UNIVERSIDADE FEDERAL DE MINAS GERAIS

Programa de Pós-Graduação em Medicina Molecular

# EFEITO DAS FUNÇÕES EXECUTIVAS NO DESEMPENHO COGNITIVO DE IDOSOS COM ENVELHECIMENTO NORMAL E PATOLÓGICO

**RAFAELA TEIXEIRA DE ÁVILA**

Belo Horizonte

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Dissertação apresentada como requisito para obtenção do título de Mestre junto ao Programa de Pós-Graduação em Medicina Molecular da Universidade Federal de Minas Gerais.

Área de concentração: Doenças Neurodegenerativas

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**RESUMO**

As funções executivas correspondem a um conjunto de processos cognitivos que de forma integrada permitem ao sujeito dirigir intencionalmente comportamento a metas. São requeridas sempre que planos de ação são formulados e quando se está adquirindo novos conhecimentos. São funções necessárias para gerenciar o comportamento humano e garantir o sucesso na vida cotidiana. O processo de envelhecimento saudável é marcado por um declínio das funções executivas, sendo esse declínio acentuado em quadros de Comprometimento Cognitivo Leve e de Demência de Alzheimer. O objetivo desta dissertação foi avaliar os efeitos das funções executivas, mesmo que indiretamente, em outros processos cognitivos em paciente idosos com envelhecimento normal, em pacientes com Comprometimento Cognitivo Leve e com Demência de Alzheimer. Foram realizados dois artigos conduzidos através da análise de mediação, objetivando investigar os mecanismos pelos quais uma variável exerce seu efeito em outra. Os resultados dos dois estudos indicaram que as funções executivas influenciam tanto direta quanto indiretamente em outros processos cognitivos, sugerindo assim que seu nível de funcionamento influencia o desempenho cognitivo de uma forma ampla e diversificada. Observamos que, especialmente no envelhecimento patológico, quando comparado ao envelhecimento normal, uma maior participação das funções executivas é requerida como recurso compensatório. Concluímos que especial atenção deve ser direcionada às funções executivas no processo de avaliação neuropsicológica do idoso, uma vez que déficits executivos podem influenciar na eficiência de outros processos cognitivos.

**Palavras-chave:** Funções Executivas, Envelhecimento normal, Envelhecimento patológico, Análise de mediação.

**ABSTRACT**

Executive functions correspond to a set of cognitive processes that when integrated permit the subject to intentionally drive behavior to goals. Are always required when plans are formulated and when is acquiring new knowledge. They are necessary to manage human behavior and to guarantee success in everyday life functions. The process of healthy aging is marked by a decline in executive functions, being this decline pronounced in Mild Cognitive Impairment (MCI) and in Alzheimer's disease (AD). The aim of this dissertation was to evaluate the effects of executive functions, even indirectly, on other cognitive processes in elderly with normal aging, with MCI and with AD. We develop two studies conducted through mediation analysis to investigate the mechanisms by which a variable exerts its effect on other. The results of both studies indicated that executive functions influence both directly and indirectly in other cognitive processes, thus suggesting that their level of functioning influences broadly and in diversified ways on cognitive performance. We observed that, especially on pathological aging group, when compared to normal aging, a greater involvement of executive functions is required as a compensatory resource. We concluded that special attention should be directed to the executive functions in the neuropsychological assessment of elderly, since executive deficits may influence the efficiency of other cognitive processes.

**Keywords:** Executive Functions, Normal Aging, Pathological Aging, Mediation analysis.

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NA: Normal Aging

MCI: Mild Cognitive Impairment

a-MCI: Amnestic Mild Cognitive Impairment

mdaMCI: Multiple Domain Amnestic Mild Cognitive Impairment

AD: Alzheimer's Disease

CCL: Comprometimento Leve Amnéstico

DA: Demência de Alzheimer

MMSE: Mine Mental State Exam

TOL: Tower of London

sTCFT: "Simplified" Taylor Complex Figure Test

FDT: Five Digit Test

OLS: Ordinary least squares

CI: confidence interval

**SUMÁRIO**

## 1. INTRODUÇÃO

O envelhecimento populacional é um fenômeno que atingiu proporções sem precedentes nas últimas décadas. A população acima dos 60 anos tem crescido mais rapidamente do que a de crianças e adultos na maior parte dos países (United Nations, 2012). Em 2009 a população idosa mundial era aproximadamente de 700 milhões, e é estimado que em 2050 ultrapasse os 2 bilhões (United Nations, 2013).

A população brasileira tem experienciado um rápido envelhecimento populacional (United Nations, 2013), sendo esperado que ultrapasse a marca de 20 milhões de idosos em 2020 (Lima-Costa & Veras, 2003). Uma das consequências do envelhecimento populacional é o aumento da prevalência de doenças relacionadas ao envelhecimento, como dos quadros demenciais, especialmente da doença de Alzheimer (Aprahamian, Martinelli & Yassuda, 2009).

O processo de envelhecimento é marcado pela redução volumétrica cerebral (Giorgio et al., 2010), especialmente do córtex pré-frontal (Maillet & Rajah, 2013) e da formação hipocampal (Raz et al., 2005). Além das alterações estruturais, alterações funcionais associadas ao processo de envelhecimento também têm sido identificadas (Leal & Yassa, 2013), como a redução do metabolismo de glicose (Apostolova et al, 2010; Herholtz et al., 2002).

Em decorrência das alterações funcionais e estruturais no cérebro, o processo de envelhecimento saudável é marcado pelo declínio de alguns processos cognitivos (Raz e Rodrigue, 2005). Os aspectos fluidos da cognição, tais como as funções executivas, tendem a ser mais vulneráveis aos efeitos do envelhecimento primário, enquanto os aspectos cristalizados, como a memória semântica, tendem a ser mais estáveis durante a velhice (Craik & Bialystok, 2006). Há evidências de que o declínio das funções executivas (Lin, et al., 2007;

Royall et al., 2004), da velocidade de processamento (Salthouse, 2000, 1996) e da memória episódica (Grady & Craik, 2000; Craik & Rose, 2012; Baddeley, 2011) sejam consequências naturais do processo de envelhecimento normal.

No envelhecimento patológico as alterações cognitivas são mais pronunciadas e ocorrem de forma mais acelerada. Na demência por Doença de Alzheimer (DA), um dos tipos mais prevalentes de demência (McKhann et al., 2011), tem sido identificado comprometimento progressivo da memória como déficit central, mas também das funções executivas, mesmo em estágios iniciais (Storandt, 2008; Bélanger et al., 2010). Essas alterações cognitivas no idoso por sua vez, resultam em comprometimento funcional, impactando a realização das atividades de vida diária (de Paula e Malloy-Diniz, 2013). Segundo Hobson e Leeds (2001) déficits executivos interferem significativamente sobre a capacidade do indivíduo de cuidar de si e sobre a sua independência. Nos quadros de Comprometimento Cognitivo Leve (CCL) e Demência de Alzheimer o desempenho nas funções executivas tem sido fortemente associado às atividades de vida diária (Royall et al., 2007; Gold, 2012) constituindo-se também em um potencial preditor de conversão do CCL para a DA (Tabert et al., 2006).

De acordo com Goldberg (2000), as funções executivas funcionam de forma a coordenar outros módulos cognitivos, sendo que déficits executivos acabam afetando o bom funcionamento de outros sistemas mentais. Assim, um aspecto importante a ser investigado na Neuropsicologia do Envelhecimento é a relação entre funções executivas e outras medidas cognitivas. Assim, no presente estudo, através de análises de mediação, será investigada a influência direta e indireta das funções na memória episódica verbal e na habilidade de visioconstrução.

## 2. REVISÃO DA LITERATURA

As funções executivas correspondem a um conjunto de processos cognitivos que permitem ao sujeito direcionar propositalmente comportamentos a metas, escolher estratégias para realizá-las e avaliar a eficiência e a adequação de tais estratégias de acordo com o seu sucesso (Lezak et al., 2004; Malloy-Diniz et al., 2014).

O desenvolvimento das funções executivas ocorre durante o processo de maturação da circuitaria do córtex pré-frontal e atinge a maturidade tardiamente quando comparada as demais funções cognitivas (Fuster, 2008). Essas funções estão principalmente relacionadas a atividade da circuitaria frontoestriatal. O córtex pré-frontal dorsolateral, orbitofrontal e o cíngulo anterior, são algumas regiões cujas atividades são comumente associadas às funções executivas. A circuitaria do córtex pré-frontal dorsolateral está relacionada aos processos ditos mais analíticos da cognição, como a habilidade de planejamento, memória operacional, categorização, monitoração da aprendizagem e da atenção, flexibilidade cognitiva e estabelecimento de metas. A atividade do córtex pré-frontal orbitofrontal está associada a alguns aspectos do comportamento social, como automonitorização, empatia, cumprimento de regras sociais e processamento das informações afetivas e emocionais. Já o circuito do cíngulo anterior é importante para aspectos da motivação, controle executivo da atenção e para a seleção e controle de respostas (Kerr & Zelazo, 2004; Fuster, 2008; Malloy-Diniz, et al., 2014).

Durante o processo de envelhecimento saudável as funções executivas apresentam um declínio lento, mas consistente, sugerindo que seu desenvolvimento segue uma curva em forma de “U” invertido (Zelazo, Craik & Booth, 2004; Lin et al., 2007; Royall et al., 2004). Há evidências de declínio da capacidade de memória operacional (Hester, Kinsella & Ong, 2004; Huntley & Howard, 2010; Hobson & Leeds, 2001), do controle inibitório (Bélanger,

Belleville & Gauthier, 2010; Penã-Casanova et al.,2009), da flexibilidade cognitiva e do planejamento (Lin et al., 2007).

A teoria do envelhecimento frontal (West, 1996) foi proposta como uma tentativa de explicar o declínio cognitivo associado ao envelhecimento. Essa teoria baseia-se em evidências de que o córtex cerebral se deteriora de forma desproporcional, e que muitas mudanças neuronais associadas ao envelhecimento ocorrem precocemente no córtex pré-frontal. Essas alterações estão associadas ao declínio dos níveis de dopamina e declínio no volume e funcionamento do córtex pré-frontal (Hedden & Gabrieli, 2004). Assim, postula-se que o declínio das funções executivas esteja associado principalmente à deterioração do córtex pré-frontal, que é considerado um importante substrato para o funcionamento executivo (Salthouse, 2003).

Diversos são os modelos teóricos que buscam conceitualizar as funções executivas. Alguns a definem como um constructo unitário, enquanto outros como sendo composta por processos relativamente independentes mas com funcionamento integrados (Letho et al., 2003; Klwe-Schiavon et al., 2012). Entre os modelos teóricos que postulam um modelo único encontramos o Sistema Atencional Supervisor de Norman e Shallice (1986) e o modelo de Memória Operacional proposto por Baddeley e Hitch (1974; Miyake et al., 2000; Klwe-Schiavon et al., 2012). Entre os modelos que propõem a existência de múltiplos processos encontramos o modelo teórico proposto por Barkley (2001), Lezak e colaboradores (2012), Miyake e colaboradores (2000).

