LUCIANO DE GOIS VASCONCELOS

MORFOMETRIA BASEADA EM VOXEL E MEDIDAS DE ESPESSURA CORTICAL DE PACIENTES COM DOENÇA DE ALZHEIMER: CORRELAÇÕES COM PERDAS FUNCIONAIS, SINTOMAS NEUROPSIQUIÁTRICOS E DISFUNÇÕES EXECUTIVAS.

Tese apresentada à Universidade Federal de São Paulo - Escola Paulista de Medicina para obtenção do Título de Doutor em Ciências

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Orientador:
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Profa. Dra. Sônia Maria Dozzi Brucki
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UNIVERSIDADE FEDERAL DE SÃO PAULO

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Esta tese de doutorado foi realizada no Departamento de Psicobiologia da Universidade Federal de São Paulo, no período de novembro/2008 a outubro/2012. O aluno foi inicialmente admitido no mestrado e converteu para doutorado em setembro de 2010. O projeto recebeu apoio financeiro da Associação Fundo de Incentivo à Pesquisa, Fundação de Amparo à Pesquisa do Estado de São Paulo (processo 2008/11282-9, vigência de 01/02/2009 a 31/01/2011) e do Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

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SUMÁRIO

ADENDO AOS LEITORES

Conforme permitem as regras da Comissão de Pós-Graduação da Universidade Federal de São Paulo, esta tese foi apresentada sob o formato alternativo.

Este modo de apresentação permite que a tese seja produzida na forma de uma compilação de pelo menos dois artigos elaborados durante o período em que o aluno esteve matriculado no programa de pós-graduação. Os artigos obrigatoriamente devem abranger o tema do projeto da tese e o aluno deve ser o primeiro autor nas duas publicações.

Esta tese compilou os artigos "Vasconcelos LG, Jackowski AP, Oliveira MO, Flor YM, Bueno OFA, Brucki SM**. Voxel-based morphometry findings in Alzheimer's disease: neuropsychiatric symptoms and disability correlations - preliminary results.** Clinics (Sao Paulo). 2011;66(6):1045-50" (ARTIGO 1) e o "Vasconcelos LG, Jackowski AP, Oliveira MO, Flor YM, Souza AAL, Bueno OFA, Brucki SM. **The thickness of the posterior cortical areas is related to executive dysfunction in Alzheimer's Disease**" (ARTIGO 2). O primeiro artigo encontra-se gratuitamente disponível no endereço eletrônico "http://www.scielo.br/pdf/clin/v66n6/21.pdf" e o segundo encontra-se em análise para publicação. Ambos estão integralmente reproduzidos nesta tese.

Durante o período de preparação deste projeto, produziram-se outros dois artigos diretamente relacionados ao tema, ambos redigidos por este aluno de pós-graduação. Os artigos "Vasconcelos LG, Brucki SMD, Bueno OFA. **Cognitive and functional dementia assessment tools: review of Brazilian literature.** Dement. Neuropsychol. 2007;1(1):18-23" e "Vasconcelos LG, Brucki SMD, Jackowski AP, Bueno OFA. **Diffusion tensor imaging for Alzheimer's disease: A review of concepts and potential clinical applicability.** Dement. Neuropsychol. 2009;3(4):268-274" estão disponíveis gratuitamente, respectivamente nos endereços eletrônicos "http://www.demneuropsy.com.br/detalhe_artigo.asp?id=127" e "http://www.demneuropsy.com.br/detalhe_artigo.asp?id=180".

LISTA DE ABREVIATURAS

DA: Doença de Alzheimer.

RM: Ressonância Magnética.

VBM: Morfometria Baseada em Voxel (“voxel-based morphometry”).

BADS: Bateria de Avaliação Comportamental das Síndromes Disexecutivas.

FAST: Escala de Estadiamento Funcional de Demência.

FLAIR: Fluid-attenuated inversion recovery.

SPM: Mapas Paramétricos Estatísticos (“Statistical Parametric Mapping”).

SVM: Correção para Pequenos Volumes (“Small Volume Correction”).

FDR: Taxa de Descoberta Falsa (“False Discovery Rate”).

RESUMO

Morfometria baseada em voxel e medidas de espessura cortical de pacientes com Doença de Alzheimer: correlações com perdas funcionais, sintomas neuropsiquiátricos e disfunções executivas. OBJETIVO: Estabelecer se as perdas funcionais e as alterações comportamentais correlacionam-se com o volume global e regional da substância cinzenta e se as disfunções executivas associam-se ao volume e espessura cortical de estruturas cerebrais. MÉTODOS: Pacientes com Doença de Alzheimer e idosos controles foram submetidos ao exame de Ressonância Magnética de crânio e a uma completa avaliação cognitiva, funcional e comportamental. Um modelo de regressão múltipla foi aplicado para avaliar as possíveis correlações entre as medidas volumétricas obtidas a partir da análise por morfometria baseada em voxel (VBM), alterações comportamentais e perdas funcionais. Uma avaliação multiparamétrica através do programa FreeSurfer forneceu o volume e espessura cortical e determinou as possíveis correlações entre as disfunções executivas e as estruturas cerebrais. RESULTADOS: A análise por VBM observou correlação negativa entre o volume do giro frontal médio bilateralmente, do giro orbitofrontal direito, do giro temporal inferior esquerdo e dos escores do Inventário Neuropsiquiátrico. Observou-se também correlação negativa entre o volume bilateral do giro fusiforme, do hipocampo esquerdo, dos giros temporais médios bilateralmente e do Questionário de Atividades Funcionais. Observou-se ainda correlação positiva entre os volumes da amigdala direita, do giro fusiforme bilateral, da insula anterior direita, do giro temporal superior direito, do giro temporal médio bilateralmente, do giro temporal inferior esquerdo e dos escores da Escala de Avaliação de Incapacidade em Demência. A avaliação através do FreeSurfer mostrou correlação negativa entre a Bateria de Avaliação Comportamental da Síndrome Disexecutiva (subteste das cartas) e o giro frontal médio direito; correlação positiva entre o teste motor de função executiva e o giro parietal superior esquerdo, o giro temporal médio esquerdo, giros supramarginais bilateralmente, o giro frontal médio direito e o precuneo direito; correlação negativa entre o Teste de Stroop Parte III, o giro parietal superior direito e o giro temporal médio direito. CONCLUSÕES: Sugere-se que, nos pacientes com Doença de Alzheimer leve, as alterações comportamentais estão associadas principalmente às reduções volumétricas frontais, e as perdas funcionais às alterações temporais. As disfunções executivas associam-se às reduções da espessura cortical de estruturas frontais e áreas temporais e parietais.

INTRODUÇÃO GERAL

Doença de Alzheimer

A população mundial está envelhecendo. Em 1950, 8% era composta por indivíduos com idade maior ou igual a 60 anos, em 2000 chegou a 10% e estima-se que em 2050 atinja 21%. A faixa etária de indivíduos com 80 anos ou mais corresponde ao seguimento de maior crescimento populacional (3.8% ao ano). Atualmente corresponde a 10% do total de idosos e estima-se que em 2050 atinja o número de 20%. O Brasil tem aproximadamente 10% da população com 60 anos ou mais e projeta-se 30% para 2050. O censo de 2010 estimava que 1,6% da população geral era composta por indivíduos com 80 anos ou mais. [1, 2]

Este processo tem ocorrido mais rapidamente nos países em desenvolvimento. Entre 2010 e 2050, a proporção de idosos nos países desenvolvidos crescerá em 56% (de 269 para 416 milhões) e nos países em desenvolvimento em 226% (de 490 para 1,6 bilhões). A transição epidemiológica mudará o padrão de adoecimento populacional, passando a prevalecer doenças crônicas. Neste novo perfil epidemiológico, destacam-se as demências, especialmente pela prevalência e incidência, morbidade, mortalidade, perdas funcionais, perda de qualidade de vida e elevação dos custos sociais. [3 - 5]

A DA é a principal causa de demência no Brasil e no mundo. Projeções estimam que em 2050 atinja-se o número de 106 milhões de pacientes, sendo que a maioria deles residirá em países em desenvolvimento. Nestes países, 20% dos indivíduos com demência vivem sozinhos ou em situação de vulnerabilidade. As altas demandas físicas, emocionais e econômicas representam um problema de saúde pública. Estima-se que mundialmente o custo anual direto seja de US$ 329 bilhões e indireto de US$ 608 bilhões. [3, 6 - 10]

O principal fator de risco para a DA é a idade avançada. A incidência aumenta de 1% aos 65 anos para 25% aos 90 anos e a prevalência de 0,1% aos 60 anos para 50% aos 90 anos. [7, 11]

Não existe atualmente tratamento aprovado para prevenção, cura ou redução significativa da taxa de declínio clínico da DA. Infelizmente os ensaios clínicos com medicamentos doença-modificadores falharam em evidenciar benefícios relevantes. [12, 13]

O diagnóstico clínico fundamenta-se em perdas cognitivas, declínio funcional e eventualmente presença de alterações neuropsiquiátricas. A maioria dos critérios diagnósticos atualmente utilizados para DA tem baixa acurácia, com sensibilidade de 80% e especificidade de 70%. Estes dados representam a experiência de centros especializados e não a realidade assistencial, possivelmente pior. [14]

As pesquisas em prevenção, diagnóstico precoce e tratamento adquirem grande relevância considerando-se o crescimento do contingente de indivíduos com perdas cognitivas, o benefício modesto das drogas disponíveis para tratamento de demência e a indisponibilidade de medicamentos doença-modificadores efetivos. [13, 15]

