Ana Isabel Pina Rodrigues

SPOTLIGHT OF ATTENTION IN DEVELOPMENTAL DYSLEXIA

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Tese no âmbito do Programa de Doutoramento em Ciências da Saúde, ramo de Ciências Biomédicas orientada pelo Professor Doutor Miguel Castelo-Branco e pela Doutora Marieke van Asselen e apresentada à Faculdade de Medicina da Universidade de Coimbra

Agosto de 2018

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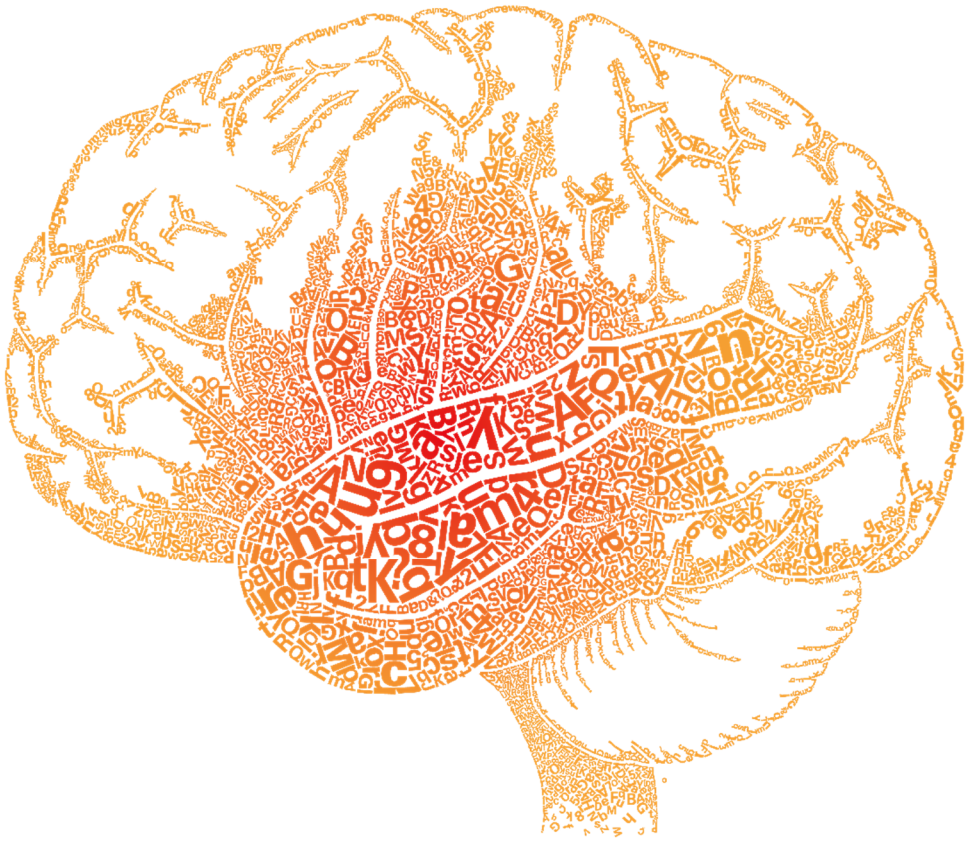

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Spotlight of attention in Developmental Dyslexia

Thesis to obtain a Ph.D. degree in Biomedical Sciencies at the Doctoral Programme in Health Sciences, supervised by Miguel Castelo-Branco and Marieke van Asselen, 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 por Miguel Castelo-Branco e Marieke van Asselen e apresentada à Faculdade de Medicina da Universidade de Coimbra

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Supervised by: Miguel Castelo-Branco, Ph.D.
Co-Supervised by: Marieke van Asselen, Ph.D.

Para a Rosa e Fernando

"You can never cross the ocean until you have the courage to lose sight of the shore".

Cristóvão Colombo

Contents

Abbreviations

ADHD	Attention Deficit and Hyperactivity Disorder
AI	Accuracy Index
ANOVA	Analysis of Variance
CCT	Cambridge Color Test
CCT-PD	Cambridge Color Test – Protan Deutan
Chr	Chromosome
D	Dorsal
dB	Decibel
DD	Developmental Dyslexia
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders IV
DSM-V	Diagnostic and Statistical Manual of Mental Disorders V
EEG	Electroencephalography
ERP	Event-Related Potential
f	Feminine
FFA	Fusiform Face Area
FI	Fluency Index
fMRI	Functional Magnetic Resonance Imaging
fROI	Functional Region of Interest
GLM	General Linear Model
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IPS	Intraparietal Sulcus
ISF	Intermediate Spatial Frequency
IQ	Intellectual Quotient
IW	Irregular Words
K	Koniocellular
LGN	Lateral Geniculate Nucleus
LOC	Lateral Occipital Complex
LSD	Local Speed Discrimination
M	Magnocellular

m	Masculine
MEG	Magnetoencephalography
MPRAGE	Magnetization-Prepared Rapid-Acquisition Gradient Echo
MRI	Magnetic Resonance Imaging
MST	Medial Superior-Temporal area
MT	Middle Temporal Area
MTM	Multi-Trace Memory
OFA	Occipital Face Area
P	Parvocellular
PALPA-P	Psycholinguist Assessments of Language Processing in Aphasia - Portuguese version
PPA	Parahippocampal Place Area
PPC	Posterior Parietal Cortex
PSA	Parietal Shape Area
PTB	Psychophysics Toolbox
PW	Pseudowords
RFX	Random Effects
ROI	Region of Interest
RPM	Ravens Progressive Matrices
RT	Response Time
RW	Regular Words
SAS	Sluggish Attentional Shifting
SD	Standard Deviation
SLD	Specific Learning Disabilities
SE	Standard Error of the mean
SMI	SensoMotoric Instruments
SOA	Stimulus Onset Asynchrony
TE	Echo Time
TMS	Transcranial Magnetic Stimulation
TPJ	Temporoparietal Junction
TR	Repetition Time
V	Ventral

VOTC	Ventral Occipito-Temporal Cortex
VWF	Visual Word Form
VWFA	Visual Word Form Area
WCR	Words Correctly Read
WISC-III	Wechsler Intelligence Scale for Children, 3rd. ed.
WR	Words Read

Summary

Developmental dyslexia (DD) is a neurodevelopmental disorder characterized by a reading impairment in spite of normal intellectual functioning and educational opportunities. Despite of the vast amount of studies, the causes of this condition and the mechanisms underlying such causes remain under debate and are still a subject of intensive research. Although phonological processing deficits are well established as core deficits in DD, it has been suggested that visuo-attentional impairments may also contribute to the pathophysiology of this condition.

The main focus of this thesis is the characterization of multiple visuo-attentional processes in DD and of the relationship between these processes and the reading deficits present in this condition. In this work, a combination of different modalities is used, such as psychophysics, eye-tracking and neuroimaging, and different dyslexic populations are studied, namely children and adults, in order to allow a comprehensive understanding of the visuo-attentional mechanisms in DD.

Since visual perception is implicated in such mechanisms, the first study of this thesis was focused on characterizing visual perception in DD. Given previous associations between abnormal dorsal stream processing and reading impairments, we used an innovative approach to infer dorsal impairments in DD population. The approach consisted of a battery of tasks following a gradient of dorsal stream contribution - a chromatic contrast sensitivity task (weak dorsal stream contribution), an intermediate spatial frequency contrast sensitivity task (mild dorsal stream contribution) and a local speed discrimination task (strong dorsal stream contribution). We confirmed that the higher the dorsal stream involvement, the higher the differences between DD children and typical readers. We also demonstrated that the higher the involvement of dorsal processing, the stronger the correlation to reading measures.

After characterizing visual perception, we went to investigate different visuo-attentional processes in DD. In the second study of this thesis, we showed, for the first time, that dyslexic adults have global temporal deficits and abnormal distribution of attention in a task requiring exogenous orienting of attention. Importantly, we also demonstrated that their attentional cueing effects are dependent on the eccentricity, with an inability to efficiently use cues to rapidly direct attention to more peripheral eccentricities. In the third study of the thesis, we addressed the perceptual noise exclusion theory by investigating how low-level visual noise interferes with lexical and sub-lexical reading processes in DD children and typical readers. Contrary to the theory's predictions, we showed that the presence of noise does not affect

reading of DD children more than that of controls. Moreover, we found a stronger effect of low-level noise in sub-lexical reading than in lexical reading, indicating that the type of reading stimuli and consequent reading strategies play an important role in determining the effects of noise interference in reading.

Finally, we conducted a fMRI study to investigate brain functioning in DD. Particularly, we studied the left ventral occipito-temporal cortex (VOTC), a region associated to memory-based visual-orthographic word recognition and that includes the Visual Word Form Area (VWFA) which has been described as an area specifically tuned to process letter strings. Based on the notion of a posterior-to-anterior gradient of increasing print specificity in VOTC, and contrary to the majority of the studies which focused exclusively on the analyses of the VWFA, we evaluated print tuning in DD along the whole VOTC. We corroborated previous studies by demonstrating an underactivation to print stimuli in the VWFA of dyslexics. Additionally, we also found differences in a more anterior area, indicating a possible role of this area in word processing and suggesting the involvement of multiple areas within VOTC in the reading impairments.

In sum, the work presented in the current thesis provides novel clues to the current understanding of DD, by demonstrating that Portuguese dyslexics have impaired visual and visuo-attentional processing and a distinct neural organization. These findings increment the current characterization of this condition, essential for the development of improved methods for diagnosis and remediation.

Sumário

A dislexia do desenvolvimento (DD) é uma perturbação do neurodesenvolvimento caracterizada pela incapacidade em descodificar e processar informação escrita, apesar de um nível intelectual normal e da existência de instrução adequada para a aprendizagem da leitura. Não obstante a extensa investigação existente sobre a DD, as suas causas, bem como os mecanismos que as subjazem, continuam a ser alvo de estudo e de debate. É comummente aceite que os défices no processamento fonológico são centrais na DD. No entanto, tem sido sugerido que défices em funções visuo-atencionais podem também contribuir para a patofisiologia desta perturbação.

Esta tese tem como principal objectivo caracterizar múltiplos processos visuo-atencionais na DD, bem como a sua relação com as dificuldades de leitura presentes nesta perturbação. No sentido de permitir uma compreensão mais abrangente desta temática, foram usados nesta tese diversos métodos, tais como testes psicofísicos, medição dos movimentos oculares e neuroimagem funcional, e foram estudadas diferentes populações, nomeadamente crianças e adultos.

Tendo em conta que a percepção visual está implicada nos processos visuo-atencionais, o primeiro estudo descrito nesta tese focou-se na caracterização da percepção visual na DD. Estudos prévios têm descrito uma associação entre alterações no processamento da via visual dorsal e os défices de leitura. Nesse sentido, usámos, neste estudo, uma abordagem inovadora para inferir alterações na via dorsal na população com DD. A abordagem consistiu no desenho de uma bateria de testes visuais que seguem um gradiente de contribuição da via dorsal – um teste de sensibilidade ao contraste cromático (fraca contribuição da via dorsal), um teste de sensibilidade ao contraste com frequências espaciais intermédias (ligeira contribuição da via dorsal) e uma tarefa de discriminação de velocidade (forte contribuição da via dorsal). O nosso estudo confirmou que quanto maior o envolvimento da via visual dorsal, maiores as diferenças entre o desempenho das crianças com DD e o das crianças sem dificuldades de leitura. Demonstrámos também que quando o envolvimento da via visual dorsal é maior, a correlação com as medidas de leitura é mais forte.

Após a caracterização da percepção visual, a nossa investigação focou-se em diferentes processos visuo-atencionais na DD. No segundo estudo desta tese, usando uma tarefa que requer orientação exógena da atenção, demonstrámos, pela primeira vez, que os adultos com dislexia exibem défices temporais na orientação exógena da atenção, bem como alterações na sua distribuição espacial. Demonstrámos também que, nos disléxicos, o efeito das pistas

atencionais é dependente da excentricidade visual, o que se traduz por uma incapacidade de usar pistas para dirigir eficaz e rapidamente a atenção em exentricidades visuais mais periféricas.

No terceiro estudo da tese, abordámos a teoria da exclusão perceptual do ruído investigando a interferência do ruído visual de baixo nível nos processos lexicais e sub-lexicais em crianças com DD e em controlos. Demonstrámos, contra as previsões da teoria, que a presença de ruído não afecta de forma mais significativa a performance das crianças com DD do que a dos controlos. Demonstrámos também que o efeito do ruído é superior na leitura sub-lexical do que na lexical. Este resultado sugere que o tipo de estímulos e estratégias de leitura têm um papel importante na determinação dos efeitos do ruído na leitura.

Por último, desenvolvemos um estudo com ressonância magnética funcional para investigar o funcionamento cerebral na DD. Estudámos, em particular, o córtice occipito-temporal ventral (VOTC) esquerdo, uma região associada ao reconhecimento das palavras baseado na memória visual ortográfica. Esta região inclui a Área da Forma Visual da Palavra (VWFA) que tem sido descrita como uma área especializada no processamento de palavras. Diferentes estudos têm sugerido um gradiente de especialização do processamento no VOTC. Contudo, a maioria da investigação do VOTC na DD focou-se exclusivamente no estudo da VWFA. O nosso estudo pretendeu analisar o processamento de estímulos de leitura em toda a extensão do VOTC. Em primeiro lugar, em consonância com outros estudos, demonstrámos hipoactivação para estímulos de leitura na VWFA dos disléxicos. No entanto, encontrámos também diferenças significativas numa área anterior do VOTC, sugerindo que esta área poderá ter também uma função no processamento de palavras. Desta forma, os resultados deste estudo sugerem o envolvimento de várias áreas no VOTC nos défices de leitura.

O trabalho aqui apresentado demonstra défices visuais e visuo-atencionais e uma organização neuronal distinta na DD, fornecendo novas pistas para a compreensão dos mecanismos envolvidos nesta perturbação. Este trabalho contribui, desta forma, para a caracterização da DD, essencial para o desenvolvimento de métodos eficazes de diagnóstico e reabilitação.

INTRODUCTION

CHAPTER 1

General Introduction

The storage and dissemination of knowledge through writing is undoubtedly a cultural landmark in the history of humankind. In modern technological societies, the ability to decode written information, i.e. to read, is a fundamental skill to reach educational and professional success. The incapacity to read can thus has important social, economic and psychological consequences.

Normal reading depends on several linguistic and non-linguistic cognitive abilities. While some people lose the ability to read due to brain injury, others cannot achieve an efficient reading despite adequate reading instruction and normal intelligence. These last cases are a considerable percentage of the population, 7%-12% (Rutter et al., 2004), and correspond to the neurodevelopmental disorder termed developmental dyslexia (DD).

In this first chapter, the clinical and neurocognitive characteristics of DD will be presented, as well as the most prominent hypotheses for its causes. Since the focus of the current work was to investigate visuo-attentional mechanisms in DD, particular emphasis will be given to attentional theories on the causes of DD and to evidence of the relationship between visuo-attentional dysfunctions and reading impairments. Finally, this chapter will introduce the general outline of the thesis and its main objectives.

Historical overview

The term "dyslexia" was coined by Rudolf Berlin, a German ophthalmologist, in 1872 and it was used to described a case of an adult with acquired reading difficulties. It was just in 1937, in the First Congress of Child Psychiatry in Paris, that Ombredanne introduced the term dyslexia to refer to non-acquired reading deficits (Guardiola, 2001).

The first description of a case of what is now referred to as developmental dyslexia dates to 1986, and it can be found in a report by W.P. Morgan published in The Lancet. This is the description of what he called "congenital word-blindness": "*Percy F. – a well-grown lad, aged 14 – is the eldest son of intelligent parents… He has always been a bright and intelligent boy, quick at games, and in no way inferior to others of his age. His greatest difficulty has been – and is now – his inability to learn to read. This inability is so remarkable, and so pronounced, that I have no doubt it is due to some congenital defect… the greatest efforts have been made to teach him to read, but, in spite of this laborious and persistent training, he can only with difficulty spell out words of one syllable… The schoolmaster who has taught him for some years says that he would be the smartest lad in the school if the instructions were entirely oral… His father informs me that the greatest difficulty was found in teaching the boy his letters, and they thought he never would learn them.*" (Morgan, 1896, p.1378 in Beaton, 2004).

Still under the term "congenital word blindness", and after publishing a series of articles in the medical press describing clinical cases, the British ophthalmologist Hinshelwood published in 1917 a treaty in which this condition is proposed as congenital and more common in boys. The cause of the reading difficulties would be, according to Hinshelwood, a deficient acquisition and storage of the visual memory of letters and words (Guardiola, 2001).

After the first works done in Europe, the study and research on reading impairments progressed mainly in the United States and especially due to the contributions of the neurologist Samuel Orton. Between the years of 1925 and 1948, he studied about three thousand children and adults, and claimed that people with non-acquired reading impairments suffered from a genetic abnormal occipital hemispheric dominance, which would lead to a deficient visual perception.

In 1971, Isabelle Liberman, started to pave the way for the phonological theories by defending that reading impairments derive from inadequate phonological representation and segmentation (Liberman, 1971 cited in Guardiola, 2001).

Despite these works, the existence of a condition characterized by specific reading deficits was still questioned. An important step to prove the existence of such condition derived from the work of Rutter and colleagues (1976), who carried out the so called epidemiological studies of the Isle of Wight. In their studies, besides finding children with concomitant reading and cognitive deficits, these authors also found children with specific reading deficits in spite of normal intelligence levels.

Since the 1970s, several theories on the causes of specific reading impairments were proposed, encompassing linguistic, perceptual, neurobiological and visual explanations. The most prominent, and still prevailing, causal theories of dyslexia are described below in detail.

Definition of Developmental Dyslexia

The first classical definition of dyslexia was provided by Knud Hermann in 1959: *"...a deficit in the acquisition of an age-appropriate level of reading and writing ability; this deficit is due to constitutional (hereditary) factors, it is often accompanied by difficulties with other kinds of symbols (numeric, musical, etc.), it exists in the absence of other cognitive or sensory deficits, and in the absence of inhibitory influences, past or present, in the internal or external environment.*" (Hermann, 1959 cited in Guardiola, 2001).

In 1968, in the report of the research group on developmental dyslexia and world illiteracy of the World Federation of Neurology, dyslexia was described as "*a disorder in children who,*

despite conventional classroom experience, fail to attain the language skills of reading, writing and spelling commensurate with their intellectual abilities" (World Federation of Neurology, 1968).

Besides the World Federation of Neurology's definition, that is still used at least in research, there are other definitions of DD that coexist nowadays. The World Health Organization, in its International Classification of Diseases, 10th Revision (ICD-10) includes DD in the specific developmental disorders of scholastic skills, sub-group of specific reading disorder: "*The main feature is a specific and significant impairment in the development of reading skills that is not solely accounted for by mental age, visual acuity problems, or inadequate schooling*...". Notably, the widely used Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) by the American Psychiatric Association, contrary to previous versions, does not comprise an explicit definition of DD. Indeed, DSM-V defines a single overarching category of Specific Learning Disabilities (SLD), being "reading impairment" a specifier to characterize a specific manifestation of learning difficulties (American Psychiatric Association, 2013). This fact has generated criticism from clinicians, researchers and practitioners in several fields. The previous version, the DSM IV-TR, defined the following diagnostic criteria for DD: a) Reading achievement, as measured by individually administered standardized tests of reading accuracy or comprehension, is substantially below that expected given the person's chronological age, measured intelligence, and age-appropriate education; b) The disturbance in Criterion A significantly interferes with academic achievement or activities of daily living that require reading skills; c) If a sensory deficit is present, the reading difficulties are in excess of those usually associated with it. It is important to note that these last criteria were used to operationally define DD in the studies described below in results' section of the current thesis.

Finally, there are other cognitive impairments that are not included in the diagnostic criteria for DD but are often observed in subjects with DD. Those include deficits in working memory (e.g. Fostick & Revah, 2018; Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005), in temporal processing (e.g. Ortiz, Estévez, Muñetón, & Domínguez, 2014; Vandermosten et al., 2010), in attentional skills (e.g. Heim et al., 2008; Menghini et al., 2010), in auditory discrimination (e.g. Amitay, Ben-Yehudah, Banai, & Ahissar, 2002), in motor or automatization skills (e.g. Nicolson, Fawcett, & Dean, 2001; Pernet, Poline, Demonet, & Rousselet, 2009), and in visual processing (e.g. Heim et al., 2010; Mascheretti et al., 2017; White et al., 2006). This heterogeneity of impairments among the dyslexic population have led to different hypothesis on the causes of this disorder. The last section of this chapter will be devoted to present different views on the etiology of DD.

Neurological basis of Developmental Dyslexia

Neuroimaging methods have shown that, in typically reading adults, the brain regions most consistently involved in single word reading are lateralized to the language-dominant left hemisphere and include inferior frontal, superior and middle temporal and temporo-parietal regions, and an area of the left fusiform gyrus (the visual word form area – VWFA) (Dehaene & Cohen, 2011; Norton, Beach, & Gabrieli, 2015; Price, 2012). Regarding impaired reading, a considerable amount of evidence showing brain structure and, in particular, function abnormalities in subjects with DD has been acquired, providing clues to understand the cognitive impairments in DD.

As already mentioned, DD is considered a neurodevelopmental disorder. This notion found particular support in the seminal work of Galaburda and colleagues (1985) who found neuroanatomical abnormalities in the postmortem brains of subjects with DD. All subjects showed an abnormal pattern of brain asymmetry in the planum temporale as well as developmental anomalies of the cerebral cortex, particularly in cortical areas devoted to language processing such as the left perisylvian regions. Based on these neuropathological findings, the authors suggested that dyslexics may suffer from abnormal cortical ontogenesis, with impaired neuron migration.

More recently, using magnetic resonance imaging (MRI) and correlating local grey matter volumes with reading performance variables, significant structural brain differences were observed between dyslexics and controls, namely in the left superior temporal cortex, the temporal visual cortex and the lateral cerebellar cortex (Pernet, Andersson, Paulesu, & Demonet, 2009). Several other studies also reported abnormal symmetry of planum temporale in dyslexic brains (see Altarelli et al., 2014 for review), as well as reduced grey matter in temporal (Silani et al., 2005; Vinckenbosch, Robichon, & Eliez, 2005) and parietal (Jednoróg, Gawron, Marchewka, Heim, & Grabowska, 2013; Xia, Hoeft, Zhang, & Shu, 2016) regions. All these regions are known to be involved in auditory/phonological, visual and attentional processing, being therefore congruent with the main causal theories of DD described below in this chapter.

In which concerns functional brain imaging studies, the functional brain differences most commonly reported are consistent with the structural differences and consist in reduced activations in left temporal, parietal and fusiform (VWFA) regions during reading related tasks (see Norton et al., 2015 for review).

Etiology of DD

When learning to read, unfamiliar orthographic codes must be associated to the familiar spoken words. This process starts by learning the matching between singular letters or groups of letters and their corresponding sounds, i.e. by acquiring phonological decoding skills. With the increase of the reading experience, children start to establish direct connections between letter strings and oral language, developing an orthographic lexicon, which supports fluent reading (Ziegler, Perry, & Zorzi, 2013). Why this process is not effortless for all children is still an open question and different views on the mechanisms of reading impairments coexist in present times. The current knowledge on the genetic basis of DD is described below, as well as some of the most important causal theories.

Genetic basis

The notion of a genetic basis of DD can be dated back to the beginning of the 20th century. In 1917, by studying a family with several members with reading deficits, Hinshelwood suggested that DD could be an hereditary condition more common in boys than in girls (Guardiola, 2001). After that, several authors corroborated the conclusion that dyslexia run in families, but only in 1950, Bertil Hallgren took this idea further by suggesting that dyslexia was an autosomal dominant disorder (Hallgren, 1950). However, several evidence in favor of genetic heterogeneity in DD has been compiled, undermining the case for an autosomal dominant mode of transmission (see Pennington, 1999, for a review).

The emergence of more sophisticated genetic techniques allowed the linkage between genes and diseases. Using such techniques, candidate regions to reading disability in chromosome 6 have been proposed (e.g. Cardon et al., 1994; Cope et al., 2012; Eicher et al., 2014; Elbert et al., 2011; Fisher et al., 1999; Gayán et al., 1999; Smith, Kimberling, & Pennington, 1991; Smith, Kimberling, Pennington, & Lubs, 1983; Warren et al., 1996), namely the DCDC2 and KIAA0319 genes whose mutations induce abnormal neural migration during cortical ontogenesis (e.g. Cope et al., 2012; Eicher et al., 2014; Elbert et al., 2011). Mutations on other chromosomes, such as 15 (e.g. Brkanac et al., 2007; Buonincontri et al., 2011; Grigorenko et al., 1997; Morris et al., 2000; Schulte-Körne et al., 1998; Schumacher et al., 2008), 1 (de Kovel et al., 2008; Grigorenko et al., 2001), 2 (de Kovel et al., 2008; Fagerheim et al., 1999), 3 (Nopola-Hemmi et al., 2001) and 18 (Fisher et al., 2002), have also been associated

with reading disabilities (see Table 1.1 and Scerri & Schulte-Körne, 2010 for a review on genetics of DD).