Miyake e colaboradores (2000) propuseram um modelo teórico hierárquico composto por três funções executivas nucleares, sendo elas a inibição, memória operacional e flexibilidade cognitiva. A partir da complexificação dessas funções nucleares, seriam formadas as funções executivas de ordem superior como o planejamento, raciocínio abstrato e a resolução de problemas (Diamond, 2013).

Os estudos que serão anexados à dissertação irão envolver três domínios nucleares das funções executivas, a Memória Operacional, o Controle Inibitório, a Flexibilidade Cognitiva e a capacidade de Planejamento, que representará as funções executivas complexas.

A memória operacional consiste em um sistema de capacidade limitada que envolve tanto o armazenamento temporário quanto a manipulação mentalmente de informações quando estas não estão mais perceptualmente presentes (Baddeley, 2012).

O modelo mais influente de memória operacional é o modelo multimodal elaborado por Baddeley e Hitch (1974). Inicialmente composto por três componentes interconectados, sendo eles a alça fonológica, o esboço visioespacial e o executivo central. Os dois tipos de memória operacional se distinguem pelo conteúdo, enquanto a alça fonológica está relacionada ao armazenamento temporário da informação de conteúdo verbal, o esboço visioespacial está relacionado ao armazenamento temporário de informações visuais e espaciais (Diamond, 2013). Esses dois sistemas são controlados pelo executivo central, componente mais complexo do modelo de memória operacional, que consiste em um sistema limitado em termos de atenção, que seleciona e manipula o material nos subsistemas (Baddeley, 2012). Posteriormente, um quarto componente foi adicionado ao modelo por Baddeley (2000), o buffer episódico. Este consiste em um sistema que permite que os componentes da memória operacional interajam e se liguem à memória de longa duração e à percepção.

O termo controle inibitório tem sido utilizado para se referir a distintos processos, tais como: a capacidade de inibir respostas prepotentes, interromper respostas que estão em curso e inibir respostas a estímulos distratores (Barkley, 2001). Entre os aspectos do controle inibitório encontra-se o controle inibitório da atenção, que permite ao sujeito focar seus recursos atencionais naquilo que foi selecionado e suprimi-los a estímulos alheios a tarefa, que possam interromper o curso eficaz de uma ação. O autocontrole que nos permite resistir

as tentações e não agir impulsivamente. Outro aspecto do autocontrole envolve a postergação de reforço, onde renuncia-se a uma gratificação imediata para uma maior recompensa posterior. Além desses aspectos, a inibição cognitiva é outro aspecto do controle inibitório. Ela está relacionada a habilidade de resistir a interferência proativa e a interferência retroativa (Diamond, 2013).

A flexibilidade cognitiva, outra função executiva considerada como estrutural, implica a capacidade de alternar o curso das ações de acordo com as exigências ambientais (Malloy-Diniz et al.,2010). Envolve também a mudança de perspectiva na abordagem de um problema, e também a flexibilidade para se adequar a novas exigências ou prioridades (Diamond, 2013). É essencial quando o plano inicial não é bem sucedido devido a imprevistos, ou quando é necessário alternar entre dois ou mais objetivos distintos. Se relaciona ainda ao pensamento abstrato e à cognição social (Diamond, 2013).

O planejamento é considerado uma função executiva de ordem superior. Refere-se à habilidade de estabelecer o melhor caminho para alcançar um objetivo, considerando as etapas necessárias para atingi-lo (Diamond, 2013). É considerado um dos mais importantes domínios das funções executivas, e requerer a colaboração de outros processos cognitivos (Lezak et al., 2004). Pulos e Denzine (2005) propõem a existência de dois tipos de planejamento. O pré-planejamento (look-ahead), o qual ocorre anteriormente ao início do comportamento para alcançar a meta estabelecida, envolvendo a elaboração da sequência de passos e a consideração de suas consequências. O segundo componente envolveria um planejamento on-line, o qual ocorre concomitante a execução do comportamento para alcançar a meta.

A ocorrência de comprometimento de funções executivas é frequente em doenças neurodegenerativas (Schroeter et al., 2012). Na DA tem sido identificado déficits executivos mesmo em seus estágios iniciais (Stopford et al., 2011; Storandt, 2008; Schroeter et al., 2012).

Tem sido proposto que o déficit em relação ao controle inibitório é um dos déficits executivos mais proeminentes nas fases iniciais da DA (Bélanger et al., 2010; Belleville, Rouleau, &Vander Linden, 2006), enquanto déficits na memória operacional e na flexibilidade cognitiva tendem a ocorrer mais tardiamente (Huntley & Howard, 2010; Salmon & Bondi, 2009).

Há evidências de comprometimento das funções executivas mesmo no CCL, o qual tem sido considerado um estágio de transição entre o envelhecimento cognitivo normal e a demência (Traykov et al., 2007; Chen et al., 2009; Brown, Devanand, Liu & Caccappolo 2011). Além disso, o comprometimento das funções executivas no CCL tem sido proposto como um possível preditor da conversão do CCL para a DA (Tabert et al., 2006; Balota et al., 2010).

Na Demência Frontotemporal variante comportamental da Degeneração Lobar Frontotemporal também tem sido identificado comprometimento de funções executivas. Os déficits executivos nesse tipo de demência geralmente estão relacionados aos domínios do planejamento, resolução de problemas, raciocínio abstrato e flexibilidade cognitiva (Neary, Snowden & Mann, 2005; Tolnay & Probst, 2001).

Em outros quadros neurodegenerativos como na Demência por Doença de Parkinson e na Demência por Corpos de Lewy, também têm sido identificado déficit das funções executivas, principalmente nos domínios do planejamento, da conceituação e do controle inibitório (Dodel et al., 2008).

As funções executivas são consideradas como um controlador de ordem superior dos demais processos cognitivos e comportamentais (Prencipe et al., 2011; Malloy-Diniz et al., 2014).). Essas funções são requeridas sempre que se está adquirindo novos conhecimentos, ou quando é necessário estabelecer um plano de ação. Desse modo, são funções necessárias para gerenciar o comportamento humano, essenciais para garantir o sucesso na vida cotidiana.

Considerando, como ressaltado a cima, a importância das funções executivas e as evidências de que o comprometimento destas funções tende a afetar variados aspectos do comportamento, o presente estudo procurou investigar a influência das funções executivas na habilidade de visioconstrução e na memória episódica no envelhecimento normal e no patológico.

A influência das funções executivas foi investigada através de análises de mediação conduzidas pelo macro PROCESS (Hayes, 2012). A análise de mediação objetiva ajudar a entender os mecanismos através dos quais uma variável preditora (X) exerce seu efeito em uma variável desfecho (Y). Para isso, tanto o efeito direto da variável X em Y é investigado, quanto o indireto através dos potenciais mediadores (M).

No primeiro estudo objetivou investigar se há efeito da habilidade de planejamento na cópia de uma figura complexa, e caso confirmado, se esse efeito ocorre apenas diretamente ou também indiretamente através de outras funções executivas. No segundo estudo foi investigado se os mecanismos pelos quais a idade influencia a memória episódica são semelhantes ou não no envelhecimento normal e patológico. Neste estudo a análise de mediação foi conduzida com o objetivo de verificar o efeito direto da idade na memória episódica e seu efeito indireto através da memória operacional.

# 3. OBJETIVOS

## 3.1. Geral

Avaliar a influência das funções executivas na memória episódica e nas habilidades visioconstrutivas em uma amostra composta por idosos com envelhecimento saudável e idosos com envelhecimento patológico.

## 3.2. Específicos

3.2.1. Avaliar o efeito do planejamento na cópia da Figura Simplificada de Taylor e o efeito indireto através da memória operacional, flexibilidade cognitiva e controle inibitório, em uma amostra heterogênea de idosos, composta por idosos com envelhecimento saudável e patológico.

- $h_0$: Não há relação de mediação entre o planejamento e a visioconstrução.

- $h_1$: Há efeito de mediação direto e indireto entre o planejamento e a visioconstrução.

3.2.2. Verificar se há diferença entre os mecanismos pelos quais a idade exerce efeito na memória episódica no envelhecimento normal e no patológico. Foi investigado o efeito direto da idade na memória episódica e indireto através da memória operacional.

- $h_0$: Não há relação de mediação entre a idade e a memória episódica nos grupos com envelhecimento normal e patológico.

- $h_1$: Há efeito de mediação entre idade e memória episódica nos grupos com envelhecimento normal e patológico.

- $h_2$: Pacientes com envelhecimento patológico e com envelhecimento normal apresentam diferentes padrões de associação entre idade e memória episódica.

## 4. PROCEDIMENTO

### 4.1. Amostra

Os dados dos dois estudos foram coletados no Centro de Referência ao idoso Professor Instituto Jenny Faria de Atenção à Saúde do Idoso, um centro público de atendimento secundário/ terciário a saúde do idoso na cidade de Belo Horizonte.

Todos os participantes passaram por uma avaliação neuropsicológica breve realizada por um neuropsicólogo, e por uma entrevista clínica realizada por um geriatra. A inclusão do participante nos estudos foi condicionada ao consenso entre os dois profissionais sobre o diagnóstico do paciente.

Os critérios de inclusão dos estudos foram idade superior a 60 anos, ausência de outras doenças neurológicas ou psiquiátricas, e ausência de deficiência sensorial ou motora grave.

O diagnóstico de Comprometimento Cognitivo Leve Amnéstico de domínio único ou de múltiplos domínios foi realizado de acordo com os critérios propostos por Winblad e colaboradores (2004; anexo 1). Os critérios diagnósticos propostos por McKhann e colaboradores (2011; anexo 2) foram utilizados para a realização do diagnóstico de provável Demência de Alzheimer.

Todos os participantes e familiares assinaram o termo de consentimento para participação na pesquisa. O presente estudo é parte de um projeto mais amplo aprovado pelo Comitê de Ética da Universidade Federal de Minas Gerais (Registro: COEP: 334/06).

# 5. WORKING MEMORY AND COGNITIVE FLEXIBILITY MEDIATES THE EFFECT OF PLANNING ON A COMPLEX FIGURE TEST COPY IN OLDER ADULTS WITH HETEROGENEOUS COGNITIVE BACKGROUNDS

Rafaela Teixeira de Ávila, Jonas Jardim de Paula, Manuel Sedó, Rodrigo Nicolato, Leandro Fernandes Malloy-Diniz

## Abstract

Planning refers to the ability to establish the best way to achieve a specific goal, considering the hierarchy of steps necessary to successfully achieve it. It is considered a higher order executive function. Many studies suggest that planning influences the performance on a complex figure test copy. The objective of the present study is to analyze whether there is a direct effect of planning, measured by the Tower of London (TOL), in The "Simplified" Taylor Complex Figure Test (sTCFT), an adaptation of the Taylor original figure. If the effect of planning on visuconstruction is confirmed, we also aim to investigate if this effect may occur indirectly through working memory, cognitive flexibility and inhibitory control. A heterogeneous sample of older adults (n= 129) composed by older with normal aging (NA), Amnestic Mild Cognitive Impairment (MCI), Amnestic Multiple Domain Mild Cognitive Impairment (amdMCI) and with Alzheimer's disease (AD) performed the TOL, sTCFT, the Corsi Block Spans and the Five Digit Test. For assess the direct and indirect effect of planning on visuoconstruction a mediation analysis was performed with all participants in the same group. We have found a significant correlation and association between all of the variables inserted in mediation model. A direct effect of planning on visuoconstruction was found, and moreover, that this effect is partially mediated by working memory and cognitive

flexibility. Our results indicate that low performance on complex figure copy is a consequence of influence of multiples factors.

