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Visuoconstructional impairment in Mild Cognitive Impairment: Diagnostic utility and predictive value in the progression to Alzheimer's disease

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Título da dissertação – *Défice visuoconstrutivo no Defeito Cognitivo Ligeiro: Utilidade diagnóstica e valor preditivo na progressão para Doença de Alzheimer*

Introdução: A visuoconstrução é um domínio cognitivo que se define pela capacidade de organizar e manipular manualmente informações espaciais, por forma criar um *design* ou copiar um modelo. Este é um domínio complexo que integra processos como a visuoperceção, a análise visuospacial, as capacidades motoras finas, a atenção e várias funções executivas. Na doença de Alzheimer (DA) a visuoconstrução é frequentemente avaliada através de provas de desenho por cópia ou de desenho livre. Tendo em conta a complexidade da visuoconstrução, e considerando o comprometimento de diversas áreas cerebrais implicado na DA, é possível observar-se défices visuoconstrutivos desde as fases iniciais da doença.

Objetivos: (1) Avaliar os défices visuoconstrutivos no Defeito Cognitivo Ligeiro (DCL) e estudar as diferenças entre doentes com DCL amnésico (DCLa) e DCL amnésico multidomínios (DCLam); (2) avaliar o valor do domínio visuoconstrutivo como preditor da conversão para DA.

Métodos: Cento e oitenta e quatro doentes diagnosticados com DCLa (n=121) e DCLam (n=63) foram avaliados anualmente (entre 2 a 11 anos) em contexto de consulta de demência ao nível da sua cognição, funcionalidade e psicopatologia, através de uma extensiva bateria neuropsicológica. A avaliação da visuoconstrução foi realizada através das seguintes tarefas: o Teste do Desenho dos Pentágonos (TDP), o Teste da Cópia do Cubo (TCC), a Tarefa de Praxia Construtiva (TPC) e a condição de desenho livre do Teste de Desenho do Relógio (TDR). O domínio visuospacial do *Montreal Cognitive Assessment* (MoCA) foi igualmente utilizado como medida visuoconstrutiva.

Resultados: Os doentes diagnosticados com DCLam apresentaram piores capacidades visuoconstrutivas que os doentes com DCLa. Apesar de as diferenças entre os dois grupos terem sido detetadas tanto em tarefas de cópia como em tarefas de desenho livre, as tarefas de cópia menos complexas (TDP e os dois itens mais simples da TPC) não reportaram diferenças estatisticamente significativas (p>.05). Em relação às diferenças entre os doentes que converteram (C) e aqueles que não converteram (NC) para demência, observou-se uma inclusão significativamente maior de doentes com inícios tardios da doença no grupo C ($t_{(135.66)}$= -4.233, p<.001). As análises de sobrevivência acusaram taxas de conversão significativamente diferentes para doentes com inícios precoces (IP) e para doentes com inícios tardios (IT) da doença ($\chi^2_{(1)}$=13.416, p<.001), com estes últimos a apresentarem sistematicamente menores probabilidades de permanecerem estáveis. As análises multinível dos doentes IP acusaram o TDR ($\chi^2_{(1)}$=5.019, p=.025) e o efeito de interação ente o TDP e o Tempo ($\chi^2_{(1)}$=6.655, p=.010) como preditores significativos da demência. Para os doentes IT, os preditores revelados foram o TDR ($\chi^2_{(1)}$=16.677, p<.001) e o domínio visuospacial do MoCA ($\chi^2_{(1)}$=4.157, p=.041). Em ambos os

modelos, piores pontuações nas tarefas de desenho implicaram um aumento da probabilidade de converter relativamente à probabilidade de não converter para demência.

Conclusões: Os resultados sugerem um comprometimento visuoconstrutivo mais acentuado nos doentes com DCLam comparativamente aos doentes com DCLa. Adicionalmente, a visuoconstrução parece constituir-se como preditor significativo da DA, com maiores défices nesta capacidade a traduzirem um incremento na probabilidade de progredir de uma condição de DCL para demência. Uma vez que os doentes com inícios tardios da doença apresentam menores probabilidades de permanecerem estáveis comparativamente aos seus homólogos com inícios precoces, doentes com inícios tardios e fracas capacidades visuoconstrutivas puderão constituir um grupo em elevado risco de conversão. Neste sentido, os défices visuoconstrutivos poderão ser utilizados como importantes sinais de aviso da probabilidade de conversão de um doente.

Palavras-chave: Visuoconstrução, Defeito Cognitivo Ligeiro, Doença de Alzheimer, Avaliação Neuropsicológica, Estudo Longitudinal.

Title of dissertation - *Visuoconstructional impairment in Mild Cognitive Impairment: Diagnostic utility and predictive value in the progression to Alzheimer's disease*

Introduction: Visuoconstruction is a cognitive domain that can be defined as the ability to organize and manually manipulate spatial information in order to create a design or copy a model. As a complex domain, visuoconstruction requires the interaction of different processes, such as visuoperception, visuospatial analysis, fine motor skills, attention and executive functions. In Alzheimer's disease (AD), this domain is frequently assessed through drawing tasks, including both copying and drawing-to-command. Given the complexity of this capacity, and since AD involves the impairment of several brain areas, visuoconstruction can be compromised in the early stages of the disease.

Objectives: (1) To assess visuoconstructional impairments in Mild Cognitive Impairment (MCI) and study differences between amnestic single-domain MCI (aMCI) and amnestic multidomain MCI (amMCI) patients; (2) to assess the value of visuoconstruction as a predictor of AD.

Methodology: One-hundred and eighty four patients diagnosed with aMCI (n=121) and amMCI (n=63) were followed in dementia consultation an evaluated annually through an extensive neuropsychological battery. All patients were assessed at a cognitive, functional and psychopathological level. To assess visuoconstruction, we applied the following tasks: the Pentagon Drawing Test (PDT), the Cube Copying Test (CCT), the Constructional Praxis Task (CPT) and the drawing-to-command condition of the Clock Drawing Test (CDT). The visuospatial domain of Montreal Cognitive Assessment (MoCA) was also used as a measure of

visuoconstruction.

Results: Overall, amMCI patients presented worst visuoconstructional abilities than aMCI patients. Although these differences were detected either by copying or drawing-to-command tasks, less complex copying tasks (PDT and the two simpler items of the CPT) could not distinguish the two groups (p>.05). Regarding the differences between patients who converted (C) and patients who did not convert (NC) to dementia, the C group included significantly more MCI patients with late-onsets than the NC group ($t_{(135.66)}$= -4.233, p<.001). Survival analysis reported significantly different patterns of conversion for patients with early-onsets (EO) and late-onsets (LO) ($\chi^2_{(1)}$=13.416, p<.001), with the latter presenting lower probabilities of remaining stable. Multilevel analysis of EO patients yelled the CDT ($\chi^2_{(1)}$=5.019, p=.025) and the interaction effect between the PDT and Time ($\chi^2_{(1)}$=6.655, p=.010) as significant predictors of dementia. For LO patients, the yelled predictors were the CDT ($\chi^2_{(1)}$=16.677, p<.001) and the visuospatial domain of MoCA ($\chi^2_{(1)}$=4.157, p=.041). In both models, worse visuoconstructional scores implied an increase in the chances of a patient converting versus the chances of not converting.

Conclusions: Our results suggest that amMCI patients present steeper visuoconstructional impairment in comparison to aMCI patients. Besides, visuoconstruction is a significant predictor of AD, with greater deficits leading to an increase in the probability to convert from MCI to dementia. Since late-onset patients are less likely to remain stable compared to their early-onset counterparts, late-onset patients with poor visuoconstructive capabilities may constitute a group at high risk of conversion. In this sense, visuoconstructive deficits may be used as an important warning sign of the probability of a patient to develop dementia.

Key Words: Visuoconstruction, Mild Cognitive Impairment, Alzheimer's Disease, Neuropsychological Assessment, Longitudinal Study.

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Content

Introduction

The current steadily increase in the average life expectancy is a remarkable achievement that is changing the age structures of societies worldwide. The ageing of the population is a current reality, and the increase of people at old and very old ages will continue. This raises challenging health and social economic costs since with advancing age the prevalence of age-related diseases, such as neurodegenerative diseases and dementia, rises. Alzheimer's disease (AD) is the most common form of dementia so it is estimated that in 2050, 115 million people across the globe will suffer from dementia due to AD. In order to face growing challenges, identification of individuals at higher risk of developing this disease is key, in order to implement prevention and intervention measures. Thus, the study of specific cognitive impairments during prodromal phases, known as Mild Cognitive Impairment (MCI), is of the utmost importance.

The present work has two main aims: (1) to study visuoconstructional impairment in MCI and (2) to evaluate its predictive value of the progression to dementia.

Firstly we will introduce main topics, such as visuoconstruction as a cognitive domain, and describe the process of neuropsychological assessment of visuoconstructional impairment. Then we will proceed to the outline of the procedures, materials and statistical analyses used. Results will be presented next, and they will be examined in the context of current literature, in the Discussion section. Finally, we will analyze the achievements and limitations of the present work, as well as propose future directions.

I – Background

Visuoconstruction

Visuoconstruction is a neuropsychological domain that can be defined as the ability to organize and manually manipulate spatial information in order to create a design or copy a model (Ruffolo, 2004). This process of copying/creating implies the transformation of mental representations into motor commands, which is achievable due to a complex interaction between different cognitive processes, such as visuoperception, visuospatial analysis, fine motor skills, attention and executive functions (including planning and organization skills, mental flexibility and working memory; Ávila et al., 2015; Benton & Tranel, 1993; Ruffolo, 2004). Furthermore, language-related abilities also exert an influence in the performance in visuoconstructional tasks (Ahmed et al., 2016; Ruffolo, 2004).

Drawing versus assembling tasks

The neuropsychological assessment of visuoconstruction relies on a wide variety of tasks that ultimately can be split into two major classes of activities – graphomotor/drawing tasks and assembling/building tasks. These

activities cannot be considered equivalent. They may vary in terms of their complexity level, as well as in the cognitive functions that they require (Angelini, Frasca, & Grossi, 1992; Fischer & Loring, 2004; Ruffolo, 2004). Furthermore, studies have shown that the inability to perform graphomotor tasks does not imply failure in three-dimensional constructional tasks and vice-versa (Dee, 1970; Kashiwagi et al., 1994), and therefore both should be included in neuropsychological assessment, in order to distinguish which deficits may be contributing to construction disability (Fischer & Loring, 2004).

Assembling and building tasks usually require the individual to put together sticks, puzzles or blocks (Ruffolo, 2004). These type of activities pose a greater load in the spatial component of perception, both at a motor execution and conceptual level. They also assess the ability to copy and reason about different movements and tactics and the ability to perform reversals in space (Fischer & Loring, 2004). These construction tasks can either be two- [e.g., *Block Design* and *Object Assembly* (Wechsler, 1955, 1981, 1997)] or three-dimensional [e.g., *Test of Three-Dimensional Block Construction* (Benton, Sivan, Hamsher, & Spreen, 1994)]. According to the evidence that some patients can set up two- or three-dimensional constructions but not both, these tasks seem to mobilize a different set of functions/capacities (Benton & Fogel, 1962; Fischer & Loring, 2004).

On the other hand, drawing tasks are rich sources of information since they are sensitive to various types of deficits, including perceptual, cognitive and motor impairments (Fischer & Loring, 2004). The ability to draw develops from simple closed geometric shapes to open geometric shapes, segmented human figures and finally complete human figures (Barret & Eames, 1996). This increasingly complex development sequence should be considered in the analysis of drawing skills of patients that may be able to produce simple geometric drawings but not complex geometric figures or common objects (Trojano & Grossi, 1998). In addition, it is crucial to assess the integrity of the visual and motor systems when evaluating drawing skills (Beaumont & Davidoff, 1992). Drawing performance is greatly influenced by the type of task, the complexity of the stimuli and individual abilities, which are dependent on age, educational level and cultural background (Rosseli & Ardila, 2003).

Copy versus free drawing

Drawing activities represent a very important part of a complete neuropsychological assessment. They include two types of tasks – copying and free drawing/drawing-to-command. Copying tasks provide the subject with a stimulus and require him to produce the most accurate copy possible; in drawing-to-command tasks the individual is instructed to draw a common item “from memory” (e.g. house, bicycle, clock) without the providence of any model (Ruffolo, 2004).