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

Table 1.1. Summary of candidate genes associated with reading disabilities

Gene	Chr	Associated Measures
KIAA0319L	1	Reading disability; Word identification and decoding; Rapid naming
MRPL19	2	Dyslexia; Reading disability; Single-word reading
ROBO1	3	Dyslexia; Reading disability; Single-word reading; Character recognition
DCDC2	6	Dyslexia; Single-word reading; Phonological awareness and decoding; Orthographic coding
KIAA0319	6	Dyslexia; Single-word reading; Phonological decoding
CYP19A1	15	Dyslexia; Phonological processing; Single-word reading; Phoneme awareness
DYX1C1	15	Dyslexia; Single-word reading; Orthographic coding
DYX6	18	Single-word reading; Phoneme awareness; Phonological decoding; Orthographic coding

Theories on the causes of DD

The phonological deficit theory

The most well studied theory on the causes of DD is the phonological theory. For its supporters, the reading problems in DD relate to a deficient representation, storage and/or retrieval of speech sounds (phonemes). In other words, reading requires the knowledge of grapheme to phoneme correspondences (i.e. the correspondence between the visual units of the words and constituent sounds). If the phonemes are deficiently represented, stored or

retrieved, it would result in an undeveloped learning of such correspondences and, consequently, in reading impairments (Snowling, 1981; Vellutino, 1979) .

This theory finds support in studies showing that dyslexics have consistent deficits on tasks requiring phonological abilities, such as phonological awareness and phonological decoding (see Snowling, 2001 and Vellutino, Fletcher, Snowling, & Scanlon, 2004 for reviews).

Pre-reading phonological skills predict later reading performance (Caravolas, Hulme, & Snowling, 2001; Law, Vandermosten, Ghesquière, & Wouters, 2017), and the majority of interventional programs in DD are grounded in this causal theory with evidence suggesting that training phonological skills leads to an improvement of reading ability (e.g. Ehri et al., 2001; Lovett, Borden, DeLuca, Kacerenza, & et al, 1994; Schneider, Roth, & Ennemoser, 2000; Shaywitz et al., 2004; Spironelli, Penolazzi, Vio, & Angrilli, 2010). However, it has been shown that not all dyslexics can benefit from such phonological interventional programs (e.g. Lovett, Ransby, Hardwick, Johns, & Donaldson, 1989; Lundberg, Frost, & Petersen, 1988; McArthur, Ellis, Atkinson, & Coltheart, 2008; Torgesen, Morgan, & Davis, 1992) and that non phonological interventions can be effective in improving reading performance (Chouake, Levy, Javitt, & Lavidor, 2012; Franceschini et al., 2013, 2017; Lorusso, Facoetti, Toraldo, & Molteni, 2005). Additionally, not all dyslexics show significant phonological deficits and not all with phonological deficits suffer from reading impairments (Caccappolo-van Vliet, Miozzo, & Stern, 2004b, 2004a; Castles & Coltheart, 2004; Ramus & Szenkovits, 2008; Tree & Kay, 2006). Thus, this theory fails to explain non phonological cases of DD, in which dyslexics only have difficulties in reading irregular words that do not follow the common phonetic rules and, thus, require lexical, rather than phonological, processing to be read (Castles & Coltheart, 1993). Indeed, a causal link between phonological skills and the ability to learn to read successfully has been challenged (Castles & Coltheart, 2004), and it has been suggested that the cause and effect may be the other way round, with reading improvement increasing phonological performance (Castro-Caldas, Petersson, Reis, Stone-Elander, & Ingvar, 1998; Facoetti, 2012; Mann & Wimmer, 2002). Thus, one can say that, besides evidence of poor phonological skills in DD, it's causal relationship with reading deficits is still under debate.

The magnocellular theory

Other important, yet controversial, causal theory in dyslexia is termed magnocellular theory (Stein, 2001; Stein & Walsh, 1997). This theory postulates that reading impairments derive from abnormal magnocellular visual processing in dyslexics. To fully understand this theory, it is important to be aware of basic principles of the human retino-cortical visual system. Therefore, the next sub-section is devoted to briefly present the neuroanatomy and functioning of the human visual system.

Visual System

When light hits the eye, the photoreceptors at the back of the retina (rods and cones) transduce optical information into electrical signals, which are projected first to bipolar cells and afterwards to a layer of cells named retinal ganglion cells. The two main types of these retinal ganglion cells are the magnocellular (M) cells and the parvocellular (P) cells. The M-cells respond strongly to movement, are highly sensitive to contrast but not very sensitive to color, and are more numerous in the periphery than in central retina. On the other hand, the smaller and most numerous P-cells, respond to changes in color but less in contrast and are not sensitive to movement. The M-cells have faster conduction velocity than P-cells, as well as higher temporal and lower spatial resolution (Kaplan & Shapley, 1986).

The axons of retinal ganglion cells form the optic nerve, and both optic nerves from each eye meet at the optic chiasm. Here, optic nerves, which are now called optic tract, project contralaterally to neurons on the Lateral Geniculate Nucleus (LGN) located in the thalamus, meaning that each optic tract contains information from the contralateral visual field. The primate LGN comprises six different layers, two M layers and four P layers, and whereas M layers receive input from M-cells, P layers receive input from P-cells (Leventhal, Rodieck, & Dreher, 1981). From LGN visual information is relayed to the primary visual cortex - V1 (see Figure 1.1)

Projections from the different layers of the LGN reach different layers in V1. The M layers of LGN project mainly to layer IVCα which projects to layer IVB and then to the higher cortical areas V2, V3 and V5. The P layers of LGN project to layer IVCβ which projects to layer IVA and then to V2 and V4 (Livingstone & Hubel, 1988). Adding to Magnocellular and

Parvocellular pathways from LGN to V1, there is also evidence of a third pathway, the Koniocellular (K), that will not be described in the current thesis.

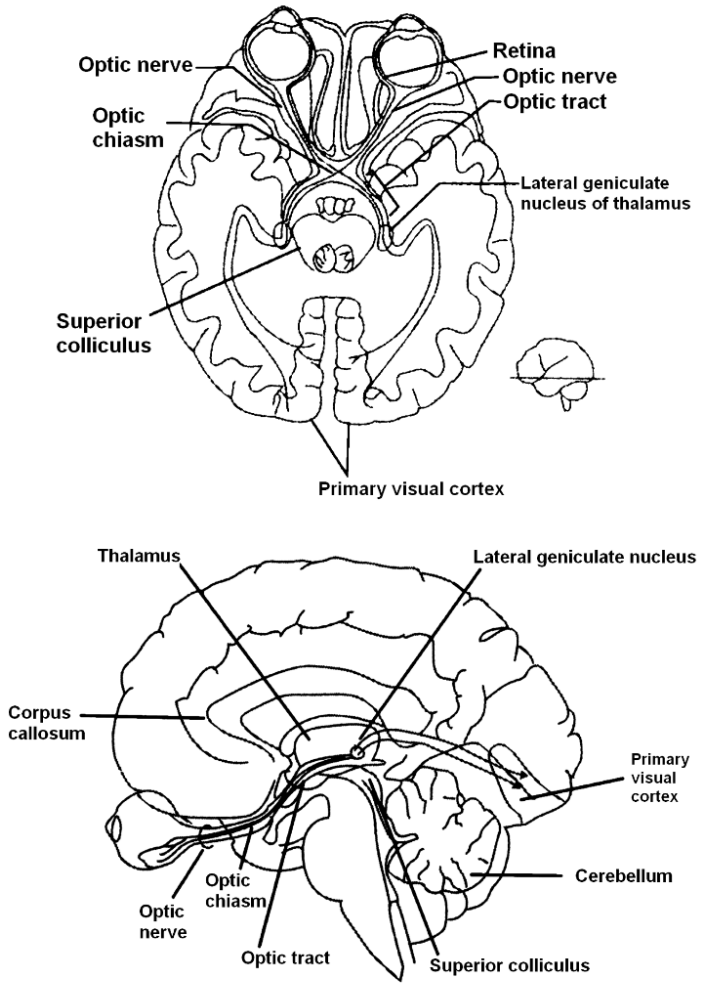

Figure 1.1. Illustration of the pathway from retina to lateral geniculate nucleus and visual cortex (From Beaton, 2004).

As described above, visual information follows parallel routes from retina to V1. When this information arrives at V1, it is redistributed to higher cortical areas, again following parallel processing streams (Ungerleider & Mishkin, 1982). According to the model of Ungerleider and Mishkin, visual information is processed in the cortex by two distinct visual streams. The route from V1 projecting to V2, V3, middle temporal (V5) and posterior parietal regions is termed dorsal (D) stream. The route from V1 projecting to V4 and on to the inferior

temporal cortex is referred as the ventral (V) stream (Ungerleider & Haxby, 1994). The dorsal and ventral visual streams are illustrated in Figure 1.2.

In terms of visual information processing, the D stream, dubbed "where" stream, is specialized in processing high temporal frequencies and low spatial frequencies, and it is essential to deal with spatial information, depth, low contrast and motion cues. The V stream, dubbed "what" stream, processes low temporal frequencies and high spatial frequencies, and it is critical for object identification, processing visual features such as shape and color (Livingstone & Hubel, 1988).

The relationship between the dorsal stream and the magnocellular pathway have been subject of debate (see Livingstone & Hubel, 1988; Maunsell, Nealey, & DePriest, 1990; Merigan & Maunsell, 1993 but also Sawatari & Callaway, 1996; Sincich & Horton, 2002). Nonetheless, considering the current knowledge, one may say that magnocellular input is thought to dominate dorsal stream (Kaplan, 2004).

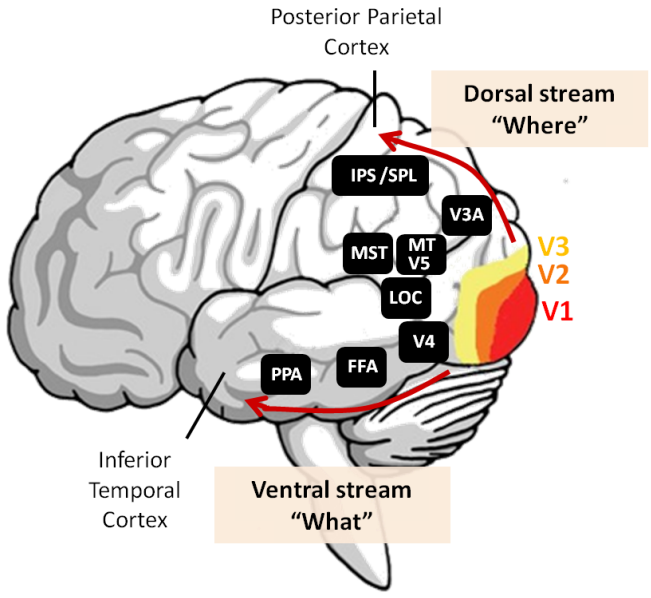

Figure 1.2. Illustration of the Dorsal and Ventral visual streams. Visual processing in the brain is mostly handled by two streams extending from primary visual cortex: the dorsal visual stream which projects from V1 to the parietal cortex and is responsible for the processing of spatial information; and the ventral visual stream which projects from V1 to the temporal lobe and is responsible for object identification (Adapted from Goebel, Muckli, & Kim, 2004).

Dyslexia and Magnocellular impairment

The magnocellular theory on the causes of reading impairments in dyslexia is grounded in evidence of an abnormal functioning of the magnocellular system. One of the first critical evidence of such magnocellular impairment was provided by anatomical post-mortem studies (Galaburda & Livingstone, 1993; Livingstone, Rosen, Drislane, & Galaburda, 1991), in which authors found anatomically abnormal M layers in the LGN of dyslexics. At that time, these studies also provided physiological evidence (visual evoked potentials) consistent with a defect in the magnocellular pathway of dyslexics.

One may say that the magnocellular theory is one of the most controversial causal theories on dyslexia, being subject of intensive research since the 80´s. Literature on this topic shows a proliferation of studies, either in favor or contradicting this theory. Stimuli with low spatial or high temporal frequency have been used to show dyslexic's decreased evoked potentials (Jednoróg, Marchewka, Tacikowski, Heim, & Grabowska, 2011; Lehmkuhle, Garzia, Turner, Hash, & Baro, 1993; Scheuerpflug et al., 2004; Shandiz et al., 2017) and in particular reduced sensitivity to magnocellular stimuli (Borsting et al., 1996; Buchholz & McKone, 2004; Cornelissen, Richardson, & Mason, 1995; Demb, Boynton, Best, & Heeger, 1998; Everatt, Bradshaw, & Hibbard, 1999; Felmingham & Jakobson, 1995; Martin & Lovegrove, 1987; Martin & Lovegrove, 1984; Pellicano & Gibson, 2008). Moreover, there is evidence that magnocellular sensitivity in pre-reading children is related to their subsequent reading skills (Boets, Wouters, van Wieringen, De Smedt, & Ghesquière, 2008; Kevan & Pammer, 2009). Nonetheless, studies using similar stimuli, report analogous magnocellular functioning between dyslexics and controls, either in terms of electrophysiological (Johannes, Kussmaul, Munte, & Mangun, 1996; Vanni, Uusitalo, Kiesilä, & Hari, 1997) or psychophysical (Gross-Glenn et al., 1995; Hayduk, Bruck, & Cavanagh, 1996; Walther-Müller, 1995; Williams, Singh, & Smith, 2003) measures. Inconsistent evidence is also found in neuroimaging studies. While some studies found functional and/or structural alterations in brain areas that are believed to receive a predominant magnocellular input, such as V5 (Demb, Boynton, & Heeger, 1997, 1998; Eden et al., 1996; Heim et al., 2010; Müller-Axt, Anwander, & von Kriegstein, 2017), others did not (Danelli et al., 2017; Olulade, Napoliello, & Eden, 2013; Tamboer, Scholte, & Vorst, 2015). Additionally, methodological issues have been raised concerning some frequent measures of magnocellular/dorsal functioning, such as high-spatial contrast sensitivity (Skottun, 2000, 2015) or coherent motion perception (Skottun & Skoyles, 2008). Despite inconsistent data on magnocellular deficits in dyslexia, some difficulties in dyslexic subjects

can be related to a deficient magnocellular system, such as erratic eye movements (Stein & Fowler, 1993; Stein & Walsh, 1997) or temporal processing deficits (Tallal, 1980b).

Notably, an important part of the dorsal stream (which receives mainly magnocellular input) is the posterior parietal cortex, which is essential for attentional skills. Indeed, some authors have put forward the hypothesis that abnormal attentional mechanisms may underlie reading impairments in dyslexia. The last part of this chapter will be dedicated to present attentional theories on the causes of dyslexia.

Attentional Theories

Visual attentional spotlight

In 1999, Vidyasagar proposed a neuronal model of a spotlight of attention guiding visual search. For this author, such modulation can occur early in visual processing, as early as at primary visual cortex (V1) (Vidyasagar, 1999).

The visual information coming in from the retina is so vast that is very likely that some kind of attentional selection is performed at a very early visual processing stage. Vidyasagar suggests that such attentional selection is performed during fixation periods by the fast dorsal visual stream which provides feedback to select regions of interest before sharp ventral stream processing. Since the large receptive fields of the ventral stream areas involved in object recognition cannot code well for location, the dorsal stream provides the location of the objects to the ventral stream (Figure 1.3).

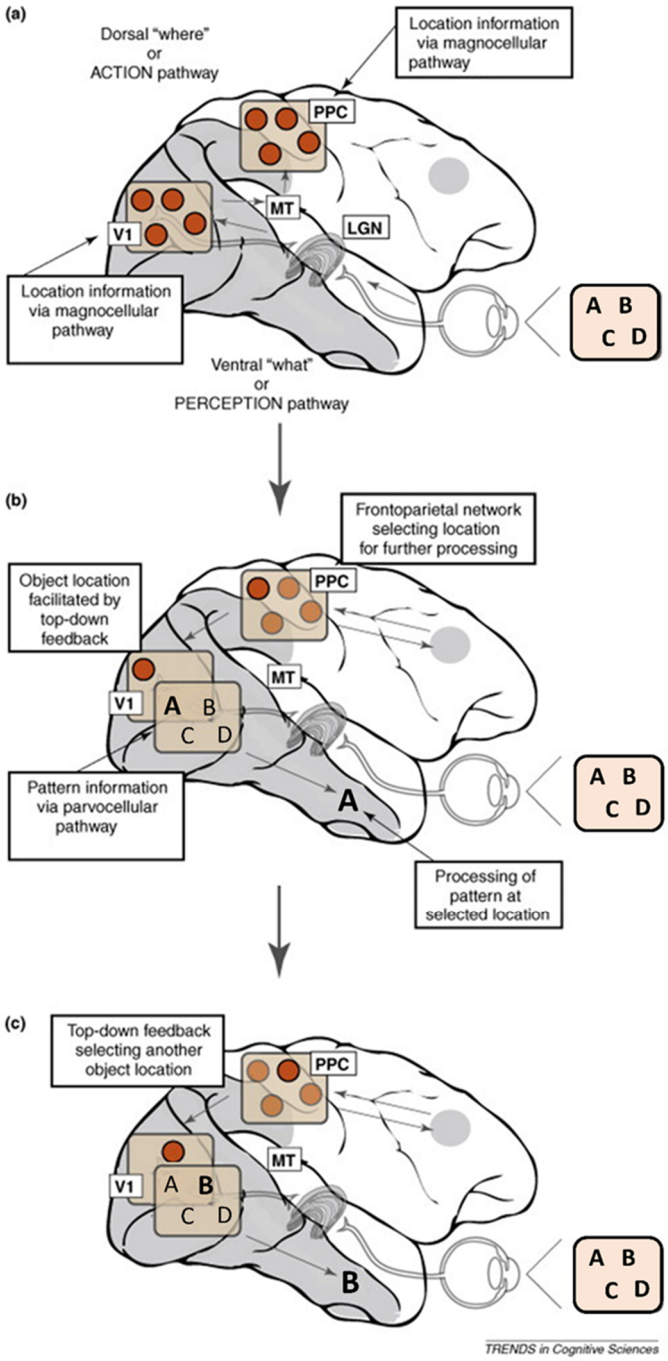

Figure 1.3. Illustration of the neuronal model of a spotlight of attention. (a) Visual pathways with signals proceeding from the eyes to the lateral geniculate nucleus (LGN) and on to primary visual cortex (V1), with the faster signals of the magnocellular channel reaching the dorsal stream areas, namely middle temporal area (MT) and the posterior parietal cortex (PPC). (b) The spatial information is used by the fronto-parietal network to select the region of interest to be processed by the slower parvocellular channel. The object in the region of interest is then processed in the ventral stream and recognized. (c) The fronto-parietal network selects another region of interest to be processed again by the ventral stream. (Adapted from Vidyasagar & Pammer, 2010).

According to this model, the attentional spotlighting is required for handling features associated with the ventral stream processing (e.g. shape) and for dealing with cluttered visual scenes. Thus, since reading involves ventral stream processing of fairly crowded stimuli, this attentional mechanism would be crucial in the ability to read effectively.

This model also aims to explain how magnocellular impairments result in reading deficits in DD. More than supporting magnocellular theory (see above), this scheme provides an alternative explanation on how the magnocellular defect leads to reading disabilities. According to this theory, the impairment does not have to be present in magnocellular cells, but it could be anywhere along the dorsal stream (Vidyasagar & Pammer, 2010), and deficiencies at different levels of the dorsal stream could result in difficulties in different aspects of reading (Kevan & Pammer, 2008). For instance, Pammer and colleagues (2006) ask participants to read words (e.g. POSTER), non-words (e.g. PESTOR) and words with individual letters shifted relative to each other (e.g. $P^{O}S^{T}E^{R}$), and used magnetoencephalography (MEG) to measure dorsal stream activity (posterior parietal cortex) across conditions. The authors found a clear signal in the posterior parietal cortex during the task, occurring in a short time interval after stimulus presentation, suggesting that dorsal stream is involved early in word reading. Moreover, the signal was stronger in the shifted words condition, indicating that one of the roles of the dorsal stream in word reading is the spatial encoding of letter features. Thus, these findings suggest that the posterior parietal cortex, and putatively the dorsal stream, processes spatial features of text, and that this occurs early in the processing sequence.

As mentioned above, the dorsal stream encompasses visuo-spatial attentional functions (Saalmann, Pigarev, & Vidyasagar, 2007). Adding to the extraction of the spatial relationships of the letters, graphemes and words, dorsal stream integrity is also essential for the flow of attentional focus that facilitates their identification by the ventral stream. Contrary to most visual search situations, in which attentional focus moves randomly, the attentional focus must move sequentially over the letters and lines to allow reading (Kermani, Verghese, & Vidyasagar, 2018). This is particularly demanding for the dorsal stream, and a failure in this mechanism would result in ventral stream deficits and reading difficulties.

A rather provocative suggestion of this theory is that even phonological deficits may steam from impairments in this visuo-attentional mechanism. If the parsing of text into graphemes units is undermined by a deficient movement of attentional focus, that would lead to deficient grapheme-phoneme correspondences. If it is the case, phonological deficits in

DD, rather than being a cause, are consequence of a poor orthographic perception (Vidyasagar & Pammer, 2010).

Adding to the indication of general magnocellular (e.g. Borsting et al., 1996; Buchholz & McKone, 2004; Conlon, Sanders, & Zapart, 2004; Iles, Walsh, & Richardson, 2000; Kevan & Pammer, 2009; Levy, Walsh, & Lavidor, 2010; Pellicano & Gibson, 2008; Talcott et al., 2002; Williams, Stuart, Castles, & McAnally, 2003) and attentional (e.g. Cestnick & Coltheart, 1999; Facoetti & Molteni, 2001; Facoetti, Paganoni, Turatto, Marzola, & Mascetti, 2000; Facoetti et al., 2003, 2006; Facoetti, Lorusso, Cattaneo, Galli, & Molteni, 2005; Franceschini, Gori, Ruffino, Pedrolli, & Facoetti, 2012; Gabrieli & Norton, 2012; Kinsey, Rose, Hansen, Richardson, & Stein, 2004; Roach & Hogben, 2008) deficits in DD, some authors have gathered evidence in favor of a specific impairment in the attentional spotlight mechanism in DD. Romani and colleagues (2011) showed a specific reduction in the attentional ability to bind together identity and position information during a serial task. In this study, two sequences of either consonants or symbols were presented side by side, and participants had to decide whether the two sequences were the same or different. In both conditions, the identity and the order of the stimuli were manipulated. The authors found that dyslexics difficulty arises from a reduction in the ability to process positional information, through a reduction in the number of attentional spotlights that can be deployed to process information at multiple locations. Moores and colleagues (2015) assessed spatial distribution and orienting of attention in adults with DD. Since DD patients showed normal eccentricity effects and use of cues but slower deployment and focusing of attention at far eccentricities, the authors argued that a smaller and weaker attention spotlight should account for their difficulties to efficiently split attention to different locations.

On the other hand, there are studies showing preserved magnocellular or dorsal stream functioning in DD (Gross-Glenn et al., 1995; Johannes et al., 1996; Kronbichler, Hutzler, & Wimmer, 2002; Roach & Hogben, 2004; Sperling, Lu, Manis, & Seidenberg, 2005, 2006b; Vanni et al., 1997; Victor, Conte, Burton, & Nass, 1993), as well as arguing against a causal role of visual attentional deficits in reading impairments (Olulade et al., 2013; Ramus, 2003; Ziegler, Pech-Georgel, Dufau, & Grainger, 2010). Ziegler and colleagues (2010), for instance, showed that when visual attention is tested with verbal and non-verbal stimuli, dyslexics only show deficits in the verbal conditions. They concluded that impaired symbol-sound mapping rather than impaired visuo-attentional processing is the core deficit underlying dyslexia.

Visual attentional span theory

The term "visual attention span" refers to the number of distinct visual elements which can be simultaneously processed in a brief multi-element visual display. In reading, the visual elements are the orthographic units in a letter string. According to the proponents of the visual attentional span theory, some DD patients show a visual attention span disorder, having a more limited capacity to process visual elements in a parallel manner, being this disorder independent from phonological deficits (Bosse et al., 2007; Valdois et al., 2004). The claim that the visual span disorder can dissociate from phonological problems in DD follows the notion of different sub-types of DD, with distinct neurobiological impairments (Peyrin, Démonet, N'Guyen-Morel, Le Bas, & Valdois, 2011). According to this theory, one of such sub-types would be characterized by impaired visual attention span but preserved phonological abilities (Peyrin et al., 2012).

This theory relates directly to a model of reading, the multi-trace memory model (MTM model), which incorporates a visual attentional process as part of the reading system (Ans, Carbonnel, & Valdois, 1998). According to this model, besides of the phonological component, reading has also a visual attentional component named visual attentional window. The amount of orthographic information that can be processed at each moment is determined by the size of this attentional window. Two types of reading procedures are considered in this model, the global and the analytic, and both procedures differ in the size of the visual attentional window necessary to extract the orthographic information. While in global reading the visual attentional window must be larger enough to incorporate the whole sequence of the input letter string, in analytic reading the window narrows down to focus on the relevant sublexical units of the input letter string. Global reading would be necessary to read irregular words, being the reading procedure more often used in expert reading. On the other hand, analytic reading would characterize inexperienced reading and it would be crucial in pseudoword reading. According to this model, a reduction on the visual attentional window would primarily affect global reading, which needs a broader window. However, in the case of a severe reduction, even the analytic reading would be disturbed, since the simultaneous processing of all units of complex graphemes would be affected. Thus, a reduced visual attention span would lead to decreased reading performance and potentially interfere with any kind of reading stimuli.

The visual attentional span theory found support in studies showing visual attention span reduction (Bosse et al., 2007; Lallier, Donnadieu, Berger, & Valdois, 2010; Lassus-Sangosse, N'guyen-Morel, & Valdois, 2008; Prado, Dubois, & Valdois, 2007; Valdois et al., 2003, 2011; Valdois, Lassus-Sangosse, & Lobier, 2012) and multi-element processing impairment (Hawelka & Wimmer, 2005; Reilhac, Peyrin, Démonet, & Valdois, 2013) in DD. However, since these authors used verbal stimuli in their tasks, the possibility that the deficits found in dyslexics may reflect a verbal-phonological impairment, rather than a visuo-attentional one, has been raised (Goswami, 2014, 2015; Ziegler, Pech-Georgel, Dufau, & Grainger, 2010). To overcome this issue, some studies used multi-element tasks with non-verbal stimuli to demonstrate that dyslexics have atypical performances even in non-verbal conditions (Jones, Branigan, & Kelly, 2008; Lobier, Peyrin, Pichat, Le Bas, & Valdois, 2014; Lobier et al., 2012; Pammer, Lavis, Hansen, & Cornelissen, 2004). Nonetheless, there are studies showing preserved visual attentional span in DD (Collis, Kohnen, & Kinoshita, 2013; Yeari, Isser, & Schiff, 2017) and, therefore, the visual attentional span theory is not free from criticism.

