MARCIO LUIZ FIGUEREDO BALTHAZAR

MEMÓRIA LÉXICO-SEMÂNTICA NO COMPROMETIMENTO COGNITIVO LEVE AMNÉSTICO E DOENÇA DE ALZHEIMER LEVE:

aspectos neuropsicológicos, de neuroimagem estrutural e modelo de organização cerebral

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Orientador: Prof. Dr. Benito Pereira Damasceno

Co-orientador: Prof. Dr. Fernando Cendes

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Dedicado a

Meus pais, Elizabeth e Jurandyr, pelo amor e apoio eternos;

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Meu filho Pedro, por existir.

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"The concept of a rose is composed of a "tactile memory image"—"an image of touch"—in the central projection field of the somesthetic cortex. It is also composed of a visual memory image located in the visual projection field of the cortex. The continuous repetition of similar sensory impressions results in such a firm association between those different memory images that the mere stimulation of one sensory avenue by means of the object is adequate to call up the concept of the object. (...) This sum total of closely associated memory images must "be aroused into consciousness" for perception not merely of sounds of the corresponding words but also for comprehension of their meaning. Following our anatomic mode of interpretation, we also postulate for this process the existence of anatomic tracts, fibers, connections, or association tracts between the sensory speech center of word-sound-comprehension and those projection fields which participate in the formation of the concept."

Carl Wernicke, 1900.

SUMÁRIO

Lista de Abreviações

βA: beta-amilóide

APOE: apolipoproteína E

CAMCOG: sessão cognitiva do CAMDEX (the Cambridge Examination for Mental Disorders of the Elderly)

CCL: Comprometimento Cognitivo Leve

CCLa: Comprometimento Cognitivo Leve amnéstico

DA: doença de Alzheimer

DLFT: degeneração lobar fronto-temporal

ENF: emaranhados neurofibrilares

FHP: filamentos helicoidais pareados

PDP: processamento distribuído em paralelo

PET: tomografia por emissão de pósitrons

PN: placas neuríticas

PPβA: proteína precursora do peptídeo beta-amilóide

RM: Ressônancia Magnética

RM-MBV: Morfometria baseada em voxels por Ressonância Magnética

SPECT: Tomografia computadorizada por emissão de fóton único

TNB: Teste de Nomeação de Boston

TAAVR: Teste de aprendizado auditivo verbal de Rey

RESUMO

A organização cerebral da memória léxico-semântica, assim como suas alterações em pacientes com doença de Alzheimer (DA) leve e Comprometimento Cognitivo Leve amnéstico (CCLa) não são completamente conhecidas.

Neste estudo, avaliamos o desempenho de pacientes com DA leve, CCLa e idosos normais em testes léxico-semânticos como o Teste de Nomeação de Boston (TNB), Teste de Similaridades do CAMCOG e Fluência Verbal (FV) para categoria animais, além de outros domínios cognitivos. Aprofundamos o estudo do desempenho dos pacientes no TNB avaliando: 1) se houve benefício com o uso de pistas semânticas e fonêmicas, após erros espontâneos de nomeação e 2) o padrão de erros de nomeação espontâneos (classificados como semânticos, fonológicos, por omissão e por paragnosia visual); e subclassificando os erros semânticos de forma hierárquica (erros superordenados, coordenados e circunlóquios).

Avaliamos também os padrões de atrofia cerebral desses pacientes em relação a controles por meio de métodos de neuroimagem estrutural por Ressonância Magnética: volumetria hipocampal e Morfometria Baseada em Voxels (RM-MBV). Ainda, correlacionamos o desempenho dos pacientes no Teste de Aprendizado Auditivo Verbal de Rey (TAAVR) com o volume hipocampal e o padrão de erros espontâneos gerais e semânticos no TNB com a densidade de substância cinzenta em todo o cérebro por RM-MBV.

Os pacientes com CCLa tiveram desempenho inferior aos controles no teste de FV para animais, enquanto que os pacientes com DA leve tiveram desempenho inferior ao grupo CCLa e controles em todos os testes léxico-semânticos. Porém, após utilizarem pista fonêmica, os pacientes com DA leve tiveram desempenho em nomeação de figuras proporcionalmente semelhante aos controles e CCLa. Também, os três grupos tiveram padrão de erros espontâneos gerais e semânticos qualitativamente iguais, embora quantitativamente tenha havido maior número de erros no grupo DA leve, seguido por CCLa e controles, respectivamente.

Quanto ao exames de neuroimagem estrutural, houve um *continuum* no volume hipocampal, porém sem diferença estatística significante entre DA leve e CCLa. Houve correlação significativa entre o volume hipocampal e o item de evocação tardia do TAAVR, considerando os três grupos em conjunto; quanto à RM-MBV, os pacientes com DA leve apresentaram mais áreas com maior grau de atrofia de substância cinzenta que

CCLa e controles; o grupo CCLa apresentou atrofia principalmente em giros parahipocampais e tálamos, quando comparados aos controles. Em relação à substância branca, o grupo DA leve apresentou atrofia em região periventricular, corpo caloso e em áreas próximas a córtices associativos. Não houve áreas de atrofia de substância branca no grupo CCLa em relação aos controles.

Encontramos diversas áreas em que houve correlação significativa entre os erros espontâneos de nomeação e a densidade de substância cinzenta, considerando os três grupos juntos. Notadamente, as regiões temporais mediais e tálamos correlacionaram-se com todos os subtipos de erros; as regiões anteriores dos lobos temporais, principalmente os giros superior e inferior, correlacionaram-se com erros coordenados e circunlóquios; os giros frontais superiores (o esquerdo mais que o direito) correlacionaram-se com erros superordenados, e os inferiores, com erros tipo circunlóquios.

Discutimos o possível papel de cada uma dessas áreas nos processos mentais léxico-semânticos e sua contribuição para o entendimento de como esse tipo de memória está organizada no cérebro humano.

ABSTRACT

Cerebral organization of lexical-semantic memory, as well as its disruption in mild Alzheimer's disease (AD) and in amnestic Mild Cognitive Impairment (aMCI) is not fully understood.

In this study, we evaluated the performance of mild AD, aMCI and normal aging subjects in lexical-semantic tests: Boston Naming Test (BNT), CAMCOG's Similarities item, Verbal Fluency (VF) for animals' category and others cognitive domains. We detailed their performance on BNT by evaluating: 1) if they needed or were benefited by semantic and phonemic cues and 2) the pattern of general errors (classified as semantic errors, visual paragnosia, phonological errors, and omission errors). The semantic errors were further subcategorized into three subclasses (coordinate, superordinate, and circumlocutory).

We also evaluated the pattern of brain atrophy in aMCI and mild AD patients by using structural neuroimaging methods: hippocampal volumetry (HV) and Voxel-based morphometry (VBM). We correlated HV with subjects' performance on Rey Auditory Verbal Learning Test (RAVLT) delayed recall item, and the pattern of spontaneous and semantic errors on BNT with grey matter density, by using VBM.

aMCI subjects performed worse than controls on VF for animals' category, while mild AD performed worse than aMCI and controls in all lexical-semantic tests. However, after phonemic cues, mild AD subjects performed similar to aMCI and control subjects. They also had the same qualitative pattern of spontaneous and semantic errors, although quantitatively, AD patients committed the most errors, controls committed the fewest errors, and aMCI subjects showed an intermediate performance.

Concerning structural neuroimaging, the three groups also presented a *continuum* pattern in HV, although there were no statistically differences between aMCI and AD HV. RAVLT delayed recall item was significantly related to HV, considering the three groups together. In relation to VBM analysis, mild AD patients had more areas with more grey matter atrophy than aMCI and control subjects. aMCI showed more atrophy mainly in parahippocampal gyri and thalami, when compared with control subjects. Considering white matter, mild AD group showed atrophy in periventricular regions, corpus callosum and areas adjacent to associative cortices. There was not white matter atrophy in aMCI patients in comparison with controls subjects.

We found several areas with significant correlations between spontaneous naming errors on BNT and grey matter density, considering the three groups together. Medial temporal structures and thalami were correlated with all subtypes of errors; anterior temporal regions, mainly superior and inferior temporal gyri, were related with coordinate and circumlocutory errors; superior frontal gyri (left more than right) were related with superordinate errors, while inferior frontal gyri (left more than right) were related to circumlocutory errors.

We discussed the possible role of each of these areas in the lexical-semantic mental processes, and their contribution to the understanding of cerebral organization of semantic memory.

1- INTRODUÇÃO

Da organização da Tese

O estudo que originou esta Tese produziu seis artigos científicos que versam sobre diferentes e complementares aspectos da organização cerebral da memória léxico-semântica na DA leve, no CCLa e no envelhecimento normal. Estes artigos podem ser divididos em três tipos: 1) estudos clínicos de alterações da memória léxico-semântica na DA e CCLa; 2) estudo em neuroimagem estrutural, avaliando os padrões de atrofia cerebral na DA e CCLa; 3) estudos em neurociência cognitiva, usando a DA, CCLa e envelhecimento normal como modelo lesional para o entendimento da organização da memória episódica e léxico-semântica no cérebro humano.

Os três primeiros artigos são exclusivamente neuropsicológicos: os artigos **1** e **2** avaliaram o desempenho dos pacientes e de idosos normais em diferentes testes léxico-semânticos; o artigo **3** aprofunda a avaliação do desempenho no TNB, investigando se os pacientes precisaram ou foram ajudados por pistas semânticas e fonêmicas e também se houve diferença no padrão de erros gerais e semânticos nas respostas espontâneas.

O artigo **4** é exclusivamente sobre neuroimagem estrutural, através do estudo dos padrões de atrofia de substâncias branca e cinzenta dos pacientes com DA leve e CCLa em relação aos controles, avaliados por meio de RM-MBV.

Os artigos **5** e **6** correlacionam os achados neuropsicológicos com neuroimagem estrutural: o artigo **5**, sobre memória episódica e volumetria hipocampal; o artigo **6**, sobre os tipos de erros gerais e semânticos nas respostas espontâneas no TNB, com a densidade de substância cinzenta cerebral avaliada por RM-MBV.

2- REVISÃO DA LITERATURA

2.1- Doença de Alzheimer

DA é uma doença neurodegenerativa com surgimento em geral após a sétima década, na qual ocorrem alterações cognitivas como déficit de memória episódica, nomeação e outros problemas de linguagem, habilidades visuo-espaciais, praxias e atenção/funções executivas. Também é comum o surgimento de distúrbios neuropsiquiátricos como agitação, depressão, alucinações e delírios (Cummings, 2003). É a principal causa de demência na população idosa, responsável por cerca de 60 a 70% de todas as demências e sua prevalência está aumentando progressivamente devido, sobretudo, ao envelhecimento da população. Essa prevalência dobra, em média, a cada 5 anos passando de 1% aos 60 anos e chegando a mais de 40% da população com mais de 85 anos de idade (Cummings e Cole, 2002). Em um estudo realizado na cidade de Catanduva/SP, Herrera et al. (2002) encontraram uma prevalência de 7,1% na população acima de 65 anos. Estima-se que, em todo o mundo, mais de 27 milhões de pessoas sofram de DA (Wilmo et al., 2006).

Há alguns fatores de risco conhecidos para a DA de início tardio, como idade, doenças vasculares e fatores genéticos como a presença do alelo ε4 da apolipoproteína E (APOE4), uma proteína carreadora de colesterol envolvida no metabolismo das placas neuríticas (PN) (Poirier et al., 2001). Existem 5 alelos para a APOE, numerados de ε1 a ε5, sendo o mais comum o ε3 (cerca de 90% da população caucasiana com 1 alelo e 60% com 2 alelos), o ε2, cuja presença pode conferir proteção contra o depósito de peptídeo β-amilóide (βA) e o ε4, com cerca de 30 % da população com 1 alelo (Corder et al., 1998).

Myers et al. (1996) mostraram que a chance de desenvolver DA em uma população caucasiana esteve diretamente relacionada à quantidade de alelos ε4. Nesse estudo, 55% do grupo homozigoto (APOE ε4/ε4) desenvolveu DA até a idade de 80 anos, contra 27% do grupo ε3/ε4 e 9% do grupo ε3/ε3 até a idade de 85 anos. Apesar do aumento do risco, apenas 10% dos indivíduos com um ou dois alelos ε4 irão desenvolver DA, o que faz com que esse exame não tenha uso clínico recomendado de forma rotineira. Diversos outros genes podem estar envolvidos no surgimento da DA (Ertekin-

Taner, 2007).

Do ponto de vista anátomo-patológico, as PN e os emaranhados neurofibrilares (ENF) são as características mais marcantes da DA. As PN são compostas por um núcleo central contendo o peptídeo βA circundada por astrócitos, micróglia e neuritos distróficos geralmente contendo filamentos helicoidais pareados (FHP) (Cummings e Cole, 2002). Resumidamente, o peptídeo βA se origina após duas clivagens proteolíticas na proteína precursora do βA (PPβA), que são realizadas pelas enzimas γ e β-secretase. A PPβA também pode ser clivada pela α-secretase, o que evita a formação do βA (Eckman e Eckman, 2007).

Foram identificadas algumas mutações genéticas, de padrão de transmissão autossômico dominante, diretamente relacionadas com o metabolismo do peptídeo βA. Essas mutações causam a DA familiar, geralmente de início precoce, cujas características clínicas e neuropatológicas são idênticas às encontradas na DA esporádica de início tardio. As principais foram verificadas em três cromossomos distintos: gene da PPβA, no cromossomo 21; gene da presenilina 1, no cromossomo 14 e gene da presenilina 2 no cromossomo 1. As presenilinas são o componente catalítico das secretases que clivam a PPβA. Todas essas mutações genéticas causam aumento do βA, particularmente do βA42 (Eckman e Eckman, 2007). Além da formação das PN, os oligômeros do βA são sinaptotoxinas potentes, e podem bloquear a função dos proteossomos, inibir a atividade mitocondrial, alterar a concentração intracelular de Ca^{2+} e ainda estimular processos inflamatórios. Podem, também, interferir na fosforilação da proteína tau (LaFerla, 2007).

O estudo da fisiopatologia do βA levou ao desenvolvimento de novas propostas terapêuticas, como a inibição da atividade das enzimas γ e β-secretase e/ou estimulação da atividade da α-secretase, ou ainda, imunoterapia com anticorpos anti-βA. Porém, apenas o depósito do βA não explica toda a fisiopatologia da DA, além de apresentar pouca correlação com a gravidade da demência (Eckman e Eckman, 2007; Poirier et al., 2001).

Os ENF contém FHP originados da hiperfosforilação da proteína tau (uma proteína associada aos microtúbulos), o que gera desestabilização do citoesqueleto celular e morte neuronal. Algumas áreas cerebrais são mais vulneráveis a esse processo patológico, como os hipocampos e os córtices frontais. É comum ocorrer nessas regiões

FHP contendo proteína tau anormalmente fosforilada, de peso molecular maior que o habitual, conhecida como proteína associada a DA (ADPA) (Poirier et al., 2001). Esse fenômeno pode justificar a maior correlação clínica dos sintomas cognitivos com a presença dos ENF. O estudo da fisiopatologia dos ENF gerou algumas possibilidades terapêuticas promissoras, como a inibição da hiperfosforilação da proteína tau, com conseqüente estabilização das proteínas microtubulares e menor dano neuronal (Morris, 2005).

Existem outros fatores causais para a DA, como resposta inflamatória local, disfunção mitocondrial, alteração de neurotransmissores secundária a perda dos neurônios colinérgicos do núcleo basal de Meynert e serotoninérgicos dos núcleos da rafe, além de perda sináptica precoce. Essa perda sináptica é a variável neuropatológica com maior correlação com o grau de demência (Scheff e Price, 2003). Essas alterações nas sinapses podem ser causadas pela presença das PN e ENF, mas também, por estresse oxidativo em genes que codificam proteínas sinápticas. Nesse caso, a disfunção sináptica seria mais precoce que o surgimento, por exemplo, das PN, e o estresse oxidativo, originado de um metabolismo energético celular anormal, teria papel predominante na gênese da DA (Forero et al., 2006).

DA, assim, é uma doença de múltiplas causas, e é possível que cada um desses fatores fisiopatológicos contribua de forma diferente para a gênese dos sintomas cognitivos de cada paciente. É presumível que, em um futuro não tão distante, a DA seja tratada de forma específica e precoce, com agentes terapêuticos que levem em conta o perfil genético e molecular de cada indivíduo.

2.2- Comprometimento Cognitivo Leve

CCL é um termo clínico aplicado a pacientes com uma ou mais alterações cognitivas objetivas, sem que haja prejuízo significativo das atividades de vida diária, ou seja, sem que sejam preenchidos critérios para diagnóstico de demência (Petersen, 2004; Winblad et al., 2004). Embora não haja um critério universalmente aceito, a maioria dos pesquisadores considera necessários: uma queixa cognitiva (geralmente memória episódica), preferencialmente confirmada por uma pessoa próxima; comprometimento cognitivo objetivo (geralmente memória episódica), com desempenho inferior ao esperado para pessoas da mesma faixa etária e escolaridade; atividades de vida diária preservadas. Enfim, é um diagnóstico que depende essencialmente do julgamento clínico e pode ser classificado de acordo com os subtipos: amnéstico (com comprometimento exclusivo de memória episódica ou com múltiplos domínios) e não-amnéstico (domínio único ou múltiplos domínios) (Kelley e Petersen, 2007).

Em relação ao CCLa, considera-se que pode haver um *continuum* no declínio cognitivo desde o envelhecimento normal até o desenvolvimento de DA. Assim, CCLa poderia ser considerado um estado intermediário entre o envelhecimento normal e DA, embora nem todos os pacientes com CCLa necessariamente evoluam para DA (Petersen, 2004). O padrão anátomo-patológico, em geral, corresponde a esse estado intermediário, havendo comprometimento principalmente de estruturas mediais do lobo temporal e menor quantidade de PN e ENF do que na DA. A quantidade e localização dos ENF, assim como na DA, também se correlacionam melhor com o quadro cognitivo (Petersen, 2006).

O conceito de CCL deixa em aberto a possibilidade de possíveis fases pré-demenciais de outras doenças neurodegenerativas, como por exemplo, CCL por comprometimento de linguagem e desenvolvimento posterior de doenças como afasia progressiva primária, ou comprometimento de atenção e funções executivas e posterior desenvolvimento de DLFT. Ainda, a investigação etiológica do CCL pode sugerir causas não-degenerativas, como doença cérebro-vascular, distúrbios psiquiátricos, traumatismo crânio-encefálico ou outras alterações clínicas (Petersen, 2001).

Como discutido acima, nem todos os pacientes com CCLa irão desenvolver DA,

o que significa que esse conceito engloba pessoas com queixas de memória de causa não-degenerativa. Nesse sentido, CCLa não pode ser considerado sinônimo de fase pré-demencial da DA e alguns autores chegaram a sugerir a extinção desse conceito para fins de pesquisa. Eles propuseram alguns critérios que tornam mais específico e precoce o diagnóstico de DA, exigindo para tal um comprometimento objetivo da memória episódica além de alguma evidência de alteração de marcadores biológicos, como atrofia de lobo temporal medial, alteração de marcadores no líquido céfalo-raquidiano (LCR), padrão específico de alteração em exames de neuroimagem funcional, como PET ou mutações genéticas com transmissão autossômica dominante para DA em familiares próximos (Dubois et al., 2007).

Estudos de neuroimagem também apontam um padrão intermediário de atrofia, notadamente em estruturas temporais mediais, como a formação hipocampal e o córtex entorrinal. Alguns autores apontam que os volumes dessas estruturas podem predizer a chance de conversão para DA (Devanand et al., 2007; Jack Jr et al., 1999). Outras modalidades de neuroimagem como PET, SPECT ou espectroscopia de prótons não mostraram evidências conclusivas de que haja um padrão típico para CCL, embora possam ser úteis em casos clínicos selecionados (Kelley e Petersen, 2007) .

Assim como na DA, ainda não há marcadores biológicos cujo uso seja recomendado na prática clínica, embora existam estudos mostrando que a dosagem de βA e proteína tau no LCR pode ser útil na diferenciação de pacientes com CCL de idosos normais (Hulstaert et al., 1999). Esses estudos apontam que os marcadores podem ser úteis também como preditores de conversão para DA, embora não haja conclusão definitiva. Ainda, a combinação desse marcadores, em especial a relação entre as concentrações de proteína tau total (aumentada) e βA42 (diminuída) apresentou em um estudo sensibilidade de 95% e especificidade de 83% como fator preditivo de conversão de CCL para DA (Hansson et al., 2006). O estudo de marcadores biológicos na CCL apresenta extrema relevância pela possibilidade de se diagnosticar que o indivíduo poderá apresentar DA antes mesmo do surgimento de demência, o que ampliaria sobremaneira a perspectiva de sucesso terapêutico.

2.3- Alterações da memória léxico-semântica na DA, no CCLa e no envelhecimento normal

As alterações patológicas descritas acima iniciam-se em nível molecular e, progressivamente, atingem redes de neurônios corticais e sub-corticais que processam informações cognitivas. O fenótipo clínico da DA e CCLa resulta da interação desse substrato anatômico disfuncionante com a história pré-mórbida do indivíduo, como por exemplo, o grau de reserva cognitiva (Alexander et al., 1997). A evolução da patologia, que se inicia em geral no córtex entorrinal e hipocampos (quando geralmente a principal queixa é amnésia para fatos recentes), chega a outras regiões cerebrais como os córtices associativos, o que acentua o comprometimento cognitivo e neuropsiquiátrico dos pacientes.

A doença que começa com alterações sutis na memória episódica leva, em sua fase mais avançada, à perda de uma das principais funções da mente humana: a capacidade de interagir com o meio-ambiente para satisfazer suas necessidades físicas, afetivas e sociais. Mesmo na fase inicial da doença já pode haver algum comprometimento das capacidades lingüísticas, e o estudo de parte dessas alterações, ainda na fase pré-demencial, é um dos objetivos de nossos trabalhos.

O aspecto semântico da linguagem é uma das aptidões humanas mais importantes para codificar, significar e reter nossa experiência do mundo. Nomear, categorizar e generalizar as características do meio à nossa volta são condições fundamentais para a nossa capacidade de gerar conhecimento e de refletir o mundo em suas relações complexas e abstratas.

A memória léxico-semântica refere-se ao armazenamento desse conhecimento no cérebro por meio de padrões de atividade neuronal interpretados como símbolos lingüísticos de conceitos concretos e abstratos. Assim, consiste no sistema de memória que torna possível guardar informações, significados, associações entre palavras, conceitos e símbolos (Papanicolaou et al., 2006; Tulving 1987). A deterioração deste tipo de memória implica na dificuldade em nomear, categorizar e generalizar: implica em perda do conhecimento.

É bem estabelecido o comprometimento da memória léxico-semântica na DA

(Hodges et.al, 1991; Hodges et.al, 1992). Os pacientes têm dificuldade em nomear e em encontrar a palavra adequada em determinado contexto (fenômeno da ponta-da-língua). Apresentam também desempenho inferior a controles em testes de categorização, julgamento de similaridades, fluência verbal para categorias e outros testes léxico-semânticos. Embora menos estudada em pacientes com CCL, a memória léxico-semântica também pode estar comprometida, como mostram alguns autores (Adlam et al., 2006; Dudas et al., 2005), principalmente em testes de fluência verbal categórica. Mesmo idosos normais apresentam desempenho inferior a adultos jovens em testes de nomeação (Albert et al., 1988; LaBarge et al., 1986; Zec et al., 2005), e alguns autores acreditam que no envelhecimento normal já ocorre dificuldade em utilizar a informação semântica para recuperar a palavra desejada (Albert et al., 1988).

Existem controvérsias em relação ao achado freqüente de dificuldade de nomeação nos pacientes com DA: alteração conceitual e comprometimento semântico ou dificuldade de acesso lexical a um campo semântico intacto? Embora possa ser metodologicamente difícil demonstrar que o deficiente desempenho em testes semânticos seja por perda conceitual, uma vez que outros problemas cognitivos (principalmente atencionais) possam explicá-lo (Storms et al., 2003), muitos autores aceitam que o grande número de erros semânticos em testes de nomeação, fluência verbal para categorias e pré-ativação semântica, por exemplo, são suficientes para demonstrar tal comprometimento (Hodges et al., 1992; Lukatela et al., 1998). Por outro lado, alguns autores demonstram através, principalmente, de estudos envolvendo *primes* (testes de pré-ativação que avaliam indiretamente o campo semântico), que o problema principal pode ser atencional e/ou de acesso lexical, nos quais os pacientes teriam dificuldade em selecionar a resposta léxico-fonológica correta depois da ativação de um campo semântico intacto (Bell et al., 2001; Milberg et al., 1999).

No artigo **3**, estudamos de forma detalhada o desempenho desses pacientes e de idosos normais no TNB.

2.4- Organização cerebral da memória léxico-semântica

Além de visar o estudo dos efeitos clínicos que a DA causa nos indivíduos, nós também pretendemos entender o funcionamento normal da organização cerebral da memória léxico-semântica. Para isso, correlacionamos os achados anatômicos de atrofia progressiva de substância cinzenta dos pacientes com DA em relação a CCLa e esses em relação aos idosos normais (descritos no artigo **4**) com o padrão de erros semânticos de nomeação, que também apresentou um padrão de continuidade entre os três grupos (artigo **3**). Postulamos que idosos normais têm menos densidade de substância cinzenta e cometem mais erros de nomeação do que adultos jovens, conforme demonstrado por outros autores. Com esse modelo de "quanto menos substância cinzenta, mais erros semânticos de nomeação", procuramos pesquisar quais áreas cerebrais podem estar envolvidas na memória léxico-semântica (artigo **6**).

