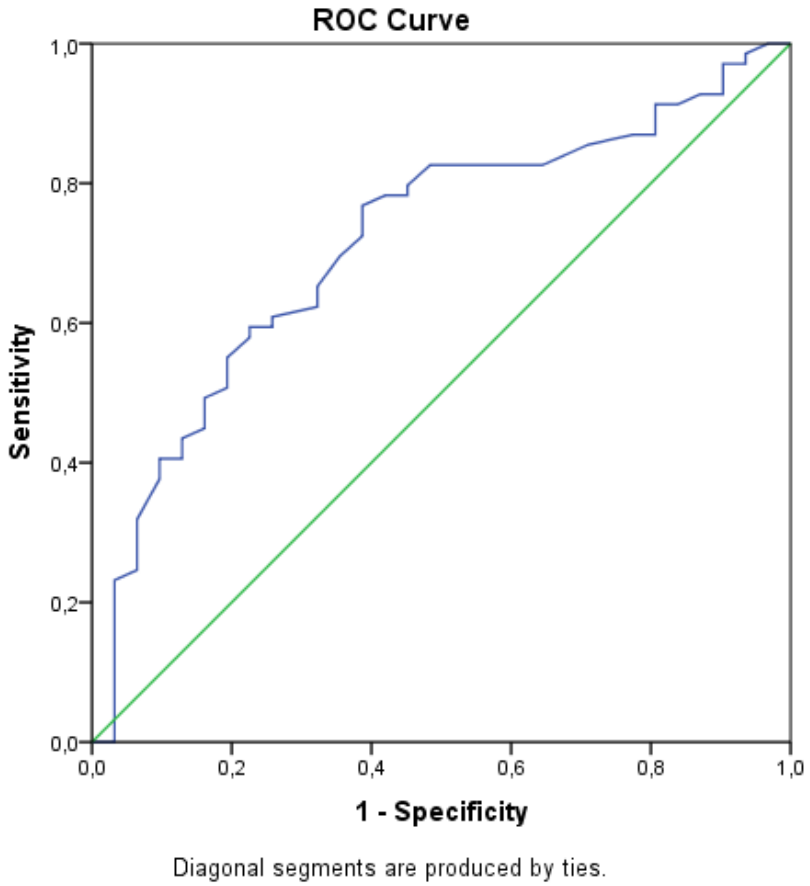

Figure 2.3.6. Diagnostic accuracy of "became-verbal". Receiver operator characteristic curve for diagnosis of "became-verbal" to expressive language based on Performance DQ.

NOTE. DQ = Developmental Quotient; ROC = receiver operating characteristic curve

Discussion

In our work, we studied the effect of the neurodevelopmental profile in the preschool period in the trend of neurodevelopment in school age, identifying predictors of later (school age) verbal development in a large sample of well-characterized children with ASD, followed from preschool to school age. For that purpose, we compared the neurodevelopmental profile measured by GMDS in two periods of time (first APSP; and second RSP).

We can conclude that the early neurodevelopmental profile of children with ASD vary widely, ranging from children with global psychomotor developmental delay to children with an adequate or superior global capacity to their chronological age. One of the most marked and diverse characteristics is the language ability, in particular, the acquisition of phrase speech and this is predicted not only by the global psychomotor development but also, particularly by the early performance (non-verbal) abilities, according to our study.

The neurodevelopmental profile of children with ASD evolves from the preschool to the school period in different manners taking into account the language abilities. In fact, there are significant statistical differences in all DQ's from GMDS between the three subgroups from preschool to school age: verbal, "became-verbal" and "never-verbal".

Despite the fact that there are no gender or maternal education differences between the three subgroups, the age of diagnosis is significantly different between them and this is probably due to the severity of symptoms at early age, with the diagnosis being later in the verbal subgroup. This is expected, as in many of these children the language delay at the first years of life is a red flag to the ASD diagnosis suspicion.

If we take into account the time, that is, the changes between preschool and school period in the DQ's, we see that only in the "never-verbal" subgroup there are differences and only in the Global DQ, Locomotor DQ and Performance DQ (decreasing from APSP to RSP). In the "became-verbal" subgroup, there are only differences in the Locomotor DQ (decreasing from APSP to RSP). In the verbal subgroup, there are no significant changes from one assessment to the other.

In the "never-verbal" subgroup, the psychomotor developmental profile is significantly worse in the school period. In this subgroup, the developmental quotients remain the same or with very few improvements, not catching up with what is expected for their chronological age (Figure 2.3.7). In the "became-verbal" subgroup the very heterogeneous developmental profile from the preschool period transformed into a homogeneous profile (Figure 2.3.8).

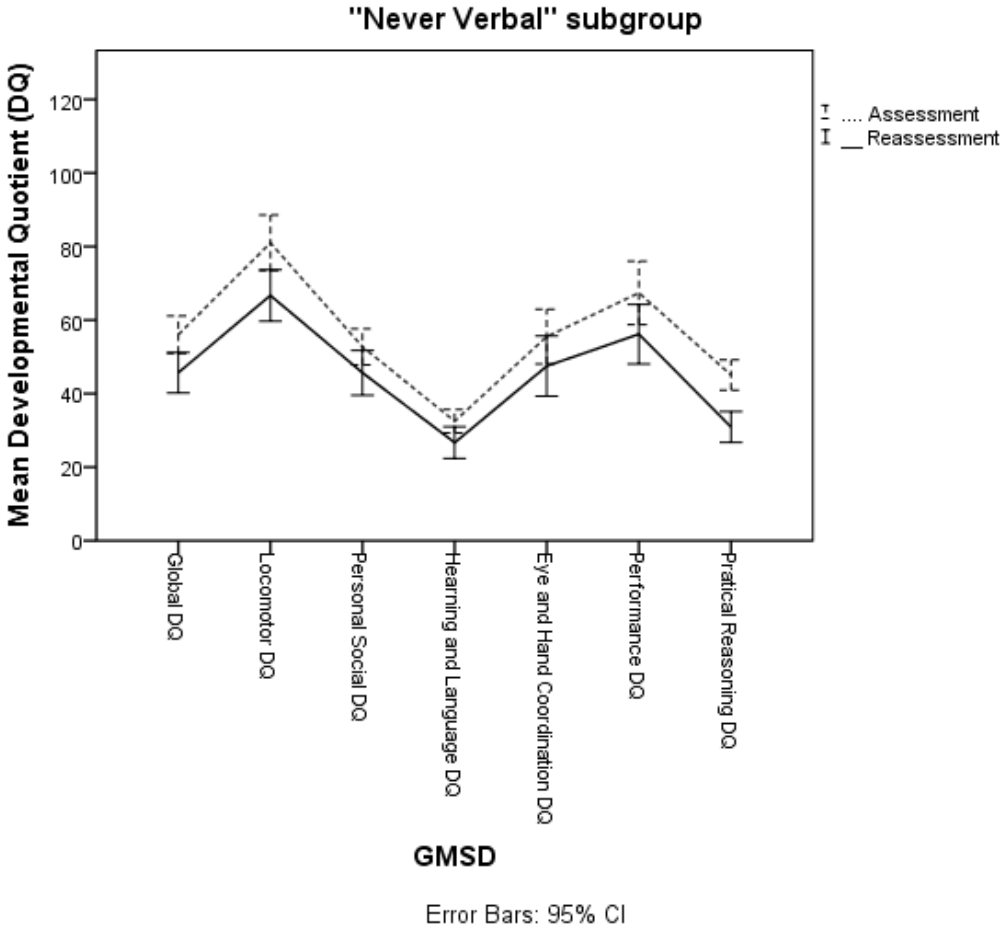

Figure 2.3.7. Differences in GMSD developmental quotients for the "never-verbal" subgroup in APSP and RSP: Line chart with error bars (95% CI).

NOTE. GMSD = Griffiths Mental Development Scales; DQ = Developmental Quotient; APSP = Assessment in the Preschool Period; RSP = Reassessment in the School Period

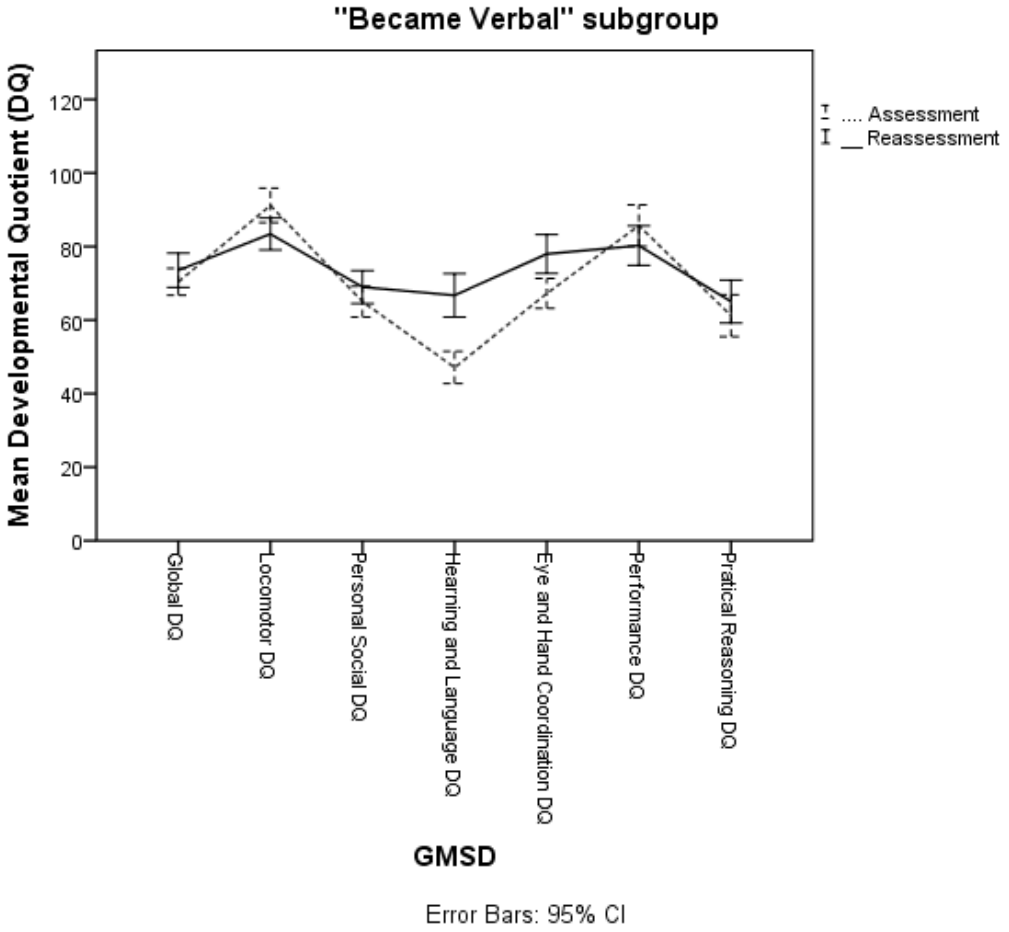

Figure 2.3.8. Differences in GMSD developmental quotients for the "became-verbal" subgroup in APSP and RSP: Line chart with error bars (95% CI).

NOTE. GMSD = Griffiths Mental Development Scales; DQ = Developmental Quotient; APSP = Assessment in the Preschool Period; RSP = Reassessment in the School Period

Importantly, our findings also demonstrate that in nonverbal preschool children with ASD normal or near normal Performance DQ (superior to 73.5) may be an index of verbal acquisition, which supports the importance of nonverbal intelligence skill as a primary predictor of later language development for children with ASD, replicating the results from other investigators (Anderson et al. 2007; Pickett et al. 2009; Wodka et al. 2013).

Our original contribution that constitutes our study as a proof of principle is related to cut-off values of DQs of GMSD that we got in this sample as early predictors of expressive language. Actually, in the clinical practice, the identification of a neurodevelopmental model in the first years of life that allows the identification of the needs of the child is very important to the adaptation of the planning of intervention and also for the adjustment of future expectations for each ASD patient and respective families (Ferreira and Oliveira 2016; Sutera

et al. 2007). Our study may provide an estimated prognosis of later language acquisition based on global developmental and nonverbal quotients scores at early age. In fact, a child with Global DQ superior to 62.5 (for a sensitivity of the 77.0% and a specificity of the 77.0%) and a Performance DQ superior to 73.5 (for a sensitivity of the 77.0% and a specificity of the 61.0%) at preschool age has a greater probability to develop phrase speech until school age. These findings also emphasise the need of a correct collection and knowledge of clinical history, with special attention to early and classic neurodevelopmental milestones. These results are in line with previous studies of our group and others (Ferreira and Oliveira 2016; Johnson et al. 2010).

In sum, focusing on all the analysis of our study, our findings suggest that these core abilities (global and nonverbal intelligence) at early age, close to diagnosis moment, have great and important information about the potential development of language in children with ASD. This knowledge could be very helpful to clarify family and educational professionals of outcome and precise and personalized educative intervention programme.

The most significant limitations of the current study were the use of a convenience sample, the absence of separate standardized cognitive and language assessments and the reliance on retrospective parent report to obtain precise age for the acquisition of phrase speech (reporting the age of first sentences). Nevertheless, we have assumed that these biases are constant through the sample. Another limitation was that specific interventions for the period between evaluations were not taken into account as predictors or moderators of language outcomes. However, our national policy for inclusion of all children with ASD at regular school in Autism Specialized Units (with special education teachers, speech therapy, occupational therapy, and psychology as interventions available) decreases this bias. Although this may be an impediment in the generalization of our results, it can also be an argument in favour of early and public intervention in ASD.

These findings have important implications for intervention programs targeting this population. With regard to treatment planning, findings further substantiate the importance of considering both nonverbal and verbal intelligence and global neurodevelopment, potentially supporting the educational intervention strategies. Considering that 69% of the children who were non-verbal acquired spoken language by the school age, the interventions should not only focus on the spoken language at the time of intervention, but also in the intention of communication. With that in mind, children at early communicative stages should be provided with augmentative and alternative communication interventions as early as possible, given the fact that there is moderate to strong evidence that augmentative and

alternative communication facilitates development of speech (Thunberg 2013). One example of this kind of intervention is the Picture Exchange Communication System (PECS) which has been linked to a positive effect on interaction and behaviour and increase in functional communication (Bondy and Frost 1994; Thunberg 2013). A combination of direct and indirect interventions, namely, the direct child-focused intervention to the child in a naturalistic context and also education and guidance to the parents, leads to better outcomes (Thunberg 2013).

In addition, given that the relative importance of nonverbal and verbal intelligence and global development depends on the outcome, the focus of treatments may also be adjusted dependent on developmental language progress.

Intervention expectations may also be adjusted, for lower functioning children with ASD, as many of them will not acquire spoken language (in our sample, 31.0% of the nonverbal children at preschool age did not acquire expressive language until school age). For the ones in this range of functioning that will have spoken language (69.0% of our sample which were nonverbal at preschool age acquired expressive language at school age) interventional gains can be expected but at a slower pace than in those with higher nonverbal intelligence.

The contribution of the current study lies in our assessment of language predictors in ASD population. This article may offer several key advantages over the previous literature by (1) using a large longitudinal sample of well characterized ASD children; (2) probing the trend of neurodevelopment profile from preschool to school age in ASD children; and (3) identifying early and exceptionally discriminative predictors of language acquisition until school age.

References

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th editio.). Arlington, US: American Psychiatric Publishing.

Anderson, D. K., Lord, C., Risi, S., DiLavore, P., Shulman, C., Thurm, A., et al. (2007). Patterns of growth in verbal abilities among children with autism spectrum disorder. *Journal of Consulting and Clinical Psychology*, *75*(4), 594–604. doi:10.1037/0022-006X.75.4.594

Associação Portuguesa de Paralisia Cerebral. (n.d.). *Instruções para aplicação das Escalas de Desenvolvimento de Ruth Griffiths, tradução e adaptação portuguesa (vol I e II)*. (A. P. de P. Cerebral, Ed.). Lisboa.

Bhat, S., Acharya, U. R., Adeli, H., Bairy, G. M., & Adeli, A. (2014). Autism: Cause factors, early diagnosis and therapies. *Reviews in the Neurosciences*, *25*(6), 841–850. doi:10.1515/revneuro-2014-0056

Billstedt, E., Carina Gillberg, I., & Gillberg, C. (2007). Autism in adults: Symptom patterns and early childhood predictors. Use of the DISCO in a community sample followed from childhood. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *48*(11), 1102–1110. doi:10.1111/j.1469-7610.2007.01774.x

Bondy, A. S., & Frost, L. A. (1994). The Picture Exchange Communication System. *Focus on Autism and Other Developmental Disabilities*, *9*(3), 1–19. doi:10.1177/108835769400900301

Carter, M. T., & Scherer, S. W. (2013). Autism spectrum disorder in the genetics clinic: A review. *Clinical Genetics*, *83*(5), 399–407. doi:10.1111/cge.12101

Centers for Disease Control and Prevention. (2009). Prevalence of autism spectrum disorders - Autism and Developmental Disabilities Monitoring Network, United States, 2006. *MMWR Surveill Summ*, *58*(10), 1–20. doi:ss5810a1 [pii]

Chakrabarti, S., & Fombonne, E. (2001). Pervasive Developmental Disorders in Preschool Children. *JAMA*, *285*(24), 3093–3099.

Chakrabarti, S., & Fombonne, E. (2005). Pervasive developmental disorders in preschool children: confirmation of high prevalence. *The American journal of psychiatry*, *162*(6), 1133–1141. doi:10.1176/appi.ajp.162.6.1133

Charman, T., Baron-Cohen, S., Swettenham, J., Baird, G., Drew, A., & Cox, A. (2003). Predicting language outcome in infants with autism and pervasive developmental disorder. *International journal of language & communication disorders / Royal College of Speech & Language Therapists*, *38*(3), 265–285. doi:10.1080/1368203100001048 30

Charman, T., Taylor, E., Drew, A., Cockerill, H., Brown, J. A., & Baird, G. (2005). Outcome at 7 years of children diagnosed with autism at age 2: Predictive validity of assessments conducted at 2 and 3 years of age and pattern of symptom change over time. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *46*(5), 500–513. doi:10.1111/j.1469-7610.2004.00377.x

Cirelli, I., Bickle Graz, M., & Tolsa, J. F. (2015). Comparison of Griffiths-II and Bayley-II tests for the developmental assessment of high-risk infants. *Infant Behavior and Development*, *41*, 17–25. doi:10.1016/j.infbeh.2015.06.004

Dunlap, W. P., Cortina, J. M., Vaslow, J. B., & Burke, M. J. (1996). Meta-analysis of

experiments with matched groups or repeated measures designs. *Psychological Methods*, *1*(2), 170–177. doi:10.1037/1082-989X.1.2.170

Ellis Weismer, S., & Kover, S. T. (2015). Preschool language variation, growth, and predictors in children on the autism spectrum. *Journal of Child Psychology and Psychiatry*, *12*, n/a-n/a. doi:10.1111/jcpp.12406

Ferreira, X., & Oliveira, G. (2016). Autism and Early Neurodevelopmental Milestones. *Acta Medica Portuguesa*, *29*(3), 168–175. doi:10.20344/amp.6790

Fombonne, E. (2003). Epidemiological surveys of autism and other pervasive developmental disorders: an update. *Journal of Autism and Developmental Disorders*, *33*(4), 365–382. doi: 10.1023/a:1025054610557

Gillberg, C., & Steffenburg, S. (1987). Outcome and prognostic factors in infantile autism and similar conditions: a population-based study of 46 cases followed through puberty. *J Autism Dev Disord*, *17*(2), 273–287. doi: 10.1007/bf01495061

Griffiths, R. (1984). *The Abilities of young children*. London: University of London press.

Howlin, P., Mawhood, L., & Rutter, M. (2000). Autism and Developmental Receptive Language Disorder—a Follow-up Comparison in Early Adult Life. II: Social, Behavioural, and Psychiatric Outcomes. *Journal of Child Psychology and Psychiatry*, *41*(5), 561–578. doi:10.1111/1469-7610.00643

Johnson, C. J., Beitchman, J. H., & Brownlie, E. B. (2010). Twenty-year follow-up of children with and without speech-language impairments: Family, educational, occupational, and quality of life outcomes. *American Journal of Speech-Language Pathology*, *19*(1), 51–65. doi:10.1044/1058-0360(2009/08-0083)

Kover, S. T., Edmunds, S. R., & Ellis Weismer, S. (2016). Brief Report: Ages of Language Milestones as Predictors of Developmental Trajectories in Young Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *46*(7), 2501–2507. doi:10.1007/s10803-016-2756-y

Le Couteur, A., Lord, C., & Rutter, M. (2003). *The Autism Diagnostic Interview-Revised (ADI-R). Los Angeles CA Western Psychological Services*. Western Psychological Services.

Lord, C., & Rutter, M. (1999). Autism diagnostic observation schedule-WPS (ADOS-WPS). *Los Angeles CA Western Psychological.*

Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., & Schopler, E. (1989). Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *J Autism Dev Disord*, *19*(2), 185–212. doi: 10.1007/bf02211841

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*, *24*(5), 659–685. doi: 10.1007/BF02172145

Luyster, R. J., Kadlec, M. B., Carter, A., & Tager-Flusberg, H. (2008). Language assessment and development in toddlers with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *38*(8), 1426–1438. doi:10.1007/s10803-007-0510-1

Muglia, P., Filosi, M., Da Ros, L., Kam-Thong, T., Nardocci, F., Trabetti, E., et al. (2018). The Italian autism network (ITAN): a resource for molecular genetics and biomarker investigations. *BMC psychiatry*, *18*(1), 369. doi:10.1186/s12888-018-1937-y

Mundy, P., Sigman, M., & Kasari, C. (1990). A longitudinal study of joint attention and

language development in autistic children. *Journal of autism and developmental disorders*, *20*(1), 115–128. doi:10.1007/bf02206861

Oliveira, G., Ataíde, A., Marques, C., Miguel, T. S., Coutinho, A. M., Mota-Vieira, L., et al. (2007). Epidemiology of autism spectrum disorder in Portugal: prevalence, clinical characterization, and medical conditions. *Developmental Medicine and Child Neurology*, *49*(10), 726–733. doi: 10.1111/j.1469-8749.2007.00726.x

Paul, R., Chawarska, K., Cicchetti, D., & Volkmar, F. (2008). Language outcomes of toddlers with autism spectrum disorders: A two year follow-up. *Autism Research*, *1*(2), 97–107. doi:10.1002/aur.12

Pickett, E., Pullara, O., O'Grady, J., & Gordon, B. (2009). Speech acquisition in older nonverbal individuals with autism: a review of features, methods, and prognosis. *Cognitive & Behavioral Neurology*, *22*(1), 1–21. doi:10.1097/WNN.0b013e318190d185

Sigman, M., & McGovern, C. W. (2005). Improvement in cognitive and language skills from preschool to adolescence in autism. *Journal of Autism and Developmental Disorders*, *35*(1), 15–23. doi:10.1007/s10803-004-1027-5

Sutera, S., Pandey, J., Esser, E. L., Rosenthal, M. A., Wilson, L. B., Barton, M., et al. (2007). Predictors of optimal outcome in toddlers diagnosed with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *37*(1), 98–107. doi:10.1007/s10803-006-0340-6

Szatmari, P., Bryson, S. E., Boyle, M. H., Streiner, D. L., & Duku, E. (2003). Predictors of outcome among high functioning children with autism and Asperger syndrome. *J Child Psychol Psychiatry*, *44*(4), 520–528. doi: 10.1111/1469-7610.00141

Tager-Flusberg, H., & Kasari, C. (2013). Minimally verbal school-aged children with autism spectrum disorder: The neglected end of the spectrum. *Autism Research*, *6*(6), 468–478. doi:10.1002/aur.1329

Thunberg, G. (2013). Early Communication Intervention for Children with Autism Spectrum Disorders. *Recent Advances in Autism Spectrum Disorders - Volume I*. doi:10.5772/54881

Thurm, A., Lord, C., Lee, L.-C., & Newschaffer, C. (2007). Predictors of Language Acquisition in Preschool Children with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *37*(9), 1721–1734. doi:10.1007/s10803-006-0300-1

Venter, A., Lord, C., & Schopler, E. (1992). A follow-up study of high-functioning autistic children. *J Child Psychol Psychiatry*, *33*(3), 489–507. doi: 10.1111/j.1469-7610.1992.tb00887.x

Wodka, E. L., Mathy, P., & Kalb, L. (2013). Predictors of Phrase and Fluent Speech in Children With Autism and Severe Language Delay. *Pediatrics*, *131*(4), e1128–e1134. doi:10.1542/peds.2012-2221

Yoder, P., Watson, L. R., & Lambert, W. (2015). Value-Added Predictors of Expressive and Receptive Language Growth in Initially Nonverbal Preschoolers with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *45*(5), 1254–1270. doi:10.1007/s10803-014-2286-4

2.4. Social attention deficits in children with autism spectrum disorder: task dependence of objects versus faces observation bias

This chapter consists in the paper: **Mouga S**, Castelhano, J, Café C, Sousa D, Duque F, Oliveira G & Castelo-Branco, M. Social attention deficits in children with autism spectrum disorder: task dependence of objects versus faces observation bias. *Frontiers in Psychiatry* (under revision)

Abstract

Social attention deficits represent a central impairment of patients suffering from autism spectrum disorder (ASD), but the nature of such patterns remains controversial.

We compared visual attention regarding social (faces) vs. non-social stimuli (objects), in an ecological diagnostic context, in 46 children and adolescents divided in two groups: ASD (N=23) and typical neurodevelopment (TD) (N=23), matched for chronological age and intellectual performance.

Our analyses revealed a three-way interaction between Group, Task and Social vs. Object Stimuli. We found a striking main effect of group and a task dependence of attentional allocation: while the TD attended first and longer to faces, ASD participants became similar to TD when they were asked to look at pictures, while telling a story. Our results suggest that social attention allocation is task dependent, raising the question whether spontaneous attention deficits can be rescued by guiding goal-directed actions.

Introduction

Autism spectrum disorder (ASD) is an early-onset neurodevelopmental disorder marked by the specificity of significant impairments in social interaction and communication, restricted interests, and the presence of repetitive and stereotyped behaviours (American Psychiatric Association, 2013). Social deficits in other domains include deviations in basic attentional processes; impairments in attention to faces or social stimuli across the lifespan, as well as attention during social exchanges, for a review see (Chita-Tegmark, 2016a, 2016b; Falck-Ytter et al., 2013; Guillon et al., 2014).

The ability to direct the attention to social stimuli is present and evident in typically developing children from early infancy (Gliga & Csibra, 2007; Goren et al., 1975; Vuilleumier, 2002). The attention to faces serves as a window into individuals' emotional and intentional states, providing critical information for social, cognitive, and communicative development and functioning (Feldman et al., 1999; Grelotti et al., 2002; Johnson, 2005; Schultz, 2005; Trevarthen & Aitken, 2001; Tronick, 1989). It has been hypothesized that deficits in social attention present in ASD, such as reduced attention to social stimuli as a whole or atypical allocation of attention to social stimuli is the cause of a compromised social functioning. Such deficits might lead to reduced social processing, loss of information necessary for the development of adaptive social functioning (Chevallier et al., 2012; Dawson et al., 2005) and

difficulties in the interpretation of emotional information (Pelphrey et al., 2002; Wagner et al., 2013).

Eye-tracking studies in ASD showed a correlation between reduced attention to social stimuli and behavioural measures (Bird et al., 2011; Chawarska et al., 2012; Klin et al., 2002; Shic et al., 2011). Klin and colleagues (Klin et al., 2002) showed, early on, that adolescents with ASD spent significantly less time attending to people when watching a segment of a movie and more time attending to the objects and the background of the scene. Deficits in social attention were thereafter replicated: i.) when looking at pictures of social scenes, participants with ASD spent less time attending to faces (Riby & Hancock, 2009); ii.) ASD children showed no difference in the time looking at people or objects, unlike in typical neurodevelopment (TD) (Wilson et al., 2010); iii.) ASD attended less to the activities of others and focused more on the background objects (Shic et al., 2011).

Atypical imbalance in the attention for social (e.g., videos of playing children) versus non-social stimuli (repeated geometrical patterns) in ASD was reported in a large-cohort study (Pierce et al., 2016). A meta-analysis on gaze patterns (Frazier et al., 2017) suggested the presence in ASD of a problem in selecting socially relevant versus irrelevant information.

Other studies, however, do not confirm this hypothesis. Kemner and colleagues (Kemner et al., 2007) found that the fixation times on face drawings embedded in an assortment of distractors of both children with ASD and TD were similar. Parish-Morris and colleagues (Parish-Morris et al., 2013) found that ASD and TD children and adolescents did not differ in the attention toward movies of faces as opposed to objects. In a study focused on magic, Kuhn and colleagues (Kuhn et al., 2010) found that ASD individuals were more susceptible to magic tricks, relying on sensitivity to social cues, than TD controls, contrary to their expectation. They found no between-group differences in fixation time on the magician's face and eyes. These studies suggest that the type of context and task may be relevant to disclose differences in social attentional allocation.

Several studies with infants suggest that innate or early-emerging attentional biases for faces or complex social scenes may be intact within the first months of life in infants who later develop ASD (Di Giorgio et al., 2016; Elsabbagh et al., 2013) in line with negative results from behavioural studies in early infancy (Macari et al., 2020).

Other important aspect to consider in the study of social attention with eye-tracking in ASD is the ecological and task relevance of the stimuli. Static stimuli have been associated to no group differences, which might indicate that they are not optimally sensitive. Adding to this information, it has been suggested that scenes depicting ecological social interactions are

the ones that evoke robust social responses (Chevallier et al., 2015; Falck-Ytter & von Hofsten, 2011; Saitovitch et al., 2013).

So far, no consensus has been reached on whether social attention is fundamentally reduced or absent in individuals with ASD. We hypothesize that the role of type of stimuli and task are critical. This may explain why a large number of studies showing significantly diminished attention to social information in ASD compared to TD controls (Kirchner et al., 2011; Klin et al., 2002; Riby et al., 2013; Riby & Hancock, 2009; Rice et al., 2012; Shi et al., 2015; Shic et al., 2011), while many others show no differences (Birmingham et al., 2011; M. Freeth et al., 2010; Megan Freeth et al., 2011; Kemner et al., 2007; Kuhn et al., 2010; Marsh et al., 2014; Parish-Morris et al., 2013; Van Der Geest et al., 2002). Given this discrepancy, it is important to understand whether the putative social attention deficits are task and stimuli dependent.

We previously showed that task and context is determinant for perceptual performance in ASD (Bernardino et al., 2012). The same might hold for the attentional bias that characterizes this population. In this study, we extended this prior work by comparing attention allocation to social vs. non-social stimuli in three tasks in ASD and TD children and adolescents. We used a paradigm based on stimuli from the Autism Diagnostic Observation Schedule (ADOS) (Lord & Rutter, 1999), a diagnostic tool that we used as a routine in the diagnostic procedure, to try to see if it can discriminate between ASD and TD children in what concerns to visual social attention and corroborate the attentional bias claim. We hypothesized that ASD children differ from TD children in which concerns visual attention to social stimuli and, in particular, demonstrate less looking towards faces than TD children.

Methods

Participants

The study comprised two groups of participants: the experimental, composed by individuals with ASD without intellectual disability (American Psychiatric Association, 2013); and the control, composed by TD individuals TD. A total of 46 children and adolescents were enrolled in the study, 23 for the ASD group (22 Male, 1 Female; mean age=13 years and 1 month) and 23 for the control group (21 Male, 2 Female; mean age=13 years and 5 months). Sample sizes were based on previously established effect sizes from other studies using eye-tracking (Riby & Hancock, 2009). Groups were matched by chronological age, gender, and performance

intelligence quotient (PIQ) (Jarrold & Brock, 2004). Further groups characterization details can be found in Table 2.4.1.

Table 2.4.1. Characterization of the clinical and control groups

	ASD	TD	
	Mean (SE)	**Mean (SE)**	
N	23	23	
Gender (M/F)	22/1	21/2	p>.05
CA (months)	156.8 (4.9)	160.5 (6.4)	p>.05
FSIQ	99.2 (3.0)	124.8 (4.1)	
VIQ	96.3 (2.7)	123.9 (4.1)	
PIQ	104.0 (3.2)	112.1 (3.6)	p>.05
ADI-R RSI	15.7 (1.1)	-	
ADI-R L/C	9.4 (0.8)	-	
ADI-R RB/I	5.1 (0.6)	-	
ADOS COM	4.6 (0.3)	-	
ADOS SI	8.0 (0.5)	-	
ADOS Total	12.6 (0.7)	-	

NOTE. ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group; SE= Standard Error of the mean; M = Male; F= Female; CA = Chronological Age; FSIQ = Full-scale intelligence quotient (IQ); VIQ = Verbal IQ; PIQ = Performance IQ; ADI-R RSI = Autism Diagnostic Interview – Revised (ADI-R) Reciprocal Social Interactions; ADI-R L/C = ADI-R Language/Communication; ADI-R RB/I = ADI-R Repetitive Behaviours/Interests; ADOS COM = Autism Diagnostic Observation Schedule (ADOS) Communication; ADOS SI = ADOS Social Interaction. *T*-tests; p>.05.

ASD participants were recruited from a sample from the Neurodevelopmental and Autism Unit, Child Developmental Centre, Paediatric Hospital, Centro Hospitalar e Universitário de Coimbra, Portugal. ASD diagnosis was assigned on the basis of the gold standard instruments: parental or caregiver interview - Autism Diagnostic Interview– Revised, ADI-R (Le Couteur et al., 2003), direct structured proband assessment - ADOS (Lord & Rutter, 1999), and clinical examination performed by an experienced neurodevelopmental Paediatrician, based on the current diagnostic criteria for autism spectrum disorder from the Diagnostic and Statistical Manual of Mental Disorders 5, DSM-5 (American Psychiatric Association, 2013). All ASD patients had positive results in the ADI-R and ADOS for autism or ASD and met the criteria for ASD from the DSM-5. A comprehensive medical observation excluded associated medical condition such as epilepsy, neurocutaneous or other genetic syndromes, or other usual comorbidities in ASD samples.

The exclusion criteria for the children who participated in this study were evaluated through an extensive anamnesis carried out with the parents or caregivers. They included neurological, neurodevelopmental, and genetic diseases, brain lesions, sensory, auditory, motor deficits, and neurodevelopmental milestones. Additionally, the parents of TD participants completed the Social Communication Questionnaire and Social Responsiveness Scale to ensure the exclusion of ASD symptomatology.

Both groups underwent an exhaustive neuropsychological evaluation and an assessment of the intelligence quotient (IQ) to exclude intellectual disabilities (all participants had a Full-Scale IQ – FSIQ>70). To be included in this study, participants also had to be able to read, describe pictures and also remain still during the task. This increased the age of the participants able to be included, despite the efforts to recruit younger subjects.

Apparatus

Eye movements were measured with a remote binocular eye tracking (SMI RED) system (SMI-SensoMotoric Instruments, Germany), with a sampling rate of 250 Hz. The tracker has a reported gaze position accuracy of 0.4° and a spatial resolution of 0.05. The participants sat approximately between 60 and 70 cm away from a 22-inch flat-screen with a resolution of 1680 × 1050 pixels. The system compensates for head movements within a 50 cm × 30 cm (at 65 cm distance), allowing the participants to look at the screen in a naturalistic manner. A 9-point calibration procedure with a fixation cross was performed before each task. The children were instructed to fixate on the cross. After the calibration, there was a validation trial to ensure the precision of the data collection. The calibration process was repeated when necessary until both eyes achieved good mapping on all nine test positions (tracking error smaller than 1° visual angle).