Copying and drawing-to-command pose different loads on different cognitive abilities. Copying performances depend greatly on visual perception and visuospatial capacities (Farah & Feinberg, 1997). Also

copying tasks may require preserved executive functions, such as planning and organizational skills, depending on their level of complexity (Freeman et al., 2000; Libon, Malamut, Swenson, Sands, & Cloud, 1996). Alternatively, drawing-to-command places the perceptual component of the task in mental imagery (Fischer & Loring, 2004). Since this type of task does not include a model, the individual is obligated to call upon a mental representation, in order to draw the requested design. This process depends on the subject's memory of the design features and his internal representation of space (Ruffolo, 2004). Thus, free drawing assesses the capacity of the individual to organize a figure as a whole with its components and provides information regarding his ability to draw complete shapes and his tendency to omit parts (Trojano & Conson, 2008; Trojano & Gainotti, 2016). Executive functioning is also crucial to the performance of free drawings. Planning and organization errors, as well as perseveration and stimulus-bound (tendency to hook on what is more perceptually evident) errors, may be more apparent and occur more frequently in the absence of a guide (Freedman et al., 1994; Royall, Cordes, & Polk, 1998; Shallice, 1982). Furthermore, drawing-to-command poses an additional load on other non-constructional cognitive abilities, such as language (since it requires the subject to comprehend the request/instructions), lexical-semantic knowledge, pictorial representations and memory (Freedman et al., 1994; Grossman, 1988; Libon et al., 1996; Price et al., 2011; Rouleau, Salmon, Butters, Kennedy, & McGuire, 1992). Hence, similarly to graphomotor and building/assembling tasks, copying and free drawing tasks cannot be considered equivalent either, despite them sharing some common features. A discrepancy between these two types of tasks became very evident with studies reporting patients that are able to produce accurate copies despite their impairment in free drawing skills (Libon et al., 1996; Rouleau et al., 1992; Rouleau, Salmon, & Butters, 1996). In addition, copying and drawing-to-command are not equally affected by ageing. While copying skills remain relatively preserved over time (especially if the given model represents a simple and/or familiar stimulus) drawing-to-command skills tend to decline, with outcomes being poorly organized and exhibiting a greater loss of details (Ska, Désilets, & Nespoulous, 1986). Regarding hemineglect, a visual inattention phenomenon characterized by the unawareness of percepts in the vision hemifield (usually left) contralateral to the brain lesion, both copying and free drawing manage to elicit it (Lezak, Howienson, Loring, Hannay, & Fischer, 2004). However, because these two types of tasks place different demands in visuospatial and attentional capacities, drawing-to-command tasks may elicit evidence of inattention more readily than copying (Frederiks, 1963), even though copying conditions may produce more spatial disorganized outcomes (Freedman et al., 1994).

As a final comment, regardless of the type of task, visuoconstruction tasks should be differentiated in terms of their complexity level. The more complex a constructional task is, the more cognitive functions it mobilizes and the more it demands from them. This leads to a greater difficulty in identifying specific deficits (Ruffolo, 2004). Thus, given the multifactorial

nature of visuoconstruction and the complexity underlying constructional performance, numerical scores are insufficient to characterize thoroughly visuoconstructional abilities. In order to differentiate between the several factors that may be contributing to an impairment (such as perceptual or visuospatial deficits, attentional impairment, motor problems or insufficient effort), it is crucial to conduct a careful observation and analysis of the performing method of the subject and the type of errors that he makes (Fischer & Loring, 2004).

Visuoconstructional Tasks

Assembling and building

As mentioned before, assembling and building tests can either be two- or three-dimensional. The *Block Design* and the *Object Assembly* tests are two Wechsler's construction tests that assess two-dimensional visuoconstruction. On *Block Design* (Wechsler, 1955, 1981, 1997), the subject receives several red and white blocks that have two completely red and two completely white faces, as well as two half-red half-white faces, whose colours are divided by a diagonal. Depending on the complexity of the item, 2, 4 or 9 blocks are provided. The subject task is to construct accurate replicas of various increasingly complex designs that are made by the examiner or printed on a smaller scale (comparatively to the blocks). Each item must be completed within a time limit. Only accurate replicas receive credit (partially correct and incorrect responses are not scored) (Wechsler, 2008). In turn, on *Object Assembly* (Wechsler, 1955, 1981, 1997) the subject is required to assemble 5 different puzzles (Man, Profile, Elephant, House and Butterfly) that represent familiar/common figures/objects, which are provided once at a time, in order of increasing difficulty. Each assembly must be completed within a time limit. Scoring takes into account both accuracy and speed, and partially complete responses are scored as well (Wechsler, 2008).

When compared to one another as well as to other tests, *Block Design* and *Object Assembly* scores may provide valuable information about the status of the different cognitive functions that play a role on the performance of these tasks. Impaired visual manipulation can be determined when an individual performs better at visuoperceptual organization tasks than in construction tests. In turn, an impaired ability for visual conceptualization unables a subject to visualize what the puzzles of the *Object Assembly* test should be and leads him to failure in *Block Design* items. Furthermore, this disability causes difficulties in the execution of purely perceptual tasks. When the ability for visuospatial conceptualization is dependent on visuomotor activity, subjects tend to perform *Object Assembly* and *Block Design*-type tasks by trial and error manipulations. Despite not being able to form visuospatial concepts before seeing the object, they can identify correct relationships that allow them to progressively develop visual concepts and hence gradually execute the task since their perception and self-correcting skills are sufficiently preserved. However, this benefit does not improve

performances in purely perceptual tasks because there is no possible manipulation. Subjects who have a disability to appreciate details perform poorly in both *Object Assembly* and *Block Design* since they rely only on overall contour. In turn, structure dependency leads individuals to perform poorly on *Object Assembly* but not on *Block Design*, since they are not able to conceptualize the construction on their own (they need a "model" to be able to perform the task). Contrastingly, concrete-mindedness leads subjects to perform better on *Object Assembly* (and poorly on *Block Design*) because it uses concrete and meaningful objects. People with concrete-mindedness have difficulties understanding abstract designs (Fischer & Loring, 2004).

Regarding three-dimensional visuoconstruction, one good example is the *Test of Three-Dimensional Block Construction* (Benton et al., 1994). This test requires the subject to produce a structure that is equal to a given model. It includes 6 block constructions, distributed by three levels of complexity – 6-block pyramid; 8-block four level construction with blocks of various sizes; 15-block four level construction with blocks of various sizes - with two equivalent forms each. Omissions, additions, substitutions and displacements are considered errors. Given the greater difficulty of this test compared to the *Block Design*, the *Test of Three-Dimensional Block Construction* may be better in detecting subtler visuoconstructive deficits (Fischer & Loring, 2004).

Drawing

In addition to the assembling/building tests, visuoconstruction can be also assessed by copying and drawing-to-command tasks. In terms of copying tests, the *Rey-Osterrieth Complex Figure test* (ROCF; Osterrieth, 1944; Rey, 1941) is one of the most widely used instruments (Knight & Kaplan, 2003). This test requires the subject to copy a complex bidimensional figure (it also has a recall trial) that is placed horizontally and cannot be rotated. The copying sequence of the subject is registered and the drawing is scored according to the selected scoring system, most commonly the Rey-Osterreith/Taylor/MCG unit scoring method (Fischer & Loring, 2004). The ROCF is a useful tool to assess various cognitive skills, namely perceptual and visuospatial abilities, executive functioning, as well as motor and visuoconstructional functions (Somerville, Tremont, & Stern, 2000).

Regarding drawing-to-command tasks, the *Clock Drawing Test* (CDT; Battersby, Bender, Pollack, & Kahn, 1956) is one of the most widely used screening tools for dementia (Kim & Chey, 2010), being particularly sensitive to AD and dementia with Lewy bodys (Duro et al., 2018). Despite being originally used to detect visuospatial hemi-inattention (Battersby et al., 1956), the CDT has been pointed as a complex task, not only sensitive to visuospatial and visuoconstructional dysfunctions, but also to executive functioning, working memory, numerical knowledge and receptive language disabilities (Freedman et al., 1994; Strauss, Sherman, & Spreen, 2006), having the potential to discriminate between MCI and dementia (Ehreke et al., 2011; Rubínová et al., 2014). On the CDT drawing-to-command condition, the subject has the task of drawing from memory the face of a

clock, its numbers and the two hands, which should be set to 10 past 11. Because this instrument is one of the most widely studied neuropsychological tests, several scoring systems have been developed. Nevertheless, although different scoring systems emphazise visuospatial and executive functions differently, evidence show that they have a remarkably similar predictive validity for dementia screening (Mainland, Amodeo, & Shulman, 2013).

The *House Drawing* is another useful drawing-to-command test that requires the subject to draw the best house possible (Fischer & Loring, 2004). According to the scoring system of Ska and colleagues (1986) drawings can be scored with 0-12 points, with each present feature receiving 1 point (e.g., one side, second side, roof, window, door, appropriate proportions, etc.). For a good performance on this test, the individual needs to work from structure to detail and to correctly handle perspective (Fischer & Loring, 2004).

Visuoconstructional Impairment

Studies have shown that impairment in visuoconstructional abilities influences the performance in various activities of daily living (Saari, Hallikainen, Hänninen, Räty, & Koivisto, 2018). Individuals with visuocontructive deficits often struggle to execute activities that are dependent on visuospatial perception and spatial/constructive skills, such as dressing, filling in forms and documents, estimating and separating amounts, grabbing objects, etcetera (Cramon & Zihl, 1988; Kerkhoff & Marquardt, 1995). In addition, impaired constructional performance seems to predict limitations in driving (Gallo, Rebok, & Lesikar, 1999; Johansson et al., 1996; Marottoli, Cooney, Wagner, Doucette, & Tinetti, 1994) and influence meal planning (Neistadt, 1993).

Focal Lesions

Since the two cerebral hemispheres differ in terms of information processing capacities and functions, many studies aimed to identify qualitative differences in visuoconstruction among patients with unilateral lesions (Fischer & Loring, 2004; Scott & Schoenberg, 2011). Generally, the right hemisphere is associated with the analysis of the overall gestalt, while the left hemisphere is associated with the appreciation of details of the visual percept (Scott & Schoenberg, 2011). Patients with right lesions tend to perform constructional tasks through disjointed and fragmented approaches that usually yell loss of the whole gestalt (Fischer & Loring, 2004). These approaches lead to drawings with a poor spatial arrangement of numerous details, characterized by sparse and imprecise graphics or highly elaborated but scattered figures that may lack important features and/or present coarse distortions (in proportions or perspective; Fischer & Loring, 2004; Scott & Schoenberg, 2011). In the scope of copying global-local stimuli (i.e., large-scale stimuli that are composed by many smaller stimuli of a different shape, such as a large “A” made by little “Ms”), right-sided lesions lead patients to reproduce only the lower-level stimuli, without processing the higher-level

form (Delis, Kiefner, & Fridlund, 1988). Regarding visual inattention (hemineglect), patients with right hemisphere dysfunction may not attend to their left hemifield, and so they may completely omit or incompletely reproduce constructional features (either lines, puzzle pieces or blocks) that are placed in the left side of the visual field (Colombo, De Renzi, & Faglioni, 1976; Fischer & Loring, 2004; Scott & Schoenberg, 2011). Finally in assembling/building tasks, even though these patients may correctly form various angles and spatial arrangements, they do not perceive the overall gestalt of the construction (Scott & Schoenberg, 2011).

On the other hand, patients with left dysfunction usually have an impaired ability to form detailed percepts, despite being able to correctly perceive the proportions and the overall appearance of a drawing/construction (Fischer & Loring, 2004). Thus, they tend to omit details and to produce overly simplistic and poorly organized drawings (Fischer & Loring, 2004; Scott & Schoenberg, 2011). Contrary to patients with right lesions, these patients perform better in copying tasks than in drawing-to-command tasks (Hécaen & Assal, 1970). In global-local tasks, patients with left dysfunction tend to focus only on the higher-level stimulus (i.e., the larger shape), ignoring the lower-level stimuli that make it up (Delis et al., 1988). Additionally, hemineglect phenomenon may also occur with left parietal lobe damage, although less frequently comparing to right damage (Colombo et al., 1976; Scott & Schoenberg, 2011). In assembling/building tasks, these patients are able to maintain the overall organization of the construction but they often rotate details (Scott & Schoenberg, 2011).

In addition to the focus of the lesion in terms of right and left cerebral hemispheres, the site of the damage in the anterior-posterior axis also influences the expression of visuoconstructional deficits. Patients with right-posterior lesions are more likely to display constructional impairments than patients who have right-anterior lesions (Black & Bernard, 1984). Furthermore, lesions in the right posterior hemisphere are more commonly associated with visual inattention (hemineglect) than the ones located in the right anterior hemisphere (Heilman, Watson, & Valenstein, 2003). Regarding the cortical-subcortical axis, evidence show that different lesions do not translate into different patterns of errors. Although subcortical lesions that affect drawing skills lead to more widespread cognitive deficits, these do not translate into more severe visuoconstructive deficits when compared to similar sized cortical lesions (Kirk & Kertesz, 1993).

Neurodegenerative Disorders: Mild Cognitive Impairment and Alzheimer's Disease

The inability to accurately copy, draw or assemble is often observed in neurodegenerative disorders despite the preservation of motor and perceptual skills (Cormack, Aarsland, Ballard, & Tovée, 2004; Trojano, Grossi, & Flash, 2009). Specifically, visuoconstructional deficits in Alzheimer's disease (AD) have been widely studied through drawing tasks. Morphometric and neurofunctional investigations have been proving a

heterogeneous basis of drawing impairment in AD, for which different cognitive mechanisms contribute (Trojano & Gainotti, 2016). Regarding morphometric evidence, a study conducted with AD and MCI patients, as well as with healthy subjects, identified an association between impaired performances on CDT and reduced grey matter density through different brain regions, namely the middle and superior temporal gyri (BA 21 and 22) bilaterally, and left entorhinal area (BA 28; Thomann, Toro, Dos Santos, Essig, & Schröder, 2008). Similarly, Serra and colleagues (2014) also found an association between drawing impairment and the distribution of the grey matter atrophy. In their study, AD patients with drawing disabilities exhibited a loss of grey matter in lateral occipital cortex bilaterally, in the posterior cingulate cortex (BA 23/31) and precuneus (BA 7) and in the right cerebellum, comparing to healthy subjects. In addition, when compared with DA patients without drawing disabilities, these patients showed a significant reduction of grey matter in cerebral regions such as angular gyrus (BA 39), precuneus (BA 7), posterior cingulate cortex bilaterally (BA 23/31), occipital cortex (BA 18) and right fusiform (BA 37) and middle temporal gyrus (BA 21). On the other hand, a study with amnestic MCI and AD patients found significant correlations between impaired performances in the copying condition of the ROCF and cortical atrophy in various right fronto-temporo-paritetal regions, such as the superior temporal gyrus, the middle frontal gyrus, the superior parietal lobule, the occipital part of the fusiform area, the lingual gyrus, and the mid-body and posterior parts of the cingulate gyrus (Ahn et al., 2011).