Sluggish attentional shifting

The sluggish attentional shifting (SAS) theory postulates that reading impairments in DD can be caused by an abnormally long attentional dwell time, meaning that the processing of a stimulus occupies the attentional capacity of dyslexics for a longer period of time than it does in normal readers. This impairment prevents an efficient attentional shifting (or orienting), i.e. prevents attention to efficiently engage onto the relevant object and disengage from that object to reengage into other (Hari, Valta, & Uutela, 1999; Hari & Renvall, 2001). Spatial orientation of attention can be goal-directed (top-down), via a mechanism known as "endogenous" orientation of attention, or automatic, stimulus-driven fashion (bottom-up) termed "exogenous" orientating of attention. Another distinguishing factor between the two is the difference in their time-courses. Whereas the effects of endogenous orientation of attention require a few hundred milliseconds to fully develop and can be maintained with effort, exogenous orientation of attention peaks within 100 to 120 ms and diminishes rapidly thereafter (Nakayama & Mackeben, 1989).

All processing levels of the visual-orthographic system are modulated by both endogenous and exogenous orientation of attention (Facoetti, 2012; Vidyasagar & Pammer, 2010 for reviews). For instance, before application of the grapheme to phoneme

correspondences, the graphemic parsing must occur, i.e. the letters string must be segmented into its constituent graphemes, and that processing requires rapid orientation of attention (Facoetti et al., 2010; Ruffino, Gori, Boccardi, Molteni, & Facoetti, 2014) combined with efficient phonological skills (Ramus, 2003; Ziegler & Goswami, 2005). Moreover, in reading, relevant graphemes must be accurately and rapidly selected among irrelevant ones. It has been shown that rapidly orienting of attention improves visual perception by intensifying the signal inside the focus of attention while diminishes the effect of noise outside the focus of attention (Carrasco, Williams, & Yeshurun, 2002; Enns & Di Lollo, 2000; Facoetti, 2012). Thus, visual attention orientation is involved in several mechanisms of letter-to-speech sound integration and, consequently, in reading (Gori & Facoetti, 2013).

According to the SAS theory, if a temporal attentional deficit is present in DD, that would reflect in a deficient perception of rapid stimulus sequences. Actually, observations of impaired processing of rapid stimulus sequences in DD started with the study of Tallal (1980a). Using a battery of nonverbal auditory perceptual tests aiming at assessing discrimination and temporal order processing, she and colleagues showed that DD children were only impaired when stimulus were presented in a rapid way. The finding of a temporal processing deficit was generalized across different sensory modalities and found to be also present in adults with DD (Fostick & Revah, 2018; Riitta Hari & Kiesilä, 1996; Johnston et al., 2017; Laasonen, Service, & Virsu, 2001). To the defenders of the SAS theory, this temporal processing deficit relates to a sluggish automatic attentional orienting and a prolonged attentional dwell time. The SAS theory also aim to be the pathophysiological link between the impairments in rapid stimulus sequences processing and the magnocellular deficits found in DD. According to it, independent effects at different processing levels may stem from the same core deficit in the magnocellular system. Such independent effects may contribute to reading impairments through a cascade of causal factors (Hari & Renvall, 2001; Vidyasagar & Pammer, 2010). While sensory impairments may stem from magnocellular deficits at earlier processing areas, temporal and orienting attentional deficits may be related to weakened or abnormal magnocellular input to the parietal dorsal visual stream. Indeed, it has been shown that DD children with magnocellular-dorsal deficits also suffer from sluggish attentional orienting. Those deficits were present specifically in dyslexics with phonological decoding deficits. These results suggest that a magnocellular-dorsal deficit linked to a dysfunction on the orientation of attention system may impair phonological decoding mechanisms that are crucial for reading acquisition (Facoetti, 2012; Ruffino et al., 2014).

Several studies addressed the hypothesis of an abnormal attentional orienting system (on visual and auditory domains) contributing to the reading impairments (Krause, 2015 for review). Studies from Franceschini and colleagues on this topic are particularly interesting. In a longitudinal study (Franceschini et al., 2012), this group followed 96 children from kindergarten until second grade, i.e. from pre-reading until 2 years of formal reading instruction. First, they assessed children in kindergarten with tests of phonemic awareness and orienting of visual attention. The last ones consisted in two tasks: a serial search performance task and an exogenous spatial cueing task. Figure 1.4 shows an example of an exogenous visuospatial cueing procedure adapted from the classical paradigm from Posner (1980). In the serial search performance task, children had to search for target symbols (not letters) among distractors. In the spatial cueing task, an ellipse was displayed at the left or at right of a central fixation cross, preceded (spatial cueing condition) or not (control condition) by a spatial cue. The spatial cue appeared either at the same side of the ellipse (valid cue condition) or at the contralateral side of the ellipse (invalid cue condition). The authors then followed this group of children for two years and found that 14 of the participants showed reading impairments after reading instruction (≅15%). Importantly, 60% of these reading impaired children had abnormal performance in the earlier tasks involving orienting of visual attention, and several analyses of the data showed that the scores on those tasks were substantial and independent predictors of future reading performance (Gabrieli & Norton, 2012). Moreover, in a very recent study, these authors showed that reading abilities in children with DD can be improved with an attentional remediation program based on the use of action videos games (Franceschini et al., 2017). They tested English-speaking children with dyslexia in regards to their reading and attentional skills before and after playing action video games. This type of games uses rapid presentation of multiple, peripheral and rapidly moving stimuli, activating spatial and temporal attention mechanisms. They were able to show improvements in both reading and attentional skills of children, replicating previous findings in a more transparent orthography (Franceschini et al., 2013). In this previous study with Italian-speaking dyslexic children (Franceschini et al., 2013), the authors measured reading, phonological and attentional skills in two groups of children with DD before and after playing action or non-action video games for 12h over the course of 2 weeks. Children who participated in playing action videos games showed an improvement on reading speed equivalent to one year of intensive traditional phonological and orthographic treatments. These studies highlight the potential of attentional remediation programs for the enhancement of reading performance.

For a review on the improvement of reading abilities using Action Video Games see Franceschini et al. (2015).

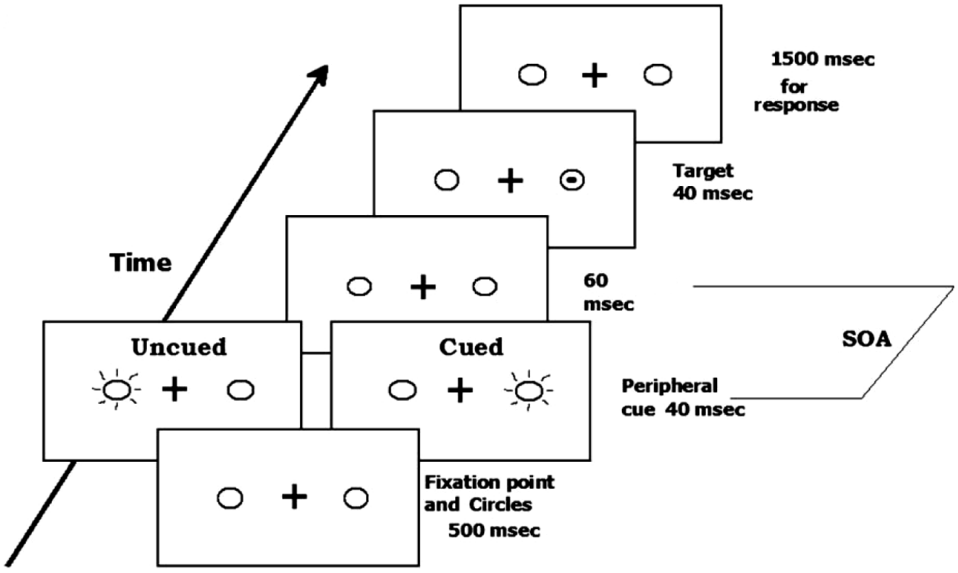

Figure 1.4. Schematic representation of an exogenous visuospatial attention task. Having the eyes fixed on a central cross, attention is oriented to different locations, using valid cues (the target appears at the cued location) or invalid cues (the target appears at the uncued location). Processing facilitation in exogenous spatial attention requires a short time interval between the onset of the cue and the onset of the target, i.e. a short stimulus onset asynchrony (SOA) (Adapted from Facoetti et al., 2010).

Regarding neuroimaging studies, it has been shown that the frontoparietal region is implicated in orienting of visual attention. Particularly, the right frontoparietal region integrates the network attending to exogenous orienting of attention (Corbetta & Shulman, 2002). Adding to studies demonstrating deficient frontoparietal activation in dyslexics while performing phonological decoding tasks (Facoetti, 2012) and right frontoparietal dysfunction in dyslexics (Grünling et al., 2004; Hoeft et al., 2006), there is also evidence that the efficacy of reading interventions is mediated by prefrontal regions (Aboud, Barquero, & Cutting, 2018).

Taken together, the behavioral and neuroimaging studies described above provide evidence that visual-attentional temporal processing deficits may be core deficits in DD. Nonetheless, some studies challenge the hypothesis of a deficient orienting of attention in DD

by showing normal effects of cueing in adults with DD (Buchholz & Aimola Davies, 2008; Judge, Caravolas, & Knox, 2007; Moores, Cassim, & Talcott, 2011; Moores et al., 2015). Additionally, it has been argued that attentional deficits in DD are a consequence, rather than a cause, of the reading difficulties (Goswami, 2003, 2014; Ramus, 2003). Such debate undermines a definitive take on the role of attention orienting in the reading deficits of DD.

Perceptual noise exclusion deficit theory

Finally, the last attentional hypothesis on the causes of DD that will be discussed in this chapter is the perceptual noise exclusion deficit hypothesis (Sperling et al., 2005, 2006b). This hypothesis is grounded in theories of signal-to-noise discrimination (Lu & Dosher, 1998), according to which there are different mechanisms by which attention improves perception, and among such mechanisms is the noise exclusion. Noise exclusion involves optimizing the perceptual filter so that signal is processed and noise is excluded. The perceptual noise exclusion deficit theory postulates that the inability to effectively filter out irrelevant information leads to poor categorization of letters and sounds, resulting in the reading deficits observed in DD.

This theory was first presented by Sperling and colleagues in 2005, in a brief communication in the journal Nature Neuroscience (Sperling et al., 2005). In this communication, the authors presented the results of children with and without DD in a task in which signal-to-noise discrimination was assessed using magnocellular and parvocellular stimuli, presented either with or without high noise (see Figure 1.5). They demonstrated that children with DD showed perceptual deficits in both magnocellular and parvocellular conditions when stimuli were presented embedded in noise. On the other hand, when stimuli were presented without noise, the same children did not show perceptual deficits on either magnocellular or parvocellular conditions. Based on these results, the authors proposed that a perceptual processing deficit related to noise exclusion, and not to magnocellular or temporal processing, is implicated in the reading deficits in DD. To further validate their theory, the authors conducted a second study in which they assessed noise interference in motion perception (Sperling et al., 2006b). They tested fifty-five adults (twenty-seven poor readers and twenty-eight good readers) and seventy-five children (thirty-two poor readers and twenty-seven good readers) with various motion perception tasks usually used to measure dorsal stream functioning. They showed that both adults and children who were poor readers

showed impaired motion perception in the presence of high external noise, but not in the presence of low or minimal external noise, suggesting deficits in noise exclusion rather than in motion perception per se. Additionally, they correlated motion perception thresholds with reading (orthographic and phonological processing) and language and verbal skills. They showed that, in adults, thresholds in high noise are related to both orthographic and phonological processing. In children, thresholds were more correlated with language and verbal abilities than with reading measures. According to authors, this indicates a developmental trajectory by which the early effects of noise-exclusion deficits on general verbal abilities are somehow fixed, leaving residual effects on reading. Similar findings were obtained in a study assessing motion coherence thresholds of DD adults under different levels of noise (Conlon, Lilleskaret, Wright, & Power, 2012). Finally, using a different approach, Sperling and colleagues showed that either adults and children with DD exhibit perception deficits in a task requiring detection of the borders of a shape placed in a perceptually noise environment, adding supportive evidence to their theory (Sperling, Lu, Manis, & Seidenberg, 2006a, 2003).

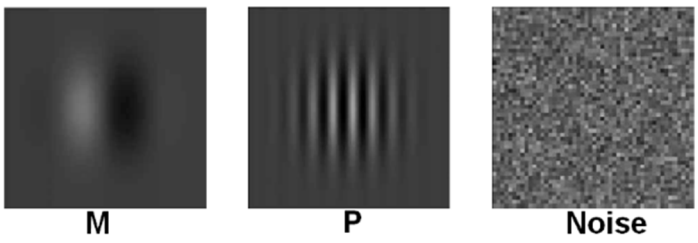

Figure 1.5. Examples of stimuli used in a study assessing noise exclusion deficits in DD. In this study, authors aimed at assess perception thresholds in children with and without DD, using magnocellular (M - left) and parvocellular (P – center) stimuli, showed either embedded or not in a white Noise patch (right). Results showed that children with DD had elevated contrast thresholds when visual stimuli were presented in noise, but performed as well as normally reading children when the visual stimuli were displayed without noise. These results underline the noise exclusion deficit hypothesis on the causes of DD (From Sperling et al., 2005).

Beattie and colleagues (2011) took the investigation of noise exclusion deficits in DD a step further by assessing visual letter detection in the presence or absence of background visual noise. They show that DD adults have higher detection thresholds than non-impaired readers only in the presence of high background noise. Their results indicate that DD's ability to categorize and represent a letter is impaired only when external noise is present, giving supportive evidence to the perceptual noise exclusion theory.

Evidence of noise exclusion deficits has also been obtained in the auditory modality. In a study by Ziegler and colleagues (2009), dyslexic children exhibited speech perception deficits when speech signals were presented with masking noise, but not when they were presented without noise. Importantly, such deficits persisted when dyslexics performance was compared to that of younger children matched on reading age, suggesting that this deficit is not consequence of the dyslexics' poor reading ability. Boets and colleagues (2011) showed that speech perception in noise deficits are present in kindergartners who were later diagnosed with DD, providing a linkage between early noise exclusion deficits and later reading difficulties.

However, it has been suggested that a disorder of automatic orienting of visual attention may underlie the perceptual noise exclusion deficit observed in DD (Facoetti, 2012; Ruffino et al., 2014). This assumption relies on the observation that spatial attention is implicated in perceptual noise exclusion since it enhances the neural representation of stimuli at the attended location (Carrasco, Ling, & Read, 2004; Carrasco et al., 2002a). This enhancement have multiple effects, including faster reaction times (Posner, 1980), improved sensitivity and spatial resolution (Carrasco & McElree, 2001; Carrasco, Williams, & Yeshurun, 2002b), reduction of flanking stimuli interference (Boyer & Ro, 2007; Carrasco, Penpeci-Talgar, & Eckstein, 2000) and, importantly, noise reduction (Dosher & Lu, 2000).

Moreover, Martelli and colleagues (2009) assessed contrast thresholds for single-letter identification in the presence or absence of white noise (see Figure 1.5 for white noise display illustration) and showed that thresholds were similar in dyslexics and controls. However, when asked to identify long words, dyslexics' thresholds were higher than that of controls, but in the same extent in the presence and absence of noise. The authors claimed that abnormal crowding effects, rather than noise exclusion deficits, was responsible for the dyslexics' impairment in long words identification. Crowding refers to impaired recognition of a target due to the presence of neighboring stimuli in the peripheral visual field. In fact, abnormal crowding effects have been reported in DD (Moores et al., 2011; Spinelli, De Luca, Judica, & Zoccolotti, 2002) and it has been shown that crowding manipulation (e.g. increasing of the

letter spacing) improves reading (Hakvoort, van den Boer, Leenaars, Bos, & Tijms, 2017; Zorzi et al., 2012).

General outline and aims of the thesis

Despite of a significant amount of research on the causes of reading impairments in DD, it's etiology and pathophysiology is not yet unveiled. Based on increasing evidence of a crucial influence of visuo-spatial attention skills on reading, the current thesis aimed at contribute to the knowledge of the visuo-attentional mechanisms involved in the reading impairments in DD.

Chapter 1 presents the current knowledge on the clinical and neurocognitive characteristics of DD. Moreover, the etiology of DD is discussed through an overview of the most prominent theories, giving a particular emphasis to the attentional theories.

Given the focus of this thesis on visuo-attentional mechanisms and the controversy about visual perception deficits in DD, in Chapter 2 we investigated visual perception of dyslexics, by comparing children with and without DD on a battery of visuoperceptual tasks probing multiple visual channels. This chapter contributes to the current debate on visual perceptual deficits in DD and probes the magnocellular deficit theory.

Chapter 3 investigates orienting of attention and its spatial distribution in dyslexic and typically reading adults. As described above, abnormal exogenous attention orienting and diffused spatial distribution of attention has been associated with reading impairments in children with developmental dyslexia. Since studies in adults have failed to replicate such relationships, this chapter helps to reconcile this inconsistency.

In Chapter 4, the perceptual noise exclusion deficit theory is tested in children with and without dyslexia, by applying the white noise displays typically used to validate this theory to a lexical decision task. Since previous works have focused on effects of noise in low-level perceptual and behavioral processes in dyslexics, this chapter takes the investigation of this theory further by looking directly at reading performance under noise.

Chapter 5 investigates patterns of activation of the ventral occipito-temporal cortex (VOTC) in dyslexics and typical reading adults. VOTC has been associated to the memory-based visual-orthographic word recognition and includes the Visual Word Form Area (VWFA). VWFA is an area specifically tuned to process letter strings and it has been widely studied in DD. This chapter adds to the current knowledge on VOTC patterns of activation in DD and provides explanatory insights into possible discrepancies in different studies as well as recommendations for future studies.

Finally, an integrative view of the main findings of the work is provided in Chapter 6 and its overall results are discussed in relation to the current knowledge on the etiology of DD and to future lines of research in this field.

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RESULTS

CHAPTER 2

Visual perception and reading:

new clues to patterns of dysfunction across multiple visual channels in developmental dyslexia

This chapter was based on: **Pina Rodrigues, A**., Rebola, J., Jorge, H., Ribeiro, M.J., Pereira, M., van Asselen, M., Castelo-Branco, M. (2017). Visual Perception and Reading: New Clues to Patterns of Dysfunction Across Multiple Visual Channels in Developmental Dyslexia. *Invest Ophthalmol Vis Sci.* 58(1):309-317. doi: 10.1167/iovs.16-20095.

Abstract

The specificity of visual channel impairment in dyslexia has been the subject of much controversy. The purpose of this study was to determine if a differential pattern of impairment can be verified between visual channels in children with developmental dyslexia, and in particular, if the pattern of deficits is more conspicuous in tasks where the dorsal system recruitment prevails. Additionally, we also aimed at investigating the association between visual perception thresholds and reading.

In the present study, we compared perception thresholds of thirty-three children diagnosed with developmental dyslexia and thirty-four controls, in a speed discrimination task, an achromatic contrast sensitivity task and a chromatic contrast sensitivity task. Moreover, we addressed the correlation between the different perception thresholds and reading performance, as assessed by means of a standardized reading test (accuracy and fluency). Group comparisons were performed by the Mann-Whitney *U* test, and Spearman's rho was used as a measure of correlation.

Results showed that, when compared to controls, dyslexics were more impaired in the speed discrimination task, followed by the achromatic contrast sensitivity task, with no impairment in the chromatic contrast sensitivity task. These results are also consistent with the magnocellular theory since the impairment profile of dyslexics in the visual threshold tasks reflected the amount of dorsal stream involvement. Moreover, both speed and achromatic thresholds were significantly correlated with reading performance, in terms of accuracy and fluency. Notably, chromatic contrast sensitivity thresholds did not correlate with any of the reading measures.

Our evidence stands in favor of a differential visual channel deficit in children with developmental dyslexia and contributes to the debate on the pathophysiology of reading impairments.

Introduction

Developmental dyslexia is a neurodevelopmental disorder characterized by a reading impairment in spite of normal intellectual functioning and educational opportunities (American Psychiatric Association, 2000). Although the prevalence of this condition is fairly high (7%) (Shaywitz, Shaywitz, Fletcher, & Escobar, 1990), its causes and mechanisms remain under debate and are currently a subject of intensive research. Phonological deficits are usually described as the core impairment in dyslexia and constitute the basis for the most dominant theory in the field: the phonological theory (Snowling, 1981). This causal hypothesis states that an inadequate correspondence between phonemes and graphemes is accountable for the reading deficits in this population. Nonetheless, the in-depth study of this condition has revealed perceptual and sensory dysfunctions (Badcock, Hogben, & Fletcher, 2011; Buchholz & McKone, 2004; Goswami, 2014) which cannot be discarded. To take these into account, a number of alternative theories have therefore been put forward. Among those, a widely discussed yet controversial sensory theory is the magnocellular account (Stein, 2001; Stein & Walsh, 1997).

The magnocellular and parvocellular retino-cortical pathways carry the majority of visual information from the retina into the cortex (Ungerleider & Mishkin, 1982). The route from primary visual cortex (V1) projecting to V5 (MT) and to posterior parietal regions is termed dorsal (D) stream and magnocellular input is thought to dominate this stream. The route from V1 projecting to V4 and on to the inferior temporal cortex is referred as the ventral (V) stream (Beaton, 2004). The two systems have distinct characteristics and while the D system is specialized in processing high temporal frequencies and low spatial frequencies, the V stream processes low temporal frequencies and high spatial frequencies (Kaplan & Shapley, 1986; Livingstone & Hubel, 1988). According to the magnocellular theory, the visual perception of dyslexics is characterized by an abnormal functioning of the D stream (Boden & Giaschi, 2007; Farmer & Klein, 1995). Several studies have provided evidence that either favor or oppose this theory. Initially, it was supported by anatomical evidence from post-mortem studies in adults with dyslexia. In their studies, Galaburda & Livingstone (1993) and Livingstone, et al. (1991), reported anatomically abnormal magno cells in the lateral geniculate nucleus (LGN), a thalamic structure that receives information from the retina and projects to V1. Electrophysiological (Jednoróg, Marchewka, Tacikowski, Heim, & Grabowska, 2011; Scheuerpflug et al., 2004) and fMRI (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2007; Demb, Boynton, & Heeger, 1997, 1998; Dhar, Been, Minderaa, & Althaus, 2010) studies have

also corroborated these findings by highlighting abnormal neural responses to magnocellular stimuli. Moreover, psychophysical studies have shown that both children and adults with dyslexia fail to reach a normal level of motion processing (Cornelissen, Richardson, & Mason, 1995; Demb, Boynton, Best, & Heeger, 1998; Demb, Boynton, & Heeger, 1998; Eden et al., 1996; Everatt, Bradshaw, & Hibbard, 1999; Iles, Walsh, & Richardson, 2000; Johnston, Pitchford, Roach, & Ledgeway, 2017; Talcott et al., 2002), attributed to the D stream. Other studies focused on the differences in contrast sensitivity thresholds between dyslexics and controls to identify D differences (Borsting et al., 1996; Buchholz & McKone, 2004; Demb, Boynton, Best, et al., 1998; Evans, Drasdo, & Richards, 1994; Kevan & Pammer, 2009; Martin & Lovegrove, 1984; Pellicano & Gibson, 2008). A study by Iles et al. (2000) raised an important question by adressing the upstream influence of low-level deficits on higher-level visual tasks that are mainly dependent on D functioning. These authors found that the dyslexics that had elevated motion coherence thresholds were also impaired on visual search tasks probing the posterior parietal function which is known to be involved in reading. Additionally, to fully understand the implications of the D impairment in reading deficits, a number of studies addressed its correlation with reading measures, finding significant links (Conlon, Sanders, & Zapart, 2004; Cornelissen et al., 1998; Demb, Boynton, Best, et al., 1998; Levy, Walsh, & Lavidor, 2010).

Nonetheless, as mentioned, the literature is not unanimous on the claim of particular D impairment in dyslexia. A number of studies report normal thresholds of motion processing (Kronbichler, Hutzler, & Wimmer, 2002; Sperling, Lu, Manis, & Seidenberg, 2006; Vanni, Uusitalo, Kiesilä, & Hari, 1997) and on other D functioning measures (Gross-Glenn et al., 1995; Johannes, Kussmaul, Munte, & Mangun, 1996; Roach & Hogben, 2004; Sperling, Lu, Manis, & Seidenberg, 2005; Victor, Conte, Burton, & Nass, 1993), as well as considerable performance variability in the population (Borsting et al., 1996; Cicchini, Marino, Mascheretti, Perani, & Morrone, 2015; Iles et al., 2000; Kubová et al., 2015; Ramus, 2003). Other studies question the specificity of visual channel impairment (Ahmadi, Pouretemad, Esfandiari, Yoonessi, & Yoonessi, 2015; Amitay, Ben-Yehudah, Banai, & Ahissar, 2002; Farrag, Khedr, & Abel-Naser, 2002; Skottun, 2000) or its mechanistic link with reading problems (Heim et al., 2010; Olulade, Napoliello, & Eden, 2013; White et al., 2006). These discrepancies are partly explained by task variability and the difficulty in isolating each visual stream (Skottun, 2000, 2015). However, by compiling multiple tasks one can build an informative test battery based on different levels of D/V contribution.