Alterações comportamentais e declínio funcional

Alterações comportamentais, problema frequente desde as fases pré-clínicas e inicias de diversas demências, relacionam-se a maior taxa de declínio cognitivo, maior dependência funcional, institucionalização precoce e maior mortalidade. Estima-se que a prevalência destes sintomas em fases iniciais varie de 35% a 85% e de 60% a 95%, quando se incluem as demências em todas as fases. [16 - 20]

Alterações comportamentais são influenciadas por fatores biológicos, psicológicos, psicossociais e ambientais. São também persistentes, têm curso flutuante, características clínicas heterogêneas e intensidade variável. O tratamento não é consensual e muitas vezes não significantemente efetivo. Quando presentes, marcam resposta positiva ao tratamento com anticolinesterásico e podem servir como parâmetro de efetividade em ensaios clínicos com novas medicações. [16]

As alterações comportamentais em pacientes com DA caracterizam-se por diferentes manifestações clínicas como apatia, ansiedade, irritabilidade, delírios e alucinações. Evidências clínicas sugerem que pacientes com padrões específicos de sintomas comportamentais apresentam evoluções clínicas diferentes. Achados neuropatológicos de pacientes com DA e alterações comportamentais são diferentes de pacientes com DA sem sintomas neuropsiquiátricos. Evidências sugerem que alterações comportamentais e perdas cognitivas da DA têm substratos neuropatológicos diferentes. [21 - 24]

Depressão e ansiedade podem preceder em vários anos os primeiros sintomas cognitivos da DA. [25] Estudos envolvendo diversos métodos de neuroimagem têm estabelecido correlações entre diferentes alterações comportamentais

e estruturas cerebrais. Apatia foi associada a estruturas frontais; [26, 27] alucinações associaram-se a estruturas frontais, parietais e temporais; [28] sintomas depressivos associaram-se ao tálamo, núcleos lentiformes e córtex temporal medial; [29] agitação associou-se a estruturas temporais e frontais. [27]

A principal causa de dependência funcional entre idosos são as demências. Ocorrem universalmente e algumas vezes dissociada dos déficits cognitivos. A alta prevalência de alterações comportamentais associa-se geralmente a maiores incapacidades, mesmo quando comparados sujeitos com desempenhos cognitivos semelhantes. [3, 15, 30, 31] Diferentemente dos sintomas neuropsiquiátricos, poucos estudos têm investigado as bases neurais das perdas funcionais em pacientes com demência. [32]

Funções executivas

Embora o conceito de que a DA seja uma doença caracterizada principalmente por alterações da memória episódica e esteja bem estabelecido, existem muitos exemplos das diferentes apresentações clínicas. [33] Aceita-se o diagnóstico de DA provável mesmo quando a disfunção executiva é o principal déficit cognitivo. [34]

Função executiva é um domínio cognitivo multidimensional que inclui atenção, volição, ações propositivas, objetividade, sequenciamento, formação de objetivos, planejamento, execução e desempenho efetivo do planejamento, autoavaliação, motivação, abstração, julgamento e processos de manuseio e retenção de informações. [35]

Disfunções executivas nos pacientes com DA são frequentes, ocorrem em todas as fases do curso clínico, associam-se à pior capacidade funcional, problemas comportamentais, maior morbidade e mortalidade, maior velocidade de progressão da doença e interferem negativamente na qualidade de vida dos doentes e respectivas famílias. [36 - 41]

Outras doenças crônicas de alta prevalência populacional como Depressão, Transtorno de ansiedade e diversas doenças clínicas também estão muito associadas às disfunções executivas. [42 - 45]

Estudos que identificam o lobo frontal como centralizador das funções executivas são controversos. O córtex pré-frontal recebe projeções de importantes áreas corticais associativas posteriores e regiões límbicas. [46] Embora a maioria dos estudos correlacione alterações de estruturas frontais e disfunções executivas, vários outros

estudos com diversos métodos de neuroimagem tem correlacionado disfunções executivas também às áreas corticais posteriores. [47 - 50] Um estudo que avaliou a espessura cortical em imagens de Ressonância Magnética (RM) estrutural de pacientes com DA demonstrou que carreadores do alelo epsilon 4 da Apolipoproteína E têm fenótipo diferente dos indivíduos não carreadores da alteração genética mencionada. Os carreadores apresentaram maiores perdas em medidas de retenção de memória e maior atrofia em regiões temporais mediais e os não carreadores maiores perdas de funções executivas e atrofia de regiões frontoparietais. [47] Outro estudo com RM funcional mostrou que pacientes com DA e sem crítica das perdas cognitivas apresentavam mais apatia, mais desinibição e perdas de funções executivas mais acentuadas. O grupo de pacientes com redução da crítica em relação aos déficits cognitivos apresentou perdas funcionais de regiões cingulofrontais e parietotemporais. [49]

Alguns resultados sustentam que a disfunção executiva na DA esteja relacionada às alterações de múltiplas estruturas encefálicas e possivelmente às desconexões entre elas. [48, 51] Um estudo de imagens com fluorodeoxiglicose por tomografia com emissão de pósitrons evidenciou hipometabolismo em regiões frontais e posteriores em pacientes com DA e disfunções executivas. Destacou-se que a integridade de diversas regiões corticais associativas e as conexões entre elas são fundamentais para o funcionamento das funções executivas. [48] Outro estudo de imagens com fluorodeoxiglicose por tomografia com emissão de pósitrons observou que a disfunção executiva de pacientes com DA leve ou "muito leve" associou-se ao hipometabolismo de regiões corticais frontais e posteriores. No grupo com DA leve as alterações ocorreram predominantemente em áreas corticais posteriores. [51] Apesar dos estudos mencionados, considera-se ainda que este campo de conhecimento possa ser mais bem investigado.

Neuroimagem e Doença de Alzheimer

Cinco dos principais biomarcadores da evolução clínica da DA como a RM estrutural (marcador de neurodegeneração), imagens de substância beta-amiloide marcada com radioisótopo por tomografia com emissão de pósitrons (marcador de deposição de placa beta-amiloide), imagens com fluorodeoxiglicose por tomografia com emissão de pósitrons (marcador de injuria neuronal) e dosagens das proteínas Abeta1-42 (marcador de deposição de placa beta-amiloide) e proteínas TAU (marcador de injuria neuronal) foram suficientemente estudados e são recomendados na seleção de pacientes

para ensaios clínicos. [12] Estas evidências permitiram que os testes mencionados fossem incorporados aos novos critérios diagnósticos da DA. [34]

Os exames mencionados são autocomplementares e trazem informações sobre a fisiopatologia do todo o curso clínico da DA, desde a fase pré-clínica até a fase de demência, 20 a 30 anos após o início do processo de adoecimento. O exame de RM estrutural pode identificar alterações relacionadas à DA vários anos antes das primeiras manifestações clínicas. [52]

Estima-se que 10% a 20% dos pacientes selecionados para ensaios clínicos não tenham realmente DA e que 30% a 40% dos indivíduos com Declínio Cognitivo Leve sejam "amiloides-negativos" e não desenvolvam DA. [53] Considerando a não utilização de testes diagnósticos adequados, problemas qualitativos de alguns centros captadores de pacientes com DA e a não utilização de medidas apropriadas de efetividade terapêutica, muitos medicamentos com potencial terapêutico podem ter o resultado diminuído ou anulado. Bons testes para os diagnósticos podem também permitir a redução do tamanho das amostras e assim tornar as pesquisas economicamente mais viáveis. [53]

Medidas volumétricas por RM estrutural e imagens com fluorodeoxiglicose por tomografia com emissão de pósitrons são consideradas por alguns estudos como os melhores métodos diagnósticos, consequentemente tendo melhores medidas de progressão clínica e efetividade terapêutica da DA. [54]

Diversos métodos de RM como a espectroscopia, a RM funcional e a imagem dos tensores de difusão foram desenvolvidos relativamente há pouco tempo e já se mostram com grande aplicabilidade clínica. [55] No entanto, a RM estrutural é o método mais estudado e consolidado. [56]

Medidas quantitativas de reduções volumétricas aferidas por RM estrutural estão validadas através de correlações com índices anatomopatológicos de gravidade neurodegenerativa. A atrofia hipocampal e reduções de volume de substância cinzenta encefálica correlacionam-se com topografia e gravidade de patologia neurofibrilar. [57]

Medidas de atrofia regional por RM estrutural identificam pacientes com déficit cognitivo, determinam risco de declínio cognitivo e avaliam adequadamente a efetividade dos medicamentos testados em ensaios clínicos. Sugere-se que a morfometria por RM tenha superioridade diagnóstica e prognóstica em relação a outros exames subsidiários. A ampliação do uso da morfometria por RM estrutural é viável

porque este exame já compõe a rotina diagnóstica de muitos centros. Quando comparada com a técnica de tomografia por emissão de pósitrons, pode ser considerada menos invasiva, menos complexa, mais disponível e mais barata. [58 - 60]

Diversas metodologias de análise de dados de RM estrutural estão disponíveis. As principais técnicas de volumetria classificam-se em visual (prática e pouco reprodutível), técnicas quantitativas baseadas em regiões de interesse (manual, com alto consumo de tempo e pouco reprodutível) e técnicas quantitativas baseadas em voxel. [52]

A MBV é uma técnica computacional automatizada muito utilizada, independente de operador, validada, altamente reprodutível e de relativamente rápida execução. É uma técnica de análise de imagens de RM utilizada para a avaliação focal e global do tecido encefálico. [61] Os resultados são obtidos após a normalização espacial de todas as imagens de RM para o mesmo espaço estereotáxico, segmentação e suavização das imagens e finalmente a realização das análises estatísticas destinadas a identificar as diferenças entre os volumes de estruturas encefálicas entre dois grupos ou entre estruturas e outras variáveis. [62 - 64] Esta técnica foi utilizada na produção do ARTIGO 1 que compõe esta tese.