Visual Stimuli and Task

The experimental protocol was created and implemented through SensoMotoric Instruments Experiment Center Version 3.2 (SMI - SensoMotoric Instruments, Germany). It was composed of three types of tasks, which integrated visual stimuli adapted from the ADOS (Lord & Rutter, 1999). The ADOS is a semi-structured, examiner's dependent, tool to assess communication, social interaction, and imagination. It allows to diagnose ASD across ages, neurodevelopmental levels, and language skills. The tasks from ADOS adapted were: "Description of a Picture", "Cartoons" and "Telling a Story from a Book". In the

"Description of a Picture" task, the participant was asked to look at a scene and tell what she/he sees. In the "Cartoons" and "Telling a story from a Book" tasks, they are asked to tell a story from the images that are presented one at a time as if they were really defoliating a book. Therefore, they were instructed to tell the researcher when they want to move to the following page. In total, they were 25 visual stimuli, representing social scenes, displayed on a screen (Figure 2.4.1).

Figure 2.4.1. RED eye-tracking system (SMI - SensoMotoric Instruments, Germany) with the image from task "Description of a Picture".

Participants were allowed to move forward to the next stimulus as soon as they had described what they were seeing and told the experimenter they wanted to move to the next picture. This choice was made instead of using a button to prevent subjects' fatigue, or boredom, and a subsequent attention decrease that may lead to just pressing the button without the description. To increase subjects' attention, involvement, and motivation, and to assure the exploration of the image begins at the same point, between each image a fixation cross was always presented. This fixation cross disappeared once the participant's gaze was detected to be within the embedded Area of interest (AOI) in it. Figure 2.4.2 illustrates the experimental procedure. There was no time constraint in each picture.

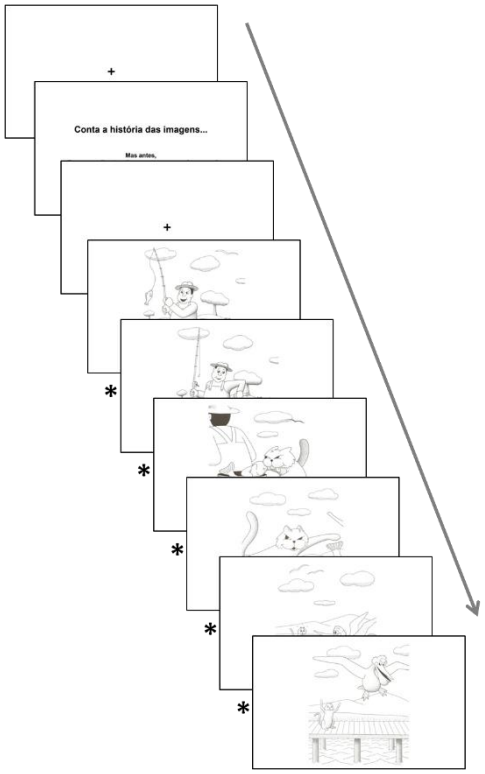

Figure 2.4.2. Acquisition protocol of the task "Cartoons". *Between each image is always presented a fixation cross to ensure that the exploration of the image begins at the same point.

Eye Tracking Recordings and Analysis

Eye movement data were recorded with iViewX™ 2.7 and analysed offline with BeGaze™ 3.7 software where different AOI's where defined in a semi-automatic procedure: "faces" and "objects"(Figure 2.4.3).

We considered the following gaze metrics: Entry Time (ET); Dwell Time Percentage (DT%); Net dwell time Percentage (NDT%); Normalized Dwell (ms/coverage) (NormD); First Fixation Duration (FFD); Fixation Time Percentage (FT%); Average Fixation Duration (AFD); Revisits.

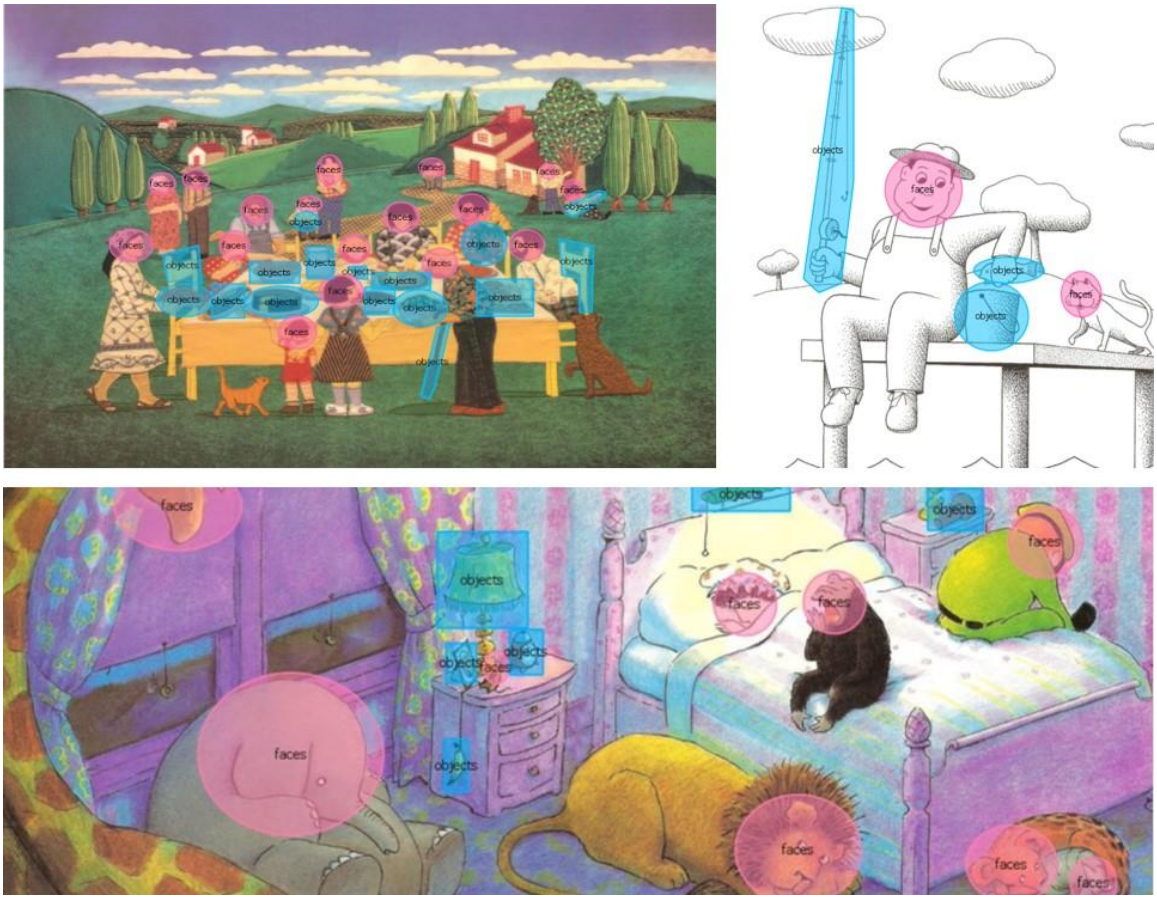

Figure 2.4.3. Example of the different areas of interest defined.

ET expresses the average interval in milliseconds (ms) from the presentation of the visual stimuli (start of the trial) to the first gaze fixation on each AOI. The DT% consists in the total duration of time (in ms) of all fixations and saccades within an AOI for all subjects, divided by the number of subjects, multiplied by 100 and divided by the difference between the current time and the start time of the trial. NDT% represents the % of the sum of durations of all fixations and saccades that hit the AOI, thus incorporating total time spent within the AOI, multiplied by 100 and divided by the difference between current time and start time of the trial. NormD (ms/coverage): is the ratio between the DT and the AOI coverage, where coverage is the AOI size (measured in pixel) in comparison to stimulus size, thus representing a percentage of the number of pixel (px). It represents a more reliable measure to understand attention distribution patterns since it adjusts the duration that a subject spent to process an item relative to its surface in the display. FFD represents the duration (in ms) of the first fixation to hit the AOI. FT% consists in the sum of the fixation durations inside the AOI multiplied by 100 and divided by the difference between current time and start time of the trial. AFD is the total duration (ms) of all fixations divided by the

number of fixations inside the AOI. A longer fixation duration is often associated with a deeper and more effortful cognitive processing. Revisits represent the number of time subjects visit an AOI.

Data analysis and statistics

Initially we conducted a descriptive statistics analysis in order to characterize the sample.

Eye-position data were analysed with a standard AOI approach. Eye tracking data were pre-processed using the SMI software - BeGaze Version 3.7 (SMI-SensoMotoric Instruments, Germany), which uses a dispersion-based algorithm for detecting fixations. The minimum fixation duration was 80 ms and the maximum dispersion value 100 pixels. Different aspects of eye movements were assessed. We included seven dependent variables in our eye-tracking analysis: ET; NDT%; NormD (ms/coverage); FFD; FT%; AFD; Revisits.

One participant in the TD group was excluded from analysis due to problems with eye-tracking data collection in tasks Picture and Book. In total, there were, therefore, valid data for 23 ASD and 22 TD participants in the Picture and Book Tasks and for 23 ASD and 23 TD participants in the Cartoons Task.

Multivariate analysis of variance (MANOVA) with a three-way interaction was used to evaluate differences in the eye-tracking measures by group, task, and AOI type (faces or objects). The goal of the three-way MANOVA was to understand if there was an interaction effect for group, AOI type and task in the eye-tracking measures. Follow up univariate three-way ANOVAs were run for each dependent variable. In the dependent variables with statistically significant interaction effects, simple two-way interactions and main effect of group were run. In the statistically significant main effect of group, pairwise comparisons were run with a Bonferroni adjustment applied. Effect sizes (partial η^2 for F statistics and Cohen's *d* for Bonferroni) are reported with *p*-values for significant main effects, interactions and pairwise comparisons.

All statistical analysis was completed with the support of the version for Microsoft Windows® of the Statistical Package for Social Sciences, version 26 (SPSS ®, Chicago, IL, USA). A significance level of 0.05 was adopted.

Ethics Statement

All the procedures in this study were reviewed and approved by the ethics committees from Faculty of Medicine from University of Coimbra, Portugal (CE-11/2013) and the Centro

Hospitalar e Universitário de Coimbra, Portugal (CHUC-102-13) and was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the parents/guardians of all participants or, when appropriate, the participants themselves. Children and adolescents also gave oral informed consent.

Results

Initial analysis was conducted to ensure that participants were matched with respect to chronological age, gender, handedness and PIQ in both groups (*t*-test, p>.05).

A three-way MANOVA was run with seven eye-tracking measures (ET, NDT%, NormD, FFD, FT%, AFD and Revisits) as dependent variables and independent variables: Group (ASD and TD), Task (Picture, Cartoons and Book) and AOI (faces and objects). There was a statistically significant three-way interaction between Group, Task and AOI in all our dependent variables together, Pillai's Trace = .092; $F(2, 260) = 1.764$, $p = .041$, partial $\eta^2 = .046$.

Follow up univariate three-way ANOVAs were run, for each dependent variable. These showed a statistically significant three-way interaction effect between group, task and AOI for ET ($F(2, 260) = 4.763$, $p = .009$, partial $\eta^2 = .035$), NormD ($F(2, 260) = 4.805$, $p = .009$, partial $\eta^2 = .036$), NDT% ($F(2, 260) = 4.693$, $p = .010$, partial $\eta^2 = .035$) and FT% , ($F(2, 260) = 3.81$, $p = .023$, partial $\eta^2 = .029$), but not for FFD, ($F(2, 260) = 0.59$, $p = .556$, partial $\eta^2 = .005$), Revisits ($F(2, 260) = 1.77$, $p = .172$, partial $\eta^2 = .013$) and AFD ($F(2, 260) = 0.28$, $p = .756$, partial $\eta^2 = .002$). The interaction effects of Group, Task and AOI in ET; NormD; and FT% are illustrated in Figures 2.4.4, 2.4.5, 2.4.6 and 2.4.7.

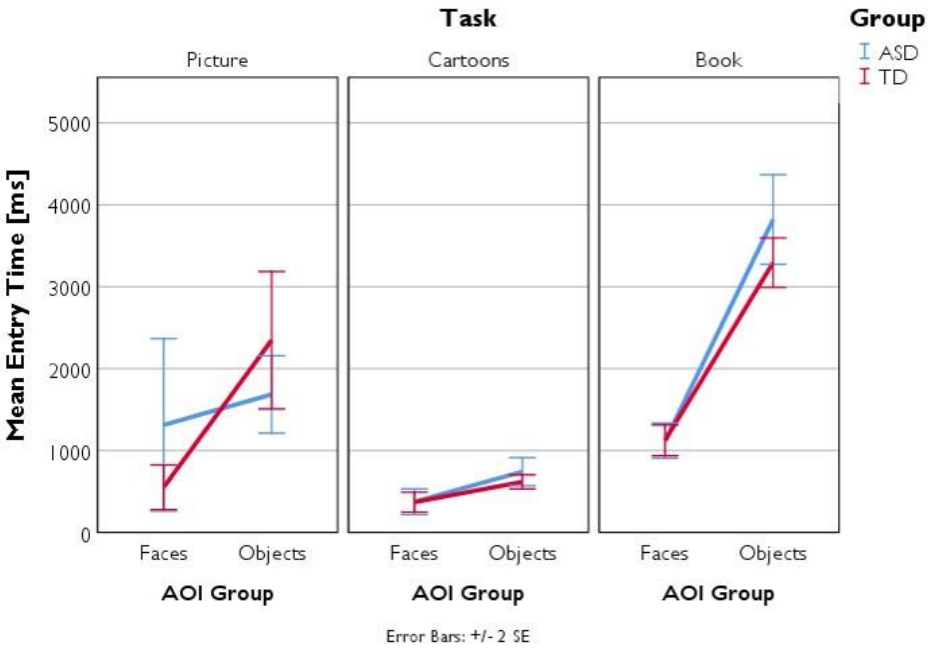

Figure 2.4.4. Interaction effects between group, task, and type of AOI. Mean Entry Time [ms]: interaction plot Group x Task x AOI. Mean Entry Time is shown for the AOI group Faces and Objects, plotted by Group (ASD and TD) in the three tasks. Lower numbers indicate the first AOI to have the first gaze fixation. NOTE. ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group; AOI = Area of Interest; SE= Standard Error

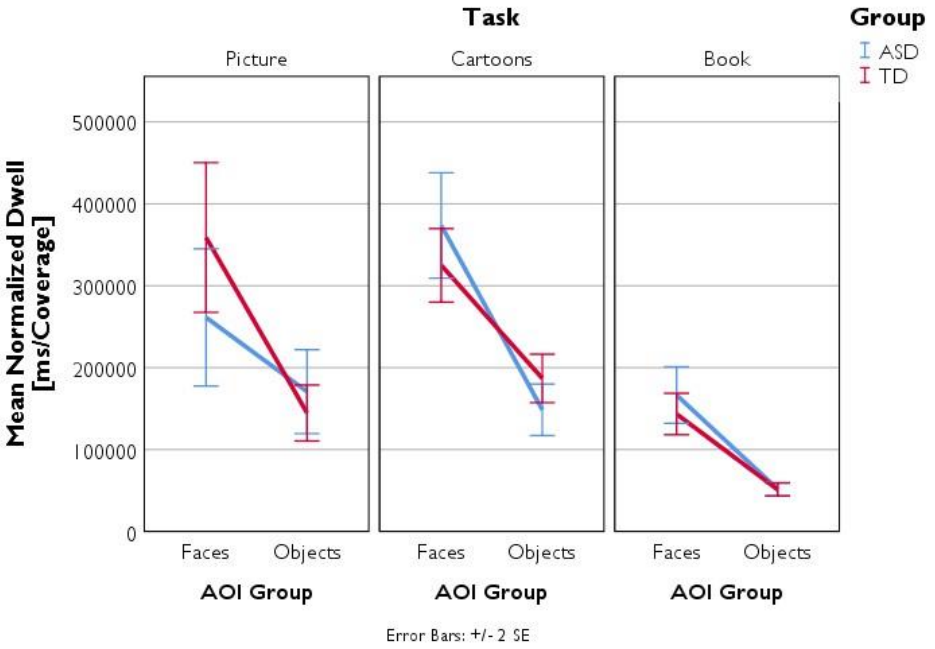

Figure 2.4.5. Interaction effects between group, task, and type of AOI. Mean Normalized Dwell [ms/Coverage]: interaction plot Group x Task x AOI. Mean Normalized Dwell is shown for the AOI group Faces and Objects, plotted by Group (ASD and TD) in the three tasks. Higher numbers indicate more time spent within the AOI, normalized by the AOI size in comparison to stimulus size, thus more time the subject spent to process the stimuli. NOTE. ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group; AOI = Area of Interest; SE= Standard Error

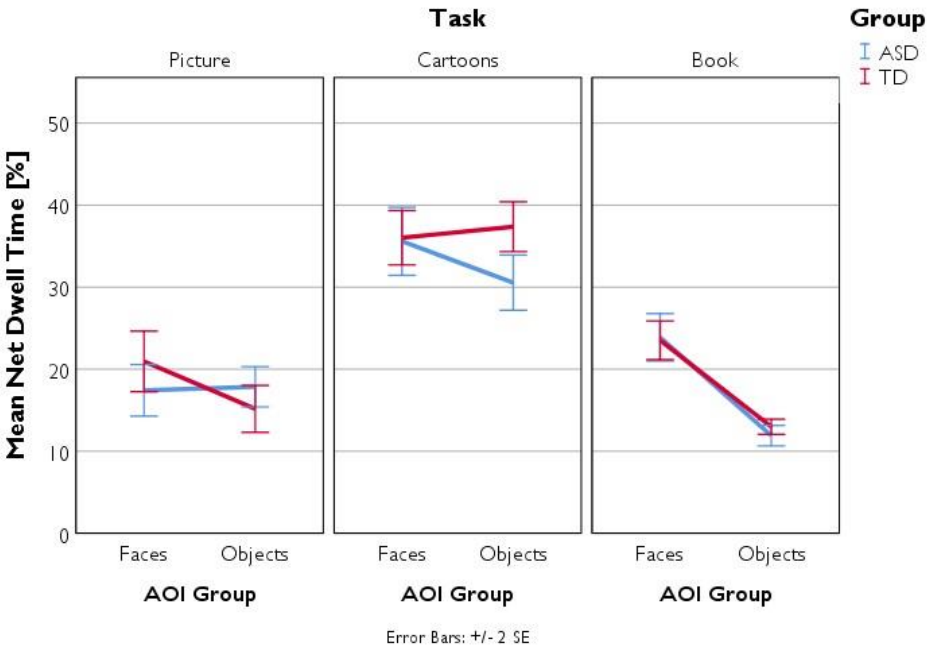

Figure 2.4.6. Interaction effects between group, task, and type of AOI. Mean Net Dwell Time [%]: interaction plot Group x Task x AOI. Mean Net Dwell Time [%] is shown for the AOI group Faces and Objects, plotted by Group (ASD and TD) in the three tasks. Higher numbers indicate more time spent within the AOI. **NOTE.** ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group; AOI = Area of Interest; SE= Standard Error

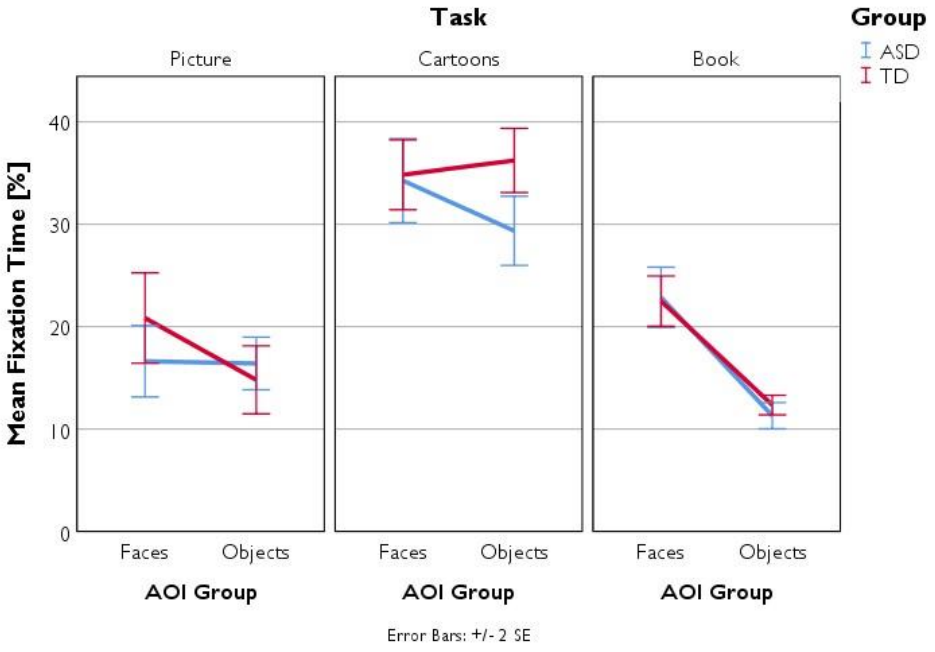

Figure 2.4.7. Interaction effects between group, task, and type of AOI. Mean Fixation Time [%]: interaction plot Group x Task x AOI. Mean Fixation Time is shown for the AOI group Faces and Objects, plotted by Group (ASD and TD) in the three tasks. Higher numbers indicate more time spent within the AOI. **NOTE.** ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group; AOI = Area of Interest; SE= Standard Error

Figures 2.4.4, 2.4.5, 2.4.6 and 2.4.7 present the interaction between Task and AOI at the different groups: ASD and TD. According to Figures 2.4.4, 2.4.5, 2.4.6 and 2.4.7, this interaction effect indicates that the relationship between task and AOI depends on the group.

For the dependent variables with the statistically significant three-way interaction effect between group, task and AOI, we now present the simple two-way interactions, main effect of group and pairwise comparisons, where needed, separately. Pairwise comparisons are summarized in Table 2.4.2.

Entry time

Follow up univariate two-way ANOVAs were run for the dependent variable ET and the main effect of group considered. These showed a statistically significant simple two-way interaction between Group and AOI in the dependent variable ET, for the Picture task $F(2, 260) = 9.08$, $p = .003$, partial $\eta^2 = .034$), but not for the Cartoons ($F(2, 260) = .07$, $p = .799$, partial $\eta^2 = .034$) and Book ($F(2, 260) = 1.27$, $p = .262$, partial $\eta^2 = .005$) Tasks. As such, a simple main effect analysis was conducted for Picture Task, and we found a statistically significant main effect of Group in the dependent variable ET, for the AOI Faces $F(2, 260) = 5.194$, $p = .023$, partial $\eta^2 = .020$ and for the AOI Objects $F(2, 260) = 3.93$, $p = .049$, partial $\eta^2 = .015$, in the Picture Task. Therefore, simple pairwise comparisons were run for the differences in mean ET score in the AOI Faces and AOI Objects between groups in the Picture Task, with a Bonferroni adjustment applied. In the Picture Task, in the AOI Faces, the mean ET in the ASD group was 1313.08 (*Standard Deviation [SD]* = 2526.63) and 551.51 (*SD* = 637.78) in the TD group, a statistically significant mean difference of 761.56, 95% CI [103.55, 1419.57], $p = .023$, $d = -.41$. In the same task, in the AOI Objects, the mean ET in the ASD group was 1685.34 (*SD* = 1134.27) and 2347.37 (*SD* = 1967.34) in the TD group, a statistically significant mean difference of -662.038, 95% CI [-1320.05, -4.03], $p = .049$, $d = .41$.

Table 2.4.2. The comparison of the Mean±SD of the Eye-tracking measures between ASD (n=23) and TD (n=23). Pairwise comparisons with a Bonferroni adjustment: significance levels and effect-sizes.

			ASD	TD	*Statistics*	
Eye-tracking measures	**Task**	**AOI**	**Mean ±SD**	**Mean ±SD**	***p***	***d***
Entry time	Picture	Faces	1313.07±2526.63	551.51±637.78	.023*	-.413
		Objects	1685.33±1134.27	2347.37±1967.34	.049*	.412
	Cartoons	Faces	375.59±375.76	370.32±291.46	.987	-.016
		Objects	742.39±410.65	617.82±207.70	.706	-.383
	Book	Faces	1120.47±514.29	1124.77±439.73	.99	.009
		Objects	3821.01±1311.36	3293.79±708.56	.116	-.497
Normalized Dwell	Picture	Faces	261306.23±200946.10	358870.71±214344.38	.006*	.47
		Objects	170705.95±122808.11	144670.91±79944.23	.457	-.251
	Cartoons	Faces	373543.36±154277.07	324851.21±107742.37	.160	-.366
		Objects	148538.82±75339.15	186859.44±70924.83	.269	.524
	Book	Faces	166567.76±82569.63	143424.55±59218.12	.509	-.321
		Objects	51705.32±19204.18	51205.75±18307.33	.989	-.027
Net Dwell Time	Picture	Faces	17.42±7.55	20.95±8.66	.091	8.66
		Objects	17.86±5.90	15.16±6.70	.197	-.428
	Cartoons	Faces	35.59±9.93	36.03±7.95	.832	.049
		Objects	30.55±8.06	37.37±7.28	.001*	.888
	Book	Faces	23.89±6.93	23.53±5.54	.861	-.057
		Objects	11.90±3.00	12.98±2.17	.605	.411
Fixation Time	Picture	Faces	16.62±8.36	20.84±10.35	.057	.449
		Objects	16.41±6.16	14.80±7.78	.469	-.229
	Cartoons	Faces	34.26±9.85	34.84±8.18	.792	.064
		Objects	29.36±8.09	36.24±7.52	.002*	.881
	Book	Faces	22.87±7.07	22.50±5.75	.867	-.057
		Objects	11.30±3.06	12.35±2.25	.636	.390

NOTE. Pairwise comparisons with a Bonferroni adjustment; * $p<.05$. All comparisons signalled with * are significant. Effect sizes were computed using Cohen's *d*; ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group; SD = Standard Deviation

Normalized Dwell

Follow up univariate two-way ANOVAs were run for the dependent variable NormD and the main effect of group considered. These showed a statistically significant simple two-way interaction between Group and AOI in the dependent variable NormD, for the Picture task $F(2, 260) = 6.25$, $p = .013$, partial $\eta^2 = .023$), but not for the Cartoons ($F(2, 260) = 3.17$, $p = .076$, partial $\eta^2 = .012$) and Book ($F(2, 260) = 0.21$, $p = .647$, partial $\eta^2 = .001$) Tasks. Afterwards, a simple main effect analysis was conducted for Picture Task, and we found a statistically significant main effect of Group in the dependent variable NormD, for the AOI Faces $F(2, 260) = 7.79$, $p = .006$, partial $\eta^2 = .029$. As such, simple pairwise comparisons were run for the differences in mean NormD score in the AOI Faces between groups in the Picture Task, with a Bonferroni adjustment applied. In the AOI faces in the Picture Task, the mean NormD in the ASD group was 261306.24 (SD = 200946.01) and 358870.71 (SD = 214344.38) in the TD group, a statistically significant mean difference of -97564.48, 95% CI [-166398.89, -28730.07], $p = .006$, $d = .47$.

Net Dwell Time

Follow up univariate two-way ANOVAs were run for the dependent variable NDT% and the main effect of group considered. These showed a statistically significant simple two-way interaction between Group and AOI in the dependent variable NDT, for the task Picture $F(2, 260) = 4.46$, $p = .036$, partial $\eta^2 = .017$ and for the task Cartoons $F(2, 260) = 4.80$, $p = .029$, partial $\eta^2 = .018$, but not for the Book ($F(2, 260) = 0.24$, $p = .625$, partial $\eta^2 = .001$) Tasks. As such, a simple main effect analysis was conducted for Picture and Cartoon Tasks, and we found a statistically significant main effect of Group in the dependent variable NDT, for the AOI Objects in the Cartoons Task $F(2, 260) = 10.97$, $p = .001$, partial $\eta^2 = .040$. Therefore, simple pairwise comparisons were run for the differences in mean NDT% score in the AOI Faces between groups in the Cartoons Task, with a Bonferroni adjustment applied. In the AOI objects in the Cartoons Task, the mean NDT in the ASD group was 30.55 (SD = 8.06) and 37.37 (SD = 7.28) in the TD group, a statistically significant mean difference of –6.82, 95% CI [-10.88, -2.77], $p = .001$, $d = .89$.

Fixation Time

Follow up univariate two-way ANOVAs were run for the dependent variable FT% and the main effect of group considered. These showed a statistically significant simple two-way

interaction between Group and AOI in the dependent variable FT%, for the task Cartoons $F(2, 260) = 4.15$, $p = .043$, partial $\eta^2 = .016$). Afterwards, a simple main effect analysis was conducted for Cartoon Task, and we found a statistically significant main effect of Group in the dependent variable FT%, for the AOI Objects in the Cartoons Task $F(2, 260) = 9.89$, $p = .002$, partial $\eta^2 = .037$. As such, simple pairwise comparisons were run for the differences in mean FT% score in the AOI Objects between groups in the Cartoon Task, with a Bonferroni adjustment applied. In the AOI objects in the Cartoons Task, the mean FT in the ASD group was 29.36 ($SD = 8.09$) and 36.24 ($SD = 7.52$) in the TD group, a statistically significant mean difference of -6.88, 95% CI [-11.18, -2.57], $p = .002$, $d = .88$.

Discussion

We studied social attention deficits in ASD, and in particular in which concerns focus on face stimuli, in the clinical context of different tasks of ADOS. For that purpose, we used eye-tracking methodology to compare the task dependence of visual attention to social stimuli (faces) *vs.* non-social stimuli (objects) in two matched groups of children and adolescents with ASD or TD.

We found significant interaction effects (between group, task, and type of AOI), when the participants are requested to perform spontaneous and simple descriptions of a picture or even a set of cartoons. When scenarios implied generating a goal-oriented narrative in the task, the pattern of attentional allocation in ASD subjects was normalized. In other words, it became similar to controls when children have to create a more complex story, such as the story of a book. The absence of interaction effects in that case corroborates similar visual search patterns in TD children. The "Description of a Picture task", despite being a painting and not a real picture, is the one depicting a more ecological social interaction: a table surrounded by people interacting while having a lunch party, playing guitar, talking to each other, which can also explain why it has the ability to better differentiate between ASD and TD. Our findings thereby provide a framework that reconciles previous literature. Scenes depicting ecological social interactions have been associated to better evoke robust social responses (Falck-Ytter & von Hofsten, 2011; Saitovitch et al., 2013).

As predicted, we found that TD children looked first to faces and during a longer period of time in the socially rich and familiar context of a gathering of people around a table ("Description of a Picture task"). The ASD children did not show a differential pattern,

between faces and objects. In other words, under these conditions interaction effects are triggered: the ASD group tends to have a similar pattern of visual search in what concerns to attention to social and non-social stimuli, that is, faces and objects, while the TD group looks first at faces and for a longer period of time, which corroborates the hypothesis that ASD participants are less attentive to faces (Kirchner et al., 2011; Klin et al., 2002; Riby et al., 2013; Riby & Hancock, 2009; Rice et al., 2012; Shi et al., 2015; Shic et al., 2011).

On the other hand, our study corroborates that children and adolescents with and without ASD show remarkably similar visual search patterns in their initial eye gaze to faces (Schauder et al., 2019). However, in our study participants are not instructed to specifically look at faces, which adds meaning and ecological importance to the result. In fact, the participants only had to describe what they were seeing and therefore, the visual search pattern is natural and more spontaneous.

Overall, our results seem to provide a unifying view of previous research. The TD group always looks at the faces first, when exploring visually the images, also spending more time looking at social stimuli. This visual search pattern is absent in the ASD group. In fact, although children with ASD look at the faces first (lower ET in the AOI faces, than in the AOI objects), there is no differential pattern in the Cartoon and Book tasks (the ones that guide a goal oriented narrative), when compared with TD.

Taken together, our results point to the fact that social attention allocation patterns in ASD population are strongly task dependent, which extends our previous work in other cognitive domains (Bernardino et al., 2012). Accordingly, the task not requiring an explicit goal-oriented narrative yields the greatest differences. This raises the question whether spontaneous attention deficits can be rescued by guiding goal-directed actions (Birmingham et al., 2011). These results are relevant for the selection of interventional strategies and in ASD children, since it stresses the importance of goal-oriented actions, which are the foundations of the structured teaching.

ASD and TD groups analyse social and non-social content differently. However, when they have to do a narrative, visual behaviour tends to normalize (that is, ASD has similar visual patterns as TD), which suggests that the narrative is used as guidance.

Entry time is an eye-tracking measure that characterize fast events, and in this measure, there are differences between ASD and TD, which can be interpreted as the best measures to distinguish the groups.

In the present study, there are some limitations to consider. Inclusion of younger children and subjects with intellectual disability was difficult because most of them were not able to make a good calibration and were therefore excluded.

In the current analysis, we focused on attention to the faces and objects in the pictures from the different tasks of ADOS (a well validated but examiner's dependent diagnosis tool for ASD) thereby trying to provide a complementary quantitative information of potential value in clinical practice to distinguish between ASD children without intellectual disability and TD. Though precise, the sensitivity of eye-tracking as a diagnostic tool remains uncertain. Here we provide evidence for task dependence, with patterns "normalizing" when a narrative is required. With this strategy, we hope to provide a tool that may help improve the course of ASD diagnostic evaluation, especially in subjects with ASD without intellectual disability, where the differential diagnosis with a typical neurodevelopment is often very difficult.

In conclusion, eye-tracking measures of visual scanning, while exploring and describing activities from the ADOS, in particular, "Description of a Picture", can discriminate between ASD and TD groups. Individuals with ASD allocated their attention to faces and objects in a similar way, while individuals from the TD group attend first and more time to faces. However, when ASD children are asked to look at pictures, organize the thought and tell a story, they attend to the same stimuli and have a similar pattern of visual search as the TD group, which raises interesting insights on the origin of this "normalization". Accordingly, when goal-directed actions are required, visual search patterns in ASD tend to resemble TD and therefore "normalize" as compared to spontaneous attention. These findings are of potential relevance to training strategies, by providing clues on learning adaptive attentional deployment. Also, they stress the importance from a diagnostic perspective point of view of observation and classification of spontaneous behaviour. Future work should confirm the value of this tool to help differential diagnosis especially in difficult cases with other neurodevelopmental disorders or typical development.

References

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). American Psychiatric Publishing.