In the present study we tested multiple visual channels to verify if a differential pattern of impairment could be found in children with and without dyslexia and to investigate whether the pattern of results can be interpreted as a function of their relative contribution to each of the visual streams. The second goal of the study was to investigate the associations between different visual thresholds and reading performance. To achieve these goals, we assessed visual function in Portuguese children with developmental dyslexia, and examined the link between low-level visual processing and reading performance. We chose a battery of low-level visual tasks ranging from color to achromatic contrast sensitivity and speed discrimination. These tasks seem to differentially involve D and V streams. In other words, they likely lead either to a preferential D activation (speed discrimination task), or V activation (chromatic contrast sensitivity task). The achromatic contrast sensitivity task using intermediate spatial frequencies probably leads to a more even pattern of activation of both streams (Kulikowski & Robson, 1999; Murav'eva, Deshkovich, & Shelepin, 2009). Our concept of a gradient of D involvement was developed to overcome the known difficulty to ensure an exclusive activation of D stream. Our battery of tasks followed, therefore, a gradient of D stream contribution (from strong in local speed discrimination, to mild in the intermediate spatial frequency contrast sensitivity task and weak in the chromatic task) which allowed us to establish a profile of low-level visual deficits in terms of a gradient of D recruitment, instead of having to rely on the assumption of exclusive activation of the stream. Finally, scores on visual function were then confronted with reading fluency and accuracy indexes, as measured through text reading.

Methods

Ethics Statement

This study and all procedures were reviewed and approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra and were conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from the legal representatives of the participants, after explanation of the nature of the study.

Participants

Participants included 33 dyslexic children (mean age: 9.88 ± 1.45 years) and 34 age-matched controls (mean age: 10.06 ± 1.39 years). Both groups were assessed in terms of IQ and reading level with the Wechsler Intelligence Scale for Children (WISC-III - Portuguese version) (Menezes Rocha, 2003) and the Fluency and Accuracy Reading Assessment Test: The King (Carvalho & Pereira, 2009), used in Portugal for reading assessment. This reading test has two outcomes that were further analyzed as reading measures: the Accuracy Index (AI) and the Fluency Index (FI). Accuracy Index was calculated using the formula (WCR / WR) x 100, where WCR stands for the number of words correctly read and WR for the total number of words read. Fluency Index was calculated using the formula (WRC / RT) x 60, where RT stands for the total time necessary to read the text (maximum of 180 seconds).

Children with dyslexia were recruited from the diagnostic and treatment center of the Faculty of Psychology and Education Sciences of the University of Coimbra. The inclusion criteria were: a 2-year lag in reading speed and/or reading accuracy on the Fluency and Accuracy Reading Assessment Test: The King (Carvalho & Pereira, 2009); and a normal level of intelligence assessed by the WISC – III, Portuguese version (IQ above 90) (Menezes Rocha, 2003). The presence of comorbid ADHD was established as exclusion criterion. The clinical sample consisted of volunteer children who fulfilled the inclusion and exclusion criteria, either assessed during the period of recruitment or previously assessed at the center. Control group were volunteer children recruited through distribution of flyers on local schools. These typically developing children had no history of learning, developmental, cognitive, neurologic, or neuropsychiatric problems. Groups were matched for age, education, gender and IQ. All participants had normal or corrected to normal vision (visual acuity of 20/20). Characteristics of participants are summarized in Table 2.1.

Table 2.1. Summary statistics for the two groups of participants

	Dyslexics (n = 33)			Controls (n = 34)			
	Mean	**Range**	**SD**	**Mean**	**Range**	**SD**	p **value**
Age (years)	9.88	7–13	1.45	10.06	7–12	1.39	.383
Education (years)	4.36	2–7	1.22	4.76	2–7	1.39	.082
IQ	104.70	90–127	8.45	107.50	92–132	9.14	.251
Reading Accuracy Index	89.76	35.7–98.2	12.59	98.90	95–100	1.61	<.001
Reading Fluency Index	58.94	14–127	28.14	138.07	93–179	20.74	<.001
Gender (m:f)	20/13			13/21			.089

NOTE. Probability values for group comparisons using Mann–Whitney U-tests (except for gender, for which the Chi square test was used) are reported (p< 0.05 values are considered significant).

Materials and Procedure

Three tasks were applied to assess low-level visual function: a speed discrimination task (Local Speed Discrimination), an achromatic contrast sensitivity task (Intermediate Spatial Frequency), and a chromatic contrast sensitivity task (Cambridge Color Test ©). The tasks took place in a darkened room. Children executed the tasks monocularly (only the dominant eye was tested) with an opaque patch occluding the other eye. A chin and forehead rest was used to ensure a stable viewing position throughout testing.

Local Speed Discrimination (LSD)

The LSD task was developed in our laboratory (adapted from Mateus et al., 2013). The task was programmed in MATLAB (MATLAB 2011a, The Mathworks Inc., Natick, MA, USA), using the Psychophysics Toolbox (PTB-3) extension. Children were seated at a viewing distance of 50 cm. All stimuli were presented on a gamma-corrected 24" LCDIPS monitor (ColorEdge CG243W, Eizo, Japan) with a resolution of 1920x1200 pixels and a refresh rate of 60 Hz. Spectral and luminance measurements were made using a spectroradiometer (PR-650 SpectraScan Colorimeter, Photo Research Inc., Chatsworth, PA, USA). The background luminance was ~0 cd/m2.

The LSD is a psychophysical task that requires the discrimination of motion speed between two separated moving single dots (a reference dot and a target dot) (see Figure 2.1 a). In each trial the reference and target dots (two white dots moving at different velocities) were simultaneously presented for 400 ms. Stimuli consisted of squared dots measuring 0.3º x 0.3º. The reference dot velocity was always 5º/s (visual degrees per second), while the target dot velocity started at 24º/s and was then adjusted by the logarithmic staircase procedure (maximum step size of 1 decibel [dB] and minimum of 0.05 dB). Children were asked to fixate a black central cross (size of 1º) during the test. After each trial, participants were asked to press a button on a keyboard indicating which dot was moving faster ("Left/Right" for the horizontal and oblique meridians or "Up/Down" for the vertical meridian). The motion was then adjusted in the following trial, driven by a correct or incorrect response, by using a logarithmic staircase procedure. The tests ended after 6 reversals and a discrimination threshold was calculated using the arithmetic mean of the last 4 reversals. This threshold represents the discriminated difference, in º/s, between test and reference stimulus. The test was repeated four times, corresponding to four different meridian/eccentricity pairs (the horizontal meridian, 0º, tested at 7.5º of eccentricity; the vertical meridian, 90º, at 10º; and the oblique meridians, 45º and 135º, at 15º). The four thresholds obtained from the four different meridians were averaged into a grand average in order to obtain a measure of the global motion perception of these children.

Intermediate Spatial Frequency (ISF)

The ISF contrast sensitivity task, developed in our laboratory (Ribeiro et al., 2012; Silva et al., 2008), uses static achromatic vertical gratings with an intermediate profile. Stimuli were static vertical gratings, with a spatial frequency of 3.5 cyc/deg (mean background luminance of 51 cd/m2, constant throughout the experiment) displayed on a 21-inch monitor (Trinitron GDM–F520 Sony monitor; Sony, Tokyo, Japan).

The width of each stimulus was 10° of visual angle (35 grating cycles) (see Figure 2.1 b). Stimulus duration was 200 ms, and the interstimulus interval varied randomly between 2300 and 2800 ms. The stimuli were presented within nine locations of the visual field. Children were seated at a viewing distance of 36 cm and were instructed to fixate the black square in the center of the screen and report the presence of the targets by pressing a button. Participants' reliability was evaluated by the inclusion of false positive (0% contrast stimuli) and false-negative (100% contrast in the central location) "catch trials." Experiments with a

false positive or false negative rate above 33% were aborted. The task was then repeated after a small rest period. If the participant still responded with a high number of false positives or false negatives, the data were not used in the analysis.

Luminance contrast of the stimulus was expressed according to Michelson. Contrast sensitivity results were expressed in terms of decibel units, dB = 20 x log (1/c), with contrast c measured as a percentage. To obtain the psychophysical thresholds, the test uses nine randomly interleaved logarithmic staircases, one for each location tested. The contrast value used for a given trial was calculated using the previous trial value plus or minus the step size in dB. The step size used was 3 dB. Staircases were run for a total of four reversals. The contrast at the final two reversals was averaged to estimate the contrast threshold. For this task, data could not be collected from one of the control children.

Cambridge Color Test (CCT)

Finally, to test chromatic contrast sensitivity we used a task that establishes a threshold of color discrimination, the Cambridge Color Test (CCT; Cambridge Research Systems, Rochester, UK). Stimuli were displayed on a 21-inch monitor (GDM-F520; Sony) and consisted of static patterns of circles of various sizes and luminances with superimposed chromatic contrast defining the letter C (gap size: 1.6°; outer diameter: 7.6°; inner diameter: 3.81°) (see Figure 2.1 c). Participants were positioned at a viewing distance of 1.8 m and were instructed to indicate the position of the C´s gap by pressing one of four buttons (up, down, left, or right). We used a color version of the test (Trivector; CCT), where the targets differ from the background along one of the three color confusion lines, each activating one type of cone receptors: protan, deutan, and tritan. We took as the threshold for the red–green (parvocellular) chromatic channel the average of the thresholds along protan and deutan lines (CCT-PD). The test uses three randomly interleaved staircases to dynamically adjust the chromaticity of the target according to the participant's performance to establish the chromaticity difference between target and background needed for reliable report of the orientation of the C. Occasional control trials, with a target presented at maximal chromatic saturation, were introduced to ensure that the participant was alert. Testing on any one staircase was terminated after 11 reversals and the mean of the last 6 reversals was taken as the threshold estimate for the direction being tested, as has been previously established (Mateus et al., 2013; Ribeiro et al., 2012). Psychophysical thresholds were expressed in CIE 1976 u'v' color space units.

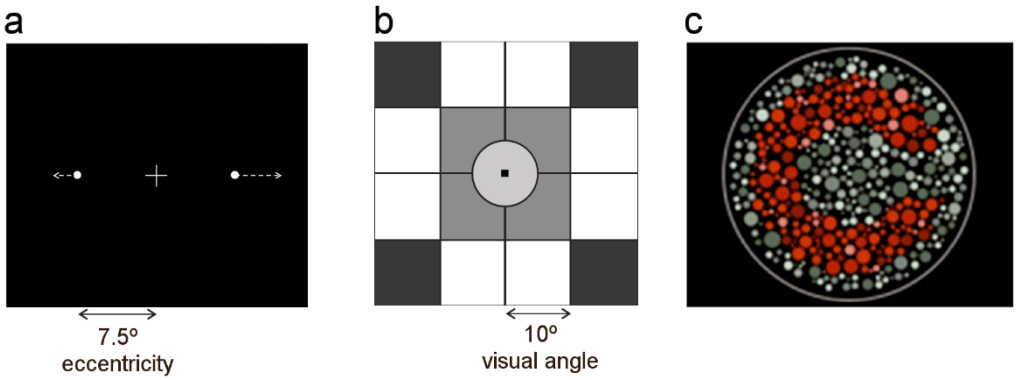

Figure 2.1. Schematic representation of the visual tests. (a) Representation of the location, at the horizontal meridian – 0º, where the moving dots were presented in the speed discrimination task. Three additional meridians were tested (vertical - 90º, tested at 10º of eccentricity; and oblique - 45º and 135º, at 15º of eccentricity). The central cross represents the fixation cross. (b) Representation of the sizes and shapes of the nine locations (represented in different shades of grey and black) within the visual field where the gratings with intermediate spatial frequency were presented. Note that in the actual experiment the shaded areas and the separating lines were not present. The stimuli were shown at these locations against an overall gray background. The black square in the middle of the figure represents the fixation square. (c) Illustration of the stimuli used in the chromatic contrast sensitivity task (Cambridge Color Test) representing a luminance noise stimulus with superimposed chromatic target (Landolt C shape, colored in red).

Statistical analysis

All statistical analyses were performed using the IBM SPSS statistical software package, version 20.0 (SPSS, Inc., Chicago, IL, USA). Since data significantly deviated from normal distributions (verified using the Kolmogorov-Smirnov normality check and Levene homogeneity tests), we applied non-parametric statistical methods. Group comparisons were performed by Mann-Whitney *U* test. Participants scoring more than 3 SD away from the group mean were considered outliers and therefore not included in the between-group analyses. This resulted in the exclusion of one participant with dyslexia from the CCT-PD task comparison. Correlational analyses were performed using Spearman rank correlation coefficient (ϱ). As in other studies (Conlon et al., 2004; Sperling, Lu, Manis, & Seidenberg,

2003), correlations were assessed for the population as a whole. Once again, participants scoring more than 3 SDs away from the overall population mean were considered outliers and therefore not included in the analyses. This was the case for five children with dyslexia: two in the ISF task, one in the CCT-PD task, and two in the AI measure.

Results

Low-level visual perception in dyslexia

The low-level visual function was assessed through a battery of tasks: the LSD, the ISF and the CCT. Results are summarized in Table 2.2. Mann–Whitney's *U* test analyses showed that dyslexics and controls had similar CCT-PD thresholds (p=0.644), indicating a preserved color discrimination in the dyslexic group (see Figure 2.2, top). In contrast, the ISF task already revealed a significant difference between groups (p=0.001; effect size r=0.410), with poorer perception thresholds for the dyslexic children (see Figure 2.2, middle). This performance difference between groups was further increased in the LSD task (p<0.0001; effect size r=0.519) (see Figure 2.2, bottom).

Taken together, results showed that dyslexics were more impaired in the LSD task, followed by the ISF task, with no impairment in the CCT-PD task and, therefore, argue against a generalized visual perception deficit.

Table 2.2. Low-level visual perception thresholds of dyslexics and controls

	Dyslexics		Controls			
	Median	**Q1-Q3**	**Median**	**Q1-Q3**	**U**	***p* value**
LSD (º/s)	3.59	2.27–4.50	1.42	0.96–2.64	222.50	<.0001
ISF (dB)	12.58	9.61–14.80	9.67	7.58–10.36	283.00	.001
CCT-PD (u'v'*10-4)	56.25	49.37–68.75	56.00	47.38–67.13	508.00	.644

NOTE. LSD = Local Speed Discrimination task; ISF = Intermediate Spatial Frequency task; CCT-PD = Cambridge Color Test task; Probability values for group comparisons using Mann–Whitney *U* tests are reported (p< 0.05 values are considered significant).

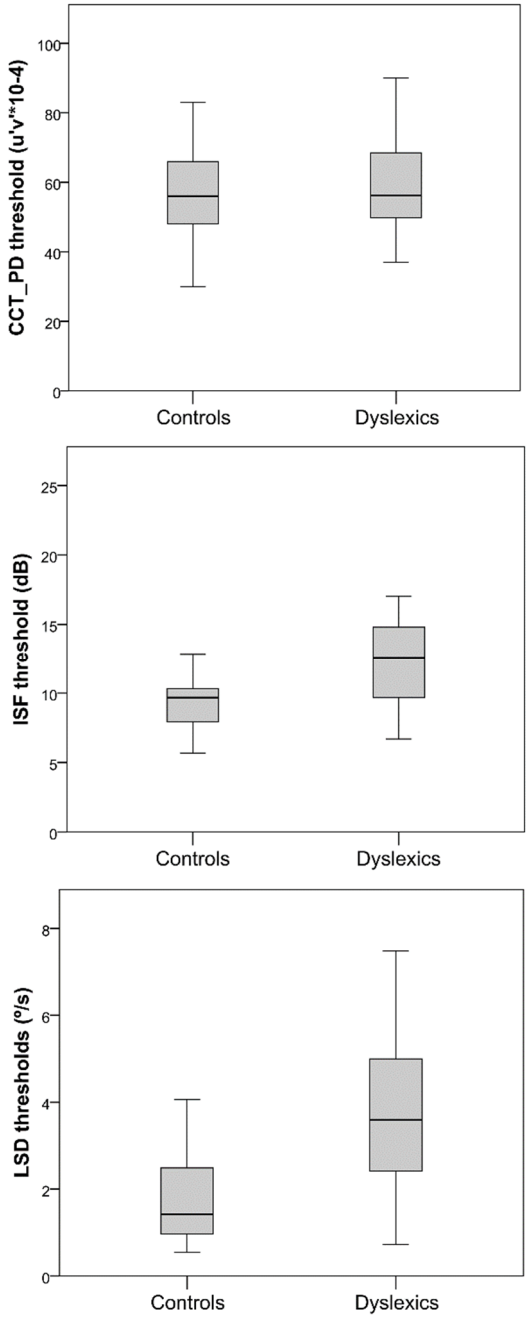

Figure 2.2. Performance of controls and dyslexics in the CCT-PD (top), ISF (middle) and LSD (bottom). Moving from top to bottom, note that dyslexics show normal chromatic contrast sensitivity, mildly impaired achromatic contrast sensitivity and considerable speed discrimination impairment. (box boundaries correspond to upper and lower 25th percentiles, outer bars to the 10th percentiles, and middle bar to the median).

Correlations between low-level visual functions and reading

In order to address the link between visual perception and reading, Spearman correlations were computed between the low-level visual thresholds (LSD, ISF and CCT-PD) and the reading measures (AI and FI).

No significant correlations were found between the CCT-PD thresholds and the reading measures [AI: ϱ= -0.054 (p=0.670); FI: ϱ= -0.148 (p=0.236)]. Thus, we did not find evidence of an association between chromatic sensitivity and reading. On the contrary, achromatic contrast sensitivity and speed discrimination were correlated with reading performance, both in terms of accuracy (AI) and fluency (FI). In the case of the ISF thresholds, the correlation coefficients were ϱ= -0.413 (p=0.0009) for the AI and ϱ= -0.412 (p=0.0007) for the FI. For the LSD task, correlation analysis identified significant correlations with the AI (ϱ = -0.440; p=0.0003) and with FI (ϱ = -0.520; p<0.0001) (Figure 2.3). Therefore, we found that the lower the achromatic contrast sensitivity and speed discrimination thresholds the better the reading performance, both in terms of accuracy and fluency.

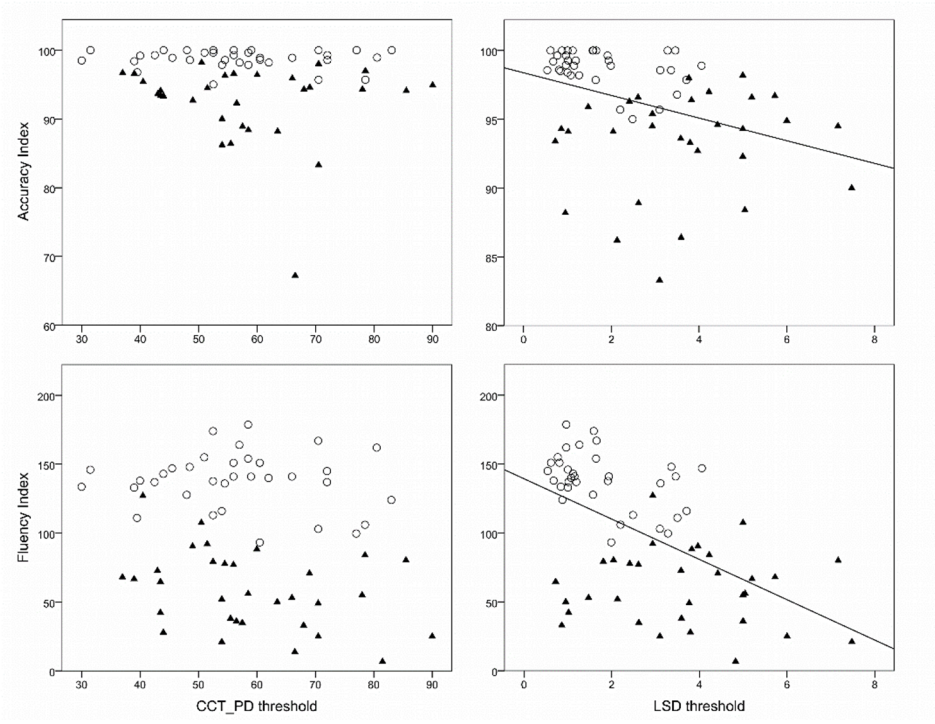

Figure 2.3. Scatter plots illustrating the correlations between the Accuracy and Fluency Indexes from the reading test with chromatic sensitivity (CCT-PD) and speed discrimination (LSD) perception thresholds. Controls (empty dots); dyslexics (filled triangles).

Discussion

The present work compared children with and without developmental dyslexia on a battery of visuoperceptual tasks assessing chromatic and achromatic contrast sensitivity and speed discrimination. The fundamental aim of this work was to probe multiple visual channels in children diagnosed with developmental dyslexia in order to verify if a differential pattern of impairment is present in these children.

We demonstrate that Portuguese children with dyslexia are substantially impaired when asked to discriminate speed, corroborating previous studies that studied motion processing (Amitay et al., 2002; Demb, Boynton, Best, et al., 1998; Demb, Boynton, & Heeger, 1998; Eden et al., 1996). It should be noted that motion perception has traditionally been assessed by coherent motion detection thresholds instead of speed discrimination. However, the output of this particular type of task across studies is contradictory (see Cornelissen et al., 1995; Everatt et al., 1999; Iles et al., 2000; Ridder, Borsting, & Banton, 2001; Talcott et al., 2002 but also Kronbichler et al., 2002; Vanni et al., 1997). Moreover, deficits in motion coherence are present in several neurodevelopmental disorders, such as autism (Pellicano, Gibson, Maybery, Durkin, & Badcock, 2005; Spencer & O'Brien, 2006) and Williams syndrome (Atkinson et al., 2006; Mendes et al., 2005). On the contrary, speed discrimination impairments seem to be preserved in, at least, some of these disorders (Chen et al., 2012; Manning, Neil, Karaminis, & Pellicano, 2015). Thus, it seems that speed discrimination deficits, may represent more specific motion deficits in dyslexia than coherent motion deficits. Additionally, recent genetic studies showed that some motion deficits, including coherent motion but not speed discrimination, are particularly strong in dyslexic individuals with a deletion in intron 2 of the DCDC2 gene rather than in the whole dyslexic population (Cicchini et al., 2015; Gori et al., 2015).

The second main finding of our study is that dyslexics have preserved chromatic contrast sensitivity. Chromatic vision in these patients, contrary to other visual functions, has not been comprehensively studied. To our knowledge there are few studies on this subject (Ahmadi et al., 2015; Bednarek & Grabowska, 2002; Dain, Floyd, & Elliot, 2008; Pammer & Wheatley, 2001; Sperling et al., 2003) and only Ahmadi et al. (2015) reported abnormal chromatic contrast thresholds in children with dyslexia. However, the task used in their study to assess chromatic contrast sensitivity consisted of chromatic natural scenes, which suggests that neural responses and performance may be distinct for natural chromatic scenes. Moreover, we must acknowledge that our chromatic contrast sensitivity testing was limited to the red-

green chromatic channel, since it also aimed at probing V stream functioning. Nonetheless, the present study endorses the majority of the previous literature by adding supportive evidence of a preserved chromatic channel in a population where other visual channels were concomitantly studied. Finally, we show, for the first time, that dyslexics are mildly affected when an intermediate spatial frequency channel was tested. Taken together, our results indicate differential low-level visual deficits in developmental dyslexia, arguing against the notion of a generalized visuoperceptual impairment.

The study of visual function in dyslexia has been mainly related to the debate on the magnocellular theory (Stein, 2001; Stein & Walsh, 1997). According to this theory, dyslexics suffer from specific D stream difficulties. Dorsal (magnocellular) stream is known to activate preferentially to stimuli with low spatial frequencies and high temporal frequencies, and many studies have used these properties to vouch for or contradict a D deficit in dyslexia (Cornelissen et al., 1995; Gross-Glenn et al., 1995; Kevan & Pammer, 2009; Lovegrove, Bowling, Badcock, Blackwood, 1980; Lovegrove, Martin, & Slaghuis, 1986; Martin & Lovegrove, 1987; Martin & Lovegrove, 1984; Sperling et al., 2005). Nonetheless, there is not a definite consensus because for most frequency ranges activation is not exclusive to this stream. In fact, the range of spatial frequencies used as a hallmark of D functioning has been a target for criticism (Skottun, 2000, 2015). Another marker that has been used to claim for D deficits in dyslexia is abnormal visual coherent motion (e.g. Cornelissen et al., 1995; Demb et al., 1997; Eden et al., 1996; Hansen, Stein, Orde, Winter, & Talcott, 2001; Iles et al., 2000; Martin & Lovegrove, 1987; Martin & Lovegrove, 1984). However, the reliability of this measure to assess D sensitivity has also been challenged (Skottun & Skoyles, 2008). Thus, the validation of the magnocellular theory is undermined by a fundamental issue: the difficulty, or even the impossibility, to exclusively activate D stream. In order to overcome this difficulty, here we designed a battery of visuoperceptual tasks with different levels of D contribution. Therefore, having a battery of three tasks, we can establish a profile of low-level visual deficits in terms of a "gradient" of D recruitment, instead of relying on the assumption of exclusive activation of this stream. In this manner, we can think of our tasks as ranging from strong (speed discrimination) to weak (chromatic sensitivity) D involvement. According to the magnocellular theory, we found that the higher the D involvement, the higher the differences between groups. Therefore, using this procedure, we report compelling evidence for a preferential D deficit in children with dyslexia.