Após o desenvolvimento das técnicas quantitativas baseadas em voxel (MBV, por exemplo), desenvolveram-se métodos de análises morfométricas complementares, capazes de avaliar a superfície e espessura cortical e subcortical, medidas não fornecidas pela MBV. Estes métodos de análise, através de programas computacionais, processam imagens estruturais de RM com pouca intervenção manual e alta reprodutibilidade. O software FreeSurfer é um dos programas mais utilizados para a análise de superfície e espessura cortical devido a objetividade, reprodutibilidade, confiabilidade e inúmeros subsídios de literatura. [65] A medida de espessura cortical é composta de um fluxo de processamento da superfície, de um fluxo de cálculo de volume e preparação dos dados para estudos de grupo. Esta técnica foi utilizada na produção do ARTIGO 2 que compõe esta tese.

Evidências sugerem que medidas de espessura cortical podem identificar indivíduos com declínio cognitivo leve e DA com grande acurácia, especificidade, consistência e reprodutibilidade. Estabeleceu-se também que a espessura cortical parece estimar o risco de conversão de declínio cognitivo leve para DA com maior acurácia que avaliações clínicas ou neuropsicológicas. [66, 67] Observou-se que as medidas mencionadas podem avaliar quantitativamente e com significância biológica

a efetividade de novos medicamentos em ensaios clínicos. A significância biológica foi subsidiada pela correlação com avaliações longitudinais do declínio cognitivo e pela associação com outros marcadores de neurodegeneração celular. [68 - 70]

JUSTIFICATIVAS

O desenvolvimento de novos instrumentos diagnósticos cria espaço para o aprimoramento destas tecnologias e ampliam a necessidade de adaptação e inclusão destes avanços nas atividades de pesquisa e assistência, especialmente em atividades envolvendo a população brasileira.

Mesmo com diversos estudos explorando as bases neurais dos sintomas neuropsiquiátricos, ainda não há consenso se alterações comportamentais e cognição são dimensões diferentes e independentes e ou se os problemas de comportamento na demência são manifestações inespecíficas, secundárias ao declínio cognitivo. Adicionalmente, poucos trabalhos analisaram as associações entre alterações estruturais, problemas comportamentais e perdas funcionais, especialmente em sujeitos com DA e baixa escolaridade.

Inconsistências sobre o papel de algumas estruturas encefálicas em determinadas funções executivas e discordâncias sobre o conceito da centralização destas faculdades no lobo frontal devem ser mais bem esclarecidas. Adicionalmente, observa-se que não existe uma clara correlação entre espessura cortical e desempenho nas funções executivas entre indivíduos saudáveis e poucos trabalhos tem estudado a espessura cortical de pacientes com DA e baixa escolaridade.

ARTIGO 1

VOXEL-BASED MORPHOMETRY FINDINGS IN ALZHEIMER'S DISEASE: NEUROPSYCHIATRIC SYMPTOMS AND DISABILITY CORRELATIONS – PRELIMINARY RESULTS.

Luciano de Gois Vasconcelos, Andrea Parolin Jackowski, Maira Okada de Oliveira, Yoná Mayara Ribeiro Flor, Orlando Francisco Amodeo Bueno, Sonia Maria Dozzi Brucki.

ABSTRACT

Introduction: The role of structural brain changes and their correlations with neuropsychiatric symptoms and disability in Alzheimer's disease are still poorly understood. Objective: To establish whether structural changes in grey matter volume in patients with mild Alzheimer's disease are associated with neuropsychiatric symptoms and disability. Methods: Nineteen AD patients (9 females; total mean age = 75.2 years old ± 4.7; total mean education level = 8.5 years ± 4.9) underwent a MRI examination and voxel-based morphometry analysis. T1-weighted images were spatially normalised and segmented. Grey matter images were smoothed and analysed using a multiple regression design. The results were corrected for multiple comparisons. The Neuropsychiatric Inventory was used to evaluate the neuropsychiatric symptoms, and the Functional Activities Questionnaire and Disability Assessment for Dementia were used for functional evaluation. Results: A significant negative correlation was found between the bilateral middle frontal gyri, left inferior temporal gyrus, right orbitofrontal gyrus and Neuropsychiatric Inventory scores. A negative correlation was found between bilateral middle temporal gyri, left hippocampus, bilateral fusiform gyri and Functional Activities Questionnaire. There was a positive correlation between the right amygdala, bilateral fusiform gyri, right anterior insula, left inferior and middle temporal gyri, right superior temporal gyrus and Disability Assessment for Dementia scores. Conclusions: The results suggest that the neuropsychiatric symptoms observed in Alzheimer's disease patients could be mainly due to frontal structural abnormalities, while disability could be associated with reductions in temporal structures.

Key words: Dementia, BPSD, functional impairment, MRI.

INTRODUCTION

The worldwide projection of Alzheimer's disease (AD) prevalence predicts that there will be approximately 106 million patients by 2050.[1] Dementia is one of the main causes of elderly cognitive decline and functional impairment,[2] leading to disastrous consequences for patients and their relatives in regard to the quality of life, and also causes immense expense for the healthcare system.[3] The neuropsychiatric symptoms, another high prevalent problem even in the pre-dementia phase,[4,5] are also correlated with additional adverse events for patients, families and caregivers, such as faster cognitive decline, earlier institutionalisation and higher mortality.[6]

Clinical evidences suggest that AD patients with different groups of neuropsychiatric symptoms have an heterogeneous clinical evolution.[7] AD patients with behavior disorders might have different pathological features when compared with AD patients without them.[8] Previous studies have shown that neuropsychiatric symptoms and cognitive function in AD patients might have separate structural pathologies.[9] Depression and anxiety can precede in years the development of cognitive decline in AD.[10]

More specific regional associations with a range of behavioral symptoms have been identified using different neuroimaging modalities. Apathy was associated to frontal structures,[11,12] delusions was correlated with frontal, parietal and temporal structures,[13] depressive symptoms with thalamus, lentiform nucleus and medial temporal cortex,[14] agitation was associated temporal and frontal structures.[12] Even with several studies, divergence if cognition and behavior are independent and heterogeneous dimensions or if behavior disorders are an inevitable and non-specific consequence in dementias still remains.[15,16] Few studies have investigated the neuropathological mechanisms of functional decline in the Alzheimer's disease. One study correlated disability with frontal, temporal and occipital structures.[17] Additionally, few studies have explored the correlation between anatomical changes, neuropsychiatric symptoms and functional losses, especially in patients of developing countries.

This study was designed to clarify whether voxel-based morphometry structural changes in grey matter volume in patients with mild AD are associated with neuropsychiatric symptoms and functional impairment.

METHODS

Subjects

Nineteen patients with mild AD (9 female) were recruited from a multidisciplinary memory clinic. Their mean age was 75.2 years (SD =4.7, range 66–86), and their mean education level was 8.5 years (SD =4.9, range 3–19). All patients in the study fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable Alzheimer's disease.

Exclusion criteria included significant symptoms of depression (Geriatric Depression Scale >=6), Functional Assessment Staging < 3 or > 4, significant radiological evidence of ischemic brain disease, Modified Hachinski Ischemia Score > 4, previous cerebrovascular event, Mini-Mental State Examination score <20 or evidence of other degenerative or secondary dementias. Other exclusion criteria included end stage chronic disease or unstable medical condition, premorbid psychiatric history, antipsychotic or psychoactive medication dose adjustments in the last two months before study enrolment, initial treatment with cholinesterase inhibitors within the two months before study enrolment, significant visual or hearing impairment, age < 60 years and any other condition that could prevent the patient from undergoing an MRI examination. Highly symptomatic depressive patients were excluded from to avoid bias in cognitive assessment. Their performance on this evaluation is strongly influenced by the level of depressive symptoms.[18]

Procedures

Each patient and their caregiver had a complete interview with a consultant geriatrician (LGV) that included assessment of demographic and medical conditions including tobacco use, diabetes mellitus, number of medications used on a daily basis, body mass index, waist-hip ratio, number of psychoactive medications and period of use of cholinesterase inhibitors. The functional status assessment was performed using the Pfeffer Functional Activities Questionnaire, which ranged from 0 points (completely independent) to 30 points (completely dependent), and the Disability Assessment for Dementia, which ranged from 0% (completely dependent) to 100% (completely independent). The neuropsychiatric symptoms were evaluated by the Neuropsychiatric Inventory, which ranged from 0 points (no behavioural problems) to 144 points (maximum of neuropsychiatric symptoms). Each participant also underwent a cognitive evaluation and had an MRI brain scan taken. The Neuropsychiatric Inventory, Disability

Assessment for Dementia and Functional Activities Questionnaire values were then correlated with grey matter volume values extracted from the patients' MRI brain scans. The Ethics Committee of the Universidade Federal de São Paulo and Hospital Santa Marceline approved the study, and informed consent was obtained from all participants (and their relative or guardian or caregiver) prior to inclusion in the study.