Bernardino, I., Mouga, S., Almeida, J., van Asselen, M., Oliveira, G., & Castelo-Branco, M. (2012). A direct comparison of local-global integration in autism and other developmental disorders: Implications for the central coherence hypothesis. *PLoS ONE*, *7*(6). https://doi.org/10.1371/journal.pone.0039351

Bird, G., Press, C., & Richardson, D. C. (2011). The role of alexithymia in reduced eye-fixation in autism spectrum conditions. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-011-1183-3

Birmingham, E., Cerf, M., & Adolphs, R. (2011). Comparing social attention in autism and amygdala lesions: Effects of stimulus and task condition. *Social Neuroscience*, *6*(5–6), 420–435. https://doi.org/10.1080/17470919.2011.561547

Chawarska, K., MacAri, S., & Shic, F. (2012). Context modulates attention to social scenes in toddlers with autism. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *53*(8), 903–913. https://doi.org/10.1111/j.1469-7610.2012.02538.x

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2012.02.007

Chevallier, C., Parish-Morris, J., Mcvey, A., Rump, K. M., Sasson, N. J., Herrington, J. D., & Schultz, R. T. (2015). Measuring social attention and motivation in autism spectrum disorder using eye-tracking: Stimulus type matters. *Autism Research*, *8*(5), 620–628. https://doi.org/10.1002/aur.1479

Chita-Tegmark, M. (2016a). Social attention in ASD: A review and meta-analysis of eye-tracking studies. *Research in Developmental Disabilities*, *48*, 79–93. https://doi.org/10.1016/j.ridd.2015.10.011

Chita-Tegmark, M. (2016b). Attention Allocation in ASD: a Review and Meta-analysis of Eye-Tracking Studies. *Review Journal of Autism and Developmental Disorders*, *3*(3), 209–223. https://doi.org/10.1007/s40489-016-0077-x

Dawson, G., Webb, S. J., & McPartland, J. (2005). Understanding the nature of face processing impairment in autism: Insights from behavioral and electrophysiological studies. In *Developmental Neuropsychology*. https://doi.org/10.1207/s15326942dn2703_6

Di Giorgio, E., Frasnelli, E., Rosa Salva, O., Maria Luisa, S., Puopolo, M., Tosoni, D., Simion, F., Vallortigara, G., Apicella, F., Gagliano, A., Guzzetta, A., Molteni, M., Persico, A., Pioggia, G., Valeri, G., & Vicari, S. (2016). Difference in Visual Social Predispositions between Newborns at Low-and High-risk for Autism. *Scientific Reports*. https://doi.org/10.1038/srep26395

Elsabbagh, M., Gliga, T., Pickles, A., Hudry, K., Charman, T., & Johnson, M. H. (2013). The development of face orienting mechanisms in infants at-risk for autism. *Behavioural Brain Research*. https://doi.org/10.1016/j.bbr.2012.07.030

Falck-Ytter, T., Bölte, S., & Gredebäck, G. (2013). Eye tracking in early autism research. *Journal of Neurodevelopmental Disorders*, *5*(1), 28. https://doi.org/10.1186/1866-1955-5-28

Falck-Ytter, T., & von Hofsten, C. (2011). How special is social looking in ASD. A review. In

Progress in Brain Research (1st ed., Vol. 189). Elsevier B.V. https://doi.org/10.1016/B978-0-444-53884-0.00026-9

Feldman, R., Greenbaum, C. W., & Yirmiya, N. (1999). Mother-infant affect synchrony as an antecedent of the emergence of self-control. *Developmental Psychology*. https://doi.org/10.1037/0012-1649.35.1.223

Frazier, T. W., Strauss, M., Klingemier, E. W., Zetzer, E. E., Hardan, A. Y., Eng, C., & Youngstrom, E. A. (2017). A Meta-Analysis of Gaze Differences to Social and Nonsocial Information Between Individuals With and Without Autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(7), 546–555. https://doi.org/10.1016/j.jaac.2017.05.005

Freeth, M., Ropar, D., Chapman, P., & Mitchell, P. (2010). The eye gaze direction of an observed person can bias perception, memory, and attention in adolescents with and without autism spectrum disorder. *Journal of Experimental Child Psychology*. https://doi.org/10.1016/j.jecp.2009.10.001

Freeth, Megan, Ropar, D., Mitchell, P., Chapman, P., & Loher, S. (2011). Brief report: How adolescents with ASD process social information in complex scenes. Combining evidence from eye movements and verbal descriptions. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-010-1053-4

Gliga, T., & Csibra, G. (2007). Seeing the face through the eyes: a developmental perspective on face expertise. In *Progress in Brain Research*. https://doi.org/10.1016/S0079-6123(07)64018-7

Goren, C. C., Sarty, M., & Wu, P. Y. (1975). Visual following and pattern discrimination of face-like stimuli by newborn infants. *Pediatrics*, *56*(4), 544–549. https://doi.org/10.1016/j.ridd.2015.10.011

Grelotti, D. J., Gauthier, I., & Schultz, R. T. (2002). Social interest and the development of cortical face specialization: What autism teaches us about face processing. *Developmental Psychobiology*. https://doi.org/10.1002/dev.10028

Guillon, Q., Hadjikhani, N., Baduel, S., & Rogé, B. (2014). Visual social attention in autism spectrum disorder: Insights from eye tracking studies. *Neuroscience and Biobehavioral Reviews*, *42*, 279–297. https://doi.org/10.1016/j.neubiorev.2014.03.013

Jarrold, C., & Brock, J. (2004). To Match or Not to Match? Methodological Issues in Autism-Related Research. *Journal of Autism and Developmental Disorders*, *34*(1), 81–86. https://doi.org/10.1023/B:JADD.0000018078.82542.ab

Johnson, M. H. (2005). Subcortical face processing. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn1766

Kemner, C., van der Geest, J. N., Verbaten, M. N., & van Engeland, H. (2007). Effects of object complexity and type on the gaze behavior of children with pervasive developmental disorder. *Brain and Cognition*. https://doi.org/10.1016/j.bandc.2006.05.006

Kirchner, J. C., Hatri, A., Heekeren, H. R., & Dziobek, I. (2011). Autistic symptomatology, face processing abilities, and eye fixation patterns. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-010-1032-9

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual Fixation Patterns During Viewing of Naturalistic Social Situations as Predictors of Social Competence in

Individuals With Autism. *Archives of General Psychiatry*, *59*(9), 809. https://doi.org/10.1001/archpsyc.59.9.809

Kuhn, G., Kourkoulou, A., & Leekam, S. R. (2010). How Magic Changes Our Expectations About Autism. *Psychological Science*. https://doi.org/10.1177/0956797610383435

Le Couteur, A., Lord, C., & Rutter, M. (2003). The Autism Diagnostic Interview-Revised (ADI-R). In *Los Angeles CA Western Psychological Services*. Western Psychological Services.

Lord, C., & Rutter, M. (1999). Autism diagnostic observation schedule-WPS (ADOS-WPS). *Los Angeles CA Western Psychological*.

Macari, S., Milgramm, A., Reed, J., Shic, F., Powell, K. K., Macris, D., & Chawarska, K. (2020). Context-Specific Dyadic Attention Vulnerabilities During the First Year in Infants Later Developing Autism Spectrum Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2019.12.012

Marsh, L. E., Pearson, A., Ropar, D., & Hamilton, A. F. C. (2014). Predictive Gaze During Observation of Irrational Actions in Adults with Autism Spectrum Conditions. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-014-2215-6

Parish-Morris, J., Chevallier, C., Tonge, N., Letzen, J., Pandey, J., & Schultz, R. T. (2013). Visual attention to dynamic faces and objects is linked to face processing skills: A combined study of children with autism and controls. *Frontiers in Psychology*, *4*(APR), 1–7. https://doi.org/10.3389/fpsyg.2013.00185

Pelphrey, K. A., Sasson, N. J., Reznick, J. S., Paul, G., Goldman, B. D., & Piven, J. (2002). Visual Scanning of Faces in Autism. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1023/A:1016374617369

Pierce, K., Marinero, S., Hazin, R., McKenna, B., Barnes, C. C., & Malige, A. (2016). Eye Tracking Reveals Abnormal Visual Preference for Geometric Images as an Early Biomarker of an Autism Spectrum Disorder Subtype Associated With Increased Symptom Severity. *Biological Psychiatry*, *79*(8), 657–666. https://doi.org/10.1016/j.biopsych.2015.03.032

Riby, D. M., & Hancock, P. J. B. (2009). Do faces capture the attention of individuals with Williams syndrome or autism? Evidence from tracking eye movements. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-008-0641-z

Riby, D. M., Hancock, P. J., Jones, N., & Hanley, M. (2013). Spontaneous and cued gaze-following in autism and Williams syndrome. *Journal of Neurodevelopmental Disorders*, *5*(1), 13. https://doi.org/10.1186/1866-1955-5-13

Rice, K., Moriuchi, J. M., Jones, W., & Klin, A. (2012). Parsing heterogeneity in autism spectrum disorders: Visual scanning of dynamic social scenes in school-aged children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(3), 238–248. https://doi.org/10.1016/j.jaac.2011.12.017

Saitovitch, A., Bargiacchi, A., Chabane, N., Phillipe, A., Brunelle, F., Boddaert, N., Samson, Y., & Zilbovicius, M. (2013). Studying gaze abnormalities in autism: Which type of stimulus to use? *Open Journal of Psychiatry*, *03*(02), 32–38. https://doi.org/10.4236/ojpsych.2013.32a006

Schauder, K. B., Park, W. J., Tsank, Y., Eckstein, M. P., Tadin, D., & Bennetto, L. (2019). Initial eye gaze to faces and its functional consequence on face identification abilities in autism spectrum disorder. *Journal of Neurodevelopmental Disorders*, *11*(1), 1–20.

https://doi.org/10.1186/s11689-019-9303-z

Schultz, R. T. (2005). Developmental deficits in social perception in autism: The role of the amygdala and fusiform face area. *International Journal of Developmental Neuroscience*. https://doi.org/10.1016/j.ijdevneu.2004.12.012

Shi, L., Zhou, Y., Ou, J., Gong, J., Wang, S., Cui, X., Lyu, H., Zhao, J., & Luo, X. (2015). Different Visual Preference Patterns in Response to Simple and Complex Dynamic Social Stimuli in Preschool-Aged Children with Autism Spectrum Disorders. *PLOS ONE*, *10*(3), e0122280. https://doi.org/10.1371/journal.pone.0122280

Shic, F., Bradshaw, J., Klin, A., Scassellati, B., & Chawarska, K. (2011). Limited activity monitoring in toddlers with autism spectrum disorder. *Brain Research*. https://doi.org/10.1016/j.brainres.2010.11.074

Trevarthen, C., & Aitken, K. J. (2001). Infant intersubjectivity: Research, theory, and clinical applications. In *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1017/S0021963001006552

Tronick, E. Z. (1989). Emotions and Emotional Communication in Infants. *American Psychologist*. https://doi.org/10.1037/0003-066X.44.2.112

Van Der Geest, J. N., Kemner, C., Camfferman, G., Verbaten, M. N., & Van Engeland, H. (2002). Looking at Images with Human Figures: Comparison between Autistic and Normal Children. *Journal of Autism and Developmental Disorders*, *32*(2), 69–75. https://doi.org/10.1023/A:1014832420206

Vuilleumier, P. (2002). Facial expression and selective attention. In *Current Opinion in Psychiatry*. https://doi.org/10.1097/00001504-200205000-00011

Wagner, J. B., Hirsch, S. B., Vogel-Farley, V. K., Redcay, E., & Nelson, C. A. (2013). Eye-tracking, autonomic, and electrophysiological correlates of emotional face processing in adolescents with autism spectrum disorder. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-012-1565-1

Wilson, C. E., Brock, J., & Palermo, R. (2010). Attention to social stimuli and facial identity recognition skills in autism spectrum disorder. *Journal of Intellectual Disability Research*, *54*(12), 1104–1115. https://doi.org/10.1111/j.1365-2788.2010.01340.x

2.5. Attentional cueing and executive deficits revealed by a virtual supermarket task coupled with eye-tracking in autism spectrum disorder

This chapter consists in the paper: **Mouga S**, Duarte CI, Café C, Sousa D, Duque F, Oliveira G, Castelo-Branco M. Attentional cueing and executive deficits revealed by a virtual supermarket task coupled with eye-tracking in autism spectrum disorder. *Journal of Autism and Developmental Disorders (under revision)*

Abstract

Executive functioning (EF) impairments are common in Autism Spectrum Disorder (ASD), having a cascading-effect on daily-life demands involving complex functions such as social cognition (SC). Tasks with high ecological validity that can assess this impact and its association with SC and contextual cueing are needed. This study aimed to assess this link between EF, attentional cueing, and SC with a novel non-immersive virtual reality task ("EcoSupermarketX"), capturing performance deficits in a realistic setting in ASD, as compared with individuals with typical neurodevelopment (TD).

Our task had three blocks of increasing executive load and incorporated social and non-social cues, with different degrees of saliency. The performance of both groups (ASD and TD) was compared using parameters reflecting item and sequencing errors, total time and distance for task completion, and head rotations, as a measure of attentional allocation.

ASD individuals showed a significant performance dependence on the presence of contextual cues, which was manifested in particular concerning item errors and head rotations (reflecting orienting). Difficulties increased as a function of cognitive load, defined as number of ordered items to be taken. Between-group differences were found both for Social and Non-Social salient cues. Eye-tracking measures showed significantly larger fixation time of salient social cues in ASD.

EcoSupermarketX task shows an impairment in ASD both in the presence of social and non-social contextual cues. In sum this novel ecological task is sensitive to detect EF and attentional cueing deficits in ASD in the context of everyday settings, which is of potential clinical relevance.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder defined by deficits in social communication and interaction, as well as repetitive patterns of behaviour and restricted interests (American Psychiatric Association, 2013). In addition to these core symptoms, it is also expressed by behavioural and cognitive alterations that have an early-onset, expressing throughout life, and which can aggravate with age in low-functioning subjects (American Psychiatric Association, 2013; Mouga et al., 2020). Several cognitive models (Baron-Cohen et al., 1985; Happé & Frith, 2006) have been proposed to explain characteristics and difficulties that ASD individuals present across the life span (Lever & Geurts, 2016; Olde Dubbelink & Geurts, 2017). The general executive dysfunction hypothesis is the basis of one of these models, which suggests that complex behavioural manifestations of ASD are consequences of impaired executive processing, with empirical studies suggesting a broad impairment in executive functions with a significant inter-individual variability (Hill, 2004b; Pennington & Ozonoff, 1996).

Until recently, executive function was used as an umbrella term to define a diversity of cognitive skills, including planning, working memory, attention, inhibition, self-monitoring, self-regulation, and initiation carried out by prefrontal areas. These have been divided as core or high-order executive functions (Goldstein & Naglieri, 2014). They are referred to as "cool" executive functions, (Zelazo & Mller, 2005) and are distinct from "hot" executive functions (Zimmerman et al., 2016), that are cognitive processes, which represent goal-oriented behaviours, mediated by affective and motivational demands (Zelazo & Carlson, 2012). Since the introduction of the executive dysfunction hypothesis in ASD, there has been a large number of studies investigating this dichotomy. These include "cool" executive functions; which have been synthesized in a number of meta-analyses (Demetriou et al., 2018; Lai et al., 2017), while the "hot" executive functions are now being increasingly investigated, in part because of the thought influence on social behavioural regulation (Kouklari et al., 2017; Zelazo & Carlson, 2012).

Impairments in executive functions are frequent in ASD individuals from early ages and are thought to have a significant influence in their social cognition, adaptive behaviour and to be major contributors to everyday deficits, disability and absence of autonomy at the most varied levels (Demetriou et al., 2018; Geurts et al., 2014; Lai et al., 2017; Leung & Zakzanis, 2014).

These deficits are attributed to atypical functional brain connectivity, with conflicting reports emphasizing either over-connectivity or under-connectivity in ASD individuals (Maximo et al., 2014). In which concerns brain regions impacted in ASD, the literature reports abnormalities across the default, salience, and executive control networks (Abbott et al., 2016), as well as cortical (unimodal and supramodal brain networks) connectivity to subcortical areas, such as thalamus and basal ganglia (Maximo & Kana, 2019), with alterations that have been reported to persist across the life span (Braden et al., 2017).

A recent systematic review and meta-analysis of impairments in non-social cognitive functioning and social cognition in adults with ASD, comparing cognitive strengths and weaknesses, showed that even the individuals with an intelligence level at the normal range, show deficits in non-social (especially in processing speed, verbal learning and memory) and social cognitive functioning (especially in theory of mind, emotion perception and processing) (Velikonja et al., 2019). This reinforces the idea that ASD is not characterized by one main type of cognitive deficit but instead by impairments in a selective range of higher-order cognitive abilities, such as executive functions (Minshew et al., 1997), which corroborates a multiple-deficit account (for a review, Rajendran & Mitchell, 2007). This approach proposes that ASD may be a complex cognitive disorder, with multiple cognitive domains being affected differentially in severity and/or number in the different individuals. Therefore, the association between non-social and social cognitive impairments is a topic of major importance. Nevertheless most studies exclusively focus on non-social or social cognition independently (Velikonja et al., 2019). For example, social attention may recruit multiple cognitive modules involved in executive function and social cognition.

Different rationales have been used to explain whether and how these social and non-social domains are linked in ASD. Some studies report that lack of cognitive flexibility or set-shifting can explain restricted and repetitive behaviours and also rigid and perseverative behaviours (Hill, 2004a; Lopez et al., 2005; South et al., 2007). Others focused on social deficits, while linking these ASD characteristics with impairments in executive functions such as inhibition, information recall, flexibility, and the ability to monitor, update, and select socially appropriate responses (Channon et al., 2001; Dennis et al., 2009; Joseph & Tager-Flusberg, 2004). Executive functioning is also associated with socialization and communication in ASD (Dichter et al., 2009; Gilotty et al., 2002; Kenworthy et al., 2009; Leung et al., 2016; McEvoy et al., 1993; Pellicano et al., 2006), and impaired executive functions may have a cascading impact on other social cognitive aspects, such as the development of the theory of mind (Jones et al., 2018; Russell et al., 1999), or joint attention

(McEvoy et al., 1993). Faja and Dawson (2014), for instance, found that an individual's flexibility to communicate with and respond to others, adjust social behaviours within interactional contexts, and to multi-task between processing dynamic social information and formulating an appropriate response, may be influenced by difficulties in set shifting or working memory. On the other hand, Ozonoff and colleagues (2004) found no significant associations between performance-based executive functions and social skills, but found that planning, a metacognitive skill, was associated with adaptive communication skills. On the contrary, Kenworthy and colleagues (2009) found performance-based measures of divided attention and verbal fluency were related to fewer social symptoms. Other studies failed to find significant connections between executive functions and the social domain of impairment in ASD (Cantio et al., 2016; Joseph & Tager-Flusberg, 2004; Landa & Goldberg, 2005).

Importantly, investigation of social and non-social cognition performance may be dependent of the context where such skills are tested. Therefore, typically developing subjects search for cues in the environment that can orient to the appropriate behaviour, and adjust their attentional focus and consequently the next action (Travers et al., 2013). This is referred to as contextual cueing, which depends on the ability to learn contingencies, associations, or probabilities that are embedded in that environment and to determine the allocation of our attention to areas that provide the most relevant information for decoding complex visual inputs (Chun & Jiang, 1998). Some studies have shown that individuals with ASD demonstrate intact contextual cueing (Barnes et al., 2008; Brown et al., 2010; Kourkoulou et al., 2012), while others show that ASD subjects have difficulties in implicitly learning the predictive relation between location of an object and the context of other objects in the environment, but not with salient spatial cues (Travers et al., 2013)

Taken together, despite the plethora of studies, there is a strong conceptual debate in the link between executive functions and social/non-social cognition research that would benefit from an integrated research methodology, taking into account ecological validity, unifying experimental approaches and neuropsychological testing. Additionally, part of the studies in the existing literature have used archival clinical data without control groups to confirm that the link between executive function and ASD symptomology (Pugliese et al., 2016; White et al., 2017). These executive deficits also need to be accurately identified and clinically assessed as they can have a significant impact on the quality of life and daily functioning of individuals with ASD (Kapp, 2018).

Moreover, such ecological contexts provide an opportunity to test the role of (social/non-social) contextual cueing in EF tasks. Our study aimed to address this research

question. To achieve these primary and secondary goals, we developed a task at our Lab: EcoSupermarketX, a non-immersive virtual reality task, monitored with eye-tracking, featuring a shopping task at a supermarket. EcoSupermarketX was based in two main premises: on the one hand, shopping is a good example of a real-world task that often draws heavily on EF, contextual cueing and social/non-social cognition and on the other hand, different assessment and rehabilitation studies of ASD populations have successfully used supermarket settings (Carr & Carlson, 1993; Lamash & Josman, 2019).

We hypothesized that the ASD subjects will show worse performance in the EcoSupermarketX task, and in particular concerning attentional contextual cueing, comparing to typical neurodevelopment (TD), and this would be associated with ASD symptom severity and with impaired executive functioning (EF) in classical neuropsychological assessments.

Methods

Participants

The study included two groups of participants: the experimental group, composed by individuals with high functioning ASD; and the control group, composed by individuals with TD. A total of 35 participants were enrolled in the study, however two ASD participants were excluded due to not being able to complete the task. A total of 17 participants in the ASD group (median age=16 years and 4 months) and 16 in the TD group (median age=15 years and 2 months) completed the protocol of the study and entered the data analysis. Groups were matched by chronological age, performance intelligence quotient (PIQ) (Jarrold & Brock, 2004), gender, and handedness (Mann-Whitney U or Pearson Chi-Square test, $p>.05$). Further groups characterization details can be found in Table 2.5.1.

ASD participants were recruited from the Neurodevelopmental and Autism Unit from Child Developmental Centre, Paediatric Hospital, Centro Hospitalar e Universitário de Coimbra, Portugal. ASD diagnosis was assigned on the basis of the gold standard instruments: parental or caregiver interview - Autism Diagnostic Interview– Revised, ADI-R (Le Couteur et al., 2003; Catherine Lord et al., 1994), direct structured proband assessment - Autism Diagnostic Observation Schedule, ADOS (C Lord et al., 1989; C Lord & Rutter, 1999), and clinical examination performed by an experienced neurodevelopmental Paediatrician, based on the current diagnostic criteria for autism spectrum disorder from the Diagnostic and Statistical Manual of Mental Disorders 5, DSM-5 (American Psychiatric Association, 2013).

All ASD patients had positive results in the ADI-R and ADOS for autism or ASD and met the criteria for ASD from the DSM-5. Parents also responded to Autism Behaviour Checklist, ABC (Krug et al., 1980), Social Communication Questionnaire (Rutter et al., 2003) and Social Responsiveness Scale (Constantino & Gruber, 2005), to better characterize the ASD participants behaviour. A comprehensive medical observation excluded associated medical condition such as epilepsy, neurocutaneous or other genetic syndromes, or other usual comorbidities in ASD samples.

Table 2.5.1. Characterization of the ASD and TD groups

	ASD	**TD**	
	Median (IQR; min-max)	**Median (IQR; min-max)**	
N	17	16	
Gender (M/F)	16/1	14/2	*
CA (years and months)	16y 4m (3y 11m; 12y 11m – 22y 4m)	15y 2m (3y 4m; 10 y 8m - 18y 6m)	*
Handedness (R/L)	16/1	14/2	*
FSIQ	93.0 (19; 71-137)	116.5 (30; 92-152)	
VIQ	92.0 (20; 78-126)	120.5 (32; 91-146)	
PIQ	101.0 (19; 73-136)	107.0 (21; 85-146)	*
ADI-R RSI	16.5 (11; 7-26)	-	
ADI-R L/C	9.5 (4; 7-22)	-	
ADI-R RB/I	5.0 (4; 3-11)	-	
ADOS COM	5.0 (2; 3-7)	-	
ADOS SI	8 (4; 4-14)	-	
ADOS Total	12.0 (5; 8-19)	-	

NOTE. ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group; IQR=Interquartile Range; min = minimum; max – maximum; M = Male; F= Female; CA = Chronological Age; R = right; L = Left; FSIQ = Full-scale intelligence quotient (IQ); VIQ = Verbal IQ; PIQ = Performance IQ; ADI-R L/C = Autism Diagnostic Interview – Revised Language/Communication; ADI-R RSI = ADI-R Reciprocal Social Interactions; ADI-R RB/I = ADI-R Repetitive Behaviours/Interests; ADOS COM = ADOS Communication; ADOS SI = ADOS Social Interaction. * Mann-Whitney U or Pearson Chi-Square p>.05.

The parents of TD participants completed the Social Communication Questionnaire (Rutter et al., 2003) and Social Responsiveness Scale (Constantino & Gruber, 2005) to exclude ASD symptomatology.

Both groups underwent an exhaustive neuropsychological evaluation and an assessment of the intelligence quotient (IQ) to exclude intellectual disabilities (all participants had a Full Scale IQ>70).

Written informed consent was obtained from the parents of the participants or, when appropriate, the participants themselves. Children and adolescents also gave oral informed consent. The study was approved by the ethics committees from Faculty of Medicine from the University of Coimbra and the Centro Hospitalar e Universitário de Coimbra and was conducted in accordance with the declaration of Helsinki.

Procedure

In the present study, an experimental task using virtual reality stimuli, named EcoSupermarketX, was conducted. The study protocol included two different components: the EcoSupermarketX task and a neuropsychological test battery, focused on EF. During the EcoSupermarketX task, the participants' eye movements were monitored (for technical details, see below).

EcoSupermarketX

EcoSupermarketX is a non-immersive virtual reality task that aims to accurately evaluate the social cognition and executive functions abilities of the participants using a realistic type of scenario mimicking everyday life – a computer-generated supermarket.

EcoSupermarketX is a new assessment tool created at our laboratory in order to add performance-based information to the other cognitive and executive measures used.

EcoSupermarketX Apparatus, Stimuli and Design

The EcoSupermarketX stimuli were generated with Vizard Virtual Reality toolkit – version 5.2 (WorldViz, Santa Barbara, USA). The task was implemented on a desktop computer and presented in a 32-inch flat-screen with a resolution of 1920 × 1080 pixels, in full screen mode. After a brief summary of the task has been given, the participant's head was immobilized via a chin and forehead support placed at the edge of the table on which the monitor was located

(at a distance of approximately 90 cm). The participant experienced the supermarket environment from a first-hand perspective and used a joystick to navigate in the scenario.

The task included a practice block, where the participants were asked to explore the scenario of the supermarket and to familiarize with the use of joystick. Following the practice block, three different condition blocks were presented with increasing executive load (increased number of items to "buy") and with or without cues (social, non-social or no cue).

In the practice block, the participant had five minutes to explore the supermarket environment freely and to familiarize with the use of joystick. The joystick was adapted to right or left-handed participants and allowed them to navigate in the scenario and to rotate the scenario to the side (as if they were turning the head and looking right or left). This practice block was designed to guarantee that each participant was completely familiarized with the apparatus before the test blocks began.

In the test blocks the participants were instructed to search and pick groceries from the supermarket shelves that were previous presented at a grocery list. The grocery list had a variable number of items (two, three or four) which defined the three different condition blocks with increased executive load. The list was presented as an instruction individually in a trial-by-trial basis: "Find strawberry cake" followed by "Find sausages" in a 2-item grocery list, for example (each item image and name appeared for three seconds, see Figure 2.5.1). The groceries were replaced randomly in the shelves on a trial-by-trial basis. For every single list, which defines a trial, the participant had one minute per item to perform the task. I.e., to find the groceries and conclude the "shopping" in a trial with a 2-items grocery list the participant had two minutes to conclude the shopping, (with a 3-items grocery list the participant had three minutes, and four minutes to the 4-items grocery list). Participants were instructed to collect all items in the sequence they appeared in the list, and as fast and accurately as possible. They had to plan and monitor their behaviour to complete the task successfully.

Additionally, participants were informed that during the task three cueing situations could happen: they could have cueing help from a person (an avatar), an arrow or no help at all. These defined the different types of cue: social, non-social, or absent cue. They were not told what specifically the person was doing or what kind of arrows were presented, so they were not expecting different saliencies a priori. In fact, there were five different conditions in each 2, 3 or 4-items conditions: non-social salient (blinking luminous arrow); non-social subtle (wooden arrow); social salient (avatar pointing to the grocery); social subtle (avatar gazing to the grocery); and no cue (Figure 2.5.1). This sequence was maintained during all the experiment. Participants underwent five trials for the 2-item grocery list condition (one trial

per cue type); 10 trials for the 3-item grocery list condition (two trials per cue type) and 15 trials for the 4-item grocery list condition (three trials per cue type), performing a total of 30 trials (with an interval between the 3 and the 4-item conditions).

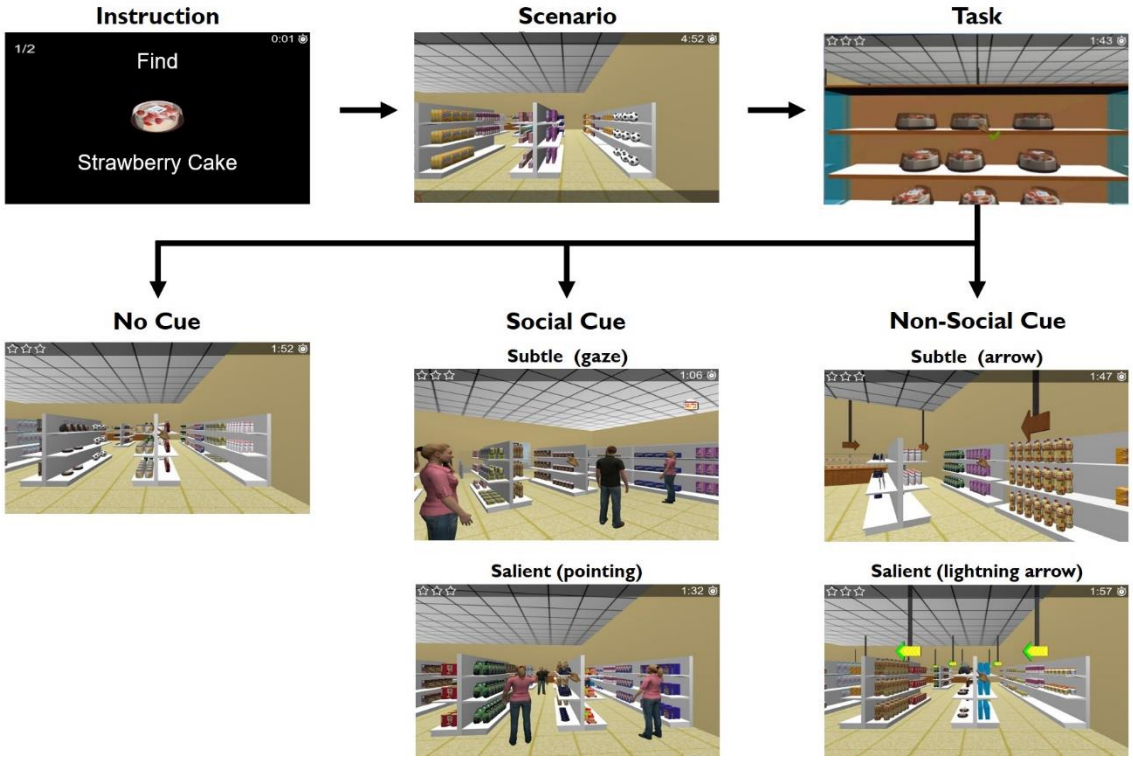

Figure 2.5.1. EcoSupermarketX task design, considering the different types of cues. The test blocks included an instruction that consisted in the grocery list the participants had to pick. The grocery list (2, 3 or 4-items) was presented as an instruction individually in a trial-by-trial basis: "Find strawberry cake" followed by "Find sausages" in a 2-item grocery list, for example (each item image and name appeared for three seconds). The grocery list had a variable number of items (two, three or four) which defined the three different condition blocks with increased executive load. The groceries were replaced randomly in the shelves on a trial-by-trial basis. Participants were instructed to collect all items in the sequence they appeared in the list, and as fast and accurately as possible. Additionally, there were five different conditions in each 2, 3 or 4-items conditions: non-social salient (blinking luminous arrow); non-social subtle (wooden arrow); social salient (avatar pointing to the grocery); social subtle (avatar gazing to the grocery); and no cue.

EcoSupermarketX aimed to analyse EF and social cognition. Therefore, to reduce mere memory constraints, an image of the requested item from the grocery list was displayed in the upper right corner after 40 seconds, giving the opportunity to the participant to conclude the trial. Focusing on the enhancement of the realism of the task and its ecological validity, realistic three-dimensional forms and commercial brands were used to depict the groceries included in the supermarket scenario.

EcoSupermarketX Data Analysis

Several parameters were defined for the analysis of the performance of each participant in the EcoSupermarketX game, considering errors, time, distance, and head rotation variables. The different behavioural measures/parameters defined were Item Errors; Sequencing Errors; Time; Distance; Head Rotation, which we describe below:

Item errors - Number of wrongly picked items of the EcoSupermarketX scenario that were not in the list of groceries divided by the number of items in the grocery list × 100 (e.g., to select a cake, when the cake was not in the list).

Sequencing errors - Number of picked items of the EcoSupermarketX scenario that were in the incorrect sequence according to the list of groceries divided by the number of items in the grocery list × 100 (e.g., to select sausages before cereals, when the cereals where first in the list).

Total time - Performance time (in seconds) - The time the participant was engaged in the execution of the trial: looking for and grabbing the products that were in the grocery list (time elapsed from the end of the grocery list memorization to the last correctly picked item).

Total distance - Performance distance - The distance the participant goes through in the execution of the task: looking for and grabbing of the products that are in the grocery list).

Number of head rotations - Sum of the number of virtual head rotations by the participant (in degrees) during the time of execution of the task.

Eye-tracking Recording and Measures

Eye movements were recorded using an infrared-emitting video-based eye tracker (EyeLink 1000 Plus, SR Research, Mississauga, ON, Canada). In terms of EyeLink tracking settings, we used mono mode and pupil corneal reflection, at a 1K sample rate. The tracker has a reported gaze position accuracy of 0.25-0.50º and a spatial resolution of 0.05. A 9-point calibration procedure with a fixation circle was performed before each block. The participants were instructed to fixate on the circle. After the calibration, there was a validation trial to ensure the precision of the data collection. The calibration process was repeated when necessary until the eye achieved good mapping on all nine test positions (tracking error smaller than 1° visual angle). As participants were performing a dynamic virtual-reality task in which they were freely walking around a supermarket, the frames in the screen were always different for all participants. In this way, the areas of interest (AOI) were defined in the virtual-reality software,

which received the participants' gaze coordinates from the eye tracking software in a real-time mode. Using those screen coordinates, we computed the time that the participant was looking to each AOI in a real time basis. The areas of interest were related to the different types of cues defined: Arm (while avatar is pointing); Head (while avatar is looking); Salient Arrow and Subtle Arrow.

Neuropsychological assessment

In addition to the assessment of intelligence quotients with the Weschler scales, we used a standard neuropsychological test battery as a baseline characterization of the executive status of the study participants. The tests were several classic executive tests widely employed in clinical and research settings, some of them included in the Coimbra Neuropsychological Assessment Battery (BANC) (M. R. Simões et al., 2016) and other classical tests. The tests selected for our study were individually administered and focused on the evaluation of executive functions, namely: Corsi Blocks assesses visuospatial short-term memory and spatial attention; Trail, that assesses attention, processing speed, and cognitive flexibility; Tower, which assesses the executive functions of planning, working memory, rule learning, the ability to inhibit responding, self-monitoring and regulation and problem solving. A used classical test that is not in the BANC is the Stroop colour-word test (Stroop, 1935) – Naming, Reading Interference tasks, which also assess cognitive flexibility and processing speed.

Data analysis and statistics

Initially we conducted a descriptive data analysis to summarize the data using graphical techniques and quantitative analysis in order to characterize the sample, detect possible extreme outliers and measurement error.

Categorical and nominal values are expressed as frequencies, and continuous data are presented as median, interquartile range (IQR) and range.

To verify the main effect of number of items, the Jonckheere-Terpstra test was used, determining if the different behavioural measures/parameters defined (Item Errors; Sequencing Errors; Total Time; Total distance; Head Rotation) results significantly increased with the increase in the number of items.

The effect of Cue in the groups was assessed, resorting to Mann–Whitney U tests comparisons of quantitative variables between the two groups (ASD and TD), first verifying if there were differences in the distribution of the different variables of the EcoSupermarketX

in the Cue vs. No Cue conditions. After identification of this main effect, planned analyses then included Social vs. Non-Social Cue, followed by Basic vs. Salient in both Social and Non-social Cues.