To conclude, we demonstrate that speed discrimination thresholds are the ones that show the strongest correlation with reading, followed by the intermediate spatial frequency

thresholds. Notably, chromatic contrast sensitivity thresholds did not correlate with any of the reading measures. These results highlight the notion that the link between low-level visual function and reading is not generalized across different visual systems. This result is in agreement with studies both in dyslexics and controls (Conlon et al., 2004; Demb, Boynton, Best, et al., 1998; Demb, Boynton, & Heeger, 1998; Levy et al., 2010). Following the D gradient mentioned above, we found that the higher the involvement of D mechanisms in the administered tasks, the stronger the correlation to both accuracy and fluency indices. This result is also in accordance with the roles that the D system may play in reading-related tasks. These include accurate letter position encoding through precise shifts in visual attention (Cornelissen et al., 1998; Stein, 2014; Vidyasagar & Pammer, 2010), the ability to process information that changes rapidly over the course of time (Sperling et al., 2003), or the rapid delivery of a low-pass representation of words to guide further processing (Chouake, Levy, Javitt, & Lavidor, 2012). Actually, a very recent study (Lawton, 2016) showed that D stream training significantly improved reading fluency and reading comprehension in individuals with dyslexia, supporting the hypothesis of a causal link between D processing deficits and dyslexia.

Finally, the link between low-level visual performance and reading is perhaps as important as the establishment of low-level visual deficits in dyslexia. In future studies, attention should be devoted to the understanding of how these particular visuoperceptual deficits underlie reading impairment. Only a clear unfolding of this issue can unequivocally establish those deficits as contributing to reading difficulties in dyslexia. Studies of indirect (Ben-Shachar et al., 2007; Chouake et al., 2012; Kevan & Pammer, 2008, 2009) and direct interference (TMS) (Laycock, Crewther, Fitzgerald, & Crewther, 2009) are already paving the way on this matter.

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CHAPTER 3

Disrupted spatial organization of cued exogenous attention persists into adulthood in developmental dyslexia

Abstract

Abnormal exogenous attention orienting and diffused spatial distribution of attention has been associated with reading impairment in children with developmental dyslexia. However, studies in adults have failed to replicate such relationships. The goal of the present study was to address this issue by assessing exogenous visual attention and its peripheral spatial distribution in adults with developmental dyslexia. In order to achieve this aim, we measured response times of 18 dyslexics and 19 typical readers in a cued discrimination paradigm, in which stimuli were presented at different peripheral eccentricities.

Results showed that adults with developmental dyslexia were slower that controls in performing the orientation discrimination task, irrespective of the attention condition. Moreover, we found that while controls became slower with the increase of eccentricity, dyslexics showed an abnormal inflexion at 10º as well as similar response times at the most distant eccentricities. Finally, contrary to controls, who showed cue effects at all levels of eccentricity, dyslexics only benefited from valid cues when stimuli were presented at less peripheral eccentricities.

Taken together, our findings indicate that, in dyslexia, the temporal deficits in orientation of attention and its abnormal peripheral spatial distribution are not restricted to childhood and persist into adulthood. Our results are, therefore, consistent with the hypothesis that the neural network underlying spatial attention is disrupted in dyslexia.

Introduction

Developmental dyslexia (DD) is characterized by a reading impairment, despite normal intelligence and adequate reading instructions. Although phonological processing deficits are well established as core deficits in DD (Snowling, 1981; Ziegler & Goswami, 2005), it has been suggested that attentional impairments may also contribute to the pathophysiology of this condition (Bosse, Tainturier, & Valdois, 2007; Cestnick & Coltheart, 1999; Facoetti et al., 2006; Facoetti, Lorusso, Cattaneo, Galli, & Molteni, 2005; Hari & Renvall, 2001; Vidyasagar, 1999; Vidyasagar & Pammer, 2010). Accordingly, several types of attention deficits have been reported in DD: narrowed visual attentional window and reduced visual attention span (Bosse et al., 2007); stronger effects of crowding (Bouma & Legein, 1977; Callens, Whitney, Tops, & Brysbaert, 2013; Martelli, Filippo, Spinelli, & Zoccolotti, 2009; Moores, Cassim, & Talcott, 2011; Pernet, Valdois, Celsis, & Démonet, 2006; Spinelli, De Luca, Judica, & Zoccolotti, 2002); noise exclusion deficits (Sperling, Lu, Manis, & Seidenberg, 2005, 2006); and, particularly relevant for this study, abnormal spatial distribution of attention (Facoetti & Molteni, 2001; Facoetti & Turatto, 2000) and impaired attention orienting (Brannan & Williams, 1987; Facoetti & Molteni, 2001; Facoetti, Paganoni, Turatto, Marzola, & Mascetti, 2000; Facoetti et al., 2003, 2006; Franceschini, Gori, Ruffino, Pedrolli, & Facoetti, 2012; Hari & Renvall, 2001; Kinsey, Rose, Hansen, Richardson, & Stein, 2004).

Fluent reading requires precise and rapid selection of relevant stimuli among distractors (Bouma & Legein, 1977; Bouma, 1970; Reynolds & Besner, 2006), which critically requires efficient orientation of attention (Cestnick & Coltheart, 1999; Facoetti et al., 2006; Perry, Ziegler, & Zorzi, 2007; Vidyasagar, 1999; Vidyasagar & Pammer, 2010). In particular, the orientation onto each sublexical unit is crucial for graphemic parsing, defined as the process determining the graphemic elements of a word, which, according to computational models of reading, precede spelling-to-sound conversion mechanisms (McCandliss, Cohen, & Dehaene, 2003; Perry et al., 2007; Whitney & Cornelissen, 2005). Indeed, before the application of the grapheme-to-phoneme correspondences, graphemes have to be accurately selected through rapid serial attentional orienting. This mechanism allows the selective processing of relevant letter-to-speech sound correspondence while suppressing the irrelevant ones.

Spatial orientation of attention can be voluntary, via a mechanism known as endogenous attention, or automatic, stimulus-driven, termed exogenous attention (Fuller, Rodriguez, & Carrasco, 2008). These two systems are also labelled as sustained (endogenous) and transient (exogenous) due to the difference in their processing time-courses. Whereas the effects of

endogenous attention require a few hundred milliseconds to fully develop and can be maintained with effort, exogenous attention peaks within 100 to 120 ms and diminishes rapidly thereafter (Cheal & Lyon, 1991; Nakayama & MacKeben, 1989).

It is worth pointing out that the attentional orienting system is anatomically based in the parietal dorsal stream, which in turn, has strong input from the magnocellular system (Gori & Facoetti, 2015). Several studies have shown temporal deficits in DD often suggested to be associated with magnocellular dysfunction (Cornelissen, Richardson, & Mason, 1995; Iles, Walsh, & Richardson, 2000; Laycock, Crewther, & Crewther, 2012; Livingstone, Rosen, Drislane, & Galaburda, 1991; Pina Rodrigues et al., 2017; Stein & Walsh, 1997; Talcott et al., 2002). Hari & Renvall (2001) proposed that parietal attentional dysfunction could underlie such deficits. Specifically, these authors suggested sluggish attentional shifting (SAS) as a causal factor for temporal processing impairment in DD. Attentional shifting refers to the engagement mechanisms onto a relevant object and subsequent disengagement from the previous object to the next one. In terms of reading processes, this failure can cause impaired speech segmentation and scanning of letter strings, which in turn can result in poor phonemic/graphemic representations and, thus, in reading difficulties (Krause, 2015; Lallier et al., 2010).

Several studies have shown that automatic exogenous orientation of attention is impaired in dyslexic children (see Facoetti, 2012; Valdois et al., 2004 for reviews). This subject was particularly explored by Facoetti and colleagues in a series of experiments (Facoetti & Molteni, 2001; Facoetti et al., 2000; Facoetti et al., 2010, 2005; Facoetti, Lorusso, Paganoni, Cattaneo, Galli, & Mascetti, 2003; Facoetti, Lorusso, Paganoni, Cattaneo, Galli, Umiltà, et al., 2003; Ruffino et al., 2014). Using cuing paradigms and manipulating the stimulus onset asynchrony (SOA) (i.e. interval between cue and target-stimulus) to activate both endogenous and exogenous systems, these authors showed that cueing effects are absent in dyslexics only at the shortest intervals, i.e. when exogenous mechanism are recruited (Facoetti et al., 2000; Facoetti, Lorusso, Paganoni, Cattaneo, Galli, & Mascetti, 2003). This impairment was found to be correlated with sublexical reading deficits in children with DD, pointing to a direct link between phonological skills and exogenous attentional mechanisms (Facoetti et al., 2010; Ruffino et al., 2010, 2014). Importantly, Franceschini et al. (2012) found, in a longitudinal study, that prereading exogenous attention orienting, assessed by cueing paradigms, predicts reading acquisition and several reading skills, such as text, word, and pseudoword reading. These authors found that the abnormality in orienting of attention is rather prevalent early in development. In their sample, 60% of future poor reader children were impaired in attention

orienting at the prereading stage. Nevertheless, the role of attentional orienting mechanisms in the reading deficits is a subject still under debate. Several studies suggested a preserved attention orienting in adults with DD (Judge, Caravolas, & Knox, 2007; Judge, Knox, & Caravolas, 2013; Moores et al., 2011; Moores, Tsouknida, & Romani, 2015), raising the hypothesis that deficits observed in DD children do not persist and hindering the claim of a causal link between such deficits and reading impairments.

The literature concerning spatial distribution of visual attention in DD is also contradictory. While some studies found an abnormal spatial distribution in these patients (Facoetti & Molteni, 2001; Facoetti & Turatto, 2000; Geiger & Lettvin, 1987; Geiger, Lettvin, & Zegarra-Moran, 1992; Geiger et al., 2008), others did not (Moores et al., 2015; Judge et al., 2007). Among the studies that favor the atypical spatial distribution hypothesis are the ones from Geiger and colleagues (Geiger & Lettvin, 1987; Geiger et al., 1992; Geiger et al., 2008), who found that, in the presence of lateral masking, dyslexics recognize letters visually farther in the periphery than typical readers. The authors suggested that dyslexics exhibited a wider visual perceptual mode. Their finding was corroborated by other studies (Dautrich, 1993; Lorusso et al., 2004; Perry, Dember, Warm, & Sacks, 1989) and found to be present across different subtypes of DD (Lorusso et al., 2004). Additionally, Facoetti et al. (2000) and Facoetti & Molteni (2001) studied attention orienting at different visual eccentricities and found that DD children did not show normal eccentricity effects as controls, corroborating a diffuse-distributed attention mode in DD. On the other hand, Judge et al. (2007), using the task used by Facoetti & Molteni (2001), showed that, unlike children, DD adults exhibit normal eccentricity effects. Their results were supported by a very recent study (Moores et al., 2015) in which results also argue against the notion of a more distributed attention in DD adults than in typical readers.

Taking into account the literature discrepancies and the ongoing debate described above, the main aim of the present study was to investigate exogenous visual attention in DD adults and its peripheral spatial distribution. To assess exogenous orienting of attention we used a classical cueing paradigm, in which peripheral pre-cues were presented, followed by a short SOA. We then adapted this paradigm to a discrimination task. Discrimination requires more attentional resources than simple detection and, therefore, is expected to be more prone to cueing effects. Since automatic orienting is supposed to occur regardless of the validity of the cue or even when subjects are not aware of the cue (McCormick, 1997; Rosen et al., 1999), uninformative cues were included in the experiment. Spatial distribution of attention was

tested by presenting the target stimuli at different peripheral eccentricities, ranging from 8º to 14º.

Methods

Participants

Eighteen developmental dyslexics and nineteen age and IQ matched controls were recruited. Individuals with dyslexia had all received a formal diagnosis of dyslexia from a qualified psychologist or an education authority official, and none had been diagnosed with any other developmental disorder (e.g. ADHD) or any neurological or psychiatric disorder. Controls were adults with no history of learning, developmental, cognitive, neurological, or neuropsychiatric disorders. All participants were assessed in terms of reading performance and intelligence level. For the reading assessment, a sub-test from the Psycholinguist Assessments of Language Processing in Aphasia - Portuguese version (PALPA-P) (Castro, Caló, & Gomes, 2007) was used. In this sub-test, participants were asked to read a list of 60 words and pseudowords as quickly as possible. The measures obtained from this sub-test were reading speed (in seconds) and accuracy (number of words correctly read). Intelligence level was measured through the Raven Progressive Matrices Test – Set 1 (RPM) (Raven, Court, & Raven, 1976). All participants had normal or corrected to normal vision. Participants' demographics and reading and intelligence scores are summarized in Table 3.1. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra. Written informed consent was obtained from the participants, after an explanation of the nature of the study.

Table 3.1. Summary statistics for the two groups of participants

	Dyslexics (n = 18)			Controls (n = 19)			
	Mean	**Range**	**SD**	**Mean**	**Range**	**SD**	p **value**
Age (years)	27.08	19–44	7.05	25.05	20–36	4.03	.443
Education (years)	15.56	13–17	1.58	16.21	14–17	1.08	.149
RPM	10.08	8-12	1.19	11.14	8-12	1.68	.063
PALPA-P reading speed (sec)	71.67	42-105	18.20	42.33	31-52	7.43	<.05
PALPA-P accuracy	50.31	42-57	4.48	57.67	56-59	1.21	<.01
Gender (m:f)	8/10			9/10			1.00

NOTE. Probability values for group comparisons using *t*-tests (except for gender, for which the Chi square test was used) are reported (p< 0.05 values are considered significant).

Materials and Procedure

The experiment was conducted in a dark room. Stimuli were delivered using the Presentation software (Neurobehavioral Systems) on a 38×30.2 cm (41.6×33.6º visual angle) computer screen with a resolution of 1280×1024 pixels and a luminance of 108 cd/m2. The distance between the subjects' eyes and the computer screen was 52 cm. A chin and forehead rest was used to ensure a stable viewing position throughout testing. To ensure that subjects fixated the center of the stimulus display during the experiment, the subject's gaze position was monitored using an eye-tracker SMI iViewX High-speed (SensoMotoric Instruments GmbH, Germany).

Stimuli and procedure

The stimuli consisted of Gabor patches, comprising a simple sinusoidal grating convolved by a Gaussian envelope (spatial frequency - 2 cpd; envelope SD - 0.25º; contrast - 50% Michelson). Stimuli were presented one at a time at four different viewing eccentricities (8º, 10º, 12º or 14º) in the four quadrants of the visual field. The patches were randomly oriented at 45 or 135 degrees from the vertical and participants were asked to discriminate, as quickly as possible, the orientation of the gratings by pressing the corresponding button of a response box (RB-834, Cedrus Corporation, San Pedro, USA). A fixation cross was presented at the center of the screen and participants were instructed to fixate the cross throughout the whole experiment. Participants' reliability was evaluated by randomly interleaving false positive and false negative catch trials. In the false negative trials stimuli were presented at the center of

the screen, in the location where subjects were instructed to fixate. False positive trials consisted in trials where only the pre-cue was presented. We excluded all participants with errors above 33% in false positive and false negative trials. The sizes of the stimuli scaled with viewing eccentricity through a magnification factor, M (Rovamo & Virsu, 1979): M=M0(1+0.29E + 0.000012E3), where E represents eccentricity and M0 represents the size of the stimuli at the smallest eccentricity. The smallest eccentricity in our experiment was the fovea where the stimulus size was 0.83º. Therefore, stimulus sizes were 2.76º, 3.24º, 3.74º and 4.2º for the 8, 10, 12 and 14 degrees of eccentricity respectively.

Exogenous orienting of attention was assessed using a variant of Posner's task (Posner, 1980) comprising visual targets preceded by spatial cues (valid, invalid and neutral). In the valid and invalid trials, the cue consisted in a salient black dot (0.23º) presented either at the same eccentricity and visual quadrant of the subsequent stimuli (valid) or at the same eccentricity but at a randomized different visual quadrant of the subsequent stimuli (invalid). In the neutral trials, four identical black dots were presented simultaneous at 14º of eccentricity in the four visual quadrants. Participants were informed of the possible appearance of black dots in the screen and were instructed to not attend to them.

Each trial began after subjects foveated the fixation cross for 500 ms. After that, the cue was presented for 30 ms, followed by a stimulus onset asynchrony (SOA) of 70 ms, after which the stimulus appeared for 100 ms. The maximum time allowed for response was 1500 ms (see Figure 3.1).

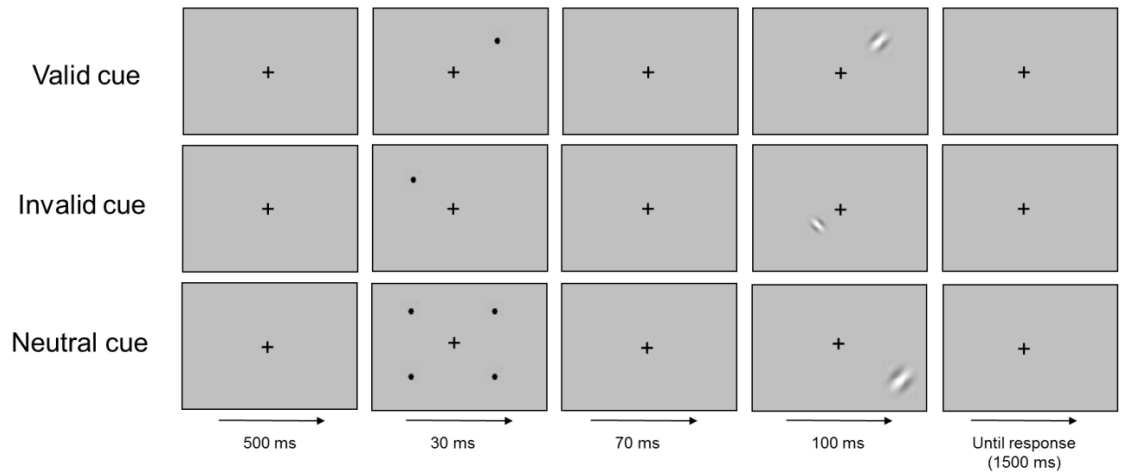

Figure 3.1. Schematic representation of the time course (left to right) of the procedure.

The experiment consisted of 2 runs of 600 trials each (1200 in total), separated by an interval in which the subjects were allowed to rest. Eye-tracker calibration was repeated after the rest period. Stimuli were randomly presented in twelve conditions (four eccentricities x three types of cue), each having 80 trials. In addition, 120 false positive and 120 false negative trials were presented. Therefore, the experiment consisted on 1200 trials, divided in 960 experimental trials and 240 control trials. Before the experiment began, participants made a practice run (80 trials) to become familiarized with the task. The dependent variable of interest was response time (RT).

Statistical analysis

All statistical analyses were performed using the IBM SPSS statistical software package, version 20.0 (SPSS, Inc., Chicago, IL). Mean correct RTs were analyzed with a mixed ANOVA, with group as the between factor (dyslexics and controls) and eccentricity (8º, 10º, 12º and 14º) and cue (valid, invalid and neutral) as within factors. Results with $p<0.05$ were considered statistically significant. Outliers, defined as RTs above or below 3 SD from the group's mean, were not detected. None of the participants scored above 33% in false positive and false negative trials and, therefore, all participants were included in the analysis.

Results

Although RTs were the variable of interest, accuracy was analysed for quality data inspection purposes. As expected, accuracy was close to ceiling, being above 90% in all conditions in both groups, which ensured that both dyslexics and controls were able to perform the task correctly.

Regarding RTs analysis, the main effect of group was significant ($F_{(1,35)} = 6.41$, $p<0.05$; $\eta_p2 =0.155$) showing that dyslexics were globally slower than controls (mean RTs were 626 ms for DD and 570 ms for controls). The main effect of cue was also significant ($F_{(2,70)} = 13.13$, $p<0.001$; $\eta_p2 =0.273$), and similar in both groups ($F_{(2,70)} = 0.04$, $p=0.958$). Participants were faster when a valid cue was presented than when invalid ($p<0.001$) or neutral ($p<0.01$) cues were displayed. Eccentricity was also found to have an effect in RTs ($F_{(3,105)} = 19.06$, $p<0.001$; $\eta_p2 =0.353$). Overall, participants became slower with increases in eccentricity, except between

8 and 10º where the RTs were equivalent. The smallest (but still significant) difference between eccentricities was found for the comparison between 10 and 12º (difference = 8 ms, $p<0.05$).

Interestingly, the eccentricity x group interaction was found to be significant ($F_{(3,105)} =3.12$, $p<0.05$; $\eta_p2 =0.082$), showing that eccentricity had a different effect on the RTs of each group. Post-hoc analysis for the different pairs of eccentricity revealed a different behavior of dyslexics at 10º of eccentricity ($F_{(1,35)} =11.38$, $p<0.01$; $\eta_p2 =0.245$ for the comparison between 8º and 10º and $F_{(1,35)} =6.25$, $p<0.05$; $\eta_p2 =0.152$ for the comparison between 10º and 12º). While the RTs of controls followed the expected increase with eccentricity, dyslexics showed an inflexion at 10º of eccentricity, increasing again at 12º. Additionally, to further investigate the effect of eccentricity in each group, one-way ANOVAs were performed in each group separately, using eccentricity (8º, 10º, 12º, 14º) as within factor. Controls showed a trend for a significant difference between 8º and 10º eccentricity (difference = 9 ms, $p=0.06$), no significant difference between 10º and 12º eccentricity, and a significant difference between 12º and 14º eccentricity (difference = 14 ms, $p<0.001$). On the contrary, DD participants only showed a significant difference between 10º and 12º eccentricity (difference = 15 ms, $p<0.05$). Importantly, controls were, as expected, faster at 8º of eccentricity than at 14º of eccentricity (difference = 27 ms, $p<0.001$). In contrast, DD adults showed no significantly different RTs at the most distant eccentricities tested.

The nonlinear behavior of DD participants, particularly at 10º of eccentricity, as well as the different distribution of the data in both groups (see Figure 3.2), motivated us to explore the effect of cue at different levels of eccentricities. Based on the different pattern of behavior in dyslexics that we observed at 10º of eccentricity, we therefore defined this eccentricity as a cutoff and collapsed the 4 degrees of eccentricity in two levels, the first comprising 8 and 10º (equal or below the identified 10º cutoff); and the second comprising 12 and 14º (above the cutoff). In order to assess cue effects at both levels of eccentricity in DD adults and controls, one-way ANOVAs were then performed separately for the two groups of participants and for each level of eccentricity, using cue (valid, invalid and neutral) as within factor. As implied by the distribution of the data, we confirmed that dyslexics have different cue effects at these two levels of eccentricity. RTs were affected by cue at 8º-10º ($F_{(2,34)} =6.11$, $p<0.01$; $\eta_p2 =0.264$), but not at 12º-14º ($F_{(2,34)} =2.48$, $p>0.05$). Valid trials were faster than invalid at the less peripheral level but not at the more peripheral. This pattern was not present in controls, which were affected in their RTs at both levels of eccentricity ($F_{(2,36)} =4.81$, $p<0.05$; $\eta_p2 =0.211$ for 8º-10º; $F_{(2,36)} =7.45$, $p<0.01$; $\eta_p2 =0.293$).

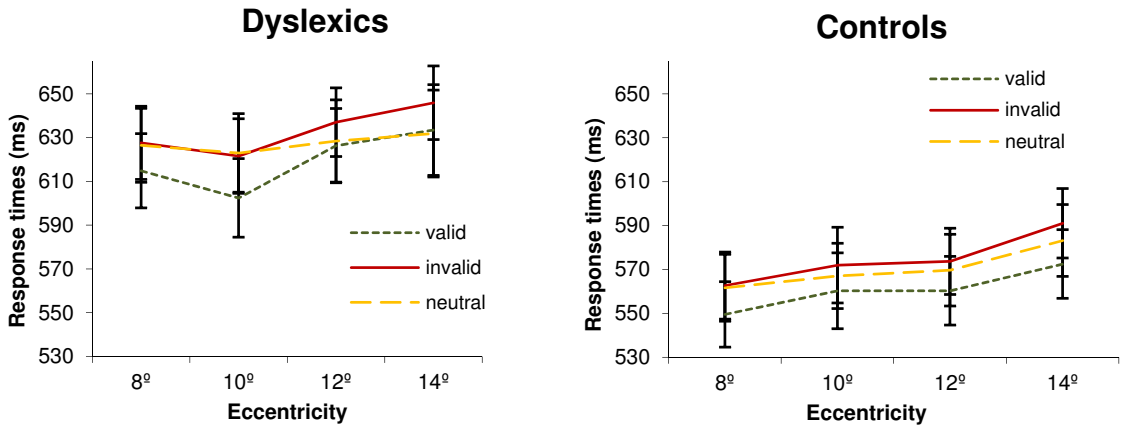

Figure 3.2. Average Response Times (ms) for the 3 types of cues (valid, invalid and neutral) at 4 eccentricities (8, 10, 12, 14º) for dyslexics and controls. NOTE. Error bars indicate ±SE.

Discussion

In the current study, we investigated the exogenous orienting of attention and its spatial distribution across the peripheral visual field in dyslexic and typically reading adults.

We showed that dyslexic adults have global temporal deficits in a task requiring orientation of attention. Although this has already been described in children with DD (Facoetti et al., 2000; Facoetti et al., 2005; Facoetti, Lorusso, Paganoni, Cattaneo, Galli, & Mascetti, 2003; Facoetti, Lorusso, Paganoni, Cattaneo, Galli, Umiltà, et al., 2003), the current study is, to our knowledge, the first to demonstrate this impairment in adults with DD. Our finding thus indicates that the temporal deficits in this population are not restricted to childhood and, therefore, persist into adulthood. Our study contrasts with recent works (Judge et al., 2007, 2013; Moores et al., 2015), which found similar RTs in adults with DD and controls in tasks requiring rapid orientation of attention. This discrepant result can be accounted in terms of spatial position of the stimuli. In these studies, the eccentricities at which the stimuli were presented ranged from 0.7º (Moores et al., 2015) to 9º (Judge et al., 2007) of visual angle. The eccentricities tested in the current study were substantially larger, with a minimum of 8º and a maximum of 14º. If DD patients suffer from anomalous peripheral spatial distribution of attention, this fact can by itself indicate that this discrepancy is only apparent, and may be due to the herein proposed distinct structure of spatial attention.