No passado, havia apenas duas formas de se pesquisar as estruturas psicológica e cerebral da memória semântica: estudar a sua aquisição na ontogênese ou examinar sua deterioração nas doenças cerebrais (método lesional), como propusemos no modelo acima.

Atualmente, há outras formas de avaliar o processamento cerebral da informação semântica, como por exemplo, estudos neurofisiológicos, modelos computacionais e, principalmente, estudos de RM funcional. A despeito dessas técnicas, ainda há significativa controvérsia no entendimento de como se dá a organização da memória léxico-semântica na anatomia cerebral. Claramente, há a necessidade de uma integração maior entre os diferentes métodos de neuroimagem estrutural e funcional no sentido de melhor compreensão do fenômeno (Hart Jr e Kraut, 2007) .

Há ainda controvérsias na forma como a memória semântica é adquirida, processada e armazenada. Por exemplo, o modelo de processamento modular assume que a codificação dos elementos que constituem a memória semântica se dá em áreas delimitadas do cérebro, em um conjunto de módulos que processam informações específicas de categorias independentes, e cada um deles realizando sua função e transferindo a informação "pronta" para outros módulos (Barrett e Kurzban, 2006).

A teoria de processamento distribuído em paralelo (PDP) defende que

existam diversas redes neurais interconectadas, que funcionam como complexas arquiteturas computacionais no processamento das informações (Mesulam, 1998; Rogers e McClelland, 2004a). Os conceitos teriam origem, dessa forma, como padrões de atividade dessas redes, que refletiriam a forma como essa informação foi adquirida através da percepção e ação. O modelo de processamento central, por outro lado, assume que a codificação dos elementos que constituem a memória semântica se dá em áreas delimitadas do cérebro. Um exemplo desse modelo, "the Organized Unitary Content Hypothesis – OUCH" foi proposto por Caramazza et al. (1990) e assume que o significado de um termo consiste de uma série de características representadas de forma amodal, abstrata.

Nenhuma dessas teorias, sozinha, explica satisfatoriamente o fenômeno, e alguns autores sugerem uma combinação de ambas (Hart Jr e Kraut, 2007). Uma das teorias mais aceitas nesse sentido, "*the distributed-plus-hub theory*", discutida por Patterson et al. (2007), combina os padrões de atividade do PDP com um centro amodal, para o qual a informação das diversas áreas cerebrais convergiria. A evidência clínica de comprometimento de todas as modalidades de conhecimento em pacientes com lesão da parte anterior dos lobos temporais (por exemplo, na Demência Semântica, nas encefalites por *Herpes simplex*, ou mesmo na DA), sugere que essas regiões cerebrais podem servir como um centro amodal que integraria as informações provenientes das áreas relacionadas a percepção, ação, linguagem, entre outras.

As características anatômicas dos lobos temporais reforçam essa hipótese. A parte anterior dos lobos temporais tem extensa conexão com os três giros temporais, os quais recebem projeções de áreas associativas secundárias; a parte anterior do giro temporal inferior é o término da via de processamento visual ventral; o giro temporal médio integra *inputs* provenientes das vias visuais, auditivas e sômato-sensitivas; o giro temporal superior, assim como o sulco temporal superior, tem papel importante na percepção auditiva, e mais especificamente no hemisfério dominante para a linguagem, na percepção do discurso verbal. Ainda, o pólo temporal e a parte anterior do giro temporal inferior enviam projeções para os córtices pré-frontal e órbito-frontal (Rogers e McClelland, 2004b). Outras áreas cerebrais também processam informações léxico-semânticas, notadamente as regiões pré-frontais, estruturas mediais temporais, tálamos,

entre outras.

Assim, no artigo **6**, procuramos integrar os achados neuropsicológicos dos pacientes com DA, CCLa e idosos normais com a anatomia cerebral, a fim de contribuir para o entendimento do que Wernicke (1900)[1] já postulara: o substrato neural da formação dos conceitos.

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3- OBJETIVOS

Foram objetivos específicos de nossos trabalhos:

1) Avaliar o desempenho de pacientes com DA leve, CCLa e idosos normais em testes léxico-semânticos de nomeação, fluência verbal categórica e categorização/similaridades (artigos **1** e **2**);

2) Avaliar o desempenho dos 3 grupos no TNB para estudar: a) a integridade do campo semântico e b) o padrão de erros espontâneos gerais e semânticos (artigo **3**);

3) Comparar as diferenças de densidade de substâncias branca e cinzenta nos 3 grupos por meio de RM-MBV (artigo **4**);

4) Correlacionar o desempenho de memória episódica no item de evocação tardia do TAAVR com o estudo volumétrico por RM dos hipocampos direito e esquerdo dos 3 grupos (artigo **5**);

5) Correlacionar os padrões de erro semântico no TNB com a densidade de substância cinzenta cerebral pelo método de RM-MBV (artigo **6**).

ARTIGO 1

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LEXICAL SEMANTIC MEMORY IN AMNESTIC MILD COGNITIVE IMPAIRMENT AND MILD ALZHEIMER´S DISEASE

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ABSTRACT - *Objective*: To study lexical semantic memory in patients with amnestic mild cognitive impairment (aMCI), mild Alzheimer's disease (AD) and normal controls. *Method*: Fifteen mild AD, 15 aMCI, and 15 normal control subjects were included. Diagnosis of AD was based on DSM-IV and NINCDS-ADRDA criteria, and that of aMCI, on the criteria of the International Working Group on Mild Cognitive Impairment, using CDR 0.5 for aMCI and CDR 1 for mild AD. All subjects underwent semantic memory tests (Boston Naming-BNT, CAMCOG Similarities item), Rey Auditory Verbal Learning Test (RAVLT), Mini-Mental Status Examination (MMSE), neuropsychological tests (counterproofs), and Cornell Scale for Depression in Dementia. Data analysis used Mann-Whitney test for intergroup comparisons and Pearson's coefficient for correlations between memory tests and counterproofs (statistical significance level was $p<0.05$). *Results*: aMCI patients were similar to controls on BNT and Similarities, but worse on MMSE and RAVLT. Mild AD patients scored significantly worse than aMCI and controls on all tests. *Conclusion:* aMCI impairs episodic memory but tends to spare lexical semantic system, which can be affected in the early phase of AD.

KEY WORDS: semantic memory, mild cognitive impairment, Alzheimer's disease, neuropsychological tests.

Memória léxico-semântica no comprometimento cognitivo leve amnéstico e doença de Alzheimer leve

RESUMO - *Objetivo:* Estudar a memória léxico-semântica no comprometimento cognitivo leve amnéstico (aCCL), doença de Alzheimer (DA) leve e controles normais. *Método*: Incluímos 15 pacientes com DA leve, 15 com aCCL e 15 controles normais, usando os critérios DSM-IV, NINCDS-ADRDA e CDR 1 para DA, e os do International Working Group on Mild Cognitive Impairment, e CDR 0,5 para aCCL. Todos os sujeitos passaram por testes de memória semântica (Teste de nomeação de Boston - TNB, item de Similaridades do CAMCOG), teste de aprendizado auditivo-verbal de Rey (TAAVR), Mini-Exame do Estado Mental (MEEM), testes neuropsicológicos (contraprovas) e Escala Cornell para Depressão em Demência. A análise dos dados usou o teste de Mann-Whitney para comparações entre os grupos e o coeficiente de Pearson para correlação entre testes e contraprovas (nível de significância $p<0,05$). *Resultados*: Os pacientes com aCCL foram semelhantes aos controles no TNB e Similaridades, mas inferiores no MEEM e TAAVR. Pacientes com DA leve tiveram performance inferior à de sujeitos com aCCL e controles em todos os testes. *Conclusão*: O aCCL prejudica a memória episódica, mas tende a poupar o sistema léxico-semântico, que pode estar afetado na fase inicial da DA.

PALAVRAS-CHAVE: memória semântica, comprometimento cognitivo leve, doença de Alzheimer, testes neuropsicológicos.

Mild cognitive impairment (MCI) is one of the most used concepts for cognitive impairment which do not fulfill criteria for dementia. It can be conceived as a clinical entity for patients in the border zone between normal aging and very early dementia, most commonly probable Alzheimer's disease (AD)[1]. It's assumed that there is a continuum in cognitive decline and, in MCI, subjects have cognitive complaints, more often forgetfulness, with intact activities of daily living[1,2]. MCI can be classified according to the clinical presentation of symptoms as amnestic MCI (aMCI), multiple domain or single non-memory domain MCI[1,2]. Like AD, its diagnosis is essentially clinic and neuropsychological assessment is a crucial part of the diagnostic process. Memory is the most studied cognitive domain, since it appears to be the

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most affected and the first to decline, but it is not a unitary system. Tulving has divided it in five principal components: episodic, semantic, working, perceptual representation system and procedural memory[3]. Episodic memory (the capacity for encoding personal experiences and conscious recollection of events) is, by far, the most studied memory system in AD and MCI, and its deficit is a *sine qua non* condition for the diagnosis of dementia.

Semantic memory can briefly be defined as the capacity to acquire and retain general knowledge about the world, its basic meanings and facts, as well as words and their meanings. Thus, its deficit signifies the loss of concepts that have been part of one's store of knowledge[3,4]. Semantic memory in MCI is not enough investigated and some studies are controversial concerning its impairment[5-7]. Several approaches can be made to study semantic memory, like tests of priming, general knowledge, category fluency and object or picture naming[8].

Our aim is to evaluate this specific kind of memory performance in patients diagnosed as aMCI and mild AD and our approach privileges the lexical aspect of the semantic memory, because language is essential to codify, signify and retain our experience[9].

METHOD

We studied 45 subjects, comprising 15 with aMCI and 15 with mild AD attended at the Unit for Neuropsychology and Neurolinguistics (UNICAMP Clinic Hospital), and 15 controls. Routine laboratory examinations for dementia assessment (including B12 and folate dosage, sorology for syphilis, thyroid hormones) and brain computed tomography was carried out in all patients. The local ethics committee approved this research.

We based the diagnosis of aMCI, on the following criteria of the International Working Group on Mild Cognitive Impairment[1]: (i) the person is neither normal nor demented; (ii) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired. We included only patients older than 50 years and CDR (Clinical Dementia Rating)[10] of 0.5.

The diagnostic process consisted of a detailed interview with the patient and informant. All patients were submitted to the Mini Mental Status Examination (MMSE; Brazilian adapted version)[11] and to the Cambridge Mental Disorders of the Elderly Examination (CAMDEX)[12], which comprises structured interviews with the patient and, separately, with an informant, evaluating the patient's current medical and psychiatric status and family history. They were also submitted to the CAMDEX cognitive test battery (CAMCOG), which includes eight subscales: memory, orientation, language, attention, abstract thinking or similarities, calculation and perception. At this phase, we didn't apply the similarities subscale.

We considered a diagnosis of aMCI if the clinical history and cognitive performance pointed to an exclusive memory deficit (poor performance on CAMCOG's memory items). For probable AD diagnosis, we used the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA)[13], including only patients classified as CDR 1. Exclusion criteria were history of other neurological or psychiatric diseases, head injury with loss of consciousness, use of sedative drugs until 24 hours before the neuropsychological assessment, drug or alcohol addiction and prior exposition to neurotoxic substances. The control group consisted of subjects with CDR 0 without previous history of neurological or psychiatric disease, or memory complaints.

Neuropsychological evaluation comprised following tests:

1) Episodic memory was evaluated with Rey auditory verbal learning test (RAVLT)[14], which consists of fifteen words read aloud for five consecutive trials (List A), followed by a free-recall test. After the fifth trial, a new interference list of fifteen words is presented (List B) followed by a free-recall test of that list. Soon afterwards, a free-recall of the first list is tested without new presentation. After a twenty-minute delay period, subjects are again required to recall words from List A. Finally, the patient must identify List A words from a list of fifty words which includes Lists A and B and twenty other words phonemically or semantically related to lists A and B.

2) Semantic memory: (a) patients were given the sixty items of the Boston Naming Test[15] (BNT- Brazilian version). BNT score was the sum of spontaneous correct responses plus correct responses following a semantic cue. (b) CAMCOG's subscale of similarities between pairs of nouns. The patients were asked " In what way are they alike?" for the pairs apple/banana, chair/table, shirt/dress and animal/vegetal. The score was calculated as the number of correct responses (zero to two for each pair; maximum score 8).

3) Control tests comprised: (a) Visual perception subtests of Luria's Neuropsychological Investigation (LNI; maximum score 20)[16]. (b) Verbal fluency (VF) for animals' category (the score was the total number of different animals' names given by patient during one minute). (c) Attention: The forward and backward digit span subtest of WAIS-R[17]. (d) Cornell Scale for Depression in Dementia (CSDD)[18].

Data analysis by means of Statistica software 6.0 used Mann-Whitney test for intergroup comparisons of demographic and cognitive scores, as well as Pearson coefficient for correlation between memory tests and counterproofs. Statistical significance considered was $p<0.05$.

RESULTS

The results of neuropsychological evaluation are shown on Table. aMCI subjects were similar to controls concerning age (p=0.343), education (p=0.578),

Table. Demographics and neuropsychological test results of amnestic mild cognitive impairment (AMCI), Alzheimer´s disease(AD), and control subjects

	MCI (n=15) Mean ± SD	AD (n=15) Mean ± SD	Controls (n=15) Mean ± SD	p value for group effect
Age	66.26±10.27[b]	75.66±7.65[a,c]	69.40±7.28[b]	< 0.05
Education (years)	5.93±4.18	4.86±4.76	6.73±3.59	NS
MMSE	26.86±2.50[a,b]	22.53±3.06[a,c]	29.06±0.70[b,c]	< 0.01
Similarities	7.00±1.19[b]	4.86±1.80[a,c]	7.33±1.04[b]	< 0.001
BNT	51.06±7.78[b]	38.73±8.64[a,c]	53.66±4.11[b]	< 0.001
Mean RAVLT	7.06±1.48[a,b]	4.60±1.12[a,c]	9.60±1.63[b,c]	< 0.001
A7- RAVLT	4.26±2.54[a,b]	1.00±1.25[a,c]	9.40±3.20[b,c]	< 0.001
VF	13.86±3.85[a,b]	10.20±3.44[a,c]	19.46±3.31[b,c]	< 0.01
fDS	4.60±0.82	4.73±1.03	4.93±0.79	NS
bDS	3.13±0.99[a]	3.13±0.51[a]	3.93±1.09[b,c]	< 0.05
Visuo-spatial LNI	18.80±1.01[b]	17.33±1.39[a,c]	18.66±1.11[b]	< 0.01

MMSE, mini-mental status examination; fDS, forward digit span; bDS, backward digit span; VF, verbal fluency; BNT, Boston naming test; A7- RAVLT, delayed recall of Rey auditory verbal learning test; a, significantly different from controls; b, significantly different from AD; c, significantly different from MCI; NS, non-significant.

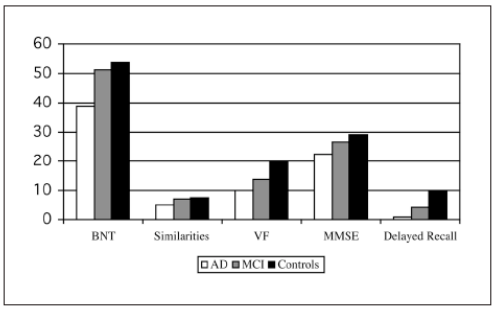

Figure. Distribution of mean scores of AD, aMCI and control subjects on main neuropsychological tests (abbreviations as in Table 1).

CAMCOG's item of similarities (p=0.42) and Boston Naming Test (p=0.56), but they performed worse on the MMSE (p=0.01), backward digit span (p<0.05), verbal fluency (p=0.0006), immediate (p=0.0004) and delayed recall (p=0.0001) of RAVLT.

AD patients were older than aMCI (p=0.01) and control subjects (p=0.03). Their educational level was inferior to that of controls (though not statistically significant). They scored lower than controls and aMCI subjects on all tests, except on forward digit span. The cognitive performance of mild AD was worse than aMCI, which was inferior to controls (Figure and Table).

The analysis of relationships between tests and counterproofs in the groups showed statistically significant correlations only between VF and RAVLT delayed recall in AD group (r=0.545; p<0.05) and between VF and BNT in aMCI group (r=0.540; p<0.05). Scores on Cornell Scale for Depression did not correlate to any of cognitive tests.

DISCUSSION

On all cognitive tests, the three groups showed a continuum of decreasing cognitive ability, with mild AD patients performing worse than aMCI subjects, who were inferior to controls. AD patients´ older age and lower educational level may have contributed to their poor test performance, at least partly. As expected, aMCI and mild AD patients were impaired on episodic memory test (RAVLT), particularly in the delayed recall task. Their low RAVLT scores could not be explained by depression (since there was no correlations with Cornell Depression Scale), but verbal fluency may have influenced this task, at least in the dementia group.

aMCI patients were similar to controls on tests of semantic memory (BNT and Similarities) but worse on verbal fluency task, which involves semantic knowledge, as well as language, executive function and short-term memory. Short-term memory may have influenced verbal fluency, since aMCI subjects had low scores on backward digit span test.

Thus, aMCI patients showed dissociation in their performance on semantic and episodic memory tasks. This finding was expected, since it is well established that these memories constitute two different subsystems of declarative memory[3,19-21], a fact confirmed by functional MRI study[22] showing that semantic and episodic tasks activate different brain

regions in patients with AD. Usually, impairment of semantic memory (semantic amnesia) is associated to dysfunction or lesion in the inferior, anterior and lateral temporal lobe, restricted to neocortex. Generally, the lesion does not include medial temporal structures, like hippocampus or any other limbic areas, which are very important for acquisition of new memories[4]. In aMCI, the initial pathologic damage is in medial temporal structures, mainly entorhinal cortex, which causes episodic memory deficits. Petersen et al.[23] showed that patients with aMCI had pathologic findings involving medial temporal lobe structures, suggesting a transitional state of evolving AD. Pennanen et al.[24], in a voxel based morphometry study, also found a unilateral medial temporal atrophy in individuals with MCI. Most of these aMCI cases (approximately 80%) will have converted to full-blown dementia syndrome after 6 years follow-up[2], thus constituting cases of very early AD. As the disease progresses, other areas are involved, including temporal neocortex, what can explain the difficulties with semantic knowledge in mild AD.

Semantic amnesia presents as difficulties in naming objects, finding words during conversation and understanding the meaning of known words and facts[4]. This is probably because most of our semantic memories are verbally coded. When we name an object, we create a code and categorize it in a complex system of relationships[9]. So, there is a superposition of language and memory concepts, especially when we are dealing with naming tests like BNT. Semantic memory deficits are commonly seen in AD, even in the early phase, but not necessarily in patients in predementia state, like aMCI[25]. For example, Delazer et al.[5] showed that retrieval of people names was normal in a group of MCI patients in comparison with healthy controls. In contrast, Dudas et al.[6] and Adlam et al.[7], by using a more comprehensive test battery, found semantic memory deficits particularly in the item recognition, cross-modal associative memory and semantic knowledge for people in MCI patients. We have found that aMCI impairs episodic memory while sparing lexical semantic system, which can be affected in the early phase of AD.

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ARTIGO 2

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Category verbal fluency performance may be impaired in amnestic mild cognitive impairment

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Abstract – To study category verbal fluency (VF) for animals in patients with amnestic mild cognitive impairment (aMCI), mild Alzheimer disease (AD) and normal controls. *Method:* Fifteen mild AD, 15 aMCI, and 15 normal control subjects were included. Diagnosis of AD was based on DSM-IV and NINCDS-ADRDA criteria, while aMCI was based on the criteria of the International Working Group on Mild Cognitive Impairment, using CDR 0.5 for aMCI and CDR 1 for mild AD. All subjects underwent testing of category VF for animals, lexical semantic function (Boston Naming-BNT, CAMCOG Similarities item), WAIS-R forward and backward digit span, Rey Auditory Verbal Learning (RAVLT), Mini-Mental Status Examination (MMSE), and other task relevant functions such as visual perception, attention, and mood state (with Cornell Scale for Depression in Dementia). Data analysis used ANOVA and a post-hoc Tukey test for intergroup comparisons, and Pearson's coefficient for correlations of memory and FV tests with other task relevant functions (statistical significance level was $p<0.05$). *Results:* aMCI patients had lower performance than controls on category VF for animals and on the backward digit span subtest of WAIS-R but higher scores compared with mild AD patients. Mild AD patients scored significantly worse than aMCI and controls across all tests. *Conclusion*: aMCI patients may have poor performance in some non-memory tests, specifically category VF for animals in our study, where this could be attributable to the influence of working memory.

Key Words: verbal fluency, mild cognitive impairment, Alzheimer disease, neuropsychological tests.

A fluência verbal para categoria pode estar alterada no comprometimento cognitivo leve amnéstico

Resumo – Estudar a fluência verbal (FV) para a categoria animais no comprometimento cognitivo leve amnéstico (aCCL), doença de Alzheimer (DA) leve e controles normais. *Método:* Incluímos 15 pacientes com DA leve, 15 com aCCL e 15 controles normais, usando os critérios DSM-IV, NINCDS-ADRDA e CDR 1 para DA, e os do International Working Group on Mild Cognitive Impairment, e CDR 0,5 para aCCL. Todos os sujeitos passaram por avaliação da FV para a categoria animais, função léxico-semântica (Teste de nomeação de Boston - TNB, item de Similaridades do CAMCOG), extensão de dígitos direto e indireto do WAIS-R, aprendizado auditivo-verbal de Rey (TAAVR), Mini-Exame do Estado Mental (MEEM), e de outras funções (contraprovas) capazes de influenciar nestes testes, como percepção visual, atenção e estado de humor (este com a Escala Cornell para Depressão em Demência). A análise dos dados usou o teste de análise de variância (ANOVA) seguido do teste de Tukey post hoc para comparações entre os grupos e o coeficiente de Pearson para correlação entre testes e contraprovas (nível de significância $p<0,05$). *Resultados:* Os pacientes com aCCL tiveram performance inferior à dos controles nos testes de FV para animais e na extensão de dígitos indireta do WAIS-R. Pacientes com DA leve tiveram performance inferior à de sujeitos com aCCL e controles em todos os testes. *Conclusão:* Pacientes com aCCL tiveram desempenho rebaixado em testes de fluência verbal para animais, o que pode ter sido influenciado pela memória operacional.

Palavras-chave: fluência verbal, comprometimento cognitivo leve, doença de Alzheimer, testes neuropsicológicos.

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Mild cognitive impairment (MCI) is a clinical entity in patients with objective cognitive problems (most often episodic memory) but without impairment in daily life activities,[1] having a greater likelihood of transforming into dementia, most often Alzheimer disease (AD), than in the normal population.[2] MCI can be classified according to the clinical presentation of symptoms into amnestic MCI (aMCI), multiple domain or single non-memory domain MCI.[1,2] Thus, by definition, aMCI presents with exclusive memory deficit, sparing other cognitive domains such as language, visuospatial perception or executive functions. Nonetheless, aMCI individuals may present some non-memory-related poor performance in specific neuropsychological tests, following a pattern similar to AD,[3] and continue to be classified as amnestic rather than multiple domains MCI. This classification is based on the clinical judgment that poor performance in one test is not enough to consider an entire cognitive domain as impaired.

Verbal fluency (VF) for animal's names is a simple and widely used task that can reveal impairment in early phases of AD,[4] where a recent study points to impairment even in aMCI.[3] Category VF involves several cognitive aspects, such as semantic knowledge, executive function and working memory. Henry et al. suggested that verbal fluency is "an excellent way of evaluating how subjects organize their thinking and ability to "organize output in terms of clusters of meaningfully related words".[5]

Our aim was to compare verbal fluency (category: animals) in healthy controls and patients diagnosed as aMCI and mild AD, hypothesizing that these two groups of patients have similar performance, because impairment of this function is common even in early stages of AD.

Methods

We studied 45 subjects, comprising 15 with aMCI and 15 with mild AD attended at the Unit for Neuropsychology and Neurolinguistics (UNICAMP Clinic Hospital), along with 15 controls. Routine laboratory examinations for dementia assessment (including B12 and folate dosage, sorology for syphilis, thyroid hormones) and brain computed tomography were carried out in all patients. The local ethics committee approved this research.

MCI in our clinic is a clinical diagnosis carried out by trained neurologists using a standardized mental status battery and was based on the following criteria of the International Working Group on Mild Cognitive Impairment:[1] (i) the person is neither normal nor demented; (ii) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired. We included only patients older than 50 years who had a CDR (Clinical Dementia Rating)[6] of 0.5. This classification was performed by using a semi-structured interview.

For probable AD diagnosis, we used the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA)[7], including only patients classified as CDR 1. Exclusion criteria were history of other neurological or psychiatric diseases, head injury with loss of consciousness, use of sedative drugs within 24 hours of the neuropsychological assessment, drug or alcohol addiction and prior exposure to neurotoxic substances. The control group consisted of subjects with CDR 0 and no previous history of neurological or psychiatric disease, or memory complaints.