Spearman rank correlation coefficients were calculated, in the clinical group, to examine the associations of EcosupermarketX behavioural parameters, eye-tracking measures and the neuropsychological tests referred to above, as well and ASD core social interaction features. Benjamini–Hochberg corrections with false positive rate established at 0.05 were used to deal with multiple comparisons, and only the correlations that survived these corrections are reported in the "Results" section and further examined in the "Discussion" section.

Differences in the eye-tracking measures were assessed, resorting to Mann–Whitney U tests comparisons of quantitative variables between the two groups (ASD and TD).

Effect sizes (Kendal's tau b for Jonckheere-Terpstra test statistics and Cohen's *d* for Mann–Whitney U tests) are reported with *p*-values for significant statistical differences.

Nonparametric statistics were carried out for all statistical analyses to avoid biases due to deviations from normality and variance heterogeneity.

All outliers were considered to be clinically and scientifically relevant, and therefore we decided not to exclude them from our main analyses presented in this paper, which is justified by the use of non-parametric statistics.

All statistical analysis was completed with the support of the Statistical Package for Social Sciences, version 26 (SPSS ®, Chicago, IL, USA). A significance level of 0.05 was adopted.

Ethics Statement

All the procedures in this study were reviewed and approved by the ethics committees from Faculty of Medicine from our University (CE-11/2013) and our Hospital (CHUC-102-13) and was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the parents/guardians of all participants or, when appropriate, the participants themselves. Children and adolescents also gave oral informed consent.

Results

EcoSupermarketX

The several behavioural measures extracted from the participants' performance in the EcoSupermarketX task gave us important indications about how well ASD participants could perform a task that mimics daily-life routines and is very demanding in terms of EF and social cognition. Moreover, the analysis of the EcoSupermarketX data gave us relevant information about the impact of increasing executive load and various cues on the behaviour of ASD and TD populations. We defined four main categories for the report of our study: effect of cognitive load (number of items); main effect of type of cue (no cue vs. cue) and then planned analyses on cue subtypes: social vs. non-social cue; subtle vs. salient cue, eye-tracking measures; correlation patterns.

Effect of cognitive load

A Jonckheere-Terpstra test for ordered alternatives showed that in the ASD group there was a statistically significant increase of item errors with increasing cognitive load (i.e. number of items in the grocery list; from "2-items", "3-items" to "4-items"), $T_{JT} = 576.50$, $z = 2.497$, $p = .013$, Kendall's tau b = 0.286, which was not present in the TD group (Figure 2.5.2).

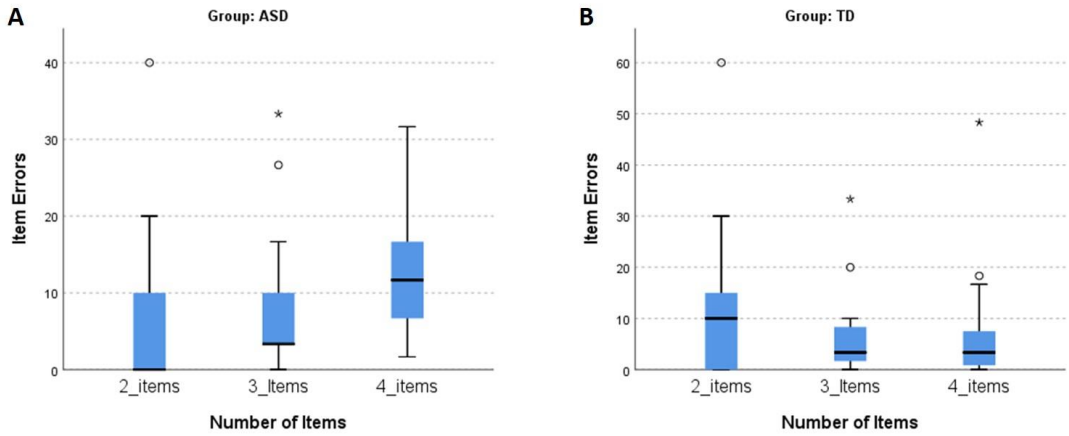

Figure 2.5.2. Trend Analysis of the number of items: item errors. (A) Association between the number of item errors with the increasing number of items in the ASD group. The number of item errors is higher with the increase of cognitive load (with higher number of items per condition) in the ASD group. (B) No association between the number of item errors with the increasing number of items in the TD group. In the TD group, the number of item errors is similar in the different conditions, despite de increasing number of items (cognitive load).

NOTE. ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group.

In the ASD group, there was a statistically significant increase of the head rotation (reflecting orienting) parameter with the increasing number of items (from "2-items", "3-items" to "4-items"), T_{JT} = 666.00, z = 4.018, p < .001, Kendall's tau b = 0.442, which was not present in the TD group (Figure 2.5.3).

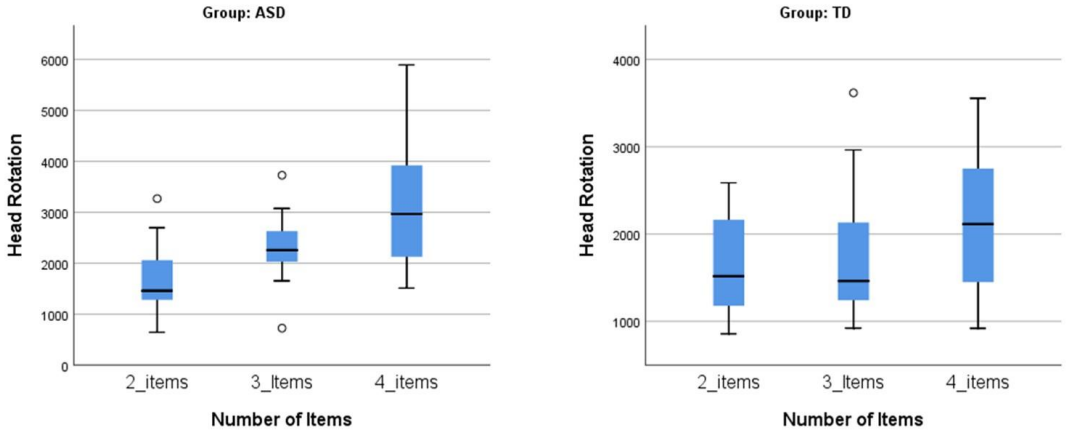

Figure 2.5.3. Trend Analysis of the number of items: head rotation. (A) The association between the head rotations with the increasing number of items in the ASD group. The head rotations increase with the increment of cognitive load (with higher number of items per condition) in the ASD group. (B) No association between the number of head rotations with the increasing number of items in the TD group. In the TD group, the head rotations are similar in the different conditions, despite de increasing number of items (cognitive load).

NOTE. ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group.

Effect of cue

The effect of Cue in the groups was assessed comparing the two groups (ASD and TD) in this order: first verifying if there were differences as function of presence versus absence of a Cue. Then follow-up analyses were performed concerning Social vs. Non-Social Cue, followed by Subtle vs. Salient in both Social and Non-social Cues.

Concerning the Cue factor , a Mann-Whitney U test indicated differences between the groups (ASD and TD) specifically for the No Cue condition, which was replicated across parameters concerning item errors , total time, total distance, and head rotation, suggesting that cue absence is very detrimental in ASD. Accordingly, item errors were statistically significantly higher for the ASD group (Mdn = 15.00) than the TD group (Mdn = 5.00), U = 67.50, p = .012, d = 0.951. The same pattern is present in the total time, with the ASD group (Mdn = 79.90) taking more time to perform the task in the No Cue condition than the TD

group (Mdn = 57.78), U = 70.00, p = .017, d =0.909. Total distance was also greater for ASD group (Mdn = 127.87) than for TD group (Mdn = 95.35), U = 81.00, p = .049, d = 0.735. Number of head rotations were statistically significantly higher for the ASD group (Mdn = 3997.20) than the TD group (Mdn = 2616.05), U = 67.00, p = .012, d = 0.960. These results are summarized in Figure 2.5.4.

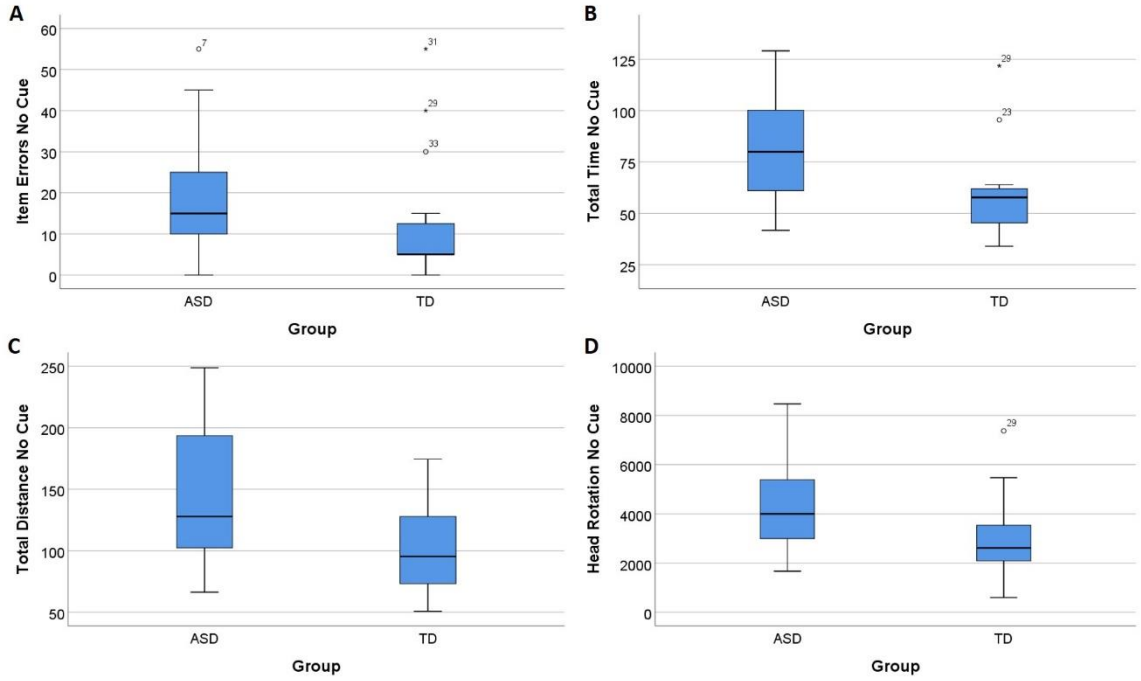

Figure 2.5.4. Significant group differences were observed in the No Cue condition (p<0.05). **A.** Mean percentage of item errors for ASD and TD groups for the No Cue condition. **B.** Total time for ASD and TD groups for the No Cue condition. **C.** Total distance for ASD and TD groups for the No Cue condition. **D.** Head rotation for ASD and TD groups for the No Cue condition. Boxplots: central mark – median; edges of box – 25th and 75th percentiles; whiskers – most extreme data points (minimum and maximum).

NOTE. ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group.

Even in the presence of a Cue, significant group differences were observed. Concerning Non-Social Cue, a Mann-Whitney U test indicated differences between the groups (ASD and TD) in this condition, specifically concerning number of head rotations. Number of head rotations were statistically significantly higher for the ASD group (Mdn = 2115.78) than the TD group (Mdn = 1644.09), U = 72.00, p = .021, d = 0.876 (Figure 2.5.5). No other significant differences were found.

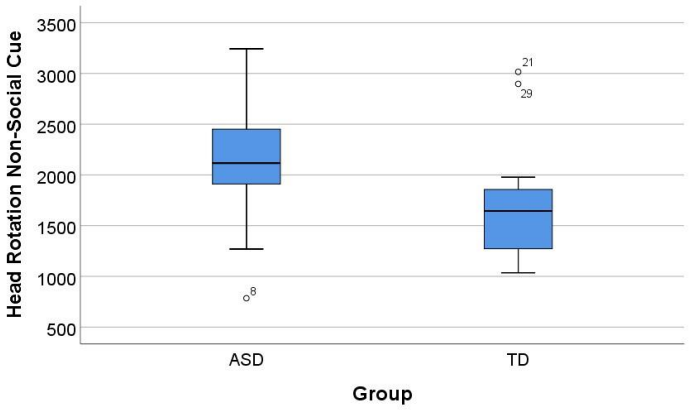

Figure 2.5.5. Significant Group differences were observed in the Non-Social Cue condition (*p* = .021). Head rotation for ASD and TD groups for the Non-Social Cue condition. Boxplots: central mark – median; edges of box – 25th and 75th percentiles; whiskers – most extreme data points (minimum and maximum). NOTE. ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group.

We also compared the performance of both groups (ASD and TD) in different types of saliency of the cues. It turned out that when cues were salient, significant group differences were present, but not for subtle cue types. A Mann-Whitney U test indicated differences between the groups (ASD and TD) in the Non-Social Salient condition, specifically in total distance and head rotation. Total distance was statistically significantly higher for the ASD group (Mdn = 68.84) than the TD group (Mdn = 55.85), U = 81.00, p = .049, d = 0.735. The same pattern is present in the number of head rotations, with the ASD group (Mdn = 2114.30) going astray in the task in the Non-Social Salient condition, contrary to the TD group (Mdn = 1462.23), U = 78.00, p = .037, d = 0.781. These results are summarized in Figure 2.5.6.

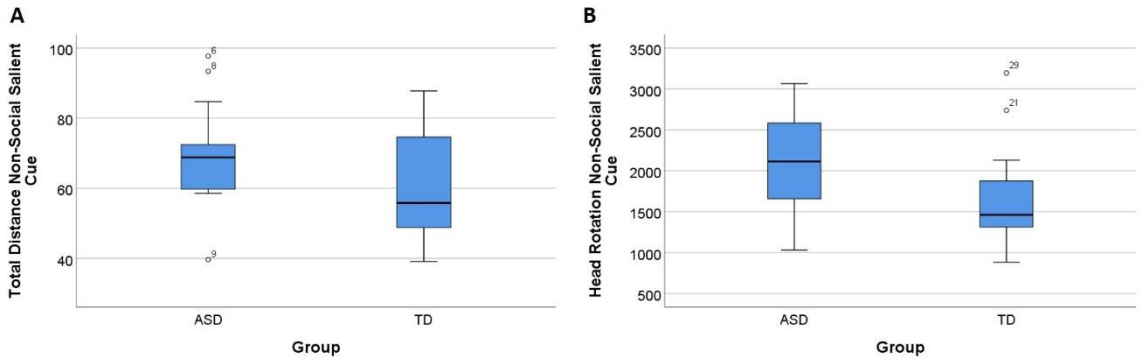

Figure 2.5.6. Group differences in the Non-Social Salient Cue condition. A. Total distance for ASD and TD groups for the Non-Social Salient Cue condition. **B.** Head rotation for ASD and TD

groups for the Non-Social Salient Cue condition. Boxplots: central mark – median; edges of box – 25th and 75th percentiles; whiskers – most extreme data points (minimum and maximum).

NOTE. ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group.

Concerning the Social Cue Salient condition, a Mann-Whitney U test indicated differences between the groups (ASD and TD) in this condition, specifically in total time and head rotation. Total time was statistically significantly higher for the ASD group, with the ASD group (Mdn = 40,71) taking more time to perform the task in the Social Salient Cue condition than the TD group (Mdn = 32,98), U = 78.00, p = .037, d = 0.781. Head rotation was also statistically significantly higher for the ASD group (Mdn = 2010,49) than the TD group (Mdn = 1582,92), U = 81.00, p = .049, d = 0.735. These results are summarized in Figure 2.5.7.

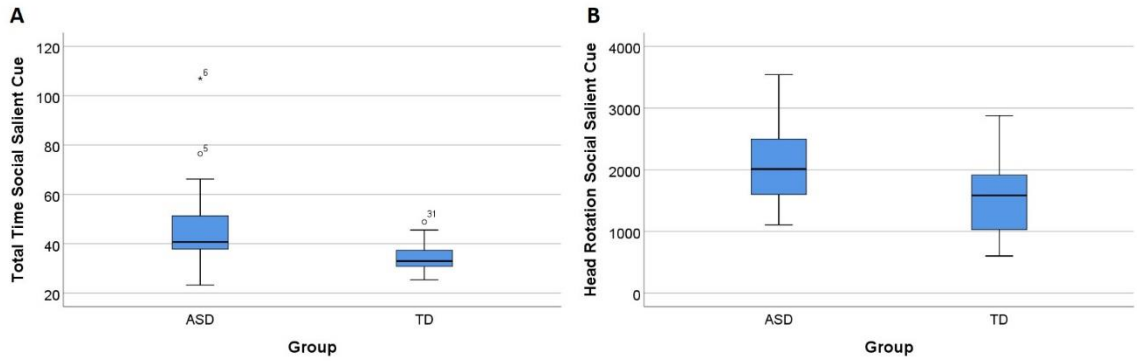

Figure 2.5.7. Group differences in the Social Salient Cue condition. A. Total time for ASD and TD groups for the Social Salient Cue condition. **B.** Head rotation for ASD and TD groups for the Social Salient Cue condition. Boxplots: central mark – median; edges of box – 25th and 75th percentiles; whiskers – most extreme data points (minimum and maximum).

NOTE. ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group.

Eye-tracking measures

The time looking at the different AOIs of social or non-social relevance (Arm; Head; Salient Arrow and Basic Arrow) that were related to the different types of cues (Social Salient; Social Basic; Non-Social Salient and Non-Social Basic, respectively) was compared between the two groups (ASD and TD).

A Mann-Whitney U test indicated differences between the ASD and TD groups in the AOI Arm, that is presented in the Social Salient condition, with the ASD group (Mdn = 13,22)

looking longer than the TD group (Mdn = 8.01) to the AOI Arm, U = 64.00, p = .009, d = 1.012 (Figure 2.5.8).

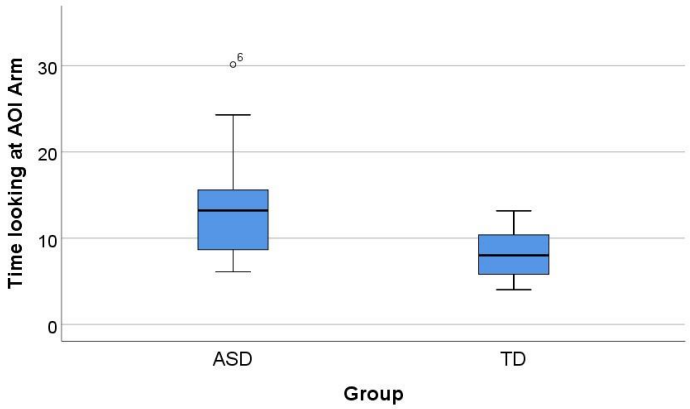

Figure 2.5.8. Group differences in the AOI Arm (U = 64.00, p = .009, d = 1.012**).** Total time for ASD and TD groups in the AOI Arm in the Social Salient Cue condition. Boxplots: central mark – median; edges of box – 25th and 75th percentiles; whiskers – most extreme data points (minimum and maximum).

NOTE. AOI = Area of Interest; ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group.

Correlation Analysis

We focused our correlational analyses between the behavioural measures/parameters of the EcoSupermarketX and the results of neuropsychological tests and diagnostic parameters and eye-tracking measures that were related with our hypothesis of a relation with executive processing and the role of attention and social cues, specifically in ASD.

Cognitive load

The cognitive load effect was evident in the total number of errors and number of head rotation, as number of items increases.

In the ASD group, the item errors in the 4-item condition were significantly correlated with the Trail Flexibility index (r_s = 0.63, p = .033). This was a positive correlation, which means that more errors in the EcoSupermarketX in the 4-item condition were associated with higher scores in the Trail Flexibility index (where higher results in the index, mean lower cognitive flexibility).

In what concerns to the number of head rotations, no significant correlations after correction were found.

Type of Cue

The no Cue condition was the one that most differentiated participants across parameters (see above) and the one where a larger pattern of significant correlations were found.

In the ASD group , in what concerns to time, in the No Cue Condition, we found significant positive correlations with scores from Tower (Total of Trials (r_s = 0.55, p = .033) and Total Errors(r_s = 0.57, p = .033)) and Reciprocal Social Interaction from ADI-R (r_s = 0.65, p = .021), and a negative correlation with Corsi Blocks (r_s = -0.66, p = .021). In addition, more difficulties in social interaction are associated with more item errors in the No Cue condition.

In this condition, regarding total distance, the ASD group showed significant correlations with Stroop - Interference (r_s = -0.63, p = .018), Corsi Blocks (r_s = -0.57, p = .021), Tower (Total of Trials (r_s = 0.59, p = .020) and Errors (r_s = 0.61, p = .018)) and Reciprocal Social Interaction level from ADI-R (r_s = 0.67, p = .018). With Tower results (Total of Trials and Errors) and Reciprocal Social Interaction from ADI-R we found positive correlations, while in the Stroop test and Corsi Blocks we found negative correlations, repeating a pattern present in the previous parameter (time).

In what concerns time, in the Social Salient Cue Condition, in the ASD group we found significant positive correlations with the eye-tracking measure (time looking at AOI Arm) (r_s = 0.65, p = .033).

In what concerns to the item errors and number of head rotations in the No Cue condition, as well as in the Non-Social Cue (head-rotation), Non-Social Salient Cue (distance and head-rotation) and Social Salient Cue (head rotation), no significant correlations after correction were found.

Discussion

In this study we investigated the link between executive functions, attentional contextual cueing, and social cognition in subjects with ASD. For that purpose, we compared the performance in a novel ecological task aimed at assessing executive functions in a daily living chore: shopping in a supermarket, with the integration of attentional social vs. non-social cues, in two matched groups of adolescents and young adults with ASD or TD. In order to answer our research question, we used markers of executive functions under distinct task constraints, with explicit manipulations of levels of cognitive load and attentional saliency of the social and non-social cues that could help in the performance of the task.

We found that ASD subjects are more affected with the increasing cognitive load of information, since they presented a significant increase of the item errors and head rotations with the increase in the number of items appearing in the grocery list. A higher value for the number of head rotations means that ASD participants struggled to find the right item, looking around (orienting) more and consequently rotating their "virtual head" during the task. This suggests a deficit in efficient deployment of attention, leading to a larger number of head turns.

Cognitive load refers to the used amount of working memory resources and is thought to be a crucial factor in learning of complex tasks (Paas et al., 2003), such as our daily living chores. Working memory is the ability to temporarily store and manipulate information, it is limited and varies from person to person (Baddeley, 2010; O'Hare et al., 2008). Working memory is also considered an essential element of cognitive control (Baddeley, 2010; Engle et al., 1999), with a critical importance for learning and academic achievement (Alloway, 2009), as well as social competency (Dennis et al., 2009). Our results, in which the ASD group presented more difficulties when the list of groceries have a higher number of items, were, therefore, in line with previous literature that report that compared to TD, individuals with ASD performed significantly worse on complex tasks related to working memory (Bennetto et al., 1996; Minshew & Goldstein, 2001; Ozonoff & Strayer, 2001; Russell et al., 1996; Williams et al., 2006). In fact, ASD subjects seemed to present difficulties in performing the task when the difficulty increases, and this does not happen in the TD group. This corroborates other studies that have also found that when performing working memory tasks of increasing complexity or cognitive load, children with ASD were impaired compared to TD children (Minshew & Goldstein, 2001; Russo et al., 2007; Williams et al., 2006).

In what concerns to the introduction of a cue as a helping feature in the task, it seems to have an important and clarifying role in the way ASD people allocate their attention in structured environments. We found that in the absence of a cue, ASD subjects perform worse and only the addition of some types of attentional cues can rescue the impaired performance of the TD individuals. In fact, our ASD participants presented more errors, took more time to perform the task, "walked" longer distances and were more adrift in the No Cue condition, when nothing would guide their actions. However, it was also of interest to verify if the type of cue (social vs. non-social) used could explain the observed behaviour. In that case, between-group differences only remained concerning non-social cues (these could not rescue performance), and one attentional parameter (head rotation), reinforcing that the use of some cues seem to have a beneficial effect in restoring overall performance.

Furthermore, ASD showed impairment specifically for salient cues, regardless of being social or non-social. , which is surprising because one would at first sight expect an effect for more subtle cues. The Enactive Mind theory stresses that cognition is embedded in experiences resulting from a body's actions upon salient aspects of its surrounding environment and that social functioning is supported by the ability to visually track socially salient information within interactions (Klin et al., 2003). Interestingly, our ASD group spend more time looking to the AOI arm (salient social cue). They seem to take more time to interpret the environment and decide what to do than TD.

The significant associations found between EcoSupermarketX parameters and the different neuropsychological assessments indicate that functional domains related to attention and executive function are captured by the measures computed from this novel ecological task. Additionally, the significant correlations found between EcoSupermarketX performance and ASD core symptomatology severity give important indications about the impact on social cognition/skills and the functional implications of ASD clinical phenotype to daily living functional abilities, going beyond previous reports (Cantio et al., 2016; Joseph & Tager-Flusberg, 2004; Landa & Goldberg, 2005).

While our results support one of the key cognitive theories of ASD: executive dysfunction (Hill, 2004b; Pennington & Ozonoff, 1996), they also stress the importance of the of attentional contextual cueing and raises questions about the nature and influence of cue saliency. We showed that ASD subjects have a deficit in the allocation of attention that seems to interact with the more general deficit in EF. On the other hand, our study reports deficits not only in non-social, but also in hot executive functions, cognitive processes, which represent goal-oriented behaviours (Kouklari et al., 2017; Zelazo & Carlson, 2012) . This emphasizes the knowledge that ASD is not characterized by one main cognitive deficit but instead by impairments in a selective range of higher-order cognitive abilities, including attention and executive function, corroborating a multiple-deficit account.

The attentional contextual cueing as a possible explanation for the difficulties in complex cognitive domains in spite of largely preserved visual spatial abilities in ASD, has been studied mostly in classic spatial-learning tasks, but much less so in the context of real life constrains and daily life chores. Some studies have suggested proficient implicit contextual cueing in individuals with ASDs as compared to TD participants (Barnes et al., 2008; Brown et al., 2010; Kourkoulou et al., 2012; Travers et al., 2013). This is in part corroborated by our study when we show that the performance of ASD group matches the TD in the presence of the cue (showing differences in the absence of cues). The contextual cueing deficit is

demonstrated by the dependence on the presence of a cue, although cue type did not show specificity in ASD. Nonetheless, we found a surprising result in what concerns to the saliency of the cues: salient cues did not rescue performance in ASD comparing to TD, contrary to subtle cues. Brown and colleagues (2010) have hypothesised that ASD problems in real-world areas expected to require implicit acquisition, such as social cognition, in spite of preserved implicit learning mechanisms, may be explained by interference due to abnormal attention or the overuse of explicit strategies. We substantiate this hypothesis in our eye-tracking result. In fact, ASD subjects show longer fixations than TD only in the social salient cue, which is associated to worse results in the Social Salient condition in the task and can explain the difficulty in daily life, where we are constant and continuously exposed to explicit salient cues in a wide range of activities we have to perform.

To the best of our knowledge, this is the first study that so far assesses attentional cueing and EF with social and non-social cues with different saliencies in an ecologic daily living chore context. The present findings help improve our understanding of the patterns of cognitive impairments in adolescents and young adults with ASD because we showed an impairment in ASD both in the presence of social and non-social contextual cues in an ecological task, capable to identify ASD deficits in EF and attentional cueing. The discrepancy between what ASD individuals can do on explicit tasks of non-social and social reasoning (when they receive specific instructions and all the task is compartmentalized), and what they are unable to do in the daily social life, when they have to apply spontaneously their abilities in a naturalistic situation, remains one of the most intriguing questions in this research field. As our previous works stated, even individuals with normal or high IQ cannot use their cognitive abilities to face the demands of daily living and social situations (Mouga et al., 2015, 2016). Our present study shows that attention deficits can be rescued by guiding goal-directed actions using explicit cues and stresses the importance of the structured or not structured context of the task and the cognitive load that implies. Taken together, our results point to the fact that attentional allocation in ASD population is context and task dependent, which extends our previous work (Bernardino et al., 2012) on contextual dependency of local vs global attentional allocation. It also shows that cognitive load may have a large impact even in these relatively simple tasks. These results are relevant for the selection of interventional strategies in ASD subjects, focused on improved attentional allocation to social and non-social cues (diminishing the need to spend more time on social attention cues, such as the arm of an avatar). They also motivate future work exploring the importance of cueing goal-oriented

actions and training of social and adaptive skills that are increasingly being done in virtual environments (Simões et al., 2014, 2018).

Our present study emphasizes that these attentional allocation impairments are associated with EF deficits, which stresses a set of important questions we already raised, related not only to the school intervention, but also full social inclusion of ASD young adults in a society that is highly competitive and requires so many social and EF abilities. Additionally, notwithstanding of a superior or average IQ, subjects with ASD experience substantial difficulties in everyday life (Mouga et al., 2015, 2016), which can lead to an overvaluation of IQ in terms of predicting adaptive behaviour skills and a misleading as good outcome without adequate assessment and consideration of EF and social skills.

Despite the fact that the use of virtual reality tasks in clinical research has several gains compared to real world settings, specifically in terms of affordability, safety, applicability, and efficiency of data collection (Parsons et al., 2017), we should have in mind that observed performance during simulated tasks may differ from what the individual does spontaneously in the real environment, since it is impossible to fully replicate the uncertainties of everyday life. And that could be pointed as one limitation of our study, however, we tried to simulate the aids that we could have in a supermarket, for instance, arrows and people helping us find what we need.

Another possible limitation of our study is that in the study of executive functions is difficult to isolate which specific type of executive functions is impaired and/or contributes to the performance deficits observed, as the tasks we used is complex and relies on multiple cognitive skills.

In sum, our results emphasize important challenges in overall attentional allocation in social/non-social cognitive processing in ASD, in the absence of overall quantitative intellectual disability. Intriguingly, social cognition impairment was further suggested by eye-tracking data on the social salient cues. The most consistent impairments in non-social cognition that we found were measured by the number of head rotations and enhanced by the increase of number of items, in the EcoSupermarketX. In fact, these was corroborated by the association of these parameters repeatedly with the Corsi Blocks and Tower in the ASD group. These tests evaluate executive functions of planning, working memory, rule learning, the ability to inhibit responding, self-monitoring and regulation and problem solving, as well as lower visuospatial short-term memory, which means that greater difficulties in our task were associated with difficulties in those areas. This provide us evidence that attention allocation and EF alterations may not only be a promising endophenotype for ASD, but also tasks that

allow to evaluate these cognitive aspects may have a determinant role in the differential diagnosis of ASD subjects without intellectual disability.

To extricate the association between attentional allocation, EF, and social vs non-social cognition and to increase our understanding of the cognitive mechanisms of impairment in ASD, future studies need to continue to consider both non-social and social cognitive domains and focus on these domains in the study of the neural correlates of executive and attentional dysfunction in ASD.

References

Abbott, A. E., Nair, A., Keown, C. L., Datko, M., Jahedi, A., Fishman, I., & Müller, R. A. (2016). Patterns of Atypical Functional Connectivity and Behavioral Links in Autism Differ between Default, Salience, and Executive Networks. *Cerebral Cortex*, *26*(10), 4034–4045. https://doi.org/10.1093/cercor/bhv191

Alloway, T. P. (2009). Working memory, but not IQ, predicts subsequent learning in children with learning difficulties. *European Journal of Psychological Assessment*, *25*(2), 92–98. https://doi.org/10.1027/1015-5759.25.2.92

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). American Psychiatric Publishing.

Baddeley, A. (2010). Working memory. *Current Biology*, *20*(4), R136–R140. https://doi.org/10.1016/j.cub.2009.12.014

Barnes, K. A., Howard, J. H., Howard, D. V., Gilotty, L., Kenworthy, L., Gaillard, W. D., & Vaidya, C. J. (2008). Intact Implicit Learning of Spatial Context and Temporal Sequences in Childhood Autism Spectrum Disorder. *Neuropsychology*, *22*(5), 563–570. https://doi.org/10.1037/0894-4105.22.5.563

Baron-Cohen, S., Leslie, A. M., & Frith, U. (1985). Does the autistic child have a "theory of mind" ? *Cognition*. https://doi.org/10.1016/0010-0277(85)90022-8

Bennetto, L., Pennington, B. F., & Rogers, S. J. (1996). Intact and Impaired Memory Functions in Autism. *Child Development*, *67*(4), 1816. https://doi.org/10.2307/1131734

Bernardino, I., Mouga, S., Almeida, J., van Asselen, M., Oliveira, G., & Castelo-Branco, M. (2012). A direct comparison of local-global integration in autism and other developmental disorders: Implications for the central coherence hypothesis. *PLoS ONE*, *7*(6). https://doi.org/10.1371/journal.pone.0039351

Braden, B. B., Smith, C. J., Thompson, A., Glaspy, T. K., Wood, E., Vatsa, D., Abbott, A. E., McGee, S. C., & Baxter, L. C. (2017). Executive function and functional and structural brain differences in middle-age adults with autism spectrum disorder. *Autism Research*, *10*(12), 1945–1959. https://doi.org/10.1002/aur.1842

Brown, J., Aczel, B., Jiménez, L., Kaufman, S. B., & Grant, K. P. (2010). Intact implicit learning in autism spectrum conditions. *Quarterly Journal of Experimental Psychology*, *63*(9), 1789–1812. https://doi.org/10.1080/17470210903536910

Cantio, C., Jepsen, J. R. M., Madsen, G. F., Bilenberg, N., & White, S. J. (2016). Exploring 'The autisms' at a cognitive level. *Autism Research*, *9*(12), 1328–1339. https://doi.org/10.1002/aur.1630

Carr, E. G., & Carlson, J. I. (1993). Reduction of severe behavior problems in the community using a multicomponent treatment approach. *Journal of Applied Behavior Analysis*, *26*(2), 157–172. https://doi.org/10.1901/jaba.1993.26-157

Channon, S., Charman, T., Heap, J., Crawford, S., & Rios, P. (2001). Real-life-type problem-solving in Asperger's syndrome. *Journal of Autism and Developmental Disorders*, *31*(5), 461–469. https://doi.org/10.1023/a:1012212824307

Chun, M. M., & Jiang, Y. (1998). Contextual Cueing: Implicit Learning and Memory of Visual Context Guides Spatial Attention. *Cognitive Psychology*, *36*(1), 28–71. https://doi.org/10.1006/cogp.1998.0681

Constantino, J. N., & Gruber, C. P. (2005). The Social Responsiveness Scale (SRS). In *Los Angeles: Western Psychological Services*.