MRI data acquisition, analysis and post-processing

Examination of the brain was performed for all subjects using a 1.5 T [Magnetom Sonata (Maestro Class) — Siemens AG, Erlangen, Germany] using an eight channel head coil. To minimise variation in head position, subjects were positioned by the same investigator using the orbito-meatal line as a landmark. Two conventional sequences were performed: (a) Axial T2-weighted FLAIR (fluid-attenuated inversion recovery) in a plane parallel to the anterior commissure-posterior commissure (AC—PC) line [TR (repetition time) = 8500 ms, TE (echo time) = 107 ms, TI (inversion time) = 2500 ms, slice thickness = 5.0 mm, slice interval = 1.5 mm, FOV (field of view) = 240 mm, matrix size = 256 X 256, NEX = 1]; and (b) Sagittal T1-gradient echo volumetric acquisition for multiplanar reconstruction (TR = 2000 ms, TE = 3.42 ms, flip angle = 15, FOV = 256 mm, 1.0 mm slice thickness with no gaps, totalling 160 slices per slab, matrix size = 256 X 256, NEX = 1).

This study used the VBM5 toolbox, which utilises and extends the new unified segmentation approach[19] implemented in Statistical Parametric Mapping (SPM5), executed in Matlab 7.0. The sagittal T1 DICOM files were converted to NIFTI-1 format. The converted files were then segmented into grey and white matter and normalised using the unified model cited above. Voxel values were modulated by Jacobian determinants derived from the spatial normalisation, thus allowing brain structures with decreased volumes after spatial normalisation to have their total counts decreased by an amount proportional to the degree of volume discounted. The final voxel resolution after normalisation was 1 mm^3. The obtained grey matter images were finally smoothed with a Gaussian filter at full width at the maximum height equal to 8 mm and entered into statistical analysis. The sum of all voxel values within the segmented images, in native-space, approximates intracranial volume within the corresponding partition. Intracranial volume was computed from the sum of grey, white and cerebral spinal fluid volume.

Statistical analysis

Demographic, clinical, cognitive, functional, and behavioural data were analysed with SPSS 13.0 (SPSS, Chicago, IL). Prior to conducting analyses, measurements were examined for normality using the Shapiro-Wilk test. The association between Neuropsychiatric Inventory, Disability Assessment for Dementia and Functional Activities Questionnaire scores was evaluated by Pearson's correlation coefficient or Spearman's rho, when appropriate. The level of statistical significance was set at $p < 0.05$.

The correlations between regional grey matter volume and the Neuropsychiatric Inventory, Functional Activities Questionnaire and Disability Assessment for Dementia scores in AD patients were evaluated using the voxel-based morphometry multiple regression model. Brain volume and age were used in the model as covariates. Resulting clusters were reported as significant at a $p < 0.001$ level, two-tailed, uncorrected for multiple comparisons. A small volume correction was applied when there was a strict a priori hypothesis that was already implicated in AD pathophysiology (hippocampus, entorhinal and perirhinal cortices, temporal gyri) emerging from whole-brain analyses. We performed small volume correction, placing a sphere with a 5 mm radius centred at the local maxima, which was equivalent to a volume of 500 mm^3, with a threshold of $p < 0.01$, corrected for multiple comparisons using False Discovery Rate. Unpredicted findings were considered to be significant only if they survived small volume correction for multiple comparisons ($p < 0.05$).

RESULTS

Demographic, clinical, cognitive, functional and behavioural data

The data description of participants is fully detailed in Table 1.

The correlation analysis of functional and behavioural scales showed a significant association between Disability Assessment for Dementia and Functional Activities Questionnaire ($r= -0.862$, $p<0.001$), Disability Assessment for Dementia and Neuropsychiatric Inventory ($r = -0.475$, $p<0.014$), and Neuropsychiatric Inventory and Functional Activities Questionnaire ($r= 0.551$, $p<0.04$).

The behavioural assessment showed that seventeen out of nineteen patients (89%) had at least one symptom in the behavioural assessment according to their caregivers. Irritability was the most frequent abnormal behaviour (63%) observed in the Neuropsychiatric Inventory symptoms field, followed by apathy (47%), agitation

(47%), delusions (42%) and euphoria (42%). The least frequent behaviour was hallucination (10%).

Neuroimaging findings and instrumental assessment correlations

The voxel-based morphometry multiple regression analysis showed that were significant negative correlations between the grey matter volume of the bilateral middle frontal gyri, right orbitofrontal gyrus and left inferior temporal gyrus and total Neuropsychiatric Inventory scores (Figure 1).

Negative correlations were found between the bilateral fusiform gyri, left hippocampus, bilateral middle temporal gyri and Functional Activities Questionnaire scores (Figure 2).

Positive correlations were seen between the right amygdala, bilateral fusiform gyri, right anterior insula, right superior temporal gyrus, left inferior temporal gyrus, left middle temporal gyrus and Disability Assessment for Dementia scores (Figure 3).

It was also observed a positive correlation between volume of frontal and temporal brain structures and cognitive tests. The detailed correlation analysis is described in Table 2.

DISCUSSION

Neuropsychiatric symptoms were very prevalent in our sample of mild AD patients. Of these symptoms, irritability was the most frequent abnormal behaviour, followed by apathy, agitation, delusions and euphoria. These behavioural problems associated with AD tend to show a trajectory of increasing prevalence and severity over time, an attribute they share with cognitive and functional decline.[4] Our paper confirms the high prevalence that was also seen in other studies.[5,20] This different prevalence of some Neuropsychiatric Inventory domains could be explained by the exclusion of highly symptomatic depressive patients, the different dementia stage of our sample, differences in cultural manifestations of behaviour and sample size. It was also observed a wide variation of Functional Activities Questionnaire scores (1-22). This assessment tool is based in the caregiver judgement, generally influenced by the burden of care and cultural aspects of reported disability.[21] Our findings also observed a positive correlations between cognitive tests scores and grey matter volume of frontal and temporal structures.

The voxel-based morphometry results showed significant negative correlations between the volume of frontal structures (middle frontal gyri and right orbitofrontal gyrus), temporal structure volume (left inferior temporal gyrus) and total Neuropsychiatric Inventory scores. Similar findings were also observed in previous studies, predominantly in the voxel-based morphometry field, molecular imaging techniques and pathological studies, confirming the role of these structures in the genesis of neuropsychiatric symptoms. Symptoms like disinhibition have been associated with grey matter volume reduction in the right middle frontal gyri,[22] depressive symptoms and bilateral atrophy of the medial orbitofrontal cortex,[23] eating disorders with perfusion changes of the orbitofrontal cortex,[24] agitation and aberrant motor behaviour with greater neurofibrillary tangle pathology of the orbitofrontal cortex,[25] apathy with left frontal structures,[11] delusions and apathy with decreased grey matter volume density in the frontal lobe,[12] neuropsychiatric symptoms with grey matter volume reduction of the right lateral middle frontal gyri and right orbitofrontal cortex[26] and neuropsychiatric symptoms with greater neurofibrillary tangle pathology of the orbitofrontal cortex.[27]

Significant correlations between the grey matter volume of temporal structures (fusiform gyri, hippocampus, amygdala, insula, temporal gyri) and functional impairment (negative correlation with Functional Activities Questionnaire and positive correlation with Disability Assessment for Dementia) were also observed. Contrary to expectations, no correlation was found between disability and frontal structures. A possible explanation for these findings is that the functions generally assessed are dependent of executive functions and prospective memory impairment, closely related to temporal structures. Studies focusing on the neuroanatomical correlation of functional impairment in AD are rare. Disability in AD subjects was associated with greater overall pathologic burden of the medial temporal, occipital, and orbital frontal regions,[17] decreased gray matter volume in the medial frontal and temporal-parietal cortices.[28] Another study observed an association of decreased cerebral activity in the bilateral parietal and temporal cortices, precuneus, and left middle frontal gyrus and the dementia scales, including instrumental activities of daily living.[29] Previous papers have demonstrated cognitive or behavioural (not functional) correlation between higher senile plaque density in the fusiform gyri and performance on visuoperceptual tests,[30] and insula pathology and behavioural abnormalities.[31]

The selective pathological involvement of some neocortical areas and ventromedial temporal lobe structures, which is common in AD,[32] was also observed in our

neuroimaging findings (middle frontal gyri, middle temporal gyri, and amygdala) and correlated with neuropsychiatric symptoms and Neuropsychiatric Inventory. Bilateral grey matter volume reduction of the fusiform gyri and left middle temporal gyri correlated with both Functional Activities Questionnaire and Disability Assessment for Dementia. The left inferior temporal gyrus was associated with both Neuropsychiatric Inventory and Disability Assessment for Dementia.

Results should be interpreted as preliminary and with caution. A few limitations of the present study warrant mentioning. A small group of AD subjects were enrolled in the study and the absence of a control group for the clinical assessment. Even though the controls were submitted to a MRI scan, the same correlational analysis on the voxel-based morphometry could not be performed as the Functional Activities Questionnaire, Disability Assessment for Dementia and Neuropsychiatric Inventory scales were designed for dementia patients.

A deeper comprehension of pathophysiological mechanisms of behavioural and functional aspects of AD and their related anatomic changes may shed light upon more effective diagnostic, prognostic and therapeutics approach.

CONCLUSIONS

The voxel-based morphometry results suggest that the neuropsychiatric symptoms observed in these AD patients could be mainly associated with abnormalities in frontal structures, while the functional impairment could be mainly associated with volume reductions in temporal structures.

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TABLES

Table 1: Description of demographic, clinical, cognitive, functional and behavioural data.