Neuropsychological evaluation comprised the following tests:

1) Verbal fluency (VF) for animals' category (the score was the total number of different animal names given the by patient in one minute).
2) Mini Mental Status Examination (MMSE),[8] Brazilian version.
3) Episodic memory was evaluated using the Rey auditory verbal learning test (RAVLT).[9]
4) Boston Naming Test (BNT- translated and culturally adapted version for Brazilian population by Dr. Cândida Camargo – Psychiatry Institute, Medicine School, University of São Paulo).[10] The BNT score was the sum of spontaneous correct responses plus correct responses following a semantic cue.
5) CAMCOG's subscale of similarities between pairs of nouns.[11] The patients were asked " In what way are they

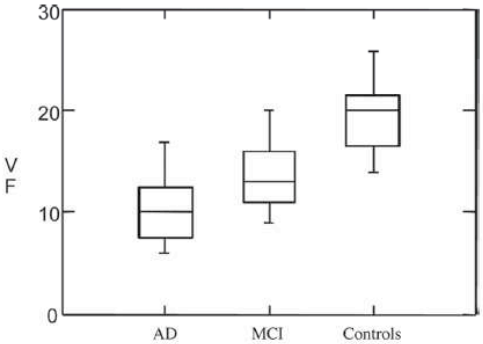

Figure 1. *Distribution of verbal fluency scores of AD, aMCI and control subjects.*

Table 1. Demographics results of amnestic mild cognitive Impairment (AMCI), Alzheimer disease (AD), and normal control subjects.

	AD (n=15) Mean±SD	MCI (n=15) Mean±SD	Controls (n=15) Mean±SD	p value for intergroup effect
Age	75.66±7.65	66.26±10.27	69.40±7.28	AD x MCI: p=0.012 AD x Controls: p=0.121 MCI x Controls: p=0.576
Education (years)	4.86±4.76	5.93±4.18	6.73±3.59	p=0.483

Table 2. Neuropsychological results of amnestic mild cognitive Impairment (AMCI), Alzheimer disease (AD), and normal control subjects.

	AD (n=15) Mean±SD	MCI (n=15) Mean±SD	Controls (n=15) Mean±SD	P value intergroups
MMSE	22.53±3.06	26.86±2.50	29.06±0.70	AD x MCI: p<0.001 AD x Controls: p<0.001 MCI x Controls: p=0.034
VF	10.20±3.44	13.86±3.85	19.46±3.31	AD x MCI: p=0.019 AD x Controls: p<0.001 MCI x Controls: p<0.001
BNT	38.73±8.64	51.06±7.78	53.66±4.11	AD x MCI: p=0.001 AD x Controls: p<0.001 MCI x Controls: p=0.582
A7- RAVLT	1.00±1.25	4.26±2.54	9.40±3.20	AD x MCI: p=0.002 AD x Controls: p<0.001 MCI x Controls: p<0.001
Similarities	4.86±1.80	7.00±1.19	7.33±1.04	AD x MCI: p<0.001 AD x Controls: p<0.001 MCI x Controls: p=0.789
fDS	4.73±1.03	4.60±0.82	4.93±0.79	p=0.583
bDS	3.13±0.51	3.13±0.99	3.93±1.09	AD x MCI: p=1.000 AD x Controls: p<0.05 MCI x Controls: p<0.05
Visuo-spatial LNI	17.33±1.39	18.80±1.01	18.66±1.11	AD x MCI: p=0.004 AD x Controls: p=0.01 MCI x Controls: p=0.949

MMSE, mini-mental status examination; fDS, forward digit span; bDS, backward digit span; VF, verbal fluency; BNT, Boston naming test; A7- RAVLT, delayed recall of Rey auditory verbal learning test.

alike?" for the pairs apple/banana, chair/table, shirt/dress and animal/vegetable. The score was calculated as the number of correct responses (zero to two for each pair; maximum score 8).

6) Visual perception subtests of Luria's Neuropsychological Investigation[12] (LNI; maximum score 20).
7) Attention: The forward and backward digit span subtest of WAIS-R.[13]
8) Cornell Scale for Depression in Dementia[14] (CSDD).

Data analysis by means of Systat software used ANOVA and a post-hoc Tukey tests for intergroup comparisons of demographic and cognitive scores, as well as Pearson coefficient for correlation between tests. Statistical significance considered was $p<0.05$.

Results

The results of demographic data are shown in Table 1 and neuropsychological evaluation in Table 2. aMCI subjects were similar to controls in age (p=0.576) and education (p=0.483). aMCI subjects performed similar to controls in CAMCOG's item of similarities (p=0.789) and Boston Naming Test (p=0.582) but performed worse than controls in verbal fluency (p<0.001), MMSE (p=0.034), backward digit span (p<0.05), delayed recall (p<0.001) of RAVLT, CAMCOG's item of similarities (p=0.789) and Boston Naming Test (p=0.582).

AD patients were older than aMCI (p=0.012) but not control subjects (p=0.121). The educational level of the AD group was lower than that of controls (though not statistically significant). These patients scored lower than controls and aMCI subjects on all tests, except the forward digit span. The cognitive performance of mild AD was worse than aMCI, which in turn was poorer than controls.

The analysis of relationships between tests in the groups showed statistically significant correlations only between VF and RAVLT delayed recall in the AD group (r=0.545; p<0.05) and between VF and BNT in the aMCI group (r= 0.540; p<0.05). In AD group, FV tended to correlate to BNT, but not reaching statistical significance (p=0.066). Scores on the Cornell Scale for Depression did not correlate to any of the cognitive tests: F (2,42)=0.929; p=0.403.

Discussion

Our findings showed that aMCI patients performed worse than controls but better than mild AD on the category VF task. This task involves not only speed and ease of word production, but also lexical-semantic field selection, executive function and working memory, in keeping track of what words have already been said. Some authors have found poor performance on category VF in MCI patients, and have interpreted this finding as a degradation of semantic networks.[15-17] We suggest that working memory and attention, rather than semantic or executive function deficits, may have influenced VF in our patients, since aMCI subjects had significantly lower scores on backward digit span test yet normal performance in semantic and executive tasks (neither anamnesis nor objective cognitive tests used in our diagnostic process showed executive dysfunction in any patients classified as aMCI). In fact, Perry et al.[18] have shown that deficits in attention are more prevalent than deficits in semantic memory in early AD. Similarly, our results on lexical semantic tests such as BNT and CAMCOG's similarities, showed no difference between aMCI and controls. Thus, our findings suggest that semantic knowledge is not impaired and cannot explain the poor performance of this group of patients in category VF.

AD patients' low VF was correlated to their impaired RAVLT delayed recall. A plausible explanation for this finding could be that our VF task partly depends on active retrieval (lexical-semantic selection) of animals' names from long-term declarative memory, also the case in the RAVLT delayed recall task. On the other hand, it is difficult to explain why VF was correlated to BNT in the aMCI group, since this group performed as well on the BNT as did controls. Nevertheless, the fact that FV was correlated to BNT in the aMCI group and also tended to correlate in the AD group, suggests that both groups may have impairment of some linguistic competence involved in lexical-semantic selection, although this was not specifically tested in our study.

We have found that aMCI patients may have poor performance in some non-memory tests, specifically category VF for animals, and that this could be attributable to the influence of working memory. However, further studies using more comprehensive testing of VF, including a phonemic task, as well as more specific tests for executive function and lexical-semantic selection in a larger sample are needed for more robust conclusions to be drawn.

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ARTIGO 3

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SEMANTIC ERROR PATTERNS ON THE BOSTON NAMING TEST IN NORMAL AGING, AMNESTIC MILD COGNITIVE IMPAIRMENT AND MILD ALZHEIMER'S DISEASE: IS THERE SEMANTIC DISRUPTION?

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ABSTRACT:

Naming difficulty is common in Alzheimer's disease (AD), but the nature of this problem is not well established. We investigated the presence of semantic breakdown and the pattern of general and semantic errors in patients with mild AD, patients with amnestic mild cognitive impairment (aMCI), and normal controls by examining their spontaneous answers on the Boston Naming Test (BNT) and verifying if they needed or were benefited by semantic and phonemic cues. The errors in spontaneous answers were classified in four mutually exclusive categories (semantic errors, visual paragnosia, phonological errors, and omission errors), and the semantic errors were further subclassified as coordinate, superordinate, and circumlocutory. aMCI patients performed normally on the BNT and needed fewer semantic and phonemic cues than mild AD patients. After semantic cues, aMCI and control subjects gave more correct answers than mild AD patients, but after phonemic cues, there was no difference between the three groups, suggesting that AD patients' low performance cannot be completely explained by semantic breakdown. Patterns of spontaneous naming errors and subtypes of semantic errors were similar in the three groups, with decreasing error frequency from coordinate to superordinate to circumlocutory subtypes.

Key words: Alzheimer's disease, mild cognitive impairment, naming test, semantic memory

Introduction

Naming tests are simple neuropsychological tools that reveal several aspects concerning how the human mind stores knowledge. They involve visual perception, activation of linguistic and executive competencies that include semantic representations, lexical access decisions, and phonological retrieval. Naming complaints are very common in mentally healthy elderly people. Over the age of seventy, individuals achieve significantly lower scores on these tests than those achieved by young adults (Albert et al., 1988; LaBarge et al., 1986; Zec et al., 2005). Some reports attribute this poor performance to difficulty in using semantic information for word retrieval, stating that lexical representation remains intact (Albert et al., 1988). Problems with naming and word finding are even more common in mild cognitive impairment (MCI) and particularly in Alzheimer's disease (AD) (Adlam et al., 2006; Dudas et al., 2005). MCI is a clinical term applied to patients with objective cognitive problems, most commonly in episodic memory, without significant impairment of daily life activities. MCI can be classified according to the clinical presentation of symptoms as amnestic MCI (aMCI), multiple domain MCI, or single non-memory domain MCI. It is assumed that there is a continuum in cognitive decline, and aMCI could be considered an intermediate stage between normal aging and AD, although not all patients will progress to dementia (Petersen, 2004; Winblad et al., 2004).

There are controversies regarding the nature of the naming deficit in AD over whether it should be considered a disruption of concepts and semantic knowledge or a difficulty in assessment of the intact lexical-semantic field. A related methodological problem is that virtually all semantic memory tests involve other cognitive domains, which makes the exclusive assessment of lexical-semantic system difficult, given the complexity of the cerebral organization of cognition. This difficulty could be overcome with procedures like the priming paradigm, which is an important way to evaluate the semantic field indirectly or implicitly by observing changes in the time and accuracy with which individuals perform simple word-nonword decisions (lexical decisions) or in overlearned language tasks such as word reading (Milberg et al, 1999).

Several authors believe that the main problem for AD patients is a breakdown in semantic processing (Garrard et al., 2005; Hodges et al., 1992; Lukatela et al., 1998), although other cognitive functions involved in the naming process, like working memory, attention, visuoperceptual skills, and lexical access, might also have an influence (Rogers et al., 2006).

Even impairment in the ability to inhibit inappropriate or no-longer-relevant information might play a main role in naming errors when patients experience increased interference from a previous stimulus (Balota et al., 1991). In early AD, poor naming performance may result from changes in attentional control and/or lexical access processes. In this case, patients might present with difficulties in selecting the correct lexical-phonological response after activation of an intact semantic field (Chenery et al., 1996). Hajilou & Done (2007) suggested that one possible cause of object recognition impairment in AD could be a deficit in processing structural aspects of visually presented items. Some authors have cited these patients' numerous semantic errors on visual confrontation naming as evidence for impaired semantic knowledge (Adlam et al., 2006; Barbarotto et al., 1998; Hodges et al., 1992), although these patients were qualitatively not so different from normal matched controls (Nicholas et al., 1996). Lukatela et al (1998), after subclassifying the semantic naming errors, found that even in early AD the semantic system is damaged and these patients tend to commit superordinate errors (by naming the category instead of the object pictured). Poor performances on other lexical-semantic tasks, like category verbal fluency (Murphy et al., 2006) and semantic priming (Chertkow et al., 1989; Giffard et al., 2005), have also been cited as evidence for disruption of the semantic field.

In the present study, we evaluated the performance on the Boston Naming Test (BNT) of patients with aMCI, patients with mild AD, and normal controls in order to verify (1) the presence of semantic breakdown and (2) the pattern of general and semantic errors in these patients. With this purpose, we examined their spontaneous answers and investigated if they needed or were benefited by semantic and phonemic cues. We assumed that, if patients did not give a correct answer spontaneously or after a semantic cue, but significantly improved after a phonemic cue, this would mean that the semantic field is not necessarily damaged. If a phonemic cue does not improve naming

performance, this indicates that semantic knowledge may be compromised. Thus, in order to study the error patterns in spontaneous answers, we classified them in four mutually exclusive categories (semantic errors, visual paragnosia, phonological errors, and omission errors) and the semantic errors were further subcategorized into three subclasses (coordinate, superordinate, and circumlocutory).

Methods

We studied 48 subjects older than 50 years (16 with aMCI, 16 with mild AD treated at the Unit for Neuropsychology and Neurolinguistics (UNICAMP Clinic Hospital), and 16 controls). Routine laboratory examinations for dementia assessment (including B12 and folate dosage, serology for syphilis, and thyroid hormone measurement) and brain computed tomography were carried out in all patients. The local ethics committee approved this research. Diagnosis of aMCI in our clinic is carried out by trained neurologists using a standardized mental status battery. The diagnostic process consisted of a detailed interview with the patient and informant (usually a close relative of the patient). All patients underwent the Cambridge Mental Disorders of the Elderly Examination (CAMDEX), which is comprised of structured interviews with the patient and, separately, with an informant, evaluating the patient's current medical condition, psychiatric status and family history. They also underwent the CAMDEX cognitive test battery (CAMCOG), which includes eight subscales: memory, orientation, language, attention, abstract thinking or similarities, calculation, and perception (Roth et al., 1988). Diagnosis of MCI was made according to the criteria of the International Working Group on Mild Cognitive Impairment (Winblad et al., 2004): (i) the person is neither normal nor demented; (ii) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired. We made a diagnosis of aMCI if the clinical history and cognitive performance pointed to an exclusive memory deficit and Clinical Dementia Rating (CDR; Morris, 1993) score of 0.5, with an obligatory and exclusive memory score of 0.5. This

classification was performed by using a semi-structured interview. All MCI subjects in this study met criteria for aMCI only.

For probable AD diagnosis, we used the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann et al., 1984), including only patients classified as CDR 1. Exclusion criteria were history of other neurological or psychiatric diseases, head injury with loss of consciousness, use of sedative drugs in the last 24 hours before the neuropsychological assessment, drug or alcohol addiction, and prior chronic exposure to neurotoxic substances. The control group consisted of subjects with CDR 0 without previous history of neurological or psychiatric disease or memory complaints.

Assessment of naming ability

The sixty-item BNT (Kaplan, Goodglass, & Weintraub, 1983; translated and culturally adapted version for the Brazilian population by Dr. Cândida Camargo – Psychiatry Institute, Medicine School, University of São Paulo) was administered to all subjects where they were asked to name the presented pictures. We determined the total score by adding the number of correct spontaneous responses to the number of correct responses after a semantic cue, which consisted of a short explanation about the picture (for example for *mask: it's part of a carnival fantasy)* or a superordinate category (for example for *elephant: it's a kind of animal*). The semantic cue was only given if the patient had failed to recognize the picture (for example: *dog* instead of *tree)* or if he/she said that they didn't know what the picture was. We gave a phonemic rather than semantic cue if the spontaneous wrong answers were semantically related to the target word (for example: *dog* instead of *camel*), or if the subject was unable to name the picture even after a semantic cue. A phonemic cue consisted of the first phonemes of the target word.

Error classification

We modified the classification system described by Lukatela et al. (1998) and divided the spontaneous errors into four mutually exclusive types: *omission* (when the subject was unable to name the picture), *visual paragnosia* (when the subject answered with an unrelated word which may or may not have shared any common characteristics with the target word), *phonologic* (when the prominent reason for naming was the similarity with another unrelated word, generally the first phonemes) and *semantic* (when the answer was semantically related to the target word). At first glance, this classification could lead to some problems, mainly when the subjects' answers contained more than one error, for example semantic and phonological (*tatu* instead of *tamanduá* – Brazilian animals whose names start with the syllable *ta* and whose pictures share similarities). In cases like this, we considered the stronger semantic relationship between these animals and the error was classified as semantic.

Semantic errors were further classified into three mutually exclusive categories: *circumlocutory* (when responses described or indicated the function of the target word), *coordinate* (when responses were of the same category as the target word), and *superordinate* (responses that belonged to a broader category than that of the target word). Two independent researchers (MLFB, BPD) performed this classification, and the discordances were solved by consensus.

Additional neuropsychological evaluation

All subjects were submitted to tests of verbal fluency (VF) for the animals category (the score was the total number of different animal names given by the subject during one minute); Mini Mental Status Examination (MMSE; Folstein et al., 1975; Brazilian version by Brucki et al., 2003); Rey auditory verbal learning test (RAVLT; Rey, 1964) to evaluate episodic memory delayed recall (RAVLT-A7); CAMCOG's subscale of similarities between pairs of nouns: the patients were asked "In what way are they alike?" for the following pairs apple/banana, chair/table, shirt/dress and animal/vegetable. The score was calculated as the number of correct responses (zero to

two for each pair; maximum score eight) (Roth et al., 1988); visual perception subtests of Luria's Neuropsychological Investigation (LNI; maximum score twenty; Christensen, 1979); the forward (FDS) and backward digit span (BDS) subtest of WAIS-R (Wechsler, 1987); and the Cornell Scale for Depression in Dementia (CSDD; Alexopoulos et al., 1988).

Data analysis was performed by means of Systat software, and we used ANOVA and a post-hoc Tukey test for intergroup comparisons of demographic and cognitive scores and G Power 3 software to calculate the effect size. In accordance with Cohen (1988), we considered partial eta-squared (η^2) and f values of 0.10 to represent a small effect, 0.25 a medium effect, and 0.4 a large effect size. With the aim of comparing the pattern of correctness after semantic and phonemic cues, we analyzed the percentage of correct answers for each participant using a separate one-way ANOVA. The same analysis was performed using the error type after spontaneous answers and the subtypes of the semantic errors. Multiple linear regressions for each group were carried out to compare the total BNT score as a dependent variable to other tests as independent variables: lexical-semantic (Similarities and VF), visual perception (LNI subtests), attention (FDS and BDS), episodic memory (RAVLT-A7), and MMSE. We also correlated BNT to age and education. In order to evaluate which cognitive problems might have possibly influenced spontaneous wrong answers for each group, we also compared the independent variables quoted above to semantic, omission, and visual paragnosia errors as separate dependent variables. We used the effect size metric f^2 for multiple regressions and, by convention, f^2 = 0.01, 0.15, and 0.35 for small, medium, and large effect sizes, respectively. P-values less than 0.05 were considered statistically significant.

Results

As shown in Table 1, there was no significant difference between the three groups with regard to age [F (2, 45) = 2.194, p = 0.123, effect size: partial η^2 = 0.08, f = 0.31] or education [F (2, 45) = 0.683, p = 0.51, partial η^2 = 0.02, f = 0.17]. With regard to the BNT total score, AD patients performed worse than aMCI patients ($p < 0.001$) and controls ($p < 0.001$), while aMCI subjects were similar to controls (p = 0.464) but

performed worse than controls on BNT spontaneous answers (without cues; $p < 0.05$). AD patients also needed more semantic and phonemic cues than aMCI patients ($p = 0.004$, and $p < 0.001$, respectively) and controls ($p < 0.001$ on both items), while there was no significant difference between aMCI patients and controls on these items ($p = 0.441$) (See Table 2).

We ran group comparisons of the mean percentages of correct answers between the 3 groups after semantic and phonemic cues in order to verify qualitatively whether there were different responses between the groups. As shown in Figure 1, AD patients answered correctly after semantic cues 21.96% of the time, while aMCI patients answered correctly at a rate of 38.98% and controls answered properly 53.03% of the time. The overall difference between the groups in the percentage of correct answers for each participant after semantic cues was significant [$F (2, 45) = 7.171$, $p = 0.002$, partial $\eta^2 = 0.24$, $f = 0.56$].

A post hoc Tukey test showed that there was a difference between AD and aMCI patients ($p = 0.023$) as well as between AD patients and controls ($p = 0.002$), but not between aMCI patients and controls ($p = 0.674$). With regard to the mean percentage of correct answers by each group after phonemic cues, AD patients answered correctly 37.02% of the time, while aMCI patients answered correctly 39.86% of the time and controls answered correctly 45.45% of the time. Analysis of variance did not show any significant differences between the percentages for each group participant [$F (2, 45) = 0.926$, $p = 0.404$, partial $\eta^2 = 0.03$, $f = 0.20$]. Another separate ANOVA was carried out to compare the percentage of each error type after spontaneous answers and there was no significant difference between the three groups for omission errors [$F (2, 45) = 0.503$, $p = 0.608$, partial $\eta^2 = 0.02$, $f = 0.14$], visual paragnosia [$F (2, 45) = 2.728$, $p = 0.076$, partial $\eta^2 = 0.10$, $f = 0.34$], and semantic errors [$F (2, 45) = 2.284$, $p = 0.114$, partial $\eta^2 = 0.09$, $f = 0.31$]. We excluded phonological errors from the analysis because the three groups made a small number of this type of error. These results are shown in Figure 2.

We also used one way analysis of variance to compare the percentages of the semantic subtype of errors among the three groups, and there were no significant differences observed for circumlocutory [$F (2, 45) = 0.620$, $p = 0.542$, partial $\eta^2 = 0.02$, $f = 0.14$], coordinate [$F (2, 45) = 0.260$, $p = 0.772$, partial $\eta^2 = 0.01$, $f = 0.10$], or superordinate

errors [F (2, 45) = 0.032, p = 0.968, partial η^2 = 0.001, f = 0.03]. These results are shown in Figure 3.

The only variables that contributed significantly to the BNT variance on multiple regression analysis were Similarities (t (10)= 2.878, p = 0.035) in the aMCI group (R^2 = 0.58, f^2 = 1.38) and Similarities (t (10)= 3.429, p = 0.019) and MMSE (t (10)= 3.553, p = 0.016) in the control group (R^2 = 0.933, f^2 = 13.92). There were no significant relationships between any variable and the BNT in the mild AD group. In the AD group, the only variable that contributed significantly to spontaneous errors was the RAVLT delayed recall on omission errors (t (7)= 2.322, p = 0.049, R^2 = 0.378, f^2 = 0.60). In the aMCI group, there was a significant relationship between omission errors (R^2 = 0.496, f^2 = 0.98) and Similarities (t (7)= - 2.949, p = 0.018) and between visual paragnosia (R^2 = 0.421, f^2 = 0.72) and Similarities (t (7)= - 2.983, p = 0.018).

Discussion

Our results showed that aMCI patients demonstrated a normal performance on the BNT and needed fewer semantic and phonemic cues than mild AD patients. After semantic cues, aMCI and control subjects correctly named more pictures than mild AD patients, but after phonemic cues there was no significant difference between the three groups. This finding suggests that AD patients may have some degree of preserved knowledge about the pictured object, but they need some help to retrieve the phonological information about the presented item. We have found that cues, like primes, could facilitate picture naming by spreading activation of semantic relations, which indicates that semantic knowledge may not be the main cognitive domain that is disrupted. Semantic errors in object naming can also arise from impairment of any level in the naming process, including input, semantic, and output levels, as shown by Hillis & Caramazza's (1995) study of aphasic patients. Picture naming deficits in AD may also be, at least in part, due to a decline in inhibitory control over phonological output processes related to phonological implementation of conceptual information (Faust et al., 2004). In addition, some studies point to preserved semantic priming as evidence that AD patients do not suffer from a degradation or loss of semantic knowledge, but rather

from a loss of retrieval or other attentionally mediated processes (Albert et al., 1988; Balota & Duchek, 1991; Ober & Shenaut, 1988). In fact, our mild AD patients' attention performance, as assessed by the backward digit span task, was lower than that of the control group, which could suggest that lexical access and attention may have played a major role in their naming deficits.

To verify the performance of our patients in other lexical-semantic tasks, we applied the VF test for category animals and the CAMCOG's item of Similarities. Both tests showed that mild AD patients performed significantly worse than aMCI patients and controls. There were no significant relations between the BNT and other tests in the AD group. In the aMCI and control groups, Similarities performance was related to the BNT overall score, which suggests that lexical-semantic field integrity is important for this naming test.

Thus, our mild AD patients demonstrated a poor performance overall on the BNT (spontaneous and semantic cued naming) and other lexical-semantic tasks, but their semantic field tended to be at least partly preserved, since they scored normally after phonemic cues. A possible explanation for this finding is provided by Butterworth et al. (1984) who, in a study of aphasic subjects, proposed that a semantic deficit with incomplete activation of semantic knowledge is likely to produce either a semantic error or a correct response (if the information available is sufficient to retrieve the correct phonological form). In a similar way, Moreaud et al. (2001), by evaluating 15 AD patients, offered a conciliatory theory that a loss of semantic knowledge for some items (as proposed by Hodges et al., 1992) may coexist with a deficit of lexical retrieval for other items (Nebes, 1992; Nicholas et al., 1996). Chenery et al (1996) found that in early AD, the main problem is attentional, but that later in the progression of the disease, naming deficits reflect increased compromise of core semantic structures and processes. It could be very difficult to demonstrate that poor performance on semantic tasks is caused by storage disorders, since disruption in other cognitive processes (mainly attention) may theoretically explain the observed outcomes as well, as discussed by Storms, Dirikx, Saerens, Verstraeten, and De Deyn (2003). Attentional problems alone, however, cannot explain the semantic errors of all AD cases. In our sample, for example, subjects with aMCI, which might be representative of very early AD, scored lower than

AD patients on digit span tests (though the difference was not statistically significant). Furthermore, there is substantial clinical heterogeneity (both cognitive and behavioral) among patients with AD, even in the early phase of the disease (Cummings, 2000). Thus, the primary initial disturbance can be attentional-executive, as well as visuospatial-apraxic or aphasic (semantic anomia), depending on which brain region is predominantly degenerated.