**Keywords**: Planning; Visuoconstruction; Working Memory; Cognitive Flexibility; Inhibitory Control; Mediation Analysis

## 5.1. Introduction

Planning refers to the ability to establish the best way to achieve a specific goal, considering the hierarchy of steps necessary to achieve it, and requires the cooperation of a number of different cognitive processes, including other aspects of executive functions (Diamond, 2013). According to Carlin and Colleagues (2000) planning include a cognitive process like "look-ahead mechanism designed to generate multiple sequences of hypothetical events and their consequences, the development of stored structured event complexes that can guide movement from an initial to a goal state, and recognition of goal attainment". According to Pulos and Denzine (2005) there are two types of planning: preplanning (or "look-ahead") occurs before the initiation of the behavior to achieve the goal, involving elaboration of a sequence of steps and their consequences, and online planning which occurs when planning and execution are commingled. On the synthetic model of executive functions proposed by Diamond (2013), based on a commonly adopted model of hierarchical structure of this cognitive processes (Miyake et al., 2000), the planning ability is a high ordered executive functions, dependent of the more structural components of working memory, inhibitory control and cognitive flexibility.

The development of executive functions occurs during the process of maturation of the striatal-limbic-prefrontal networks (Fuster, 2009) and functions reach maturity later when compared with other cognitive functions. The executive functions follows an inverted U-

shaped curve across the lifespan, following the pattern of fluid aspects of cognition (Zelazo, Craik & Booth, 2004). Its development continues until early adulthood, and shows a slow, but consistent decline during aging (Zelazo, Craik & Booth, 2004). They are related to several aspects of daily life and self-regulation, including health (Miller et al., 2011), quality of life (Davis et al., 2010) and performance in Activities of Daily Living (de Paula et al., 2013).

A classic measure of planning abilities usually adopted in research and clinical settings is the Tower of London (TOL), developed by Shallice (1982). On this seminar paper the author, working on the concept of a Supervisory Attentional System, developed a cognitive test where the subject had to plan a series of steps (movements performed on a wooden tower) to achieve a specific goal (a target stimulus shown on a card). The test quickly becomes one of the most used paradigms for the assessment of planning, and several versions of the task were developed. Krikorian, Bartok and Gay (1994) adapted and validated the original Shallice task for the use with children, version that is one of the most used nowadays. Later, this version was modified by Portella and Colleagues (2003), aiming to reduce the ceiling effect found on the original version and, therefore, increasing its efficiency in identifying impairments of planning on a broader range of clinical conditions. This new version (Portella et al., 2003) was validated for the assessment of older adults with mild cognitive impairment and dementia (de Paula et al., 2012).

Other neuropsychological paradigm commonly adopted on clinical practice is the "Complex Figure Test" (Rabin, Barr & Burton, 2005). From this paradigm, Rey-Osterrieth Complex Figure Test is the most used test on clinical practice (Shin et al., 2004), where the subject must copy and later recall a complex geometrical figure. The test is a well-validated measure of visuospatial abilities and episodic memory (Shin, Park, Park, Seol & Kwon, 2006) and is sensitive in the detection of clinical conditions such as head injury (Schwartz, Penna & Novack, 2009), dementia (Ardila et al., 2000) and medial temporal lobe damage (Kixmiller et

al., 2000). Visuoconstructional ability requires a several processes that together transforms a mental representation into motor commands, and has a prominent spatial component (Smith, 20009; Fischer and Loring, 2004). Alternate versions of Rey-Osterrieth Complex Figure Test were developed, with the Taylor variant as the most commonly reported (Strauss, Sherman and Spreen, 2006). Complex Figure Tests generally consists of a copy trial followed by immediate and delayed recalls. This kind of test evaluates predominantly visuoconstructional ability and non-verbal episodic memory.

A common clinical interpretation of Complex Figure Tests involves the assessment of how much the subject planning abilities influences the copy performance. Previous studies reported significant associations between different measures of executive functions and the copy accuracy of Complex Figure Tests, but with conflicting results. A study with traumatic brain injury patients revealed that 11% to 16% of Rey-Osterrieth Complex Figure performance was accounted by executive functions (Schwarz, Penna & Novack, 2009). Watanabe and Colleagues (2005) suggests that Complex Figure Tests might be used as measures of executive functions in children with neurological disorders, but these results were not replicated in a recent paper (Weber, Riccio & Cohen, 2013). A more specific association between a specific scoring system of the Rey-Osterrieth Complex Figure Test and measures of planning (a maze task) was reported by Ogino and Colleagues (2009) in a study of children with neuropsychological disorders. These clinical data suggests an important association between executive functions and drawing.

Proposing a consensual cognitive model of drawing, Guérin, Ska and Belleville (1999) hypothesized three systems that together underlie the processing of drawing: visual perception, visual imagery and graphic production. Visual perception and visual imagery are required when doing an unfamiliar drawing, and comprise a bottom-up pathway, which includes visual memory, encoding of coordinates and categorical relations of the picture

grapho-elements and working memory. These processes are complemented by a top-down pathway, which includes attentional shifting, planning and action programming for the graphic reproduction. The authors state the need to clarify what aspects of planning would mediated the visuoconstructional abilities (Guérin et al., 1999). On the perspective of Diamond (2013) inhibitory control, working memory and cognitive flexibility are components of executive functions that allow the complex aspects of this construct, including planning. On a synthesis of these two models, the working memory and cognitive flexibility (which involves the attentional shifting) are potential mechanisms of the association between planning and drawing, while inhibitory control might not be significantly associated to drawing performance.

The present study aims to investigate the nature of the association of Planning with a complex figure copy. We tested a model, based on a hierarchical perspective of executive functions (Diamond, 2013), where planning is a high ordered component. We hypothesized that the effect of planning on visuoconstruction might be mediated by more basic components of these functions.

## 5.2. Methods

### *Participants*

We evaluated a heterogeneous sample of older adults referred for cognitive assessment enrolled on the present study on a secondary/tertiary public health center for older people in the city of Belo Horizonte, Brazil. There were 129 participants (68 women's) divided in four groups: Normal Aging (NA; n=26), Amnestic Mild Cognitive Impairment (aMCI; n=38), Multiple Domain Amnestic Mild Cognitive Impairment (mdaMCI; n=29) and Mild probable Alzheimer's disease (AD; n=36). We adopted the Winblad and Colleagues (2004) criteria for aMCI and mdaMCI, and the Mckhann and Colleagues for AD (2011). For the MCI patients,

the clinical course and symptom manifestation was typical of Alzheimer's disease (primary cognitive complaint related to memory, insidious onset and slow progression). All the demented patients scored between, 0.5 and 1 on the Clinical Dementia Rating (Morris, 1993), while all MCI participants scored below 1 and all healthy controls scored 0. The exclusion criteria were presence of other neurologic or psychiatric diseases, and absence of severe sensory or motor disabilities. All the MCI and healthy controls showed Mini-Mental State Examination scores above the Brazilian cut-off for dementia, according to education (Brucki et al., 2003). All the participants and their caregivers, when necessary, signed the informant consent for participation. The study is part of a broader project approved by the Universidade Federal de Minas Gerais Ethical Board (Registry: COEP: 334/06).

***Neuropsychological Assessment***

For the present study the participants performed a copy-recall Complex Figure Test adapted for Brazilian elderly patients with low formal education. The "Simplified" Taylor Complex Figure Test (sTCFT) is an adaptation of the Taylor original figure where some grapho-elements were excluded, reducing the components from 18 to 12 specific elements. The task seems a validity measure of visuoconstructional and non-verbal memory on older adults with low formal education according to preliminary studies (Melo et al, 2011; Ávila et al., 2013). The copy was followed by an immediate recall (3 minutes) and a delayed recall (25-30 minutes). The scoring criteria were based on the Taylor figure, considering the element accuracy and precision, ranging from 0 to 2 points. The total score of the test ranges from 0 to 24, and higher scores indicates better performance. Preliminary data shows good reliability, construct and criterion related validity for the Brazilian elderly population (de Paula et al. submitted).

As a measure of Planning abilities we used the TOL version proposed by Portella's and Colleagues (2003). The test consists of twelve problems of growing complexity where in a wooden tower with three pins of different length and three balls of different colors, starting from a fixed position, the subject must match a different configuration showed by the examiner. This version is valid for Brazilian older adults (de Paula et al., 2012). The total score ranges from 0 to 46. Higher scores indicate better planning abilities.

For the assessment of Working Memory we used the backward component of the Corsi Blocks Span (Kessels, van den Berg, Ruis & Brands, 2008). This task assess the visuospatial sketchpad component of the Baddelley (2013) working memory model. In the present study, we used the product score between the maximum span achieved and the total of correct trials, as proposed by Kessels et al. (2008), with scores ranging from 0 to 144. Higher scores indicates better working memory efficiency. The task was validated for this population (de Paula et al., 2013).

We adopted the Five Digit Test (FDT), proposed by Sedó (2004), as a measure of Inhibitory Control and Cognitive Flexibility. It is a stroop paradigm test involving numbers from 1 to 5 and quantities from 1 to 5 divided in four trials. The third trial involves a conflict situation where the subject must not read the numbers shown on the stimulus but tell how many digits are written (Ex.: in the stimulus 3-3-3-3 the correct answer is "four"). This component assesses selective attention - an important aspect of inhibitory control according to Diamond (2013). On the fourth component the same procedure is adopted, but along the previous stimulus the participant must shift the responses (what number and how many digits) along the stimulus, assessing the cognitive flexibility component. To reduce the usually high multicolinearity between timed tasks, we used the FDT Inhibition errors as a measure of Inhibitory Control and the FDT Shifting errors as a measure of Cognitive Flexibility.

***Statistical Procedures***

Once our data distribution were predominantly non-parametric, differences between groups were analyzed by non-parametric tests: the Kruskal-Wallis test for general group comparisons and Bonferroni-corrected for six specific group comparisons ($p = 0.008$ ). Bivariate correlations between planning, working memory, cognitive flexibility, inhibitory control, and sTCFT Copy were tested using Spearman correlation analysis. This analysis was conduct with all sample in the same group.