Variable	Mean	SD; range	Median
Age (years)	75.2	4.7; 66–86	74
Education (years)	8.5	4.9; 3–19	8
Time of cholinesterase inhibitor use (months)	41.9	26; 4–106	36
Mini Mental State Examination	24.21	2.78; 20-29	24
Verbal fluency for letters F, A and S	22.15	11.22; 8-56	19
Verbal fluency for animals	10.52	2.76; 6-16	11
Clock drawing test	6.10	2.67; 2-10	6
Functional Activities Questionnaire	8.89	4.5; 1-22	10
Disability Assessment for Dementia	89.36	9.96; 60-100	92
Neuropsychiatric Inventory	20.36	19.25; 0-77	16

Table 2: Neuroimaging findings, cognitive, behavioural and functional scores correlations.

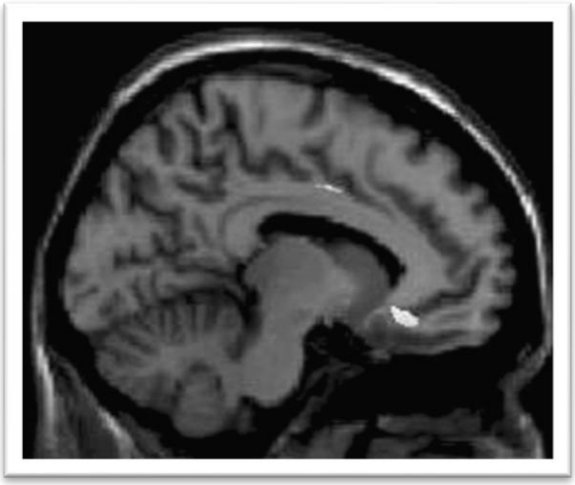
Instrument [Positive (PC) or negative (NC) correlation]	Brain region (R=right, L=left)	MNI coordinates	KE	Z-score
MMSE [PC]	R Inferior temporal gyrus	56 -2 -36	190	3.64
	L Inferior temporal gyrus	-45 1 -40	259	3.51
	L Fusiform gyrus	-36 -12 -41	61	3.27
	L Insula	-35 -12 -5	94	3.26
FAS [PC]	L Inferior frontal gyrus	-46 12 18	473	3.63
CDT [PC]	R Putamen	22 16 -1	786	3.51
	L Putamen	-20 17 0	39	3.23
	L Insula	-40 20 11	200	3.99
	R Insula	41 20 -11	70	3.50
NPI [NC]				
	R Middle frontal gyrus	43 52 -5	4493	4.34
	L Middle frontal gyrus	-32 57 -12	12260	3.76
	R Orbitofrontal gyrus	9 50 -24	4493	74.32
	L Inferior temporal gyrus	-48 -59 -19	19433	3.65
FAQ [NC]				
	R Fusiform gyrus	39 -12 -39	4914	5.01
	L Fusiform gyrus	-27 -8 -35	9813	4.66
	L Hippocampus	-34 -21 -15	9813	3.30
	L Middle temporal gyrus	-57 -29 -9	9488	3.91
	R Middle temporal gyrus	-31 20 -17	1769	3.51
DAD [PC]				
	R Amygdala	29 9 -28	4102	4.72
	R Fusiform gyrus	37 -17 -31	4102	4.11
	L Fusiform gyrus	-32 -16 -32	2955	4.33
	R Anterior insula	42 -15 -1	2324	4.09
	L Inferior temporal gyrus	-48 -59 -19	433	3.65
	L Middle temporal gyrus	-60 -22 -8	929	4.38
	R Superior temporal gyrus	58 -6 -17	1237	3.98

Positive correlation = PC; Negative correlation = NC; Mini Mental State Examination = MMSE; Verbal fluency for letters F, A and S = FAS; Clock drawing test = CDT; Functional Activities Questionnaire = FAQ; Disability Assessment for Dementia = DAD; Neuropsychiatric Inventory = NPI; MNI = Montreal Neurologic Institute

coordinates of peak effect; voxel extent threshold = KE; R = right; L = left; Results are reported at p for small volume correction < 0.05.

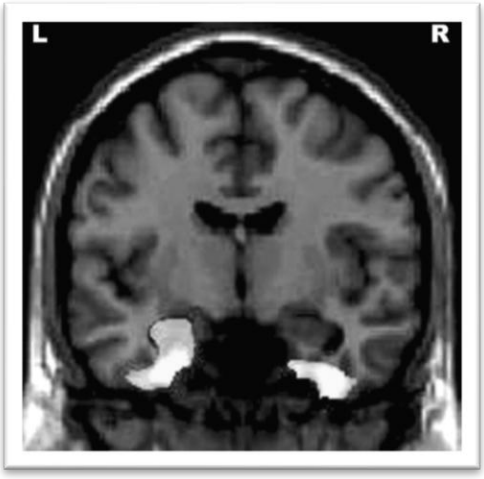
FIGURES

Figure 1



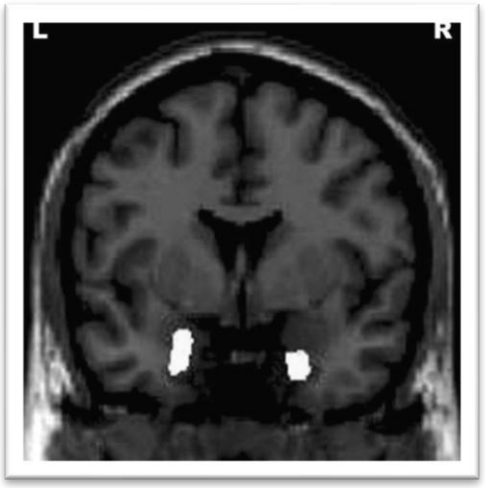
Correlations between Neuropsychiatric Inventory scores and reduced gray matter volume in different areas of the brain. The results are displayed at an uncorrected p level <0.001 and plotted onto the SPM5 canonical T1 image for the purpose of illustration.

Figure 2



Correlations between Functional Activities Questionnaire scores and reduced gray matter volume in different areas of the brain. The results are displayed at an uncorrected p level <0.001 and plotted onto the SPM5 canonical T1 image for the purpose of illustration. R = right; L = left.

Figure 3



Correlations between Disability Assessment for Dementia scores and reduced grey matter volume in different areas of the brain. Results are displayed at an uncorrected p level <0.001 and plotted onto the SPM5 canonical T1 image for the purpose of illustration. R = right; L = left.

ARTIGO 2

THE THICKNESS OF THE POSTERIOR CORTICAL AREAS IS RELATED TO EXECUTIVE DYSFUNCTION IN ALZHEIMER'S DISEASE

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ABSTRACT

Background: Executive dysfunction is associated with negative outcomes. The neural basis of executive deficits in Alzheimer's disease is still unclear and should be better evaluated. Aim: To establish whether alterations of brain structures in Alzheimer's disease are associated with executive dysfunction. Methods: Nineteen patients with Alzheimer's disease and 22 older control subjects underwent a comprehensive evaluation. The clock drawing test, the digit span test, the executive motor function test, the Behavioural Assessment of Dysexecutive Syndrome battery (Rule Shift Cards test), and the Stroop test were used to evaluate executive dysfunction. A multiparametric approach using Freesurfer image analysis suite provided a description of volumetric and geometric features of the gray matter structures. Results: The cortical thickness maps showed a negative correlation between the Behavioural Assessment of Dysexecutive Syndrome battery (Rule Shift Cards test) and the right middle frontal gyrus; a positive correlation between the executive motor function test and the left superior parietal gyrus, left middle temporal gyrus, bilateral supramarginal gyri, right middle frontal gyrus and right precuneus; a negative correlation between the Stroop test (part III) and the right superior parietal gyrus; and a negative correlation between the Stroop test (part III) and the right middle temporal gyrus. Conclusions: Executive dysfunction in Alzheimer's disease is correlated to alterations not only in the frontal areas but also within many temporal and parietal regions.

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of late-onset dementia worldwide [1]. Dementia is one of the main causes of cognitive decline and functional impairment in the elderly [2], leading to impaired quality of life and high costs on the healthcare system [3].

Although the prevailing concept of AD as an episodic memory disorder is well supported, there are many examples of clinical heterogeneity [4]. Several non-amnestic presentations of the pathophysiological process of AD exist, and probable AD is diagnosed even if executive function is the main cognitive deficit [5].

Executive function is a multidimensional cognitive domain that includes attention, sequencing, goal formation, planning, carrying out goal-directed plans, effective performance, insight, will, abstraction, and judgment [6]. The executive dysfunctions have heterogeneous manifestations, and they occur almost universally in all stages of dementia [7]. Furthermore, these dysfunctions are associated with greater risk for development of AD [8]. Executive dysfunction is also associated with greater dementia severity, rapid disease progression, disability, behavioral disorders, and higher mortality [9 - 12].

Approaches that focus on the localization of executive abilities within the frontal lobe have often been criticized, and these critics have favored a perspective that emphasizes the connectivity between the frontal regions and the more posterior and subcortical brain areas [6]. Prefrontal cortex receives inputs from high-order association cortical areas like the posterior parietal lobe, superior temporal lobe, and paralimbic regions [13].

Many studies have explored the neural basis of executive dysfunction in AD. Although most of them correlate changes in the frontal structures with executive performance impairment, many others have correlated executive dysfunction with posterior cortical areas [14 - 18].

Automated magnetic resonance imaging (MRI) thickness measures of individual brain regions can identify mild cognitive impairment and AD with great accuracy, specificity, consistency and reproducibility across multiple independent cohorts. These measures correlate strongly with clinical measures of decline, as well as cellular biomarkers [19 - 21]. Using software tools, a single volumetric T1-weighted MRI scan can be completely processed with little to no manual intervention in a relatively short amount of time. Evidences from literature suggest that cortical thickness

can predict the risk of conversion from mild cognitive impairment to AD with a higher degree of accuracy than can clinical and neuropsychological assessments [22, 23]. Therefore, this automated measure provides a cost-effective and efficient method for the early diagnosis of AD and mild cognitive impairment. Furthermore, these measurements may be able to serve as a quantitative and biologically meaningful endpoint in therapeutic trials.