With regard to spontaneous naming errors, there was a continuum between the three groups, with AD patients committing the most errors, controls committing the fewest errors, and aMCI subjects showing an intermediate performance. Nevertheless, when we analyzed the percentage of naming errors, the three groups were similar regarding the pattern of errors: each group committed semantic errors most frequently, followed by visual paragnosias and omissions. Phonological spontaneous errors were very uncommon. Analysis of relationships between spontaneous errors and other cognitive tests showed a significant correlation only between RAVLT delayed recall and omission errors in the AD group. A plausible explanation for this finding could be that naming partly depends on active retrieval (lexical-semantic selection) from long-term declarative memory, as in the RAVLT delayed recall task. In the aMCI group, Similarities was negatively related to omission and visual paragnosia errors (that is, committing fewer omission and visual paragnosia errors implied a better performance on Similarities), suggesting that these errors might have been influenced by semantic field integrity.

Analysis of the semantic subtype of errors showed that the three groups had a similar pattern of errors: they differed quantitatively, but not qualitatively. They made the most coordinate errors, followed by superordinate and circumlocutory errors. Why did this pattern of errors exist even among controls? Why did our AD patients not make more superordinate than coordinate errors when compared to aMCI and controls? A plausible explanation for this pattern of errors even among controls is that naming of basic level entities (e.g., house, chair, hammer, dog) as well as of unique or subordinate entities (e.g., White House, rocking chair, sledgehammer, collie) requires finer-grained discrimination and access to more information than the naming of higher level categories (e.g., animal, fruit, tool), as suggested by Martin & Chao (2001). The predominance of coordinate errors made by our AD patients (whose mean MMSE score was 22.5 ± 2.9) is

in disagreement with the higher frequency of superordinate errors found by Lukatela et al. (1998) in their AD group with similar MMSE scores (23.9 ± 3.2), although we used a slightly different classification. In spite of this discordance, our findings support the theory of Lukatela et al.(1998) and earlier proposals (Chertkow & Bub, 1990; Hodges et al., 1991) that, in AD, differentiation of within-category exemplars is impaired, whereas knowledge of broader semantic categories is preserved. The varied findings and controversies concerning coordinate versus superordinate errors as well as lexical retrieval deficit versus semantic knowledge loss found by several authors are probably related to variations in the dementia stage and, in the early stages, to the heterogeneous distribution of regional degeneration. In different AD patients, this could affect predominantly *stricto sensu* language areas for lexical access (naming) and/or higher level cortical association areas related to semantic (conceptual) organization. An additional plausible explanation for these varied findings in early AD is Milberg et al.'s (1999) Gain/Decay hypothesis, which represents a further development based upon Collins and Loftus's (1975) model of dynamic spreading activation and Hasselmo's (1994) theory of AD pathology as characterized by changes in synaptic density and deregulations of connectivity, which occur early in the course of the disease. According to this hypothesis, knowledge is stored in a semantic network made up of a series of representational (conceptual) units which vary in how "active" they are and when activated beyond some threshold, will produce a wave of activation that spreads to other units within the network. The central assumption is that a reduction in the time constant of spreading activation in AD produces dynamic changes that allow semantic representations to be either more available or less available than normal, depending on the time frame in which this information has to be accessed. In AD, there may be a change in the modulation of activation, rather than the loss of activation proposed by models that claim a degradation of semantic knowledge associated with brain atrophy (cf. Martin & Fedio, 1983; Farah & Tippett, 1996). Knowledge degradation attributable to neural atrophy and loss of representational units cannot be a plausible explanation for the semantic deficits found in early AD, since (1) many other degenerative conditions (Parkinson's disease, Huntington disease, alcoholism) are not associated with such an extensive impairment of semantic memory as seen in this disease (as argued by Milberg

et al., 1999), and (2) there is increasing evidence that the earliest pathological change in AD is an intraneuronal accumulation of Aβ oligomers (not fibrils) leading to mitochondrial abnormalities, a decreased rate of glucose utilization, oxidative damage, and synaptic dysfunction, which can impair cognition long before the appearance of neuritic plaques, neurofibrillary tangles, and brain atrophy (Reiman et al., 1996; Dodart et al., 1999; Selkoe, 2002; Kelly & Ferreira, 2006). Early synaptic changes plus a reduction in the number of longer axons and dendrites by the disease process (tangles and plaques) would have the effect of reducing the total resistance and capacitance of the dendritic membrane, thus reducing the time constants of both excitatory and inhibitory postsynaptic potentials arriving at affected neural cell bodies while increasing the gain and the decay rate of activation within the neural network (Milberg et al., 1999).

Another relevant aspect of our findings is that our subjects answered correctly after a phonemic cue, even if they had spontaneously made a semantic error. In such cases, for example, making a semantic-coordinate error on spontaneous naming might imply semantic integrity at this and higher levels and maybe a disruption at a more basic level. Semantic disruption would be expected to occur from the more detailed nodes of the semantic network to the more generic levels of semantic hierarchical organization as aging leads to the progression of aMCI and AD. Chenery et al. (1996) showed that the naming responses of subjects severely affected by the disease reflect increased compromise of core semantic structures and processes, which is not necessarily true in the early phases. It is possible that if we had included patients with moderate and severe AD, they would not have answered properly even after phonemic cues. Should this be the case, we could have found a different pattern of semantic errors, maybe with a higher prevalence of the superordinate subtype.

In conclusion, we have found that aMCI subjects performed similarly to controls with regard to the BNT total score (spontaneous plus cued naming), while there was a significantly decreased performance from normal aging to aMCI to AD on BNT spontaneous naming (without cues). The poor performance of AD patients cannot be completely explained by semantic breakdown, since they performed as well as aMCI and control subjects after phonemic cues, and this relative sparing of semantic knowledge could be due to the early disease phase of our patients. We also found that the overall

pattern of spontaneous naming errors and the subtypes of semantic errors were similar in the three groups, with decreasing frequency of errors from coordinate to superordinate to circumlocutory subtypes. These naming difficulties are most likely explained by a combination of loss of semantic knowledge, impaired lexical access, and higher taxing of cognitive resources for finer-grained discrimination between basic level lexical-semantic fields. Further studies with larger sample sizes and a more comprehensive battery of tests to assess the cognitive architecture of the semantic system, including lexical access and appropriate control tasks, are needed for more reliable conclusions.

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Table1. Demographic and additional neuropsychological data

Variable	AD (n = 16) Mean ± SD	MCI (n =16) Mean ± SD	Controls (n =16) Mean ± SD
Age (years)	76.25 ± 7.75	70.87 ± 9.79	70.62 ± 7.77
Education (years)	5.31 ± 4.98	5.18 ± 3.16	6.50 ± 2.75
MMSE	22.56 ± 2.96 $^{a***, b***}$	26.50 ± 2.28^{a**}	29.12 ± 0.71
VF	10.12 ± 3.34$^{a***, b*}$	13.62 ± 3.46^{a***}	19.37 ± 3.22
RAVLT-A7	1.00 ± 1.21$^{a***, b**}$	3.56 ± 2.15^{a***}	9.00 ± 3.05
Similarities	4.87 ± 1.74$^{a***, b***}$	6.93 ± 1.18	7.37 ± 1.02
FDS	4.62 ± 1.08	4.50 ± 0.81	5.00 ± 0.81
BDS	3.12 ± 0.50^{a*}	2.93 ± 0.57^{a**}	3.93 ± 1.12
Visuo-spatial LNI	17.31 ± 1.35^{a**,b**}	18.68 ± 0.94	18.62 ± 1.08

Data presented as means ± SD. MMSE: mini-mental status examination; VF: verbal fluency; RAVLT-A7: delayed recall of Rey auditory verbal learning test; FDS: forward digit span; BDS: backward digit span; Visuo-Spatial-LNI: visuospatial perception item of Luria's neuropsychological investigation.

a: significantly different from controls; b: significantly different from aMCI

*** $p < 0.001$

** $p < 0.007$

* $p < 0.01$

Table 2. Boston Naming Test scores

Variable	AD (n = 16) Mean ± SD	aMCI (n =16) Mean ± SD	Controls (n =16) Mean ± SD
BNT- total score	38.37 ± 8.70[a***,b***]	51.12 ± 7.11	53.81 ± 3.90
Spontaneous answers	34.87 ± 9.71[a***, b***]	48.25 ±9.13[a*]	51.62 ± 5.87
Semantic cues	15.93 ± 7.76[a***,b**]	7.37 ± 7.50	4.12 ± 4.70
Phonemic cues	21.43 ± 8.63[a***,b***]	8.93 ± 7.06	6.18 ± 3.90

a: significantly different from controls; b: significantly different from aMCI

*** $p < 0.001$

** $p < 0.005$

* $p < 0.05$

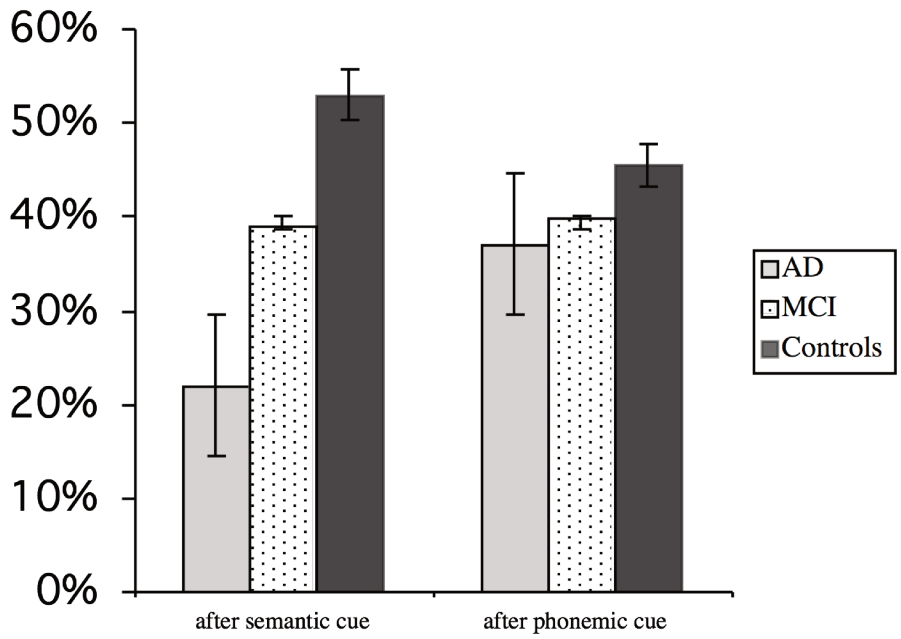

Figure 1. Percentage of correct answers by each group after semantic and phonemic cues.

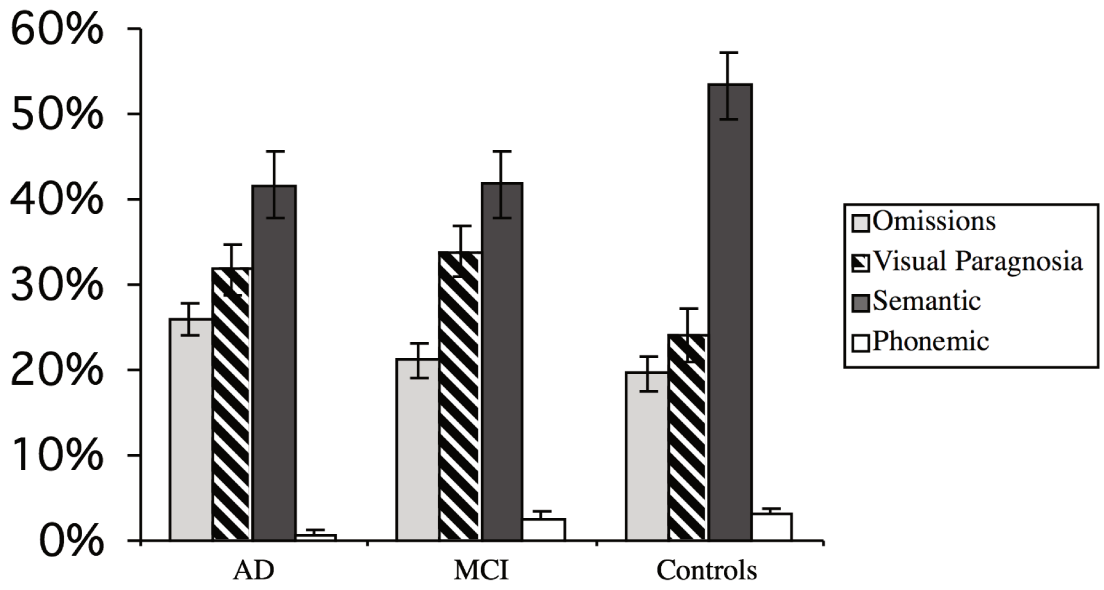

Figure 2. Percentage of subtypes of errors from total naming errors among AD, AMCI, and control subjects.

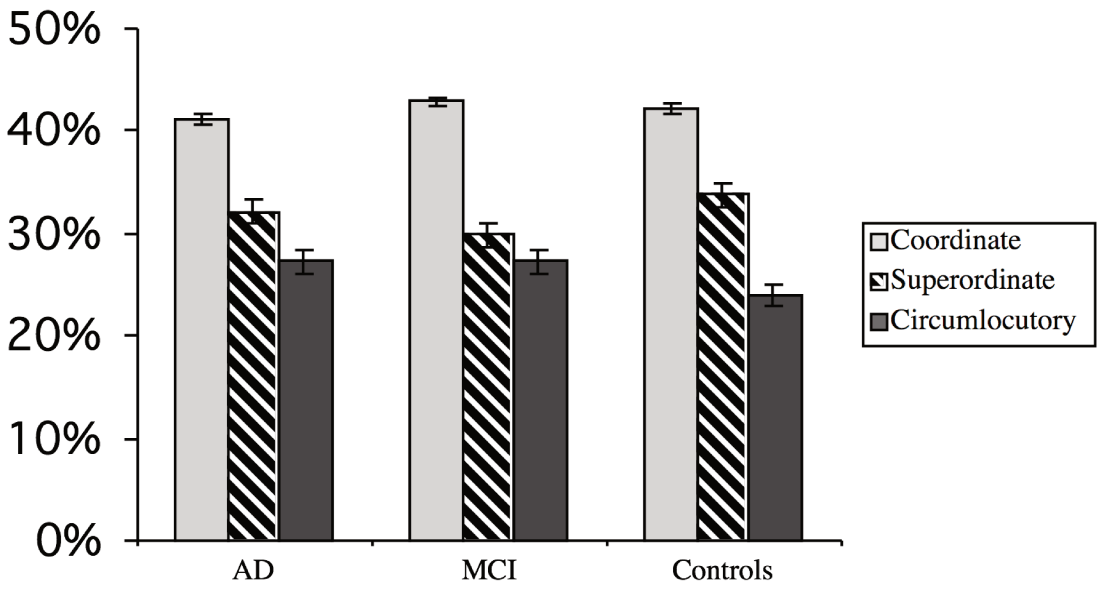

Figure 3. Percentage of subtypes of semantic errors from total semantic errors.

ARTIGO 4

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Differences in grey and white matter atrophy in amnestic Mild Cognitive Impairment and mild Alzheimer's disease

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Abstract

Background:Grey matter (GM) atrophy has been demonstrated in amnestic mild cognitive impairment (aMCI) and mild Alzheimer's disease (AD), but the role of white matter (WM) atrophy has not been well characterized. In spite of these findings, the validity of aMCI concept as prodromal AD has been questioned.

Methods: We performed brain MRI with voxel-based morphometry (VBM) analysis in 48 subjects, aiming to evaluate the patterns of GM and WM atrophy among mild AD, aMCI and age-matched normal controls.

Results: aMCI GM atrophy was similarly distributed but less intense than that of mild AD group, mainly in thalami and parahippocampal gyri. There were no difference between aMCI and controls concerning WM atrophy. In the mild AD group, we found WM atrophy in periventricular areas, corpus callosum and WM adjacent to associative cortices.

Discussion: We demonstrated that aMCI might be considered a valid concept to detect very early AD pathology, since we found a close proximity in the pattern of atrophy. Also, we showed the involvement of WM in mild AD, but not in aMCI, suggesting a combination of Wallerian degeneration and microvascular ischemic disease as a plausible additional pathological mechanism for the discrimination between MCI and AD.

Key-words: amnestic mild cognitive impairment, Alzheimer's disease, white matter, voxel-based morphometry

Introduction

Mild cognitive impairment (MCI) is considered a clinical entity for patients with objective cognitive problems (most often episodic memory) without impairment on daily life activities [1] and their chance to convert to dementia, most commonly Alzheimer's disease (AD), is greater than normal population [2]. As research in MCI has evolved, it has become clear that several clinical subtypes exist: amnestic MCI (single and multi-domain), and non-amnestic (single and multiple-domain). Several neuroimaging, genetic and cerebrospinal fluid (CSF) biomarkers studies have focused their attention on amnestic MCI (aMCI), because it might be representative of very early AD [3-6]. However, some aMCI cases will not convert to AD, what means that this concept may include patients who have memory problems associated to non-neurodegenerative diseases, like depression and anxiety, or drug induced states [7]. In this sense, we cannot consider aMCI as synonym of very early AD. A recent position paper suggested to eliminate MCI construct for research purposes and considered for probable AD diagnosis just an objective episodic memory deficit plus a supportive feature, like medial temporal lobe atrophy measured by magnetic resonance imaging (MRI) [8].

Several authors found a similar pattern of grey matter (GM) atrophy among MCI and early AD patients, mainly on medial temporal structures, but the role of white matter (WM) atrophy has not been well characterized, in particular in mild or initial stages of disease. Histopathologic studies in more advanced AD have shown evidence of WM change, including axonal and oligodendrocyte loss coincident with a reactive astrocytosis [9]. Axonal damage attributed to Wallerian degeneration and microvascular ischemic disease are the main proposed etiological agents to justify WM atrophy in AD [10-13], and in vivo MRI WM changes can be found even in early AD phases or in its prodromal states like MCI [14]. We applied a MRI Voxel-based morphometry (VBM) technique that maps the entire brain instead of being restricted to single regions. Voxels, or volume picture elements, are represented mathematically in the three dimensions of height, width and depth, and correspond to units of tissue volume. This method is very useful in the study of neurodegenerative diseases like AD (in which neuronal density is primarily affected), and allows detecting changes even in its earliest stage or possible prodromal states like aMCI. In the present study, we used this VBM approach to evaluate the

patterns of atrophy in GM and WM of aMCI and mild AD patients in comparison to control subjects and, based on our findings, we will discuss the advantages and limitations of considering aMCI as prodromal AD.

Methods

Subjects

We studied 48 subjects older than 50 years, comprising 17 with aMCI, 15 with mild AD attended at the Unit for Neuropsychology and Neurolinguistics at University of Campinas, UNICAMP, and 16 healthy controls. Routine laboratory examinations for dementia assessment, including B12 and folate serum levels, serology for syphilis, dosage of thyroid hormones, brain computed tomography and MRI were carried out in all patients. The local ethics committee approved this research and all patients signed an informed consent for this study.

aMCI in our clinic is a diagnosis carried out by trained neurologists using a standardized mental status battery. The routine diagnostic process consisted of a detailed interview with the patient and informant. All patients were submitted to the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) [15], which comprises structured interviews with the patient and, separately, with an informant, evaluating the patient's current medical and psychiatric status and family history. They were also submitted to the CAMDEX cognitive test battery (CAMCOG), which includes eight subscales: memory, orientation, language, attention, abstract thinking or similarities, calculation and perception. MCI diagnosis followed the criteria of the International Working Group on Mild Cognitive Impairment [1]: (i) the person is neither normal nor demented; (ii) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired. We considered a diagnosis of aMCI if the clinical history and cognitive performance pointed to an exclusive memory deficit and Clinical Dementia Rating (CDR) [16] score of 0.5, with obligatory memory score of 0.5. This classification was performed by using a semi-structured interview.

For probable AD diagnosis, we used the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA) [17] including only patients classified as CDR 1. Exclusion criteria were history of other neurological or psychiatric diseases, Hachinski ischemic score [18] greater than 4, head injury with loss of consciousness, use of sedative drugs in the last 24 hours before the neuropsychological assessment, drug or alcohol addiction and prior chronic exposure to neurotoxic substances. The control group consisted of subjects with CDR 0 without previous history of neurological or psychiatric disease, or memory complaints.

Neuropsychological evaluation

Alls subjects were submitted to the Mini Mental Status Examination (MMSE) [19, 20], as a measure of global cognitive impairment, as well as Rey auditory verbal learning test (RAVLT) [21] to evaluate episodic memory delayed recall (RAVLT-A7); Boston Naming test (BNT) [22]; verbal fluency (VF) for animals' category; visual perception subtests of Luria's Neuropsychological Investigation (LNI) [23]; the forward (FDS) and backward digit span (BDS) subtest of WAIS-R [24] and Cornell Scale for Depression in Dementia (CSDD) [25,26]. For data analysis we used Systat software 12.0. We performed Kruskall-Wallis test for inter-group comparisons of demographic and cognitive scores. Statistical significance considered at $p < 0.05$.

MRI scanning protocol, imaging processing and statistical analysis

High-resolution MRI was performed using a 2.0 T scanner (Elscint, Haifa, Israel). T1- and T2-weighted images were acquired in axial, coronal, and sagittal planes with thin cuts. In addition, volumetric (3D) T1 gradient echo (GRE) images were acquired in the sagittal plane with 1 mm thick (flip angle = 35°, time to repeat = 22 ms, echo time = 9 ms, matrix = 256 X 220, field of view = 23 X 25 cm). We used Analyze® format images that were generated from raw Dicom images using MRIcro software (http://www.sph.sc.edu/comd/rorden/mricro.html). The anterior commissure was selected for the normalization process. Using SPM2 software (Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk) we normalized, segmented, and smoothed all images [27]. We also used the optimized VBM code described in previous studies to modulate the images [28]. All images were spatially

normalized using SPM2 built-in routines, in order to perform the comparisons between groups. This step reduces individual brain size variability by spatially normalizing each image to a template. Then, images underwent automatic segmentation of GM using SPM2 built-in routines, which estimate the probability that each voxel is GM. The images also underwent: modulation, a technique which preserves the quantity of tissue that was deformed during the normalization process; and smoothing: segmented GM images were convolved with an Isotropic Gaussian Kernel of 10 mm to reduce interindividual gyral variation. The same process was done for WM analysis. For statistical analysis, we used the software Non-Parametric Mapping (NPM) (http://www.sph.sc.edu/comd/rorden/npm) and the results of these comparisons are displayed as statistical non-parametric map of Brunner-Munzel test with the number of standard deviations compared to controls (z score) [29]. The statistical analysis for all comparisons was performed with grand mean scaling, proportional threshold masking (0.8 for GM and 0.4 for WM) and implicit masking. We defined the contrast searching for areas of reduced WM and GM. The results were corrected for multiple comparisons using a false discovery rate (FDR) of 1% with an extended threshold looking for clusters with at least 32 contiguous voxels.

Results

There were no statistically significant differences between the 3 groups concerning age or education. Neuropsychological and demographic data are shown on Table 1. aMCI subjects were similar to controls concerning Boston Naming Test and visuospatial perception subtests of LNI, but they performed worse on the MMSE ($p = 0.01$), backward digit span ($p < 0.05$), verbal fluency ($p = 0.0006$), and delayed recall ($p = 0.0001$) of RAVLT. AD patients scored lower than controls and aMCI subjects on all tests, except on forward digit span.

Concerning aMCI, we found atrophy mainly on bilateral: thalami (left: z score = 5.30; right: $z = 5.63$), parahippocampal gyri (right: $z = 4.39$; left: $z = 4.12$) and caudate nuclei (right: $z = 4.15$; left: $z = 4.17$). We also found significant GM atrophic areas in right hemisphere: anterior cingulate gyrus ($z = 4.06$), and superior ($z = 4.50$) and middle ($z = 4.17$) frontal gyrus (figures 1A and 2).

As compared to normal controls, AD subjects presented a similar pattern of GM atrophy

seen in aMCI, though more intense, in bilateral thalami (right: z = 6.54; left: z = 5.35) and parahippocampal gyri (right: z = 4.95; left: z = 4.12). In the AD group, there was more significant atrophy in other medial temporal structures, including bilateral hippocampi (right: z = 4.09; left: z = 3.95), amygdales (right: z = 4.15; left: z= 3.54) and left insula (z = 4.10) and in several other areas shown on figures 1 and 2 (mainly on bilateral: inferior parietal lobule, inferior and superior frontal gyrus, anterior cingulated gyrus, caudate nucleus; right hemisphere: precuneus, uncus, middle frontal gyrus, lingual gyrus and cerebellum). In comparison to aMCI, mild AD group showed significant GM atrophy in bilateral superior frontal gyri (right: z = 3.12; left: z = 2.46), right inferior frontal gyrus (z = 2.18), left middle temporal gyrus (z = 2.60), right lingual gyrus (z = 2.35) and right cerebellar tonsil (z = 2.46).