Actually, the hypothesis of abnormal spatial distribution of attention in the peripheral visual field of DD adults is supported by the two additional main findings of this study. First, DD adults showed abnormal eccentricity effects, reflecting a wider distribution of attention than controls. Such pattern has been already described in children with DD (Facoetti et al., 2000). However, previous studies (Judge et al., 2007; Moores et al., 2015) have found similar effects of eccentricity in adults with and without DD. Nonetheless, the eccentricities tested corresponded to foveal, parafoveal and perifoveal processing, while the present study used more peripheral eccentricities, outside of the macular zone (Strasburger, Rentschler, & Jüttner, 2011). Our finding, therefore, adds to previous evidence by showing that the abnormal distribution of peripheral visual attention observed is present in adults thereby persisting beyond development.

The second finding that supports an atypical spatial distribution of visual attention in DD adults is that attentional cueing effects in DD are dependent on viewing eccentricity. In accordance with previous studies (Posner, 1980; Posner, Snyder, & Davidson, 1980), normal reading adults showed cue effects at all levels of eccentricity. On the contrary, RTs of dyslexic adults could only benefit from valid cues when stimuli were presented at less peripheral eccentricities. Thus, DD adults are not efficiently using cues to rapidly direct attention to more peripheral eccentricities, again suggesting abnormal peripheral processing. This result is in accordance with that of Moores et al. (2015) who found an indication that DD adults need more time to focus attention to far eccentricities. However, it is important to note that Roach & Hogben (2004) found a similar impairment at lower eccentricities. Nonetheless, their task included distractor stimuli in set sizes up to 16 elements, which likely brought an increment of difficulty to DD adults since it is known that crowding affects DD more than controls (Moores et al., 2011).

Our findings are consistent with the notion that covert attention mechanisms, as measured by Posner-like paradigms, operate in a distinct manner in central and peripheral vision in health and disease, as also observed in a previous study from our group in Parkinson disease (Sampaio et al., 2011). In that study we found impaired high-level attentional modulation of contrast sensitivity in the visual periphery (up to 15 degrees), where mechanisms of covert attention are at higher demands. A critical role for peripheral vision is justified by the fact that it can be used to make a snapshot of the local context (van Asselen & Castelo-Branco, 2009).

We speculate that our results may be interpreted within the framework of the role of right posterior parietal cortex in spatial attention. Particularly, the right temporo-parietal junction

(TPJ) is known to be involved in the network responsible for exogenous orienting of attention (Corbetta & Shulman, 2002, 2011). Consistent with the hypothesis of a right posterior parietal dysfunction in dyslexia (e.g. Facoetti, Turatto, Lorusso, & Mascetti, 2001; Hari, Valta, & Uutela, 1999), some studies observed deficient activations in the right TPJ in dyslexics when performing phonological decoding tasks (e.g. Hoeft et al., 2006). Overall, the findings of the present study endorse this hypothesis by showing that the mechanisms of rapid orienting of spatial attention are impaired in adults with DD.

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CHAPTER 4

Evidence for a differential interference of noise in sub-lexical and lexical reading routes in healthy participants and dyslexics

This chapter was based on: **Pina Rodrigues, A.**, Rebola, J., Jorge, H., Ribeiro, M. J., Pereira, M., Castelo-Branco, M., & van Asselen, M. (2017). Evidence for a differential interference of noise in sub-lexical and lexical reading routes in healthy participants and dyslexics. *Cognitive Neuropsychology,* 29, 1-10. https://doi.org/10.1080/02643294.2017.1299001

Abstract

The ineffective exclusion of surrounding noise has been proposed to underlie the reading deficits in developmental dyslexia. However, previous studies supporting this hypothesis focused on low-level visual tasks, providing only an indirect link of noise interference on reading processes. In this study, we investigated the effect of noise on regular, irregular and pseudoword reading in 23 dyslexic children and 26 age and IQ matched controls, by applying the white noise displays typically used to validate this theory to a lexical decision task. Reading performance and eye movements were measured. Results showed that white noise did not consistently affect dyslexic readers more than typical readers. Noise affected more dyslexic than typical readers in terms of reading accuracy, but it affected more typical than dyslexic readers in terms of response time and eye movements (number of fixations and regressions). Furthermore, in typical readers, noise affected more the speed of reading of pseudowords than real words. These results suggest a particular impact of noise on the sub-lexical reading route where attention has to be deployed to individual letters. The use of a lexical route would reduce the effect of noise. A differential impact of noise between words and pseudowords may therefore not be evident in dyslexic children if they are not yet proficient in using the lexical route. These findings indicate that the type of reading stimuli and consequent reading strategies play an important role in determining the effects of noise interference in reading processing and should be taken into account by further studies.

Introduction

Written language is a very important cultural landmark and is essential for disseminating information. Problems in decoding it may lead to communication deficits, with significant implications in processes such as social interaction and educational development (Beaton, 2004).

Although fluent reading is normally achieved during childhood, some children (5-17,5%) (Shaywitz, 1998) show significant reading difficulties. A proportion of these children are diagnosed with developmental dyslexia (DD). Diagnostic criteria for this developmental disorder include poor reading skills with otherwise normal intellectual functioning and educational opportunities (American Psychiatric Association, 2000). Despite the apparently simple diagnostic criteria of DD, symptomatology can be highly heterogeneous. The phonological deficits are often described as the core impairments of dyslexics (Snowling, 1981), but visual and auditory perceptive deficits (Badcock, Hogben, & Fletcher, 2011; Buchholz & McKone, 2004; Stein, 2001), as well as attentional deficits (Facoetti & Molteni, 2001; Facoetti, Lorusso, Cattaneo, Galli, & Molteni, 2005; Ruffino et al., 2010) have also been associated with this condition.

Due to this heterogeneity of symptoms, several theories have been put forward to account for the causes of dyslexia. The most accepted and well-studied theory is the phonological theory (Snowling, 2001), which postulates that reading problems are due to an ineffective correspondence between graphemes and phonemes that leads to the misreading. More recently, it has been suggested by the noise exclusion theory that the problem with these children is the deficient processing of relevant stimuli in the presence of surrounding visual noise (Sperling, Lu, Manis, & Seidenberg, 2005, 2006). Sperling and colleagues presented dyslexic and non-dyslexic children with stimuli designed to preferentially activate either magnocellular or parvocellular pathways, shown in the presence or absence of visual noise. They concluded that the dyslexics' performance on both pathways was only worse in the presence of visual noise. Based on these results, the authors claimed that a noise exclusion deficit may underlie the reading deficits in dyslexia. According to their interpretation, dyslexic children are not able to efficiently extract the relevant visual information from the scene, leading to poor categorization of letters and sounds, and consequently, to reading deficits.

A number of studies have been conducted on the relation between reading difficulties and processing of visual noise. However, it is vital to distinguish between low (white noise) and high (semantic level noise), as well as between high level reading processes and low level

perceptual mechanisms related to reading. Taking this into account, the majority of the studies can be grouped in two categories. At one end of the spectrum, studies have looked at the interference of low level noise on lower-level visual tasks (Beattie, Lu, & Manis, 2011; Conlon, Lilleskaret, Wright, & Power, 2012; Sperling et al., 2005, 2006). At the other end of the spectrum, other authors have successfully established links between the manipulation of high level visual noise and reading or reading related processes (Moll & Jones, 2013; Schneps et al., 2013). However, to fully understand the interference of visual noise on reading, it is also important to investigate how low-level visual noise interferes with high level reading processes. In order to achieve this goal, and directly look at the effect of low level noise on reading performance, the current study builds upon the methodology of Beattie and colleagues (Beattie et al., 2011) and applies it to a lexical decision task. For this purpose, we design a paradigm in which dyslexics and normal readers were shown words and pseudowords in two possible backgrounds: no noise and white noise. Children were then asked to decide, without time constrains, if each stimulus was a real word or not.

Adding to this matter, we investigated two other questions which derive from our main goal. First, during the task, we recorded the participants' eye movements. Eye movement measures have been widely used to assess reading and visual functions in DD (Bednarek, Tarnowski, & Grabowska, 2006; Bellocchi, Muneaux, Bastien-Toniazzo, & Ducrot, 2013; Bucci, Nassibi, Gerard, Bui-Quoc, & Seassau, 2012; De Luca, Borrelli, Judica, Spinelli, & Zoccolotti, 2002; Eden, Stein, Wood, & Wood, 1994; Hawelka, Gagl, & Wimmer, 2010; Hutzler & Wimmer, 2004; Kunert & Scheepers, 2014; Trauzettel-Klosinski et al., 2010). It is well known that dyslexics have non-typical eye movements when reading (De Luca, Borrelli, Judica, Spinelli, & Zoccolotti, 2002), and thus it is important to investigate if a possible difference in performance due to noise is already reflected in modulations at this level. Second, given the presence of irregularities in the Portuguese language, we divided real words into the same number of regular and irregular words. Regular words are the ones that follow the grapheme-phoneme conversion rules of a language, in this case the Portuguese language. Irregular words are words that do not follow the common phonetic rules and, thus, require holistic processing to be successfully read. The inclusion of these two types of words along with pseudowords allowed us to understand putative differences regarding noise interference in respect to the recruitment of different reading routes. According to the dual-route model of reading (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001; Coltheart, Curtis, Atkins, & Haller, 1993), two major processing routes can be used to read written language, namely the lexical and sub-lexical routes. The lexical route refers to the ability to process the word as a

whole, by comparing the word that is being read with the internal lexicon of the reader. This route is essential to read irregular words. In contrast, the sub-lexical route allows the reading of pseudowords and refers to grapheme-by-grapheme reading. This last route can also be used to read regular words, particularly during reading acquisition, when their processing is usually made in a more piecemeal and phonological dependent manner, in contrast to irregular words that require the processing of larger visual units.

To our knowledge, this is the first study probing dyslexics' reading performance under low-level visual noise and investigating noise interference with different reading stimuli. Results will add to the characterization of dyslexia and its underlying causes, as well as to the understanding of noise interference within different reading routes.

Methods

Participants

Participants included 23 developmental dyslexic children (mean age: 10.26 ± 1.21, mean educational level: 4.74 ± .75) and 26 age-matched normal readers (mean age: 10.54 ± .81, mean educational level: 5.12 ± .71). Dyslexic children were recruited from the diagnostic center of the Faculty of Psychology and Education Sciences of the University of Coimbra. For the control group, typically developing children with no history of learning, developmental, cognitive, neurologic, or neuropsychiatric problems were recruited from local schools. Both groups were assessed in terms of IQ and reading level with the Wechsler Intelligence Scale for Children (WISC-III - Portuguese version; Menezes Rocha, 2003) and the Fluency and Accuracy Reading Assessment Test: The King (Carvalho & Pereira, 2009), used in Portugal for reading assessment. The output of this reading test consists of two indices: the Accuracy Index (AI) and the Fluency Index (FI).

The inclusion criteria for the dyslexics group were: a 2-year lag in reading speed and/or reading accuracy on the Fluency and Accuracy Reading Assessment Test: The King (Carvalho & Pereira, 2009); and a normal level of intelligence as assessed by the WISC – III, Portuguese version - IQ above 90 (Menezes Rocha, 2003).

All participants had normal or corrected to normal vision. Participants' characteristics are summarized in Table 4.1.

The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine of the University of

Coimbra. Written informed consent was obtained from the legal representatives of the participants, after an explanation of the nature of the study.

Table 4.1. Summary statistics for the two groups of participants (means and standard deviation in brackets)

	Dyslexics (23)	**Controls (26)**	***p* value**
Age	10.26 (1.21) [9-13]	10.54 (.81) [9-12]	n.s.
Reading Instruction/School Grade	4.74 (.75) [4-6]	5.12 (.71) [3–6]	n.s.
Gender (Males/Females)	14/9	9/17	n.s.
IQ	105.13 (9.20)	106.88 (12.70)	n.s.
Reading Accuracy Index	91.11 (12.68)	99.08 (.85)	<.01
Reading Fluency Index	67.41 (26.69)	142.95 (14.02)	<.001

NOTE. Age (in years, with range in square brackets); reading instruction/school grade (in years, with range in square brackets); Gender; IQ; Accuracy and Fluency Indexes from the reading test "The King". Probability values for group comparisons using *t*-tests (except for gender, for which the Chi square test was used) are reported ($p < 0.05$ values are considered significant).

Materials and Procedure

Apparatus

The task was conducted on a 22-inch computer screen with a resolution of 1680×1050 pixels. Participants sat at 70 cm from the screen. The stimuli were delivered using the Presentation software package (Version 14.9, Neurobehavioral Systems, Inc., Berkeley, CA, USA).

Eye movements were measured using an SMI © Red remote eye tracker (SensoMotoric Instruments GmbH, Germany), with a sampling rate of 500 Hz, an accuracy of 0.4° and a spatial resolution of 0.03°. A nine-point calibration from the SMI software and a 5-point validation method built in-house were used, in order to ensure the precision of the data collection.

Stimuli

The set of stimuli was composed of 60 regular words, 60 irregular words and 60 pseudowords. The selection and classification of the words was done by a professional linguist. Words were selected from a Portuguese words data base (CORLEX) and classified into regular and irregular according to the grapheme to phoneme conversions necessary to read them properly. In the case of regular words, the conversions followed the common Portuguese phonetic rules. For the irregular words, which contain at least one grapheme that can be converted to different phonemes being the conversion not deductible by any rule, the selection was done according to four irregularity criteria (some of them quite specific for the Portuguese language): QU > /kø/ [e.g. equipamento (ekipɐˈmẽtu)] or /kw/ [e.g. cinquenta (sĩkwˈẽtɐ)] and GU > /gø/ [e.g. sportinguista (spɔrtĩˈgiʃtɐ)] or /gw/ [e.g. ambiguidade (ɐ̃bigwidˈadɨ)] before the E, I and O vowels; ii. Intervocalic X > /ks/ [e.g. sexualidade (sɛkswɐliˈdad(ə))] or /ʃ/ [e.g. embaixador (ẽbɐjʃɐdˈoɾ)] or /s/ [e.g. aproximar (ɐpɾɔsimˈaɾ)]; iii. O > /ɔ/ [e.g. caixote (kajˈʃɔt(ə))] or /o/ [e.g. gafanhoto (gɐfaɲˈotu)] in stressed syllable; and iv. E > /ɛ/ [e.g. completo (kõˈplɛtu)] or /e/ [e.g. gabinete (gɐbinˈetɨ)] in stressed syllable (Alves, Martins, & Simões, 2010; Festas, Martins, & Leitão, 2007; Martins & Festas, 2012). The selected words were all more than 5 letters long (mean = 8.63) and of high frequency according to the CORLEX database of Portuguese words (Nascimento, 2003). The mean frequency for our sample was 1298.25, in a scale where values above 100 indicate high frequency. Even though we made efforts to select high frequent words and this were matched across noise conditions, regular words were overall still more frequent than irregular words.

The list of words was initially presented to 10 children from the 3rd grade and only the words that were recognized by more than 70% of these children were included. This resulted in our final set of 120 words. The pseudowords were constructed based on the regular words used by changing three of their letters, including the first one.

Stimuli were presented one by one in black letters (font Courier New). Lowercase letters of the reading material were 5.7 mm in height which corresponded to a visual angle of 0.47º. The inter-letter spacing was 7.5 mm.

Procedure

The experiment consisted of 3 runs of 60 trials each (180 in total), separated by intervals in which the participants were allowed to rest. Eye-tracker calibration and validation were repeated after each rest period.

The words and pseudowords were randomly presented in the center of the screen in two noise conditions: no noise/baseline (white background) and white noise. These conditions were matched for the number and length of stimuli of each type (regular and irregular words and pseudowords), as well as for word frequency.

Figure 4.1 illustrates the noise conditions of this task. In the white noise condition, the stimuli were superimposed on an image composed of random white and black dots, which was generated using MATLAB (MATLAB 2011a, The Mathworks Inc., Natick, MA, USA). This condition was similar to the noise patterns used in the Sperling and colleagues study (Sperling et al., 2005). Both conditions were well above the luminance contrast required for reading and each stimulus was only presented after the participant fixated a cross for 500 ms, positioned over the first letter of each word or pseudoword.

Children were instructed to discriminate between words and pseudowords, without time constraints, in a two-alternative forced-choice task, by pressing one of two response box buttons (RB-834, Cedrus Corporation, San Pedro, USA). The instructions given to participants were as follows: "You will see some words on the screen. They will appear one at a time. After reading each word, if you think that the word is real, press the right button. If you think that the word is invented, press the left button. Each time you press one of the buttons, the next word will appear." Therefore, children were neither instructed to respond as soon as possible nor were they instructed to respond only when they were absolutely confident about their decision. Response times (latencies) were collected and accuracy (hit-rate) was calculated. When referring to a given class of stimuli, the hit-rate represents the percentage of correct trials for that class of stimuli (e.g., correctly identified regular words in respect to the total number of regular words). When all classes of stimuli are collapsed, the hit-rate represents the overall percentage of correct trials. Throughout the task, the number and duration of fixations, the number of regressions and the saccadic amplitude were obtained, using the Begaze 3.2 © software (SensoMotoric Instruments GmbH, Germany). Event detection was accomplished using the software's high-speed algorithm for saccade detection. The parameters used were a minimum peak velocity of 40º/s as well as a minimum fixation duration of 75 ms. Minimum saccade duration was set to automatic.

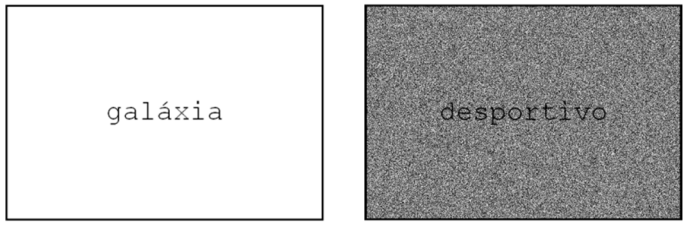

Figure 4.1 – Illustration of the two conditions in the word/pseudoword discrimination task - no noise (baseline) in the left; white noise (random black and white dots) in the right.

Statistical analysis

When studying the response latencies of groups that vary greatly for general levels of performance (such as dyslexics vs normal readers in a reading task), standard analysis may yield spurious interactions between group and experimental factors (Faust, Balota, Spieler, & Ferraro, 1999). Typically, groups that are slower to begin with will show larger effects for more difficult conditions independently of the characteristics of the experimental manipulation (Paizi, De Luca, Zoccolotti, & Burani, 2013).

In order to control for such potential effects of over-additivity, an individually based z-score transformation proposed by Faust and colleagues (Faust et al., 1999) was performed. This transformation was applied to the response latencies of correct trials only. Z scores were obtained by taking each individual's response latencies, subtracting the overall mean averaged across all trials and dividing them by their SD. Non-transformed latencies are nonetheless included in the Figures to allow for inspection of the raw data. One should note that this type of transformation is only applicable to open scales and not to closed scales such as accuracy. Therefore, z-score analyses were only performed on response latencies while results on accuracy might bear a potential contribution of an over-additive effect.

All statistical analyses were performed using the IBM SPSS Statistics version 20 software. Data were analyzed through mixed ANOVA analyses, followed by the Bonferroni correction for multiple comparisons. For the variable with more than two levels (word type), when data did not meet assumptions of sphericity, the Greenhouse-Geisser correction procedure was employed, with original degrees of freedom and corrected confidence probabilities (p) being reported.

Results

Three-way 2x3x2 mixed ANOVAs were performed separately for accuracy (hit rate), response latencies and eye movement measures (number of fixations, fixation duration, number of regressions and saccadic amplitude). Noise condition (no noise, whites noise) and word type (regular, irregular, pseudowords) were used as within subject factors, and group (dyslexics, controls) as between subject factor.

Reading performance

Concerning reading performance, results showed: 1) A main effect of group both in terms of hit rate ($F_{(1,46)} = 16.39$, $p < 0.001$; $\eta_p2 = 0.263$; Figure 4.2a) and raw response latencies ($F_{(1,46)} = 63.05$, $p < 0.001$; $\eta_p2 = 0.578$; Figure 4.2b). As expected, dyslexics were less accurate and slower than controls; 2) A main effect of noise both in terms of hit rate ($F_{(1,46)} = 62.12$, $p<0.001$; $\eta_p2 = 0.575$; Figure 4.2a) and z transformed response latencies ($F_{(1,46)} = 445.93$, $p<0.001$; $\eta_p2 = 0.906$; Figure 4.2c). Responses were less accurate and slower in the noise than in the no noise condition; 3) A main effect of word type, again in both terms of hit rates ($F_{(2,92)} = 16.28$, $p<0.001$; $\eta_p2 =0.261$; Figure 4.3) and z transformed response latencies ($F_{(2,92)} = 394.12$, $p<0.001$; $\eta_p2 =0.895$; Figure 4.4). Post-hoc analyses showed that pseudowords were responded to more accurately than the irregular words ($t_{(94)} = 3.01$, $p<0.001$; Figure 4.3), but were also responded to more slowly than irregular words ($t_{(94)} = 24.00$, $p<0.01$; Figure 4.4). This might suggest a speed accuracy trade-off. When participants did not recognize a word, they took longer to respond, but made no errors when the stimulus was a pseudoword.

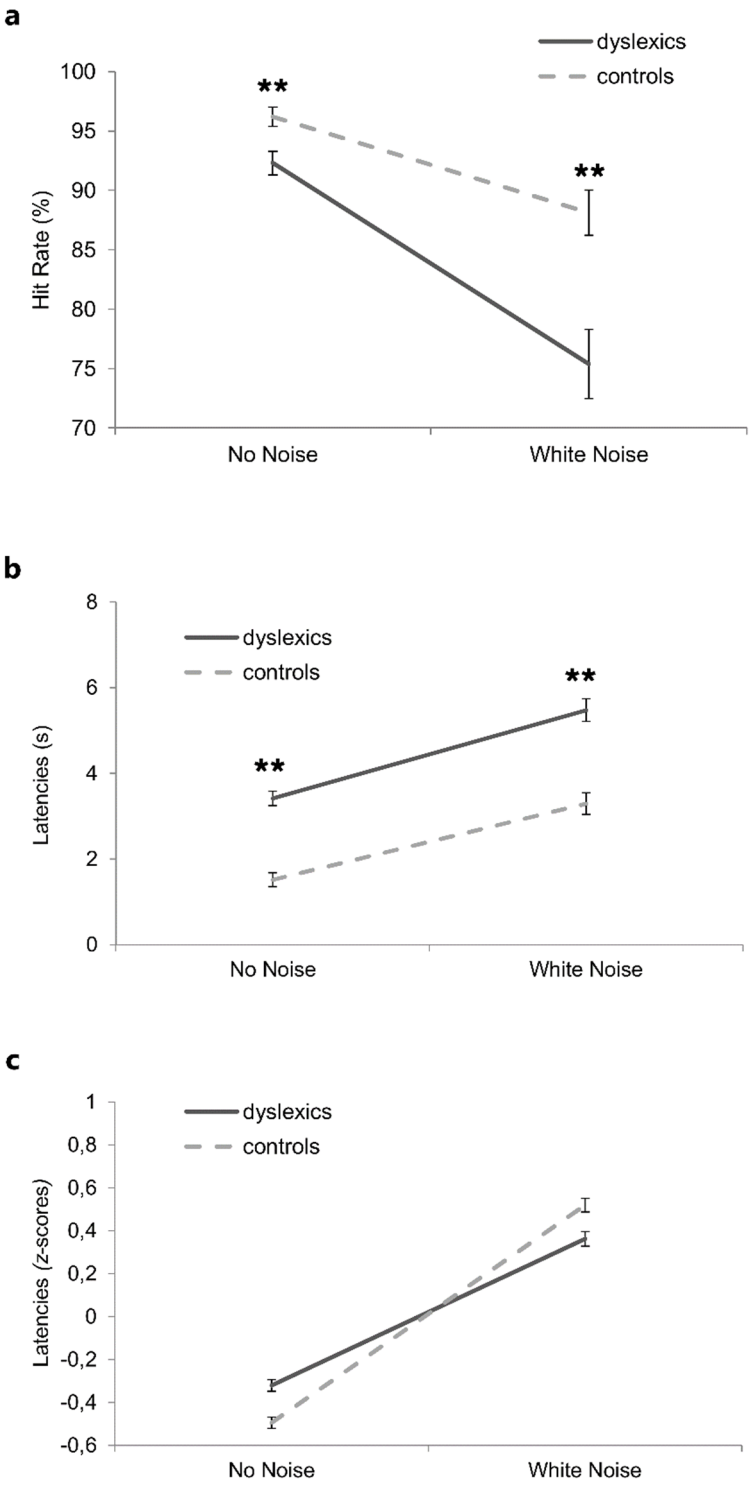

Figure 4.2. – Reading performance on the words/pseudowords discrimination task, under the two levels of noise (No Noise and White Noise), for dyslexics and controls. **(a)** Percentage and SE of the correct responses (hit rate); **(b)** Mean latencies (raw data, in seconds) and SE; **(c)** Mean latencies (z scores) and SE. NOTE. ** $p<0.01$

There was also an interaction group x noise for hit rates ($F_{(1,46)} = 7.40$, $p<0.001$; $\eta_p 2 = 0.139$; Figure 4.2 a), and for response latencies ($F_{(1,46)} = 16.94$, $p<0.001$; $\eta_p 2 = 0.269$; Figure 4.2c). These two interactions, however, were in opposite directions. White noise reduced accuracy more in dyslexics than in controls possibly due to accuracy being closer to ceiling in controls. Instead, noise impacted speed more in controls than in dyslexics when results were considered in terms of z scores. This second interaction, however, is largely mediated by response latencies to pseudowords as shown by a significant three-way group x noise x word type interaction ($F_{(2,92)} = 22.87$, $p<0.001$; $\eta_p 2 = 0.332$; Figure 4.4). In controls, white noise had a particularly strong effect in reducing the speed of response to pseudowords (Figure 4.4b). Instead, in dyslexics, white noise had a similar impact on both words and pseudowords (Figure 4.4a). This suggests that, in controls, the proficiency in using the lexical route hampers the effect of noise on processing speed. Pseudoword processing is more affected probably because white noise has a particularly strong impact on the ability to attend and process individual letters. Differences are attenuated in dyslexics in which the lexical route is less well established.