In terms of brain activity, a study conducted by Matsuoka and colleagues (2013) aimed to identify the neural correlate of the different components of CDT, namely clock face, numbers and hands. They found that while total CDT scores correlated positively with activity in the bilateral parietal and posterior temporal lobes, as well as in the right middle frontal gyrus, partial scores on placing numbers correlated positively with activity in the right posterior temporal lobe and in the left posterior middle temporal lobe. In turn, scores for the placement of hands correlated positively with activity in bilateral parietal lobes, the right posterior temporal lobe, the right middle frontal gyrus, and the right occipital lobe. Similarly, Nakashima and colleagues (2016) assessed the relationship between different error types on CDT and regional cerebral blood flow in a sample of AD patients and pointed various associations between different CDT error types and different brain regions. They discovered significant correlations between reduced blood flow in the right parietal lobe (right inferior parietal lobule, BA 40) and the error "missing numbers", right parietal and temporal lobes (right inferior and superior parietal lobules, BA 40 and BA 7; right superior temporal gyrus, BA 39) and "uneven number distance from edge", bilateral temporal lobe (left superior temporal gyrus, BA 42; right transverse temporal gyrus, BA 41) and "same length hands", left temporal lobe (left superior temporal gyrus, BA 13) and "unclosed circle", bilateral frontal lobe (right and left middle frontal gyrus, BA 10) and "uneven number spacing", and left frontal lobe (left middle frontal gyrus, BA 9) and "absence of or not

pointing towards number 2" and "deviation of the clock center". A study comparing cerebral activity during copying and drawing-to-command CDT conditions in a population of AD patients (Shon et al., 2013) showed that both performances correlated positively with bilateral temporo-parietal regions activations. However, these relations changed with the increase of the severity of the disease, going from left temporal to right temporo-parietal activity in the drawing-to-command conditions, and from no correlation to correlation with diffuse right fronto-temporo-parietal regions in the copying condition. Together, these evidence show why AD can lead to impaired drawing skills even in its early stages, considering the involvement of several brain areas in the disease.

Free drawing abilities appear to be impaired in the early stages of AD, probably due to the heavy demand that they pose on semantic memory, whereas copying skills remain relatively preserved for longer (Rouleau et al., 1996). Errors such as simplifications, impaired perspective and spatial alteration are the most common among the drawings of AD patients (Bonoti, Tzouvaleka, Bonotis, & Vlachos, 2015; Kirk & Kertesz, 1991). Nevertheless, the detection of early copying disabilities may be achievable through more complex stimuli (Binetti et al., 1998). For instance, copy accuracy of the ROCF can discriminate DA from MCI patients, and MCI patients from healthy subjects (Ahn et al., 2011). Similarly, in the Beery Developmental Test of Visual-Motor Integration (VMI; Beery, 1989), which requires an individual to copy a series of 24 increasingly complex figures, AD patients tend to make more constructive errors than MCI patients, who in turn make more errors than healthy subjects (Malloy, Belanger, Hall, Aloia, & Salloway, 2003). However, in this task, qualitative errors such as stimulus-bound, perseveration and intrusion errors are only distinguishable between AD and MCI/Controls groups, and not between MCI patients and healthy subjects (Malloy et al., 2003).

Therefore, drawing-to-command tasks may be more sensitive to cognitive decline and conceptual deficits in AD (Rouleau et al., 1996). In a CDT drawing-to-command condition study, Allone and colleagues (2018) observed significant differences between AD and amnestic MCI patients regarding clock face integrity, sequencing of numbers, presence and placement of hands, clock size and graphic difficulties, which were all worse for AD than for MCI patients. In addition, qualitative errors such as misrepresentation of the clock face, stimulus-bound, misrepresentation of the time and perseveration were also more frequent in the AD group. Parsey and Schmitter-Edgecombe (2011) reported similar results. Accordingly, longitudinal studies with the CDT reported an increase of conceptual errors with the progression of AD (Lee et al., 2011; Rouleau et al., 1996). Over time, the error type frequency seems to be spatial/planning deficits, conceptual errors, stimulus-bound errors and perseveration, with conceptual deficits becoming the most frequent type of error 18 months after the baseline (Lee et al., 2011). Conceptual errors appear to be present since the early stages of the AD and revealed to be very sensitive to cognitive decline in this disease (Amodeo, Mainland, Herrmann, & Shulman, 2015).

There are various evidence supporting the predictive value of the CDT for dementia (Amodeo et al., 2015; López et al., 2016). The CDT appears to be an instrument that is sensitive to cognitive decline over time and that can differentiate, at baseline, cognitively preserved subjects (Chen et al., 2000; Ehreke, Luppa, König, Villringer, & Riedel-Heller, 2011) and MCI patients (Lee et al., 2014; López et al., 2016) that may convert to dementia in the future. Regarding the predictive value of other free drawing tasks, a study conducted by Maserati and colleagues (2018) showed that in drawing human figures, the productions of MCI patients are intermediate in body height (an independent predictor of cognitive impairment) between the drawings of AD patients and the drawings of healthy controls.

AD patients may present different clinical features according to their age at onset of the disease. Althoug both early- and late-onset patients present deficits in memory, executive functions, language, visuoconstruction and praxis, late-onset patients tend to perform more poorly in semantic memory tasks than early-onset patients, while the latter exhibit more deficits in executive functions and visuoconstructional abilities (Joubert et al., 2016). Therefore, there has been some interest in studying drawing disorders in these two types of AD patients. Investigations have been pointing a higher frequency of visuoconstructive deficits assessed with ROCF in early-onset patients comparing to late-onset patients (Fujimori et al., 1998; Joubert et al., 2016; Koedam et al., 2010; Serra et al., 2014), which appear to be associated with visuospatial impairment (Fujimori et al., 1998; Koedam et al., 2010; Serra et al., 2014).

Finally, when studying drawing disorders in neurodegenerative diseases, it is crucial to take into consideration the etiological heterogeneity of MCI, since it represents a great source of variability (Petersen et al., 2014; Trojano & Gainotti, 2016). In this line, a study conducted by Ahmed and colleagues (2016) aiming to assess CDT performances in three different types of MCI (amnestic, dysexecutive and multidomain) revealed that dysexecutive and multidomain MCI patients, but not amnestic MCI patients, committed significantly more errors than healthy subjects.

II - Objectives

Visuoconstruction has been widely studied in AD through drawing tasks. However, we found few studies comparing visuoconstructional deficits between different subtypes of MCI, and even less that evaluated existing differences through copying tasks other than the copying condition of the CDT. Additionally, to our knowledge, the study of the value of visuoconstructional measures in predicting future dementia has been mainly focused on drawing-to-command tasks. Given the heterogeneous basis of drawing, a predictive study investigating both drawing-to-command and copy tasks is necessary.

Hereupon, the present work has two main aims. Firstly, we intend to evaluate the visuoconstructional impairment in MCI and to assess possible differences between amnestic single-domain (aMCI) and amnestic multidomain (amMCI) forms of MCI. This will provide a better

understanding of visuoconstruction in MCI and how it can be helpful in the diagnostic process. Given the features of each condition, we expect amMCI patients to present worse visuoconstructional abilities than aMCI patients. Secondly, we aim to assess the value of different visuoconstructional measures (copying and drawing-to-command tasks) in predicting the progression from MCI to dementia due to AD. We expect both types of tasks to have explanatory value of the conversion.

III - Methodology

Population

Our sample was collected at the Neurology Department of the Centro Hospitalar e Universitário de Coimbra. This sample included 184 patients followed at the Dementia Consultation. In this consultation all patients underwent a series of examinations composed by: (1) medical exam performed by a neurologist; (2) complementary diagnostic exams such as the genetic study for detection of the e4 variant of Apolipoprotein E gene and imaging exams [such as functional and structural magnetic resonance (MRI) and Single-Photon Emission Computed Tomography (SPECT)]; (3) biomedical analysis to exclude infeccious or treatable forms of dementia; (4) biomarkers study through the Amyloid Positron Emission Tomography, with the use of the ^{11}C-Pittsburg compound B (^{11}C-PiB-PET) and analysis of the cerebrospinal fluid (CSF; through Lumbar Puncture); and (5) comprehensive neuropsychological assessment through the application of the Lisbon Battery for Dementia Assessment (*Bateria de Lisboa para a Avaliação das Demências* – BLAD; Guerreiro, 1998).

The final diagnosis of "MCI due to AD" counted on the input of a multidisciplinary team and was performed by a neurologist considering all the data from the abovementioned examinations. This process followed the international criteria of the National Institute on Aging-Alzheimer's association (NIA-AA) workgroups (Albert et al., 2011). Only patients diagnosed with aMCI and amMCI were included in our study, given the association between this sub-types of MCI and the conversion to AD (Petersen, 2004). Furthermore, only patients with a minimum of 2 years of follow-up post-diagnosis were included. Illiteracy was considered an exclusion criterion for the selection of the patients due to the lack of normative data for this segment of the population in several instruments (as described below).

Procedures

For diagnosis purposes, patients performed two brief global cognitive assessment tests – the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; Guerreiro et al., 1994) and the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; Simões et al., 2008) - as well as the BLAD (Guerreiro, 1998), for neuropsychological characterization. Performances on these tests were considered the baseline capacities of the patients, for analysis purposes.

Post-diagnosis, all participants underwent a comprehensive evaluation once per year. The aim of these annual evaluations performed in the consultation background was to determine the progression of the disease and the effects of the therapeutics applied. The assessment battery used included the cognitive, functional and psychopathological status of the patients considering both self-reports and reports from a reliable informant. The protocol was composed by the following tests: (1) MMSE (Folstein et al., 1975; Guerreiro et al., 1994), MoCA (Nasreddine et al., 2005; Simões et al., 2008) and Alzheimer 's Disease Assessment Scale – Cognitive subscale (ADAS-Cog; Mohs, Rosen, & Davis, 1983; Rosen, Mohs, & Davis, 1984; Guerreiro, Fonseca, Barreto, & Garcia, 2008), to assess cognitive status; (2) Clinical Dementia Rating Scale (CDR; Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993; Garrett et al., 2008) for disease staging/severity; (3) Subjective Memory Complaints Scale (SMC; Schmand, Jonker, Hooijer, & Lindeboom, 1996; Ginó, Guerreiro, & Garcia, 2008) for cognitive complaints of the patient and the informant/caregiver; (4) Blessed Dementia Scale (BLESSED; Blessed, Tomlinson, & Roth, 1968; Garcia, 2008) and Disability Assessment for Dementia Scale (DAD; Gélinas, Gauthier, McIntyre, & Gauthier, 1999; Leitão & Santana, 2008) for functional status; (5) Geriatric Depression Scale – 30 (GDS-30; Yesavage et al., 1983; Barreto, Leuschner, Santos, & Sobral, 2008; Simões & Firmino, 2013), the Hamilton Anxiety Scale (HAMILTON; Hamilton, 1959) and the Neuropsychiatric Inventory (NPI; Cummings et al., 1994; Leitão & Nina, 2008) to assess psychopathology.

The application of the protocol was discontinued upon conversion of the patients. Thus, the first assessment considered in longitudinal analyses corresponded to the first protocol applied after the diagnosis establishment, while the last assessment was operationalized as the assessment at the time of the conversion (for patients who progressed from MCI to AD) or the most recent one (for patients who remained stable or whose decline still did not meet the criteria for dementia). According to the disease evolution outcome, patients were divided into two groups: conversion (C=72) and non-conversion (NC=112).

Materials

In this section, we will describe the measures used to assess visuoconstruction abilities, as well as their respective scoring systems. These measures were integrated into more global tests that will be briefly described as well.

Mini-Mental State Examination (MMSE) – The Pentagon Drawing Test

The MMSE (Folstein et al., 1975; Guerreiro et al., 1994) is a screening tool widely used in the assessment of cognitive impairment (Freitas, Simões, Alves, & Santana, 2015a). It is composed of 30 dichotomous items (0 – incorrect; 1- correct) that translate into a 30-point scale. This tool evaluates 5 cognitive domains: Orientation (5 points for temporal and 5 points for special orientation), Memory (3 points for

retention and 3 points for delayed recall), Attention and Calculus (5 points), Language (2 points for naming, 1 point for sentence repetition, 3 points for oral comprehension, 1 point for written order comprehension, 1 point for written expression), and Visuoconstruction (1 point; Freitas, Simões, Alves, & Santana, 2015b). Visuoconstructive abilities are assessed through the Pentagon Drawing Test (PDT).

The PDT is a copying task that requires the patient to accurately reproduce two intersecting pentagons, whose intersection area forms a rhombus (Fountoulakis et al., 2011). In the MMSE, drawings with two overlapping 5-sided figures whose common area forms a rhombus are scored with 1 point. Any other drawing receives 0 points. Given the simplicity of this scoring system, others systems have been developed. In the present study, we also included the scoring system of Bourke, Castleden, Stephen and Dennis (1995). This system consists of a 6-point scale that was developed based on possible errors (Table 1), and that is able to discriminate AD patients from healthy controls when the binary score of MMSE cannot (Martinelli, Cecato, Martinelli, Melo, & Aprahamian, 2018).