Comparing WM concentration of AD patients against that of controls, we found atrophy in the mild AD group in the corpus callosum (CC), mainly in its anterior part (z = 3.55) as well as in the WM adjacent to: right and left fusiform gyrus (z = 4.01), left superior temporal gyrus (z = 3.67), left (z = 3.85) and right (z = 3.80) parahippocampal gyri and periventricular regions bilaterally (figures 3 and 4). Comparisons between aMCI and controls did not disclose any statistically significant area of WM atrophy in the aMCI group.

Discussion

Our findings support the idea of a continuum in the brain pathology between normal aging, aMCI and mild AD [30]. With regard to aMCI, we found a similar and less intense GM atrophy pattern in comparison to mild AD group, mainly in thalami and parahippocampal gyri (Figures 1B and 2). Interestingly, if we consider that our aMCI patients do represent prodromal AD, it could indicate that the atrophy might begin in these areas (thalami and parahippocampal gyri), as seen in aMCI group (Figure 1B, in green and yellow), and then spreads to other temporal medial structures like hippocampi and amygdales and other thalamic nuclei, as seen in mild AD group (Figure 1B, in red). It is well established the involvement of medial temporal structures in AD, and also in aMCI [30]. Thalamic atrophy as demonstrated by other VBM studies [31, 32], although less emphasized by anatomopathologic studies, may contribute to memory loss in AD, mainly if anterior and dorsomedial nuclei are involved [33, 34]. Chételat et al., in a

longitudinal VBM study, also found significant GM loss in left thalamus over the 18-month follow-up period common to both converters and non-converters [35]. Maybe, thalamic atrophy in MCI could have some prognostic value in the conversion to AD, since thalamus, as well as medial temporal lobes, neocortical association areas, basal ganglia and basal forebrain might be part of a brain network whose atrophy is significantly correlated with the diagnosis of AD, as suggested by Teipel et al., in a multivariate deformation-based study developed to predict conversion to AD [36]. Moreover, we found atrophy in aMCI group on right superior and middle frontal gyri, right anterior cingulate gyrus and bilateral caudate nuclei. Our aMCI patients could be compared to another aMCI group that progressed to AD (aMCI-P) in a recent longitudinal VBM study that compared patterns of GM atrophy between "converters and non-converters to AD" [37]. Differently from our patients, the aMCI group that remained clinically stable (aMCI-S) did not show any GM atrophy when compared to controls. Although we did not evaluate the progression of our aMCI patients, they showed a pattern of GM atrophy very similar to that of aMCI-P subjects. This fact may reflect our exclusion criteria, which possibly allowed us to evaluate just "real" prodromal AD subjects.

Concerning WM, our findings are in accordance with other reports of atrophy in AD, mainly in periventricular areas, corpus callosum and areas adjacent to cortical associative regions [10-13, 38]. We did not find any consistent asymmetry between WM atrophy areas, except for those adjacent to superior temporal gyrus, which were more atrophic in the left side. In disagreement with other authors, we did not find areas of WM atrophy in aMCI group as compared to controls [14, 39, 40].

WM atrophy may be caused by different etiologies, mainly Wallerian degeneration secondary to cortical atrophy and/or ischemic disease and these different causes may coexist in AD pathology. In the periventricular region, for example, microinfarcts may play a major role, since it has been reported that there is a single watershed WM area extending between 3 and 13 mm from the ventricular surface, what makes this area more susceptible to vascular injury [10]. On the other hand, several authors, by using different MRI methods like Diffusion Tensor Imaging (DTI), have shown that there is WM selective damage in areas associated to cortical atrophy, with relative sparing of areas

related to motor or visual function [12-14]. The selective impairment of WM was probably associated to the pathologically proved distribution of neurofibrillary tangles and amyloid plaques in the cortex and among the interconnecting WM fibers. Wallerian degeneration is the most accepted mechanism to explain these findings. In support of this mechanism, we found a significant atrophy in the WM close to associative cortices like fusiform and superior temporal, and also parahipoccampal gyri, which concurs with data from another study of WM abnormalities in bitemporal medial structures associated to hippocampi and amigdalae atrophy [41]. We also demonstrated that atrophy in anterior CC portions, responsible for the anatomical inter-hemispheric cortico-cortical connection of prefrontal regions, is more intense than that of posterior regions, as shown by others [42, 43]. Other authors have found a different atrophy pattern affecting predominantly posterior CC, whose fibers connect temporo-parietal associative cortices [41]. It is tempting to speculate that the WM atrophy in our mild AD patients may have led to a cortico-cortical and/or cortico-subcortical disconnection of cognitive neurofunctional networks and thus contributed to the poor neuropsychological performance of these patients, as proposed by others [9].

Recently, the concept of MCI has been questioned, and even some authors have proposed new AD research criteria that makes its concept unnecessary [8]. An important argument against MCI concept is its clinical heterogeneity, with inclusion of individuals that will not evolve to a full dementia syndrome, and therefore, do not represent preclinical AD. On the other hand, MCI is still a very useful concept if we consider the present diagnostic criteria for AD. For research purposes, we can achieve a high level of specificity (that is, aMCI could really be thought as prodromal AD) if exclusion of other possible causes of memory decline in the elderly were more precise (psychiatric conditions, thyroidal disturbances, nutritional deficiency, use of sedative drugs, etc.).

Our study had some limitations: AD patients were older than aMCI and controls, with a trend to statistical significance ($p = 0.065$); we did not correlate the WM findings to neuropsychological data, which prevented us from getting better insight into the cognitive implications of WM damage in our mild AD patients. Another limitation of our VBM approach was the presence, in rare cases, of some imprecision in the points of maximal difference between groups, with clusters of voxels that did not correspond to

any specific GM area. In these cases, we considered the coordinates of nearest GM area (± 5 mm) as the maximal significance point. Despite such limitations, we demonstrated that aMCI might be considered a valid concept to detect very early AD pathology, since we found a close proximity in the pattern of atrophy, predominantly in temporal medial structures and thalami. Furthermore, there were no statistically significative differences when we compared GM density between aMCI and mild AD subjects in areas like medial temporal lobes. We also found involvement of WM in mild AD, but not in aMCI, suggesting a combination of Wallerian degeneration and microvascular ischemic disease as a plausible additional pathological mechanism for the discrimination between MCI and AD.

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Table 1. Demographic and neuropsychological data

	AD	aMCI	Controls	p
Age	74.26±6.33	68.29±9.93	69.12±7.55	0.170
Education	6.00±5.52	5.88±4.32	6.87±3.66	0.315
MMSE	22.93±2.65	26.41±2.76	29.12±0.71	< 0.0001
A7-RAVLT	1.26±1.28	4.17±2.40	9.56±3.03	< 0.0001
BNT	39.33±9.98	50.82±7.66	53.75±4.18	< 0.0001
VF	10.60±3.39	13.64±3.92	19.43±3.03	< 0.0001
VSP-LNI	17.20±1.42	18.76±0.97	18.81±0.98	0.002
fDS	4.46±1.06	4.58±0.79	5.06±0.85	0.108
bDS	3.20±0.77	3.11±0.92	4.12±1.02	0.004

Data presented as means ± SD. MMSE: mini-mental status examination; A7- RAVLT: delayed recall of Rey auditory verbal learning test; BNT: Boston naming test; VF: verbal fluency; VSP-LNI: visuospatial perception item of Luria's neuropsychological investigation; fDS: forward digit span; bDS: backward digit span.

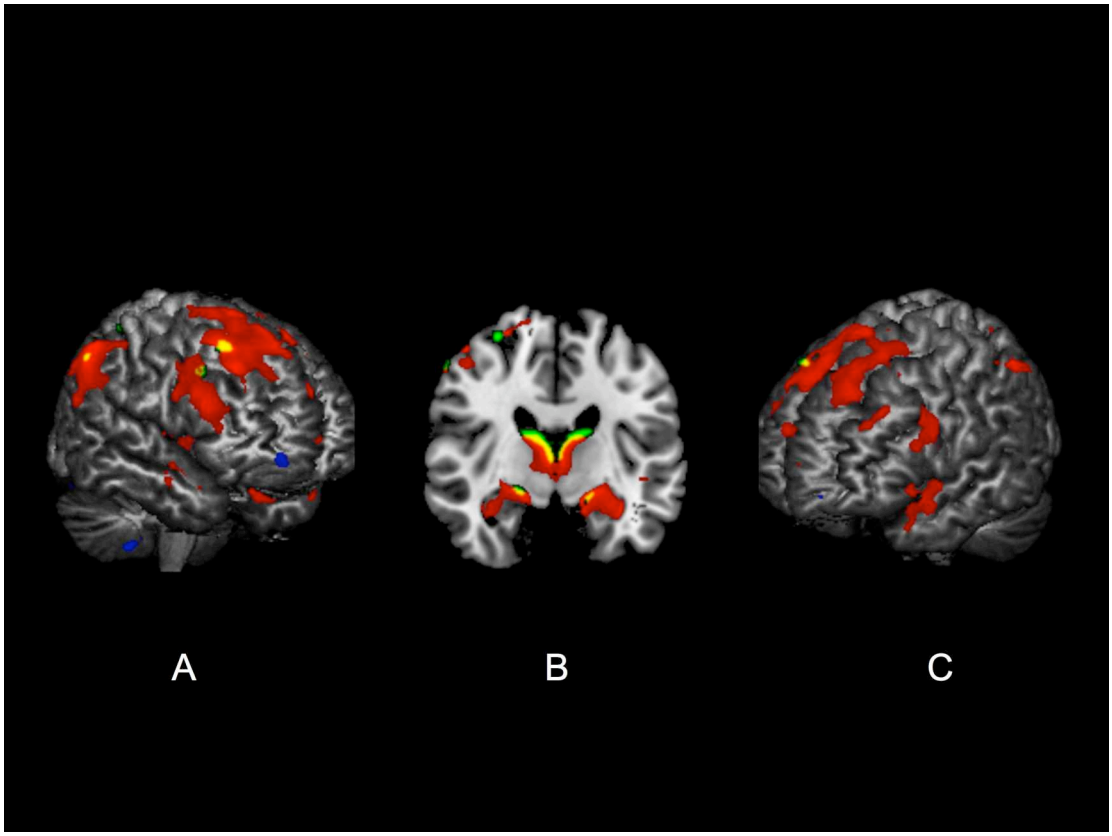

Figure 1. Patterns of grey matter atrophy in aMCI and mild AD. A: Right hemisphere view; B. Coronal view; C. Left hemisphere view. Red: mild AD in comparison with controls; Green: aMCI in comparison with controls; Blue: mild AD in comparison with aMCI; Yellow: common areas of atrophy among aMCI and mild AD.

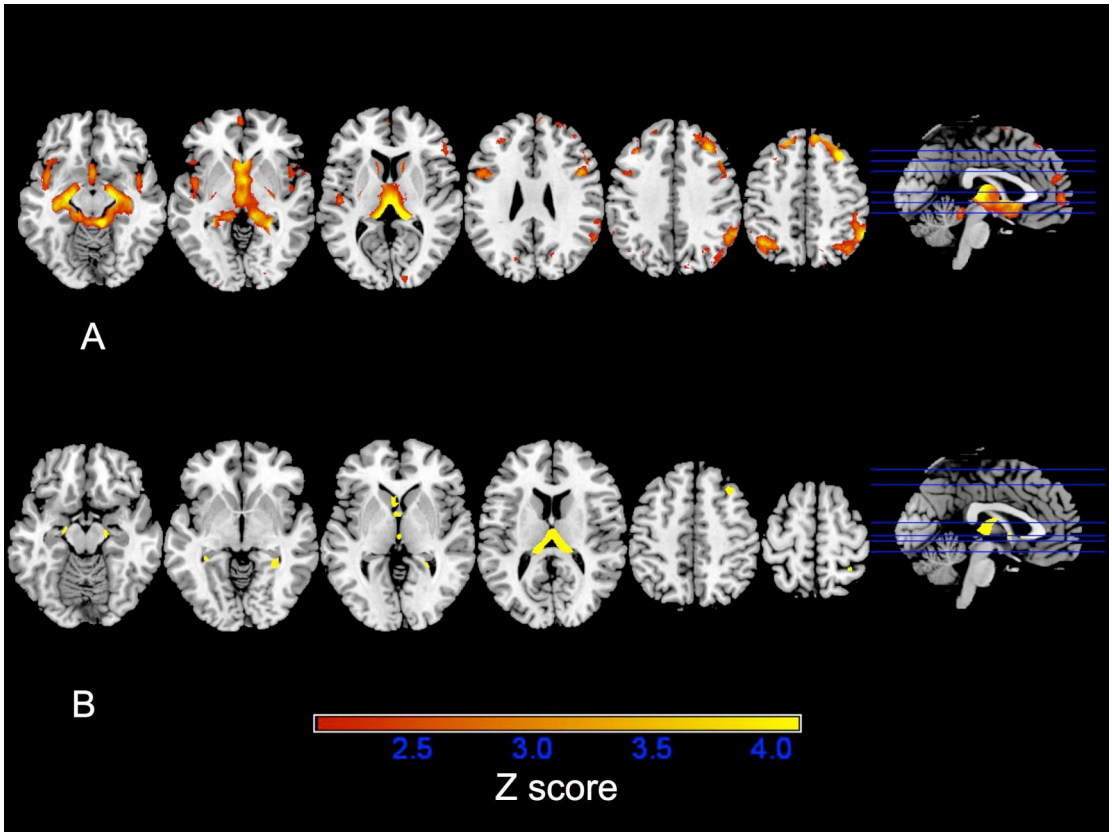

Figure 2. Axial slices of grey matter atrophy in relation to controls in: A. mild AD; B. aMCI. The colorbar indicates the number of standard deviations compared to controls (z score). The level of significance selected was $p < 0.05$ corrected for multiple comparisons (false discovery rate). All slices are in neurological orientation (left on the left side).

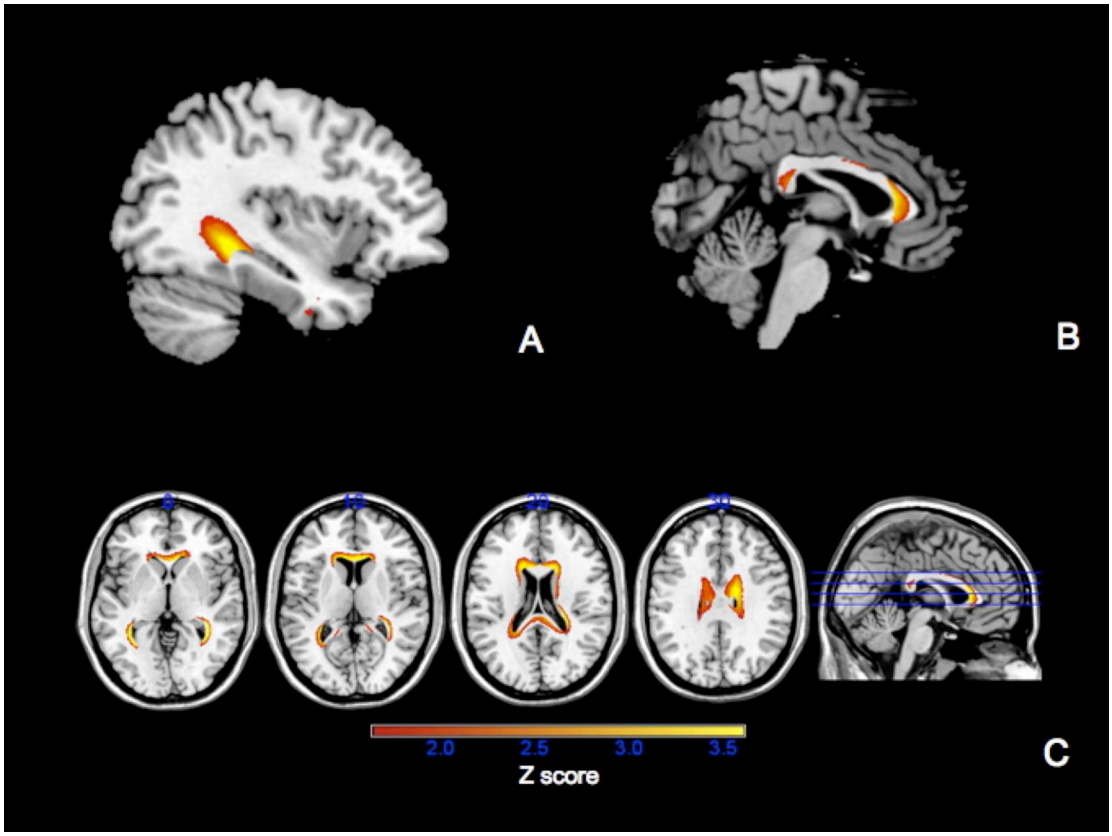

Figure 3. Results of VBM WM analysis of mild AD patients and normal controls. A. WM atrophy adjacent to left fusiform gyrus; B. Atrophy of corpus callosum, mainly in its anterior part; C. Axial slices at corpus callosum level. All slices are in neurological orientation (left on the left side).

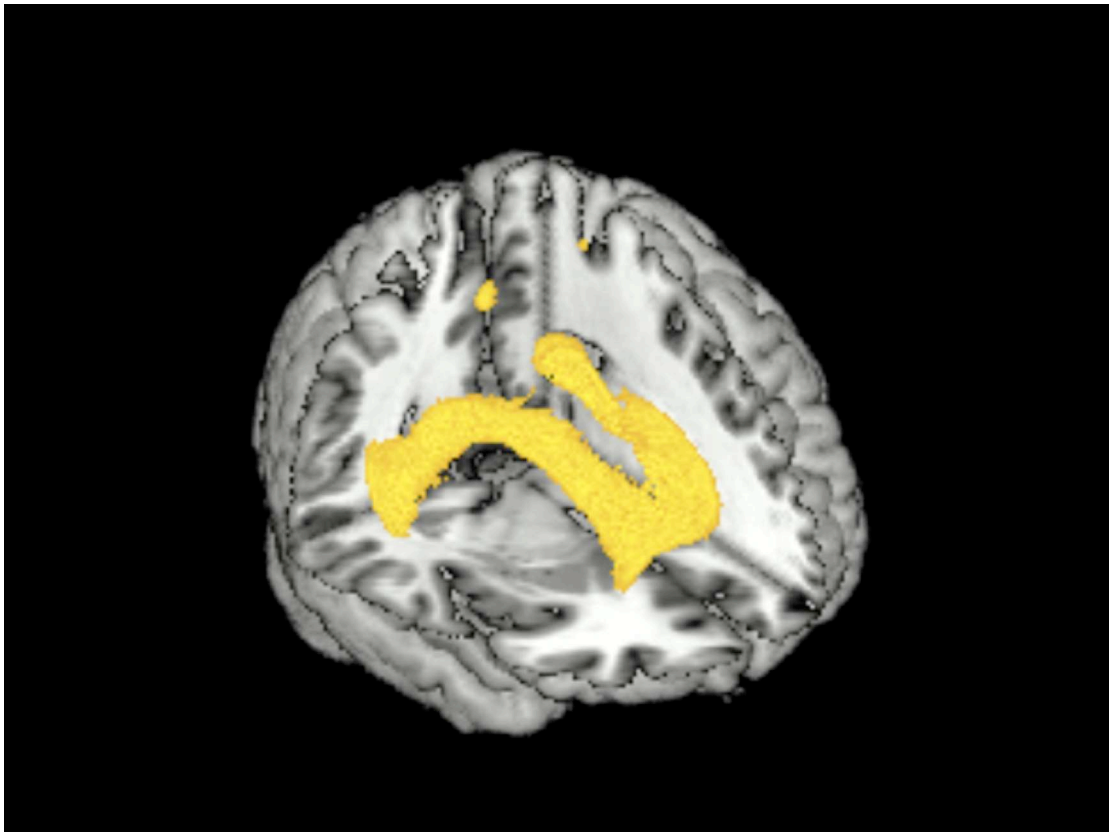

Figure 4. 3D reconstruction of WM atrophy on AD group at significance level of $p < 0.05$ (z score =2).

The authors report no conflicts of interest

ARTIGO 5

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Hippocampal atrophy and verbal episodic memory performance in amnestic mild cognitive impairment and mild Alzheimer's disease

A preliminary study

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Abstract – To evaluate hippocampal volume in patients with AD and aMCI, and correlate its atrophy with verbal episodic memory performance. ***Methods:*** We studied 42 individuals older than 50 years, including 14 with amnestic mild cognitive impairment (aMCI), 14 with mild Alzheimer's disease (AD) and 14 normal controls. All individuals were submitted to the Rey auditory verbal learning test (RAVLT) to evaluate episodic memory. They were also submitted to the forward (FDS) and backward digit span (BDS) subtest of WAIS-R to evaluate working memory and attention, and to the Mini Mental State Examination (MMSE). Hippocampal volumetric measurements were performed according to anatomic guidelines from a standard protocol using high-resolution T1-inversion recovery 3-mm coronal MRI slices. Hippocampal volumes (HV) were corrected for the variation in total intracranial volume. There was no significant difference between the three groups concerning age and education. ***Results:*** On RAVLT, there was a continuum between the three groups, with AD recalling less words, controls more, and aMCI subjects showing an intermediate performance on all sub-items. We found an asymmetry between HVs, with smaller mean left HV for all groups. ANOVA and *post hoc* Tukey's test for comparisons of HV showed a significant difference among groups, with difference between controls and both AD and aMCI, although there was no significant difference between AD and aMCI groups. ***Conclusions:*** There was a significant correlation between hippocampal volumes and scores on RAVLT, confirming that medial temporal structures are closely associated with memory performance in normal ageing as well as in aMCI and AD.
Key words: hippocampal atrophy, MRI, memory, Alzheimer's disease, mild cognitive impairment.

Atrofia hipocampal e desempenho na memória verbal episódica no comprometimento cognitivo leve amnéstico e na doença de Alzheimer leve

Resumo – Avaliar os volumes hipocampais (VH) em pacientes com doença de Alzheimer (DA) leve e comprometimento cognitivo leve amnéstico (aCCL). ***Métodos:*** Estudamos 42 sujeitos maiores de 50 anos, incluindo 14 com DA leve, 14 com aCCL e 14 controles. Todos foram submetidos ao teste de aprendizado auditivo verbal de Rey (TAAVR) para avaliação de memória episódica, ao teste de extensão de dígitos direto e indireto do WAIS-R, para avaliação de memória operacional e atenção e ao Mini Exame do Estado Mental (MEEM). As medidas de volumetria hipocampal foram obtidas de acordo com as diretrizes anatômicas de um protocolo padrão usando imagens coronais ponderadas T1 inversion-recovery de 3 mm. Os VH foram corrigidos para a variação do volume intracraniano total. Não houve diferença significativa entre os 3 grupos quanto a idade e escolaridade. ***Resultados:*** No TAAVR houve um *continuum* no desempenho dos 3 grupos, com os pacientes com DA leve evocando menos palavras, os controles mais e os aCCL mostrando um desempenho intermediário em todos os subitens.

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Encontramos também uma assimetria entre os VH, com o lado esquerdo menor que o direito nos 3 grupos. O teste de análise de variância (ANOVA) seguido do teste *post hoc* de Tukey para comparações entre os VH dos grupos mostrou diferença significativa entre controles e DA e aCCL, mas não entre DA e aCCL. Encontramos também correlação estatística significativa entre os VH e o desempenho no TAAVR. ***Conclusões:*** As estruturas do lobo temporal medial estão intimamente ligadas ao desempenho de memória episódica tanto no envelhecimento normal quanto no aCCL e DA.

Palavras-chave: atrofia hipocampal, MRI, memória, doença de Alzheimer, transtorno cognitivo leve.

Memory is a complex psychological function that is closely associated with medial temporal lobe structures. Since the H.M. case described in the early 1950s, it has been known that circumscribed brain lesions within the limbic system may deteriorate the ability to form new memories.[1]

Patients with Alzheimer's disease (AD) and amnestic mild cognitive impairment (aMCI) show a markedly reduced ability to retain new information: they often have difficulty in recalling appointments, shopping list items, names of people, and perform poorly on verbal episodic memory tests. This memory impairment is the earliest clinical symptom and a prominent feature throughout the course of AD.[2,3]

The hippocampus is a central component of the medial temporal lobe memory system, and its structural integrity is necessary for declarative memory.[1,2] There are several neuroimaging evidences for loss of hippocampal tissue in human diseases associated with memory impairments, and findings of magnetic resonance imaging (MRI) studies have established that volumetry of the hippocampus is useful in assisting the clinical diagnosis of AD.[4-6] In patients with aMCI, a condition that is often transitional to AD, hippocampal cortex pathology lies between the values measured in controls and mild AD.[7]

In the present study, our aim was to evaluate hippocampal volume in patients with AD and aMCI, and correlate its atrophy with verbal episodic memory performance.

Patients and methods

We studied 42 individuals older than 50 years, comprising 14 with aMCI, 14 with mild AD attended at the Unit for Neuropsychology and Neurolinguistics (UNICAMP Clinic Hospital), and 14 normal controls. Routine laboratory examinations for dementia assessment (including B12 and folate dosage, serology for syphilis, thyroid hormones) and brain computed tomography were carried out in all patients. The local ethics committee approved this research.

aMCI in our clinic is a diagnosis carried out by trained neurologists using a standardized mental state battery. The diagnostic process consisted of a detailed interview with the patient and informant. All patients were submitted to the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) which comprises structured interviews with the patient and, separately, with an informant, along with evaluation of patient's current medical and psychiatric status and family history. Participants were also submitted to the CAMDEX cognitive test battery (CAMCOG), which includes eight subscales: memory, orientation, language, attention, abstract thinking or similarities, calculation and perception.[8]

MCI diagnosis followed the criteria of the International Working Group on Mild Cognitive Impairment,[9] and was classified as follows: (i) the person is neither normal or demented; (ii) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective self-report of decline and/or by informant in conjunction with objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired.