Demetriou, E. A., Lampit, A., Quintana, D. S., Naismith, S. L., Song, Y. J. C., Pye, J. E., Hickie, I., & Guastella, A. J. (2018). Autism spectrum disorders: a meta-analysis of executive function. *Molecular Psychiatry*, *23*(5), 1198–1204. https://doi.org/10.1038/mp.2017.75

Dennis, M., Agostino, A., Roncadin, C., & Levin, H. (2009). Theory of mind depends on domain-general executive functions of working memory and cognitive inhibition in children with traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*, *31*(7), 835–847. https://doi.org/10.1080/13803390802572419

Dichter, G. S., Lam, K. S. L., Turner-Brown, L. M., Holtzclaw, T. N., & Bodfish, J. W. (2009). Generativity abilities predict communication deficits but not repetitive behaviors in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *39*(9), 1298–1304. https://doi.org/10.1007/s10803-009-0742-3

Engle, R. W., Laughlin, J. E., Tuholski, S. W., & Conway, A. R. A. (1999). Working memory, short-term memory, and general fluid intelligence: A latent-variable approach. *Journal of Experimental Psychology: General*, *128*(3), 309–331. https://doi.org/10.1037/0096-3445.128.3.309

Faja, S., & Dawson, G. (2014). Performance on the dimensional change card sort and backward digit span by young children with autism without intellectual disability. *Child Neuropsychology*, *20*(6), 692–699. https://doi.org/10.1080/09297049.2013.856395

Geurts, H. M., van den Bergh, S. F. W. M., & Ruzzano, L. (2014). Prepotent response inhibition and interference control in autism spectrum disorders: Two Meta-Analyses. *Autism Research*, *7*(4), 407–420. https://doi.org/10.1002/aur.1369

Gilotty, L., Kenworthy, L., Sirian, L., Black, D. O., & Wagner, A. E. (2002). Adaptive Skills and Executive Function in Autism Spectrum Disorders. *Child Neuropsychology*, *8*(4), 241–248. https://doi.org/10.1076/chin.8.4.241.13504

Goldstein, S., & Naglieri, J. A. (2014). Introduction: A History of Executive Functioning as a Theoretical and Clinical Construct. In S. Goldstein & J. A. Naglieri (Eds.), *Handbook of Executive Functioning* (pp. 1–567). Springer New York. https://doi.org/10.1007/978-1-4614-8106-5

Happé, F., & Frith, U. (2006). The weak coherence account: Detail-focused cognitive style in autism spectrum disorders. In *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-005-0039-0

Hill, E. L. (2004a). Executive dysfunction in autism. *Trends in Cognitive Sciences*, *8*(1), 26–32. https://doi.org/10.1016/j.tics.2003.11.003

Hill, E. L. (2004b). Evaluating the theory of executive dysfunction in autism. *Developmental Review*, *24*(2), 189–233. https://doi.org/10.1016/j.dr.2004.01.001

Jarrold, C., & Brock, J. (2004). To Match or Not to Match? Methodological Issues in Autism-Related Research. *Journal of Autism and Developmental Disorders*, *34*(1), 81–86. https://doi.org/10.1023/B:JADD.0000018078.82542.ab

Jones, C. R. G., Simonoff, E., Baird, G., Pickles, A., Marsden, A. J. S., Tregay, J., Happe, F., & Charman, T. (2018). The association between theory of mind, executive function, and the symptoms of autism spectrum disorder. *Autism Research : Official Journal of the*

International Society for Autism Research, *11*(1), 95–109. https://doi.org/10.1002/aur.1873

Joseph, R. M., & Tager-Flusberg, H. (2004). The relationship of theory of mind and executive functions to symptom type and severity in children with autism. *Development and Psychopathology*, *16*(1), 137–155. https://doi.org/10.1017/S095457940404444X

Kapp, S. K. (2018). Social Support, Well-being, and Quality of Life Among Individuals on the Autism Spectrum. *Pediatrics*, *141*(Supplement 4), S362–S368. https://doi.org/10.1542/peds.2016-4300N

Kenworthy, L., Black, D. O., Harrison, B., Della Rosa, A., & Wallace, G. L. (2009). Are executive control functions related to autism symptoms in high-functioning children? *Child Neuropsychology*, *15*(5), 425–440. https://doi.org/10.1080/09297040802646983

Klin, A., Jones, W., Schultz, R., & Volkmar, F. (2003). The enactive mind, or from actions to cognition: lessons from autism. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *358*(1430), 345–360. https://doi.org/10.1098/rstb.2002.1202

Kouklari, E.-C., Thompson, T., Monks, C. P., & Tsermentseli, S. (2017). Hot and Cool Executive Function and its Relation to Theory of Mind in Children with and without Autism Spectrum Disorder. *Journal of Cognition and Development*, *18*(4), 399–418. https://doi.org/10.1080/15248372.2017.1339708

Kourkoulou, A., Leekam, S. R., & Findlay, J. M. (2012). Implicit Learning of Local Context in Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *42*(2), 244–256. https://doi.org/10.1007/s10803-011-1237-6

Krug, D. A., Arick, J., & Almond, P. (1980). Behavior Checklist for Identifying Severely Handicapped Individuals With High Levels of Autistic Behavior. *Journal of Child Psychology and Psychiatry*, *21*(3), 221–229. https://doi.org/10.1111/j.1469-7610.1980.tb01797.x

Lai, C. L. E., Lau, Z., Lui, S. S. Y., Lok, E., Tam, V., Chan, Q., Cheng, K. M., Lam, S. M., & Cheung, E. F. C. (2017). Meta-analysis of neuropsychological measures of executive functioning in children and adolescents with high-functioning autism spectrum disorder. *Autism Research*, *10*(5), 911–939. https://doi.org/10.1002/aur.1723

Lamash, L., & Josman, N. (2019). A metacognitive intervention model to promote independence among individuals with autism spectrum disorder: Implementation on a shopping task in the community. *Neuropsychological Rehabilitation*, *0*(0), 1–22. https://doi.org/10.1080/09602011.2019.1682621

Landa, R. J., & Goldberg, M. C. (2005). Language, social, and executive functions in high functioning autism: A continuum of performance. *Journal of Autism and Developmental Disorders*, *35*(5), 557–573. https://doi.org/10.1007/s10803-005-0001-1

Le Couteur, A., Lord, C., & Rutter, M. (2003). The Autism Diagnostic Interview-Revised (ADI-R). In *Los Angeles CA Western Psychological Services*. Western Psychological Services.

Leung, R. C., Vogan, V. M., Powell, T. L., Anagnostou, E., & Taylor, M. J. (2016). The role of executive functions in social impairment in Autism Spectrum Disorder. *Child Neuropsychology*, *22*(3), 336–344. https://doi.org/10.1080/09297049.2015.1005066

Leung, R. C., & Zakzanis, K. K. (2014). Brief Report: Cognitive Flexibility in Autism Spectrum Disorders: A Quantitative Review. *Journal of Autism and Developmental Disorders*, *44*(10), 2628–2645. https://doi.org/10.1007/s10803-014-2136-4

Lever, A. G., & Geurts, H. M. (2016). Age-related differences in cognition across the adult lifespan in autism spectrum disorder. *Autism Research*. https://doi.org/10.1002/aur.1545

Lopez, B. R., Lincoln, A. J., Ozonoff, S., & Lai, Z. (2005). Examining the relationship between executive functions and restricted, repetitive symptoms of Autistic Disorder. *Journal of Autism and Developmental Disorders*, *35*(4), 445–460. https://doi.org/10.1007/s10803-005-5035-x

Lord, C, & Rutter, M. (1999). Autism diagnostic observation schedule-WPS (ADOS-WPS). *Los Angeles CA Western Psychological*.

Lord, C, Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., & Schopler, E. (1989). Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *Journal of Autism and Developmental Disorders*, *19*(2), 185–212. https://doi.org/10.1007/BF02211841

Lord, Catherine, Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *24*(5), 659–685. https://doi.org/10.1007/BF02172145

Maximo, J. O., Cadena, E. J., & Kana, R. K. (2014). The Implications of Brain Connectivity in the Neuropsychology of Autism. *Neuropsychology Review*, *24*(1), 16–31. https://doi.org/10.1007/s11065-014-9250-0

Maximo, J. O., & Kana, R. K. (2019). Aberrant "deep connectivity" in autism: A cortico–subcortical functional connectivity magnetic resonance imaging study. *Autism Research*, *12*(3), 384–400. https://doi.org/10.1002/aur.2058

McEvoy, R. E., Rogers, S. J., & Pennington, B. F. (1993). Executive Function and Social Communication Deficits in Young Autistic Children. *Journal of Child Psychology and Psychiatry*, *34*(4), 563–578. https://doi.org/10.1111/j.1469-7610.1993.tb01036.x

Minshew, N. J., & Goldstein, G. (2001). The Pattern of Intact and Impaired Memory Functions in Autism. *Journal of Child Psychology and Psychiatry*, *42*(8), 1095–1101. https://doi.org/10.1111/1469-7610.00808

Minshew, N. J., Goldstein, G., & Siegel, D. J. (1997). Neuropsychologic functioning in autism: Profile of a complex information processing disorder. *Journal of the International Neuropsychological Society*, *3*(4), 303–316. https://doi.org/10.1017/s1355617797003032

Mouga, S., Almeida, J., Café, C., Duque, F., & Oliveira, G. (2015). Adaptive Profiles in Autism and Other Neurodevelopmental Disorders. *Journal of Autism and Developmental Disorders*, *45*(4), 1001–1012. https://doi.org/10.1007/s10803-014-2256-x

Mouga, S., Café, C., Almeida, J., Marques, C., Duque, F., & Oliveira, G. (2016). Intellectual Profiles in the Autism Spectrum and Other Neurodevelopmental Disorders. *Journal of Autism and Developmental Disorders*, *46*(9), 2940–2955. https://doi.org/10.1007/s10803-016-2838-x

Mouga, S., Correia, B. R., Café, C., Duque, F., & Oliveira, G. (2020). Language Predictors in Autism Spectrum Disorder: Insights from Neurodevelopmental Profile in a Longitudinal Perspective. *Journal of Abnormal Child Psychology*, *48*(1), 149–161. https://doi.org/10.1007/s10802-019-00578-7

O'Hare, E. D., Lu, L. H., Houston, S. M., Bookheimer, S. Y., & Sowell, E. R. (2008). Neurodevelopmental changes in verbal working memory load-dependency: An fMRI investigation. *NeuroImage*, *42*(4), 1678–1685. https://doi.org/10.1016/j.neuroimage.2008.05.057

Olde Dubbelink, L. M. E., & Geurts, H. M. (2017). Planning Skills in Autism Spectrum Disorder Across the Lifespan: A Meta-analysis and Meta-regression. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-016-3013-0

Ozonoff, S., Cook, I., Coon, H., Dawson, G., Joseph, R. M., Klin, A., McMahon, W. M., Minshew, N., Munson, J. A., Pennington, B. F., Rogers, S. J., Spence, M. A., Tager-Flusberg, H., Volkmar, F. R., & Wrathall, D. (2004). Performance on Cambridge neuropsychological test automated battery subtests sensitive to frontal lobe function in people with autistic disorder: Evidence from the Collaborative Programs of Excellence in Autism network. *Journal of Autism and Developmental Disorders*, *34*(2), 139–150. https://doi.org/10.1023/B:JADD.0000022605.81989.cc

Ozonoff, S., & Strayer, D. L. (2001). Further evidence of intact working memory in autism. *Journal of Autism and Developmental Disorders*, *31*(3), 257–263. https://doi.org/10.1023/a:1010794902139

Paas, F., Tuovinen, J. E., Tabbers, H., & Van Gerven, P. W. M. (2003). Cognitive Load Measurement as a Means to Advance Cognitive Load Theory. *Educational Psychologist*, *38*(1), 63–71. https://doi.org/10.1207/S15326985EP3801_8

Parsons, T. D., Carlew, A. R., Magtoto, J., & Stonecipher, K. (2017). The potential of function-led virtual environments for ecologically valid measures of executive function in experimental and clinical neuropsychology. *Neuropsychological Rehabilitation*, *27*(5), 777–807. https://doi.org/10.1080/09602011.2015.1109524

Pellicano, E., Murray, M., Durkin, K., & Maley, A. (2006). Multiple cognitive capabilities/deficits in children with an autism spectrum disorder: "Weak" central coherence and its relationship to theory of mind and executive control. *Development and Psychopathology*, *18*(1), 77–98. https://doi.org/10.1017/S0954579406060056

Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. In *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1111/j.1469-7610.1996.tb01380.x

Pugliese, C. E., Anthony, L. G., Strang, J. F., Dudley, K., Wallace, G. L., Naiman, D. Q., & Kenworthy, L. (2016). Longitudinal Examination of Adaptive Behavior in Autism Spectrum Disorders: Influence of Executive Function. *Journal of Autism and Developmental Disorders*, *46*(2), 467–477. https://doi.org/10.1007/s10803-015-2584-5

Rajendran, G., & Mitchell, P. (2007). Cognitive theories of autism. *Developmental Review*, *27*(2), 224–260. https://doi.org/10.1016/j.dr.2007.02.001

Russell, J., Jarrold, C., & Henry, L. (1996). Working memory in children with autism and with moderate learning difficulties. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *37*(6), 673–686. https://doi.org/10.1111/j.1469-7610.1996.tb01459.x

Russell, J., Jarrold, C., & Hood, B. (1999). Two intact executive capacities in children with autism: Implications for the core executive dysfunctions in the disorder. *Journal of Autism and Developmental Disorders*, *29*(2), 103–112. https://doi.org/10.1023/A:1023084425406

Russo, N., Flanagan, T., Iarocci, G., Berringer, D., Zelazo, P. D., & Burack, J. A. (2007). Deconstructing executive deficits among persons with autism: Implications for cognitive neuroscience. *Brain and Cognition*, *65*(1), 77–86. https://doi.org/10.1016/j.bandc.2006.04.007

Rutter, M., Bailey, A., & Lord, C. (2003). *Social Communication Questionnaire*. Western

Psychological Services.

Simões, M., Bernardes, M., Barros, F., & Castelo-Branco, M. (2018). Virtual Travel Training for Autism Spectrum Disorder: Proof-of-Concept Interventional Study. *JMIR Serious Games*, *6*(1), e5. https://doi.org/10.2196/games.8428

Simões, M., Mouga, S., Pedrosa, F., Carvalho, P., Oliveira, G., & Branco, M. C. (2014). Neurohab: A Platform for Virtual Training of Daily Living Skills in Autism Spectrum Disorder. *Procedia Technology*, *16*(June 2015), 1417–1423. https://doi.org/10.1016/j.protcy.2014.10.161

Simões, M. R., Albuquerque, C. P., Pinho, M. S., Vilar, M., Pereira, M., Lopes, A. F., & Coimbra, et al. (2016). *Bateria de Avaliação Neuropsicológica de Coimbra (BANC) [Coimbra Neuropsychological Assessment Battery]*. CEGOC-TEA.

South, M., Ozonoff, S., & Mcmahon, W. M. (2007). The relationship between executive functioning, central coherence, and repetitive behaviors in the high-functioning autism spectrum. *Autism*, *11*(5), 437–451. https://doi.org/10.1177/1362361307079606

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*. https://doi.org/10.1037/h0054651

Travers, B. G., Powell, P. S., Mussey, J. L., Klinger, L. G., Crisler, M. E., & Klinger, M. R. (2013). Spatial and identity cues differentially affect implicit contextual cueing in adolescents and adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *43*(10), 2393–2404. https://doi.org/10.1007/s10803-013-1787-x

Velikonja, T., Fett, A.-K. K., & Velthorst, E. (2019). Patterns of Nonsocial and Social Cognitive Functioning in Adults with Autism Spectrum Disorder: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *76*(2), 135–151. https://doi.org/10.1001/jamapsychiatry.2018.3645

White, E. I., Wallace, G. L., Bascom, J., Armour, A. C., Register-Brown, K., Popal, H. S., Ratto, A. B., Martin, A., & Kenworthy, L. (2017). Sex differences in parent-reported executive functioning and adaptive behavior in children and young adults with autism spectrum disorder. *Autism Research*, *10*(10), 1653–1662. https://doi.org/10.1002/aur.1811

Williams, D. L., Goldstein, G., & Minshew, N. J. (2006). The profile of memory function in children with autism. *Neuropsychology*, *20*(1), 21–29. https://doi.org/10.1037/0894-4105.20.1.21

Zelazo, P. D., & Carlson, S. M. (2012). Hot and Cool Executive Function in Childhood and Adolescence: Development and Plasticity. *Child Development Perspectives*, *6*(4), 354–360. https://doi.org/10.1111/j.1750-8606.2012.00246.x

Zelazo, P. D., & Mller, U. (2005). Executive Function in Typical and Atypical Development. In *Blackwell Handbook of Childhood Cognitive Development* (Vol. 3, Issue 1, pp. 445–469). Blackwell Publishers Ltd. https://doi.org/10.1002/9780470996652.ch20

Zimmerman, D. L., Ownsworth, T., O'Donovan, A., Roberts, J., & Gullo, M. J. (2016). Independence of Hot and Cold Executive Function Deficits in High-Functioning Adults with Autism Spectrum Disorder. *Frontiers in Human Neuroscience*, *10*, 24. https://doi.org/10.3389/fnhum.2016.00024

2.6. Concomitant hyperactivation of the central executive, saliency and social cognition networks in autism spectrum disorder as revealed by an ecological paradigm

This chapter consists in the paper: **Mouga S**, Duarte IC, Café C, Sousa, D., Duque F, Oliveira G & Miguel Castelo-Branco. Concomitant hyperactivation of the central executive, saliency and social cognition networks in autism spectrum disorder as revealed by an ecological paradigm. (in preparation).

Abstract

The identification of major networks in the brain such as the Central Executive Network (CEN), the Saliency and Social Cognition networks in independent studies raises relevant questions of their relative involvement in autism spectrum disorder (ASD). Here we addressed this question using an ecological goal-oriented daily-life virtual reality task, with relevant executive demands, with social and non-social conditions.

A total of 34 adolescents participated in the study: 18 ASD patients without intellectual disability and 16 individuals controls with typical neurodevelopment (TD). We recorded functional magnetic resonance imaging (fMRI) data while participants performed the virtual reality EcoSupermarketX, task, monitored with eye-tracking, consisting of going shopping to a supermarket, with three types of sub-tasks that include no cues, non-social cues and social cues.

We found that in terms of performance, ASD group only differed from TD in two social cue condition: total time and distance taken to do the task. In fact, our ASD participants did not differ from TD in item errors, sequencing errors, and total head rotation (orienting response) irrespective of cue type measures. ASD were also matched to the TD group in the eye-tracking measures. When performing this ecological task, we found surprising evidence for hyperactivation across all three networks: social, executive, and the saliency circuits. Between group comparisons showed indeed increased activity in pivotal social brain circuits, namely the temporoparietal junction, ventromedial prefrontal cortex and inferior parietal lobule, differential recruitment of areas of the executive network, namely in the middle frontal gyrus, and also the pregenual anterior cingulate cortex which is part of the salience network. Contrarily, ASD showed surprisingly reduced activation in the parahippocampal gyrus, involved in scene recognition, which is a key feature in our task.

We can conclude that ASD adolescents, when performing a virtual shopping task matched to performance of controls, need to hyperactive three main core circuits in the brain: executive, saliency and social cognition networks. Our results corroborate the notion that hyperactivation may provide a compensatory mechanism in neurodevelopmental disorders and extend it to a remarkable multi-circuit level.

Introduction

Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by a varied severity of symptoms reflecting deficits in social communication and interaction, and repetitive patterns of behaviour and interests (American Psychiatric Association, 2013).

The central core symptom of ASD is impairment of social cognition abilities (Baron-Cohen et al., 1985; Happé et al., 2017). Social cognition is a complex adaptive cognitive process that involves implicit and explicit mental processes and encompasses our capacity to store, process and apply information about other people and social contexts, as well as the ability to attribute mental states to one self and others (Happé et al., 2017; Heyes & Frith, 2014). This allows one to predict other's people behaviour and adapt accordingly (Happé et al., 2017; Pinkham et al., 2008). Social cognition depends on a plethora of cognitive processes, including emotion recognition and processing, focus of attention, social stimuli encoding, social orienting, social motivation, learning from others, and verbal processing which are critical to our lives since early childhood and in a daily basis (Pino et al., 2020).

As detailed below, neuroimaging research in general separately studied the role of different neural networks in ASD and found variable activation patterns. These circuits include the core social cognition, the Central Executive Network (CEN) and the Saliency networks. However, a unified framework addressing the integrated recruitment of these networks is lacking. In this work we aim to address the relative role of these networks in an ecological daily-life task, with relevant executive demands.

The specific brain regions that are most frequently involved in social cognition have been identified by previous neuroimaging studies (Arioli & Canessa, 2019; Park et al., 2018). The brain network that supports these skills, also known as the "social brain", includes the prefrontal cortex (PFC), the amygdala, the anterior thalamus, the anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC), the superior temporal sulcus (STS) and temporo-parietal junction (TPJ) (Arioli & Canessa, 2019; Kennedy & Adolphs, 2012; Müller & Fishman, 2018; Schurz et al., 2014; Wolf et al., 2010). Differences between individuals with ASD and with typical neurodevelopment (TD) have been reported in several studies that used tasks operationalizing social cognition. Some of these studies reported distinct activation of these regions in ASD (Kana et al., 2014; Kim et al., 2016; Patriquin et al., 2016; White et al., 2014), combined with structural differences of some of these areas, including the STS, insula, fusiform face area and inferior frontal gyrus (Patriquin et al., 2016). There is growing

consensus that the impairments in ASD are usually not due to abnormalities in a specific unique area, but rather to particular brain networks (Chen et al., 2017; Eack et al., 2017; Müller & Fishman, 2018; Park et al., 2018).

In spite of the fact that functional network–level investigations of ASD pathophysiology have focused primarily on social cognition, impairments in other behavioural and cognitive domains, such as alterations in the relative perceptual salience of social and non-social stimuli, as well as differences in executive functioning (EF) have also been reported in ASD (Chita-Tegmark, 2016; Lai et al., 2017; Lai et al., 2014; Ruta et al., 2017). How changes in these cognitive domains relate to social cognition and other impairments that are typical of ASD remains an open question. These alterations, in particular the impairments in executive functions, have also an early-onset, are present throughout life, and can aggravate with age (especially in low-functioning subjects), and persists despite amelioration of other ASD symptoms (American Psychiatric Association, 2013; Mouga et al., 2020).

It remains an open question how executive network interrelates with the salience network in health and disease and into which extent it overlaps with social networks. For example, TPJ, which is related to the theory of mind and the distinction between self and other, is also associated with the direction of attention for salient cues. The fact that executive areas activate in social cognition paradigms suggests an important joint contribution of these areas in the explanation of these impairments.

Executive functions are cognitive skills, including planning, working memory, attention, inhibition, self-monitoring, self-regulation, and initiation (Goldstein & Naglieri, 2014). These high-level cognitive processes entail the modulation of lower-level processes, enabling one to behave flexibly and at the same time enhance the approach to unfamiliar circumstances and adaptation to new environments. In our everyday life one has to deal with unexpected situations and adapt behaviour accordantly, making plans for the future, switching from one activity to other, and for that one has to engage in such processes defined as executive functions, essential for successful daily living, which allow one to lead independent, purposeful lives (Gilbert & Burgess, 2008). In ASD individuals, executive functions are impaired from early ages and are thought to have a significant influence in their social cognition, adaptive behaviour and to be major contributors to everyday deficits, disability and absence of autonomy at the most varied levels (Demetriou et al., 2018; Geurts et al., 2014; Lai et al., 2017; Leung & Zakzanis, 2014).

Prior functional neuroimaging studies of executive functions in individuals with ASD indicated reduced activation of some brain areas in ASD, namely, the dorsolateral prefrontal

cortex (DLPFC) (Dichter & Belger, 2008; Luna et al., 2002; Shafritz et al., 2008), superior and inferior parietal lobules (Just et al., 2007; Schmitz et al., 2006; Shafritz et al., 2008; Solomon et al., 2009, 2014), anterior frontal (Solomon et al., 2009). Other activation patterns were found depending on the cognitive and emotional context (Schmitz et al., 2006). Despite these results, there is no consensus in the literature, which can be attributed to the type of task used, contextual demands, group heterogeneity and ASD comorbidity (Gilbert & Burgess, 2008; Minshew & Keller, 2010). A recent meta-analysis that analysed data from sixteen functional magnetic resonance imaging (fMRI) studies with executive functions tasks, including 739 participants (356 ASD, 383 TD individuals) aged from 7 to 52 years, revealed that both TD and ASD participants had significant activity in PFC regions, although with ASD presenting greater activation, comparing to TD participants, in left anterior cingulate cortex (ACC) and left cingulate gyrus, and lesser activation in the bilateral inferior parietal lobule (IPL), left middle frontal gyrus (MFG), right precuneus, left putamen, left thalamus, left medial prefrontal cortex (MPFC), and right superior parietal lobule (SPL) (May & Kana, 2020). These authors concluded that the EF impairments present in ASD subjects are due to changes in the overall executive network, instead of the unique PFC recruitment that they concluded that is similar in both ASD and TD groups. The wider brain network that is responsible for the processes involved in EF, as active maintenance and manipulation of information in working memory, judgment and decision making in the context of goal directed behaviour, is the CEN (Sridharan et al., 2008).

ASD has also been linked to alterations in the salience network (Monk et al., 2009). The salience network is a set of brain regions, including primarily the anterior cingulate and ventral anterior insular cortices, that is thought to play a role in detecting and coordinating a response to salient interoceptive and exteroceptive stimuli. It is therefore involved in selecting which stimuli are deserving of our attention, playing a role in switching between internally (for example, the default mode network) and externally focused networks (for example, the central executive network) (Menon & Uddin, 2010; Seeley, 2019; Seeley et al., 2007; Sridharan et al., 2008).

Most of the neuroimaging studies of salience network in ASD focused on the resting-state functional connectivity, and showed inconsistent results (Chen et al., 2017; Elton et al., 2016; Uddin, 2015; von dem Hagen et al., 2013). It was proposed that ASD and TD participants can be discriminated based on hyperconnectivity within the salience network (Uddin et al., 2013). However, little is known about how this altered resting-state connectivity

relates to brain activity during information processing (Green et al., 2016). Task-based experimental designs are therefore needed.

The relevance of focusing on identifiable brain networks to help understand mechanisms of disease in ASD has increased. Considering the symptoms that better characterize ASD, there are three brain networks which joint action is of special interest: social cognitive network or "social brain", central executive network and salience network. The last one partially overlaps task positive and task negative networks while the first two are dominantly task positive networks. How these networks interact in health and disease remains an intriguing question.

Cognitively demanding goal-directed tasks in the human brain are thought to involve the dynamic interplay of these large-scale neural networks, in particular the salience network and the CEN (Chand & Dhamala, 2016). In these types of tasks ASD subjects tend to struggle to successfully perform, especially in real-life, where there is, most of the times, the interference of social interaction difficulties and lack of motivation.

The neural correlates of social cognition processing and EF in ASD have been largely studied, but mainly in separate approaches, with mixed results. Our research question therefore asked how appropriate EF relates to activation in these different networks during a goal-oriented ecologic task where social and non-social conditions are present.

To this date, no fMRI study of ASD has examined the brain activity of ASD and TD subjects while performing a task that requires social cognition, EF, and cue saliency processing, at the same time, in the context of an ecological social situation. Such a task enabled us to study the function of the above mentioned three main networks. To address this question, we recorded fMRI data while participants performed a task developed at our Lab: the EcoSupermarketX, a virtual reality task, monitored with eye-tracking, consisting of going shopping to a supermarket, with three types of sub-tasks that include social cues, non-social cues, or no cue (see Methods section for detailed information). EcoSupermarketX was based in two main premises: on the one hand, shopping is a good example of a real-world task that often draws heavily on EF, contextual cueing and social/non-social cognition and on the other hand, different assessment and rehabilitation studies of ASD populations have successfully used supermarket settings (Carr & Carlson, 1993; Lamash & Josman, 2019).

We thereby sought to characterize the neural circuitry associated with the performance of a goal-oriented ecologic task with social and non-social conditions in ASD and TD individuals. We also hypothesized that this experimental approach will be able to show the

relative role of executive, social and saliency brain networks when performing a task related to impairments that are a central problem in ASD patient's daily life.

Methods

Participants

A total of 34 participants took part in the study, namely 18 ASD patients without intellectual disability and 16 TD controls. Due to exclusion criteria concerning excessive head movement during the fMRI acquisition (see details below) or inability to remain inside the scanner until the end of the acquisition, 5 participants (3 ASD and 2 TD) were excluded from the analysis. As a result, 15 ASD patients aged between 12 and 22 years (median age = 16 years 4 months) and 14 chronological age matched control participants aged between 10 and 18 years (median age = 15 years 2 months) were included for the final analysis.

The ASD participants were identified from a large sample of participants who had previously participated in our studies (chapters 2.4 and 2.5) and recruited from the Unit of Neurodevelopment and Autism, Child Developmental Centre, Paediatric Hospital, Centro Hospitalar e Universitário de Coimbra, Portugal. The selection was based on the chronological age (≥ 10 years) and on the ability to cooperate in the fMRI acquisition.

ASD diagnosis was assigned on the basis of the gold standard instruments: parental or caregiver interview - Autism Diagnostic Interview– Revised, ADI-R (Le Couteur et al., 2003; Catherine Lord et al., 1994), direct structured proband assessment - Autism Diagnostic Observation Schedule, ADOS (Lord et al., 1989; Lord & Rutter, 1999) , and clinical examination performed by an experienced neurodevelopmental Paediatrician, based on the current diagnostic criteria for autism spectrum disorder from the Diagnostic and Statistical Manual of Mental Disorders 5, DSM-5 (American Psychiatric Association, 2013). All ASD participants had positive results in the ADI-R and ADOS for autism or ASD and met the criteria for ASD from the DSM-5. A comprehensive medical observation excluded associated medical conditions such as epilepsy, neurocutaneous or other genetic syndromes, or other usual comorbidities in ASD samples, such as Attention Deficit Hyperactivity Disorder (ADHD) or intellectual disability.

The TD group included 14 participants with typical neurodevelopment who were matched for chronological-age, Performance Intelligence Quotient (PIQ) (Jarrold & Brock, 2004), gender, and handedness with the ASD group (Mann-Whitney U or Pearson Chi-Square

test, p>.05). The Social Communication Questionnaire which is a screening test for ASD symptoms was completed by the TD group participants' parents to exclude ASD (Rutter et al., 2003). The positive cut-off for ASD is equal or above 15 and all participants scored below.

Two ASD patients and one TD participant demonstrated left-hand dominance as it was measured using the Edinburgh Inventory (Oldfield, 1971). When necessary, correction to normal vision was ensured using specific eyeglasses compatible with the magnetic field. Given that some ASD patients exhibited hypersensitivity to the sound, we worked with each patient, so they were previously familiarized with the magnetic resonance imaging (MRI) sounds and were able to attend and perform experimental tasks inside the scanner. Nonetheless, all participants used hearing protection.

Both groups underwent a comprehensive neuropsychological evaluation and an assessment of the intelligence quotient (IQ) to exclude Intellectual disability (full-scale IQ>70). All participants included in the study received the Portuguese adapted version of the Wechsler Intelligence Scale for Children – third edition (WISC-III) (Wechsler, 2003) or the Wechsler Adult Intelligence Scale – third edition (WAIS-III) (Wechsler, 2008), according to the participant's age.

The demographic characterization of both groups is summarized in Table 2.6.1.

Table 2.6.1. Characterization of the ASD and TD groups			
	ASD	**TD**	
	Median (IQR; min-max)	**Median (IQR; min-max)**	
N	15	14	
Gender (M/F)	14/1	12/2	p =.501*
CA (years and months)	16y 5m (4y 5m; 12y 2m – 22y 4m)	15y 9m (2y 8m; 10y 8m - 18y 6m)	p =.290*
Handedness (R/L)	14/1	13/1	p =.960*
FSIQ	100.0 (24; 71-137)	116.5 (24; 92-152)	p =.004
VIQ	97.0 (17; 78-126)	120.5 (29; 98-145)	p<.001
PIQ	101.0 (35; 73-136)	107.0 (21; 85-146)	p =.172*
ADI-R RSI	16.0 (11; 7-26)	-	
ADI-R L/C	10.0 (4; 3-22)	-	
ADI-R RB/I	4.0 (2; 2-11)	-	
ADOS COM	5.0 (2; 3-7)	-	
ADOS SI	8 (3; 4-14)	-	
ADOS Total	12.0 (5; 8-19)	-	

NOTE. ASD = Autism Spectrum Disorder group; TD = Typical neurodevelopment group; IQR= Interquartile Range; min = minimum; max – maximum; M = Male; F= Female; CA = Chronological Age; R = right; L = left; FSIQ = Full-scale intelligence quotient (IQ); VIQ = Verbal IQ; PIQ = Performance IQ; ADI-R RSI = ADI-R Reciprocal Social Interactions; ADI-R L/C = Autism Diagnostic Interview – Revised Language/Communication; ADI-R RB/I = ADI-R Repetitive Behaviours/Interests; ADOS COM = ADOS Communication; ADOS SI = ADOS Social Interaction. * Mann-Whitney U or Pearson Chi-Square p>.05.

Procedure

In the present study, an experimental task using virtual reality stimuli, named EcoSupermarketX, was conducted. The acquisition session comprised one structural MRI

sequence and three fMRI sequences (three EcoSupermarketX runs). The EcoSupermarketX stimulus was presented on a liquid crystal display (LCD) monitor (48.5 × 87.8 cm, 1920 × 1080 pixel resolution, 60 Hz refresh rate) which the participants viewed through a mirror mounted above their eyes at an effective distance of 178 cm. The participants could actively navigate the scenario and select the response using an MR-compatible joystick (Hybridmojo, San Mateo CA, USA). During the acquisition session, individually calibrated eye tracking data (sample frequency of 1K) were recorded inside the scanner using Eyelink 1000 software (EyeLink 1000 Plus, SR Research, Mississauga, ON, Canada).

EcoSupermarketX

EcoSupermarketX is a non-immersive virtual reality task that aims to accurately evaluate the social cognition and executive functions abilities of the participants using a realistic quotidian scenario – a computer-generated supermarket.

EcoSupermarketX is a new assessment tool created at our laboratory in order to add performance-based information to the other cognitive and executive measures used.

EcoSupermarketX Stimuli and Design

The EcoSupermarketX stimuli were generated with Vizard Virtual Reality toolkit – version 5.2 (WorldViz, Santa Barbara, USA).

The task in the MRI was preceded by a similar task (explained in the chapter 2.5), so the participants were already familiarized with the scenario of the supermarket and with the use of joystick. The joystick was adapted to right or left-handed participants and allowed them to navigate in the scenario and to rotate the scenario to the side (as if they were turning the head and looking right or left).

The experimental task consisted of 3 separate runs with a variable duration (since it was dependent of the performance of each subject). A boxcar design was employed in which 3 experimental conditions (No Cue, Non-Social Cue and Social Cue) were randomly presented. A total of 6 trials per condition were obtained. The participants viewed a black screen with a central cross between each trial. In each trial the participants were instructed to search and pick groceries from the supermarket shelves that were previous presented at a grocery list. The grocery list had three items. The list was presented as an instruction individually in a trial-by-trial basis: "Find strawberry cake" followed by "Find sausages" and then "Find olive oil", for example (each item image and name appeared for three seconds, see

Figure 2.6.1). The groceries were replaced randomly in the shelves in a trial-by-trial basis. For every single list with 3 items, which defines a trial, the participant had a maximum of 3 minutes to perform the task, i.e., to find the groceries and conclude the "shopping". Nevertheless, the trial ends as the participant completes the list. Participants were instructed to collect all items in the sequence they appeared in the list, and as fast and accurately as possible. They had to plan and monitor their behaviour to complete the task successfully.

Additionally, participants were informed that during the task three situations could happen: they could have help from a person (an avatar), an arrow or no help at all; these were the different cues respectively: Social Cue, Non-Social and No Cue. They were not told what specifically the person (avatar gazing to the grocery) was doing or what kind of arrows (wood arrow) were presented (Figure 2.6.1). Participants underwent 3 runs, six trials for each run, performing a total of 18 trials (six trials per cue type). The are 30 seconds of baseline and between the instruction (encoding) and the beginning of the task there is 12, 14 or 16 seconds.