Table 1. Six-point scoring system of Bourke and colleagues (1995)

Score	Drawing Description	Equivalent score of MMSE
6	Correctly copied	1
5	Two intersecting figures, with only one being a pentagon or additional lines intersecting two pentagons	0
4	Two intersecting figures were neither are pentagons	0
3	Two not intersecting figures (they can be adjoining)	0
2	One closed figure	0
1	Drawn lines that do not form a closed figure, closing-in occurance or no attempt	0

Note. Adapted from "A comparison of clock and pentagon drawing in Alzheimer's disease", by J. Bourke, C. M. Castleden, R. Stephen, & M. Dennis, 1995, *International Journal of Geriatric Psychiatry*, *10*(8), pp. 703-705. Copyright 1995 by John Wiley & Sons, Ltd.; and from "Performance of the Pentagon Drawing test for the screening of older adults with Alzheimer's dementia", by J. E. Martinelli, J. F. Cecato, M. O. Martinelli, B. A. R. de Melo, & I. Aprahamian, 2018, *Dementia & Neuropsychologia*, *12*(1), pp. 54-60.

Montreal Cognitive Assessment (MoCA) – The Cube-Copying Test & The Clock Drawing Test

The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; Simões et al., 2008) is a brief cognitive screening tool that was specifically developed to detect milder forms of cognitive decline, namely MCI (Freitas, Simões, Alves, & Santana, 2011). This tool assesses 6 different cognitive domains – Executive Functions (4 points), Visuospatial Abilities (4 points), (short-term) Memory (5 points), Language (5 points), Attention,

Concentration and Working Memory (6 points) and (spatial and temporal) Orientation (6 points) - and whose global score may vary from 0 to 30 points (Freitas, Simões, Alves, & Santana, 2015c). In this test, visuospatial/visuoconstructive abilities are assessed through a copying task – the Cube-Copying Test (CCT) – and a drawing-to-command task – the Clock Drawing Test (CDT).

The CCT requires the patient to accurately copy a Necker cube. According to the scoring system of the MoCA, a drawing must exhibit three-dimensionality, the same perspective and all the edges to be considered correct (and scored with 1 point). If the drawing does not respect these criteria it will be scored with 0 points (Simões et al., 2008). This test is usually used to detect visuoconstructive deficits as well as visuospatial perception and motor programming abnormalities (Hirabayashi, Sakatsume, & Hirabayashi, 1992).

On the other hand, the CDT (Battersby et al., 1956; Santana, Duro, Freitas, Alves, & Simões, 2013) is often used as a screening tool for dementia and assesses visuoconstructive, visuospatial and executive dysfunction (Santana, Duro, Freitas, Alves, & Simões, 2015). In the present study, we applied the drawing-to-command condition of this test, which requires the patient to draw a round clock from memory, with all the numbers, and to set the time for 11 hours and 10 minutes. Two scoring systems were used to analyze the clock drawings - the scoring system of Cahn and colleagues (1996) and the 18-point scoring system of Babins, Slater, Whitehead and Chertkow (2008). The scoring system of Cahn and colleagues (1996) is a composite of a quantitative and a qualitative score, respectively based on the 10-point scoring system of Rouleau and colleagues (1992) and on the analysis of error types. Briefly, the quantitative score, as developed by Rouleau and colleagues (1992), corresponds to the sum of the scores of three separate features – the clock face (0-2 points), the placement of the numbers (0-4 points) and the placement of the hands (0-4 points).The qualitative score is based on the absence/presence (0/1 point) of stimulus-bound responses, conceptual errors, perseveration signs and spatial arrangement errors (such as neglect of left hemisphere, planning deficits, non-specific spatial errors, numbers written on the outside of the clock and numbers written counterclockwise). The total CDT score corresponds to the subtraction of the qualitative score (0-8 points) from the quantitative score (0-10 points). On the other hand, the scoring system of Babins and colleagues (2008) can be divided into five major categories that comprise different errors. They are: (1) integrity of the clock face (0-2 points), which assesses drawing abilities; (2) placement of the center (0-2points), which evaluates spatial capacities, (3) numbering (0-6 points), which assesses visuospatial and drawing abilities, planning skills and number generation capacity; (4) placement and size of the hands (0-6 points), which assesses executive skills and language comprehension, and encloses aspects regarding the exhibited time and the construction of the hands; and (5) overall clock Gestalt (0-2 points), that evaluates more gross planning abilities. This 18-point system is able to detect stimulus-bound errors (e.g.

hands misplaced for 10 minutes to 11), conceptual deficits (e.g. absence of the numbers, absence of the hands – misrepresentation of the clock), visuospatial dysfunction (e.g. missing numbers, numbers outside the clock face), planning deficits (e.g. hemineglect, poor spacing of the numbers, additional marks) and perseveration errors (e.g., number repetitions, use of more than 2 hands). Our choice of analyzing the CDT drawings according to these two scoring systems was based on their psychometric differences. While the system of Cahn and colleagues (1996) is very useful in detecting dementia of the Alzheimer's type, the system of Babins and colleagues (2008) was developed with the aim of enhancing the CDT utility in the detection and prognostication of MCI. Also, both scoring systems have normative data for the Portuguese population (Santana et al., 2013).

Alzheimer's Disease Assessment Scale (ADAS-Cog) – Constructional Praxis (Geometric Figures Copying Test)

The ADAS-Cog (Mohs et al., 1983; Rosen et al., 1984; Guerreiro et al., 2008) is a brief battery developed to assess the cognitive performance of AD patients. It is composed by 7 performance tasks (word recall, naming, commands, constructional praxis, ideational praxis, orientation and word recognition) and 4 clinical scales (remembering test instructions, spoken language ability, word finding difficulty and comprehension of oral language), whose scores are based on the number of committed errors. This instrument assesses the core characteristics of the cognitive decline in AD in terms of memory, language, praxis, constructive skills and orientation. With a score between 0-72, the ADAS-Cog has an inverse socring method with higher scores indicating a greater degree of cognitive impairment.

In this scale, the visuoconstructive abilities are assessed by the Constructional Praxis Task (CPT). Specifically, this task assesses the ability to copy geometric forms, as well as visual planning skills. In CPT, the patient is presented with four images of different geometric figures – a circle, two intersecting rectangles, a rhombus and a cube - that are progressively more complex in terms of their shape. The patient is then asked to copy each figure once at a time, in the most accurate way possible. A drawing is considered correct (and receives 0 points) when the overall shape is reproduced. Differences in size or small gaps are not considered errors. Each incorrect drawing receives the score of 1 point. The CPT total score may range from 0 points, when all the drawings are copied correctly, to 5 points, in cases in which the patient does not draw any forms/write letters (Connor & Schafer, 1998).

Lisbon Battery for Dementia Assessment (BLAD) – Cube, House and Daisy Copying Test

Primarily used to evaluate the cognitive capacities of older adults with suspected cognitive impairment/dementia, the BLAD (Guerreiro, 1998) is a neuropsychological battery that assesses orientation, crystallized intelligence/episodic memory/acquired factual knowledge, attention, working memory, oral language, abstraction and logical reasoning ability,

visuoperceptive and two-dimensional constructive capacities, initiative, calculation, executive functions and praxis (Simões, 2012).

Regarding the assessment of visuoconstruction abilities, we analyzed three copying tasks integrated into this battery – the cube-copying task, the house-copying task and the daisy-copying task. In the cube-copying task (CUBE), the patient is required to draw a cube according to a given model. For each correct edge, 1 point is scored. Since this cube is not "transparent" (so it only has 9 edges), total scores may range from 0 to 9 points. In turn, the house- and daisy-copying tasks are administrated at the same time and require the patient to accurately copy a house and its seal, as well as a flower with eight petals. Hemineglect, planning dysfunction, micro/macrography, loss of elements and deficits in the overall gestalt are detectable in these tasks. In the present study, accurate copies were scored with 1 point, while distorted reproductions received 0 points.

Statstical Analyses

All statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS), Version 22 for Windows. The characterization of sociodemographic and clinical features of the sample was performed through descriptive statistics. The study of visuoconstruction in MCI was accomplished through analysis of frequencies, and differences between aMCI and amMCI patients were analyzed using the Student's *t* test. Similarly, differences between NC and C groups, regarding either sociodemographic and clinical features, as well as differences at baseline, were analyzed using the same methods. Chi-square was used to assess qualitative differences between groups. The estimates and analyses of effect size were based on Cohen's *d* (Cohen, 1988).

To estimate survival curves we applied the Kaplan-Meier method, while log rank test was used two compare the survival curves of two groups. In Kaplan-Meier analysis, the median value corresponds to the time when the event (conversion) occurred in 50% of the sample. To evaluate survival patterns while contemplating more than one factor, we performed a Cox regression. The Cox's proportional hazards model is a class of survival models that relates the time prior to an event occurence to one or more covariates, which effect of a unit increase multiples the hazard rate. In the present study, the hazard corresponds to the risk for conversion at a given moment. In other words, it is the probability of converting given that patients have not converted up to that point in time (Bewick, Cheek, & Ball, 2004). The variable "Time" used on these analyses corresponded to the time since the onset (i.e., beginning of the complaints) until the event occurence.

Generealized Estimating Equations (GEE) were used to analyze longitudinal data (neuropsychological assessments over time). This method performs average estimates of odds ratios for each parameter of the model, meaning that it quantifies the association of each parameter with the occurence of the defined event (outcome) in a population. An odds ratio corresponds to the odds of an outcome (e.g. conversion to dementia) given property A (e.g. failure in PDT), in comparison to the odds of that outcome

in the absence of that property (Szumilas, 2010). Given the nature of our outcome variable (binary), GEE have to accommodate logistic regression. Therefore, regression coefficients indicate the estimated increase in the log odds of the outcome for a unit increase in the parameters. Thus, the exponential function of the regression coefficients corresponds to the odds ratios (Szumilas, 2010). Since in IMB SPSS, GEE only accommodates models with a two-level hierarchy (repeated measures nested in individuals; Heck, Thomas, & Tabata, 2012), we estimated separate models according to our necessity of accounting for higher-level groups. The selection of the best models was based on the analysis of fit statistics (quasi-likelihood) using the "smaller-is-better" criteria.

IV - Results

Sociodemographic and clinical characterization of the sample

The present study included 184 participants. The sample was composed by 121 aMCI patients (65.8%) and 63 amMCI patients (34.2%). For sociodemographic and clinical characterization we considered the following variables: age, gender, education, age of onset of the disease (and if it was prior or post the 65 years-old mark, considered early versus late onset; the onset corresponds to the beginning of the complaints), family history of dementia, being a homozygous/heterozygous carrier of the ApoE4 allele, number of assessments, outcome [conversion, non-conversion and others (drop-out and death)], disease duration since the onset (for participants who did not convert to dementia) and the number of years until conversion (Table 2).

Table 2. Sociodemographic and clinical characteristics of the total sample (*n*=184)

	N	**%**	
Gender (Female)	111	60.3	
Early age of onset (<65)	72	41.4	
Positive family history	84	48.6	
ApoE4 carriers (heterozygous)	76	43.2	
ApoE4 carriers (homozygous)	13	7.4	
Conversion	72	39.1	
Non-conversion	75	40.8	
Other outcomes	37	20.1	
	M	***SD***	**Min - Max**
Age	70.26	8.471	46 – 90
Education	6.90	4.398	1 – 22
Age of onset	66.69	8.832	39 – 88
Number of assessments	3.76	1.768	2 – 11
Time to conversion	6.29	3.304	2 – 20
Disease duration	8.15	4.278	1 – 18

Characterization of visuoconstruction in MCI

In order to characterize the visuoconstructional domain in MCI, we

analyzed all the collected drawings (copying and drawing-to-command) in terms of frequency of errors, as well as the scores of the visuospatial domain of the MoCA. Considering these measures, we compared the scores of aMCI patients with the scores of amMCI patients. Different outcomes were not discriminated.

Drawing errors frequencies

Regarding the copying tasks, the majority of MCI patients were able to accurately perform the PDT. From the 655 tests applied, 444 (68%) of them were scored with 1 point/6 points (depending on the scoring system used) and only 211 (32%) received 0 points, when scored according to the MMSE. According to the scoring system of Bourke, 63% of the 211 failed drawings were scored with 5 points, since they exhibited (1) two intersecting figures with one of them not being a pentagon, or (2) presented two pentagons but with additional intersecting lines (Figure 1).

In CCT, of the 555 tests applied, 208 (37.5%) were scored with 1 point, while 347 (62.5%) were scored with 0 points.

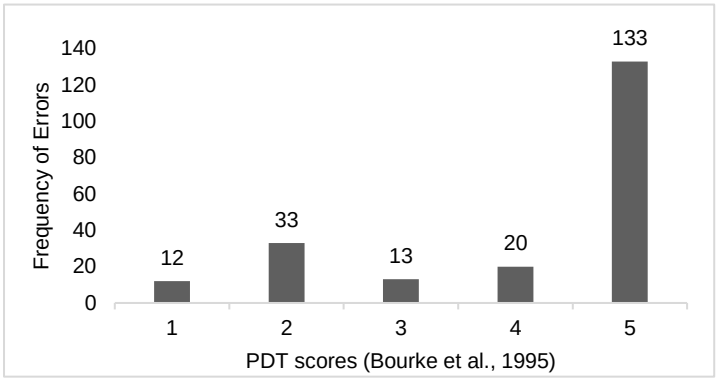

Figure 1. Distribution of frequencies of different error types, according to the scoring system of Bourke and colleagues (1995). PDT=Pentagon Drawing Test.