To estimate the direct and indirect effect of planning through mediators on sTCFT copy, we performed a mediation analysis. The objective of mediation analysis is to help answer how an predictor (X) influences an outcome (Y) directly and indirectly through one or more mediator variables, and to investigate how a causal agent X transmits its effect on Y (Hayes, 2013; Preacher and Hayes, 2008). In the present study we assessed the effect of planning (X) on sTCFT Copy (Y) directly and indirectly through multiples mediators being $M_1$=*working memory*, $M_2$= *cognitive flexibility* and $M_3$= *inhibitory control* using a macro (PROCESS) developed for SPSS by Hayes (2012). We used a parallel multiple mediator model analysis using Ordinary Least Squares (OLS) regression-based path analysis, once our mediators are supposed to be in the same hierarchical level. The significance for the potential specific indirect effect was assessed by a bootstrapping strategy (K=5000), once bootstrap confidence intervals respect the irregularity of the sampling distribution of indirect effect. This procedure also reduces the bias of a predominantly non-parametric data. We also conduct a percentile-based bootstrap confidence interval (CI) for the indirect effect. If the confidence interval do not contain the number zero, it provides evidence of a significant indirect effect. Whereas, if the confidence interval contain zero there is no sufficient evidence that the predictor affects outcome through mediators. A pairwise comparisons between specific indirect effects was used to test whether one indirect effect is statistically different

from another. All the procedures were performed on SPSS 20.0. The criterion for statistical significance was $p < 0.05$.

### 5.3. Results

Participants' description, group comparisons and the post-hoc analysis are reported in Table 5.1. The groups differed significantly on age and education, and as expected, on all neuropsychological measures.

**Table 5.1: Participants' description and group comparisons**

| | NC (1) | | aMCI (2) | | mdaMCI (3) | | AD (4) | | Group comparisons | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **M** | **SD** | **M** | **SD** | **M** | **SD** | **M** | **SD** | **K-W** | **p-value** | **Post-hoc*** |
| **Age** | 70.58 | 7.17 | 73.03 | 7.00 | 77.00 | 7.43 | 76.17 | 7.11 | 13.59 | 0.004 | 1 < 3, 1 < 4 |
| **Education** | 6.23 | 4.38 | 6.97 | 5.53 | 3.97 | 3.65 | 3.75 | 3.19 | 16.36 | 0.001 | 1 > 4, 2 > 3, 2 > 4 |
| **MMSE** | 26.85 | 3.04 | 26.58 | 2.03 | 23.52 | 3.17 | 21.33 | 3.25 | 53.02 | <0.001 | 1 > 3, 1 > 4, 2 > 3, 2 > 4 |
| **TOL** | 21.54 | 9.14 | 25.79 | 8.85 | 22.28 | 9.78 | 16.28 | 8.13 | 17.35 | 0.001 | 2 > 4 |
| **sTCFT Copy** | 19.23 | 5.53 | 19.84 | 4.47 | 15.41 | 5.63 | 14.81 | 6.20 | 23.45 | <0.001 | 1 > 3, 1 > 4, 2 >3, 2 > 4 |
| **CSB** | 16.31 | 12.29 | 17.32 | 10.30 | 11.21 | 8.19 | 10.44 | 8.63 | 11.83 | 0.008 | 2 > 4, 3 > 4 |
| **FDT Inhibition** | 3.19 | 5.11 | 3.05 | 3.63 | 7.21 | 7.54 | 5.86 | 7.09 | 8.82 | 0.032 | - |
| **FDT Shifting** | 6.88 | 6.97 | 5.42 | 5.06 | 11.03 | 5.88 | 11.28 | 6.44 | 26.20 | <0.001 | 1 < 3, 1 < 4, 2 < 3, 2 <4 |

MMSE: Mini-Mental State Examination, TOL: Tower of London Test, sTCFT: "Simplified" Taylor Complex Figure Test, CSB: Corsi Span Backward, FDT Inhibition: Five Digit Test Inhibition errors, FDT Switching: Five Digit Test Flexibility errors, 1: Normal Controls, aMCI: Amnestic Mild Cognitive Impairment, mdaMCI: Multiple Domain Amnestic Mild Cognitive Impairment, AD: Alzheimer's disease, k-w: Kruskal-Wallis.*Bonferroni-corrected p-values for specific comparisons (p = 0.008).

Table 5.2 shows the correlations between the executive functions tests and the sTCFT. All the correlations were significant, and effect sizes ranged from small to moderate.

**Table 5.2: Correlations between independent variable and the outcome variables (n=129)**

| Measures | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| **1. Visuoconstruction[1]** | 0.367** | 0.413** | -0.502** | -0.420** |
| **2. Planning[2]** | | 0.386** | -0.260** | -0.212* |
| **3. Working Memory[3]** | | | -0.293** | -0.299** |
| **4. Cognitive Flexibility[4]** | | | | 0.470** |
| **5. Inhibitory Control[5]** | | | | 1.000 |

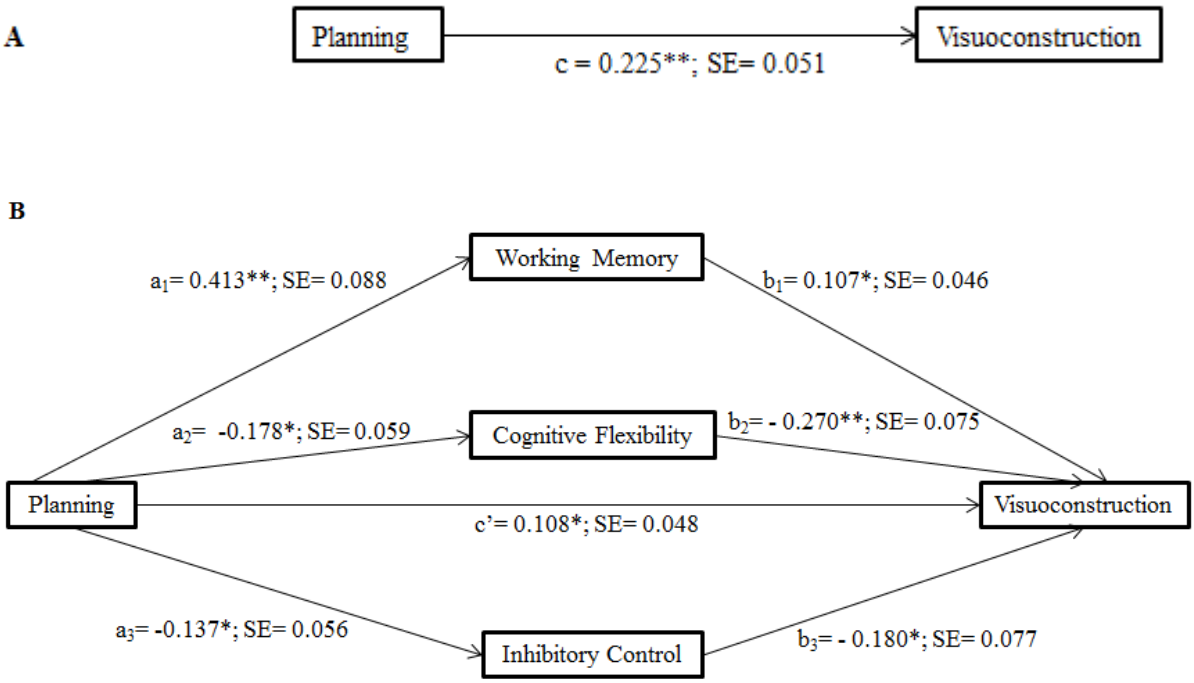
* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
1 – Simplified Taylor Complex Figure Test, 2- Tower of London, 3- Corsi Blocks Span Backward, 4- Five Digits Test Flexibility errors, 5- Five Digits Test Inhibition errors.

The first step of mediation analysis tested the association of the independent predictor (planning) with the mediator variables (working memory, cognitive flexibility and inhibitory control). When controlling for others variables, planning was associated with all of our potential mediators. As can be seen in table 5.3, all of ours potential mediators also have associated significantly with our outcome, the visuoconstructional ability measured by the sTCFT copy, when controlling for others variables.

The parallel multiple mediation analysis using the ordinary least square method assessed the direct influence of planning and it's indirect influence by the proposed mediators on the visuoconstruction ability. The total effect of our model ($c = 0.225$, $t = 4.449$, $p < 0.001$) was larger than the direct effect of planning on visuoconstruction ($c' = 0.108$, $t = 2.262$, $p = 0.025$). When all mediators were controlled, we found a significant direct effect of planning on sTCFT copy as can be seen in table 5.3 and figure 5.1. Because the direct effect did not decrease to zero when the mediators were entered in the model, we have found a

partial mediation. Thereby, our parallel mediation model does not explain all mechanisms by which planning affects complex copy drawing.

**Figure 5.1:** Panel A – Total effect of planning on visuoconstruction; Panel B – Direct and indirect effects of planning on visuoconstruction through mediators




* p<0,05; ** p<0.001

*Note.* Planning: Tower of London, Visuoconstruction: sTCFT copy, Working Memory: Corsi Blocks Span Backward, Cognitive Flexibility: Five Digits Test Flexibility errors, Inhibitory Control: Five Digits Test Inhibition errors.

Our results suggest that sTCFT Copy differs as function of planning. Planning was positively associated to working memory, and negatively associated to cognitive flexibility and inhibitory control (paths a in figure 5.1). It should be noted that these two negative associations are due the fact that scores used as measure of cognitive flexibility and inhibitory control were in different metric in relation to the others. Each specific mediator on our analysis predicted the sTCFT copy when controlling for planning and the others mediators (Figure 5.1, paths b). However, there is significant evidence that planning affects

visuoconstruction indirectly only through two of our potential mediators. For this analysis, we used a 5.000 resampling approach by the PROCESS macro. Statistical significance was assessed by the CI values: if its positive or negative (lower and upper bound of the CI entirely above or below zero) the effect is significant, if straddle "0" it is not considered significant. As can be seen in table 5.4, we found a significant positive indirect effect of planning on sTCFT Copy through working memory (point estimate= 0.050, 95% percentile CI= 0.017 to 0.091), and through cognitive flexibility (point estimate= 0.049, 95% percentile CI= 0.015 to 0.093), as the confidence intervals are entirely above zero. However, the indirect effect through inhibitory control was not significant since it straddles zero (point estimate= 0.025, 95% percentile CI= -0.0003 to 0.062). We performed a pairwise comparison between the indirect effects of planning through working memory and through cognitive flexibility to test if one of these effects is significantly larger (which may indicate a stronger mediator in this analysis). The results did not indicate significant differences between them (point estimate= -0.004, 95% percentile CI= -0.059 to 0.0489).