The questionable description of executive functions as higher-level cognitive functions that are mediated primarily by the frontal lobes and the lack of a definitive role of specific brain structures in certain executive tasks should be better clarified. Also, the lack of a clear correlation between cortical thickness and executive function performance in healthy subjects and the limited number of papers assessing the correlation between the posterior associative cortical thickness and executive functions should be evaluated.

The aim of this study was to establish whether alterations in gray matter volume and cortical thickness of brain structures are associated with executive dysfunction in patients with mild AD and healthy controls.

METHODS

Ethics Statement

This study was approved by the Joint Ethics Committee of Universidade Federal de Sao Paulo and participants (or the guardian or caregiver for the patients with AD) gave written informed consent in accordance with the declaration of Helsinki.

Subjects

Nineteen patients with mild AD and twenty-two older control subjects were recruited from a multidisciplinary memory clinic. The control subjects did not have any cognitive complaints, and all of the participants in the patient group fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria for probable AD [24]. Patients had Functional Assessment Staging [25] score of 3 or 4 and were receiving a stable dose of a cholinesterase inhibitor for at least 2 months. Controls had a Functional Assessment Staging score of 1 or 2.

Exclusion criteria included significant symptoms of depression (Geriatric Depression Scale - 15 items - score of >= 6) [26], significant radiological

evidence of ischemic brain disease, a Modified Hachinski Ischemia Score of > 4 [27], a previous cerebrovascular event, a Mini-Mental State Examination score of < 20 [28] or evidence of other degenerative or secondary dementias, end-stage chronic disease or an unstable medical condition, a psychiatric history, antipsychotic or psychoactive medication adjustments in the 2 months prior to study enrollment, significant visual or hearing impairment, age < 60 years, schooling of less than 2 years and any other condition that could prevent the patient from undergoing an MRI examination or cognitive assessment. Very depressed patients were excluded to avoid bias in the cognitive evaluation because depressive symptoms strongly influence performance on cognitive assessments [29].

Procedures

Each subject and the caregivers of the patients with AD underwent a complete interview with a consultant geriatrician. The physician collected demographic and medical information, including whether the patient had a history of hypertension or diabetes mellitus, the body mass index, and the waist-hip ratio.

Functional status assessment was performed using the Functional Activities Questionnaire [30] and the Disability Assessment for Dementia (only in patients) [31]. Neuropsychiatric symptoms were evaluated using the Neuropsychiatric Inventory (only in patients) [32]. The comprehensive cognitive evaluation included executive tests, such as the clock drawing test [33]; the digit span test [34]; an executive motor function test [35]; the Behavioral Assessment of the Dysexecutive Syndrome – BADS (Rule Shift Cards subtest) [36]; and the Stroop test [37]. Each participant also underwent a MRI.

To evaluate executive motor function, a modified version of the Neuropsi battery subtest was used [35]. Each subject was asked to pay attention to a sequence of 3 hand positions which were performed 3 times by the examiner. The subject should reproduce the sequence in the correct order 3 times. No verbal cues were given, but the examiner did indicate whether the reproduction was correct or incorrect. To perform this task, the subject should place his dominant hand in three different positions sequentially: a fist resting horizontally, a palm resting vertically, and a palm resting horizontally. If the subject was unable to reproduce the sequence after 3 attempts, the score was 1. If the subject was able to reproduce the sequence after 2 attempts, the score was 2. If the subject was able to reproduce the sequence in the first attempt, the score was 3.

MRI data acquisition, analysis and post-processing

MRI of the brain was obtained from all subjects using a 1.5 T scanner [Magnetom Sonata (Maestro Class) Siemens AG, Medical Solutions, Erlangen, Germany] with an eight-channel head coil. To minimize variation, a single investigator positioned all of the subjects using the orbito-meatal line as a landmark. Two conventional sequences were performed to exclude structural lesions: a) Axial T2-weighted FLAIR (fluid-attenuated inversion recovery) in a plane parallel to the anterior commissure-posterior commissure (AC-PC) line [TR (repetition time) = 8500 ms, TE (echo time) = 107 ms, IT (inversion time) = 2500 ms, slice thickness = 5.0 mm, slice interval = 1.5 mm, FOV (field of view) = 240 mm, matrix size = 256 x 256, NEX = 1] and b) Sagittal T1-gradient echo volumetric acquisition for multiplanar reconstruction (TR = 2000 ms, TE = 3.42 ms, flip angle = 15 degrees, FOV = 245 mm, 1.0-mm slice thickness with no gaps, totaling 160 slices per slab, matrix size = 256 x 256, NEX = 1). Scans of low image quality were excluded.

T1-weighted images were processed using the recon-all pipeline of the Freesurfer package, which is documented and freely available to be downloaded online [38]. The main steps of this pipeline are gray/white matter segmentation, pial and white matter surface modeling, transformation of the cortical surface to spherical coordinates, nonlinear surface registration based on curvature (gyrus and sulcus) allowing for analysis of multiple subjects and automated parcellation of cortical areas. The technical details of such procedures are described in the pivotal study [39].

A set of five morphometric parameters per vertex was used as an input to the multimodal classifier: average convexity or concavity, mean radial curvature, metric distortion, cortical thickness and surface area. The average convexity or concavity was used for quantifying the primary folding pattern of a surface. This parameter can capture large-scale geometric features, indicating the depth-height above the template surface of the Freesurfer (fsaverage) and measuring sulcal depth or gyral height. The mean radial curvature was used to assess folding of the cortical surface. Metric distortion (Jacobian) was calculated as the degree of displacement of the cortical surface when registered to the Freesurfer template (fsaverage). Finally, cortical thickness and surface area were used to quantify volumetric differences. Statistical difference maps were constructed using a general linear model, assuming a significance level of 5% corrected for multiple comparisons using the false discovery rate. Further technical details of these parameters are better described in prior publication [39].

Statistical analysis

Volume of brain structures (supplementary material), demographic, clinical, and neuropsychological data were presented as mean +- standard deviation. The Student's t-tests (at a significant level of $p < 0.05$) was used to compare the data of AD patients and controls.

To correlate executive function with brain structures, the volumetric measures were previously transformed to Z scores using the formula [(value - mean)/SD], and a stepwise linear regression was performed. The scores of the executive function tests represented the independent variables used to predict alterations in brain structures. All the correlations were controlled for age, gender, and intracranial volume. Type I errors for the follow-up multiple comparisons were controlled via Bonferroni adjustment (at significance level of 0,015). All statistical analyses were performed using SPSS 18.0.

RESULTS

Demographic, clinical, cognitive, functional, and behavioral data

Table 1 shows the baseline characteristics of the study population. The mean age of the total sample was 72.5 years (SD 5.8, range 60–86 years).

One patient scored 29 in the MMSE. This subject was followed over the previous two years because of executive mild cognitive impairment. During the follow-up period, a progressive cognitive and functional decline was observed in neuropsychological and clinical evaluations. The patient converted to dementia and was therefore included in the study.

The mean scores for the geriatric depression scale of patients and controls were 2 (range 0-5) and 1.3 (range 0-5), respectively, without significant differences being observed between the groups. The mean score of patients on the Functional Activities Questionnaire was 9.8 (SD 4.7, range 2-22). The control group did not show any functional impairment. The Disability Assessment for Dementia and Neuropsychiatric Inventory tests were also used in patients with AD to complete the functional and behavioral assessment. The mean scores were 87% (SD 11, range 60 - 100%) and 22 (SD 19, range 0 – 77), respectively.

Volumetric assessment

Compared to controls, patients with AD exhibited significantly smaller volumes of bilateral caudal middle frontal gyri, and isthmus of cingulate, left

pars opercularis, right pars orbitalis, left pars triangularis, rostral middle frontal gyri bilaterally, superior frontal gyri bilaterally and frontal pole bilaterally, middle temporal gyri bilaterally, precuneus bilaterally, superior parietal gyri bilaterally, inferior parietal gyri bilaterally, supramarginal gyri bilaterally, and left fusiform gyrus. The description of the volumetric neuroimaging data of the participants is fully detailed as Supplementary Material.

The volume of the right superior parietal gyrus correlated negatively with results of the Stroop test Part III - errors (beta = -0.093, t = -0.359, p = 0.012) and differentiated the AD group from healthy controls (beta = -0.986, t = -3.071, p = 0.005). All the correlations were controlled for age, gender, and intracranial volume.

Cortical thickness maps

The cortical thickness maps of patients and control subjects showed a negative correlation between the BADS score (rule shift cards test, rule 2, errors) and thickness of the right rostral middle frontal gyrus; see Figure 1, images 1A and 2A. A positive correlation between the executive motor function test and the left superior parietal gyrus, left middle temporal gyrus, bilateral supramarginal gyri, right caudal middle frontal gyrus and right precuneus thickness was noted; see Figure 1, images 1B, 2B, 1C and 2C. There was a negative correlation between results of the Stroop test Part III (errors) and the right superior parietal gyrus; see Figure 1, image 1D. There was a negative correlation between results of the Stroop test Part III (time) and the right middle temporal gyrus; see Figure 1, image 2D.

DISCUSSION

Our results showed that executive dysfunctions in mild AD may be correlated to the thinning of the parietal and temporal cortices.

A correlation between the volume and cortical thickness of the right superior parietal gyrus with executive function tests was observed. The volumetric correlation could be used to differentiate AD patients from controls.