Accordingly, in terms of the CPT from the ADAS-Cog, 316 of the 658 tasks were scored with 1 point (48%). The geometric figure where MCI patients failed the most was the cube, with 56.4% (371) of the copies being incorrect/inaccurate (Figure 2).

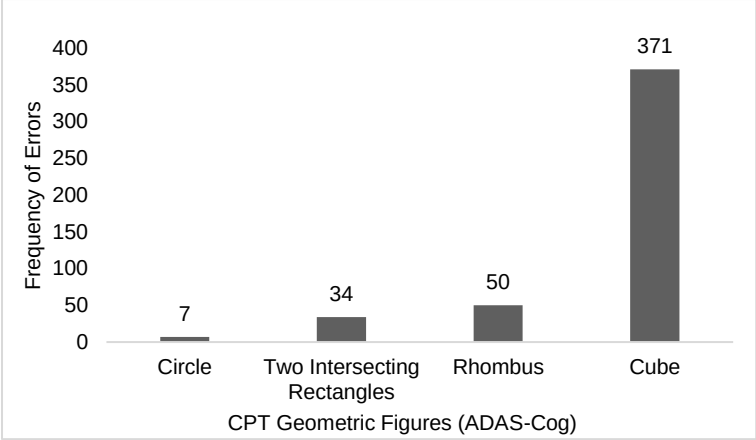

Figure 2. Distribution of frequencies of errors for each geometric figure from the CPT of the ADAS-Cog. CPT=Constructional Praxis Task.

Regarding the drawing-to-command tasks, particularly the CDT, the obtained total scores were very diverse. According to the scoring system of Cahn, the most frequent scores were 10, 9/7, and 8 points (Figure3).

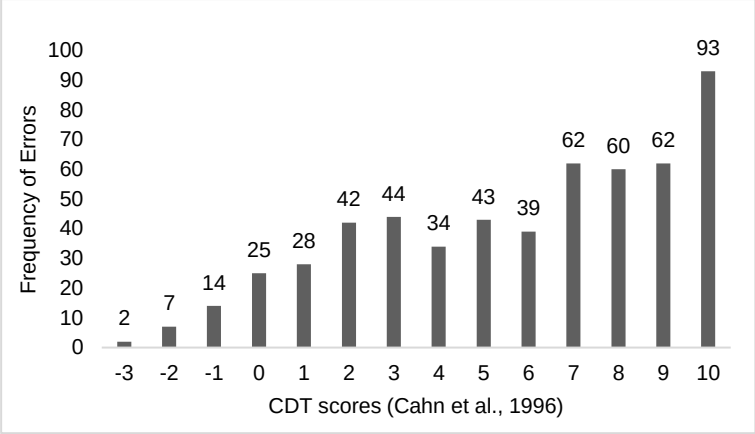

Figure 3. Distribution of frequencies of CDT scores, according to the scoring system of Cahn and colleagues (1996). CDT=Clock Drawing Test.

Considering the quantitative and qualitative scores separately, the most frequent quantitative scores were 10 (*N*=105), 8 (*N*=91) and 9 points (*N*=87), wherein the face of the clock, the placement of the numbers and the placement of the hands commonly received the maximum scores: 80.9% scored 2 points on the clock face; 34.8% scored 4 points on numbers; 33.5% scored 4 points on hands. The most frequent qualitative scores were 1 (32.3%), 0 (30.6%) and 2 points (22.5%). The most common types of errors were the planning deficit (44.3%), the conceptual deficit (33.4%) and the stimulus-bound error (12.1%; Figure 4).

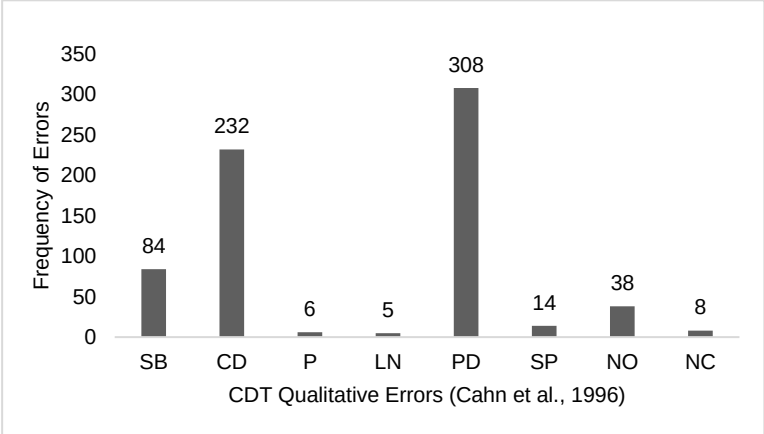

Figure 4. Distribution of frequencies of CDT scores, according to the scoring system of Cahn and colleagues (1996). SB=Stimulus-bound; CD=Conceptual deficit; P=Perseveration; LN=Left hemineglect; PD=Planning deficit; SP=Non-specific spatial error; NO=Numbers outside the clock; NC=Numbers counterclockwise; CDT=Clock Drawing Test.

With the scoring system of Babins, the most frequently observed global scores were 15 (11.7%), 14 (10.5%) and 17 points (8.5%; Figure 5). The majority of patients were able to correctly draw the clock face (81.3%)

and to correctly place the center of the clock (2 points: 60%). Regarding numbering, the most frequent attributed score was 4 points (37.3%), followed by the scores 6 (19.3%) and 3 (16.4%). The most common errors were related to spacing, specifically the spacing between the numbers 1-2-4-5-7-8-10-11 (75.7%) and between the numbers 12-3-6-9 (63.2%). The existence of missing/added numbers was the third most frequent type of numbering error (28.1%; Figure 6).

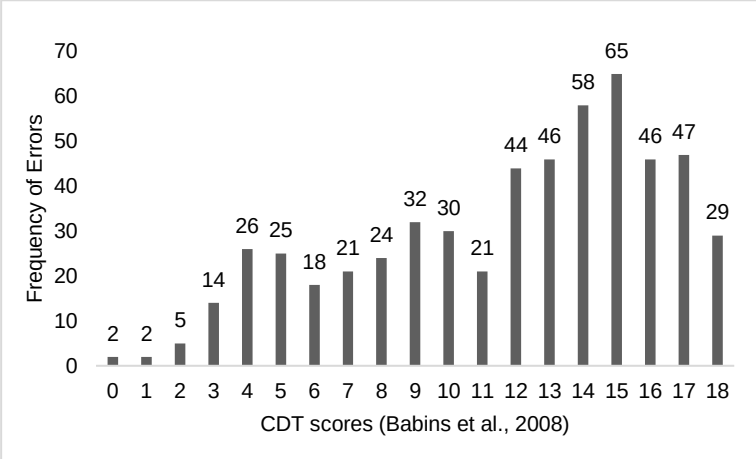

Figure 5. Distribution of frequencies of the CDT scores, according to the scoring system of Babins and colleagues (2008). CDT= Clock Drawing Test.

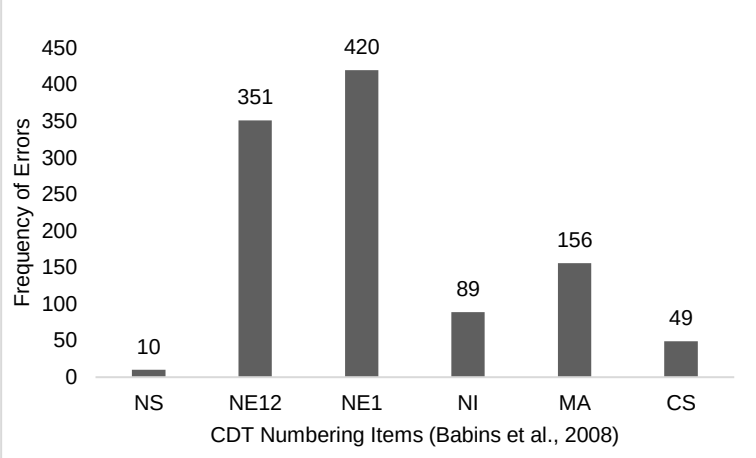

Figure 6. Distribution of frequencies of the CDT errors in the numbering items, according to the scoring system of Babins and colleagues (2008). NS=Numbers are all the same; NE12=Numbers equally spaced (12-3-6-9); NE1=Numbers equally spaced (1-2-4-5-7-8-10-11); NI=Numbers inside the clock; MA=No missing or added numbers; CS=Correct clockwise sequence; CDT=Clock Drawing Test.

Regarding the hands of the clock, the most frequent scores were 5 (29.4%), 0 (21.4%) and 4 points (18.6%). The wrong placement of the minute hand was the most frequent error in time setting (38.9%). Among the items referring to the construction of the hands, the drawing of arrows and the size difference between the two hands were the ones with the highest frequency of errors (77.1% and 60.5% respectively; Figure 7).

Lastly, in terms of the gestalt, the majority of the clock drawings

presented at least 1 gestalt error (47.2%). The second most frequent score was 2 points, with 211 (38%) drawings presenting a perfect gestalt.

Finally, in the assessment of the visuospatial/visuoconstructive domain by MoCA (which includes the 0/1 point scoring of CCT and a 0-3 points scoring of CDT), only 11 (2%) of the 555 scores were null. However, the remaining frequencies were scattered by the different scores: 1 point representing 25.9%, 3 points representing 25.4%, and 4 points representing 23.8% of all scores (Figures 8).

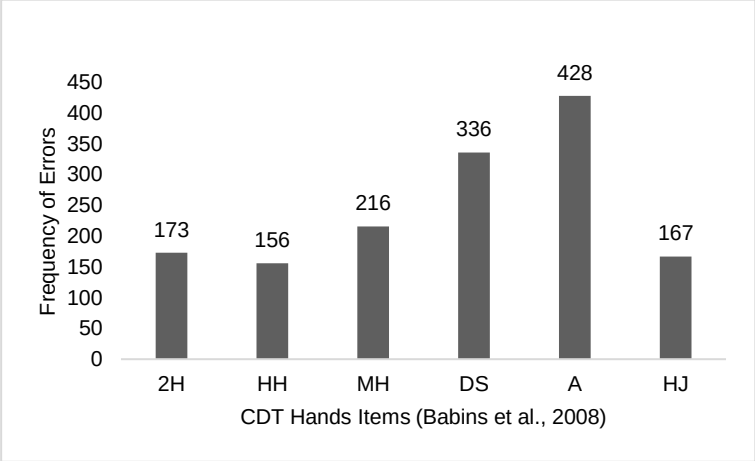

Figure 7. Distribution of frequencies of CDT errors in the hand items, according to the Babins and colleagues' (2008) scoring system. The chart includes time setting items (2H=Two hands; HH=Hour hand is correct; MH=Minute hand is correct) and construction of the hands items (DS=Difference in hands' size; A=Arrows; HJ=Hands are joined). CDT=Clock Drawing Test.

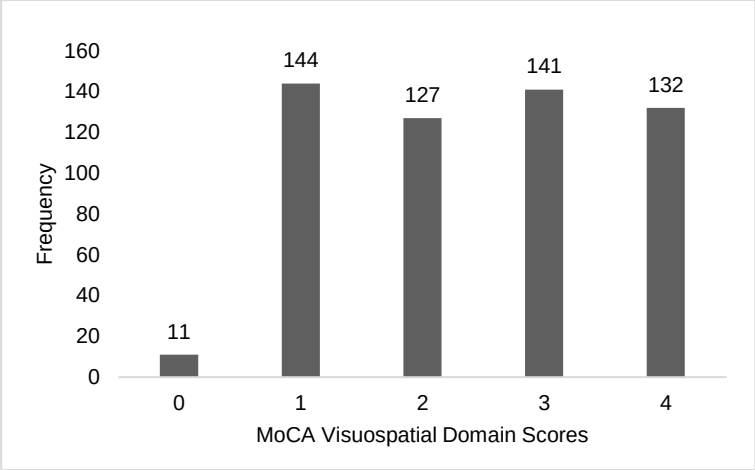

Figure 8. Distribution of the frequencies of scores in the visuospatial domain of MoCA.

Differences between aMCI and amMCI drawing errors

Comparisons between aMCI and amMCI drawing scores show that, overall, amMCI patients had poorer performances than aMCI. Regarding copying tasks, this was true for the CCT and the total score of CPT (measure with greater effect size). Specifically on CPT, the two groups were different in performing the copy of the rhombus and the cube. The two groups did not differ in the PDT (Table 3).

Table 3. Differences between aMCI and amMCI groups in visuocontructive copying tasks.

	aMCI	amMCI	Differences	Effect size
	M (SD)	***M (SD)***	**between groups**	**(Cohen's *d*)**
CCT	.43 (.496)	.26 (.439)	$t_{(388.04)}$= 4.113, *p*<.001	.36
CPT total score	.60 (.680)	.93 (.741)	$t_{(346.18)}$= -5.404, *p*<.001	.46
CPT rhombus	.05 (.218)	.14 (.343)	$t_{(269.38)}$= -3.253, *p*=.001	.31
CPT cube	.50 (.501)	.70 (.459)	$t_{(405.16)}$= -4.932, *p*<.001	.42

Abbreviations. CCT=Cube Copying Test; CPT=Constructional Praxis Task; aMCI=amnestic single-domain Mild Cognitive Impairment; amMCI=amnestic multi-domain Mild Cognitive Impairment;

Relatively to the drawing-to-command tasks, amMCI patients scored significantly lower than aMCI patients in the total score of CDT, as well as in the drawing of the clock face, in the placement of the numbers and in the placement of the hands, independently of the scoring system used (Table 4). According to the scoring system of Babins, the two groups also differed in the placement of the clock center and in gestalt. The measures with greater effect sizes were the three CDT total scores (of the three scoring systems) and the two numbering scores of the soring systems of Chan and Babins (Table 4).