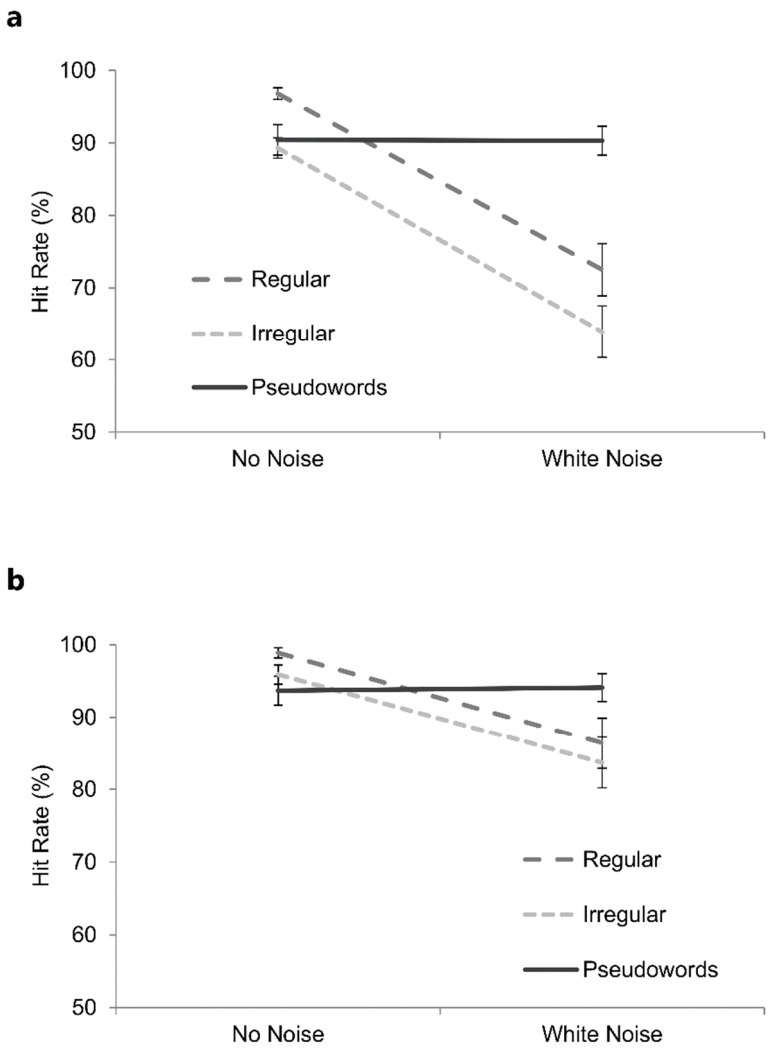

Figure 4.3. – Percentage and SE of the correct responses (hit rate) of (a) dyslexics and (b) controls on the words/pseudowords discrimination task, under the two levels of noise (No Noise and White Noise), for the three types of words (Regular, Irregular and Pseudowords).

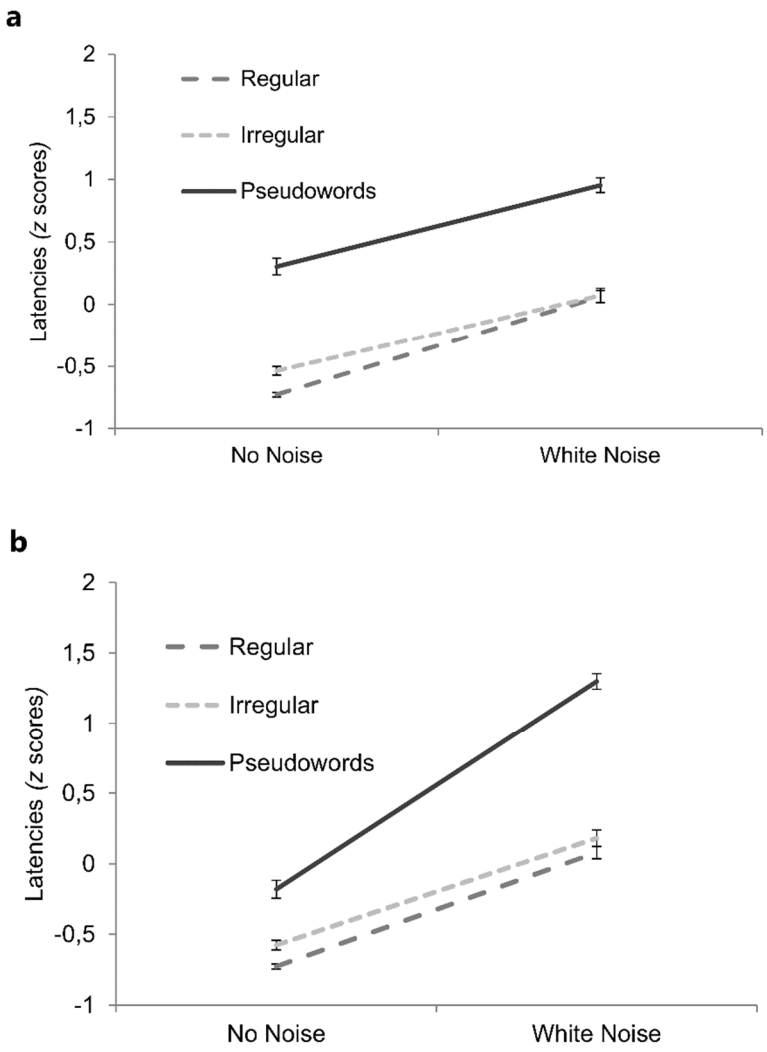

Figure 4.4. – Mean latencies (z scores) and SE of (a) dyslexics and (b) controls on the words/pseudowords discrimination task, under the two levels of noise (No Noise and White Noise), for the three types of words (Regular, Irregular and Pseudowords).

Eye movements

Concerning eye movements, results showed: 1) A main effect of group both for number of fixations ($F_{(1,46)}$ = 50.60, p<0.001; η_p2 =0.524) and regressions ($F_{(1,46)}$ = 21.02, p<0.001; η_p2 =0.314). Dyslexics exhibited a higher number of fixations and regressions. No significant effect of group was found for fixation duration and for saccadic amplitude; 2) A main effect of noise for all eye movement measures: number of fixations ($F_{(1,46)}$ = 105.24, p<0.001; η_p2 =0.696); number of regressions ($F_{(1,46)}$ = 91.73, p<0.001; η_p2 =0.666); fixation duration ($F_{(1,46)}$ = 157.63, p<0.001; η_p2 =0.774); and saccadic amplitude ($F_{(1,46)}$ = 8.10, p<0.01; η_p2 =0.150). The presence of white noise elicited a higher number of fixations and regressions, longer fixations and smaller saccades; 3) A main effect of word type, for number of fixations ($F_{(2,92)}$ = 117.31, p<0.001; η_p2 =0.718), number of regressions ($F_{(1,46)}$ = 136.38, p<0.001; η_p2 =0.748) and fixation duration ($F_{(2,92)}$ = 10.03, p<0.001; η_p2 =0.179). Post-hoc analyses showed a higher number of fixations ($t_{(94)}$ = 7.29, p<0.001) and regressions ($t_{(94)}$ = 8.36, p<0.001), as well as longer fixation durations ($t_{(94)}$ = 2.83, p<0.01), with pseudowords than with irregular words. The means and standard deviations of eye movements of dyslexics and controls for the two experimental conditions are shown in Table 4.2.

Notably, there was an interaction group x noise x word type for number of fixations ($F_{(2,92)}$ = 10.44, p<0.001; ηp2 =0.185) and for number of regressions ($F_{(2,92)}$ = 15.40, p<0.001; η_p2 =0.251). As for response latencies, in controls, white noise had a particularly strong impact in the increase of the number of fixations and regressions on pseudowords, while in dyslexics it had a similar effect on both words and pseudowords.

Table 4.2 – Means and standard deviation (in brackets) of the eye movements of dyslexics and controls for the two noise conditions (no noise and white noise) and for the three word types (regular, irregular and pseudowords).

	Dyslexics						**Controls**					
	No Noise			**White Noise**			**No Noise**			**White Noise**		
	RW	**IW**	**PW**	**RW**	**IW**	**PW**	**RW**	**IW**	**PW**	**RW**	**IW**	**PW**
Fixation Number	6.05 (1.28)	6.26 (1.45)	10.90 (3.56)	7.39 (3.13)	6.34 (2.78)	13.74 (5.16)	3.70 (.51)	4.42 (.74)	5.59 (1.35)	5.80 (1.59)	5.91 (1.61)	10.15 (3.15)
Fixation Duration (ms)	347.51 (78.11)	343.97 (75.54)	373.20 (76.36)	462.55 (125.84)	463.60 (115.84)	454.50 (103.86)	306.31 (46.98)	315.26 (51.08)	343.07 (68.65)	417.15 (92.15)	412.43 (87.53)	437.51 (86.65)
Regression Number	.89 (.38)	.98 (.36)	2.40 (.90)	1.18 (.64)	1.15 (.64)	2.84 (1.42)	.38 (.19)	.62 (.29)	1.08 (.43)	1.04 (.42)	1.13 (.44)	2.44 (.83)
Saccadic Amplitude (degrees)	2.41 (.73)	2.54 (.63)	2.59 (.98)	2.28 (.56)	2.24 (.67)	2.28 (.39)	2.28 (.73)	2.42 (.95)	2.34 (.86)	2.20 (.73)	2.09 (.65)	2.27 (.62)

NOTE. The number of fixations, the fixation durations (in milliseconds), the number of regressions and the saccadic amplitudes (in degrees) are reported. RW = regular words. IW = irregular words. PW = pseudowords.

Discussion

In this work we aimed at defining the role of the noise exclusion deficit in reading impairments by using a lexical decision task under two different visual noise conditions: no noise and white noise. Previous studies have shown an effect of white noise in lower level perceptual and behavioral processes in dyslexics (Beattie et al., 2011; Conlon et al., 2012; Sperling et al., 2005, 2006). The present study took this approach one step further by looking directly at reading performance under this type of noise. To our knowledge, this is the first study in which the direct effect of low-level visual noise on actual reading processes was studied.

Contrary to noise exclusion theory predictions (Sperling et al., 2005, 2006), we did not find a consistently stronger effect of noise on reading times or eye movements of dyslexics when compared to those of controls. Indeed, only the accuracy measure showed such an effect. Nevertheless, this last result should be interpreted with caution since it probably reflects a ceiling effect in the hit rate of controls. Hence, taken together, our results indicate that when one investigates how low-level visual noise interferes with high level reading processes, one no longer finds a selective deficit for noise exclusion in children with dyslexia. Therefore, for this particular combination of noise type and reading task, one can conclude that there was no noise exclusion deficit specific to the dyslexic population.

The second goal of the study was to understand if the effect of visual noise is modulated by the type of reading material, and, therefore, words and pseudowords were included in the experiment. Interestingly, we found that the effect of noise was larger on pseudoword than word reading speed, particularly in controls, indicating that white noise affected sub-lexical reading more than lexical reading. This suggests that, for real words, lexical information can be used to reconstruct the input and counteract the effect of noise. This interaction was verified with all measures in which significant effects were found (response latencies and number of fixations and regressions), except in the accuracy measure. This exception may reflect a mechanism of asymmetric ambiguity. Children were asked to decide if each stimulus was a real word or a pseudoword. Thus, even if errors in pseudoword reading were being committed, it is very unlikely that those errors would turn a pseudoword into a real word. In this manner, pseudoword accuracy would be constant across conditions, as we observed, and less indicative of actual noise interference. The fact that the particular influence of noise on the reading of pseudowords was observed exclusively in controls can be explained by the poorer reading experience of dyslexics. Our sample consisted of children exposed to few years of reading instruction and it is known that the development of reading is grounded in

sub-lexical processing whereas the recruitment of the lexical route evolves in parallel with reading experience (Ziegler & Goswami, 2005). Thus, while controls were already recruiting the lexical route for reading real words (regular and irregular) and the sub-lexical route for reading pseudowords, dyslexic children could still have been heavily relying on the sub-lexical route for reading all class of stimuli (real words and pseudowords).

The finding that visual noise affects sub-lexical reading more than the lexical is not in itself obvious. Low-level visual noise putatively affects reading at a very early visual stage. In the classical view of the dual route model (Coltheart et al., 2001; Coltheart et al., 1993) the visual analysis is neutral to the involvement of the two reading routes. However, two possible and complementary interpretations for our finding can be put forward.

First, one can hypothesize that slowing down the early visual processing may produce a cascade effect with differential impacts on the two reading routes, with particular repercussion on the sub-lexical route. Indeed, this hypothesis goes in line with several studies suggesting a link between abnormal early visual functioning and sub-lexical reading impairments. In their studies with dyslexic patients, Borsting et al. (1996), Cestnick & Coltheart (1999) and Gori et al. (2014) showed that dyslexics with deficits in sub-lexical reading (i.e. phonological dyslexics) exhibit abnormal performance in some early visual tasks, while dyslexics with impaired lexical reading (i.e. surface dyslexics) have normal early visual functioning. Thus, according to this interpretation, our evidence reinforces the notion that the existence of early visual interference (e.g. presence of low-level visual noise) has a stronger impact on the sub-lexical route than on the lexical route. This finding suggests that distinct noise exclusion deficits may be found within the dyslexic population according to specific reading impairments (lexical vs sub-lexical). Unfortunately, the distribution and characteristics of our dyslexic sample was not ideal for a detailed analysis on dyslexic sub-groups. Nonetheless, future studies should take into account the heterogeneity of reading impairments before drawing definitive conclusions on noise exclusion deficits in DD.

Another distinct, although not incompatible, interpretation for our results relates to the different attentional mechanisms involved in each of the reading routes. According to some authors (Cestnick & Coltheart, 1999; Rastle & Coltheart, 1998), lexical reading entails parallel letter processing, whereas sub-lexical reading is a serial left-to-right sequential process across letters. While the lexical route receives input from all the letters in a word simultaneously, the sub-lexical route receives input from each letter separately in a left-to-right serial manner. Thus, the two reading routes may require distinct orienting of attention and attentional shifting. Attentional shifting consists in moving attention between stimuli or between

features of the same stimulus, with or without the involvement of gaze shifts (Kustov & Robinson, 1996; Stoet, Markey, & López, 2007). Since the sub-lexical route is a sequential process, it demands an attentional shifting from letter to letter which is not present, at least in the same extent, in the parallel lexical route. Adding visual noise to reading stimuli, as in the current study, poses additional visuospatial attentional constraints which in turn may result in an increase of the number of attentional shifts necessary to process it. Since attentional shifting is involved primarily in sub-lexical reading, this would explain why this route is more affected by visual noise, either in terms of reading fluency as in number of eye movements (fixations and regressions).

Additional studies are needed to elucidate the mechanisms that underlie visual noise interference on sub-lexical reading. However, independently of its underlying causes, the finding that white noise affects sub-lexical reading more than lexical reading suggests that the type of reading stimuli and consequent different reading strategies play an important role when studying noise interference in reading processes.

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CHAPTER 5

Neural responses of the ventral occipito-temporal cortex in developmental dyslexia

Abstract

For the past two decades, neuroimaging studies in dyslexia have pointed towards an hypoactivation of the ventral occipito-temporal cortex (VOTC), a region that has been closely associated to reading through the extraction of a representation of words which is invariant to position, size, font or case.

However, most of the studies are confined to the VWFA, while recent studies have demonstrated a posterior-to-anterior gradient of print specificity along the VOTC. In our study, the whole VOTC, partitioned into three main patches of cortex, is assessed in dyslexic and control adults.

Thirty participants were included in this study (14 developmental dyslexics and 16 age and education matched controls). The design consisted of alternately viewed blocks of stimuli from a given class (words, consonant strings, phase scrambled words, phase scrambled consonant strings, small checkerboards, large checkerboards). The analyzed contrast was print stimuli (words and consonants) vs scrambled stimuli and checkerboards.

Corroborating previous findings, our results showed underactivation to print stimuli in the VWFA of dyslexics. Additionally, differences between dyslexics and controls were also found particularly in an area of the anterior partition of the VOTC, suggesting a relevant role of this area in word processing.

In sum, our study corroborates an underactivation in the VWFA of dyslexics and suggests the involvement of multiple areas within VOTC in the reading impairments.

Introduction

Developmental dyslexia is a high prevalence neurodevelopmental disorder characterized by a reading impairment in spite of a normal intellectual functioning and educational opportunities (American Psychiatric Association, 2000). Typically, it affects the accuracy and/or fluency of word recognition as well as spelling and decoding abilities (Shaywitz & Shaywitz, 2005).

Recent neuroimaging methods, including functional magnetic resonance imaging (fMRI), electroencephalography (EEG, and event-related potentials or ERPs), and magnetoencephalography (MEG), have consistently revealed the brain regions dominantly involved in single word reading (Norton, Beach, & Gabrieli, 2015), which are likely important to the characterization and understanding of the dyslexic brain. Three major circuits contributing to different aspects of reading have been identified (Pugh et al., 2000). A left dorsal temporo-parietal circuit around the classically termed Wernicke's area is associated with phonology-based reading processes (i.e., grapheme–phoneme conversion, phonological assembly). Additionally, a left inferiorfrontal circuit around the classically termed Broca's area, including inferofrontal and precentral gyri, is thought to be involved in speech-gestural articulatory recoding of print. Finally, a left ventral occipito-temporal circuit including lateral extrastriate, fusiform, and inferior temporal regions is linked to memory-based visual-orthographic word recognition (Martin, Schurz, Kronbichler, & Richlan, 2015). The latter includes the Visual Word Form Area (VWFA), which has been widely studied after being identified and described by Cohen et al. (2002) as an area specifically tuned to process letter strings (Cohen et al., 2000; Cohen et al., 2002; Cohen & Dehaene, 2004; Dehaene & Cohen, 2011; Dehaene, Le Clec'H, Poline, Le Bihan, & Cohen, 2002).

In particular, this last area belongs to the visual route known as the ventral "what" pathway (Ungerleider & Mishkin, 1982), contributing to reading through the extraction of a representation of words which is invariant to position, size, font or case. This representation has been referred to in literature as the Visual Word Form (VWF) (Warrington & Shallice, 1980).

Because activation in this region increases with reading skill, Shaywitz et al. (2002) referred to the left ventral occipito-temporal cortex (VOTC) as a "reading skill zone". Since reading skills are impaired in dyslexia, it would be expected to find an underactivation of this region in this condition (Sandak, Mencl, Frost, & Pugh, 2004; Shaywitz & Shaywitz, 2005). In fact, in the last two decades, neuroimaging studies comparing fMRI activations of dyslexic and typical readers have identified an hypoactivation to print in the left VOTC compared to

control subjects, particularly in the VWFA (Boros et al., 2016; Brunswick, 1999; Cao, Bitan, Chou, Burman, & Booth, 2009; Kronbichler & Kronbichler, 2018; Martin, Kronbichler, & Richlan, 2016; Maurer et al., 2007; Paulesu et al., 2001; Rumsey et al., 1997; Salmelin, Service, Kiesilä, Uutela, & Salonen, 1996; Shaywitz et al., 2002; van der Mark et al., 2011).

Although some authors have suggested that the dysfunctional activation of the VOTC is secondary to a primary dysfunction of the temporoparietal reading system (Boros et al., 2016; McCandliss & Noble, 2003; Pugh et al., 2001), the relevance of this region is highlighted in a study by Richlan, Kronbichler, & Wimmer (2011), which reports the VOTC as the only area underactivated in dyslexics compared with non dyslexics in meta-analyses conducted in children as well as in adults.

Despite recent reports confirming that visual tuning follows a posterior-to-anterior gradient of increasing print specificity in the left occipitotemporal network in adults and adolescents (Brem et al., 2006, 2009; Vinckier et al., 2007) as well as in children (Brem et al., 2009), most VOTC studies restrict themselves to the analysis of the VWFA, even when coordinates deviate from the ones defined by the early work by Cohen et al. (Barton, Fox, Sekunova, & Iaria, 2010; Cavina-Pratesi, Large, & Milner, 2015; James, James, Jobard, Wong, & Gauthier, 2005; Reinke, Fernandes, Schwindt, O'Craven, & Grady, 2008), who advert that this area is accurately found near Talairach coordinates -43; -54; -12, with a standard deviation of only ~0.5cm in the healthy brain. In fact, this diversity was a concern already expressed by these authors, by highlighting an overview of 20 imaging studies reporting activations that fell within the following boundary coordinates: $-50<x<-30$; $-80<y<-30$; $z<0$. The authors made a distinction between more posterior peaks, typically elicited by non-visual verbal stimuli (or common to the visual and non-visual stimuli), and the more anterior ones, consistent with their VWFA, observed when contrasting alphabetic strings with non-alphabetic stimuli such as false fonts or fixation. Posterior to this site, another word-tuned region has been identified by Stroher et al. (2016) who coined the name Occipital Word Form Area (see also Szwed et al., 2011), and advocated a role analogous to that of the Occipital Face Area (OFA) (Gauthier et al., 2000), which focuses on processing lower-level components or parts of the face, which are bounded further upstream in the face-processing network.

According to this framework, in the present study we evaluate print tuning in dyslexic adults along multiple regions within the VOTC.

Methods

Participants

14 developmental dyslexics (mean age: 30.50 ± 8.73, mean educational level: 15.64 ± 1.86) and 16 age matched controls (mean age: 29.44 ± 6.72, mean educational level: 16.38 ± 2.03) were recruited. The inclusion criterion for the dyslexics group was a previous clinical diagnosis of developmental dyslexia and no prior history of other developmental, cognitive, neurologic, or neuropsychiatric disorders. In the control group we included adults with no history of learning, developmental, cognitive, neurologic, or neuropsychiatric disorders.

All participants were assessed in terms of reading performance and intelligence level. For the reading assessment, a sub-test from the Psycholinguist Assessments of Language Processing in Aphasia - Portuguese version (PALPA-P) (Castro, Caló, & Gomes, 2007) was used. In this sub-test, participants were asked to read a list of 60 words and pseudowords as quickly as possible. The measures obtained from this sub-test were reading speed (in seconds) and accuracy (number of words correctly read). Intelligence level was measured through the Raven Progressive Matrices Test – Set 1 (RPM) (Raven, Court, & Raven, 1976).

The groups were matched for age, gender, years of education and IQ (as assessed by RPM), and statistically different in the reading measures (speed and accuracy). All participants were right-handed and had normal or corrected to normal vision. Participants' demographics and reading and intelligence scores are summarized in Table 5.1. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra. Written informed consent was obtained from the participants, after an explanation of the nature of the study.

Table 5.1. Summary statistics for the two groups of participants

	Dyslexics (n = 14)			Controls (n = 16)			
	Mean	**Range**	**SD**	**Mean**	**Range**	**SD**	p **value**
Age (years)	30.50	20–45	8.73	29.44	21–48	6.72	.710
Education (years)	15.64	12–17	1.86	16.38	9–17	2.03	.315
RPM	10.29	9-12	.99	10.93	10-12	.73	.062
PALPA-P reading speed (sec)	75.85	46-101	16.58	39.31	29-47	6.43	<.001
PALPA-P accuracy	50.00	42-57	4.72	56.46	54-58	1.27	<.001
Gender (m:f)	6/8			12/4			.078

NOTE. RPM = Raven Progressive Matrices; PALPA-P = Psycholinguist Assessments of Language Processing in Aphasia - Portuguese version. Probability values for group comparisons using t-tests (except for gender, for which the Chi square test was used) are reported (p< 0.05 values are considered significant).

Task and Stimuli

During fMRI acquisition participants were asked to pay attention to presented words, consonants strings, checkerboards, and phase scrambled versions of the words and consonant strings. Implicit processing by passive viewing was chosen to avoid confounds driven by potential differences in task performance. Though the participants are not instructed to read the word during this task, reading occurs implicitly and without conscious effort in skilled readers (Price, Wise, & Frackowiak, 1996). Various studies involving children and adults have demonstrated implicit processing activation in reading-related brain regions, including those thought to be involved in orthographic, phonological and semantic processing (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2011; Price et al., 1996; Turkeltaub et al., 2004; Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003).

Word stimuli consisted of 60 five-letter words selected from the Portuguese Corlex database. Words with frequency values above 100 are considered to be highly frequent with the mean word frequency values for our sample being 1758.30.

Consonant strings were built by combining 60 random series of five consonants (example: 'vcbtx'). All of the consonant strings were unpronounceable in Portuguese.

Phase-scrambled versions were built for every word and consonant stimuli, in a total of 120.