We considered a diagnosis of aMCI if the clinical history and cognitive performance pointed to an exclusive memory deficit and Clinical Dementia Rating[10] score of 0.5, with obligatory memory score of 0.5. This classification was achieved using a semi-structured interview.

For probable AD diagnosis, we used the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA)[11] including only patients classified as CDR 1. Exclusion criteria were history of other neurological or psychiatric diseases, head injury with loss of consciousness, use of sedative drugs in the last 24 hours before the neuropsychological assessment, drug or alcohol addiction and prior chronic exposure to neurotoxic substances. The control group consisted of subjects with CDR 0 without previous history of neurological or psychiatric disease, or memory complaints.

All individuals were submitted to the Rey auditory verbal learning test (RAVLT)[12] to evaluate episodic memory, which consists of fifteen words read aloud for five consecutive trials (List A), followed by a free-recall test. We considered immediate memory the mean of these five trials. After the fifth trial, a new interference list of fifteen words is presented (List B) followed by a free-recall test of that list. Soon afterwards, a free-recall of the first list is tested without representation. After a twenty-minute delay period,

subjects are again required to recall words from List A (delayed recall). Finally, the patient must identify List A words from a list of fifty words which includes Lists A and B and twenty other words phonemically or semantically related to lists A and B (recognition). They were also submitted to the forward (FDS) and backward digit span (BDS) subtest of WAIS-R[13] to evaluate working memory and attention, as well as to the Mini Mental State Examination (MMSE).[14]

MRI volumetry

MRI acquisition was performed on a 2-T scanner (Elscint Prestige®, Haifa, Israel), in three orthogonal planes, and a volumetric saggital T1 acquisition for multiplanar reconstruction. Hippocampal volumetric measurements were performed according to anatomic guidelines from a standard protocol[15] in T1-IR 3-mm coronal slices (flip angle=200°; TR=2800, TE=14, inversion time (TI)=840, matrix 130×256, FOV=16 cm×18 cm). We performed manual delineation of the entire extension of hippocampal formation using the NIH-Image program® (developed at the United States National Institutes of Health and available on the Internet at http://www.rsb.info.nih.gov/nih-image/).

Hippocampal volumes (HV) were corrected for the variation in total intracranial volume, and asymmetry indexes were determined for each subject as the ratio of the smaller to the larger hippocampus. Volumes were transformed into Z scores: number of standard deviations from the mean of control group. Z scores below –2.0 were indicative of atrophy. The investigators who interpreted MRIs and performed MRI volumetric measurements were blinded to patients' clinical and neuropsychological information.

Data analysis by means of Systat software used ANOVA and a post-hoc Tukey test for group comparisons of demographic, cognitive and volumetric scores. Multiple linear regressions were used to compare RAVLT scores with other relevant variables. Statistical significance considered was $p<0.05$.

Results

As shown in Table 1, there was no significant difference between the three groups concerning age [$F(3,39)=3.105$, $p=0.056$] and education [$F(3,39)=0.196$, $p=0.822$]. On RAVLT, there was a continuum between the three groups, with AD recalling less words, controls more, and aMCI sub-

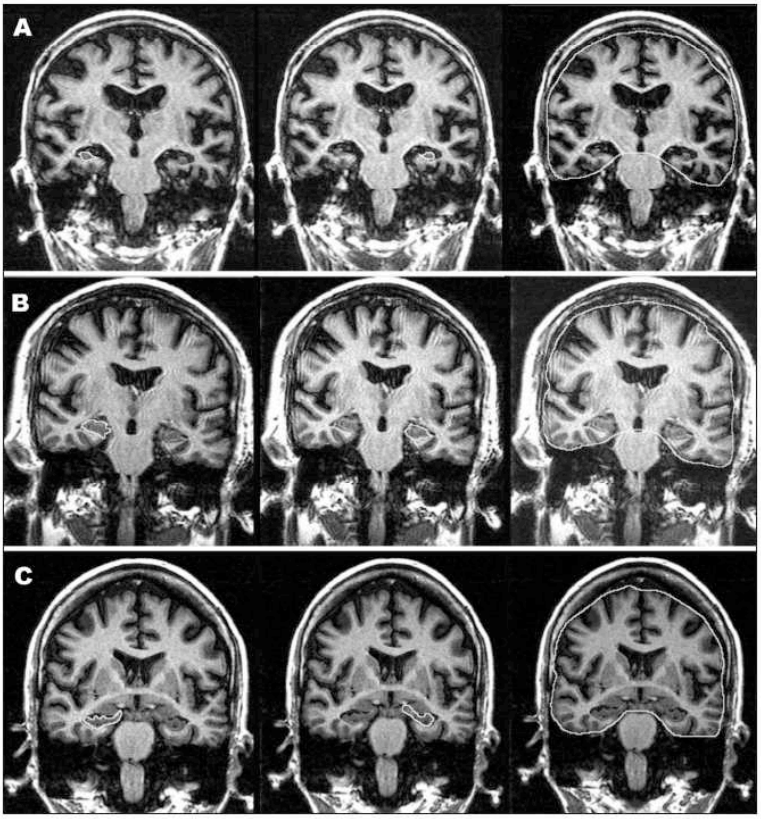

Figure 1. *Illustrative pictures of T1-IR coronal slice delineation of the entire extension of right and left hippocampal formation and intracranial volume. (A) Mild AD; (B) aMCI; (C) Normal controls.*

Table 1. Demographic and neuropsychological data.

	AD (mean±SD)	aMCI (mean±SD)	Controls (mean±SD)
Age	75.07±6.90	68.14±9.75	69.00±7.09
Education	6.14±5.71	6.43±4.54	7.21±3.56
MMSE	22.86±2.74[a***,b***]	26.93±2.59[b*]	29.07±0.73
Delayed recall RAVLT	1.36±1.28[a***,b***]	4.14±2.60[b**]	9.57±3.25
Recognition RAVLT (correct response - false positive)	–1.07±6.33[a***,b***]	4.36±4.55[b**]	11.86±1.88
Immediate memory	5.00±1.12[a***,b***]	7.01±1.41[b**]	9.86±1.33
FDS	4.50±1.09	4.50±0.76	4.93±0.73
BDS	3.21±0.80[b*]	3.14±1.03[b*]	4.14±1.10

[a]Significantly different to aMCIs; [b]Significantly different to controls; ***p<0.0001; **p<0.001; *p<0.05

Table 2. Hippocampal volume (mm^3).

	AD (mean±SD)	aMCI (mean±SD)	Controls (mean±SD)
Right hippocampus	2545.18±433.49[a***]	2720.05±291.94[a***]	3245.14±266.31
Left hippocampus	2406.07±410.89[a***]	2550.41±294.87[a***]	3058.03±217.93

[a]Significantly different to controls; ***p<0.0001

jects showing an intermediate performance in all subitems (immediate memory, delayed recall and recognition).

We found an asymmetry between HVs, with smaller mean left HV for all groups (Table 2). ANOVA and *post hoc* pairwise comparisons of hippocampal volumes using Tukey's test, showed a significant difference among groups, with difference between controls, AD and aMCI (ANOVA; p<0.00001), although there was no difference between AD and aMCI groups (Table 2).

Multiple regression analysis including hippocampal volumes from all subjects (AD, aMCI and controls) as independent variables and RAVLT, FDS, BDS and MMSE as dependent variables, showed a significant relationship between volumes and scores on RAVLT subitems and MMSE (p<0.00001). Pearson's correlation coefficients for left and right hippocampal volumes and each test are shown in Table 3.

Table 3. Pearson's correlation coefficients (r) for left and right hippocampal volumes and each test.

Test	Right HV	Left HV
MMSE	0.62	0.62
FDS	0.22	0.16
BDS	0.35	0.27
Delayed recall RAVLT	0.66	0.65
Recognition RAVLT	0.51	0.51

Discussion

Our results tended to confirm previous studies in which AD patients had a smaller HV compared to normal controls, while aMCI patients had intermediate atrophy (though not statistically significant in our sample). This finding is in accordance with neuropathological studies in which aMCI subjects showed an intermediate pattern of neurofibrillary changes of aging and pathologic features of very early AD, since they showed neurofibrillary tangles in the entorhinal cortex and hippocampal formation.[7,16] One possible reason for the fact that we did not find significant hippocampal volume differences between mild AD and aMCI HV is the clinical proximity between these two clinical entities and their close pathological relationship. Petersen et al showed that neuropathologists often characterized MCI cases as having prodromal or incipient AD, meaning that they did not fulfill the criteria for AD but were suggestive of being in transition (diffuse amyloid in the neocortex and frequent neurofibrillary tangles in medial temporal lobe structures).[7] In all groups, there was an asymmetry among left (more atrophic) and right hippocampus, a fact that is in disagreement with other studies, where a right-greater-than-left asymmetry is seen in normal controls, but is in accordance with other papers where MCI cases may present a reversal of this normal hippocampal asymmetry.[4,17,18]

We found a correlation between episodic memory and right and left HVs, confirming that quantitative assessment of medial temporal structures may serve as a surro-

gate marker of memory performance in normal ageing as well as in AD.[6,19,20] Measurement of other medial temporal structures such as amigdala, parahippocampal formation, entorhinal and perirhinal cortices, as well as regional hippocampal shape differences (head *versus* body, for example) may help further in differentiating mild cognitive impairment from initial stages of AD.[1,18,19,21] Some authors have shown that hippocampal and entorhinal cortex volumes can contribute to the prediction of MCI conversion to AD, although cognitive tests provide better accuracy.[22,23] Attention may have influenced delayed recall performance in the AD group, since there was significant correlation with the BDS.

In conclusion, our preliminary findings show that there is a significant HV difference between AD, aMCI and controls, but not between AD and MCI; the 3 groups showed more left than right hippocampal atrophy; and episodic memory correlated with left and right HV. Our study had some limitations including the small sample size and the fact that AD patients were older than MCI patients and controls where this approached statistical significance (p= 0.056). Further studies employing larger sample of patients and controls as well as measures of other medial temporal structures are needed to reach definitive conclusions.

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ARTIGO 6

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NEURAL CORRELATES OF LEXICAL-SEMANTIC MEMORY IN NORMAL AGING, AMCI AND MILD AD: A MRI-VBM STUDY

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Abstract

Neuroanatomical correlation of lexical-semantic memory is not fully understood. The most influential positions about semantic memory organization share the view that semantic representations reflect the manner in which information has been acquired through perception and action, and that each brain area processes different modalities of semantic representations. Despite these anatomical differences in semantic processing, generalization across different features that have similar semantic significance is one of the main characteristics of human cognition. We evaluated the brain regions related to the hierarchical semantic generalization of visually presented object drawings of the Boston Naming Test (BNT), which comprises different categories, such as animals, vegetables, tools, food, and furniture. In order to create a model of lesion method, we studied a sample of subjects that represent a continuous decrease both in cognitive functions, including naming skills, and in grey matter density (GMD) relatively to normal young people: normal aging, amnestic mild cognitive impairment (aMCI) and mild AD. We correlated their semantic errors in BNT, hierarchically organized in three levels (superordinate, coordinate and circumlocutory/subordinate errors) with the whole GMD as measured by voxel-based morphometry (VBM). The only areas that related to all semantic tasks were the medial temporal structures and thalami. Superior (STG) and inferior (ITG) temporal gyri, especially in their anterior parts, as well as prefrontal cortices (inferior and superior frontal gyri) were involved in more specific semantic errors subtypes. We discuss the possible role of each of these areas in the lexical-semantic networks, and their contribution to the models of semantic memory organization.

Key-words: semantic memory, voxel-based morphometry, Alzheimer's disease, mild cognitive impairment

Introduction

Language is one of the most important characteristics that allows us to codify, signify, and retain our experience of the world (Luria, 1986). Naming the many aspects of our environment is an essential attribute for the evolution of human complex adaptive ability and reveals the capacity to learn and share knowledge. Lexical-semantic memory refers to the storage of this knowledge in the brain by means of patterns of neuronal activity interpreted as linguistic symbols of concrete and abstract concepts. The relationship between brain anatomy and the storage of these patterns of information is not well understood. There are several hypotheses that have been proposed to explain how lexical-semantic memory is acquired, processed, and stored in the brain, and they have been guided by two main general models: a parallel distributed representation (McClelland and Rumelhart, 1985) comprising a homogeneous network of equivalent neuronal units that process every aspect of semantics, and a center processing model, which assumes that all memory elements are encoded in a delimited area of the brain. Neither of these models in its pure form explains satisfactorily the phenomena, and a combination of these two theories has been proposed (Martin, 2007). The most influential theories regarding semantic memory organization share the view that semantic representations reflect the manner in which information has been acquired through perception and action, in a way that the features which define an object are stored close to the primary sensory and motor areas that were active when information about that object was acquired (Martin, 2000; Gainotti, 2007; Patterson *et al*., 2007). This view is supported by many studies using electrophysiological methods, functional neuroimaging, and computational models (Farah *et al.*1991), although there remain controversies and unanswered questions as to how the acquired knowledge is stored and processed. Even the different neuroimaging approaches (functional and structural/lesion method) need a more homogeneous methodology, since these studies have frequently disagreed over the role of specific brain regions in semantic memory (Martin, 2007). Functional neuroimaging (PET, fMRI) makes a map of regional metabolic and perfusion changes that follow neural events elicited by cognitive tasks in an attempt to disclose what parts of the brain are related to specific mental operations. PET images depend on the regional distribution of radiotracers, while fMRI is based on the blood-oxygenation-

level dependent (BOLD) contrast produced by minute regional changes of oxyhemoglobin/deoxyhemoglobin levels that influence the magnetic signal. Both techniques allow visualization of levels of brain activity in normal subjects and focal involvement during different conditions (Huettel *et al.*, 2004).

Lesion models, on the contrary, which are based on a detailed syndrome analysis, are used to attempt to determine which basic mental operation is impaired by a circumscribed brain lesion. This approach has been extensively used in clinical neuropsychology and, according to the concept of the "complex functional system" (Luria, 1973) or "neurofunctional network" (Mesulam, 1990), every complex mental function or task is carried out by various basic operations (processes, components) organized in a dynamic assembly of interconnected brain regions, each region giving its specific contribution to the functioning of the system as a whole. A focal brain lesion disrupts a specific mental operation associated to that particular brain region, which commonly leads to disruption of all of the functional systems or tasks for which that particular operation is required (Luria, 1973).

Since Warrington (1975) proposed that semantic memory is categorically organized, showing that patients with specific brain lesions may have category-specific deficits (most commonly, difficulty in identifying living beings, but not tools), the majority of studies have investigated the possible implications of these dissociations in the cerebral organization of semantic memory. Functional neuroimaging studies, for example, have focused mainly on the evaluation of brain regions involved in specific categorical aspects of naming: animals, tools, nouns, verbs, imageability and concreteness of words, conceptual properties of action verbs, and so on (Binder *et al.,* 2005; Devlin *et al.*, 2002; Gainotti, 2007; Perani *et al*., 1995; Tyler *et al.,* 2001). These studies have solidified the notion that each brain area processes different modalities of semantic representations, but there is no consensus among researchers as to whether these dissociation approaches are robust enough to explain the whole body of functional and clinical data. One of the main characteristics of human cognition is the capacity to generalize across concepts that have similar semantic significance but not necessarily similar specific (physical or behavioral) attributes. The most striking evidence of deterioration of this generalizing capacity is semantic dementia (SD), in which there is a

degeneration of the anterior portions of the temporal lobes, more intense on the left side. These patients have difficulties in naming everyday objects and knowing their properties, with impairment of all kinds of concepts in the context of otherwise well-preserved cognition, including episodic memory. Other diseases associated with lesions in the anterior parts of temporal lobe show the same pattern of loss of knowledge, particularly in *Herpes simplex* virus encephalitis, stroke, and Alzheimer's disease (AD). In this sense, as proposed by other authors, the temporal lobe, particularly its anterior part, may represent a convergence zone for information coming from brain regions responsible for processing different aspects of knowledge (Hodges *et al*., 1995; Patterson *et al*., 2007). It has also been suggested that the temporal lobe object representation system may be organized hierarchically, with increasing convergence and integration of information occurring along its posterior to anterior axis (Martin *et al.,* 2001).

Our aim was to evaluate the brain regions related to the hierarchical semantic generalization of visually presented object drawings of the Boston Naming Test (BNT) (Kaplan *et al.*, 1983), which comprises different categories, such as animals, vegetables, tools, food, and furniture. In order to create a model of the lesion method, we studied a sample of subjects that experienced a continuous decrease both in cognitive functions, including naming skills, and in grey matter density (GMD) relative to normal young people: normal aging, amnestic mild cognitive impairment (aMCI), and mild AD. We correlated their semantic errors on the BNT, hierarchically organized in three levels (superordinate, coordinate, and circumlocutory/subordinate errors) with the whole GMD as measured by voxel-based morphometry (VBM). We also performed this correlation with BNT total score (correct responses). Naming complaints are very common in mentally healthy elderly people. Over the age of seventy, individuals achieve significantly lower scores on these naming tests than those achieved by young adults (Albert *et al*., 1988; LaBarge *et al*., 1986; Zec *et al*., 2005). Problems with naming and word finding are even more common in mild cognitive impairment (MCI) and are most common in Alzheimer's disease (AD) (Adlam *et al*., 2006; Dudas *et al*., 2005). MCI is a clinical entity applied to patients with objective cognitive problems, most commonly in episodic memory, without significant impairment of daily life activities. We assumed that our sample would constitute a continuum of cognitive decline and brain atrophy,

with aMCI being considered as an intermediate stage between normal aging and AD. Thus, this study may be regarded as counterproof of functional studies: instead of imaging normal young people as they think about the names of presented pictures, we evaluated the patterns of naming errors in this sample of subjects in correlation with their progressive, continuous brain atrophy.

Methods

We studied 48 subjects older than 50 years [17 with aMCI, 15 with mild AD treated at the Unit for Neuropsychology and Neurolinguistics (UNICAMP Clinic Hospital), and 16 controls]. Routine laboratory examinations for dementia assessment (including B12 and folate dosage, serology for syphilis, and thyroid hormone measurement) and brain computed tomography were carried out in all patients. The local ethics committee approved this research. Diagnosis of aMCI in our clinic is carried out by trained neurologists using a standardized mental status battery, which includes evaluation of episodic memory, orientation, language, attention, abstract thinking, calculation, and visual perception. The diagnostic process consists of a detailed interview with the patient and informant (usually a close relative of the patient). Diagnosis of MCI was made according to the criteria of the International Working Group on Mild Cognitive Impairment (Winblad *et al*., 2004): (i) the person is neither normal nor demented; (ii) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired. We made a diagnosis of aMCI if the clinical history and cognitive performance pointed to an exclusive memory deficit and Clinical Dementia Rating (CDR; Morris, 1993) score of 0.5, with an obligatory and exclusive memory score of 0.5. This classification was performed using a semi-structured interview.

For probable AD diagnosis, we used the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann *et al*., 1984), including

only patients classified as CDR 1. Exclusion criteria were history of other neurological or psychiatric diseases, head injury with loss of consciousness, use of sedative drugs in the last 24 hours before the neuropsychological assessment, drug or alcohol addiction, and prior chronic exposure to neurotoxic substances. The control group consisted of subjects with CDR 0 without previous history of neurological or psychiatric disease or memory complaints.

Assessment of naming ability

The sixty-item BNT (Kaplan, 1983; translated and culturally adapted version for the Brazilian population by Dr. Cândida Camargo – Psychiatry Institute, Medicine School, University of São Paulo), for which subjects were asked to name the presented pictures, was administered to all subjects. We determined the BNT total score by adding the number of correct spontaneous responses to the number of correct responses after a semantic cue, which consisted of a short explanation about the picture (for example, for *mask: it's part of a carnival fantasy)* or a superordinate category (for example, for *elephant: it's a kind of animal*). The semantic cue was only given if the patient had failed to recognize the picture (for example: *dog* instead of *tree)* or if he/she said that they did not know what the picture was.

We modified the classification system described by Lukatela *et al*.(1998) and divided the spontaneous errors into four mutually exclusive types: *omission* (when the subject was unable to name the picture), *visual paragnosia* (when the subject answered with an unrelated word which may or may not have shared any common characteristics with the target word), *phonologic* (when the prominent reason for naming was a similarity with another unrelated word, generally the first phonemes) and *semantic* (when the answer was semantically related to the target word). At first glance, this classification could lead to some problems, mainly when the subjects' answers contained more than one error, for example semantic and phonological (*<u>ta</u>tu* instead of *<u>ta</u>manduá* – Brazilian animals whose names start with the syllable *ta* and whose pictures share similarities). In cases like this, we considered the stronger semantic relationship between these animals and the error was classified as semantic.

Semantic errors were further classified into three mutually exclusive categories: *circumlocutory* (when responses described or indicated the function of the target word), *coordinate* (when responses were of the same basic category as the target word), and *superordinate* (responses that belonged to a broader category than that of the target word). Two independent researchers (MLFB, BPD) performed this classification, and the discordances were solved by consensus.

Additional neuropsychological evaluation

All subjects were submitted to tests of verbal fluency (VF) for the animals category (the score was the total number of different animal names given by the subject during one minute); Mini Mental Status Examination (MMSE; Folstein *et al*., 1975; Brazilian version by Brucki *et al*., 2003); Rey auditory verbal learning test (RAVLT; Rey, 1964) to evaluate episodic memory delayed recall (RAVLT-A7); and CAMCOG's subscale of similarities between pairs of nouns, in which the patients were asked "In what way are they alike?" for the following pairs: apple/banana, chair/table, shirt/dress, and animal/vegetable. The score was calculated as the number of correct responses (zero to two for each pair; maximum score eight) (Roth *et al*., 1988); visual perception subtests of Luria's Neuropsychological Investigation (LNI; maximum score twenty; Christensen, 1979); the forward (FDS) and backward digit span (BDS) subtest of WAIS-R (Wechsler, 1987); and the Cornell Scale for Depression in Dementia (CSDD; Alexopoulos *et al.*, 1988; Carthery-Goulart *et al.,* 2007). Data analysis was performed using Systat software 12.0. We performed Kruskall-Wallis and Mann-Whitney tests for inter-group comparisons of demographic and cognitive scores. In order to evaluate which cognitive problems might have possibly influenced omission wrong answers in the group, we carried out a multiple linear regression to compare spontaneous omission errors as a dependent variable to other tests as independent variables: lexical-semantic (Similarities and VF), visual perception (LNI subtests), attention (FDS and BDS), episodic memory (RAVLT-A7), and MMSE. Statistical significance was considered when $p < 0.05$.

MRI scanning protocol and imaging processing

High-resolution MRI was performed using a 2.0 T scanner (Elscint, Haifa, Israel). T1- and T2-weighted images were acquired in axial, coronal, and sagittal planes with thin cuts. In addition, volumetric (3D) T1 gradient echo (GRE) images were acquired in the sagittal plane with 1 mm thick slices (flip angle = 35°, time to repeat = 22 ms, echo time = 9 ms, matrix = 256 X 220, field of view = 23 X 25 cm). We used Analyze® format images that were generated from raw Dicom images using MRIcro software (http://www.sph.sc.edu/comd/rorden/mricro.html). The anterior commissure was selected for the normalization process. Using SPM2 software (Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk), we normalized, segmented, and smoothed all images (Friston *et al*., 1995). We also used the optimized VBM code described in previous studies to modulate the images (Good *et al.,* 2001). All images were spatially normalized using SPM2 built-in routines, in order to perform the comparisons between groups. This step reduces individual brain size variability by spatially normalizing each image to a template. Then, images underwent automatic segmentation of GM using SPM2 built-in routines, which estimate the probability that each voxel is GM. The images also underwent modulation, a technique that preserves the quantity of tissue that was deformed during the normalization process, and smoothing, in which segmented GM images were convolved with an Isotropic Gaussian Kernel of 10 mm to reduce interindividual gyral variation. For statistical analysis, we used Non-Parametric Mapping (NPM) software (http://www.sph.sc.edu/comd/rorden/npm), and the results of these comparisons are displayed as a statistical non-parametric map of the Brunner-Munzel test with the number of standard deviations compared to controls (z score). The statistical analysis for all comparisons was performed with grand mean scaling, proportional threshold masking (0.8), and implicit masking. The results were corrected for multiple comparisons using a false discovery rate (FDR) of 1% with an extended threshold looking for clusters with at least 32 contiguous voxels.

Voxel-based correlation analysis

We performed a multiple regression analysis using NPM software to identify brain regions whose GMD values were significantly correlated with the scores on the BNT and the pattern of naming errors: spontaneous (semantic errors, visual paragnosia, phonological errors and omission errors) and semantic subtypes (superordinate, coordinate, and circumlocutory). Age and education were also included in the analysis as dependent variables. The results of these comparisons are displayed as statistical maps with the number of standard deviations (z score) representing the strength of correlation. Because NPM only carries out positive correlations, we inverted the magnitude of our data by attributing a rating in which the subject who made the greatest number of errors scored zero and the other subjects who made fewer errors scored proportionally better. NPM is based on MNI templates. We converted MNI to Talairach coordinates using the GingerALE 1.1 software (http://www.brainmap.org/ale/index.html).