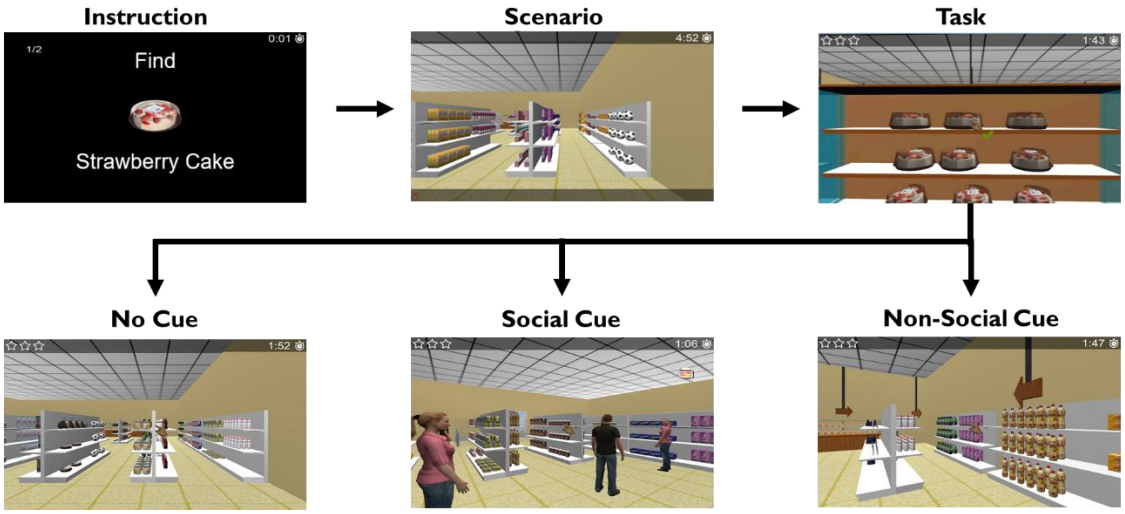

Figure 2.6.1. EcoSupermarketX task design, considering the different types of cues. The task blocks included an instruction that consisted in the grocery list the participants had to pick. The grocery list (3 items) was presented as an instruction individually in a trial-by-trial basis: "Find strawberry cake" followed by "Find sausages" and "Find Olive Oil", for example (each item image and name appeared for three seconds). The groceries were replaced randomly in the shelves on a trial-by-trial basis. Participants were instructed to collect all items in the sequence they appeared in the list, and as fast and accurately as possible. Additionally, there were three different conditions related to cues: No Cue; Non-Social Cue (wooden arrow) and Social Cue (avatar gazing to the grocery). The task blocks were divided in three runs with an interval between each run.

To reduce merely memory constraints, an image of the requested item from the grocery list was displayed in the upper right corner after 40 seconds, giving the opportunity to the participant to conclude the trial. Focusing on the enhancement of the realism of the task and its ecological validity, realistic three-dimensional (3D) forms and commercial brands were used to depict the groceries included in the supermarket scenario.

Eye-tracking Recording and Measures

Eye movements were recorded using an infrared-emitting video-based eye tracker (EyeLink 1000 Plus, SR Research, Mississauga, ON, Canada). In terms of EyeLink tracking settings, we used mono mode and pupil corneal reflection, at a 1K sample rate. The tracker has a reported gaze position accuracy of 0.25-0.50º and a spatial resolution of 0.05. A 9-point calibration procedure with a fixation circle was performed before each run. The participants were instructed to fixate on the circle. After the calibration, there was a validation trial to ensure the precision of the data collection. The calibration process was repeated when necessary until the eye achieved good mapping on all nine test positions (tracking error smaller than 1° visual angle). As participants were performing a dynamic virtual-reality task in which they were walking around a supermarket, the frames in the screen were always different for all participants. In this way, the areas of interest (AOI) were defined in the virtual-reality software, which received the participants' gaze coordinates from the eye tracking software in a real-time mode. Using those screen coordinates, we computed the time that the participant was looking to each AOI in a real time basis. The areas of interest related to the different types of cues were defined: Head (because the avatar is looking to the item) and Arrow.

Imaging data acquisition parameters and pre-processing

MRI experiments were performed on a 3 Tesla (3T) Magnetom Prisma Fit MRI scanner (Siemens, Erlangen, Germany), at the Institute of Nuclear Sciences Applied to Health (ICNAS), Universidade de Coimbra, Portugal, using a 12-channel head coil. The scanning session started with the acquisition of one T1-weighted 3D anatomical magnetization-prepared rapid acquisition gradient echo (MPRAGE) pulse sequence, with repetition time (TR) = 2530 ms, echo time (TE) = 3.5 ms, resolution 1 mm^3 (voxel size 1.0 × 1.0 × 1.0 mm), flip angle = 7°, 192 slices, field of view (FOV) = 256 × 256 mm and a slice thickness of 1mm.

Afterward, three functional runs were acquired using a T2*-weighted gradient echo-planar imaging (EPI) sequence, with slice thickness of 3 mm and voxel size 3 mm^2, 37

interleaved slices without gap, acquired parallel to the AC-PC line, TR = 2000 ms, TE = 30 ms, fip angle of 75° and FOV of 210×210. In average, the scanning session lasted 45 minutes. Data pre-processing was performed on BrainVoyager 21.4 software (Brain Innovation, Maastricht, The Netherlands). Pre-processing included slice-scan time correction, 3D head-motion correction and temporal high-pass filtering (general linear model [GLM] - Fourier, 2 cycles). Participants exceeding 6 mm of movement in any axis were excluded from further analysis (n=5; 3 ASD and 2 TD). Data were normalized to Montreal Neurological Institute (MNI) space and spatially smoothed using a gaussian kernel with FWHM of 6 mm.

Data Analysis

All statistical analysis was completed with the support of the version for Microsoft Windows® of the Statistical Package for Social Sciences, version 26 (SPSS ®, Chicago, IL, USA) and the BrainVoyager 21.4 software (Brain Innovation, Maastricht, the Netherlands).

Behavioural EcoSupermarketX data analysis

Several parameters were defined for the analysis of the EcoSupermarketX performance of each participant: considering errors, time, distance, and head rotation variables. Information about the executive functions that, in our perspective, are reflected by each EcoSupermarketX behavioural measure was added, despite our knowledge that the daily-life routines, and therefore the tasks that simulate them, require multiple cognitive and executive functions that are difficult to extricate. The different behavioural measures/parameters defined were Item Errors; Sequencing Errors; Time; Distance; Head Rotation, which we describe below:

Item errors - Number of picked items of the EcoSupermarketX scenario that were not in the list of groceries divided by the number of items in the grocery list × 100 (e.g., select a toy, when the toy was not in the list).

Sequencing errors - Number of picked items of the EcoSupermarketX scenario that in the incorrect sequence in the list of groceries divided by the number of items in the grocery list × 100 (e.g., to select sausages before cereals, when the cereals where first in the list).

Total time - Performance time (in seconds) - The time the participant was engaged in the execution of the task: looking for and grabbing the products that were in the grocery list (time elapsed from the end of the grocery list memorization to the last picked item).

Total distance - Performance distance - The distance the participant goes through in the execution of the task: looking for and grabbing of the products that are in the grocery list).

Head rotation (orienting response) - Sum of virtual head rotations by the participant (in degrees) during the time of execution of the task. This parameter aims to reflect attentional control, psychomotor and processing speed, planning, and motor time.

Nonparametric statistics (Mann-Whitney U tests) were carried out for all statistical analyses to avoid biases due to deviations from normality and variance heterogeneity.

Functional Magnetic Resonance data analysis

Statistical analysis was performed at group level using a GLM approach. The predictor's model was obtained by convolution of the boxcar time course (the individual block duration was defined up to the participant's response) with a two-gamma hemodynamic response function.

First, to compute a whole brain statistical maps for group effect, an overlay random-effects (RFX) ANOVA with within-factors "Cue" (No cue, Non-Social Cue, Social Cue) and between-factor "group" (ASD vs. TD) was conducted. These statistical maps were corrected for multiple comparisons using a cluster threshold method with a fixed p-value of .05 and an estimated minimum cluster extension of 70 contiguous voxels. The extension estimation was made using Monte Carlo simulations (1000 iterations). This map revealed areas for which there are fundamental differences between groups irrespective of other factors.

In addition, for each identified region, post-hoc *t*-tests were computed whenever significant group effects were found.

Ethics Statement

All the procedures in this study were reviewed and approved by the ethics committees from Faculty of Medicine from Coimbra University (CE-11/2013) and Centro Hospitalar e Universitário de Coimbra (CHUC-102-13) and was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written

informed consent was obtained from the parents/guardians of all participants or, when appropriate, the participants themselves. Children and adolescents also gave oral informed consent.

Results

Behavioural Results

Behavioural analysis revealed that ASD and TD groups achieved similar performances in all EcoSupermarketX task parameters (p>.05, Mann-Whitney U), except for total time and total distance in the Social Cue Condition. The total time taken to perform the task was statistically significantly higher for the ASD group (Mdn = 34.5) than the TD group (Mdn = 26.9), U = 58.00, p = .041, d = .824. The same pattern is present in the total distance, with the ASD group (Mdn = 50.1) walking longer distances in the Social Cue condition, than to the TD group (Mdn = 43.0), U = 44.00, p = .007, d = 1.137. These results are summarized in Figure 2.6.2.

However, since there are no significant statistical differences in other measured parameters: item errors, total sequencing errors and head rotation, both in No Cue, Non-Social, and Social Cue conditions, we can assume that both groups are performance matched.

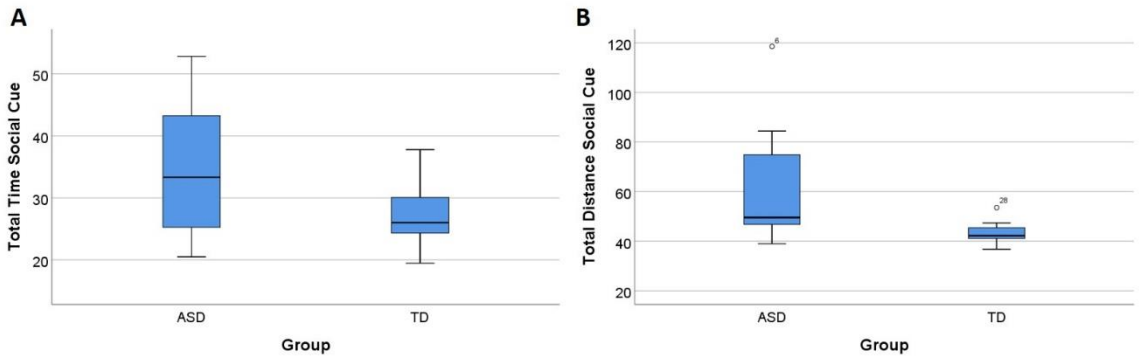

Figure 2.6.2. Performance across time and distance in Social Cue Condition in ASD and TD groups. **A.** Total time for ASD and TD groups for the Social Cue condition. **B.** Total distance for ASD and TD groups for the Social Cue condition. Boxplots: central mark – median; edges of box – 25th and 75th percentiles; whiskers – most extreme data points (minimum and maximum). NOTE. ASD= Autism spectrum disorder, TD= Typical neurodevelopment.

Eye-tracking measures

The time looking at the different AOIs of social or non-social relevance (Head and Arrow) that were related to the different types of cues (Social and Non-Social, respectively) was compared between the two groups (ASD and TD).

A Mann-Whitney U test indicated no differences between the ASD and TD groups in the AOIs Head ($U = 99.00$, $p = 1.000$) and Arrow ($U = 114.00$, $p = .482$).

fMRI: Whole-brain analysis of between group effects in EcoSupermarketX task

The whole-brain RFX ANOVA revealed significant group effects in prefrontal (including ventromedial, orbitofrontal and anterior cortex), temporal (in particular the temporoparietal junction and the temporal pole), and visual areas (ASD showed higher Blood-Oxygen-Level-Dependent contrast [BOLD] activity than TD, see below). It worth noting that in parahippocampal areas TD showed higher BOLD activity than ASD participants (see below). The differences between the pattern observed in ASD and in TD are detailed in Table 2.6.2. ($F \geq 4.21$; $p < .05$, corrected for multiple comparisons) and further highlighted in Figure 2.6.3.

ROI-based post-hoc *t*-tests confirmed higher BOLD activity for ASD compared with TD in response across EcosupermarketX task conditions in particular in regions involved in EF, perception, social cognition and error monitoring. The executive areas with higher BOLD activity for ASD were the Middle Frontal and Ventrolateral PFC (vlPFC) which was associated with activations in other regions involved also in social and emotional cognition (Ventromedial PFC [vmPFC] and Orbitofrontal Cortex). Increased Inferior Frontal Gyrus (a region involved in inhibitory control) activation was also observed. Other regions involved in social cognition with higher BOLD activity for ASD found included the Middle temporal cortex, Temporal Pole, TPJ, including the Supramarginal Gyrus as well. The same analysis revealed higher BOLD activity for TD compared to ASD in Parahippocampal Gyrus (PHG), which is believed to be involved in contextualizing of scene and social background as well as in memory encoding and retrieval which is a dominant feature of the EcosupermarketX task (for further details on statistical significance, see Table 2.6.2.

Table 2.6.2. Whole brain RFX ANOVA analysis: summary of RFX-GLM contrasts, outputs, and statistics

Region	BA	Peak MNI Coordinates			No of voxels	F	p	No Cue		Non-Social Cue		Social Cue	
		X	Y	Z				t	p	t	p	t	p
ASD>TD													
RH Middle Temporal/Occipital Gyrus	37	53	-55	-2	1190	12.12	**.002**	4.006	**<.001**	4.969	**<.001**	3.943	**.001**
RH Temporal Pole	38	41	20	-22	664	11.51	**.002**	3.242	**<.001**	4.812	**<.001**	3.668	**<.001**
RH Primary Somatosensory Cortex/Somatosensory Association Cortex/Supramarginal Gyrus	1/7/40	32	-37	57	2726	16.02	**<.001**	5.114	**<.001**	6.073	**<.001**	5.820	**.001**
RH Primary Somatosensory Cortex Primary Motor Cortex	1/4	19	-31	57	710	10.13	**.004**	4.373	**<.001**	4.421	**<.001**	3.943	**.001**
L/RH Supplementary Motor Area	6	-2	-28	54	2285	15.15	**<.001**	5.162	**<.001**	5.721	**<.001**	5.467	**<.001**
L/RH Ventromedial Prefrontal Cortex/ Pregenual Anterior Cingulate Cortex Orbitofrontal Cortex	32 10/11	-6	50	-8	4439	19.04	**<.001**	4.575	**<.001**	5.611	**<.001**	3.690	**<.001**
LH Middle Frontal Gyrus	10	-33	51	-1	1979	13.69	**.001**	3.509	**.002**	3.391	**.003**	3.692	**.001**
LH Middle Temporal Gyrus	21/22	-60	-19	5	10826	22.10	**<.001**	5.405	**<.001**	7.688	**<.001**	4.703	**<.001**
LH Middle Frontal Gyrus	8/9	-30	24	42	1347	14.18	**<.001**	4.040	**<.001**	4.389	**<.001**	4.040	**.001**
LH Inferior Parietal Lobule	40	-38	-49	53	805	12.02	**.002**	5.114	**<.001**	6.073	**<.001**	5.820	**<.001**
Claustrum		-37	-2	-18	618	10.42	**.003**	2.152	**<.001**	4.530	**<.001**	3.367	**<.001**
LH Inferior Frontal Gyrus/Ventrolateral Prefrontal Cortex	45/46/47	-50	-2	-18	3552	15.38	**<.001**	4.512	**<.001**	5.440	**<.001**	3.851	**.001**
LH Temporal Parietal Junction	22/40	-60	-27	21	1937	19.70	**<.001**	5.108	**<.001**	4.747	**<.001**	4.928	**<.001**
TD>ASD													
RH Parahippocampal Gyrus	19	26	-49	-7	586	11.18	**.002**	-4.008	**.001**	-4.318	**.001**	-4.198	**.001**
LH Parahippocampal Gyrus	18/19	-16	-72	1	1810	15.41	**<.001**	-8.547	**<.001**	-9.091	**<.001**	-8.479	**<.001**

◄**NOTE.** Brain regions showing significant whole brain RFX-ANOVA group effect ($p<.05$, corrected for multiple comparisons) and ROI-based GLM-RFX contrasts for group differences between responses to Social, Non-Social and No Cue conditions. Positive *t*-tests indicate higher β values for the ASD group than for TD. Negative *t*-tests indicate higher β values for the TD group than for ASD. X, Y and Z represent MNI coordinates. Significant comparisons are marked in bold. BA = Brodmann Area; ASD= Autism spectrum disorder group, TD= typical neurodevelopment group, RH=right hemisphere, LH=left hemisphere.

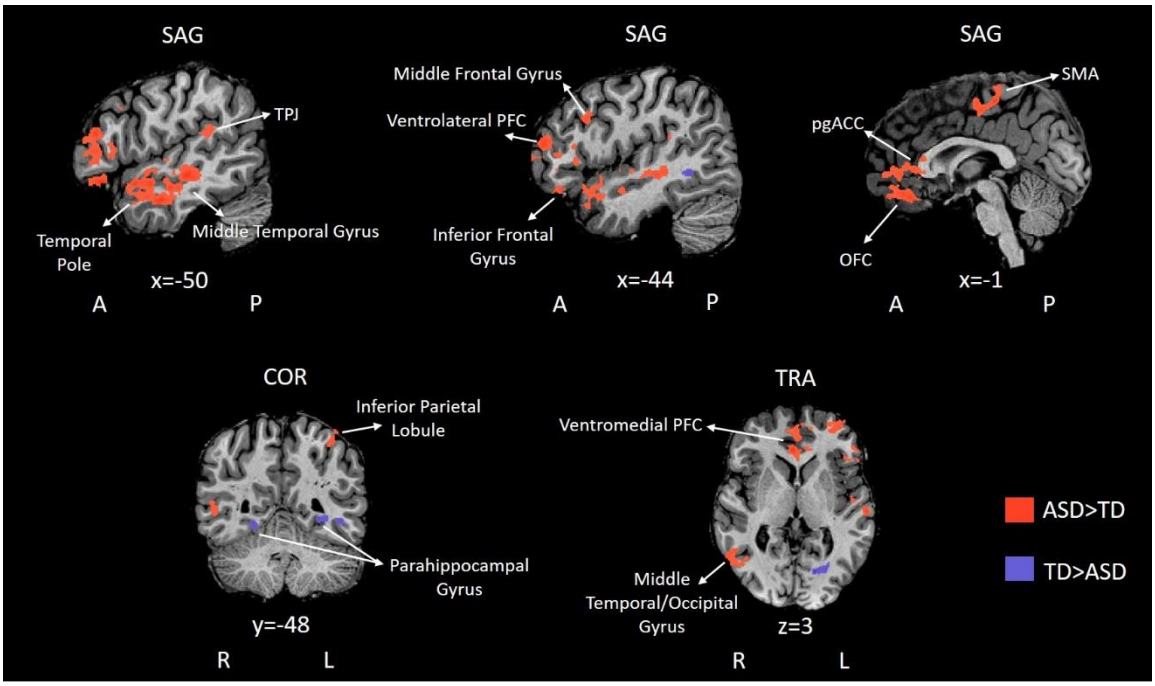

Figure 2.6.3. RFX ANOVA group effects for EcoSupermarketX Task. Statistical maps from group analysis overlaid on sagittal, coronal, and transversal slices of a representative subject. Red clusters depict regions where BOLD activity was higher for individuals with ASD than TD. Blue clusters depict regions where BOLD activity was lower for individuals with ASD than TD. Slice locations are given in MNI coordinates. **NOTE.** ASD= Autism Spectrum Disorder group, TD= Typical neurodevelopment group, TPJ= Temporal Parietal Junction, PFC= Prefrontal Cortex, pgACC= Pregenual Anterior Cingulate Cortex; OFC= Orbitofrontal Cortex, SMA= Supplementary Motor Area, A= Anterior; P= Posterior, R= right, L= left; SAG = Sagittal plane; COR = Coronal plane; TRA = Transversal Plane; MNI = Montreal Neurological Institute.

Discussion

In this study we investigated the differential involvement of executive, saliency and social cognition networks when ASD and healthy participants engage in a demanding goal-oriented task. To achieve this goal, we developed a novel ecologic task, the EcoSupermarketX. Going shopping to a supermarket is an essential daily living chore for independent life. Our EcoSupermarketX experiment drives heavily on social cognition, EF, and saliency of cues in terms of social and non-social content, in the context of this realistic social situation (shopping). In this scenario participants had to memorize a small list of three items, and they were instructed to find and "grab" each item in the supermarket. Like in real life, they had the possibility to have: a) no help at all (No Cue); b) the help of an arrow (Non-Social Cue) that pointed to the right route, or c)the help of a "person", an avatar (Social Cue) that pointed the right way to find the grocery. The current work is, to our knowledge, the first fMRI study with

an ecologic paradigm explicitly designed to investigate brain activity in three different networks: social, central executive, and salience.

In order to answer our main research question, we used markers of EF under distinct task constraints, with explicit manipulations of the types of cues that could help in the performance of the task. We also monitored the visual attention of the individuals going shopping to specific AOI's social (avatar's head) and non-social (arrow) cues.

Preserved ASD performance for non-social conditions

We found that in the absence of a cue or with the non-social cue, ASD subjects' performance did not differ from the TD group. ASD group only performed worse than the TD in two specific behavioural measures of the social cue condition: total time and distance taken to do the task. In fact, our ASD participants did not differ from TD in item errors, sequencing errors, and total head rotation in all conditions (No Cue, Non-Social Cue and Social Cue), reinforcing the notion that participants were overall matched in terms of error performance.

Pattern of higher brain activity in ASD in executive, saliency and social cognition networks while performing EcoSupermarketX

When performing this ecological daily living task – going shopping, we found differential activation across three main networks: social, executive, and the saliency circuits. Accordingly, we found higher activity by the ASD group when compared with the group of healthy individuals (without ASD) in areas that are pivotal in social brain circuits, namely the TPJ, vmPFC and IPL. Importantly, the TPJ has also being implicated in social and emotional processing (Bilek et al., 2015; Frith & Frith, 2003; Krall et al., 2015; Schulte-Rüther et al., 2011), including joint attention (Oberwelland et al., 2016; Redcay et al., 2010; Schilbach et al., 2010), as well as to attentional reorienting to salient cues (Carter & Huettel, 2013) and visually triggered shifts of attention that share common neural substrates with gaze perception (Itier & Batty, 2009). These aspects are quite important in our task design. Moreover, it is also known that the TPJ is most reliably activated when participants engage in tasks involving the inference of goals or end states for described actions (Van Overwalle, 2009).

It is interesting to point out that differential recruitment of areas of the executive network were found with larger activation in ASD, namely in the middle frontal gyrus, and also pregenual ACC which is part of the salience network. These areas were found to present higher activity in the ASD group while performing the EcoSupermarketX.

The only region that showed reduced activation in ASD as compared to controls was the parahippocampal gyrus, involved in scene recognition. It is indeed known that parahippocampal gyrus is recruited for spatial navigation and memory encoding and retrieval (Aminoff et al., 2013), which is required to perform the presented task.

We speculate that the opposite pattern observed for the parahippocampal gyrus may reflect the fact that relative over-recruitment observed for the three main networks reflects task difficulty but given that ASD are quite functional in terms of scene recognition and navigation, under-recruitment in comparison to controls may even occur in this case of relative proficiency. A study comparing TD adolescent girls before and after practice on a visual-spatial problem-solving computer game, Tetris, showed that brain activity decreases after practice (Haier et al., 2009). We may speculate that is what occurred in our study, since our fMRI tasks preceded by a similar task (explained in the chapter 2.5), so the participants were already familiarized with the scenario of the supermarket and with the use of joystick and had a period of practice. Additionally, a recent study (Cardillo et al., 2020) showed that no impairments emerged in visuospatial working memory in ASD, as compared with TD controls, which corroborates our previous work (Bernardino et al., 2012), showing that this ability is relatively spared.

Interestingly, this pattern of higher activity in all brain areas recruited to do the task, except the parahippocampal gyrus which showed lower activity in ASD group, is common to the three conditions in the task, either using structured cues (social and non-social), or performing the shopping without no cues about the object location. As the final performance of the task is quite similar between the groups, we may speculate that the ASD groups maintain a higher neural effort level, a putative compensatory mechanism, to reach similar performance levels as the TD group. Although neural compensation mechanisms are still controversial, this task combined with fMRI showed that ASD group use the structured cues as TD do in goal-oriented behaviour.

Considering that shopping is a challenging task for the majority of ASD patients and our results showed they are engaged in an extra mental effort in the executive, saliency and social brain networks to perform the task; we may assume that they had to make more effort, with ensuing larger pressure and stress level, than the TD group. If this is true it would explain why there is higher activity in the OFC, an area that is part of the limbic system, being involved in control emotional reactions in certain social situations, as well as process of decision making and self-control (Adolphs, 2009). OFC has also been thought to contain a "cognitive map" of task space in which the current state of the task is represented, and that this representation is

especially critical for behaviour when states are unobservable from sensory input (Schuck et al., 2016).

Similar performance scores and different patterns of brain activation relative to controls which may actually occur in a compensatory way to provide preserved performance have already been reported (Graewe et al., 2013). In functional neuroimaging studies that focused on response inhibition in adults with ASD (Kana et al., 2007; Schmitz et al., 2006). Kana et al (2007) found that the adults with ASD relative to controls had decreased activity, namely the anterior cingulate cortex, while Schmitz et al. (Schmitz et al., 2006) found increased activity for the ASD group in several brain regions known to be involved in response inhibition, including the inferior frontal gyrus and the OFC during a simple Go/NoGo task using non-social stimuli.

However, most of the studies differ from ours in two very important areas: ecologic set up and multiple task demands (social, attentional, executive) that are inherent to the paradigm.

We found that ASD subjects could understand the shopping task and that besides the behavioural results, ASD did not presented differences comparing to the TD group in the eye-tracking measures. Our results are consistent with a body of literature suggesting that hyperactivation of particular networks may provide a compensatory mechanism to preserve performance (Graewe et al., 2013). It is remarkable that, in the current study this was observed across executive, saliency and social cognition networks.

References

Adolphs, R. (2009). The Social Brain: Neural Basis of Social Knowledge. *Annual Review of Psychology*, *60*(1), 693–716. https://doi.org/10.1146/annurev.psych.60.110707.163514

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). American Psychiatric Publishing.

Aminoff, E. M., Kveraga, K., & Bar, M. (2013). The role of the parahippocampal cortex in cognition. *Trends in Cognitive Sciences*, *17*(8), 379–390. https://doi.org/10.1016/j.tics.2013.06.009

Arioli, M., & Canessa, N. (2019). Neural processing of social interaction: Coordinate-based meta-analytic evidence from human neuroimaging studies. *Human Brain Mapping*, *40*(13), 3712–3737. https://doi.org/10.1002/hbm.24627

Baron-Cohen, S., Leslie, A. M., & Frith, U. (1985). Does the autistic child have a "theory of mind" ? *Cognition*. https://doi.org/10.1016/0010-0277(85)90022-8

Bernardino, I., Mouga, S., Almeida, J., Van Asselen, M., Oliveira, G., & Castelo-Branco, M. (2012). A Direct Comparison of Local-Global Integration in Autism and other Developmental Disorders: Implications for the Central Coherence Hypothesis. *PLoS ONE*, *7*(6), e39351. https://doi.org/10.1371/journal.pone.0039351

Bilek, E., Ruf, M., Schäfer, A., Akdeniz, C., Calhoun, V. D., Schmahl, C., Demanuele, C., Tost, H., Kirsch, P., & Meyer-Lindenberg, A. (2015). Information flow between interacting human brains: Identification, validation, and relationship to social expertise. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1421831112

Cardillo, R., Vio, C., & Mammarella, I. C. (2020). A comparison of local-global visuospatial processing in autism spectrum disorder, nonverbal learning disability, ADHD and typical development. *Research in Developmental Disabilities*, *103*(April), 103682. https://doi.org/10.1016/j.ridd.2020.103682

Carr, E. G., & Carlson, J. I. (1993). Reduction of severe behavior problems in the community using a multicomponent treatment approach. *Journal of Applied Behavior Analysis*, *26*(2), 157–172. https://doi.org/10.1901/jaba.1993.26-157

Carter, R. M. K., & Huettel, S. A. (2013). A nexus model of the temporal-parietal junction. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2013.05.007

Chand, G. B., & Dhamala, M. (2016). Interactions Among the Brain Default-Mode, Salience, and Central-Executive Networks During Perceptual Decision-Making of Moving Dots. *Brain Connectivity*, *6*(3), 249–254. https://doi.org/10.1089/brain.2015.0379

Chen, H. H., Uddin, L. Q., Duan, X., Zheng, J., Long, Z., Zhang, Y. Y., Guo, X., Zhang, Y. Y., Zhao, J., & Chen, H. H. (2017). Shared atypical default mode and salience network functional connectivity between autism and schizophrenia. *Autism Research*. https://doi.org/10.1002/aur.1834

Chita-Tegmark, M. (2016). Social attention in ASD: A review and meta-analysis of eye-tracking studies. *Research in Developmental Disabilities*, *48*, 79–93. https://doi.org/10.1016/j.ridd.2015.10.011

Demetriou, E. A., Lampit, A., Quintana, D. S., Naismith, S. L., Song, Y. J. C., Pye, J. E., Hickie, I., & Guastella, A. J. (2018). Autism spectrum disorders: a meta-analysis of

executive function. *Molecular Psychiatry*, *23*(5), 1198–1204. https://doi.org/10.1038/mp.2017.75

Dichter, G. S., & Belger, A. (2008). Atypical modulation of cognitive control by arousal in autism. *Psychiatry Research: Neuroimaging*, *164*(3), 185–197. https://doi.org/10.1016/j.pscychresns.2007.12.005

Eack, S. M., Wojtalik, J. A., Keshavan, M. S., & Minshew, N. J. (2017). Social-cognitive brain function and connectivity during visual perspective-taking in autism and schizophrenia. *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2017.03.009

Elton, A., Di Martino, A., Hazlett, H. C., & Gao, W. (2016). Neural Connectivity Evidence for a Categorical-Dimensional Hybrid Model of Autism Spectrum Disorder. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2015.10.020

Frith, U., & Frith, C. D. (2003). Development and neurophysiology of mentalizing. In *Philosophical Transactions of the Royal Society B: Biological Sciences*. https://doi.org/10.1098/rstb.2002.1218

Geurts, H. M., van den Bergh, S. F. W. M., & Ruzzano, L. (2014). Prepotent response inhibition and interference control in autism spectrum disorders: Two Meta-Analyses. *Autism Research*, *7*(4), 407–420. https://doi.org/10.1002/aur.1369

Gilbert, S. J., & Burgess, P. W. (2008). Executive function. *Current Biology*, *18*(3), R110–R114. https://doi.org/10.1016/j.cub.2007.12.014

Goldstein, S., & Naglieri, J. A. (2014). Introduction: A History of Executive Functioning as a Theoretical and Clinical Construct. In S. Goldstein & J. A. Naglieri (Eds.), *Handbook of Executive Functioning* (pp. 1–567). Springer New York. https://doi.org/10.1007/978-1-4614-8106-5

Graewe, B., Lemos, R., Ferreira, C., Santana, I., Farivar, R., De Weerd, P., & Castelo-Branco, M. (2013). Impaired Processing of 3D Motion-Defined Faces in Mild Cognitive Impairment and Healthy Aging: An fMRI Study. *Cerebral Cortex*, *23*(10), 2489–2499. https://doi.org/10.1093/cercor/bhs246

Green, S. A., Hernandez, L., Bookheimer, S. Y., & Dapretto, M. (2016). Salience Network Connectivity in Autism Is Related to Brain and Behavioral Markers of Sensory Overresponsivity. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(7), 618-626.e1. https://doi.org/10.1016/j.jaac.2016.04.013

Haier, R. J., Karama, S., Leyba, L., & Jung, R. E. (2009). MRI assessment of cortical thickness and functional activity changes in adolescent girls following three months of practice on a visual-spatial task. *BMC Research Notes*, *2*(1), 174. https://doi.org/10.1186/1756-0500-2-174

Happé, F., Cook, J. L., & Bird, G. (2017). The Structure of Social Cognition: In(ter)dependence of Sociocognitive Processes. *Annual Review of Psychology*, *68*(September 2016), 243–267. https://doi.org/10.1146/annurev-psych-010416-044046

Heyes, C. M., & Frith, C. D. (2014). The cultural evolution of mind reading. In *Science*. https://doi.org/10.1126/science.1243091

Itier, R. J., & Batty, M. (2009). Neural bases of eye and gaze processing: The core of social cognition. *Neuroscience and Biobehavioral Reviews*, *33*(6), 843–863. https://doi.org/10.1016/j.neubiorev.2009.02.004

Jarrold, C., & Brock, J. (2004). To Match or Not to Match? Methodological Issues in Autism-

Related Research. *Journal of Autism and Developmental Disorders*, *34*(1), 81–86. https://doi.org/10.1023/B:JADD.0000018078.82542.ab

Just, M. A., Cherkassky, V. L., Keller, T. A., Kana, R. K., & Minshew, N. J. (2007). Functional and Anatomical Cortical Underconnectivity in Autism: Evidence from an fMRI Study of an Executive Function Task and Corpus Callosum Morphometry. *Cerebral Cortex*, *17*(4), 951–961. https://doi.org/10.1093/cercor/bhl006

Kana, R. K., Keller, T. A., Minshew, N. J., & Just, M. A. (2007). Inhibitory Control in High-Functioning Autism: Decreased Activation and Underconnectivity in Inhibition Networks. *Biological Psychiatry*, *62*(3), 198–206. https://doi.org/10.1016/j.biopsych.2006.08.004

Kana, R. K., Libero, L. E., Hu, C. P., Deshpande, H. D., & Colburn, J. S. (2014). Functional brain networks and white matter underlying theory-of-mind in autism. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nss106

Kennedy, D. P., & Adolphs, R. (2012). The social brain in psychiatric and neurological disorders. *Trends in Cognitive Sciences*, *16*(11), 559–572. https://doi.org/10.1016/j.tics.2012.09.006

Kim, E., Kyeong, S., Cheon, K. A., Park, B., Oh, M. K., Chun, J. W., Park, H. J., Kim, J. J., & Song, D. H. (2016). Neural responses to affective and cognitive theory of mind in children and adolescents with autism spectrum disorder. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2016.04.026

Krall, S. C., Rottschy, C., Oberwelland, E., Bzdok, D., Fox, P. T., Eickhoff, S. B., Fink, G. R., & Konrad, K. (2015). The role of the right temporoparietal junction in attention and social interaction as revealed by ALE meta-analysis. In *Brain Structure and Function*. https://doi.org/10.1007/s00429-014-0803-z

Lai, C. L. E., Lau, Z., Lui, S. S. Y., Lok, E., Tam, V., Chan, Q., Cheng, K. M., Lam, S. M., & Cheung, E. F. C. (2017). Meta-analysis of neuropsychological measures of executive functioning in children and adolescents with high-functioning autism spectrum disorder. *Autism Research*, *10*(5), 911–939. https://doi.org/10.1002/aur.1723

Lai, M.-C., Lombardo, M. V., & Baron-Cohen, S. (2014). Autism. *The Lancet*, *383*(9920), 896–910. https://doi.org/10.1016/S0140-6736(13)61539-1

Lamash, L., & Josman, N. (2019). A metacognitive intervention model to promote independence among individuals with autism spectrum disorder: Implementation on a shopping task in the community. *Neuropsychological Rehabilitation*, *0*(0), 1–22. https://doi.org/10.1080/09602011.2019.1682621

Le Couteur, A., Lord, C., & Rutter, M. (2003). The Autism Diagnostic Interview-Revised (ADI-R). In *Los Angeles CA Western Psychological Services*. Western Psychological Services.