In terms of errors, considering the scoring system of Cahn, the average of the qualitative scores for aMCI was significantly different from the average scores for the amMCI patients. The amMCI group presented significantly more stimulus-bound errors, conceptual deficits and planning deficits, comparatively to the aMCI group. Regarding the scoring system of Babins, the amMCI patients committed significantly more mistakes than the aMCI patients in the following items of numbering: numbers equally spaced (12-3-6-9), numbers equally spaced (1-2-4-5-7-8-10-11) and no missing or added numbers. For the placement of the hands, amMCI showed worst performances than aMCI patients in the items "two hands", "hour hand is correct" and "minute hand is correct", as well as in the items "difference in hands' size" and "hands are joined" (Table 4).

Table 4. Differences between aMCI and amMCI groups in visuocontructive drawing-to-command tasks.

	aMCI	amMCI	Differences	Effect size
	M (SD)	***M (SD)***	**between groups**	**(Cohen's *d*)**
CDT (Cahn et al., 1996)	6.28 (3.273)	4.66 (3.456)	$t_{(553)}$= 5.345, *p*<.001	.48
CDT (Rouleau et al., 1992)	7.39 (2.374)	6.23 (2.474)	$t_{(553)}$= 5.292, *p*<.001	.48
Clock face$_{10}$	1.84 (.379)	1.70 (.505)	$t_{(276.77)}$= 3.278, *p*=.001	.31
Numbers$_{10}$	2.99 (1.043)	2.54 (1.200)	$t_{(309.98)}$= 4.329, *p*<.001	.40

$Hands_{10}$	2.55 (1.531)	1.98 (1.523)	$t_{(553)}$= 4.068, p<.001	.37
Qualitative score (Cahn et al., 1996)	1.10 (1.062)	1.56 (1.185)	$t_{(318.05)}$= -4.422, p<.001	.41
$Stimulus\text{-}bound_{10}$	.12 (.322)	.22 (.418)	$t_{(282.14)}$= -3.010, p=.003	.27
$Conceptual\ deficit_{10}$	.36 (.481)	.54 (.500)	$t_{(338.27)}$= -3.892, p<.001	.37
$Planning\ deficit_{10}$	.52 (.500)	.63 (.485)	$t_{(359.89)}$= -2.346, p=.020	.22
CDT (Babins et al., 2008)	12.37 (4.327)	10.44 (4.336)	$t_{(553)}$= 4.919, p<.001	.45
$Clock\ face_{18}$	1.85 (.376)	1.71(.502)	$t_{(276.40)}$= 3.225, p=.001	.32
$Center_{18}$	1.40 (.855)	1.15 (.925)	$t_{(326.68)}$= 3.094, p=.002	.28
$Numbers_{18}$	4.25 (1.303)	3.66 (1.370)	$t_{(553)}$= 4.931, p<.001	.44
Numbers equally spaced $(12\text{-}3\text{-}6\text{-}9)_{18}$	.41 (.492)	.28 (.450)	$t_{(380.19)}$= 3.091, p=.002	.28
Numbers equally spaced $(1\text{-}2\text{-}4\text{-}5\text{-}7\text{-}8\text{-}10\text{-}11)_{18}$	.29 (.453)	.15 (.359)	$t_{(432.41)}$= 3.834, p<.001	.34
$No\ missing/added\ numbers_{18}$	.77 (.424)	.62 (.487)	$t_{(310.58)}$=3.436, p=.001	.33
$Hands_{18}$	3.56 (2.067)	2.88 (2.184)	$t_{(333.39)}$= 3.508, p=.001	.32
$Two\ hands_{18}$	.74 (.440)	.58 (.495)	$t_{(315.74)}$=3.651, p<.001	.34
$Hour\ hand\ is\ correct_{18}$	.75 (.434)	.65 (.477)	$t_{(321.85)}$=2.289, p=.023	.22
$Minute\ hand\ is\ correct_{18}$	.65 (.477)	.53 (.501)	$t_{(335.35)}$=2.823, p=.005	.25
Difference in hands' $size_{18}$	.42 (.496)	.32 (.467)	$t_{(369.66)}$= 2.597, p=.010	.23
$Hands\ are\ joined_{18}$	.75 (.435)	.60 (.492)	$t_{(314.68)}$=3.473, p=.001	.32
$Gestalt_{18}$	1.32 (.688)	1.06 (.660)	$t_{(363.66)}$= 4.291, p<.001	.17

Note. Items followed by "10" refer to the scoring system of Cahn, and items followed by "18" refer to the scoring system of Babins.

Abbreviations. CDT=Clock Drawing Test; aMCI=amnestic single-domain Mild Cognitive Impairment; amMCI=amnestic multi-domain Mild Cognitive Impairment.

Finally, in the visuospatial/visuoconstructive domain of the MoCA, amMCI patients presented significantly lower scores (M=2.07, SD=1.118), comparing to the aMCI patients (M=2.60, SD=1.151; $t_{(553)}$=5.155, p<.001, d=.47).

Conversion and Non-Conversion group differences

In order to understand the disease evolution profile of our sample and to study the impact of visuoconstruction in this context, we analyzed the differences between NC and C groups.

Sociodemographic and clinical features

The analysis of the differences between the NC and C groups yelled no statistically significant differences regarding gender ($\chi^2_{(1)}$=.138, p=.711) or education ($t_{(145)}$=.602, p=.548, d=.06). Neverthless, some clinical variables significantly differed between the two groups. The patients from the C group were significantly older than NC patients at the onset of the disease. Also, there were significantly more patients classified with late-onset (≥65) on the C group than on the NC group. Patients who converted also had a significantly shorter disease evolution time than those who did not convert (Table 5). We did not found other significant differences, including in the MCI type (p≥.05).

Table 5. Differences between Conversion (C) and Non-conversion groups (NC) regarding clinical features

	NC	C	Differences	Effect size
	M (SD)	***M (SD)***	**between groups**	**(Cohen's *d*)**
Age of onset	62.94 (8.443)	70.51 (7.143)	$t_{(138)}$= -5.715, p<.001	.97
Early vs. Late onset	.44 (.499)	.77 (.425)	$t_{(135.66)}$= -4.233, p<.001	.71
Disease duration/Time to conversion	8.15 (4.278)	6.29 (3.304)	$t_{(131.35)}$= 2.892, p=.004	.48

Abbreviations. NC=Non-conversion group; C=Conversion group.

Differences at Baseline

Analysis of the baseline performances yelled significant differences between C and NC patients (Table 6). In terms of the overall cognitive functioning, C patients presented a significantly worse status than their counterparts. Specifically, memory, visuospatial/visuoconstructional abilities, and orientation were the three cognitive domains that discriminated the two groups. Regarding visuoconstruction tasks, patients differed at baseline only on the CDT. Namely, differences between the two groups were statistically significant for the CDT total scores (independently of the scoring system applied), for the placement of the numbers and the hands, for the gestalt and for two qualitative errors (conceptual and planning deficits), where C patients consistently presented poorer performances.

Table 6. Differences between Conversion (C) and Non-conversion groups (NC) at baseline.

	NC	C	Differences	Effect size
	M (SD)	***M (SD)***	**between groups**	**(Cohen's *d*)**
MMSE	28.28 (1.947)	26.02 (2.912)	$t_{(95.96)}$=4.963 , p<.001	.91

MoCA	19.81 (4.661)	16.00 (4.043)	$t_{(75)}$= 3.677, p<.001	.87
MoCA_M	1.32 (1.422)	.36 (.621)	$t_{(58.703)}$= 3.821, p<.001	.87
MoCA_VS	2.83 (1.070)	2.21 (1.101)	$t_{(67)}$= 2.317, p=.024	.57
MoCA_O	5.78 (.525)	5.14 (.891)	$t_{(39.81)}$= 3.405, p=.002	.88
ADAS-Cog	8.19 (3.211)	11.03 (4.258)	$t_{(63)}$= -2.924, p=.005	.75
CDT (Cahn et al., 1996)	7.40 (3.084)	5.84 (2.760)	$t_{(94)}$= 2.580, p=.011	.53
CDT (Rouleau et al., 1992)	8.15 (2.070)	7.05 (2.138)	$t_{(94)}$= 2.562, p=.012	.52
$Numbers_{10}$	3.34 (.919)	2.91 (1.019)	$t_{(94)}$= 2.185, p=.031	.44
$Hands_{10}$	3.00 (1.177)	2.37 (1.328)	$t_{(94)}$= 2.454, p=.016	.50
Total of qualitative errors (Cahn et al., 1996)	.75 (1.072)	1.21 (.833)	$t_{(94)}$= -2.277, p=.025	.48
Conceptual $deficit_{10}$	.21 (.409)	.40 (.495)	$t_{(81.357)}$= -1.996, p=.049	.42
Planning $deficit_{10}$	.42 (.497)	.70 (.465)	$t_{(92.10)}$= -2.870, p=.005	.58
CDT (Babins et al., 2008)	14.09 (3.537)	12.33 (3.902)	$t_{(94)}$= 2.326, p=.022	.53
$Numbers_{18}$	4.79 (1.199)	3.98 (1.185)	$t_{(94)}$= 3.333, p=.001	.68
Numbers equally spaced $(12\text{-}3\text{-}6\text{-}9)_{18}$	.51 (.505)	.23 (.427)	$t_{(93.81)}$= 2.910, p=.005	.60
Numbers equally spaced $(1\text{-}2\text{-}4\text{-}5\text{-}7\text{-}8\text{-}10\text{-}11)_{18}$	.45 (.503)	.23 (.427)	$t_{(93.77)}$= 2.320, p=.023	.47
No missing/added $numbers_{18}$	.92 (.267)	.77 (.427)	$t_{(67.29)}$= 2.101, p=.039	.42
Two $hands_{18}$	.89 (.320)	.72 (.454)	$t_{(73.09)}$= 2.023, p=.047	.43
$Gestalt_{18}$	1.68 (.510)	1.30 (.638)	$t_{(94)}$= 3.218, p=.002	.66

Note. Items followed by "10" refer to the scoring system of Cahn, and items followed by "18" refer to the scoring system of Babins.

Abbreviations. MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; MoCA_M=Memory domain; MoCA_VS=Visuospatial domain; MoCA_O=Orientation domain; ADAS-Cog=Alzheimer's Disease Assessment Scale – Cognitive subscale; CDT=Clock Drawing Test; NC=Non-conversion group; C=Conversion group.

Considering the previous finding that NC and C patients differ in terms of their early/late age of onset, we decided to perform the same comparative analysis separately for both early-onset (EO) and late-onset (LO) patients. For EO patients, C and NC patients differed significantly on overall cognitive status and on certain cognitive domains, such as memory, visuospatial abilities and orientations. They also differed on the CCT and on

the CDT (global scores, placement of the hands, conceptual and planning deficits and gestalt). Patients who converted were consistently worse than NC patients (Table 7).

Table 7. Differences between NC and C subgroups of EO group at baseline.

	NC	C	Differences	Effect size
	M (SD)	***M (SD)***	**between groups**	**(Cohen's *d*)**
MMSE	28.68 (1.226)	26.21 (2.259)	$t_{(15.99)}$= 3.867, p=.001	1.35
MoCA	20.22 (4.410)	14.40 (2.510)	$t_{(26)}$= 2.824, p=.009	1.62
MoCA_M	1.33 (1.328)	.00 (.000)	$t_{(17)}$= 4.258, p=.001	-
MoCA_VS	3.17 (.857)	1.60 (.894)	$t_{(21)}$= 3.584, p=.002	1.79
MoCA_O	5.72 (.575)	4.40 (.548)	$t_{(21)}$= 4.593, p<.001	2.35
ADAS-Cog	6.93 (2.052)	11.27 (3.409)	$t_{(24)}$= -4.047, p<.001	1.54
CCT	.44 (.511)	.00 (.000)	$t_{(17)}$= 3.688, p=.002	-
CDT (Cahn et al., 1996)	8.52 (1.827)	6.00 (2.793)	$t_{(13.63)}$= 2.760, p=.016	1.07
CDT (Rouleau et al., 1992)	8.89 (1.219)	7.36 (1.963)	$t_{(13.27)}$= 2.395, p=.032	.94
$Hands_{10}$	3.26 (.859)	2.45 (1.036)	$t_{(36)}$= 2.468, p=.018	.85
Total of qualitative errors (Cahn et al., 1996)	.37 (.688)	1.36 (1.027)	$t_{(13.81)}$= -2.950, p=.011	1.13
$Conceptual\ deficit_{10}$	.07 (.267)	.45 (.522)	$t_{(12.19)}$= -2.297, p=.040	.60
$Planning\ deficit_{10}$	.26 (.447)	.64 (.505)	$t_{(36)}$= -2.275, p=.029	.80
CDT (Babins et al., 2008)	15.26 (2.443)	12.91 (3.145)	$t_{(36)}$= 2.473, p=.018	.83
$Gestalt_{18}$	1.85 (.362)	1.27 (.467)	$t_{(36)}$= 4.109, p<.001	1.39

Note. Items followed by "10" refer to the scoring system of Cahn, and items followed by "18" refer to the scoring system of Babins.