**Table 5.3: Regression Coefficients, Standard Errors, and Model Summary Information for the Parallel Multiple Mediator Model**

| | | Consequent | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $M_1$ (Working Memory) | | | $M_2$ (Cognitive Flexibility) | | | $M_3$ (Inhibitory Control) | | | | Y (sTCFT Copy) | | |
| **Antecedent** | | **Coeff.** | **SE** | **P** | **Coeff.** | **SE** | **p** | **Coeff.** | **SE** | **p** | | **Coeff.** | **SE** | **p** |
| **X (Planning)** | $a_1$ | 0.413 | 0.09 | <0.001 | $a_2$ - 0.178 | 0.06 | 0.003 | $a_3$ - 0.137 | 0.06 | 0.016 | **c'** | 0.108 | 0.05 | 0.025 |
| **$M_1$** | | - | - | - | - | - | - | - | - | - | **$b_1$** | 0.107 | 0.05 | 0.022 |
| **$M_2$** | | - | - | - | - | - | - | - | - | - | **$b_2$** | - 0.270 | 0.07 | <0.001 |
| **$M_3$** | | - | - | - | - | - | - | - | - | - | **$b_3$** | - 0.180 | 0.08 | 0.021 |
| **Constant** | | 4.940 | 2.06 | 0.018 | 12.445 | 1.38 | <0.001 | 7.74 | 1.32 | <0.001 | | 16.701 | 1.42 | <0.001 |
| | | $R^2 = 0.15$ | | | $R^2 = 0.07$ | | | $R^2 = 0.04$ | | | | $R^2 = 0.37$ | | |
| | | F(1,127)=22.17,p=<0.001 | | | F(1,127)=9.24,p=0.003 | | | F(1,127)=5.96,p=0.016 | | | | F(4,124)=18.46,p<0.001 | | |

*Note.* Coeff: Coefficient; SE: Standard error. Mediation model using OLS regression.

1- Corsi Blocks Span Backward, 2- Five Digits Test Flexibility errors, 3- Five Digits Test Inhibition errors, X – Tower of London,Y- Simplified Taylor Complex Figure Test.

**Table 5.4: Conditional indirect effect of working memory, cognitive flexibility and inhibitory control on visuoconstruction**

| | Point estimate | Bootstrap SE | 95% percentile bootstrap CI |
|---|---|---|---|
| **Working Memory[1]** | 0.044 | 0.019 | 0.012 to 0.082 |
| **Cognitive Flexibility[2]** | 0.048 | 0.020 | 0.014 to 0.094 |
| **Inhibitory Control[3]** | 0.025 | 0.015 | -0.0003 to 0.062 |

*Note.* 5.000 bootstrap samples. 1 - Corsi Blocks Span Backward, 2 - Five Digits Test Flexibility errors, 3 - Five Digits Test Inhibition errors., SE: Standard Error, Ci: Confidence Interval.

### 5.4. Discussion

The aim of this work was to investigate how the planning abilities, a high-ordered executive functions, associates with a complex figure test copy. We have found a partial parallel multiple mediator model where planning affects sTCFT copy directly and indirectly through working memory and cognitive flexibility in a heterogeneous sample of older adults with different cognitive background.

We found that the relationship between planning and complex figure copy is more complex than suggested by the literature. Although we found a direct effect of planning on visuoconstrution, this association was driven in part by visuospatial working memory and cognitive flexibility. These indirect effects are in line with the proposal that different aspects of executive's functions are related to complex drawing, more specifically, the working memory and cognitive flexibility (Guérin et al., 1999). A positive direct and indirect effects was found, results that are consistent with the proposal that better functioning of some executive functions relates to higher accuracy on a complex drawing test (Guérin et al., 1999). Although, several studies have investigated the association between planning and visuoconstruction (Ogino et al., 2009; Schwarz, Penna & Novack, 2009; Watanabe et al., 2005), the current work, to our knowledge, is the first study to investigate the mechanisms by which planning transmits its effect, based on a cognitive model of drawing.

As stated by Guérin and Colleagues (1999) there is a need to clarify which aspects of planning are associated with drawing copy. From a hierarchical perspective, we tested these associations using basic aspects of executive functions. Since the direct effect of planning remained significant when the potential mediators were included in the model, the association between planning and visuoconstruction in our model is not fully mediated by working memory and cognitive flexibility. This result also demonstrates that planning measured by TOL has an independent contribution in explaining variance on figure copy. Is important to emphasize that we have found a partial multiple mediator model, therefore, other factors besides working memory and cognitive flexibility may account for influence of planning on drawing copy.

In agreement with the literature, we have found association between planning, measured by the TOL, and complex figure copy when all mediators were controlled. The positive indirect effect of planning on sTCFT copy indicates that better planning ability is associated with better accuracy in figure copy. Guérin and Colleagues (1999) suggest that impairment on planning could result in difficulties on drawings copy, evidence that is supported by other studies with different neuropsychological measures (Schwarz, et al., 2009; Ogino et al., 2009). Our work is in line with clinical studies that found association between inefficient planning and inaccurate drawing performance. Elderkin-Thompson and colleagues (2004) assessed older adults with depression and found an association between poor planning and a more inefficient organization complex figure copy, compromising its quality. As we, Freeman and cols. (2000) found association between planning and quality of copy of a complex figure test in a study with healthy elderly and demented patients. They have found that healthy elderly had better planning, reproducing better the configural elements and having better performance on copy of a complex figure.

Although only two of our three mediators were significant, we have found association between all of our potential mediators (working memory, cognitive flexibility and inhibitory control) with our independent variable, planning (paths a). This finding is consistent with the literature which indicates that these cognitive processes contribute to the performance on TOL (Carlin et al., 2000; Köstering et al., 2014; Welsh, Satterlee-Cartmell and Stine, 1999). Previous studies shows that during the execution of TOL, working memory is required once is necessary keep a sequence of subgoals in the working memory during execution to accomplish the objective, especially when doing preplanning (Gilhooly et al., 2002; Welsh et al., 1999). The demand of cognitive flexibility must be related to TOL performance once during this task is necessary generates several alternative move subgoals to select the most appropriate to achieve the goal (Köstering et al., 2014). The literature suggests that the contribution of inhibitory control is also required because is necessary to inhibit the automatic behavior of moving a ball directly into its goal position to plan the moves to solve the problem successfully (Koppenol-Gonzalez, Bouwmeester & Boonstra, 2010). These results suggest that poor performance on TOL might not represent a core planning deficit, whereas multiple factors influence performance on this task.

We also have found significant association between ours potential mediators with our outcome, visuoconstruction (paths b). According to Guérin, and Colleagues. (1999) the involvement of the visuospatial scketchpad is required on drawing tasks, once is necessary to process the position and orientation of the elements. The visuospatial working memory might involve two components, a passive and an active process (Millet et al., 2009). Passive is related to temporary information retention of form and location of visual stimuli, and active is related to retention and execution of movement sequences and to the ability to operate mental rotation. In this sense, the copy of a complex figure would demand the use of the passive component to store the figure elements and its organization, while the active component

would allow the mental imagery of the organization and its expression by motor routines. In agreement to this proposal, in a study with a heterogeneous elderly sample, Freeman and cols. (2000) found an association between visual working memory test and copy of a modified Rey Complex Figure. When considering the inhibitory control, opposite to our results, Freeman and cols. (2000) did not found any relationship of this cognitive domain with copy of a complex figure in a heterogeneous sample of elderly. No work investigating the association between complex figure copy and cognitive flexibility was found. We hypothesized that the aspects of cognitive flexibility of being able to change perspective spatially and the ability of flexibly switch the course when needed might be related to a complex copy drawing test.

Some limitations of our study comprise a small sample size limiting the generalization of the finds. Although our sample size is sufficient to detect a moderate or large effect size, it may not be sensitive to small effects. We could not say whether the direct effect is larger or smaller than the indirect effects, because there is no consensus as to which method is the most appropriate to measure the effect sizes on multiple mediators model (Preacher and Kelley, 2011; Hayes, 2013). We have to emphasize that a partial mediation model was found, therefore our model do not explain all mechanisms by which planning exert its effect on a complex figure test copy. In the present study, we do not control the effect of age. According to other studies advancing age is a cognitive process that influence performance on TOL and on complex figure copy (Strauss et al., 2006; Gallagher and Burke, 2007). We also did not analyze the effect of intelligence. As reported by previous articles, intelligence predicts performance on TOL and on complex figure copy (Zook et al., 2004; 2006; Köstering et al., 2014). Therefore, intelligence and age might account for part of the mechanisms that our mediation model did not explain. Ours results indicate that low performance on complex figure copy is a consequence of influence of multiples factors.

To our knowledge our study is the first to an attempt to understand how planning exert its effect on a complex figure copy through different paths in a heterogeneous sample of elderly. We found a significantly direct effect of planning on sTCFT copy. We also demonstrated that the relationship between planning and sTCFT was partially mediated by working memory and cognitive flexibility. Future studies must be performed with larger samples trying to reach a model where all mechanisms of influence can be explained.

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## 6. WORKING MEMORY MEDIATES THE ASSOCIATION BETWEEN AGE AND MEMORY RECALL ON PATHOLOGICAL AGING BUT NOT ON NORMAL AGING

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**Abstract:** Is well established in the literature that episodic memory declines with the processing of aging. Studies suggest that this decline might be mediated by age-related decline of executive functions. In the present study we aim to investigate whether age affects directly episodic memory on normal aging and on pathological aging. If confirmed, we also want to investigate if this effect may occur indirectly through executive functions, and if the mechanisms by which age influences episodic memory differ between normal and pathological aging. 74 older adults with normal aging and 97 with pathological aging were submitted to a neuropsychological protocol that includes Digit Span, Five Digit Test and Rey Auditory Verbal Learning Test (RAVLT). From the executives measures, only working memory correlated significantly with age and memory recall in each group. Thus, a simple mediation model was conduct for each group, where age was the predictor variable, memory recall the outcome and working memory the potential mediator. The result of our mediation models differed between the two groups. On normal aging, we have found only a significant direct effect of age on episodic memory. However, on pathological group a significant direct effect was found, and also that part of this direct effect of age on episodic memory is partially mediated by working memory. Our results show that the mechanisms by which age exerts its effect on memory varies between normal aging and pathological aging.

**Keywords:** Episodic Memory; Executive Functions; Working Memory; Normal Aging; Mild Cognitive Impairment; Mediation Analysis

## 6.1. Introduction

Episodic memory is a long-term declarative memory that involves the ability to learn, store and retrieve the acquired information temporally determined (Stebbins et al., 2012; Dickerson & Eichenbaum, 2010; Craik & Rose, 2012). It also involves the ability to remember past experiences with temporal label, including information such as where and when an event occurred, and requires rapid encoding of association among different aspects of an event that have been experienced (Henke, 2010; Tulving, 2002).

Considering the brain areas, episodic memory is supported by a network including the medial temporal lobe, with important role of hippocampus and parahippocampal strctures in the acquisition of new information, and by neocortical association areas (Dickerson & Eichenbaum, 2010). Beyond the medial temporal lobe, the prefrontal cortex seems to have a significant participation on memory with the ventrolateral region playing an important role on episodic memory (Simons & Spiers, 2003). Studies have shown that interaction between medial temporal lobe and the prefrontal cortex is extremely important to an efficient memory function (Dickerson et al., 2007; Simons & Spiers, 2003).