Leung, R. C., & Zakzanis, K. K. (2014). Brief report: Cognitive flexibility in autism spectrum disorders: A quantitative review. *Journal of Autism and Developmental Disorders*, *44*(10), 2628–2645. https://doi.org/10.1007/s10803-014-2136-4

Lord, C, & Rutter, M. (1999). Autism diagnostic observation schedule-WPS (ADOS-WPS). *Los Angeles CA Western Psychological.*

Lord, C, Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., & Schopler, E. (1989). Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *Journal of Autism and Developmental Disorders*, *19*(2),

185–212. https://doi.org/10.1007/BF02211841

Lord, Catherine, Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *24*(5), 659–685. https://doi.org/10.1007/BF02172145

Luna, B., Minshew, N. J., Garver, K. E., Lazar, N. A., Thulborn, K. R., Eddy, W. F., & Sweeney, J. A. (2002). Neocortical system abnormalities in autism: An fMRI study of spatial working memory. *Neurology*, *59*(6), 834–840. https://doi.org/10.1212/WNL.59.6.834

May, K. E., & Kana, R. K. (2020). Frontoparietal Network in Executive Functioning in Autism Spectrum Disorder. *Autism Research*, *13*(10), 1762–1777. https://doi.org/10.1002/aur.2403

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, *214*(5–6), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Minshew, N. J., & Keller, T. A. (2010). The nature of brain dysfunction in autism: Functional brain imaging studies. *Current Opinion in Neurology*, *23*(2), 124–130. https://doi.org/10.1097/WCO.0b013e32833782d4

Monk, C. S., Peltier, S. J., Wiggins, J. L., Weng, S. J., Carrasco, M., Risi, S., & Lord, C. (2009). Abnormalities of intrinsic functional connectivity in autism spectrum disorders,. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2009.04.069

Mouga, S., Correia, B. R., Café, C., Duque, F., & Oliveira, G. (2020). Language Predictors in Autism Spectrum Disorder: Insights from Neurodevelopmental Profile in a Longitudinal Perspective. *Journal of Abnormal Child Psychology*, *48*(1), 149–161. https://doi.org/10.1007/s10802-019-00578-7

Müller, R. A., & Fishman, I. (2018). Brain Connectivity and Neuroimaging of Social Networks in Autism. *Trends in Cognitive Sciences*, *22*(12), 1103–1116. https://doi.org/10.1016/j.tics.2018.09.008

Oberwelland, E., Schilbach, L., Barisic, I., Krall, S. C., Vogeley, K., Fink, G. R., Herpertz-Dahlmann, B., Konrad, K., & Schulte-Rüther, M. (2016). Look into my eyes: Investigating joint attention using interactive eye-tracking and fMRI in a developmental sample. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2016.02.026

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*. https://doi.org/10.1016/0028-3932(71)90067-4

Park, M. T. M., Raznahan, A., Shaw, P., Gogtay, N., Lerch, J. P., & Mallar Chakravarty, M. (2018). Neuroanatomical phenotypes in mental illness: Identifying convergent and divergent cortical phenotypes across autism, ADHD and schizophrenia. *Journal of Psychiatry and Neuroscience*. https://doi.org/10.1503/jpn.170094

Patriquin, M. A., DeRamus, T., Libero, L. E., Laird, A., & Kana, R. K. (2016). Neuroanatomical and neurofunctional markers of social cognition in autism spectrum disorder. *Human Brain Mapping*. https://doi.org/10.1002/hbm.23288

Pinkham, A. E., Hopfinger, J. B., Pelphrey, K. A., Piven, J., & Penn, D. L. (2008). Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. *Schizophrenia Research*, *99*(1–3), 164–175. https://doi.org/10.1016/j.schres.2007.10.024

Pino, M. C., Vagnetti, R., Masedu, F., Attanasio, M., Tiberti, S., Valenti, M., & Mazza, M. (2020). Mapping the Network of Social Cognition Domains in Children With Autism Spectrum Disorder Through Graph Analysis. *Frontiers in Psychiatry*, *11*(October), 1–10. https://doi.org/10.3389/fpsyt.2020.579339

Redcay, E., Dodell-Feder, D., Pearrow, M. J., Mavros, P. L., Kleiner, M., Gabrieli, J. D. E., & Saxe, R. (2010). Live face-to-face interaction during fMRI: A new tool for social cognitive neuroscience. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.01.052

Ruta, L., Famà, F. I., Bernava, G. M., Leonardi, E., Tartarisco, G., Falzone, A., Pioggia, G., & Chakrabarti, B. (2017). Reduced preference for social rewards in a novel tablet based task in young children with Autism Spectrum Disorders. *Scientific Reports*. https://doi.org/10.1038/s41598-017-03615-x

Rutter, M., Bailey, A., & Lord, C. (2003). *Social Communication Questionnaire*. Western Psychological Services.

Schilbach, L., Wilms, M., Eickhoff, S. B., Romanzetti, S., Tepest, R., Bente, G., Shah, N. J., Fink, G. R., & Vogeley, K. (2010). Minds made for sharing: Initiating joint attention recruits reward-related neurocircuitry. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2009.21401

Schmitz, N., Rubia, K., Daly, E., Smith, A., Williams, S., & Murphy, D. G. M. (2006). Neural correlates of executive function in autistic spectrum disorders. *Biological Psychiatry*, *59*(1), 7–16. https://doi.org/10.1016/j.biopsych.2005.06.007

Schuck, N. W., Cai, M. B., Wilson, R. C., & Niv, Y. (2016). Human Orbitofrontal Cortex Represents a Cognitive Map of State Space. *Neuron*, *91*(6), 1402–1412. https://doi.org/10.1016/j.neuron.2016.08.019

Schulte-Rüther, M., Greimel, E., Markowitsch, H. J., Kamp-Becker, I., Remschmidt, H., Fink, G. R., & Piefke, M. (2011). Dysfunctions in brain networks supporting empathy: An fMRI study in adults with autism spectrum disorders. *Social Neuroscience*. https://doi.org/10.1080/17470911003708032

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., & Perner, J. (2014). Fractionating theory of mind: A meta-analysis of functional brain imaging studies. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2014.01.009

Seeley, W. W. (2019). The Salience Network: A Neural System for Perceiving and Responding to Homeostatic Demands. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *39*(50), 9878–9882. https://doi.org/10.1523/JNEUROSCI.1138-17.2019

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Shafritz, K. M., Dichter, G. S., Baranek, G. T., & Belger, A. (2008). The Neural Circuitry Mediating Shifts in Behavioral Response and Cognitive Set in Autism. *Biological Psychiatry*, *63*(10), 974–980. https://doi.org/10.1016/j.biopsych.2007.06.028

Solomon, M., Ozonoff, S. J., Ursu, S., Ravizza, S., Cummings, N., Ly, S., & Carter, C. S. (2009). The neural substrates of cognitive control deficits in autism spectrum disorders. *Neuropsychologia*, *47*(12), 2515–2526. https://doi.org/10.1016/j.neuropsychologia.2009.04.019

Solomon, M., Yoon, J. H., Ragland, J. D., Niendam, T. A., Lesh, T. A., Fairbrother, W., & Carter, C. S. (2014). The development of the neural substrates of cognitive control in adolescents with autism spectrum disorders. *Biological Psychiatry*, *76*(5), 412–421. https://doi.org/10.1016/j.biopsych.2013.08.036

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences*, *105*(34), 12569–12574. https://doi.org/10.1073/pnas.0800005105

Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn3857

Uddin, L. Q., Supekar, K., Lynch, C. J., Khouzam, A., Phillips, J., Feinstein, C., Ryali, S., & Menon, V. (2013). Salience network-based classification and prediction of symptom severity in children with autism. *JAMA Psychiatry*, *70*(8), 869–879. https://doi.org/10.1001/jamapsychiatry.2013.104

Van Overwalle, F. (2009). Social cognition and the brain: A meta-analysis. In *Human Brain Mapping*. https://doi.org/10.1002/hbm.20547

von dem Hagen, E. A. H., Stoyanova, R. S., Baron-Cohen, S., & Calder, A. J. (2013). Reduced functional connectivity within and between "social" resting state networks in autism spectrum conditions. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nss053

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children–Third Edition (WISC-III) - Portuguese Version (M. R. Simões, A. M. Rocha, and C. Ferreira)*. Cegoc-Tea.

Wechsler, D. (2008). *Manual for intelligence scale for adults. Portuguese version (M.R. Simões, A. M. Rocha, and C. Ferreira)*. (Cegoc-Tea (ed.); Third Edit).

White, S. J., Frith, U., Rellecke, J., Al-Noor, Z., & Gilbert, S. J. (2014). Autistic adolescents show atypical activation of the brain's mentalizing system even without a prior history of mentalizing problems. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2013.12.013

Wolf, I., Dziobek, I., & Heekeren, H. R. (2010). Neural correlates of social cognition in naturalistic settings: A model-free analysis approach. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2009.08.060

CONCLUDING REMARKS

CHAPTER 3

CHAPTER 3

General Discussion, Conclusion and Future Work

General Discussion

In the current thesis a combination of neuropsychological assessment, psychophysics, eye-tracking and neuroimaging tools was employed with the purpose to better understand the clinical and biological phenotypes of Autism Spectrum Disorder (ASD) and the nature and the extent of the executive dysfunction and its link with the social cognition phenotype.

The comprehension of executive dysfunction and its link with the social cognition in ASD benefits from the characterization of its clinical phenotype in what concerns to neurodevelopmental, intellectual and functional profile. In fact, since the ASD diagnosis is outlined on behaviour, the first symptoms to arise are the ones that are observable in adaptive behaviour, especially in what concerns to communication and socialization. Since the pioneering descriptions of ASD, by Kanner and Asperger in the forties of the past century, specific ASD core features and difficulties were evident. Both stressed what really differentiates ASD from other neurodevelopmental disorders (OND) and individuals with typical neurodevelopment (TD) and that was, in 2013, merged in consensual diagnostic criteria: deficits in social communication and social interaction (American Psychiatric Association, 2013). Nevertheless, despite the core features of ASD being clear, the complex phenotype is far from being totally and truly known and understood, and that is what led us to characterize this disorder, beginning from what we see every day in our clinical work and constitutes one of the major concerns of parents, caregivers, therapists and teachers: adaptive behaviour. From the functional part we went to see how the intellectual profile of ASD is characterized in our population and then went one step back, to see how the neurodevelopmental profile evolved from preschool to school years and how informative it could be.

Only a careful characterization of the ASD phenotype allows us to know the impact of ASD diagnosis in daily living and inform us about the next steps to improve quality of life. Our research questions were created from the clinic perspective and experience, and then narrowed to basic, technological and ecological approaches. From the neuropsychological and behavioural approach to psychophysics, eye-tracking and neuroimaging techniques, we ascribed particular importance to tasks where ecological validity is enhanced.

Functional phenotype of ASD

To characterize the functional profile of ASD individuals, we compared the adaptive behaviour measured by the most studied and widely used instrument, the Vineland Adaptive Behaviour Scales (VABS). It is widely accepted that individuals with ASD exhibit deficits in their adaptive skills, however the precise relevance of intelligence quotient (IQ) to the symptomatic expression of ASD and direct involvement in the subject's adaptive behaviour remains unclear.

In Chapter 2.1 - *Adaptive profiles in autism and other neurodevelopmental disorder,* we found that ASD individuals exhibit more deficits in their adaptive behaviour than individuals with OND and that their IQ would predict.

ASD population was characterized by significantly lower scores in the daily living skills (DLS) and Socialization domains, particularly in the Personal and Domestic DLS and in Interpersonal Relationships and Coping Skills subdomains. These results are in part in line with the typical profile of individuals with ASD (Bolte & Poustka, 2002; A. S. Carter et al., 1998; Fenton et al., 2003; Paul et al., 2004; Tomanik et al., 2007; Volkmar et al., 1987). Nevertheless, other studies report relative strengths in DLS in ASD samples, and we did not found this pattern. A surprising result was that ASD showed higher results than OND, however, with no statistical significance, for the Communication domain, which we attribute to the greater percentage of adequate receptive communication in the ASD population, presented in the subdomains scores.

Our study showed that co-occurring intellectual disability (ID) result in further debilitating effects on overall functioning and adjustment in real life, especially in ASD patients which is line with previous studies (Di Nuovo & Buono, 2007; Gabriels et al., 2007; Perry et al., 2009). Particularly, ASD with ID showed lower scores for all domains of VABS, including Communication as compared with OND with ID. In what concerns to subdomains, Personal DLS, Interpersonal Relationships and Coping Skills remain as a core distinctive factor from subjects without ASD but with ID. This corroborates previous findings that reported that individuals with ASD tend to have lower overall adaptive skills when compared with chronological age (CA) and IQ matched peers without ASD (Di Nuovo & Buono, 2007; Gabriels et al., 2007; Kraijer, 2000).

Surprisingly, we did not find lower Communication scores or preserved DLS in the ASD group without ID when compared to age and mental-age matched individuals without ID as was previous shown by other authors (Carpentieri & Morgan, 1996; Kraijer, 2000;

Loveland & Kelley, 1991; Perry et al., 2009; VanMeter et al., 1997; Volkmar et al., 1987). This may be explained by the fact that we have studied school-age children, which can have better results in written domain. This may be due to the hyperlexic profile in autistic population with normal or above normal IQ (Newman et al., 2007) or to the structured teaching approach usually implemented in schools in Portugal (Decreto-Lei n.º 54/2018) focused on ASD children's needs, that may improve these specific skills.

On the other hand, our study demonstrated that the socialization deficits found in the ASD population cannot be explain only by the ID and constitute the core domain in which ASD group is distinctive as assessed by the VABS.

Verbal abilities seem to determine the adaptive functioning in the school aged ASD individuals, highlighting the importance of the development of functional language skills for later outcome (Howlin et al., 2014), which not happens in the OND sample, where the verbal abilities have not a determining value in the adaptive behaviour.

One disturbing finding of our study was the association between CA and Communication, Socialization and global adaptive ability in the ASD population, which may suggest that ASD subjects, compared to OND peers, where CA was associated only with Socialization, may fall behind with respect to adaptive functioning as they grow older, enhancing the gap between cognitive skills and adaptive behaviour (Kanne et al., 2011; Klin et al., 2007; Szatmari et al., 2003). This information has a prognostic value, which should be used not only to inform parents, caregivers, and therapists, but more importantly to target the areas of intervention.

Taken together, our findings, and specifically the impact of socialization impairment on the functional skills, which is a distinctive factor between ASD and OND, independently of cognitive ability, contributes to help differential diagnosis in a clinical set and reinforces the need for a targeted intervention focused on social skills. This raises a set of important questions related not only to the intervention that is being given to school-aged children and adolescents with ASD, but also to the future integration of ASD young adults in a society that is highly competitive and requires so many social abilities. To the research field, the need for tasks that could assess the impact of social cognition in the adaptive behaviour skills, that is also related to the executive functioning (EF), stresses the importance of the ecological validity.

Intellectual phenotype of ASD

To characterize the intellectual profile of ASD we compared the cognitive profile measured by one of the most studied and widely used tools, Weschler Intelligence Scale for Children – third edition (WISC-III), between two groups, one with ASD and another without ASD, the OND sample, controlled for CA and global intellectual level - Full-Scale IQ (FSIQ).

In Chapter 2.2. we found that ASD has a distinctive profile, when compared to OND individuals, which was more evident when the WISC-III results were analysed in a further complex view of their indexes and subtests. In fact, FSIQ, Verbal IQ (VIQ) and Performance (PIQ) were unable to discriminate accurately the ASD subjects when we looked at the main groups and at individuals with no ID. Nevertheless, the verbal abilities of groups with ID were significantly lower in the ASD sample, and it was possible to conclude that this phenotypic marker will help signalize ASD.

However, despite our study show that ASD was characterized by significantly lower scores in the VIQ than PIQ, which became even more evident whenever ID was present, corroborating, in part, the typical VIQ-PIQ discrepancies of individuals with ASD (Charman et al., 2011; Minshew et al., 1992; Ryland et al., 2014; Szatmari et al., 1990), we did not find associations with ASD symptomatology from the scores from ADI-R and ADOS, as in many of the previous studies(Black et al., 2009; Kaufman & Lichtenberger, 2000).

In what concerns index scores the one that was able to differentiate between ASD and OND was Processing Speed Index (PSI), with ASD presenting lower scores, which means more difficulties in this cognitive capacity, consistent with previous studies(Mayes & Calhoun, 2004). This index requires persistence and planning ability, which is sensitive to motivation, to difficulties in working under a time pressure, and motor coordination, deficits that are usually features in the ASD symptomatology. These abilities are related to reading performance and working memory: increased processing speed can decrease the load placed on working memory, while decreased processing speed can impair the effectiveness of working memory, an executive function (Wechsler, 2003). Therefore, difficulties in processing speed and EF are related., stressing the importance of a more profound study of EF in ASD.

However, when we took into account the presence or absence of ID, the results differed. The ASD individuals with ID showed lower scores for Verbal Comprehension Index (VCI) and PSI as compared to OND, while ASD individuals without ID (compared with OND without ID), showed also lower results for PSI, but no difference in VCI and higher results in Perceptual Organization Index (POI). This emphasis that the core distinctive index

from subjects with or without ASD was the ability to focus attention and quickly scan, discriminate between, and sequentially order visual information.

Regarding the specific subtests of WISC-III, we found that the subtests that better discriminate between ASD and OND are "Comprehension" and "Coding", which were significantly lower in all ASD individuals. Although some previous studies tried to differentiate the ASD subjects by their strengths, these difficulties were the ones which could separate ASD from the OND in our large sample. We can also conclude that our ASD patients exhibit a more heterogeneous intellectual profile than OND.

In chapter *Intellectual profiles in the autism spectrum and other neurodevelopmental disorders* (2.2), we also replicate the results on adaptive behaviour (chapter 2.1). In fact, the associations between WISC standard scores, Kaufman's Factors and Bannatyne's categories with VABS domains show that adaptive functioning is positively correlated with intellectual profile, especially in the Communication domain from VABS. The Communication domain relates not only to the ability to use the spoken language, but also to learning capabilities, especially in school-aged children. Therefore, it was expected that the cognitive ability, in some way, would modulate this domain - communication learning.

The characterization of the intellectual profile of ASD children is of the utmost importance, namely because it has proven to be a good predictor of outcome in terms of academic progress(Gillberg & Steffenburg, 1987), in the selection of the intervention type, school adaptations and curriculum, but also to adopt realistic perspectives for the future. On the contrary, an underestimation of intelligence may further increase the stigma that some individuals with ASD experience and may negatively affect opportunities in everyday life, for instance the opportunity of having an employment.

Our results also reinforce the use of Wechsler scales in the clinical set and research, although they are not a diagnostic measure for ASD, because they are used as a criterion to match ASD individuals in research studies and affect how their potential and progress are assessed and predicted in the clinical practice.

Neurodevelopmental phenotype of ASD

After the characterization of the adaptive and intellectual profile, we clarified how the neurodevelopmental profile evolves from the preschool period to school age and identified predictors of verbal development of children with ASD. For that purpose, we compared the

neurodevelopmental profile measured by Griffiths Mental Developmental Scales (GMDS) in two periods of time (first in the preschool; and second in the school).

In the study reported in chapter 2.3 - *Language Predictors in Autism Spectrum Disorder: Insights from Neurodevelopmental Profile in a Longitudinal Perspective*, we found that one of the most marked characteristics of ASD individuals is the presence of alterations in the language ability, in particular, the acquisition of phrase speech and this is predicted not only by the global psychomotor development but also, by the early performance (non-verbal) abilities at preschool age.

The neurodevelopmental profile of children with ASD evolves from the preschool to the school period in different manners taking in account the language abilities. In the children that were nonverbal in the preschool period and remained nonverbal at school age, the psychomotor developmental profile is significantly worse in the school period, not catching up with what is expected for their CA. In the subgroup of children that became verbal from the preschool to the school period, only the Locomotor Developmental Quotient is decreased. In this subgroup the very heterogeneous developmental profile from the preschool age transformed into a homogeneous profile later at school years. Conversely, in the group of children that were already verbal in the preschool period, there were no significant changes from one assessment to the other.

Additionally to this characteristic pathway we stressed the importance of nonverbal intelligence skills as a primary predictor of later language development for children with ASD, replicating the results from others(Anderson et al., 2007; Pickett et al., 2009; Wodka et al., 2013), but adding cut-off values of Developmental Quotients (DQs) of GMSD as early predictors of expressive language. Importantly, our findings also demonstrate that, in nonverbal preschool children with ASD, normal or near normal Performance DQ (superior to 73.5) and a Global DQ superior to 62.5 may be an index of future verbal acquisition.

Our findings suggest that these core abilities (global and nonverbal intelligence) at early age, close to the diagnosis moment, have great and important information about the potential development of language in children with ASD. This knowledge could be very helpful to clarify family and educational professionals of outcome and precise and personalized therapeutic and educative intervention programmes.

Social attention in ASD

After the characterization of the functional and cognitive phenotype of ASD, where social impairments where highlighted, we focused on social attention deficits, in particular in which concerns to focus on face or object stimuli, in the clinical context of different tasks of Autism Diagnostic Observation Schedule (ADOS), with eye-tracking methodology.

We found that TD children looked first to faces and during a longer period of time in the socially rich and familiar context of a gathering of people around a table ("Description of a Picture task"), being this task the one that better differentiate between ASD and TD. Our findings thereby provide a framework that reconciles previous literature, that stated that scenes depicting ecological social interactions have been associated to better evoke robust social responses (Falck-Ytter & von Hofsten, 2011; Saitovitch et al., 2013).

Contrarily, when scenarios implied generating a goal-oriented narrative in the task, the pattern of attentional allocation in ASD subjects was normalized. In other words, under these conditions, interaction effects are not triggered. The ASD group tends to have a similar pattern of visual search in what concerns to attention to social and non-social stimuli, that is, faces and objects. In turn, the TD group looks first at faces and for a longer period of time, which corroborates the hypothesis that ASD participants are less attentive to faces, one extensively studied aspect regarding deficits in social cognition(Kirchner et al., 2011; Ami Klin et al., 2002; Riby et al., 2013; Riby & Hancock, 2009; Rice et al., 2012; Shi et al., 2015; Shic et al., 2011).

Our study also corroborates that children and adolescents with and without ASD show remarkably similar visual search patterns in their initial eye gaze to faces (Schauder et al., 2019). However, in our study participants are not instructed to specifically look at faces, which adds meaning and ecological validity to the result.

Overall, our results seem to provide a unifying view of previous research. The TD group always looks at the faces first, when exploring visually the images, also spending more time looking at social stimuli. This visual search pattern is absent in the ASD group. In fact, although children with ASD look at the faces first, there is no differential pattern in the Cartoon and Book tasks (the ones that guide a goal oriented narrative), when compared with TD.

Taken together, our results point to the fact that social attention allocation patterns in ASD population are strongly task dependent, which extends our previous work in other cognitive domains (Bernardino et al., 2012). Accordingly, the task not requiring an explicit goal-oriented narrative yields the greatest differences. This raises the question whether

spontaneous attention deficits can be rescued by guiding goal-directed actions in the ASD population (Birmingham et al., 2011). These results are relevant for the selection of interventional strategies and in ASD children, since it stresses the importance of goal-oriented actions, which are the foundations of the structured teaching with proven positive results (D'Elia et al., 2014; Panerai et al., 2002; Siu et al., 2019).

We also add to the body of knowledge, that entry time, an eye-tracking measure that characterize fast events, is the best measures to distinguish both groups (ASD versus TD). The use of this particular measure in the analysis of the attention to social and non-social stimuli of the different tasks of ADOS (a well validated but examiner's dependent diagnosis tool for ASD) may potentially provide a complementary quantitative information of potential value in clinical practice to discriminate between ASD children without ID and TD.

The fact that we provide evidence for task dependence, with patterns "normalizing" when a narrative is required, may help to improve the course of ASD diagnostic evaluation, especially in subjects with ASD without ID, where the differential diagnosis with a TD is often very difficult. This stresses the importance, from a diagnostic perspective point of view, of observation and classification of spontaneous behaviour. This can also inform training strategies, by providing clues on learning adaptive attentional deployment.

The link between executive functioning and social cognition in ASD revealed by an ecological task

Based on our characterization of the functional and cognitive phenotype of ASD individuals, we were able to emphasise that the core difficulties in social communication and interaction extend to social adaptive skills. In fact, ASD subjects present marked difficulties in daily living skills and socialization, particularly in what concerns to personal and domestic autonomy and in interpersonal relationships and coping skills. On the other hand, ASD are also characterized by difficulties in processing speed index, that affects the effectiveness of working memory, a key executive function. We also highlighted the relevance on the "marker" of non-verbal abilities at early age in the later acquisition of verbal abilities, a central aspect in the ASD communication deficits. Additionally, we stressed the importance of the task/context and use of eye-tracking in the study of social and non-social stimuli. Taken together, all this information leads to the need of an ecological task that may assess the link between EF, attentional contextual cueing, and social cognition in subjects with ASD.

For that purpose, we developed a novel ecological task – EcoSupermarketX aimed which measures EF in a daily living chore: shopping in a supermarket, with the integration of attentional social vs. non-social cues, and compared the performance of two matched groups of adolescents and young adults with ASD and TD in the task. In order to answer our research question, we used markers of EF under distinct task constraints, with explicit manipulations of levels of cognitive load and attentional saliency of the social and non-social cues that could help in task solving.

We found that ASD subjects are more affected with the increasing cognitive load of information, which is linked to a deficit in efficient deployment of attention. This is a crucial factor in learning of complex tasks (Paas et al., 2003), such as our daily living chores, and essential element of cognitive control (Baddeley, 2010; Engle et al., 1999), with a critical importance for learning and academic achievement (Alloway, 2009), as well as social competency (Dennis et al., 2009). Our results, were in line with previous literature that report that compared to TD, individuals with ASD performed significantly worse on complex tasks related to working memory (Bennetto et al., 1996; Nancy J. Minshew & Goldstein, 2001; Ozonoff & Strayer, 2001; Russell et al., 1996; Williams et al., 2006).

We also found ASD subjects perform worse in the absence of helping cues and only the addition of some types of attentional cues can rescue the impaired performance compared with TD individuals. In fact, our ASD participants presented more errors, took more time to perform the task, "walked" longer distances and were more adrift when nothing would guide their actions. These findings, along with the fact that between-group differences only remained concerning non-social cues (these could not rescue performance), and one attentional parameter (head rotation), reinforces that the use of some cues seems to have a beneficial effect in restoring overall performance in ASD population.

One surprising finding concerns to impairment that ASD presented specifically for salient cues, regardless of being social or non-social. The Enactive Mind theory stresses that cognition is embedded in experiences resulting from body's actions upon salient aspects of its surrounding environment and that social functioning is supported by the ability to visually track socially salient information within interactions (Ami Klin et al., 2003). Interestingly, our ASD group spent more time looking to the salient social cue, which we can speculate as they take more time to deduce the environment and decide what to do than TD.

The significant associations found between EcoSupermarketX parameters and the different neuropsychological assessments indicate that functional domains related to attention and executive function are captured by the measures computed from this novel ecological

task. Moreover, the significant correlations found between EcoSupermarketX performance and ASD core symptomatology severity give important indications about the impact on social cognition/skills and the functional implications of ASD clinical phenotype to daily living functional abilities, going beyond previous reports (Cantio et al., 2016; Joseph & Tager-Flusberg, 2004; Landa & Goldberg, 2005).

Our findings support one of the key cognitive theories of ASD: executive dysfunction (Hill, 2004; Pennington & Ozonoff, 1996). Nonetheless, they add to the body of knowledge the importance of the attentional contextual cueing and raises questions about the nature and influence of cue saliency. On the other hand, our study reports deficits not only in non-social, but also in hot executive functions, cognitive processes, which represent goal-oriented behaviours (Kouklari et al., 2017; Zelazo & Carlson, 2012) . This emphasizes the knowledge that ASD is not characterized by one main cognitive deficit but instead by impairments in a selective range of higher-order cognitive abilities, including attention and executive function, corroborating a multiple-deficit account.

The study of attentional contextual cueing, as a possible explanation for the difficulties in complex cognitive domains in spite of largely preserved visual spatial abilities in ASD, has focused mostly in classic spatial-learning tasks, but much less so in the context of real life constrains and daily life chores. Some studies have suggested proficient implicit contextual cueing in individuals with ASDs as compared to TD participants (Barnes et al., 2008; Brown et al., 2010; Kourkoulou et al., 2012; Travers et al., 2013). This is, in part, corroborated by our study when we show that the performance of ASD group matches the TD in the presence of the cue (showing statistical differences in the absence of cues). Nonetheless, we found a surprising result in what concerns to the saliency of the cues: salient cues did not rescue performance in ASD comparing to TD, contrary to subtle cues. Brown and colleagues (2010) have hypothesised that ASD problems in real-world areas expected to require implicit acquisition, such as social cognition, in spite of preserved implicit learning mechanisms, may be explained by interference due to abnormal attention or the overuse of explicit strategies. We substantiate this hypothesis in our eye-tracking result. In fact, ASD subjects show longer fixations than TD only in the social salient cue, which is associated to worse results in the Social Salient task condition and can explain the difficulty in daily life, where we are constantly and continuously exposed to explicit salient cues in a wide range of activities.

To the best of our knowledge, this is the first study that, so far, assessed attentional cueing and EF with social and non-social cues, with different saliencies, in an ecologic daily living chore context. The present findings help to improve our understanding of the patterns

of cognitive impairments in our sample of adolescents and young adults with ASD because we showed an impairment in ASD both in the presence of social and non-social contextual cues in an ecological task, capable to identify ASD deficits in EF and attentional cueing. The discrepancy between what ASD individuals can do on explicit tasks of non-social and social reasoning (when they receive specific instructions and all the task is compartmentalized), and what they are unable to do in the daily social life, when they have to apply spontaneously their abilities in a naturalistic situation, remains one of the most intriguing questions in this research field. As our previous chapters stated, even individuals with normal or high IQ cannot use their cognitive abilities to face the demands of daily living and social situations (Chapters 2.1 - *Adaptive profiles in autism and other neurodevelopmental disorders* and 2.2 - *Intellectual profiles in the autism spectrum and other neurodevelopmental disorders*). In this study, we demonstrate that attention deficits can be rescued by guiding goal-directed actions using explicit cues and stress the importance of the structured or not structured context of the task and the required cognitive load. Taken together, our results point to the fact that attentional allocation in ASD population is context and task dependent, which, again, extends our previous work (Bernardino et al., 2012) on contextual dependency of local vs global attentional allocation. It also shows that cognitive load may have a large impact even in these relatively simple tasks. These results are relevant for the selection of interventional strategies in ASD subjects, focused on improved attentional allocation to social and non-social cues

Our work emphasizes that these attentional allocation impairments are associated with EF deficits, which stresses a set of important questions we already raised, related not only to the school intervention, but also full social inclusion of ASD young adults in a society that is highly competitive and requires so many social and EF abilities. Additionally, notwithstanding of a superior or average IQ, subjects with ASD experience substantial difficulties in everyday life (Chapters 2.1 - *Adaptive profiles in autism and other neurodevelopmental disorders* and 2.2 - *Intellectual profiles in the autism spectrum and other neurodevelopmental disorders*) which can lead to an overvaluation of IQ in terms of predicting adaptive behaviour skills and a misleading as good outcome without adequate assessment and consideration of EF and social skills, specifically involved in solving everyday problems.

Neural correlates executive functioning and social cognition in ASD revealed by ecological task

To extricate the association between EF and social vs non-social cognition and to increase our understanding of the cognitive mechanisms of impairment in ASD, we studied the neural correlates of executive dysfunction and social cognition in ASD, with an adapted version of EcoSupermarketX.

The current work is, to our knowledge, the first fMRI study with an ecologic task explicitly designed to investigate brain activity in three different networks: social, central executive, and salience, when performing this ecological daily living task – going shopping.

We found higher activity by the ASD group when compared with the group of healthy individuals (without ASD) in areas that are pivotal in social brain circuits, namely the temporo-parietal junction (TPJ), ventromedial prefrontal cortex (vmPFC) and inferior parietal lobule (IPL). Importantly, this brain region has also being implicated in social and emotional processing (Bilek et al., 2015; Frith & Frith, 2003; Krall et al., 2015; Schulte-Rüther et al., 2011), including joint attention (Oberwelland et al., 2016; Redcay et al., 2010; Schilbach et al., 2010), as well as to attentional reorienting to salient cues (R. M. K. Carter & Huettel, 2013) and visually triggered shifts of attention that share common neural substrates with gaze perception (Itier & Batty, 2009). These aspects are quite important in our task design. Moreover, it is also known that the TPJ is most reliably activated when participants engage in tasks involving the inference of goals or end states for described actions (Van Overwalle, 2009).

It is interesting to point out that differential recruitment of areas of the executive network were found with larger activation in ASD, namely in the middle frontal gyrus, and also pregenual anterior cingulate cortex (pgACC), which is part of the salience network.

A pattern of higher activity was found in the ASD group for all the three brain networks recruited to complete the task, except, the parahippocampal gyrus (presenting lower activity in ASD group). Interestingly, the ultimate performance of the task was quite similar between the groups, which leads to the suggestion that these findings are due to the fact that the ASD group maintains a higher neural effort in order to reach similar performance levels as the TD group.

Patterns of brain activation that may actually occur in a compensatory way to provide preserved performance have already been reported in other conditions such as mild cognitive impairment (Graewe et al., 2013).

A relevant point for this discussion relies on the fact that most of the studies in ASD differ from ours in two very important areas: ecologic validity and social demands that are task inherent.

We found that ASD subjects could understand and perform the shopping task Additionally, the introduction of a cue as a helping feature seems to have a clarifying role in the way ASD people allocate their attention in structured environments. Besides the behavioural results, ASD did not present differences comparing to the TD group in the eye-tracking measures (corroborating what we have already found in chapter 2.5 - *Attentional cueing and executive deficits revealed by a virtual supermarket task coupled with eye-tracking in autism spectrum disorder*). Our results are consistent with a body of literature suggesting that hyperactivation of articular networks may provide a compensatory mechanism to preserve performance (Graewe et al., 2013). It is remarkable that in our experimental studies this was observed across executive, saliency and social cognition networks.

Conclusions

The research work presented in the current thesis, confirmed the importance of a comprehensive characterization of the functional and cognitive phenotype of ASD individuals. Our findings underlined that the core difficulties in social communication and interaction extend to social adaptive skills. In fact, the major weakness in ASD subjects is the presence of marked difficulties in daily living skills and socialization, indispensable abilities to survive on their own. Additionally, ASD are also characterized by impairments in processing speed index, that affects the effectiveness of working memory, an important executive function. We also emphasized the importance on non-verbal abilities as a mark for later acquisition of verbal abilities, a central aspect in the ASD communication profile. The relevance of the task/context and use of eye-tracking in the study of attention to social and non-social stimuli was also highlighted. Our results also put prominence on important challenges in overall attentional allocation in social/non-social cognitive processing in ASD, despite the absence of overall quantitative ID. This provides evidence that attention allocation and EF alterations deserve consideration as promising endophenotypes for ASD. Furthermore, ecological tasks that allow to evaluate these cognitive aspects may have a determinant role in the differential diagnosis of ASD subjects without ID, as well as to inform approaches to therapeutic and educational interventions. We also went further in the understanding of the neural correlates of these impairments by demonstrating a

hyperactivation of three simultaneous brain networks (executive, saliency and social cognition networks) in an ecological demanding task in our ASD sample. This finding could be interpreted as a compensatory effort for the ASD population to achieve the same performance in executive and social demanding tasks as the TD individuals.