The cortical thickness of the left superior parietal gyrus, bilateral supramarginal gyri, right precuneus, and left middle temporal gyrus correlated positively with performance on the executive motor function test. The executive functions assessed by this cognitive test, such as working memory, planning and praxis, did not correlate with the structures mentioned in previous studies.

The right superior parietal gyrus and the right middle temporal gyrus correlated negatively with the scores of the Stroop test Part III, supporting the role of these structures in inhibitory control. Similar results were not found in the literature. One study correlated response inhibition and the right parietal cortices of bipolar disorder type 1 patients [40].

The anatomical correlations of the Stroop test and the executive motor function test occurred predominantly and with higher intensity in the right hemisphere, confirming previous studies [40, 41]. These findings highlight the capacity of the practical cognitive tests (mentioned above) to detect executive dysfunction in patients with mild AD.

Many other studies using different neuroimaging methods have correlated parietal and temporal structures with executive functions. Few of these studies used cortical thickness as a variable (14, 18). Voxel-based morphometry studies revealed that patients with AD without the epsilon 4 allele of apolipoprotein had poorer executive tasks performance and greater frontoparietal atrophy [14] and that grey matter reduction of the bilateral insula and left lateral temporal lobe was a predictor of clinical progression of dysexecutive mild cognitive impairment [42]. Radionuclide studies have found correlations between executive functions and the parietal and temporal regions [15, 43]. Functional MRI studies have correlated the right frontal regions and the associative parietotemporal areas with executive deficits in patients with AD [16, 44].

The relationship between cortical thickness and performance on cognitive tests has not been fully elucidated and warrants further investigation. We found positive correlations between cortical thickness and cognitive test performance, both in controls and patients. However, previous studies have found different results that showed an inverse relationship between cortical thickness and performance on executive function tests in control subjects [45, 46].

The differential aspects of this study should be mentioned. The selective pathological involvement of some neocortical areas and temporal lobe structures, which is common in AD [47], was also observed in our neuroimaging findings and correlated with executive dysfunction. Cardiovascular risk, and important factor in cognitive decline and executive impairment, and a possible confounder in AD studies, was considered and controlled in this investigation [48, 49].

The populations in developing countries are exposed to various adverse conditions. A combined vulnerability in education, income, wealth and

occupation was associated with poor cognitive function in late life. [50] Education has been found to be the most consistent socioeconomic factor associated with cognitive dysfunction. [51] Our sample showed a mean education level of 8 years, higher than the average schooling of the adult Brazilian population, which is estimated at 6 years. [52] Most of the studies in this field were_performed in developed countries with more highly educated individuals than our sample (14, 18, 21, 42). Although our study population had a higher education level than much of the country, our sample is a better representation of the local population than those in other studies, and our results could be used as reference for future studies evaluating the cortical thickness of AD patients with a low education level.

The results should be interpreted with caution because there are a few limitations to our study. The main limitations include the small sample size and the age difference between patients and control subjects. The poor ecological validity of some executive tests and the complex dependence of the executive functions of other cognitive domains should be mentioned as a potential problem in the assessment of the executive functions of AD patients [6].

Cholinesterase inhibitors have been shown to decrease hippocampal and cortical atrophy [53, 54] and improve cognitive performance in AD patients [55]. Although the treatment time had varied for the patients (4 to 107 months), they had similar clinical staging (Functional Assessment Staging score of 3 or 4). To the best of our knowledge, no studies assessed the effects of cholinesterase inhibitors on cortical thickness.

This study has implications for our understanding of how functional deficits in patients are associated with their underlying structural basis. Neuroimaging techniques have demonstrated that executive abilities are not confined to the frontal area of the brain but instead consist of complex interactions among different brain regions [56]. Our results are consistent with other studies of AD which have suggested that executive function may not depend entirely on the prefrontal cortex but on other posterior cortical areas, as well.

The association between modern neuroimaging methods and practical tests, such as the Stroop test and executive motor function test, could be very useful for identifying executive dysfunction in patients with AD. Future neuroimaging studies addressing the connection between these posterior cortical areas and the relationships

between cortical thickness and education level would add to the understanding of the neural basis of AD.

CONCLUSIONS

Executive dysfunction in mild Alzheimer's disease is associated not only with abnormalities of the frontal areas but also with many temporal and parietal regions. The pathophysiology of executive dysfunction is complex and includes abnormalities in multiple brain regions and, probably, in the connections among them.

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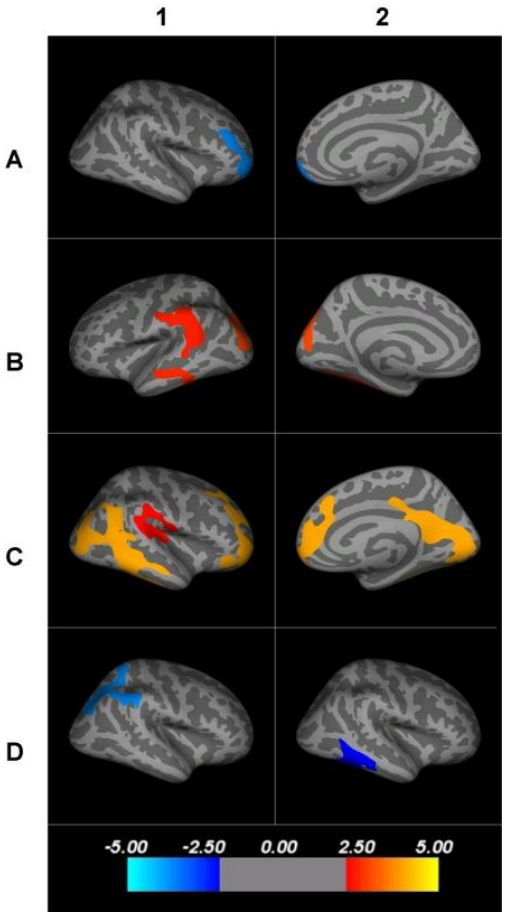
Table 3: Demographic, medical and cognitive data description.

Variable	Controls (n=22, 12 female): Mean (SD); range.	Alzheimer's disease (n=19, 10 female): Mean (SD); range.	Differences between groups (t; p value)
Age (years)	70.14 (5.67); 60-80.	75.42 (4.81); 66-86.	-3.187; 0.003*
Education (years)	9.14 (5.26); 2-18.	7.68 (4.42); 3-16.	0.947; 0.349
Diabetes (%)	22	21	0.126; 0.900
Hypertension (%)	64	58	0.367; 0.715
Waist-hip ratio	0.94 (0.81); 0,7-1.1.	0.92 (0.71); 0.8-1.1.	-1.037; 0.306
Body mass index	27.21 (3.71); 19– 32	26.10 (3.62); 21-36.	0.965; 0.340
Modified Hachinski Scale	0.95 (0.84); 0-3.	0.68 (0.58); 0-2.	1.175; 0.247
Time of cholinesterase inhibitor use (months)	NA	42.63 (27.35); 4-106.	NA
Mini Mental State Examination	28.82 (0.90); 27-30.	24.00 (2.62); 20-29.	8.083; 0.000*
Stroop test Part III (time - seconds)	48.77 (19.96); 25-103.	67.63 (28.50); 35-155.	-2.480; 0.018*
Stroop test Part III (errors)	1.59 (2.30); 0-9.	4.95 (4.50); 0-18.	-3.067; 0.004*
Digit Span Backwards	3.86 (1.32); 0-6.	3.00 (1.29); 0-4.	2.110; 0.041*
Executive motor function test	2.45 (0.67); 1-3.	1.26 (1.14); 0-3.	4.127; 0.000*
Behavioural Assessment of Dysexecutive Syndrome: Rule Shift Cards test - rule 2 (time - seconds)	37.00 (8.25); 25-60.	41.21 (12.70); 26-76.	-1.275; 0.210
Behavioural Assessment of Dysexecutive Syndrome: Rule Shift Cards test - rule 2 (errors)	3.32 (3.92); 0-10.	7.05 (3.45); 0-11.	-3.211; 0.003*
Clock drawing test	7.95 (2.36); 4-10.	6.11 (2.74); 2-10.	2.319; 0.026*

NA: not available; * significant statistical difference.

Figure 1:

Cortical thickness maps of associations between brain regions and executive functions.



Red, orange and yellow colors represent positive correlations. Blue color represents negative correlations. 1A and 2A illustrate the negative correlation between the BADS score (rule shift cards test, rule 2, errors) and thickness of the right rostral middle frontal gyrus; 1B, 2B, 1C, 2C illustrate the positive correlation between the executive motor function test and the left superior parietal gyrus, left middle temporal gyrus, bilateral supramarginal gyri, right caudal middle frontal gyrus and right precuneus thickness; 1D illustrate the negative correlation between results of the Stroop test Part III (errors) and the right superior parietal gyrus; 2D illustrate the negative correlation between results of the Stroop test Part III (time) and the right middle temporal gyrus The scale is graded in z-score.

Supplementary material

Volumes [mm3] of different brain structures measured with an automated volumetric method (FreeSurfer).