Functional neuroimaging studies have shown regularity on encoding and retrieving, as defined in the HERA model (hemispheric encoding/retrieval asymmetry). That model is based on empirical regularity that shows that the left prefrontal cortex is more involved than the right in encoding information into episodic memory, whereas the right prefrontal cortex is more involved than the left in memory retrieval (Tulving, 2002). This model shows the importance of the frontal lobes to episodic memory.

It is well documented that there is age-related changes on episodic memory during the process of aging (Baddeley, 2011; Grady & Craik, 2000). Decline of episodic memory on older adults with normal aging must be related to changes in the functioning of neural systems that support this memory processes (Stebbins et al., 2002). Craik and Rose (2012) suggest that once encoding and retrieval operations share some features, age-related memory decline may reflect impairment on mechanisms underlying these two processes. Impairment of episodic memory is pronounced in patients with pathological aging, as in dementia caused by Alzheimer's disease (AD), which have memory impairment as one of the most prominent deficit (McKhann et al., 2011).

There are many attempts to explain cognitive mechanisms underlying age-related memory deficits. Craik and Rose (2012) concluded in a review article that many problems on encoding memory during aging derive principally from decline of certain processing operations, like of attention and working memory. Salthouse (1996) proposes that the decline of processing speed is a major factor contributing for decline of cognitive functions with increasing age, including of memory performance. Another mechanism proposed to account to age-related decrement of memory is the reduced processing resources. This theory proposes an age-related decline of attentional resources available for cognitive processing, which in consequence compromises memory efficiency (Luo & Craik, 2008).

The frontal aging theory is also suggested as a potential mechanism underlying the age-related decline of episodic memory (Parks et al., 2011). According to this hypothesis the cerebral cortex deteriorates disproportionately, with the frontal lobe, especially the prefrontal cortex, being one of the first brain area affected (West, 1996; Hedden & Gabrieli, 2004).

Executive functions are related to frontoestriatal circuitry, and as the episodic memory, declines in normal aging (Lin et al., 2007). Have been postulated that decline of executive functions with advancing aging could affect the memory performance of elderly

(Bouazzaoui et al., 2013). Decline of working memory capacity, for instance, has been related to a worse episodic memory performance (Craik & Rose, 2012; Unsworth et al., 2011).

Neuroimaging studies suggests that decline of memory on older adults is related to reduced activity of cortical brain areas, especially of the prefrontal cortex and temporal medial (Grady & Craik, 2000). Studies have shown that healthy older adults have reduced left pre-frontal cortex activation during encoding of new information when compared to young adults (Daselaar, Dennis & Cabeza, 2007; Stebins et al., 2002). However, increase activity of the right prefrontal cortex during retrieving on healthy elderly has been demonstrated (Grady and Craik, 2000). This different pattern of activation in older adults with a reduction of lateralization has been called as Hemispheric Asymmetry Reduction in Older Adults (HAROLD).

In the current study we aim to investigate how age exerts its effect on memory recall. We investigate the direct effect of age on memory recall on normal and pathological aging, and if this effect may occur through executive functions. We also want to verify if the mechanisms by which age exerts its effect on memory differ between normal and pathological aging.

## 6.2. Methods

### *Participants*

We studied a total of 74 older adults with normal aging (55 women) and 97 with pathological aging (51 women). The pathological group was composed by patients with amnestic Mild Cognitive Impairment (aMCI; n= 61) and Multiple Domain Amnestic Mild Cognitive Impairment (mdaMCI; n= 36). For MCI diagnosis the criteria proposed by Winblad and Colleagues (2004) was used. The Clinical Dementia Rating of all MCI patients was

below 1, and of normal aging was 0. None of the participants had other neurological or psychiatric diseases, according to exclusion criteria adopted.

All patients underwent a medical assessment performed by a geriatrician, and were also assessed by a brief neuropsychological protocol conduct by a neuropsychologist. The neuropsychological protocol included several neuropsychological tests previously validated for older adults (de Paula et al., 2013) and the Five Digit Test. The diagnoses were performed by consensus of both professionals. The participants were assessed at the Instituto Jenny Faria de Atenção à Saúde do Idoso, a secondary/tertiary public health center for older adults in the city of Belo Horizonte, Brazil.

This study is part of a broader project approved by the Research Ethics Committee of the Universidade Federal de Minas Gerais (Registry: COEP: 334/06). All patients and their families gave written consent for participation.

***Neuropsychological Assessment***

*Rey Auditory Verbal Learning Test (RAVLT):* In the present study the Brazilian version of the test for older adults proposed by Malloy-Diniz and cols. (2007) and validated by de Paula and Colleagues (2012) was adopted. This test measures the processes of learning, recall and recognition of verbal episodic memory. It consists of five learning trials of a fifteen word list followed by an interference list, an immediate recall (RAVLT IR), a 25-minutes delayed recall (RAVLT DR) and a recognition trial (RAVLT Rec). In the present study we adopted the delayed recall as measure of episodic memory.

*Digit Span Test:* It is a test where the participant is required to repeat a series of digits of increasing length in the forward or backward order. We used the backward order product score between the maximum span achieved and the total of correct trials of the Digit Span for

the assessment of verbal working memory (Kessesl, van den Berg, Ruis & Brands, 2008). The reverse order measures the phonological loop, a component of the working memory model (Baddeley, 2011). This test is validated for this population (de Paula et al., 2013).

*Five Digit Test (FDT):* It is a stroop paradigm test proposed by Sedó (2004) composed by four successive parts: decoding (reading numbers), retrieving (counting figures), inhibiting (saying the number of digits instead of reading the digit) and shifting (switch between counting and reading). The test involves automatic process (parts 1 and 2) and controlled process (parts 3 and 4). It is composed by numbers from 1 to 5 and also by quantities from 1 to 5. In the present study we used the FDT Inhibition errors as measure of inhibitory control, and FDT Switching errors as measure of cognitive flexibility.

***Statistical Procedures***

The first objective was to investigate the direct effect of age on memory, and if it may occur indirect through multiple executive functions mediators: Working Memory, Cognitive Flexibility and Inhibitory Control. One condition to conduct mediation analysis is having correlation between the independent variable, mediators and outcome variable. Our first step was conduct bivariate correlations between age, working memory, cognitive flexibility, inhibitory control and memory recall using Pearson correlation analysis in each group, once our data showed predominantly parametric distributions. This analysis showed that in both groups only age, working memory and memory recall were significantly correlated. No significantly correlation between cognitive flexibility and inhibitory control with age and memory recall were found neither on normal aging nor in pathological aging ($p>0.05$). Therefore, we conduct a simple mediation analysis in each group, where working memory was the unique potential mediator.

In the present study we used for simple mediation analysis the macro PROCESS developed by Hayes (2012). This macro estimates the direct and indirect effects using Ordinary Least Squares (OLS), and provides constituents components through standard regression statistics such as $R^2$. The mediation analysis aims to help understand the mechanisms by which a predictor influences (X) an outcome (Y) (Hayes, 2013).

We conduct the mediation analysis with the same variables for the normal and pathological aging groups. For both groups our predictor was age (X), the potential mediator was working memory (M) and the outcome variable was memory recall (Y). The group division was made because we wanted to verify whether age affects memory through the same mechanisms on normal and on pathological aging. The bootstrapping strategy (K=5000) was used to assess the significance of the indirect effect. Bias corrected-based bootstrap confidence interval (CI) for the indirect effect was conduct. An indirect effect is statistically significant if zero does not lies within the interval range. If zero does not occur in the confidence interval then we can conclude that the indirect effect is significant.

All the procedures were performed on SPSS 20.0. The criterion for statistical significance was $p< 0.05$.

**6.3. Results**

Groups' description and group comparisons are reported in Table 6.1. The groups differed significantly on age and on all neuropsychological measures, but not on schooling. The Table 6.2 shows the correlations between age, working memory and memory recall for each group. All correlations were significant.

**Table 6.1: Groups' description and group comparisons**

| | NA | | PA | | Anova (Sig.) |
|---|---|---|---|---|---|
| | **M** | **DP** | **M** | **DP** | |
| **Age** | 72.46 | 7.27 | 76.00 | 7.62 | 0.003 |
| **Education** | 6.74 | 4.27 | 5.43 | 4.56 | 0.058 |
| **MEEM** | 27.21 | 2.51 | 24.55 | 4.56 | <0.001 |
| **DSB** | 16.09 | 10.29 | 12.31 | 7.93 | 0.007 |
| **RAVLT - A7** | 8.62 | 2.73 | 3.47 | 1.92 | <0.001 |

MMSE: Mini-Mental State Examination, DSB: Digit Span Total Backward, RAVLT – A7: delayed recall, NA: normal aging, PA: pathological aging composed by aMCI and mdaMCI.

**Table 6.2: Correlations between independent variable and the outcome variables**

**6.2.1: Normal aging**

| **Measures** | **2** | **3** |
|---|---|---|
| **1. Age** | -0.287* | -0.333** |
| **2. Working Memory** | | 0.234* |
| **3. Memory recall** | | 1.000 |

**6.2.2: Pathological aging**

| **Measures** | **2** | **3** |
|---|---|---|
| **1. Age** | -0.230* | -0.207* |
| **2. Working Memory** | | -0.220* |
| **3. Memory recall** | | 1.000 |

*Note.* *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). 2- Digit Span Total Backward, 3 – RAVLT delayed recall.

The simple mediation analysis conduct with normal aging group showed a negative association of age with working memory when the other variable was controlled (figure 6.1.1 path $a_1$). A negative association between age and memory recall was also found (path $c_1$'). These results indicate that increase age is associated with worse working memory and memory recall performance. No significant association between working memory and memory recall was found (path $b_1$), as can be seen in table 6.3.1. The simple mediation analysis using ordinary least square analysis assessed the direct effect of age on memory recall. Our results show a negative direct effect of age on memory recall (point estimate= -0.109, CI= -0.195 to -0.022, p= 0.014). As no significant association between working memory and memory recall was found, we cannot consider working memory as a mediator,

since it is necessary that constituents paths (a and b) differ from zero. However, a confidence interval to test the statistical significance of the indirect effect was generated. For this analysis, we used a 5.000 resampling approach by the PROCESS macro. The result of this analysis corroborated the previous finding. The indirect effect of aging on memory through working memory recall in normal aging group was not significant because the confidence interval straddles zero (point estimate= -0.016, 95% bias corrected CI= -0.059 to 0.002).

The mediation analyses conduct with pathological aging group followed the same procedures adopted for normal aging. The results showed a significant negative association between age and working memory ($a_2$), a negative association between working memory and memory recall ($b_2$), and also a negative association between age and memory recall ($c_2$') when the other variable was controlled, as can be seem in table 6.3.2. A negative direct effect of age on memory recall was found (point estimate= -0.068, CI= -0.118 to -0.018, p= 0.007). Contrary to what occurred with the normal aging group, we have found a significant positive indirect effect of age on memory recall through working memory (point estimate= 0.016, CI= 0.0005 to 0.047). When the potential mediator was introduced in the model, the direct effect did not reduce to zero. So, we have a partial mediation model that did not explain all mechanisms by which age influence memory recall in this group.