Taken together, this multimodal study allowed the development of tools that can lead to a more 'real-life' behavioural assessment, which is essential to develop interventions that may have effective beneficial results. Our findings show that in these task conditions, that are closer to the daily-life challenges, the executive and social cognition skills should be the main target of intervention. However, the population in this study is not representative of the entire spectrum of ASD since some individuals are not able to collaborate in eye-tracking and fMRI studies (non-verbal individuals and/or with ID or at younger ages), precisely where the intervention would have the greatest impact. In this line, the study of nonverbal skills proved to be essential to obtain an early indicator of development.

In sum, we provided novel clues to the current understanding of the neurocognitive and functional profile of ASD, namely in which concerns EF and social cognition. By using different approaches and methodologies and studying different ASD samples, we added to current knowledge by characterizing, for the first time, the adaptive, neurodevelopmental and intellectual profiles of Portuguese ASD population.

Future Work

Extending our work, particularly in what respects to findings in social attention, social cognition and EF, to toddlers, young children and elderly adults with ASD will be an important following step in future studies to expand the understanding of the disorder mechanisms underlying these deficits. In addition, the use of other fMRI approaches, like ecological task-induced brain connectivity patterns may promote the detection of individual differences in brain-behaviour relationships. This line of research may identify individual specificities of connectivity patterns underlying these relevant cognitive traits, providing strong evidence for the validity and robustness of our results. Finally, our findings motivate future work exploring the importance of cueing goal-oriented actions and teaching of social and adaptive skills that are increasingly being done in virtual environments.

References

Alloway, T. P. (2009). Working memory, but not IQ, predicts subsequent learning in children with learning difficulties. *European Journal of Psychological Assessment*, *25*(2), 92–98. https://doi.org/10.1027/1015-5759.25.2.92

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). American Psychiatric Publishing.

Anderson, D. K., Lord, C., Risi, S., DiLavore, P., Shulman, C., Thurm, A., Welch, K., & Pickles, A. (2007). Patterns of growth in verbal abilities among children with autism spectrum disorder. *Journal of Consulting and Clinical Psychology*, *75*(4), 594–604. https://doi.org/10.1037/0022-006X.75.4.594

Baddeley, A. (2010). Working memory. *Current Biology*, *20*(4), R136–R140. https://doi.org/10.1016/j.cub.2009.12.014

Barnes, K. A., Howard, J. H., Howard, D. V., Gilotty, L., Kenworthy, L., Gaillard, W. D., & Vaidya, C. J. (2008). Intact Implicit Learning of Spatial Context and Temporal Sequences in Childhood Autism Spectrum Disorder. *Neuropsychology*, *22*(5), 563–570. https://doi.org/10.1037/0894-4105.22.5.563

Bennetto, L., Pennington, B. F., & Rogers, S. J. (1996). Intact and Impaired Memory Functions in Autism. *Child Development*, *67*(4), 1816. https://doi.org/10.2307/1131734

Bernardino, I., Mouga, S., Almeida, J., van Asselen, M., Oliveira, G., & Castelo-Branco, M. (2012). A direct comparison of local-global integration in autism and other developmental disorders: Implications for the central coherence hypothesis. *PLoS ONE*, *7*(6). https://doi.org/10.1371/journal.pone.0039351

Bilek, E., Ruf, M., Schäfer, A., Akdeniz, C., Calhoun, V. D., Schmahl, C., Demanuele, C., Tost, H., Kirsch, P., & Meyer-Lindenberg, A. (2015). Information flow between interacting human brains: Identification, validation, and relationship to social expertise. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1421831112

Birmingham, E., Cerf, M., & Adolphs, R. (2011). Comparing social attention in autism and amygdala lesions: Effects of stimulus and task condition. *Social Neuroscience*, *6*(5–6), 420–435. https://doi.org/10.1080/17470919.2011.561547

Black, D. O., Wallace, G. L., Sokoloff, J. L., & Kenworthy, L. (2009). Brief report: IQ split predicts social symptoms and communication abilities in high-functioning children with autism spectrum disorders. *J Autism Dev Disord*, *39*(11), 1613–1619. https://doi.org/10.1007/s10803-009-0795-3

Bolte, S., & Poustka, F. (2002). The relation between general cognitive level and adaptive behavior domains in individuals with autism with and without co-morbid mental retardation. *Child Psychiatry Hum Dev*, *33*(2), 165–172.

Brown, J., Aczel, B., Jiménez, L., Kaufman, S. B., & Grant, K. P. (2010). Intact implicit learning in autism spectrum conditions. *Quarterly Journal of Experimental Psychology*, *63*(9), 1789–1812. https://doi.org/10.1080/17470210903536910

Cantio, C., Jepsen, J. R. M., Madsen, G. F., Bilenberg, N., & White, S. J. (2016). Exploring 'The autisms' at a cognitive level. *Autism Research*, *9*(12), 1328–1339. https://doi.org/10.1002/aur.1630

Carpentieri, S., & Morgan, S. B. (1996). Adaptive and intellectual functioning in autistic and nonautistic retarded children. *J Autism Dev Disord*, *26*(6), 611–620.

Carter, A. S., Volkmar, F. R., Sparrow, S. S., Wang, J. J., Lord, C., Dawson, G., Fombonne, E., Loveland, K., Mesibov, G., & Schopler, E. (1998). The Vineland Adaptive Behavior Scales: supplementary norms for individuals with autism. *J Autism Dev Disord*, *28*(4), 287–302.

Carter, R. M. K., & Huettel, S. A. (2013). A nexus model of the temporal-parietal junction. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2013.05.007

Charman, T., Pickles, A., Simonoff, E., Chandler, S., Loucas, T., & Baird, G. (2011). IQ in children with autism spectrum disorders: data from the Special Needs and Autism Project (SNAP). *Psychol Med*, *41*(3), 619–627. https://doi.org/S0033291710000991 [pii]10.1017/S0033291710000991

D'Elia, L., Valeri, G., Sonnino, F., Fontana, I., Mammone, A., & Vicari, S. (2014). A Longitudinal Study of the Teacch Program in Different Settings: The Potential Benefits of Low Intensity Intervention in Preschool Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *44*(3), 615–626. https://doi.org/10.1007/s10803-013-1911-y

Dennis, M., Agostino, A., Roncadin, C., & Levin, H. (2009). Theory of mind depends on domain-general executive functions of working memory and cognitive inhibition in children with traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*, *31*(7), 835–847. https://doi.org/10.1080/13803390802572419

Di Nuovo, S. F., & Buono, S. (2007). Psychiatric syndromes comorbid with mental retardation: differences in cognitive and adaptive skills. *J Psychiatr Res*, *41*(9), 795–800. https://doi.org/S0022-3956(06)00055-0 [pii]10.1016/j.jpsychires.2006.02.011

Engle, R. W., Laughlin, J. E., Tuholski, S. W., & Conway, A. R. A. (1999). Working memory, short-term memory, and general fluid intelligence: A latent-variable approach. *Journal of Experimental Psychology: General*, *128*(3), 309–331. https://doi.org/10.1037/0096-3445.128.3.309

Falck-Ytter, T., & von Hofsten, C. (2011). How special is social looking in ASD. A review. In *Progress in Brain Research* (1st ed., Vol. 189). Elsevier B.V. https://doi.org/10.1016/B978-0-444-53884-0.00026-9

Fenton, G., D'Ardia, C., Valente, D., Del Vecchio, I., Fabrizi, A., & Bernabei, P. (2003). Vineland adaptive behavior profiles in children with autism and moderate to severe developmental delay. *Autism*, *7*(3), 269–287.

Frith, U., & Frith, C. D. (2003). Development and neurophysiology of mentalizing. In *Philosophical Transactions of the Royal Society B: Biological Sciences*. https://doi.org/10.1098/rstb.2002.1218

Gabriels, R. L., Ivers, B. J., Hill, D. E., Agnew, J. A., & McNeill, J. (2007). Stability of adaptive behaviors in middle-school children with autism spectrum disorders. *Research in Autism Spectrum Disorders*, *1*(4), 291–303. https://doi.org/DOI 10.1016/j.rasd.2006.11.004

Gillberg, C., & Steffenburg, S. (1987). Outcome and prognostic factors in infantile autism and similar conditions: a population-based study of 46 cases followed through puberty. *J Autism Dev Disord*, *17*(2), 273–287.

Graewe, B., Lemos, R., Ferreira, C., Santana, I., Farivar, R., De Weerd, P., & Castelo-Branco,

M. (2013). Impaired Processing of 3D Motion-Defined Faces in Mild Cognitive Impairment and Healthy Aging: An fMRI Study. *Cerebral Cortex*, *23*(10), 2489–2499. https://doi.org/10.1093/cercor/bhs246

Hill, E. L. (2004). Evaluating the theory of executive dysfunction in autism. *Developmental Review*, *24*(2), 189–233. https://doi.org/10.1016/j.dr.2004.01.001

Howlin, P., Savage, S., Moss, P., Tempier, A., & Rutter, M. (2014). Cognitive and language skills in adults with autism: a 40-year follow-up. *J Child Psychol Psychiatry*, *55*(1), 49–58. https://doi.org/10.1111/jcpp.12115

Itier, R. J., & Batty, M. (2009). Neural bases of eye and gaze processing: The core of social cognition. *Neuroscience and Biobehavioral Reviews*, *33*(6), 843–863. https://doi.org/10.1016/j.neubiorev.2009.02.004

Joseph, R. M., & Tager-Flusberg, H. (2004). The relationship of theory of mind and executive functions to symptom type and severity in children with autism. *Development and Psychopathology*, *16*(1), 137–155. https://doi.org/10.1017/S095457940404444X

Kanne, S. M., Gerber, A. J., Quirmbach, L. M., Sparrow, S. S., Cicchetti, D. V, & Saulnier, C. A. (2011). The role of adaptive behavior in autism spectrum disorders: implications for functional outcome. *J Autism Dev Disord*, *41*(8), 1007–1018. https://doi.org/10.1007/s10803-010-1126-4

Kaufman, A. S., & Lichtenberger, E. O. (2000). *Essentials of WISC-III and WPPSI-R Assessment*. Wiley.

Kirchner, J. C., Hatri, A., Heekeren, H. R., & Dziobek, I. (2011). Autistic symptomatology, face processing abilities, and eye fixation patterns. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-010-1032-9

Klin, A, Saulnier, C. A., Sparrow, S. S., Cicchetti, D. V, Volkmar, F. R., & Lord, C. (2007). Social and communication abilities and disabilities in higher functioning individuals with autism spectrum disorders: the Vineland and the ADOS. *J Autism Dev Disord*, *37*(4), 748–759. https://doi.org/10.1007/s10803-006-0229-4

Klin, Ami, Jones, W., Schultz, R., & Volkmar, F. (2003). The enactive mind, or from actions to cognition: lessons from autism. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *358*(1430), 345–360. https://doi.org/10.1098/rstb.2002.1202

Klin, Ami, Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual Fixation Patterns During Viewing of Naturalistic Social Situations as Predictors of Social Competence in Individuals With Autism. *Archives of General Psychiatry*, *59*(9), 809. https://doi.org/10.1001/archpsyc.59.9.809

Kouklari, E.-C., Thompson, T., Monks, C. P., & Tsermentseli, S. (2017). Hot and Cool Executive Function and its Relation to Theory of Mind in Children with and without Autism Spectrum Disorder. *Journal of Cognition and Development*, *18*(4), 399–418. https://doi.org/10.1080/15248372.2017.1339708

Kourkoulou, A., Leekam, S. R., & Findlay, J. M. (2012). Implicit Learning of Local Context in Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *42*(2), 244–256. https://doi.org/10.1007/s10803-011-1237-6

Kraijer, D. (2000). Review of adaptive behavior studies in mentally retarded persons with autism/pervasive developmental disorder. *J Autism Dev Disord*, *30*(1), 39–47.

Krall, S. C., Rottschy, C., Oberwelland, E., Bzdok, D., Fox, P. T., Eickhoff, S. B., Fink, G. R.,

& Konrad, K. (2015). The role of the right temporoparietal junction in attention and social interaction as revealed by ALE meta-analysis. In *Brain Structure and Function*. https://doi.org/10.1007/s00429-014-0803-z

Landa, R. J., & Goldberg, M. C. (2005). Language, social, and executive functions in high functioning autism: A continuum of performance. *Journal of Autism and Developmental Disorders*, *35*(5), 557–573. https://doi.org/10.1007/s10803-005-0001-1

Loveland, K. A., & Kelley, M. L. (1991). Development of adaptive behavior in preschoolers with autism or Down syndrome. *Am J Ment Retard*, *96*(1), 13–20.

Mayes, S. D., & Calhoun, S. L. (2004). Similarities and differences in Wechsler Intelligence Scale for Children--Third Edition (WISC-III) profiles: support for subtest analysis in clinical referrals. *Clin Neuropsychol*, *18*(4), 559–572. https://doi.org/10.1080/13854040490888530

Minshew, N J, Goldstein, G., Muenz, L. R., & Payton, J. B. (1992). Neuropsychological functioning in nonmentally retarded autistic individuals. *J Clin Exp Neuropsychol*, *14*(5), 749–761. https://doi.org/10.1080/01688639208402860

Minshew, Nancy J., & Goldstein, G. (2001). The Pattern of Intact and Impaired Memory Functions in Autism. *Journal of Child Psychology and Psychiatry*, *42*(8), 1095–1101. https://doi.org/10.1111/1469-7610.00808

Newman, T. M., Macomber, D., Naples, A. J., Babitz, T., Volkmar, F., & Grigorenko, E. L. (2007). Hyperlexia in children with autism spectrum disorders. *J Autism Dev Disord*, *37*(4), 760–774. https://doi.org/10.1007/s10803-006-0206-y

Oberwelland, E., Schilbach, L., Barisic, I., Krall, S. C., Vogeley, K., Fink, G. R., Herpertz-Dahlmann, B., Konrad, K., & Schulte-Rüther, M. (2016). Look into my eyes: Investigating joint attention using interactive eye-tracking and fMRI in a developmental sample. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2016.02.026

Ozonoff, S., & Strayer, D. L. (2001). Further evidence of intact working memory in autism. *Journal of Autism and Developmental Disorders*, *31*(3), 257–263. https://doi.org/10.1023/a:1010794902139

Paas, F., Tuovinen, J. E., Tabbers, H., & Van Gerven, P. W. M. (2003). Cognitive Load Measurement as a Means to Advance Cognitive Load Theory. *Educational Psychologist*, *38*(1), 63–71. https://doi.org/10.1207/S15326985EP3801_8

Panerai, S., Ferrante, L., & Zingale, M. (2002). Benefits of the Treatment and Education of Autistic and Communication Handicapped Children (TEACCH) programme as compared with a non-specific approach. *Journal of Intellectual Disability Research*, *46*(4), 318–327. https://doi.org/10.1046/j.1365-2788.2002.00388.x

Paul, R., Miles, S., Cicchetti, D., Sparrow, S., Klin, A., Volkmar, F., Coflin, M., & Booker, S. (2004). Adaptive behavior in autism and Pervasive Developmental Disorder-Not Otherwise Specified: microanalysis of scores on the Vineland Adaptive Behavior Scales. *J Autism Dev Disord*, *34*(2), 223–228.

Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. In *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1111/j.1469-7610.1996.tb01380.x

Perry, A., Flanagan, H. E., Dunn Geier, J., & Freeman, N. L. (2009). Brief report: the Vineland Adaptive Behavior Scales in young children with autism spectrum disorders at different

cognitive levels. *J Autism Dev Disord*, *39*(7), 1066–1078. https://doi.org/10.1007/s10803-009-0704-9

Pickett, E., Pullara, O., O'Grady, J., & Gordon, B. (2009). Speech acquisition in older nonverbal individuals with autism: a review of features, methods, and prognosis. *Cognitive & Behavioral Neurology*, *22*(1), 1–21. https://doi.org/10.1097/WNN.0b013e318190d185

Redcay, E., Dodell-Feder, D., Pearrow, M. J., Mavros, P. L., Kleiner, M., Gabrieli, J. D. E., & Saxe, R. (2010). Live face-to-face interaction during fMRI: A new tool for social cognitive neuroscience. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.01.052

Riby, D. M., & Hancock, P. J. B. (2009). Do faces capture the attention of individuals with Williams syndrome or autism? Evidence from tracking eye movements. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-008-0641-z

Riby, D. M., Hancock, P. J., Jones, N., & Hanley, M. (2013). Spontaneous and cued gaze-following in autism and Williams syndrome. *Journal of Neurodevelopmental Disorders*, *5*(1), 13. https://doi.org/10.1186/1866-1955-5-13

Rice, K., Moriuchi, J. M., Jones, W., & Klin, A. (2012). Parsing heterogeneity in autism spectrum disorders: Visual scanning of dynamic social scenes in school-aged children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(3), 238–248. https://doi.org/10.1016/j.jaac.2011.12.017

Russell, J., Jarrold, C., & Henry, L. (1996). Working memory in children with autism and with moderate learning difficulties. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *37*(6), 673–686. https://doi.org/10.1111/j.1469-7610.1996.tb01459.x

Ryland, H. K., Hysing, M., Posserud, M. B., Gillberg, C., & Lundervold, A. J. (2014). Autistic features in school age children: IQ and gender effects in a population-based cohort. *Research in Autism Spectrum Disorders*, *8*(3), 266–274. https://doi.org/http://dx.doi.org/10.1016/j.rasd.2013.12.001

Saitovitch, A., Bargiacchi, A., Chabane, N., Phillipe, A., Brunelle, F., Boddaert, N., Samson, Y., & Zilbovicius, M. (2013). Studying gaze abnormalities in autism: Which type of stimulus to use? *Open Journal of Psychiatry*, *03*(02), 32–38. https://doi.org/10.4236/ojpsych.2013.32a006

Schauder, K. B., Park, W. J., Tsank, Y., Eckstein, M. P., Tadin, D., & Bennetto, L. (2019). Initial eye gaze to faces and its functional consequence on face identification abilities in autism spectrum disorder. *Journal of Neurodevelopmental Disorders*, *11*(1), 1–20. https://doi.org/10.1186/s11689-019-9303-z

Schilbach, L., Wilms, M., Eickhoff, S. B., Romanzetti, S., Tepest, R., Bente, G., Shah, N. J., Fink, G. R., & Vogeley, K. (2010). Minds made for sharing: Initiating joint attention recruits reward-related neurocircuitry. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2009.21401

Schulte-Rüther, M., Greimel, E., Markowitsch, H. J., Kamp-Becker, I., Remschmidt, H., Fink, G. R., & Piefke, M. (2011). Dysfunctions in brain networks supporting empathy: An fMRI study in adults with autism spectrum disorders. *Social Neuroscience*. https://doi.org/10.1080/17470911003708032

Shi, L., Zhou, Y., Ou, J., Gong, J., Wang, S., Cui, X., Lyu, H., Zhao, J., & Luo, X. (2015). Different Visual Preference Patterns in Response to Simple and Complex Dynamic Social Stimuli in Preschool-Aged Children with Autism Spectrum Disorders. *PLOS*

ONE, *10*(3), e0122280. https://doi.org/10.1371/journal.pone.0122280

Shic, F., Bradshaw, J., Klin, A., Scassellati, B., & Chawarska, K. (2011). Limited activity monitoring in toddlers with autism spectrum disorder. *Brain Research*. https://doi.org/10.1016/j.brainres.2010.11.074

Siu, A. M. H., Lin, Z., & Chung, J. (2019). An evaluation of the TEACCH approach for teaching functional skills to adults with autism spectrum disorders and intellectual disabilities. *Research in Developmental Disabilities*, *90*, 14–21. https://doi.org/10.1016/j.ridd.2019.04.006

Szatmari, P., Bryson, S. E., Boyle, M. H., Streiner, D. L., & Duku, E. (2003). Predictors of outcome among high functioning children with autism and Asperger syndrome. *J Child Psychol Psychiatry*, *44*(4), 520–528.

Szatmari, P., Tuff, L., Finlayson, M. A., & Bartolucci, G. (1990). Asperger's syndrome and autism: neurocognitive aspects. *J Am Acad Child Adolesc Psychiatry*, *29*(1), 130–136.

Tomanik, S. S., Pearson, D. A., Loveland, K. A., Lane, D. M., & Bryant Shaw, J. (2007). Improving the reliability of autism diagnoses: examining the utility of adaptive behavior. *J Autism Dev Disord*, *37*(5), 921–928. https://doi.org/10.1007/s10803-006-0227-6

Travers, B. G., Powell, P. S., Mussey, J. L., Klinger, L. G., Crisler, M. E., & Klinger, M. R. (2013). Spatial and identity cues differentially affect implicit contextual cueing in adolescents and adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *43*(10), 2393–2404. https://doi.org/10.1007/s10803-013-1787-x

Van Overwalle, F. (2009). Social cognition and the brain: A meta-analysis. In *Human Brain Mapping*. https://doi.org/10.1002/hbm.20547

VanMeter, L., Fein, D., Morris, R., Waterhouse, L., & Allen, D. (1997). Delay versus deviance in autistic social behavior. *J Autism Dev Disord*, *27*(5), 557–569.

Volkmar, F. R., Sparrow, S. S., Goudreau, D., Cicchetti, D. V, Paul, R., & Cohen, D. J. (1987). Social deficits in autism: an operational approach using the Vineland Adaptive Behavior Scales. *J Am Acad Child Adolesc Psychiatry*, *26*(2), 156–161. https://doi.org/S0890-8567(09)65643-4 [pii]10.1097/00004583-198703000-00005

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children–Third Edition (WISC-III) - Portuguese Version (M. R. Simões, A. M. Rocha, and C. Ferreira)*. Cegoc-Tea.

Williams, D. L., Goldstein, G., & Minshew, N. J. (2006). The profile of memory function in children with autism. *Neuropsychology*, *20*(1), 21–29. https://doi.org/10.1037/0894-4105.20.1.21

Wodka, E. L., Mathy, P., & Kalb, L. (2013). Predictors of Phrase and Fluent Speech in Children With Autism and Severe Language Delay. *Pediatrics*, *131*(4), e1128–e1134. https://doi.org/10.1542/peds.2012-2221

Zelazo, P. D., & Carlson, S. M. (2012). Hot and Cool Executive Function in Childhood and Adolescence: Development and Plasticity. *Child Development Perspectives*, *6*(4), 354–360. https://doi.org/10.1111/j.1750-8606.2012.00246.x

List of Publications

Mouga, S., Duarte, CI., Café, C., Sousa, D., Duque, F., Oliveira, G. & Castelo-Branco, M. Attentional cueing and executive deficits revealed by a virtual supermarket task coupled with eye-tracking in autism spectrum disorder. *Journal of Autism and Developmental Disorders*. Under revision

Mouga, S., Castelhano, J., Café, C., Sousa, D., Duque, F., Oliveira, G. & Castelo-Branco, M. Social attention deficits in children with autism spectrum disorder: task dependence of objects versus faces observation bias. *Frontiers in Psychiatry*. Under revision

Direito, B.*, **Mouga, S.***, Sayal, A, Simões, M., Quental, H., Bernardino, I. , Playle, R., et al. Training the social brain - clinical and neural effects of an 8-week real-time functional Magnetic Resonance Imaging neurofeedback Phase IIa Clinical Trial in Autism. *Autism: International Journal of Research and Practice* (2021). Under revision

Simões, M., **Mouga, S.**, Pereira, A. C., de Carvalho, P., Oliveira, G., Castelo-Branco, M. (2020). Virtual Reality Immersion Rescales Regulation of Interpersonal Distance in Controls but not in Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, 50(12):4317-4328. doi: 10.1007/s10803-020-04484-6.

Mouga, S., Correia, B. Regadas, Café, C., Duque, F., Oliveira, G. (2020). Language Predictors in Autism Spectrum Disorder: Insights from Neurodevelopmental Profile in a Longitudinal Perspective. *Journal of Abnormal Child Psychology*, 48(1):149-161. http://dx.doi.org/10.1007/s10802-019-00578-7.

Simões, M., Monteiro, R., Andrade, J., **Mouga, S.**, França, Felipe, Oliveira, G., Carvalho, P., Castelo-Branco, M. (2018). A Novel Biomarker of Compensatory Recruitment of Face Emotional Imagery Networks in Autism Spectrum Disorder. *Frontiers in Neuroscience*, 1;12:791. http://dx.doi.org/10.3389/fnins.2018.00791.

Amaral, C., **Mouga, S.**, Simões, M., Pereira, H. C., Bernardino, I., Quental, H., Playle, R., McNamara, R., Oliveira, G., Castelo-Branco, M. (2018). A Feasibility Clinical Trial to Improve Social Attention in Autistic Spectrum Disorder (ASD) Using a Brain Computer Interface. *Frontiers in Neuroscience,* 13;12:477. http://dx.doi.org/10.3389/fnins.2018.00477.

Castelhano, J., Tavares, Paula, **Mouga, S.**, Oliveira, G., Castelo-Branco, M. (2018). Stimulus dependent neural oscillatory patterns show reliable statistical identification of autism spectrum disorder in a face perceptual decision task. *Clinical Neurophysiology*, 129(5):981-989. http://dx.doi.org/10.1016/j.clinph.2018.01.072.

Carvalho Pereira, Andreia, Violante, I. R., **Mouga, S.**, Oliveira, G., Castelo-Branco, M. (2017). Medial Frontal Lobe Neurochemistry in Autism Spectrum Disorder is Marked by Reduced N-Acetylaspartate and Unchanged Gamma-Aminobutyric Acid and Glutamate+Glutamine

Levels. *Journal of Autism and Developmental Disorders* 48(5):1467-1482. http://dx.doi.org/10.1007/s10803-017-3406-8.
Amaral, C. P., Simões, M. A., **Mouga, S.**, Andrade, J., Castelo-Branco, M. (2017). A novel Brain Computer Interface for classification of social joint attention in autism and comparison of 3 experimental setups: A feasibility study. *Journal of Neuroscience Methods*, 1;290:105-115. http://dx.doi.org/10.1016/j.jneumeth.2017.07.029.

Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium (2017). Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. *Molecular Autism,* 22;8:21. http://dx.doi.org/10.1186/s13229-017-0137-9.

Weiner, D. J., Wigdor, E. M., Ripke, S., Walters, R. K., Kosmicki, J. A., Grove, J., Samocha, K. E., Goldstein, J. I., Okbay, A., Bybjerg-Grauholm, J., Werge, T., Hougaard, D. M., Taylor, J.; iPSYCH-Broad Autism Group, **Psychiatric Genomics Consortium Autism Group**, Skuse, D., Devlin, B., Anney, R., Sanders, S. J., Bishop, S., Mortensen, P. B., Børglum, A. D., Smith, G. D., Daly, M. J., Robinson, E. B. (2017). Polygenic transmission disequilibrium confirms that common and rare variation act additively to create risk for autism spectrum disorders. *Nature Genetics,* 49(7):978-985. http://dx.doi.org/10.1038/ng.3863.

Conceição, I. C., Rama, M. M., Oliveira, B., Café, C., Almeida, J., **Mouga, S.**, Duque, F., Oliveira, G., Vicente, A. M. (2017). Definition of a putative pathological region in PARK2 associated with autism spectrum disorder through in silico analysis of its functional structure. *Psychiatric Genetics*, 27(2):54-61. http://dx.doi.org/10.1097/ypg.0000000000000159.

Loureiro, S., Almeida, J., Café, C., Conceição, I., **Mouga, S.**, Beleza, A., Oliveira, B., Sá, J., Carreira, I., Saraiva, J., Vicente, A., Oliveira, G. (2017) Copy number variations in chromosome 16p13.11-the neurodevelopmental clinical spectrum. *Current Pediatric Research*, 21(1): 116-129. https://www.alliedacademies.org/articles/copy-number-variations-in-chromosome-16p1311the-neurodevelopmental-clinical-spectrum.pdf.

Mouga, S., Café, C., Almeida, J., Marques, C., Duque, F., Oliveira, G. (2016). Intellectual Profiles in the Autism Spectrum and Other Neurodevelopmental Disorders. *Journal of Autism and Developmental Disorders*, 46(9):2940-55. http://dx.doi.org/10.1007/s10803-016-2838-x.

Tavares, P., **Mouga, S.**, Oliveira, G., Castelo-Branco, M.. Preserved face inversion effects in adults with autism spectrum disorder: an event-related potential study (2016). *NeuroReport*, 25;27(8):587-592. http://dx.doi.org/10.1097/wnr.0000000000000576.

Mouga, S., Almeida, J., Café, C., Duque, F., Oliveira, G. (2015). Adaptive Profiles in Autism and Other Neurodevelopmental Disorders. *Journal of Autism and Developmental Disorders,* 45(4):1001-1012. http://dx.doi.org/10.1007/s10803-014-2256-x.

Correia, F., Café, C., Almeida, J., **Mouga, S.**, Oliveira, G. (2015). Autism Spectrum Disorder: FRAXE Mutation, a Rare Etiology. *Journal of Autism and Developmental Disorders,* 45(3):888-92. http://dx.doi.org/10.1007/s10803-014-2185-8.

Hadley, D., Wu, Z. L., Kao, C., Kini, A., Mohamed-Hadley, A., Thomas, K., Vazquez, L., Qiu, H., Mentch, F., Pellegrino, R., Kim, C., Connolly J; **AGP Consortium**, Glessner J, Hakonarson H. (2014). The impact of the metabotropic glutamate receptor and other gene family interaction networks on autism. *Nature Communications,* 13;5:4074. http://dx.doi.org/10.1038/ncomms5074.

Pinto, D., Delaby, E., Merico, D., Barbosa, M., Merikangas, A., Klei, L., Thiruvahindrapuram, B., Xu, X., Ziman, R., Wang, Z., Vorstman, J. A., Thompson, A,, Regan, R., Pilorge, M., Pellecchia, G., Pagnamenta, A. T., Oliveira, B., Marshall, C. R., Magalhaes, T. R., Lowe, J. K., Howe, J. L., Griswold, A. J., Gilbert, J., Duketis, E., Dombroski, B. A., De Jonge, M. V., Cuccaro, M., Crawford, E. L., Correia, C. T., Conroy, J., Conceição, I. C., Chiocchetti, A. G., Casey, J. P., Cai, G., Cabrol, C., Bolshakova, N., Bacchelli. E., Anney, R., Gallinger, S., Cotterchio, M., Casey, G., Zwaigenbaum, L., Wittemeyer, K., Wing, K., Wallace, S., van Engeland. H., Tryfon, A., Thomson, S., Soorya, L., Rogé, B., Roberts, W., Poustka, F., **Mouga, S.**, Minshew, N., McInnes, L. A., McGrew, S. G., Lord, C., Leboyer, M., Le Couteur, A. S., Kolevzon, A., Jiménez González, P., Jacob, S., Holt, R., Guter, S., Green, J., Green, A., Gillberg, C., Fernandez, B. A., Duque, F., Delorme, R., Dawson, G., Chaste, P., Café, C., Brennan, S., Bourgeron, T., Bolton, P. F., Bölte, S., Bernier, R., Baird, G., Bailey, A. J., Anagnostou, E., Almeida, J., Wijsman, E. M., Vieland, V. J., Vicente, A. M., Schellenberg, G. D., Pericak-Vance, M., Paterson, A. D., Parr, J. R., Oliveira, G., Nurnberger, J. I., Monaco, A. P., Maestrini, E., Klauck, S. M., Hakonarson, H., Haines, J. L., Geschwind, D. H., Freitag, C. M., Folstein, S. E., Ennis, S., Coon, H., Battaglia, A., Szatmari, P., Sutcliffe, J. S., Hallmayer, J., Gill, M., Cook, E. H., Buxbaum, J. D., Devlin, B., Gallagher, L., Betancur, C., Scherer, S. W. (2014). Convergence of Genes and Cellular Pathways Dysregulated in Autism Spectrum Disorders. *The American Journal of Human Genetics*, 1;94(5):677-694. http://dx.doi.org/10.1016/j.ajhg.2014.03.018.

Correia, C. T, Conceição, I. C, Oliveira, B., Coelho, J., Sousa, I., Sequeira, Ana F, Almeida, J., Café, C., Duque, F., **Mouga, S.**, Roberts, W., Gao, K., Lowe, J. K., Thiruvahindrapuram, B., Walker, S., Marshall, C. R., Pinto, D., Nurnberger, J. I., Scherer, S. W., Geschwind, D. H., Oliveira, G., Vicente, A. M. (2014). Recurrent duplications of the annexin A1 gene (ANXA1) in autism spectrum disorders. *Molecular Autism*, 10;5(1):28. http://dx.doi.org/10.1186/2040-2392-5-28.

Bernardino, I., **Mouga, S.**, Castelo-Branco, M., van Asselen, M. (2012). Egocentric and Allocentric Spatial Representations in Williams Syndrome. *Journal of the International Neuropsychological Society,* 19(1):54-62. http://dx.doi.org/10.1017/s1355617712000963.

Bernardino, I., **Mouga, S.**, Almeida, J., van Asselen, M., Oliveira, G., Castelo-Branco, M. (2012). A Direct Comparison of Local-Global Integration in Autism and other Developmental

Disorders: Implications for the Central Coherence Hypothesis. *PLoS ONE* (7): 6: e39351. http://dx.doi.org/10.1371/journal.pone.0039351.

J. Tarroso, M., Almeida, J., Lontro, R., Marques, C., S M., T., Lobo, C., Café, C., **Mouga, S**., Lapa, L., Duque, F., Correia, C., Vicente, A., Oliveira, G. (2010). Os efeitos da risperidona nos níveis de prolactina numa amostra de crianças e adolescentes com autismo. *Acta Pediátrica Portuguesa* 41 (3): 111-116. https://pjp.spp.pt//article/view/4356.

Curriculum Vitae

Susana Mouga was born on January 19, 1984 in Lisbon, Portugal. In 2002, she completed her secondary school education at Escola Secundária do Bombarral in Bombarral, after which she studied Psychology at the Faculty of Psychology and Educational Sciences of the University of Coimbra. For her master degree, she did a clinical and research internship at the Centro de Desenvolvimento da Criança (CDC), Hospital Pediátrico (HP), Centro Hospitalar e Universitário de Coimbra (CHUC). In December 2007 she attained her master's degree and at the same time started to work as a psychologist and research assistant in an international project: Autism Genome Project (AGP)/The Autism Simplex Collection (TASC), supported by Autism Speaks in UNDA/HP/CHUC (under supervision of Professor G. Oliveira) and in collaboration with Instituto Gulbenkian de Ciência. In December 2009 she started to work as research assistant at the IBILI, Faculty of Medicine of the University of Coimbra, under the supervision of Professor Miguel Castelo-Branco and always in collaboration with UNDA/HP/CHUC (under supervision of Professor Guiomar Oliveira). In 2011, she successfully applied to the Doctoral Programme in Health Sciences of the Faculty of Medicine of the University of Coimbra, completing the courses with Excellent (19/20). In 2013 she started her PhD research project entitled Testing a specific link between Executive Functions and Social Cognition in Autism Spectrum Disorders at CNC.IBILI, CIBIT-ICNAS and UNDA/HP/CHUC, under the supervision of Professor Guiomar Oliveira and Professor Miguel Castelo-Branco. In 2015 she was awarded an Individual PhD Scholarship from the Portuguese Foundation for Science and Technology (FCT): SFRH/BD/102779/2014, to pursue her PhD. During the past thirteen years she has been collaborating in research projects in the area of neurodevelopmental disorders, namely, autism spectrum disorder, always combining basic research and clinical work.