Finally, two versions of checkerboards were built. A small version spanned the exact size of the word and consonant stimuli. A larger version had a threefold increase in the horizontal dimension and a four-fold increase in the vertical dimension. This span was used to equate the number of acquired volumes per condition. The horizontal spatial frequency of the

checkerboard stimuli was equated to the word and consonant stimuli (one black and white square for each letter).

fMRI Scanning

Images were obtained on a Siemens Tim Trio 3T scanner using a 12 channel head coil. Structural images were collected using a T1 weighted MPRAGE (magnetization prepared rapid-acquisition gradient echo) (TR=2530 ms, TE=3.42 ms, flip angle=7, matrix size = 256 x 256, voxel size= 1 mm3 isotropic). Standard T2 n-weighted gradient-echo echo planar imaging was used for the functional task runs (TR=1500 ms; TE=30 ms; 3.6 x 3.6 mm in-plane resolution; 3.6 mm slice thickness with no gap; flip angle=76; matrix size=64 x 64; number of slices=28; 285 measurements were used for the functional run). The slices were oriented to obtain a brain coverage spanning from the cerebellum to the motor cortices, ensuring ventral occipito-temporal coverage. Image processing was performed using BrainVoyager QX v2.6 (Brain Innovation, Maastricht, The Netherlands). Pre-processing steps included motion correction, slice scan-time correction, linear trend removal and temporal high-pass filtering of 0.00980 Hz (3 cycles in time course). Functional data was registered to each individual's anatomical scan and transformed to a common Talairach space.
The functional scan consisted of alternately viewed blocks of stimuli from a given class (words, consonant strings, phase scrambled words, phase scrambled consonant strings, small checkerboards, large checkerboards). The run had 18 blocks (3 for each category) and each block lasted 20s (20 images, 800 ms each, 200 ms gap), separated by 10s fixation baseline intervals. The run started with a period of fixation for 10s and ended with a period of fixation for 30s. Block presentation order was pseudorandomized within each repetition (there had to be a block of each stimulus category before a second block of a given category could be presented) and then the same order was used for all participants.

Data analysis

GLMs and contrasts

A GLM with 6 predictors, one for each stimulus category was built for each participant. We focused on a contrast similar to the one used by Cohen to identify the VWFA, although we also included scrambled versions of words and consonant strings. In this manner, contrast

was PRINT STIMULI (WORDS and CONSONANTS) vs SCRAMBLED STIMULI and CHEKERBOARDS.

VOTC partitions

Following the reasoning outlined in the introduction, we parceled the VOTC into three regions-of-interest (ROI), which approximately encompass the VWF system (among other dedicated areas): an anterior portion centered on x=-35; y=-40; z=-20, a middle portion centered on x=-43; y=-60; z=-15, and a posterior portion centered on x=--40; y=-85; z=-5. The regions span 25mm along the x dimension; 20mm along the y dimension and 30mm along the z dimension. The posterior region was allowed a larger span along the y dimension to include posterior occipital activations.

The employment of a three-fold division of this region in word processing studies is not new and has been successfully used by other authors (Mei et al., 2015; Seghier & Price, 2011). Furthermore, individual data corroborates this approach, as exemplified in Figure 5.1 for both dyslexic and control subjects. An illustration of the ROIs center and span is shown in Figure 5.2.

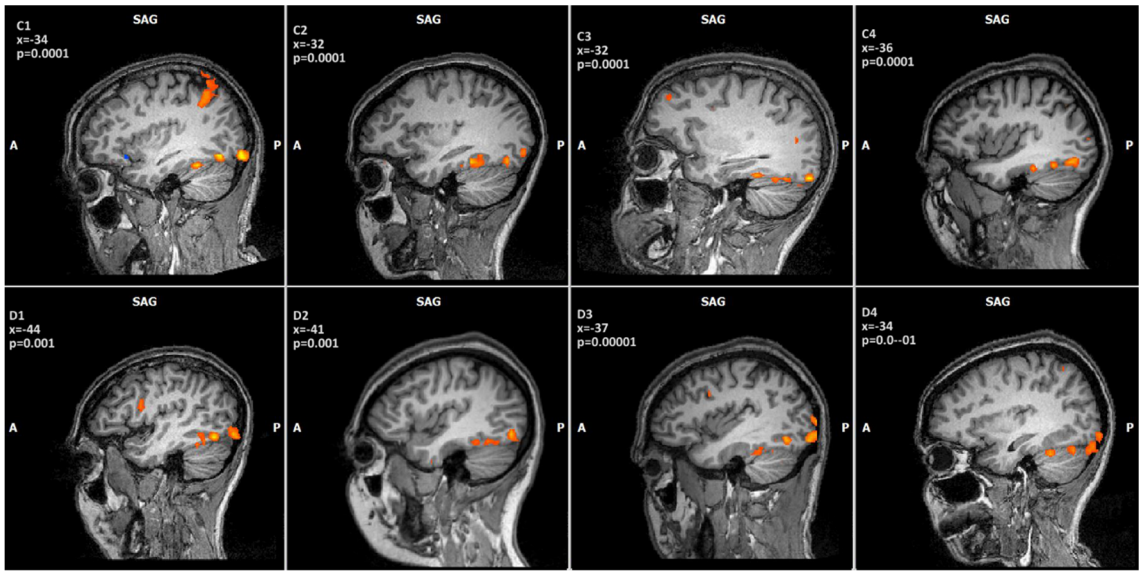

Figure 5.1. – Example individual activations to the contrast words and consonants vs scrambled stimuli and checkerboards. 4 controls (top row) and 4 dyslexics (bottom row) are shown. Note the pattern of the three identifiable clusters.

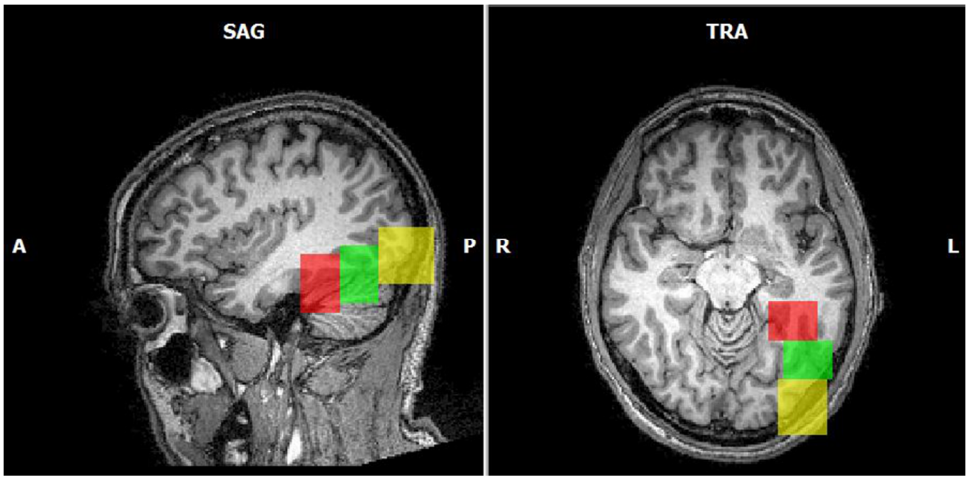

Figure 5.2. – Illustration of the three selected ROIs, corresponding to three broad regions of the VOTC.

Statistical Analysis

A standard RFX-GLM to check for areas with significant differences between groups was performed. Results are evaluated for each of the three VOTC partitions, at a significance threshold of $p<.05$ and a cluster threshold of 8mm3 (2x2x2).

Results

For every VOTC partition, areas could be identified with greater activation for controls than dyslexics which are in concordance with coordinates previously reported in literature for word-processing relevant areas (see Table 5.2).

The significance map for the anterior partition is clearly dominated by an area centered on Talairach coordinates -31; -35; -18. In the middle partition, an area with greater activity for controls than dyslexics was identified in close accordance to the reported coordinates of the VWFA (-43, -53, -6). For the posterior partition, dyslexics showed significant hypoactivation for print stimuli in an area centered on Talairach coordinates -34; -83; -12.

Thus, according to previous findings, we found underactivation to print stimuli in the VWFA of dyslexics. Nonetheless, the major differences between dyslexics and controls were found in the anterior partition of the VOTC, indicating that the underactivation is not restricted to the VWFA. Taken together, our results show that there seem to be areas differentially recruited by controls and dyslexics in word-reading processes.

Table 5.2. - Mean contrast differences in the three VOTC partitions

	Anterior Partition					Middle Partition					Posterior Partition				
	Controls > Dyslexics (-31; -35; -18)					Controls > Dyslexics (-43; -53; -6)					Controls > Dyslexics (-34, -83, -12)				
	Controls	**Dyslexics**	**t**	***p***	**Cluster size**	**Controls**	**Dyslexics**	**t**	***p***	**Cluster size**	**Controls**	**Dyslexics**	**t**	***p***	**Cluster size**
Print vs scrambled and checkerboards	0.845	-0.256	3.728	0.0008	786	1.021	0.141	2.483	0.0193	48	1.354	-0.079	2.318	0.0280	7

Discussion

Since the early description of the VWFA in 2002, and the claim of a word tuning gradient in the VOTC, an intense debate has been generated concerning its preservation in dyslexia. Previous work has identified hypoactivation of the VOTC in the dyslexic brain, particularly in the VWFA.

In his seminal VWFA study, Cohen and colleagues reviewed word-tuned activations that ranged from y=-80 to y=-30 (Cohen et al., 2002). In 2007, Vinckier et al. (2007) exploited the full range of this extension to argue in favor of a hierarchical coding of letter streams in the VOTC, from y=-96 to y=-40. They established that activation became more selective for higher-level stimuli toward the anterior fusiform region. Further research confirmed both the diversity and the posterior to anterior (ranging from low-level to high-level) direction of the word-tuned gradient (Barton et al., 2010; Olulade, Flowers, Napoliello, & Eden, 2015; Szwed et al., 2011; van der Mark et al., 2009; Zemmoura, Herbet, Moritz-Gasser, & Duffau, 2015). With this in mind, in the present study, we probed print-specificity in the whole VOTC, partitioned into three regions: anterior, middle and posterior.

Corroborating previous studies (e.g. Boros et al., 2016; Martin et al., 2016; van der Mark et al., 2011), we demonstrated that dyslexics show hypoactivation to print stimuli in the VWFA (Talairach coordinates -43; -53; -6). Interestingly, we identified other areas in which print-specific activity is significantly larger for controls than dyslexics, particularly in the anterior partition of the VOTC (Talairach coordinates -31; -35; -18), a region which sits at the top of the VOTC visual gradient and may bridge with nearby semantic and multimodal regions (see Binder, Desai, Graves, & Conant, 2009; Jobard, Vigneau, Mazoyer, & Tzourio-Mazoyer, 2007). In fact, the most robust differences were observed in this particular region, suggesting a possible role of this area for reading related processes in health and disease. Other studies had located the brain region showing greater selectivity for letter strings in more anterior VOTC regions, rather than in the VWFA (Olulade, Flowers, Napoliello, & Eden, 2013; Turkeltaub et al., 2003). Our study thus reinforces the involvement of multiple areas within VOTC in reading processes.

According to the hierarchical coding of letter streams in the VOTC (Barton et al., 2010; Olulade et al., 2015; Szwed et al., 2011; van der Mark et al., 2009; Vinckier et al., 2007; Zemmoura et al., 2015), bilateral early visual cortices extract the early features of the letters which are then recombined into increasingly abstract letter string representations up to the VWFA. The areas identified in the present study would therefore lie towards greater

integration of print units, being responsible for whole word processing (VWFA) and even multimodal/semantic representation of words (anterior temporal). Applying this framework to reading error analysis, disrupted neural activity at lower levels would predict errors on similar words (e.g., misreading "farm" as "form"), whereas noise at higher levels could lead to errors on increasingly larger units such that eventually the whole word is difficult to access (Glezer, Jiang, & Riesenhuber, 2009). In this manner, the dyslexic pattern of activation in our sample would be more associated with difficulties at the whole-word higher perceptual levels whereas lower-level perception seems to be more preserved.

Nevertheless, the functional posterior-to-anterior hierarchy in the left VOTC has recently been challenged. In a very recent work, Lochy and colleagues (2018) report an extensive functional mapping of the VOTC for selective responses to visual letter strings and words with intracerebral recordings. Besides showing letter-selective responses across all the VOTC, they found responses to real words in a region extending more anteriorly than the VWFA. Moreover, a distinct spatial organization for prelexical and lexical processing in the left fusiform gyrus was not observed.

The fine grained spatial organization of the VOTC for processing letters and words is, therefore, still under debate, although our study and others suggest that the contribution of multiple areas, in particular in anterior VOTC, is relevant. In addition to the VWFA, future studies are needed to unveil the specific contribution to reading of other areas along the VOTC.

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CONCLUDING REMARKS

CHAPTER 6

Discussion and Conclusions

Discussion

The current thesis aimed at investigate mechanisms of disease in developmental dyslexia (DD), particularly in which concerns the possible etiological involvement of visuo-attention abnormalities in the reading impairments observed in this condition.

In the last years a vast amount of evidence trying to unveil the causes of DD have been gathered. The importance of this research topic is fairly obvious: the increased knowledge about the causes of the condition can result in earlier and more accurate diagnosis, as well as in more effective remediation programs. However, and despite all research, there is still an ongoing controversy concerning the etiology of this condition and different hypothesis coexist nowadays. The influence of visual and visuo-attentional mechanisms in reading difficulties is considered by several of those hypothesis. Combining different approaches and techniques, the work presented on this thesis addressed some of the current causal theories of DD, namely the magnocellular theory (Stein & Walsh, 1997), the sluggish attentional shifting theory (Hari & Renvall, 2001) and the perceptual noise exclusion theory (Sperling, Lu, Manis, & Seidenberg, 2005). The implications of the current findings for the understanding of visual and visuo-attentional mechanisms underlying reading impairments in DD will be pointed out in this chapter.

Visual perception in DD

The main objective of the current thesis was to investigate the influence of visuo-attentional mechanisms in DD. Therefore, the first research question of this work focused on characterizing visual perception in children with DD. The nature of putative visual perception deficits in DD is a controversial issue with contradictory evidence. Cortical visual information processing is routed in two main visual streams: the dorsal (D) and the ventral (V) streams. Whereas some authors claim for a visuo-perceptual deficit in DD, namely in which concerns D stream processing (e.g. Pellicano & Gibson, 2008; Shandiz et al., 2017), others do not (e.g. Gross-Glenn et al., 1995; Vanni, Uusitalo, Kiesilä, & Hari, 1997). One of the possible reasons for such discrepancies is the difficulty in isolating the function of each visual processing stream. The work described in Chapter 2 provides an innovative approach by assessing visual perception through a battery of tasks following a gradient of D stream contribution, providing a comprehensive and multifaceted perspective instead of relying on the assumption of

exclusive activation of the stream. The battery comprised three different low-level visuo-perceptual tasks: a chromatic contrast sensitivity task (weak D stream contribution), an intermediate spatial frequency contrast sensitivity task (mild D stream contribution) and a local speed discrimination task (strong D stream contribution).

We showed that children with DD have deficits in speed discrimination and in contrast sensitivity in intermediate spatial frequencies, but preserved chromatic contrast sensitivity. These results are globally in line with previous studies which had already shown isolated motion perception deficits (e.g. Amitay, Ben-Yehudah, Banai, & Ahissar, 2002; Talcott et al., 2002) and typical chromatic perception (e.g. Dain, Floyd, & Elliot, 2008; Sperling, Lu, Manis, & Seidenberg, 2003) in DD. Notably, our study was the first to test an intermediate spatial frequency visual channel in DD and to demonstrate an impairment in this channel. Moreover, and following the gradient of dorsal stream contribution, our comprehensive approach allowed to demonstrate that the higher the dorsal stream involvement, the higher the differences between DD children and typical readers. Concerning the relationship between low-level visual functions and reading, we also showed that the higher the involvement of dorsal stream mechanisms, the stronger the correlation to reading measures. Taken together, the results of the work described in Chapter 2 add supportive evidence for a dorsal (magnocellular) deficit in children with DD.

Orienting and spatial distribution of attention in DD

Based on the findings of the first study described in this thesis in which we demonstrated a dorsal stream deficit in DD, and given the fact that the dorsal stream also integrates parietal functions essential for visuo-spatial attentional skills (Saalmann, Pigarev, & Vidyasagar, 2007), we went to investigate visuo-spatial attention in DD.

Some of the visuo-spatial attentional abnormalities described in children with DD concern impaired exogenous attention orienting (e.g. Facoetti, Lorusso, Cattaneo, Galli, & Molteni, 2005; Franceschini, Gori, Ruffino, Pedrolli, & Facoetti, 2012; Hari & Renvall, 2001) and diffused spatial distribution of attention (Facoetti & Molteni, 2001; Facoetti, Paganoni, & Lorusso, 2000). However, studies in adults have failed to replicate such results (e.g. Judge, Caravolas, & Knox, 2007; Moores, Tsouknida, & Romani, 2015), hindering the claim of a causal link between these attentional impairments and the reading deficits in DD.

The study described in Chapter 3 of the current thesis aimed at further investigate orienting and spatial distribution of attention in adults with DD, adding to the debate on the relationship between these attentional mechanisms and reading impairments. Attention orienting can be goal-directed, via a mechanism known as "endogenous" orientation of attention, or automatic, rapid and in a stimulus-driven fashion termed "exogenous" orientating of attention (Nakayama & MacKeben, 1989). By measuring reaction times of adults with and without DD in a cued discrimination task with stimuli presented at four degrees of visual eccentricity, we showed for the first time that dyslexics adults have global temporal deficits in a task requiring exogenous orienting of attention. Moreover, we demonstrate that adults with DD have an abnormal distribution of attention. Along with the different effect of eccentricity on the reaction times of dyslexics and controls, we also showed that attentional cueing effects in DD adults are dependent on the eccentricity. While normal reading adults showed cue effects at all levels of eccentricity, corroborating previous studies (Posner, 1980; Posner, Snyder, & Davidson, 1980), the reaction times of dyslexic adults could only benefit from valid cues when stimuli were presented at less peripheral eccentricities. Thus, DD adults are not efficiently using cues to rapidly direct attention to more peripheral eccentricities. Such findings can have important implications for the understanding of reading impairments in DD. Exogenous orienting of attention is involved in the precise and rapid selection of relevant stimuli among distractors by intensifying the signal inside the focus of attention (Carrasco, Williams, & Yeshurun, 2002; Enns & Di Lollo, 2000; Facoetti, 2012). In addition, it is also important to visually determine the graphemic elements of a word, i.e. for graphemic parsing, which, combined with efficient phonological skill, is a crucial process for the letter-to-speech integration (Facoetti et al., 2010; Ruffino, Gori, Boccardi, Molteni, & Facoetti, 2014).
In sum, the work described in Chapter 3 reconciles previous studies in children and in adults and provides evidence of the persistence of the attention orienting deficits into adulthood.

Noise exclusion and reading

While some authors claim that deficits in attentional orienting and abnormal spatial distribution of attention underlie reading impairments in DD (e.g. Facoetti & Molteni, 2001; Facoetti et al., 2000; Facoetti et al., 2005; Franceschini et al., 2012; Gad Geiger & Lettvin, 1987; Gad Geiger, Lettvin, & Zegarra-Moran, 1992; Gadi Geiger et al., 2008; Hari & Renvall, 2001), others raised the hypothesis that DD may be due to a deficient processing of relevant

stimuli in the presence of surrounding visual noise (Sperling, Lu, Manis, & Seidenberg, 2005, 2006). That theory was named perceptual noise exclusion theory.

In Chapter 4 we addressed this hypothesis by probing, for the first time, dyslexics' reading performance under low-level visual noise and by investigating noise interference with different reading stimuli (regular and irregular words and pseudowords). For that, we design a paradigm built upon previous works (Beattie, Lu, & Manis, 2011) in which DD children and normal readers had to discriminate between words and pseudowords under two different backgrounds: no noise and white noise. Besides measuring accuracy and response times, we also recorded the participants' eye movements.

We showed that, contrary to noise exclusion theory predictions, the presence of noise does not consistently affect DD children more than controls. Particularly, we demonstrated that when one investigates how low-level visual noise interferes with high level reading processes, one no longer finds a selective deficit for noise exclusion in children with DD.

Additionally, other interesting finding emerged from our work. We found that the effect of low-level noise was larger on pseudoword than word reading speed. This stronger effect of low-level noise in sub-lexical reading than in lexical reading, suggests that, for real words, lexical information can be used to reconstruct the input and counteract the effect of noise. Two possible interpretations for this result can be put forward. First, a low-level visual interference may produce a cascade effect with particular repercussion on the sub-lexical route. This explanation goes in line with previous findings showing concomitant deficits in sub-lexical reading and in low-level visual tasks (Borsting et al., 1996; Cestnick & Coltheart, 1999; Gori, Cecchini, Bigoni, Molteni, & Facoetti, 2014). The second interpretation relates to the orienting of attention mechanisms investigated in Chapter 3. Since the lexical route receives simultaneous input from all the letters in a word, while the sub-lexical route receives input from each letter separately in a left-to-right serial manner (Cestnick & Coltheart, 1999; Rastle & Coltheart, 1998), the sub-lexical route is more demanding in which concerns attentional shifting. By adding visual noise to reading stimuli we might have posed additional visuospatial attentional constraints, increasing the number of attentional shifts, thereby increasing the time and the number of eye movements necessary to process the stimuli.

The major implication of this study for the understanding of DD is, therefore, the notion that the presence of noise may indeed play a role in the reading deficits, however, particularly in dyslexics exhibiting sub-lexical reading deficits rather than in the whole dyslexic population. Since, unfortunately, the distribution and characteristics of our DD sample was not ideal for a detailed analysis on dyslexic sub-groups, future studies on noise exclusion deficits in DD

should take into account the heterogeneity of reading impairments to fully understand the plausible noise exclusion deficits in DD.

Brain functioning in DD

Reading is a highly demanding task for the brain. It involves several processes which, in turn, recruit different cortical circuits. One of those circuits is in the left ventral occipito-temporal cortex (VOTC) and is has been associated to memory-based visual-orthographic word recognition (Martin, Schurz, Kronbichler, & Richlan, 2015). The VOTC includes the Visual Word Form Area (VWFA) which has been described as an area specifically tuned to process letter strings (e.g. Cohen et al., 2002; Dehaene & Cohen, 2011). Despite the knowledge of a posterior-to-anterior gradient of increasing print specificity in VOTC (Brem et al., 2006, 2009; Vinckier et al., 2007), the majority of the studies which have identified underactivation to print stimuli in the VOTC of dyslexics focused exclusively on the analyses of the VWFA. The work described in Chapter 5 adds to the current knowledge by evaluating print tuning in DD along the whole VOTC. For such purposes, words, consonants strings, checkerboards, and phase scrambled versions of the words and consonant strings were presented to participants during fMRI acquisition. Given the posterior-to-anterior gradient in VOTC, we parceled the VOTC into three partitions (posterior, middle and anterior). We then investigated areas, along the three partitions, with significant different activations to print stimuli in dyslexics and controls. According to previous literature, we found underactivation to print stimuli in the VWFA (VOTC middle partition) of dyslexics. However, the underactivation was not restricted to this area, being also present in other areas of the VOTC, particularly in its anterior region. This results is in line with other studies which had located the areas with greater selectivity for letter strings in more anterior VOTC regions, rather than in the VWFA (Olulade, Flowers, Napoliello, & Eden, 2013; Turkeltaub et al., 2003).

These work, therefore, corroborates an underactivation in the VWFA of dyslexics and suggests the involvement of multiple areas within VOTC in the reading impairments.

Conclusions

The work presented in the current thesis provides novel clues to the current understanding of the neurocognitive profile of DD, namely in which concerns visual and visual-attention characteristics. By using different approaches and studying different dyslexic populations, we added to current knowledge by demonstrating, for the first time, that Portuguese dyslexics have impaired visual and visuo-attentional processing and a distinct neural organization. Despite the complexity of the relationship between visuo-attention skills and reading, also stressed in our work, our findings increment the understanding of this condition, a fundamental premise to improve diagnosis and remediation strategies.

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Pina Rodrigues, A., Rebola, J., Jorge, H., Ribeiro, M. J., Pereira, M., Castelo-Branco, M., & van Asselen, M. (2017). Evidence for a differential interference of noise in sub-lexical and lexical reading routes in healthy participants and dyslexics. Cognitive Neuropsychology, 29, 1–10. https://doi.org/10.1080/02643294.2017.1299001

Pina Rodrigues, A., Rebola, J., Jorge, H., Ribeiro, M. J., Pereira, M., van Asselen, M., & Castelo-Branco, M. (2017). Visual Perception and Reading: New Clues to Patterns of Dysfunction Across Multiple Visual Channels in Developmental Dyslexia. Investigative Ophthalmology & Visual Science, 58(1), 309–317. https://doi.org/10.1167/iovs.16-20095

van Asselen, M., Sampaio, J., **Pina, A.**, & Castelo-Branco, M. (2011). Object based implicit contextual learning: a study of eye movements. Attention, Perception, & Psychophysics, 73(2), 297–302. https://doi.org/10.3758/s13414-010-0047-9

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Ana Pina Rodrigues, 2018

Curriculum Vitae

Ana Pina Rodrigues was born on December 23, 1981 in Viseu, Portugal. In 1999, she completed her secondary school education at Escola Secundária Alves Martins in Viseu, after which she studied Psychology at the Faculty of Psychology and Education Sciences of the University of Coimbra. She finished her Degree in 2004 and, in 2007, 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. In 2010, she successfully applied to the Doctoral Programme in Health Sciences of the Faculty of Medicine of the University of Coimbra and in 2011 she started her PhD research project entitled "Spotlight of Attention in Developmental Dyslexia" at CNC.IBILI and CIBIT-ICNAS, under the supervision of Professor Miguel Castelo-Branco and Professor Marieke van Asselen.