Abbreviations. MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; MoCA_M=Memory domain; MoCA_VS=Visuospatial domain; MoCA_O=Orientation domain; ADAS-Cog=Alzheimer's Disease Assessment Scale – Cognitive subscale; CCT=Cube Copying Test; CDT=Clock Drawing Test; NC=Non-conversion group; C=Conversion group.

On the other hand, LO-NC and -C patients significantly differed on global and specific-domain cognitive measures, but not on any drawing task. The two groups were statistically different at the MMSE and the MoCA (global score, memory and orientation), wherein C patients exhibited poorer scores, once again (Table 8).

Table 8. Differences between NC and C subgroups of LO group at baseline.

	NC	C	Differences	Effect size
	M (SD)	*M (SD)*	between groups	(Cohen's *d*)
MMSE	27.81 (2.593)	25.98 (3.142)	$t_{(65}$= 2.483, p=.016	.64
MoCA	19.52 (5.035)	16.43 (4.326)	$t_{(44)}$= 2.230, p=.031	.66
MoCA_M	1.36 (1.529)	.43 (.676)	$t_{(29.20)}$= 2.613, p=.014	.79
MoCA_O	5.82 (.501)	5.33 (.913)	$t_{(30.74)}$= 2.145, p=.040	.67

Abbreviations. MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; MoCA_M=Memory domain of MoCA; MoCA_O=Orientation domain of MoCA; NC=Non-conversion group; C=Conversion group.

Survival Analysis

To assess the disease evolution of our sample, we performed log rank tests for each sociodemographic and clinical variable, in order to compare Kaplan-Meier survival curves of each category of the variables. Neither gender (male/female: $\chi^2_{(1)}$=.166, p=.684), education level (1-4/5-9/>10 years: $\chi^2_{(1)}$=1.620, p=.445), family history (negative/positive: $\chi^2_{(1)}$=.128, p=.721), being a homozygous ApoE4 carrier (no/yes: $\chi^2_{(1)}$=3.237, p=.072) or type of MCI (aMCI/amMCI: $\chi^2_{(1)}$=.183, p=.669) significantly affected the survival profile of the sample. On the other hand, the probability of survival (i.e. of not converting to dementia) over time was not equivalent for EO and LO patients, neither for non-carriers and heterozygous carriers of ApoE4 (Table 9).

Table 9. Probabilities of survival over time.

	EO	LO	ApoE4 non-carrier	ApoE4 heterozygous carrier
2 years	.986	.950	.979	.943
5 years	.958	.782	.830	.792
10 years	.722	.370	.606	.347
15 years	.671	.239	.519	.220
20 years	.671	.000	.000	.220

Abbreviations. EO=Early-onset patients; LO=Late-onset patients.

Regarding the age of onset of the disease, while EO patients took a mean of 14.307 years (*SD*=.793) since the onset to convert, the LO patients took 10.329 years (*SD*=.783), with each group presenting a conversion rate at year 5 of 11.11% and 20.59%, respectively. This translates a significant effect of the type of onset (early/late; $\chi^2_{(1)}$=13.416, p<.001; Figure 9) in the risk of converting to dementia. The LO patients presented a median of 9

years (*SD*=.661), meaning that it took 9 years for 50% of the late-onset patients to convert. In turn, the EO group never reached the 50% mark.

Being a heterozygous ApoE4 carrier also had a significantly impact in the probability of survival ($\chi^2_{(1)}$=5.587, *p*=.018; Figure 10), with non-carriers presenting a mean survival time of 13.76 years (*SD*=.913; *Mdn*=20; SD_{Mdn}=.000) and heterozygous carriers exhibiting a mean of 12.134 years (*SD*=.674; *Mdn*=10, SD_{Mdn}=.992). The two groups presented conversion rates of 15.79% and 19.72% at year 5, respectively.

Given the significant effects of these two clinical features, we proceeded with a cox regression (since the proportional hazards assumption was fulfilled), where the two variables were analyzed simultaneously. The qui-squared test yelled a significant improvement in fit of our model containing the two predictors, relatively to the null model ($\chi^2_{(2)}$=17.120, *p*<.001). The analysis of the regression coefficients indicated that being a heterozygous ApoE4 carrier was not a significant explanatory variable, i.e., did not significantly affect the time to conversion ($\chi^2_{(1)}$=3.022, *p*=.082, 95% CI [.946, 2.505]), while the type of the onset (early/late) was/did ($\chi^2_{(1)}$=10.376, *p*=.001, 95% CI [1.453, 4.645]). Late-onset patients had a greater risk of conversion, being 2.598 times more likely to convert to dementia than EO patients (β=.955, *p*=.001).

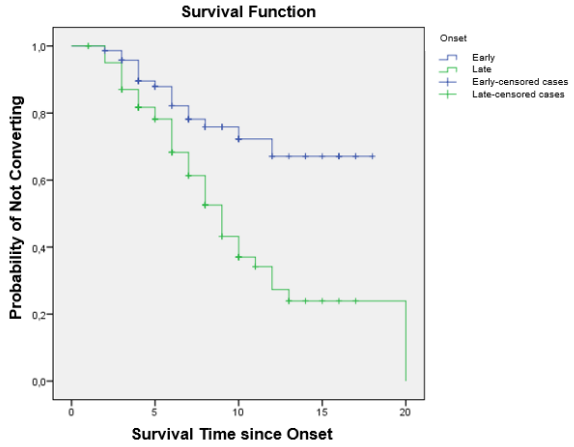

Figure 9. Plot of the survival curves for type of onset (early versus late).

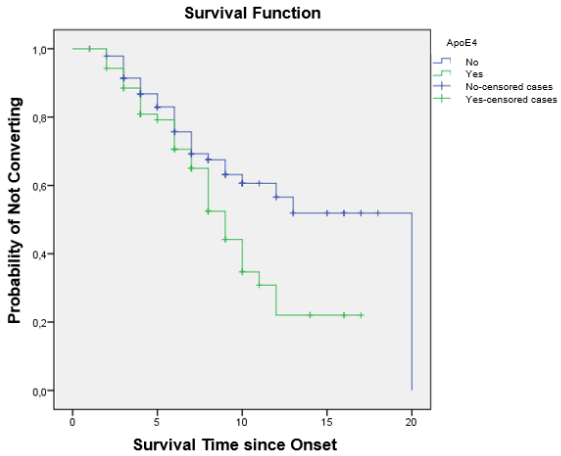

Figure 10. Plot of the survival curves for ApoE4 carrying (single allele: no versus yes).

Visuocontructive predictors

After the survival analyses, we performed GEE separately for both EO and LO patients, in order to examine if any visuoconstructive variables explained the likelihood of the patients to convert over time, and in a positive case, which ones contributed for it. The achieved model for the EO patients included the time (i.e. annual assessments), the CDT (Cahn scoring system total score) and the interaction effect between Time and the PDT (scoring system of MMSE; Table 10). At the beginning of the study (i.e., first assessment), for the EO patients the probability of not converting to dementia was greater than the probability to convert (β= -1.68, OR=.186). Furthermore, the probabilities of conversion did not seem to change over time for these patients (p>.05). On the other hand, patients with greater CDT total scores were more likely to fall in the non-conversion group, while patients with lower scores were more likely to convert to dementia (β= -.015). For each point less on the CDT total score, there were 1.015 times more chances for patients to convert. Regarding the interaction effect PDT*Time, the log odds of -.052 translates the difference between the slopes of PDT when the score was equal to 0 and when it was equal to 1. In other words, while the log odds for PDTs scored 0 was .011, the log odds for PDTs scored 1 was -.041. This means that for patients who failed to correctly perform the PDT, the odds ratio associated to this predictor was bigger than 1 (OR=1.011), and therefore we observed an increase in the probability of converting. For patients who were able to perform the PDT, the odds ratio associated to the predictor was smaller than 1 (OR=0.960), and therefore there was a decrease in the probability of converting.

Table 10. GEE parameter estimates for EO patients.

	Log Odds (β)	*SE*	95% CI	Wald Chi-Square	Odds Ratio (OR)	95% CI
Intercept	-1.68	.288	[-2.245, -1.115]	$\chi^2_{(1)}$=33.990, p<.001	.186	[.106, .328]
Time	.011	.018	[-.024, .046]	$\chi^2_{(1)}$=.387, p=.534	1.011	[.976, 1.047]
CDT (Cahn et al., 1996)	-.015	.007	[-.028, -.002]	$\chi^2_{(1)}$=5.019, p=.025	.985	[.972, .998]
PDT*Time	-.052	.020	[-.092, -.013]	$\chi^2_{(1)}$=6.655, p=.010	.949	[.912, .988]

Abbreviations. CDT=Clock Drawing Test; PDT=Pentagon Drawing Test.

For the LO patients, the model with the best goodness of fit included the following predictors: the time, the CDT (Babins scoring system) total score and the visuospatial domain total score of MoCA (Table 11). At the beginning of the study (i.e. first assessment), LO patients had 1.625 times more changes to convert than to not convert to dementia. The time exerted an opposite effect, since patients with longer follow-ups were more likely to not convert. Per new assessment, there was 0.953 times the chance of the previous assessment of patients to convert. Regarding the CDT total scores, for each one unit decrease, the odds of converting (versus not converting)

increased by a factor of 1.06. Similarly, for a one unit decrease in the visuospatial domain of the MoCA, there was 1.09 times more chance to convert.

Table 11. GEE parameter estimates for LO patients.

	Log Odds (β)	*SE*	95% CI	Wald Chi-Square	Odds Ratio (OR)	95% CI
Intercept	.485	.247	[.002, .969]	$\chi^2_{(1)}$=3.875, *p*=.049	1.625	[1.002, 2.635]
Time	-.048	.020	[-.087, -.010]	$\chi^2_{(1)}$=6.011, *p*=.014	.953	[.917, .990]
CDT (Babins et al., 2008)	-.058	.014	[-.086, -.030]	$\chi^2_{(1)}$=16.677, *p*<.001	.943	[.917, .970]
MoCA_VS	-.087	.043	[-.170, -.003]	$\chi^2_{(1)}$=4.157, *p*=.041	.917	[.844, .997]

Abbreviations. CDT=Clock Drawing Test; MoCA_VS=Visuospatial domain of MoCA.

V - Discussion

We present an original research study that aimed to evaluate and characterize the presence of visuoconstructional impairment in MCI patients. Our purpose was to provide a better understanding of the status/functioning of this domain in this clinical group, determining if there were early indicators of future conversion to dementia related with this particular capacity/ability.

The analysis of the frequency and types of errors related with visuoconstruction showed that the majority of MCI patients were able to correctly perform simple copying tasks, such as the Pentagon Drawing Test and the copy of the three less complex geometric figures of the Constructional Praxis Task from ADAS-Cog (the circle, two intersecting pentagons and the rhombus). However, when the performance of the Cube-Copying Test was requested, 62.5% of the copies were inaccurate. Because more complex copying tasks may require preserved executive functioning (e.g., Freeman et al., 2000), this observation suggests that the visuoconstructional impairment in MCI is more likely related to an impairment on planning and organizational abilities, than it is to visuoperceptual or visuospatial deficits (Freeman et al., 2000; Libon et al., 1996). Regarding drawing-to-command tasks, the performances in the Clock Drawing Test exhibited more diversity. Regardless of the scoring system used, total scores appeared distributed across all the range of possible scores, and the most commonly made errors were related to conceptual and executive deficits. The main difficulties of these patients were to equally space the numbers of the clock and to correctly construct its hands, differentiating their size and including the arrows. The time setting was also frequently misconfigured. It is important to note that the administration of the Clock Drawing Test disclosed several different deficits among MCI patients. Because drawing-to-command tasks pose additional load on other cognitive abilities, such as language and memory, that copying tasks do not

(e.g., Freedman et al., 1994; Price et al., 2011; Rouleau et al., 1992; Strauss et al., 2006), the CDT seems to be able to detect deficits that the Pentagon Drawing Test or the Constructional Praxis Task are not. Therefore, this test may be useful in discriminating different specific cognitive decline profiles. Nevertheless, more complex tasks may hamper the identification of specific deficits (Ruffolo, 2004) and therefore we advise the usage of both types of tasks, copying and free drawing, with different degrees of complexity.

Regarding the discrimination of different types of MCI, the analysis of the differences between aMCI and amMCI patients showed that amMCI patients presented overall worse visuoconstructional abilities, detected in both copying and drawing-to-command tasks. From the copying tasks, the Pentagon Drawing Test was the only test that did not yell statistically significant differences. This may be due to its low degree of complexity given that in Constructional Praxia Task, although there were significant differences on the total score, they were solely due to differences in the rhombus and in the cube, the two items with higher complexity. These findings suggest that copying tasks that utilize stimuli with greater levels of complexity can discriminate between aMCI and amMCI patients, contrary to more simple tasks.

Regarding drawing-to-command tasks, amMCI patients presented lower total scores in the CDT, in all three scoring systems (Babins et al., 2008; Cahn et al., 1996; Rouleau et al., 1992), suggesting that the choice of one scoring system over the others may not be important to distinguish aMCI from amMCI patients. Amnesic-multidomain MCI patients performed worse than aMCI patients in the production of all components of the clock (face, center, numbers and hands), specifically exhibiting more difficulties in equally spacing the numbers, generating the correct numbers, constructing the hands and setting the time. Additionally, these patients committed more gestalt errors, as well as more stimulus-bound, conceptual and planning errors. These results show that amMCI patients presented a greater impairment not only in their pure drawing abilities, but also in their visuospatial capacities, planning skills, organization abilities and language comprehension, in comparison to aMCI patients. Together, such evidence highlight the potential of the CDT to discriminate not only between dysexecutive MCI/multidomain MCI and amnestic MCI patients (Ahmed et al., 2016) but also between amnestic multidomain MCI and pure amnestic MCI patients.