**Table 6.3: Regression Coefficients, Standard Errors, and Model Summary Information for the Simple Mediator Model**

### 6.3.1: Normal aging

| | | Consequent | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | $M_1$ (Working Memory) | | | | Y (Memory Recall) | | |
| **Antecedent** | | **Coeff.** | **SE** | **P** | | **Coeff.** | **SE** | **p** |
| **X (Age)** | $a_1$ | -0.405 | 0.16 | 0.013 | $c_1$' | -0.109 | 0.043 | 0.014 |
| $M_1$ | | - | - | - | $b_1$ | 0.040 | 0.031 | 0.195 |
| **Constant** | | 45.477 | 11.64 | <0.001 | | 15.880 | 3.334 | <0.001 |
| | | $R^2 = 0.08$ | | | | $R^2 = 0.13$ | | |
| | | F(1,72)=6.43, p=0.013 | | | | F(2,11)=5.39, p=0.006 | | |

*Note.* Coeff: Coefficient; SE: Standard error. Mediation model using OLS regression.
1 – Digit Span Backward, Y – RAVLT delayed recall.

### 6.3.2: Pathological aging

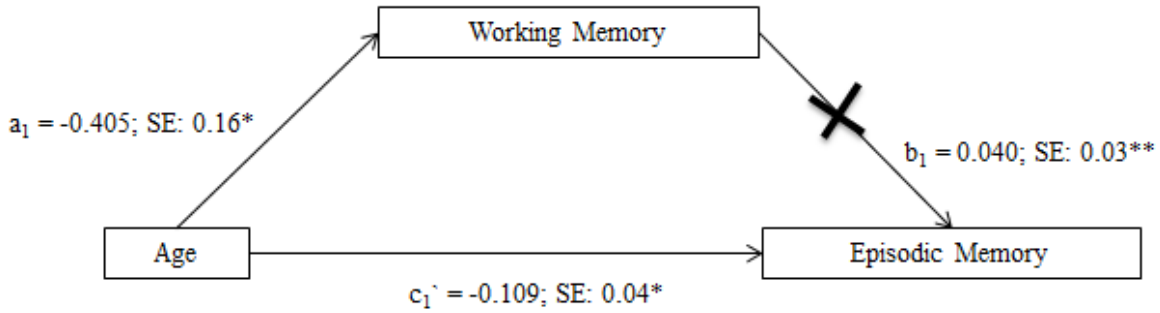
| | | Consequent | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | $M_1$ (Working Memory) | | | | Y (Memory Recall) | | |
| **Antecedent** | | **Coeff.** | **SE** | **p** | | **Coeff.** | **SE** | **p** |
| **X (Age)** | $a_2$ | -0.239 | 0.10 | 0.024 | $c_2$' | -0.068 | 0.02 | 0.007 |
| $M_2$ | | - | - | - | $b_2$ | -0.069 | 0.02 | 0.006 |
| **Constant** | | 30.460 | 793 | <0.001 | | 9.541 | 2.01 | <0.001 |
| | | $R^2 = 0.05$ | | | | $R^2 = 0.12$ | | |
| | | F(1,95)=5.28, p=0.024 | | | | F(2,94)=6.28, p=0.002 | | |

*Note.* Coeff: Coefficient; SE: Standard error. Mediation model using OLS regression.
1 – Digit Span Backward, Y – RAVLT delayed recall.

**Figure 6.1. 6.1.1: Panel A – Direct and indirect effects of age on memory recall on normal aging group; 6.1.2: Panel B – Direct and indirect effects of age on episodic memory on pathological aging group**

**Figure 6.1.1: Normal aging**

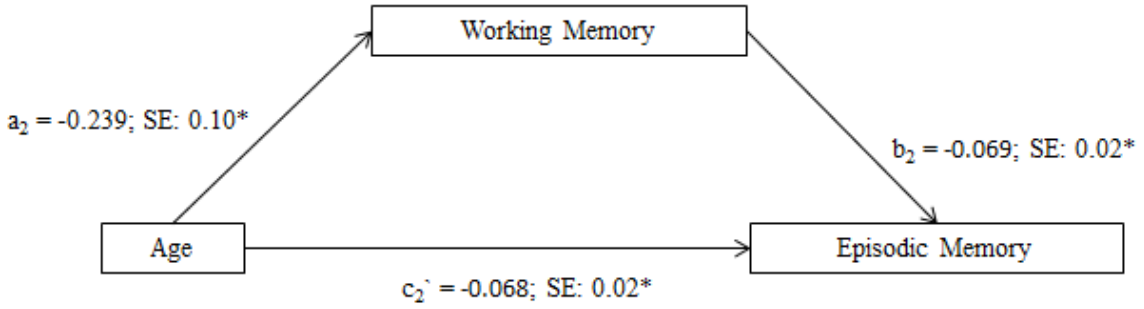
**A**




* p<0.05; ** p>0.05

**Figure 6.1.2: Pathological aging**

**B**




* p<0.05

## 6.4. Discussion

The objective of the current study was to investigate the mechanisms by which age exerts its effect on memory recall, and whether these mechanisms differ between normal and pathological aging. Our first idea was to conduct a parallel multiple mediator model, but only one of our potential mediators correlated significantly with age and memory recall. We then

conduct a simple mediation model for each group where age was the predictor, working memory the potential mediator and memory recall the outcome variable. The mediation model found for each group differed, showing a different pattern of association between age and memory recall on these groups.

While for normal aging group was found only a negative direct effect of aging on memory recall, for pathological aging we found a partial mediation model where age exerts a negative direct effect on memory recall, and moreover, we have found a positive indirect effect of aging on memory through working memory. We found that the relation between age and memory recall is more complex on pathological aging group than in normal aging, with this association been in part driven by working memory. Considering the compensatory theory, these results suggests that our pathological group places greater demand on executive functioning as an attempt to compensate for their episodic memory difficulties (Bouazzaoui et al., 2013; Reuter- Lorenz & Cappell, 2008). Neuroimaging studies suggests that the recruitment of additional brain areas of prefrontal cortex during retrieving reflects an attempt to compensate for memory decline and for other reduced cognitive resources, such as attention (Daselaar, Dennis & Cabeza, 2007). Our results suggest that working memory mediates memory accuracy only on older with pathological aging, with this greater involvement of working memory may serving as a compensatory process to their memory difficulties. However, this over recruitment of executive functions is not related with an efficient memory performance on our pathological aging group. One possible explanation to this finding is that besides memory impairment they also have a significant decline of working memory.

Although significant correlation between working memory and memory recall has been found, no association between working memory and memory recall on normal aging group was found in our mediation model. We also did not found an indirect effect of age

through working memory on memory recall on this group. One hypothesis to explain this result is that our normal aging group does not present a significant decline of memory, so they do not need an over recruitment of executive functions as compensatory mechanism to an efficient memory performance. This group does not require executive functions to memory performance to the same extent as our pathological aging group. This result is opposite to the findings of Lee and Colleagues (2012). In their study they found executive functions (a score composed by working memory and cognitive flexibility) as indirect mediator of the relationship between age and memory, but that processing speed is a stronger mediator than executive function. In another recent mediation study, Kim, Kwon and Shin (2013) did not found a direct effect of age on memory, but that age-related verbal memory decrement is principally related to problems with executive functions. One possible reason to our results differ from this last work is that the sample of our study is apparently older.

In the current study in both normal aging and in pathological group, we have found a significant direct effect of age on memory recall. It is well established in the literature this association. These results suggests that memory recall varies as function of age, as age increase the capacity to remember past events decreases. These finding is in line with previous articles that have reported this association (de Paula et al., 2012; Cansino, 2009; Nyberg et al., 2012; Dickerson & Eichenbaum, 2010).

We also have found significant association among age and working memory performance. The results of the present study confirm the general expectation that verbal working memory decline with increasing age, and support previous research findings (Hester, Kinsella & Ong, 2004; Huntley & Howard, 2010; Hobson & Leeds, 2001).

Some limitations of our study comprise the small sample size limiting the generalization of our finds, and a significant difference on age across the groups. Another limitation is that we have not found a complete mediation model on pathological aging, thus

our model did not explain all mechanisms by which age affects memory recall on this group. It is necessary to emphasize that on pathological group we have found a partial mediation model. Our mediation model did not explain all mechanisms by which age affects memory recall, therefore, others factors, besides working memory, might account for the variance on the model. In the current study we did not controlled the effect of processing speed, whose decline has been associated with decline of episodic memory on older adults (Salthouse, 1996). This cognitive process might account for part of the variance that is not explained by our mediation model. We also cannot determine whether the direct effect is smaller or larger than indirect effect on pathological aging group.

In summary, we found that the mechanisms by which age exerts its effect on memory varies between normal aging and pathological aging. On normal aging we found only a direct effect of age on memory, whereas on pathological aging group we have found this same association, and moreover, that working memory is a mediator of the relationship between age and memory recall.

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## 7. DISCUSSÃO GERAL

Os resultados do presente estudo evidenciam que um funcionamento executivo eficiente é essencial para um bom desempenho em atividades que envolvam as habilidades visioconstrutivas e a memória episódica. Esses achados vão de encontro com as teorias que definem as funções executivas como um gerenciador metacognitivo dos demais processos cognitivos e do comportamento (Prencipe et al., 2011; Goldberg, 2001), ressaltando assim sua importância para um bom funcionamento cotidiano.

Consistente com a literatura foi identificado no primeiro estudo que a habilidade de planejamento exerce um efeito direto na cópia de uma figura complexa (Elderkin-Thompson et al., 2004; Schwarz, et al., 2009). Um importante achado é que uma relação mais complexa entre o planejamento e a visioconstrução foi encontrada, com parte do efeito do planejamento ocorrendo parcialmente através da memória operacional e da flexibilidade cognitiva. Para nosso conhecimento, esse é o primeiro estudo que investigou os mecanismos pelos quais o planejamento exerce seu efeito em uma tarefa de visioconstrução em uma amostra heterogênea de idosos com envelhecimento normal e patológico.

Outro achado relevante do presente estudo é o padrão distinto de associação entre idade e memória episódica entre os grupos com envelhecimento normal e com envelhecimento patológico. Enquanto no grupo com envelhecimento normal foi identificado apenas efeito direto da idade na memória, no grupo com envelhecimento patológico foi identificado que esse efeito ocorre parcialmente através da memória operacional. A ausência de efeito indireto da idade na memória episódica através da memória operacional no grupo com envelhecimento normal é contrária ao que foi apresentado por estudos prévios (Lee et al., 2012; Kim et al., 2013). Provavelmente, este achado está relacionado ao fato de que nossos pacientes com envelhecimento saudável não apresentam um declínio significativo da memória

episódica, não sendo necessário o recrutamento das funções executivas. Nossa hipótese para explicar o modelo de mediação encontrado no grupo com envelhecimento patológico é que a ativação das funções executivas ocorre como uma tentativa compensatória que busca melhorar o desempenho da memória.