For multiple regression analysis, we considered the three groups together (normal aging, aMCI, and mild AD) for three main reasons. First, theoretically there is a continuum both in GMD and in the naming performance in the three groups, which could explain the correlation between brain regions and their psychological functions (that is, the denser the grey matter, the fewer the naming errors). In this sense, aMCI may be considered to be a prodromal stage of AD, which means that both conditions have the same pathological process in distinct phases. Second, we showed in a previous study with the same subjects (Balthazar *et al*., in press) that the three groups had the same pattern of spontaneous errors ($p = 0.503$ for omission errors, $p = 0.076$ for visual paragnosia, $p = 0.114$ for semantic errors) and of semantic subtypes of errors ($p = 0.62$ for circumlocutory, $p = 0.772$ for coordinate and $p = 0.968$ for superordinate), which means that, considering the qualitative pattern of errors, the three groups were not different. Third, our aim was not to study normal aging, aMCI, and AD *per se*, as separated clinical conditions, but to use this continuum of diseases as a lesion model to study lexical-semantic memory.

Results

As shown in Table 1, there was no significant difference among the three groups with regard to age ($p = 0.17$) or education ($p = 0.31$). There was a continuum in neuropsychological performance in all tests, except in backwards digit span. With regard to the BNT total score, AD patients performed worse than aMCI patients and controls ($p < 0.001$), while aMCI subjects performed worse than controls on BNT spontaneous answers (those without cues; $p < 0.05$). The absolute values of spontaneous errors are shown in Table 1, and the total number of semantic errors and subtypes are shown in Table 1 and Figure 1. We excluded phonological errors from the analysis because the three groups made a small number of this type of error. The only variables that contributed significantly to the spontaneous omission errors variance on multiple regression analysis ($R^2 = 0.515$) were Similarities ($t = - 2.66$, $p = 0.011$) and MMSE ($t = -3.09$, $p = 0.004$).

Regarding brain atrophy, we also found a continuum among the groups, as shown in Figure 2. In comparison to normal controls, the aMCI group showed atrophy bilaterally, mainly in the thalami (left: z score = 5.30; right: z = 5.63), parahippocampal gyri (right: z = 4.39; left: z = 4.12), and caudate nuclei (right: z = 4.15; left: z = 4.17). Significant GM atrophic areas were also found in the right hemisphere: anterior cingulate gyrus (z = 4.06) and superior (z = 4.50) and middle (z = 4.17) frontal gyrus. As compared to controls, AD subjects had a pattern of GM atrophy similar to that seen in aMCI, though more intense, in the bilateral thalami (right: z = 6.54; left: z = 5.35) and parahippocampal gyri (right: z = 4.95; left: z = 4.12). In the AD group, there was more significant atrophy in other medial temporal structures, including the bilateral hippocampi (right: z = 4.09; left: z = 3.95), amygdales (right: z = 4.15; left: z= 3.54), left insula (z = 4.10), and several other areas shown in Figure 2. In comparison to the aMCI group, the mild AD group showed significant GM atrophy in the bilateral superior frontal gyri (right: z = 3.12; left: z = 2.46), right inferior frontal gyrus (z = 2.18), left middle temporal gyrus (z = 2.60), right lingual gyrus (z = 2.35), and right cerebellar tonsil (z = 2.46).

Multiple regression analysis revealed significant correlations between GMD

and BNT score, mostly in the thalami: right lateral dorsal nucleus (z score = 3.22) and left medial dorsal nucleus (z = 3.11); hippocampi: right (z = 2.47) and left (z = 2.32); parahippocapal gyri: right (z = 2.30) and left (z = 2.28); left superior temporal gyrus (z = 2.62); left inferior frontal gyrus, Brodmann areas: 9 (z = 2.75), 46 (z = 2.33); bilateral superior frontal gyri: left (z = 3.06) and right (z = 2.76); left middle frontal gyrus (z = 2.17); and other areas shown in Figure 3. Areas of correlations with spontaneous errors are shown in Figure 4. Semantic errors (in red, violet and yellow) were related mainly to the bilateral anterior part of the temporal lobe: left (z = 3.03) and right (z = 2.89) superior temporal gyrus; left inferior temporal gyrus (z = 2.17); thalami: left (z = 3.01) and right (z = 2.85) dorsomedial nuclei; hippocampi: left (z = 2.29) and right (z = 2.12); and left caudate nucleus (z = 2.29). Intersections between semantic and omission errors (in yellow) were found in the right hippocampus, left inferior frontal gyrus, right superior frontal gyrus, left precuneus, and right superior and middle temporal gyrus. Other correlations with omission errors are shown in Figure 4 (in green). Visual paragnosia errors were related to the primary visual area, in left inferior occipital gyri (Brodmann areas 17 and 18), other than those shown in Figure 4 (in blue). Semantic error subtype correlations are detailed in Figure 5 and Tables 2 (superordinate), 3 (coordinate), and 4 (circumlocutory).

Discussion

Our results support the hypothesis of a continuum in brain pathology and cognitive decline among the three groups, particularly regarding their spontaneous answers as they named BNT pictures, which indicates that our lesion model could be satisfactorily tested. We found that several brain regions were negatively correlated with the errors on the BNT; that is, the more errors that were made, the lower the GMD in that particular area. The main areas of significant correlations between GMD and semantic tasks are shown in Table 5. The only areas that were related to all semantic tasks were the medial temporal structures and thalami (positive correlation with BNT total score and negative with semantic errors). The superior (STG) and inferior (ITG) temporal gyri, especially their anterior parts, as well as the prefrontal cortices (inferior and superior

frontal gyri) were associated with more specific semantic errors subtypes. We shall discuss the possible role of each of these areas in the lexical-semantic networks and their contribution to the models of semantic memory organization.

Medial temporal structures like the hippocampus and parahippocampal gyri have a well-known role in episodic memory processes. Recently, they have also been associated with semantic memory. In fact, episodic and semantic memories, as conceived by Tulving (1987), are highly interactive. It is well established that episodic memory for events encoded during semantic categorization is better remembered than when subjects do not associate the target event with a particular previously learned characteristic, which indicates a close relationship between semantic and episodic memories. Menon *et al*. (2002) suggested that semantic processing during episodic encoding might create a stronger or more elaborate memory trace. It is also possible that, through repetition and rehearsal, new information could be abstracted from its episodic context and represented as semantic memory, as proposed by Squire *et al*. (1993). In addition, Gabrieli *et al.* (1988) demonstrated that amnesic patients with lesions in the medial temporal lobes are impaired in the acquisition of new semantic memories. Our results concur with those of a recent VBM study in patients with early AD (Venneri *et al*, 2008), which also found strong GMD correlations with the medial temporal structures, mainly with the most anterior part of the parahippocampus and other parts of the perirhinal cortex. As proposed by these authors, the primary role of this region would be the combination of the different representations of a given object, as part of a process of multimodal synthesis spread over different cortical areas. Thus, lesion of these brain structures in early AD would isolate the hippocampus from the multisensory input of the neocortex, resulting in reduction of retrieval efficiency, rather than loss of representation.

The role of the thalamus in lexical-semantic memory is less understood than that of other significant areas demonstrated in our study. Recent electrophysiological and functional neuroimaging studies have established the involvement of the thalamus in the process of feature binding, which results in the recall of the object in semantic memory (Hart and Kraut, 2007). Slotnick *et al.* (2002) proposed that the thalamus could modulate the mechanism for semantic object recall via synchronizing electrical brain rhythms. They performed an experiment in a subject with depth electrodes implanted bilaterally in

the thalamic medial nuclei for electrical stimulation treatment of refractory epilepsy. Prior to the electrical stimulation, a word-word feature binding and a control association task were presented to the subject, while a scalp electroencephalogram (EEG) and event-related thalamic field potentials were recorded. In all trials of the feature binding task, there was a spatially widespread thalamocortical decrease in alpha band EEG power, which was followed by an increase in spatially more focal gamma band power in the thalamus and occipital scalp electrodes for only those trials that resulted in semantic object recall. The early reduction in low-frequency EEG power probably reflects a process of cortical disinhibition and preparedness for the subsequent phase of high-frequency (gamma) rhythm, which may mediate feature binding via synchronization of neural regions that represent different features of the object to be recalled (Slotnick *et al*., 2002)

Unfortunately, the Slotnick *et al*. (2002) study could not establish the role played by brain regions other than the thalamus and occipital cortex in feature binding, since scalp electrodes did not cover most of the head. For this reason, the same group of authors (Kraut *et al*., 2003) studied the same word-word feature-binding task using event-related fMRI. With this technique, they found two distinct loci of thalamic signal change (one anterior in the dorsomedial nucleus, and the other posterior in the pulvinar) and two different time courses of signal changes in each of the following regions of interest: Brodmann area 6 (BA 6), ventral temporo-occipital region, primary visual cortex, dorsomedial nucleus, and pulvinar nucleus. The BA 6 waveform was the earliest to raise, peak, and return to baseline, while that of the pulvinar region was the latest to do so. Based on these findings and previous electrophysiological studies, the authors proposed a neural mechanism in which the dorsomedial nucleus would be involved in the early search or object generation in conjunction with BA 6 or could activate other prefrontal regions specifically involved in task-related working memory or language functions. The pulvinar would be engaged later, in the process of feature binding, by acting as a mediator or modulator of the selective gamma rhythm, which would subserve the fusing of features in the instance of object recall (Kraut *et al*., 2003). In our study, the thalamus was one of the regions most effectively correlated with all types of semantic errors. Our findings support the idea that the thalamus is directly involved in semantic

memory activities, possibly with an integrative role, since its nuclei were correlated with BNT total score and with all kinds of semantic errors subtypes, predominantly the pulvinar with superordinate errors and the dorsomedial nucleus with coordinate and circumlocutory errors.

The involvement of neocortical temporal regions in semantic memory is better understood and has been extensively demonstrated (Damasio *et al.*, 1996; Gorno-Tempini *et al*., 1998; Damasio *et al*., 2004; Grossman *et al*., 2004). Grossman et al. (2004) studied VBM and confrontation naming in AD, frontotemporal dementia, and corticobasal degeneration, and left lateral temporal atrophy was a common source of impaired naming across these patient groups. Another VBM study of semantic dementia (Mummery *et al*., 2000) showed that ATL activation peaks aligned closely with areas of strongest grey matter reduction, mostly with atrophy of the left anterior temporal lobe. We found correlations especially in the anterior parts of the STG, bilaterally but stronger on the left side, and in the anterior parts of the ITG, here in a weaker and less spread outline than in the STG. Our findings support the idea that the anterior temporal lobe (ATL), predominantly its superior part, is robustly related to higher-order semantic generalization, since the subjects were asked to name pictures of different categories and there was a close relationship between coordinate and circumlocutory errors, regardless of their specific categories. In this sense, our results are in agreement with the "distributed-plus-hub" view, which considers the ATL as an amodal "hub" dedicated to encoding the similarity relations among various concepts in all modalities and for all semantic categories, in a way that semantically related items (e.g., different kinds of birds) are encoded with similar patterns across a common set of ATL neurons and synapses, regardless of the task (Patterson *et al*., 2007). This view may be mechanistically explained by the parallel distributed processing approach, in which the input-output units would have a correspondence in different parts of the brain which processes different types of information. Also, PDP approach calls for a set of shared representation units that tie together all of an object's properties across different information types (Rogers et *al*, 2004). In our study, we also found that the STG and ITG were related to all subtypes of errors, except for the superordinate subtype. This could mean that the anterior portions of the temporal lobe may be involved in retrieval of more

unique aspects of objects (basic and subordinate levels), independent of their categories, as shown by others (Damasio *et al*., 1996). In Grabowski *et al*.'s (2001) study, the specificity of word retrieval was verified in a PET experiment by asking normal subjects to name at unique level entities from two conceptual categories: famous faces and famous landmarks presented as photographs. They found increased activity in the left temporal pole as the subjects retrieved names of unique entities in both categories. Our results also support to some extent Martin and Chao's (2001) hypothesis that the temporal lobe object representation system may be organized hierarchically, with increasing convergence and integration of information occurring along its posterior to anterior axis, since we did not find correlations between superordinate errors and more posterior regions of the temporal lobe.

The prefrontal cortex is also related to the semantic system, often in an asymmetrical way, with the left more involved than the right side. The left inferior prefrontal cortex (LIPFC) has been considered as a "semantic working memory system" responsible for retrieving, maintaining, monitoring, and manipulating semantic representations stored elsewhere (Martin and Chao, 2001), as put in evidence by functional neuroimaging, transcranial magnetic stimulation, and lesion studies (Gabrieli *et al*., 1998; Devlin *et al.*, 2003; Thompson-Schill *et al*., 1998). In functional imaging studies, the LIPFC is more active when subjects make semantic judgments regarding words than when they make non-semantic judgments for the same words (Gabrieli *et al.,* 1998), and even when they make semantic judgments for line drawings (Vandenberghe *et al.*, 1996). The role of the LIPFC is crucial when the semantic tasks require cognitive control of semantic or lexical retrieval, particularly during selection among competing alternatives (Thompson-Schill *et al*., 1997). As compared to the bottom-up, automatic retrieval, the top-down, controlled retrieval can facilitate activation of weakly associated, task-relevant information even in the presence of more strongly associated but task-irrelevant information, and can even inhibit the retrieval of this preponderant, task-irrelevant information (Bunge *et al.*, 2005). Thompson-Schill et al.'s (1997) study suggests that the LIPFC does not support retrieval of semantic knowledge *per se*. Rather, this retrieval is done entirely by the posterior neocortex based upon cues presented through bottom-up processes, and the specific role of the LIPFC would be to select those

retrieved representations that are task-relevant from among competing, irrelevant representations.

Our results have confirmed the contribution of prefrontal cortices, mainly the left inferior frontal gyrus. This area was related to all semantic tasks, though not to the spontaneous semantic errors. The superior frontal gyrus was more related to superordinate errors bilaterally, particularly on the left side. The inverse relation between prefrontal cortex density and the number of superordinate errors might be interpreted as a characteristic function of that area in retrieving lexical and semantic information. Patients with left prefrontal lesions often have difficulty retrieving words in response to specific cues (e.g. words beginning with a specific letter or names of objects belonging to a specific semantic category), even when there is no aphasia (Baldo *et al.*, 1998). In such cases, making a superordinate error (for example, naming "animal" instead of the target word "dog") might indicate difficulty in selecting the appropriate phonological response to answer a particular semantic question. In fact, activation of the LIPFC has been elicited by phonological tasks such as discrimination of visually and auditorily presented words (Fiez *et al*., 1995) with the greatest activation more posteriorly, near Broca's area (Gabrieli *et al*., 1998). These and other studies (Poldrack *et al*., 1999) even suggested a domain-specificity of the anterior LIPFC (BA 45/47) for controlled semantics and of the posterior LIPFC (BA 44/6) for controlled phonology. However, more recent studies (Gold *et al*., 2005; Snyder *et al.,* 2007) have argued against domain-specificity and for domain-preferentiality in LIPFC. Thus, it may be hypothesized that the LIPFC is activated to the extent that lexical and semantic information must be rehearsed, temporarily stored, and selected in working memory to perform a particular task.

Additionally, we also found a significant correlation of superordinate errors with the left inferior frontal gyrus (BA 44, $z = 2.02$) and right anterior cerebellum ($z = 3.79$). This finding is in accordance with the idea that left-prefrontal and right-cerebellar regions are components of an interactive network, as indicated by clinical reports of crossed cerebellar diaschisis (Boni *et al.*, 1992;Liu *et al.,*2007; Miura *et al.,*1994) and by observations of left prefrontal and right cerebellar activation elicited by lexical and semantic tasks (Gabrieli *et al.*, 1998). Unlike these authors, we also found correlations,

especially of coordinate and circumlocutory errors, with the right inferior frontal gyrus.

In a previous study with the same sample of patients (Balthazar *et al*. 2008, *in press*), we verified that they named BNT pictures correctly after a phonemic cue, even if they had spontaneously made a semantic error. We interpreted this finding as indicating that their semantic fields tended to be at least partly intact and that making a circumlocutory error implies that the subject preserves some degree of specific attributes of the presented picture but fails in the retrieval at the specific level. In the same way, making a semantic-coordinate error on spontaneous naming might imply semantic integrity at this and higher levels and possibly a disruption at a more basic level. Therefore, our hierarchical classification of semantic errors (superordinate, coordinate, and circumlocutory) indicates a gradually increasing difficulty in retrieval of the expected phonological response, from the subordinate to the superordinate level of organization, rather than directly assessing loss of knowledge. Based on the PDP approach proposed by Rogers *et al.* (2004), it might be possible that these phonemic cues were enough to activate another verbal units in the neural networks responsible for processing semantic information. This event could change the network state, by summing the activation of the visual units to the new phonological information, what would be compatible to the improvement in the answers of AD patients. We suggest that these neural networks are disrupted in AD patients, and their anatomical correlates might correspond to the areas related to spontaneous naming errors, as we showed in anterior temporal lobe or left prefrontal cortex.

Our study has some limitations: the small sample size and the presence, in rare cases, of some imprecision in the points of maximal correlation between GM and neuropsychological data, with clusters of voxels that did not correspond to any specific GM area in the Talairach atlas. This fact might be due to approximation in the conversion from MNI to Talairach coordinates. In these cases, we considered the coordinates of the nearest GM area (± 5 mm) as the maximal significance point. Notwithstanding the limitations of this study, we found evidence that several brain areas are related to the process of higher-order semantic generalization, mainly the thalamus, medial temporal lobe, prefrontal cortex (left more than right), and bilateral anterior temporal lobes (mostly STG and ITG).

In conclusion, we propose an integrative model of semantic memory, in which the *rationale* is based on connectionist parallel distributed processing of semantic information, acquired during reciprocal interaction between the organism and the environment, throughout perception and action activities. Our findings suggest that the structures that were related to all semantic tasks (thalamus and medial temporal structures) might play a mediator role: the thalamus may act as a synchronizer of brain rhythms needed for co-activation of different brain regions, as proposed by Kraut *et al.* (2003), and medial temporal structures like the hippocampus and parahippocampal gyrus might be responsible for the combination of the different representations of a given object, playing an essential role to achieve retrieval of particular mental content. The ATL could be interpreted as an amodal hub, as suggested by Patterson *et al*. (2007), which is essential to achieve the unique aspects that ultimately define the target word; the left prefrontal cortex would act to select the most relevant semantic aspect in a given circumstance and maybe convert that semantic representation to its phonological form: the most appropriate word to be said in that specific context.

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Table 1. Demographic and neuropsychological data

	AD	aMCI	Controls	p
Age	74.26 ± 6.33	68.29 ± 9.93	69.12 ± 7.55	0.170
Education	6.00 ± 5.52	5.88 ± 4.32	6.87 ± 3.66	0.315
MMSE	22.93 ± 2.65	26.41 ± 2.76	29.12 ± 0.71	< 0.0001
BNT- total score (spontaneous + cued correct answers)	39.33 ± 9.98	50.82 ± 7.66	53.75 ± 4.18	< 0.0001
BNT- spontaneous answers	34.87 ± 9.7	48.25 ± 9.13	51.62 ± 5.87	< 0.05
Omission errors	6.43 ± 5.39	2.50 ± 2.65	1.62 ± 2.50	0.006
Visual paragnosia	7.87 ± 3.72	4.18 ± 4.73	2.00 ± 2.19	< 0.0001
Semantic errors	10.31± 4.06	4.81 ± 3.16	4.43 ± 2.44	< 0.0001
Superordinate errors	3.31 ± 2.65	1.53 ± 1.45	1.50 ± 1.26	0.037
Coordinate errors	4.25 ± 1.84	2.06 ± 1.94	1.87 ± 1.31	0.001
Circumlocutory errors	2.81 ± 1.27	1.31 ± 1.01	1.06 ± 0.92	< 0.0001
A7-RAVLT	1.26 ± 1.28	4.17 ± 2.40	9.56 ± 3.03	< 0.0001
VF	10.60 ± 3.39	13.64 ± 3.92	19.43 ± 3.03	< 0.0001
VSP-LNI	17.20 ± 1.42	18.76 ± 0.97	18.81 ± 0.98	0.002
fDS	4.46 ± 1.06	4.58 ± 0.79	5.06 ± 0.85	0.108
bDS	3.20 ± 0.77	3.11 ± 0.92	4.12 ± 1.02	0.004

Data presented as means ± SD. MMSE: mini-mental status examination; A7- RAVLT: delayed recall of Rey auditory verbal learning test; BNT: Boston naming test; VF: verbal fluency; VSP-LNI: visuospatial perception item of Luria's neuropsychological investigation; fDS: forward digit span; bDS: backward digit span.

Table 2: Brain areas of statistically significant correlation with Superordinate errors

Region	Number of voxels in cluster	Talairach Coordinates			Z score
Right anterior cerebellum	58	7	-42	-9	3.79
Left Parahippocampal gyrus	97	-28	-40	-5	2.82
Left Thalamus, pulvinar	84	-13	-30	11	2.59
Right Thalamus, pulvinar	87	9	-28	9	2.35
Left Thalamus, ventral anterior nucleus	99	-12	-7	13	2.17
Left Thalamus, lateral dorsal nucleus	95	-10	-17	17	2.09
Left Inferior Frontal Gyrus (BA 44)	73	-50	5	19	2.02
Left Superior Frontal Gyrus (BA 9)	84	-1	55	25	2.07
Right Precuneus (BA 19)	81	10	-78	40	2.19
Left Precuneus	96	-17	83	40	2.00
Left Superior Frontal Gyrus (BA 8)	77	-17	36	51	3.05
Right Superior Frontal Gyrus (BA 6)	79	17	26	58	2.66
Right Inferior Parietal Lobule (BA 40)	83	47	-40	50	2.90
Right Middle Frontal Gyrus (BA 6)	91	29	13	54	2.20

BA: Brodmann area

Table 3: Brain areas of most statistically significant correlation with Coordinate errors

Region	Number of voxels in cluster	Talairach Coordinates			Z score
Left Superior Temporal Gyrus (BA 38)	100	-29	6	-28	4.32
Right Superior Temporal Gyrus (BA 38)	88	38	10	-28	3.45
Right Middle Temporal Gyrus (BA 21)	109	44	3	-34	3.48
Left Middle Temporal Gyrus (BA 21)	72	-48	1	-21	2.90
Left Inferior Temporal Gyrus (BA 20)	119	-49	-4	-37	2.21
Right Inferior Temporal Gyrus (BA 20)	83	45	-12	-37	3.16
Left Hippocampus	79	-29	-15	-18	2.35
Right Hippocampus	80	34	-12	-20	2.11
Left Uncus	54	-21	-7	-37	3.00
Right Uncus	78	20	1	-20	2.11
Left Amygdala	82	-18	-3	-13	2.21
Left Globus pallidus	103	-21	-3	-6	2.67
Left Mammillary Body	99	-4	-13	-6	2.11
Right Anterior Cingulate (BA 25)	51	1	10	-3	2.33
Left Thalamus, Medial Dorsal Nucleus	55	-1	19	10	2.70
Right Thalamus, Medial Dorsal Nucleus	87	3	-20	6	2.39
Left Thalamus, Lateral Dorsal Nucleus	95	-11	-19	14	2.44
Right Thalamus, Lateral Dorsal Nucleus	95	11	-19	14	2.09
Right Caudate nucleus	84	9	17	1	2.40
Left Caudate nucleus	86	-6	4	1	2.36
Left Putamen	104	-23	-2	1	2.81
Left Inferior Frontal Gyrus (BA 44)	91	-51	9	20	2.16
Right Inferior Frontal Gyrus (BA 44)	83	52	4	20	2.12
Left Precuneus (BA 7)	101	-3	-76	44	2.73
Left Superior Parietal Lobule (BA 7)	95	-29	-58	44	3.11

BA: Brodmann area

Table 4: Brain areas of statistically significant correlation with Circumlocutory errors

Region	Number of voxels in cluster	Talairach Coordinates			Z score
Left Uncus (BA 28)	60	-21	6	-25	2.68
Right Uncus (BA 28)	80	21	6	-35	3.24
Left Hippocampus	80	-35	-19	-36	2.52
Left Amygdala	75	-17	-3	-16	2.87
Right Amygdala	81	17	-3	-16	2.33
Left Inferior Temporal Gyrus (BA 20)	61	-45	-36	-16	2.46
Right Parahippocampal gyrus (BA 28)	60	16	-3	-13	2.48
Left Parahippocampal gyrus (BA 28)	79	-16	-3	-13	2.37
Right Superior Temporal Gyrus (BA 38)	77	43	5	-17	2.26
L Superior Temporal Gyrus (BA 38)	81	-46	-3	-2	2.64
L Thalamus, Medial Dorsal Nucleus	92	-3	-15	6	3.02
Right Thalamus, Medial Dorsal Nucleus	92	6	-12	6	2.55
Right Anterior Cingulate Gyrus (BA 25)	47	1	13	-4	2.45
L Anterior Cingulate Gyrus (BA 25)	82	-2	13	-4	2.58
Right Insula (BA 13)	81	46	9	-4	2.49
L Inferior Frontal Gyrus (BA 9)	86	-49	5	26	3.22
L Inferior Frontal Gyrus (BA 44)	112	-49	13	19	2.14
Right Inferior Frontal Gyrus (BA 44)	90	53	9	22	2.16
L Superior Parietal Lobule (BA 7)	108	-30	-60	-43	2.88
Right Inferior Parietal Lobule (BA 39)	107	34	-62	42	2.34