The second aim of the present study was to assess the value of visuoconstructional measures in predicting the progression of MCI patients to dementia due to AD. Specifically, we intended to test drawing measures (copying and drawing-to-command tasks) since they are widely used with AD patients (Trojano & Gainotti, 2016).

The analysis of differences between the patients who converted and the patients who did not progress to AD reported that the majority of C patients had a late onset of the disease (i.e., posterior to the 65 years mark). At the time of the diagnosis, the C patients were also in a more debilitated cognitive state than NC patients. Specifically, these patients had worst

memory capacity, visuoconstructive skills and orientation abilities. Furthermore, they exhibited worst performances in the Clock Drawing Test. These patients made more mistakes in the placement of numbers and in the construction and placement of the hands. They also committed more conceptual and planning errors than NC patients and exhibited a poorer gestalt. Such evidence suggests that MCI patients who have greater visuoconstructional impairment (as assessed by the CDT) at the time of diagnosis tend to progress to dementia more than patients with milder deficits. This is congruent with studies that reported greater severity of CDT errors in AD patients, in comparison to MCI patients (Allone et al., 2018; Parsey & Schmitter-Edgecombe, 2011), and proposes that an early impairment in this task may indicate prodromic AD. The fact that the NC and C groups did not differed in any copying task at baseline supports the idea that drawing-to-command tasks are more sensitive to milder cognitive decline than copying tasks (Rouleau et al., 1996).

Because the proportions of EO and LO patients were not equivalent in the C and NC groups, it was important to analyze the differences between these two groups while controlling the type of onset. Analyses of differences within the EO and LO groups reported that, once again, C patients had, at baseline, significantly worse global cognitive status than NC patients. However, only EO-C and EO-NC patients differed significantly in visuoconstructive measures (e.g. visuospatial domain of MoCA, CCT and CDT), and their differences were detected in both copying and drawing-to-command tasks. The fact that EO patients, but not LO patients, differed in visuoconstructive measures at baseline may be due to the differences in the clinical features of these two types of individuals. While early-onset AD patients tend to exhibit more deficits in executive functions and visuoconstructional abilities, late-onset patients tend to have more difficulties in semantic memory tasks, despite both presenting deficits in memory, executive functions, language, visuoconstruction and praxis (e.g., Joubert et al., 2016; Koedam et al., 2010; Serra et al., 2014). Also, the fact that the CCT was the only copying task to report differences between EO-C and EO-NC patients may have to do with its degree of complexity, since there is a bigger likelihood of detecting early copying disabilities through the use of a more complex stimulus (Ahn et al., 2011; Binetti et al., 1998).

Survival analyses reported significant differences in the conversion rates of EO and LO patients. The probabilities of not converting over time for the LO group were consistently lower than the probabilities for the EO group. Late-onset patients converted more rapidly than early-onset patients, taking 9 years since onset for 50% of this group to convert. On the other hand, the EO group never reached the 50% mark, therefore exhibiting a much lower conversion rate than the LO group. These data are in line with studies showing that the risk for cognitive decline increases with age (Langa & Levine, 2014) and suggest that the MCI patients with initial cognitive complaints after the 65 years old are at higher risk of conversion. Therefore, these patients should be targeted for a rapid implementation of intervention measures, such as counseling, optimization of functional status, cognitive

training and exercise (Langa & Levine, 2014; Vega & Newhouse, 2014), as well as for a more close medical follow-up/care. The low number of conversions in the EO group may be an indicator of a possible high prevalence of "worried well" individuals among younger patients. Although all MCI patients included in the present study were well characterized in terms of their diagnosis and, indeed, presented an objective cognitive impairment, it is possible that the extended medical follow-up of these patients has been motivated by their complaints, and not by an objective cognitive decline over time, leading to the study of subjects whose cognitive impairment is not due to neurodegenerative causes. Another important aspect of these analyses is the time until conversion reported for each group. In contrast to several studies reporting considerable conversion rates up to 5 years of follow-up (e.g. Fischer et al., 2007; Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006), our EO and LO groups reported mean times until conversion of 10 and 14 years, and conversion rates of 11.11% and 20.59% at year 5, respectively. This is due to our operationalization of time. In the survival analyses, "Time" corresponded to the number of years past since the onset of cognitive complaints, a subjective data provided by the patient and informant/caregiver. We consider this operationalization of time to be more accurate, given that it is recognized that prodromal phases of AD are particularly long and progressive, and that the first signs of cognitive decline can appear as early as 12 years prior dementia (Amieva et al., 2008).

In addition to the differences caused by the type of onset, we also observed different survival patterns of heterozygous ApoE4 carriers and non-carriers, with carriers converting more rapidly than non-carriers. However, when joined in the same model as the type of onset (early/late) and analyzed simultaneously, the effect of the ownership of one ApoE4 allele lost its statistical significance. This result may be due to two possible mechanisms: (1) the effect of an interaction between age and possessing an ApoE4 allele and (2) an unbalanced distribution of the ApoE4 carriers through the EO and the LO groups. According to a longitudinal study conducted by Bonham and colleagues (2016), where they assessed the effects of ApoE4 and age in the progression from a healthy cognitive state to MCI or AD, the highest risk for ApoE4 carriers to convert is between the ages of 70-75 years. This translates the age as major risk factor for dementia that influences the effect of the strongest known genetic risk factor, the allele ε4 of ApoE. Furthermore, since the assembly of our sample was conducted in a clinical context and was solely based on the type of MCI diagnosis, we did not take into account the distribution of ApoE4 carriers across the different groups, so the possibility of an uneven distribution across the NC and the C groups cannot be ruled out. Hereupon, despite the effects of the allele ε4 in the probabilities of not converting to dementia being not-significant, they should not be disregarded.

To evaluate the value of different visuoconstructional tasks in predicting dementia, we built 2-level models for groups who reported statistically significant differences in their survival curves, namely the EO group and the LO group. These models accommodate within- and between-

subjects changes, where repeated measures appear nested within individuals. Generalized Estimating Equations analyses reported two optimal models that included time and stated visuoconstructional measures as significant predictors of dementia. Regarding analysis of the achieved model for the EO group, we observed that time was not a significant predictor of conversion for these patients. This is congruent with the observed survival pattern of this group (that translates a small rate of conversion) and highlights the importance of considering other factors (e.g. risk factors, cognitive decline even if very mild) when contemplating the cession of medical follow-up of individuals with early-onsets of the disease, given that the duration of the follow-up is not informative. Contrastingly, time was reported as a significant predictor of dementia for the LO group, however with a beneficial effect. According to the model, there was a decrease in the probability of these patients to convert (over the probability of not converting) at every new neuropsychological assessment. This is in line with the survival curve of the group, which shows that the steep decline of the probabilities of not converting is followed by a plateau, suggesting that patients with late-onsets tend to convert in the first years of follow-up, otherwise having more chances of remaining stable.

Regarding visuoconstructive measures, the model of the EO group reported the CDT as a significant predictor of dementia, with lower scores increasing the probability of these patients to convert. In other words, worst visuoconstruction abilities in the CDT may predict the conversion from MCI to dementia. We also observed a significant effect of the interaction between the PDT and time. This interaction effect stated that EO patients who were unable to correctly perform the PDT task had their probability to convert increased over time (relatively to their probability of not converting), while patients who could correctly copy the two pentagons suffered a decrease in their probability of converting to dementia. Given that PDT is a relatively simple copying task and therefore tends to remain preserved for longer (Rouleau et al., 1996), failures in this task should be carefully accounted, since they are suggestive of more severe cognitive deteriorations and indicate an increase in the risk to dementia over time.

Similarly to the EO group, the achieved model for the LO group also reported the CDT as a significant predictor of dementia, once again indicating that lower scores implicated an increase in the probability to convert. Nevertheless, it is important to highlight the fact that the CDT appeared as a significant predictor in both models, but with different scoring systems. While for EO patients the scoring system of Cahn was the one with better predictive value, the 18-point scoring system of Babins was the one that better fitted the predictive model for LO patients. The observation that the CDT is included in both models suggests that predictive value of this task is not influenced by differences associated with the type of onset of the disease, which brings robustness to previous findings on the capacity of the CDT to predict dementia in the generality of MCI patients (e.g. Amodeo et al., 2015; López et al., 2016). However, a scoring system that includes qualitative elements (Cahn et al., 1996) seems to be better in predicting

conversion of EO patients, while a more detailed scoring system that is better suited to detect early markers of dementia (Babins et al., 2008) appears to be a better predictor for LO patients. Given that EO patients tend to exhibit more visuoconstructive and executive functioning deficits and that EO-C and EO-NC subjects already differed in the CDT at baseline, it may be advantageous to apply a more informative scoring system that accommodates qualitative errors and strategies when assessing the visuoconstruction in these patients. On the other hand, considering that LO patients tend to fail more in semantic memory tasks, and given that LO-C and LO-NC did not differ in any visuoconstructional task at baseline, it may be more advantageous to assess these patients with a more exhaustive scoring system that is able to detect more subtle changes. Neverthless we advise the appliance of both scoring systems in clinical context, regardless the type of patient, since they exhibit different advantages by providing distinctively valuable data (Spenciere, Alves, & Charchat-Fichman, 2017).

Along with the CDT, the optimal model for LO patients also yelled the total score of the visuospatial domain of MoCA as a significant predictor of dementia, with lower scores implying, once again, an increase in the probability to convert from MCI to AD. As a more general visuoconstructive measure, the visuospatial domain of MoCA is a composite of a copying and a drawing-to-command task – the CCT (scored as correct or incorrect) and the CDT (scored with a 3-point system that translates the correct/incorrect drawing of the face of the clock, and the correct/incorrect placement of the numbers and the hands). The observation that the optimal models for EO and LO patients accommodate the two types of drawing tasks highlights the importance of including both copying and drawing-to-command tasks in the assessment of visuoconstructional abilities of MCI patients, especially if this assessment is carried-out in a monitoring over time context. This goes against the idea that copying conditions may be secondary when drawing-to-command conditions are administrated (Ruffolo, 2004). The fact that the copying tasks only showed predictive value indirectly through interaction effects or composite measures may be associated with their degrees of complexity. The copying tasks used in the present study are rather simple, particularly when compared with more complex tasks such as the ROCF (Osterrieth, 1944; Rey, 1941). Since the detection of copying impairments in MCI is more likely to happen with more complex tasks (Binetti et al., 1998), future longitudinal studies should consider including tasks similar to the ROCF, in order to attempt the detection of main predictive effects of copying tasks.

The present study has some limitations. One can be considered the lack of a complex copying task that could allow us to produce more complete predictive models. Another limitation relates to the assemble of the sample, which was performed without considering the distribution of ApoE4 carriers across the EO and LO groups and therefore, did not allow an accurate assessment of the effects of this variable in the progression to dementia. Lastly, the main limitation of our study refered to the inability to control variables such as individual drawing abilities and cultural

background, aspects that greatly influence drawing performances (Rosseli & Ardila, 2003). Although NC and C patients did not differ in terms of educational level, variables such as the starting drawing abilities of the patients and the familiarity that they have with writing-like tasks could not be assessed. Despite these limitations, the present study also presented various strengths. The reliable characterization of the patients that was made by a multidisciplinary team and defined by a neurologist, and the annual comprehensive evaluations performed through a complete (neuro)psychological battery assured the accuracy of the distributions of our patients across groups and the validity of our results. Furthermore, our study assessed the value of visuoconstruction in predicting dementia through a quick, economic-friendly and easy to apply set of drawing tasks, very suitable for medical settings. Lastly, the main strength of the present study relies on the GEE analysis. The Generalized Estimating Equations approach is a multilevel modelling technique that allows the analysis of both continuous and categorical repeated measures in a logistic regression within a two-level model that accommodates repeated measures nested in individual. It can handle complex longitudinal designs with more than two repeats while allowing for unbalanced repeats and missings (Heck et al., 2012). To better assess visuoconstruction, future studies should include both copying and drawing-to-command tasks with different levels of complexity, as well as consider the evaluation of individual drawings skills and the analysis of individual cultural background.

VI - Conclusions

The present study highlighted the importance to assess visuoconstruction in monitoring the cognitive decline of MCI patients at risk of developing AD. Drawing tasks are quick and easy to apply and allow the detection of various deficits in different cognitive abilities. Generally, the visuoconstructional impairment of MCI patients appeared to be more related to deficits in executive functioning and in accessing knowledge than to pure visuoperceptual or visuospatial impairments, since it was better detected by more complex copying and free drawing tasks. Regarding the differences between different subtypes of MCI, amMCI and aMCI patients could be distinguished by both copying and drawing-to-command tasks, and amMCI patients presented overall greater visuoconstructional impairment.

One of the main conclusions of this study is that visuoconstruction had significant value as a predictor of dementia, with greater deficits being associated with a greater risk of converting. Indeed, the EO patients who converted presented worse performances in visuoconstructional tasks at baseline, than those who remained stable until the end of the study. In addition to the predictive value of visuoconstruction, MCI patients with late-onsets had less probabilities than patients with early-onsets of remaining stable, which points late-onset MCI patients with visuoconstructional impairments as a group at high-risk of converting. Therefore, visuoconstructive deficits may be utilized as an important warning sign of the probability to dementia.

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