Estudos apontam que embora as regiões pré-frontais apresentem uma atrofia associada ao processo de envelhecimento, é nessas regiões que têm sido identificados os maiores focos de superativação como mecanismo compensatório (Reuter-Lorenz e Cappell, 2008). Embora a superativação seja geralmente acompanhada de um melhor desempenho (Reuter-Lorenz e Cappell, 2008), não foi encontrado tal padrão no estudi 2. Esse fato provavelmente ocorreu porque nossos pacientes do grupo clínico, além de comprometimento da memória episódica, também apresentavam comprometimento da memória operacional.

Esses resultados trazem uma importante implicação para a prática clínica, evidenciando a importância de se realizar uma avaliação neuropsicológica detalhada das funções executivas, uma vez que seu bom funcionamento além de influenciar no desempenho funcional, pode influenciar positivamente o funcionamento dos demais processos cognitivos.

É estabelecido na literatura o declínio de funções executivas associado ao envelhecimento (Lin et al., 2007) e seu comprometimento em quadros de CCL e DA (Brown, Devanand, Liu & Caccappolo 2011; Storandt, 2008; Bélanger et al., 2010). Assim como demonstrado na literatura, nos dois estudos presentes neste trabalho, os pacientes do grupo clínico apresentaram pior desempenho nas funções executivas quando comparados ao grupo de idosos com envelhecimento normal. O funcionamento das funções executivas em idosos tem sido proposto como um importante preditor do desempenho funcional nas atividades de vida diária, especialmente em quadros demenciais (Hobson & Leeds, 2001; Pereira et al., 2008).

O presente estudo apresenta algumas limitações. O pequeno tamanho amostral nos limita realizar generalizações dos achados. Nos dois artigos foram encontrados modelos parciais de mediação não sendo assim possível explicar todos os mecanismos pelos quais uma variável exerce seu efeito em outra.

## 8. CONCLUSÃO

Nossos resultados evidenciam a importância de uma caracterização detalhada das funções executivas na avaliação neuropsicológica do idoso. Foi identificada influencia tanto direta quanto indiretamente destas funções em outros domínios cognitivos. Assim, nossos resultados sugerem que déficits executivos podem influenciar na eficiência de outros processos cognitivos, consequentemente influenciando no cotidiano do idoso.

## 9. PERSPECTIVAS FUTURAS

- Novos estudos com amostra maior de idosos com envelhecimento saudável, com Comprometimento Cognitivo Leve e com provável Demência de Alzheimer, buscando verificar se esses grupos apresentam um padrão diferente de associação entre a habilidade de planejamento e a visoconstrução.

- Novos estudos buscando verificar os mecanismos pelos quais a idade exerce sua influência na memória episódica em uma amostra de idosos com provável Demência de Alzheimer.

- Novos estudos com amostras maiores de idosos com envelhecimento normal, com Comprometimento Leve Amnéstico e com provável Demência de Alzheimer buscando replicar os dados.

## 10. ANEXOS

**10.1. Anexo:** Critérios diagnósticos para Comprometimento Cognitivo Leve (Adaptado de Winblad et al., 2004)

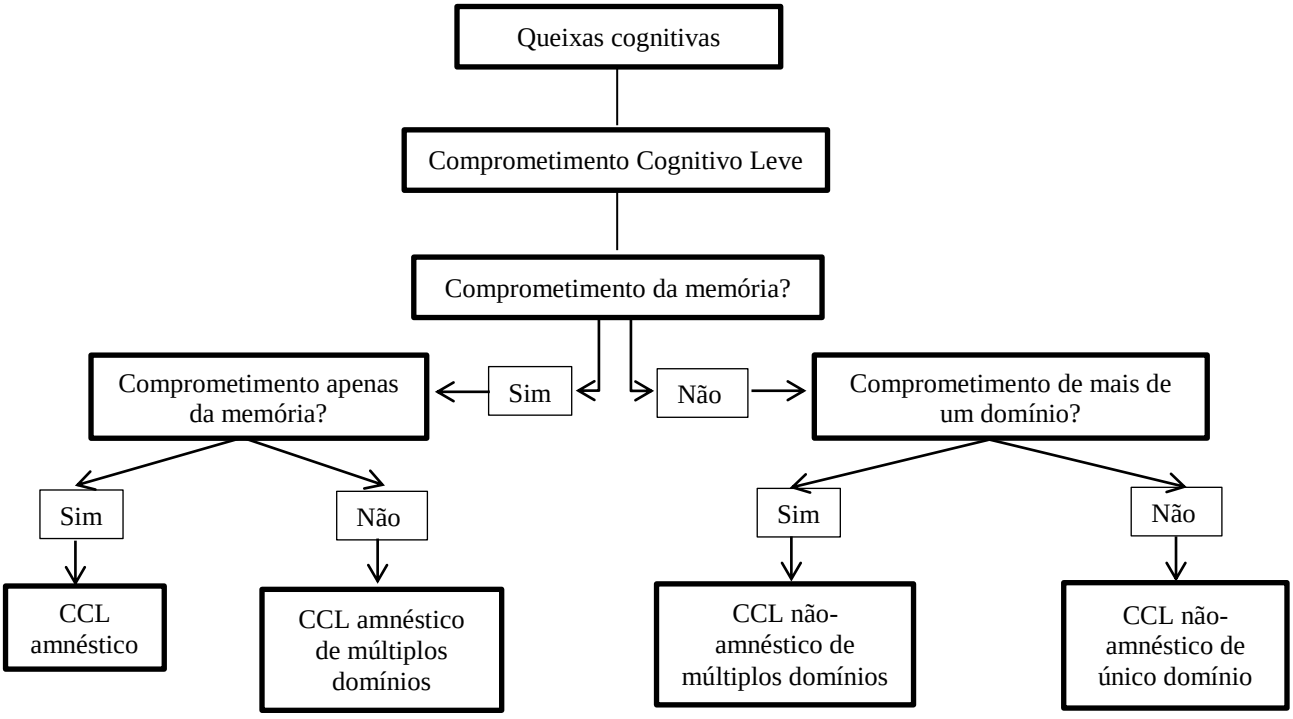
Recomendações gerais para o diagnóstico de CCL:

- Os sintomas apresentados pelo paciente não cumprem os critérios diagnósticos do DSM-IV ou CID-10 para demência.

- Evidência de declínio cognitivo avaliado tanto através do relato do paciente e/ou de um informante próximo quanto do desempenho em testes cognitivos, ou evidência de declínio ao longo do tempo em testes neuropsicológicos.

- Preservação das atividades de vida diária básicas, e comprometimento mínimo nas atividades de vida diária instrumentais.

Processo de classificação do CCL



**10.2. Anexo:** Critérios diagnósticos para provável Demência de Alzheimer (Adapatado de McKhann et al., 2011)

**A –** Diagnóstico de Demência definido por sintomas cognitivos e comportamentais que:

1. Interferem na habilidade de desempenhar normalmente o trabalho ou atividades habituais;

2. Representam um declínio significativo frete aos níveis anteriores de funcionamento;

3. Não são mais bem explicados por um quadro de delirium ou transtorno psiquiátrico grave;

4. O comprometimento cognitivo é identificado e diagnosticado através de uma combinação da história clínica relatada pelo paciente e por um informante próximo, e de uma avaliação cognitiva objetiva;

5. O comprometimento cognitivo ou alterações do comportamento afetam pelo menos dois dos seguintes aspectos: memória, funções executivas e/ou julgamento, habilidades visioespaciais, linguagem, personalidade e/ou comportamento.

**B.** Início insidioso, com os sintomas se instalando de forma gradual, ao longo de meses ou anos, e não de forma súbita.

**C.** Histórico claro de piora cognitiva evidenciada através de relato ou observação.

**D.** Os déficits cognitivos iniciais e mais proeminentes são evidentes história, com início em uma das seguintes categorias:

1. Apresentação amnéstica: É a mais comum apresentação sindrômica de DA. Os déficits envolvem comprometimento da capacidade de aprendizado e de evocação de informações aprendidas recentemente. Além disso, deve haver evidência de disfunção cognitiva em pelo menos um outro domínio cognitivo.

2. Apresentação não-amnéstica:

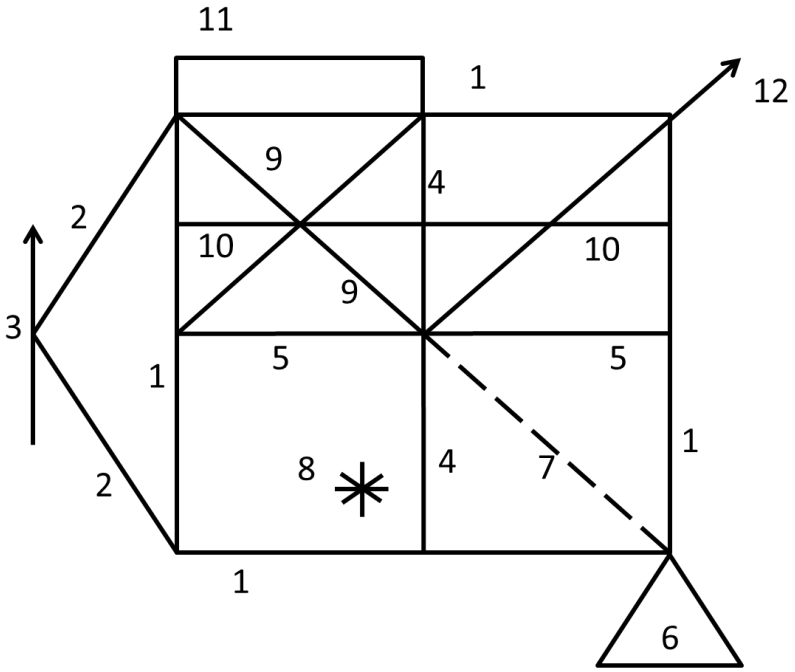
a. Linguística: O comprometimento mais proeminente é na busca de palavras, mas déficits em outros domínios cognitivos devem estar presentes.

b. Visioespacial: O déficit mais proeminente é na cognição espacial, incluindo agnosia para objetos, comprometimento do reconhecimento de face e alexia. Déficits em outros domínios cognitivos devem estar presentes.

c. Disfunção executiva: Os déficits mais proeminentes envolvem o raciocínio, a capacidade de julgamento e de resolução de problemas. Déficits em outros domínios cognitivos devem estar presentes.

**E.** O diagnóstico de provável Demência de Alzheimer não deverá ser realizado quando existe evidência de doença cerebrovascular concomitante; sintomas de Demência por Corpúculos de Lewy; características proeminentes de Demência Frontotemporal; características proeminentes de afasia progressiva primária; evidência de outra doença neurológica concorrente ou comorbidade médica incluindo uso de medicações que possam um efeito expressivo sobre a cognição.

**Anexo 10.3:** Figura Simplificada de Taylor



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