Brain structures volume (mm3)		Left Hemisphere: Mean (SD).	Differences between groups (t; p value)	Right Hemisphere: Mean (SD).	Differences between groups (t; p value)
Caudal anterior cingulate	Control	1685.23 (434.84)	-0.087; 0.931	2056.09 (506.72)	1.513; 0.138
	Patient	1697.74 (483.08)		1832.26 (428.73)	
Caudal middle frontal	Control	5849.32 (980.91)	2.902; 0.006*	5346.50 (1132.18)	2.207; 0.033*
	Patient	4940.79 (1021.33)		4701.26 (626.98)	
Isthmus cingulate	Control	2509.59 (484.52)	2.428; 0.020*	2379.59 (377.58)	2.631; 0.012*
	Patient	2181.74 (358.88)		2083.11 (337.96)	
Lateral orbitofrontal	Control	7392.73 (883.47)	1.797; 0.080	7416.23 (855.54)	0.832; 0.411
	Patient	6934.47 (724.62)		7192.89 (859.13)	
Medial orbitofrontal	Control	5382.05 (898.86)	1.527; 0.135	4976.59 (596.86)	1.472; 0.149
	Patient	4983.89 (747.20)		4669.37 (739.16)	
Paracentral	Control	2938.86 (593.83)	1.941; 0.059	3392.91 (579.42)	1.523; 0.136
	Patient	2609.79 (472.53)		3139.37 (469.71)	
Pars opercularis	Control	4435.59 (851.00)	2.521; 0.016*	3542.05 (717.96)	1.844; 0.073
	Patient	3853.21 (577.81)		3196.21 (419.41)	
Pars orbitalis	Control	2007.95 (373.62)	1.983; 0.054	2612.77 (373.91)	2.893; 0.006*
	Patient	1822.16 (175.96)		2300.37 (307.44)	
Pars triangularis	Control	3307.91 (581.73)	2.088; 0.043*	3917.32 (641.66)	1.701; 0.097
	Patient	2966.84 (441.38)		3592.79 (568.64)	
Rostral anterior cingulate	Control	2720.32 (470.85)	1.432; 0.160	2222.45 (465.68)	1.498; 0.142
	Patient	2513.68 (448.79)		2042.42 (257.33)	
Rostral middle frontal	Control	14221.68 (1798.14)	2.834; 0.007*	15501.50 (2029.12)	2.794; 0.008*
	Patient	12770.32 (1422.34)		13800.11 (1840.23)	
Superior frontal	Control	19761.64 (2997.74)	2.791; 0.008*	19168.27 (2624.50)	3.779; 0.001*
	Patient	17521.11 (1936.71)		16500.89 (1722.51)	
Frontal pole	Control	713.41 (181.72)	3.527; 0.001*	952.59 (178.94)	5.105; 0.000*
	Patient	542.89 (114.51)		686.16 (151.06)	

Superior temporal	Control	11017.32 (1678.8)	1.874; 0.68	10467.68 (1396.09)	1.244; 0.221
	Patient	10161.68 **(**1146.63)		9937.89 (1326.80)	
Middle temporal	Control	9677.50 **(**1394.84)	2.031; 049*	10797.59 (1296.25)	4.130; 0.000*
	Patient	8686.00 (1729.73)		9025.37 (1451.89)	
Inferior temporal	Control	10044.91 (1718.88)	1.843; 0.73	10144.77 (1779.39)	1.631; 0.111
	Patient	9104.84 **(**1515.960		9217.16 (1846.91)	
Para- hippocampal	Control	1984.68 (278.07)	2.041; 0.48	1886.32 (351.04)	1.441; 0.261
	Patient	1804.53 (285.11)		1763.37 (335.98)	
Postcentral	Control	8457.32 (1209.36)	0.479; 0.634	8230.00 (1060.68)	1.294; 0.203
	Patient	8246.05 (1608.57)		7789.89 (1115.48)	
Precuneus	Control	8381.86 (872.34)	3.710; 0.001*	8882.95 (1015.76)	3.900; 0.000*
	Patient	7256.16 (1070.60)		7612.00 (1068.80)	
Superior parietal	Control	11734.91 (1091.82)	3.382; 0.002*	11404.82 (1242.52)	3.439; 0.001*
	Patient	10278.68 **(**1644.83)		9844.47 (1657.50)	
Inferior parietal	Control	11814.50 (2018.33)	2.267; 0.029*	137299.55 (20629.7)	2.607; 0.013*
	Patient	10474.37 **(**1722.94)		121180.53 (18645.8)	
Supra – marginal	Control	9614.05 **(**1476.46)	2.575; 0.014*	9000.36 (1232.09)	2.507; 0.016*
	Patient	8496.47 (1272.31)		8084.63 (1084.58)	
Fusiform	Control	9403.27 (1293.04)	3.404; 0.002*	87853.64 (13171.89)	1.750; 0.088
	Patient	8161.11 (995.04)		81200.00 (10807.03)	
Intracranial	Control	1520000.31 (167.94)	0.354; 0.726		
	Patient	1501000.57 (170.88)			

* Significant statistical difference.

DISCUSSÃO GERAL

O envolvimento seletivo de áreas neocorticais frontais, parietais e temporais, comum na DA, [71] foi também observado nas análises de ambos os artigos e correlacionaram-se às alterações comportamentais, perdas funcionais e disfunções executivas.

O artigo 1 confirmou evidências sobre as bases neurais das alterações comportamentais na DA. Ao associar sintomas neuropsiquiátricos e alterações de estruturas frontais, reproduziu os resultados de vários outros estudos que utilizaram diversos métodos de neuroimagem. No entanto, trouxe novas evidências ao estabelecer associações entre estruturas temporais e perdas funcionais. Até onde podemos avaliar, somente um trabalho baseado em análises de MBV identificou resultados semelhantes. [72]

O artigo 2 diferencia-se da maioria dos trabalhos na área ao estabelecer correlações entre atrofia cortical de regiões posteriores e disfunções executivas de pacientes com DA. Os achados são valorizados ao se evidenciar a avaliação do risco cardiovascular entre os sujeitos da pesquisa, um importante fator relacionado ao declínio cognitivo e disfunção executiva. [73, 74] Os resultados estão em consonância com estudos de neuroimagem mais recentes que incluem, juntamente com as estruturas temporais mediais, alterações de regiões corticais posteriores como possíveis biomarcadores precoces da DA. [75]

As populações de países em desenvolvimento estão expostas a várias condições adversas. Vulnerabilidades em educação, renda, qualidade de vida e ocupação associaram-se a baixo funcionamento cognitivo durante o envelhecimento. [76] Educação foi identificada como o principal fator socioeconômico associado à disfunção cognitiva. [77] A escolaridade média da amostra deste estudo foi de 8 anos, maior que a média nacional, estimada em 6 anos. [78] A maioria dos estudos nesta área foi realizada em países desenvolvidos, envolvendo sujeitos com escolaridade muito maior que a observada em nossa amostra (variação de 14.4 a 16.4 anos). [47, 70, 79] Embora a média de escolaridade dos sujeitos deste estudo seja maior que a média nacional, os resultados observados no artigo 2 podem ser uma melhor referência para futuros estudos que avaliem espessura cortical de pacientes com baixa escolaridade.

Além dos dois artigos já apresentados nesta tese, o projeto global permitiu que fossem produzidos, ainda na etapa de preparação desta tese, outros dois artigos. [80, 81] O primeiro fez uma revisão da literatura visando identificar os

instrumentos de avaliação cognitiva e funcional da DA adaptados para o Brasil. O segundo artigo revisou conceitos e aplicabilidade clínica da imagem dos tensores de difusão na DA. Pretendemos utilizar esta técnica, em uma próxima publicação, para estudar o papel da integridade das interconexões neuronais entre as diversas áreas corticais associadas às disfunções executivas.

Limitações

O tamanho da amostra é o principal problema observado nos 2 artigos.

Observa-se também no artigo 1 a ausência de um grupo controle. Embora os indivíduos controles tenham sido submetidos à RM de crânio, não foram avaliados pelo Inventário Neuropsiquiátrico Modificado e Escala de Avaliação de Incapacidade em Demência, instrumentos desenvolvidos para a avaliação de cuidadores de pacientes com demência, dificultando assim possíveis comparações entre os grupos.

Em relação ao artigo 2, observa-se a diferença de idade entre os grupos. A validade ecológica dos testes de funções executivas e a complexa relação de interdependência entre as várias funções cognitivas também limitam a avaliação das funções executivas.

Implicações práticas

Os resultados destes artigos implicam em uma melhor compreensão das bases neurais dos sintomas neuropsiquiátricos, perdas funcionais e disfunção executiva em pacientes com DA leve.

Diversas manifestações de sintomas cognitivos e comportamentais, diferentes evoluções clínicas e respostas heterogêneas aos tratamentos instituídos tornam importante o conhecimento adequado das bases neurais da DA. A constatação de diferentes genótipos e fenótipos relacionados à DA trazem implicações diretas para o diagnóstico, prognóstico, intervenções terapêuticas e novas linhas de pesquisa. [24, 79, 82] Pesquisas sobre os mecanismos da DA permitem o aprimoramento do processo diagnóstico e o desenvolvimento de novas abordagens terapêuticas e preventivas. [83]

Avaliações por técnicas baseadas em MBV e análise de volume e espessura cortical permitem tradicionalmente a diferenciação de grupos de indivíduos como pacientes e controles. Técnica de classificação multivariada (“Support Vector Machines”, por exemplo) pode permitir a utilização de dados obtidos através das

análises automatizadas no diagnóstico individualizado de pacientes com DA, aprimorando o diagnóstico e a capacidade prognóstica. [68]

Além das evidências já estabelecidas do papel de estruturas frontais no desempenho de funções executivas, os resultados do artigo 2 demonstram a íntima participação de estruturas corticais posteriores no funcionamento adequado deste domínio cognitivo. Pesquisas dirigidas para o estudo das conexões entre as áreas corticais mencionadas e também para as correlações entre a espessura cortical e escolaridade trarão importantes informações para o conhecimento das bases neurais da DA.

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