BA: Brodmann area

Table 5. Main areas of significant correlations between GMD and Semantic tasks

Brain areas	BNT and Semantic errors subtypes				
	BNT total score	Semantic errors	Superordinate	Coordinate	Circumlocutory
Thalamus	R > L	L > R	L > R	L > R	L > R
Hippocampus	R > L	L > R	X	L > R	L
Superior Temporal gyri	L	L > R	X	L > R	L > R
Inferior Frontal gyri	L	X	L	L > R	L = R
Parahippocampal gyri	R = L	X	L	X	R > L
Superior Frontal gyri	L > R	X	L > R	X	X
Anterior Cingulate	X	X	X	L > R	L > R
Inferior Temporal gyri	X	L	X	R > L	L
Uncus	X	X	X	L > R	R > L
Amigdalae	X	X	X	L	L > R
Precuneus	X	X	R > L	L	X

R: correlation in the right side. L: correlation in the left side. R > L: bilateral correlation, higher in the right side. L > R: bilateral correlation, higher in the left side. X: no correlation

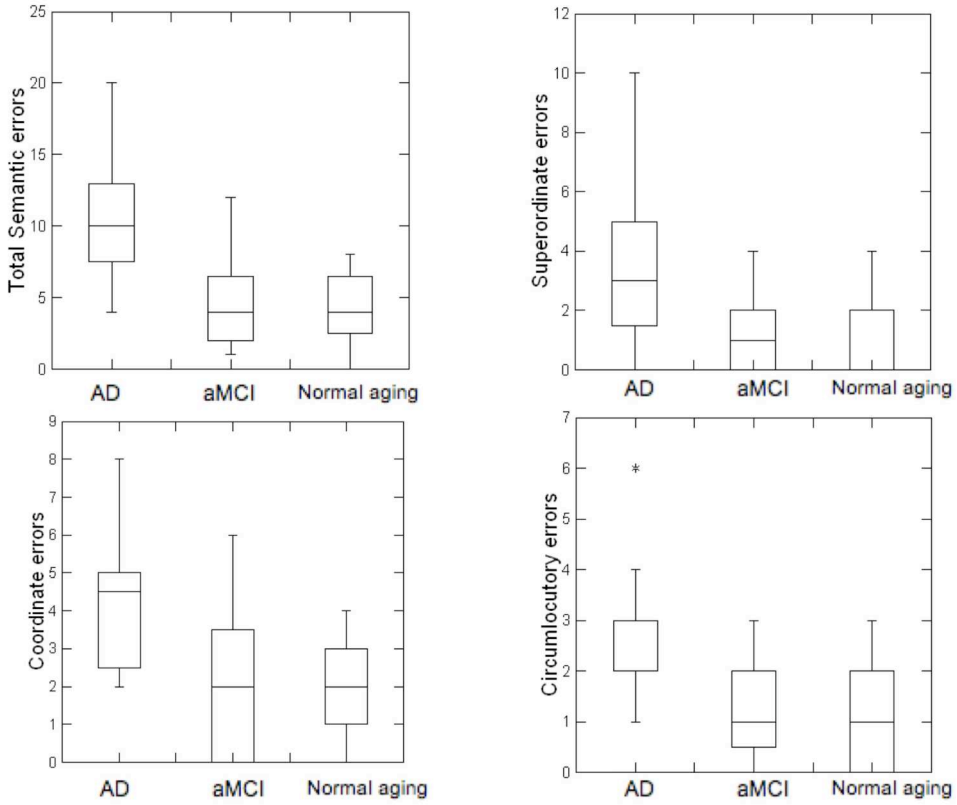

Figure 1. Box-and-whiskers plot showing total semantic and semantic subtypes errors (superordinate, coordinate and circumlocutory) in the different groups (mild AD, aMCI and normal aging). The box extends from the 25th percentile to the 75th percentile, with a horizontal line at the median. Whiskers extend down to the smallest value and up to the largest.

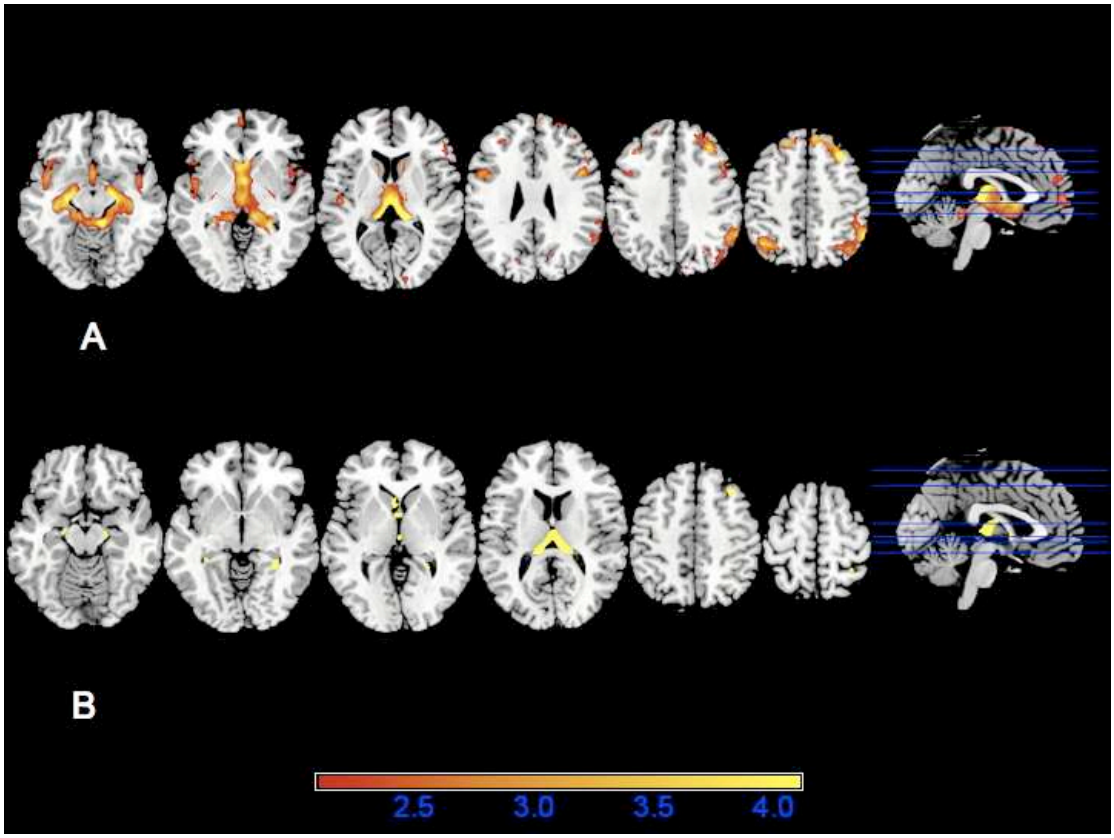

Figure 2. Patterns of grey matter atrophy in relation to controls in: A. mild AD; B. aMCI. The colorbar indicates the number of standard deviations compared to controls (z score). The level of significance selected was $p < 0.05$ corrected for multiple comparisons (false discovery rate). All slices are in neurological orientation (left on the left side).

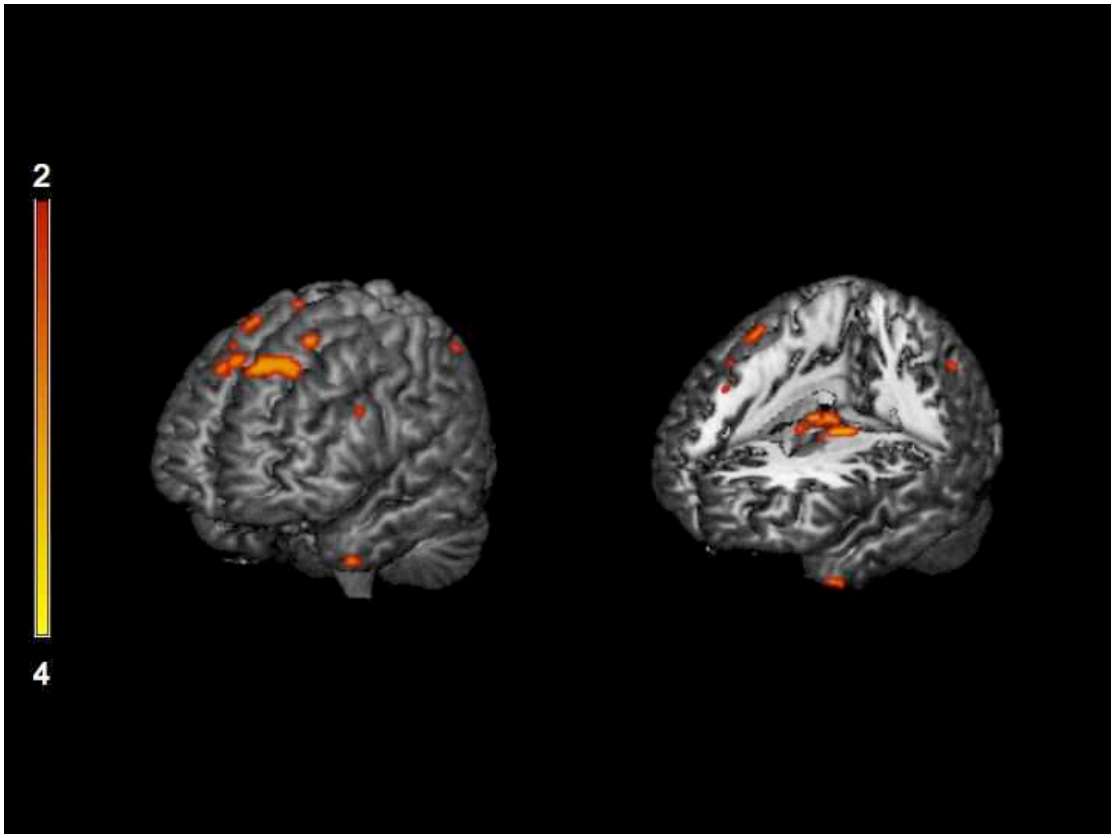

Figure 3. Areas of significant correlations with BNT total score, mainly on left superior frontal girus, left inferior frontal gyrus, left anterior temporal pole and bilateral thalami ($p < 0.05$).

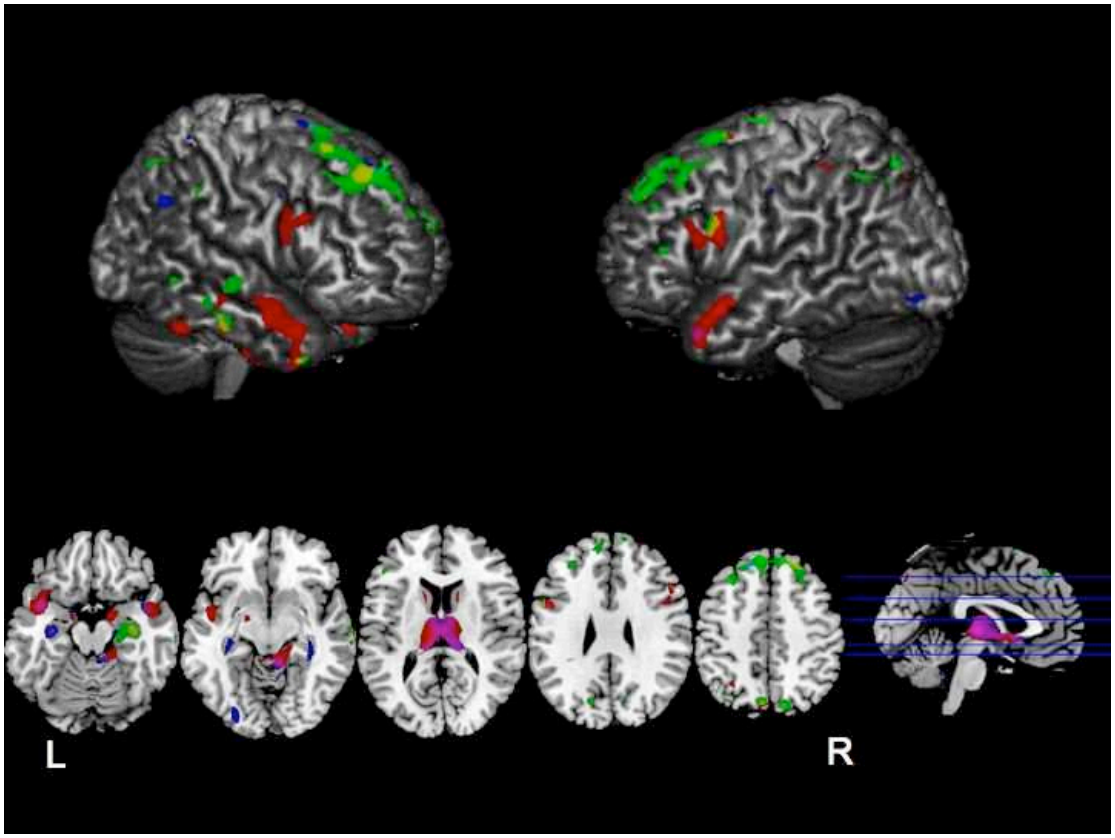

Figure 4. Areas of significant correlations with spontaneous errors on BNT. Red: semantic errors; Green: omission errors; Blue: Visual paragnosia; Violet: intersection between semantic errors and visual paragnosia; Yellow: intersection between semantic and omission errors ($2 < z$ score < 4; $p < 0.05$). All slices are in neurological orientation (left on the left side).

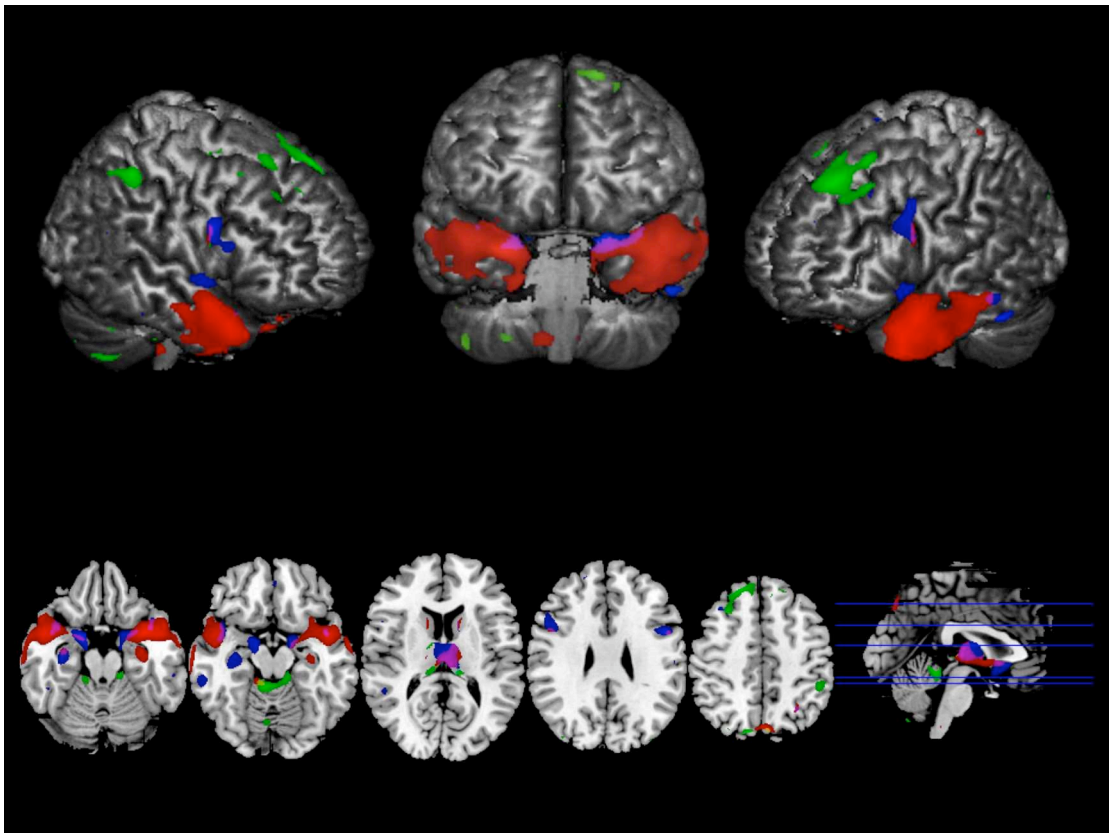

Figure 5. Areas of significant correlation with Semantic errors. Red: coordinate errors; Green: superordinate errors; Blue: circumlocutory errors. Violet: intersection between coordinate and circumlocutory errors ($2 < z$ score < 4; $p < 0.05$). All slices are in neurological orientation (left on the left side).

5- DISCUSSÃO e CONCLUSÕES

Nossos trabalhos avaliaram diferentes aspectos da memória léxico- semântica no CCLa, DA e envelhecimento normal. Discutiremos um modelo baseado tanto em nossos achados, como na literatura pertinente, que integre os diferentes achados neuropsicológicos, anatômicos, neurofisiológicos e moleculares envolvidos no processamento e na alteração da informação semântica.

Como discutido na introdução, DA é uma doença heterogênea, com vários possíveis fatores causais, sendo que um dos principais achados precoces é alteração na função e densidade sinápticas, deposição de PN e ENF, seguidos por atrofia cerebral. Ou seja, há alteração funcional precoce tanto na comunicação entre as redes de neurônios secundárias à degradação sináptica, quanto por perda neuronal direta.

Essas alterações em nível molecular levam a uma desorganização gradual e progressiva de parte das redes neurofuncionais responsáveis pelo processamento da informação cognitiva, o que origina alterações clínicas como as estudadas nessa Tese: dificuldade de nomeação e perda conceitual.

No **artigo 1**, mostramos que os pacientes com DA apresentaram desempenho inferior aos controles em todos os testes léxico-semânticos: nomeação, categorização/julgamento de similaridades e fluência verbal para categoria animais, o que sugeriu que há comprometimento direto dessa função psicológica nesses pacientes. Porém, numa avaliação mais detalhada do desempenho dos pacientes com DA no TNB (a**rtigo 3**), mostramos que, embora eles cometam mais erros espontâneos de nomeação se comparados aos outros grupos, não há diferença no seu desempenho quando fornecemos uma pista fonêmica correspondente à primeira sílaba da palavra-alvo. Concluímos com esse achado que não há necessariamente perda do conceito correspondente à figura mostrada, mas sim, predomina a dificuldade em acessar a informação semântica que produziu a resposta correta após a pista fonêmica. Mostramos também que os pacientes com DA e CCLa, assim como os idosos normais, tiveram o mesmo padrão tanto de erros espontâneos (semânticos, paragnosia visual, omissão e fonológicos) quanto de hierarquia semântica (coordenado, superordenado e circunlóquio). Observamos ainda que o desempenho no TNB foi influenciado pelo teste de Similaridades tanto nos pacientes com CCLa como nos controles, o que sugeriu que a integridade do campo semântico influenciou no teste de nomeação de figuras.

Esses achados parecem, à primeira vista, contraditórios: por um lado, os pacientes com DA parecem ter o campo semântico preservado, pois acertam após a pista fonêmica; por outro lado, têm desempenho abaixo do normal nos outros testes léxico-semânticos, o que sugere degradação conceitual. Os problemas atencionais, que poderiam justificar os erros nos testes semânticos, não foram os maiores responsáveis pelo desempenho dos pacientes com DA, visto que: 1) não houve diferença estatística, por exemplo, no teste de extensão de dígitos ("digit span", ordem direta) entre os três grupos e 2) não houve correlação estatística entre os testes de extensão de dígitos (em ordem direta e inversa) com os testes léxico-semânticos.

Assim, os pacientes com DA parecem apresentar um padrão misto de comprometimento e preservação do campo semântico. Alguns autores encontraram um padrão semelhante. Moreaud et al. (2001), por exemplo, propuseram que a perda semântica para alguns itens pode coexistir com dificuldade de acesso lexical a outros itens. Butterworth et al. (1984) propuseram que um déficit semântico, com ativação incompleta do conhecimento semântico pode produzir tanto um erro semântico quanto uma resposta correta (se a informação disponível for suficiente para evocar a resposta fonológica adequada). Propusemos que essa preservação relativa pode se dever à fase inicial da doença em nossos pacientes.

Nesse artigo, encontramos também uma inesperada semelhança no padrão qualitativo dos erros semânticos de nomeação: tanto DA, quanto CCLa e idosos normais cometeram mais erros coordenados, seguidos por erros superordenados e, por último, circunlóquios. Sugerimos que, no decorrer do *continuum* patológico entre os três grupos, há uma crescente produção quantitativa dos erros, porém, até a fase leve da DA, o dano não é suficiente para produzir erros qualitativos mais genéricos como os erros superordenados. Possivelmente, isso ocorre em fases mais avançadas da doença onde, talvez, haja predominância da informação mais genérica em detrimento da informação mais específica dos objetos.

Essa análise do processo mental levou-nos ao questionamento sobre a organização estrutural da memória léxico-semântica e como a doença ocasiona sua degradação. Em busca dessa resposta, duas teorias destacaram-se: a Hipótese do Ganho/Declínio (Milberg et al., 1999) e o Processamento Distribuído em Paralelo, uma

teoria conexionista aperfeiçoada por Rogers e McClelland (2004a).

A Hipótese do Ganho/Declínio baseia-se na premissa de que a primeira e mais importante alteração cognitiva na DA se deve à disfunção sináptica. Assume que o sistema de memória semântica se comporta como uma rede de representações associadas à propagação de ativação dos impulsos elétricos a partir das sinapses e, alterações nessa dinâmica da propagação podem levar a dificuldade de acesso à informação semântica. Na DA, ocorreriam mudanças como a redução da constante do tempo de ativação. Estas mudanças alterariam a disponibilidade das representações semânticas, as tornando mais ou menos disponíveis que o normal. Assim, a redução sináptica precoce associada à diminuição no número de axônios e dendritos teria o efeito de reduzir a resistência e capacitância da membrana dendrítica. Esse fenômeno reduziria as constantes de tempo dos potenciais pós-sinápticos excitatórios e inibitórios que chegam aos corpos celulares, o que causaria um aumento do padrão de ganho e declínio de ativação dentro da rede neural (Milberg et al., 1999). O principal mérito dessa teoria é explicar os efeitos de "*hyperpriming*" nos pacientes com DA, mostrado por vários autores (Chertkow et al. 1994; Giffard et al., 2001), ou seja, o fato de eles terem desempenho melhor que os controles em alguns testes de *priming* semântico, notadamente de decisão lexical. A teoria prediz que no tempo típico em que o *priming* semântico pode ser observado (50 a 2000 ms), os pacientes com DA mostrarão inicialmente um aumento acima do normal do padrão de ativação (correspondente ao "*hyperpriming*"), seguido por uma posterior queda para abaixo do limiar de normalidade (Milberg et al., 1999). Isso ocorre nos testes em que as respostas podem ser dadas de forma rápida (com baixa assincronia do início de estímulo), e prediz que as relações em que haja forte associação de palavras (gato-cachorro, por exemplo) fiquem inicialmente ainda mais fortes, e aquelas em que haja fraca associação, fiquem ainda mais fracas na DA. A aplicação dessa teoria em nosso estudo pode ajudar, em parte, a compreender o porquê de os pacientes com DA apresentarem desempenho normal após a pista fonêmica ou, ao contrário, cometerem erros quando a relação entre categoria semântica com seu fonema é mais forte do que a relação entre a figura apresentada e o fonema inicial correspondente. Por exemplo, ao ser mostrada a figura de um tamanduá para os pacientes com DA, seguida pela pista semântica "animal brasileiro" e pela pista fonêmica "- é um *ta*...", a resposta

invariavelmente foi “tatu”, um animal cujo nome é mais amplamente conhecido da população.

Apesar desse mérito, a teoria do Ganho/Declínio baseia-se quase exclusivamente na hipótese de perda de densidade sináptica na DA e leva pouco em consideração a atrofia cerebral, ou seja, a perda das unidades processadoras de informação, os neurônios. No **artigo 4**, mostramos claramente a presença de atrofia de substância cinzenta, tanto na DA quanto no CCLa. Essa teoria não oferece explicação satisfatória, também, para o padrão de erros semânticos encontrados em nosso estudo.

A teoria do Processamento Distribuído em Paralelo, se baseia num modelo computacional de redes neurais, no qual os neurônios são representados por unidades de processamento não-lineares interconectadas e organizadas em grupo. Cada unidade está associada a um estado de ativação, que depende da força do *input* proveniente de outra unidade. Nesse modelo, cada grupo de unidades pode representar uma região distinta do córtex. Assim, é possível simular a atividade do córtex visual associativo criando um grupo de unidades neuronais chamado, por exemplo, grupo “visual”, que receberia e processaria estímulos que primariamente são provenientes do meio externo; o grupo “verbal” representaria áreas corticais relacionadas ao processamento lingüístico e, da mesma forma, pode receber informações lingüísticas provenientes do meio externo, como nome de objetos ou sua descrição. Assim, os grupos de unidades são divididos em subgrupos, compreendendo aqueles que recebem estímulos externos (camadas visíveis, no exemplo acima “visual”e “verbal”) e aqueles que processam apenas as informações provenientes dos grupos com os quais estão conectados (camada oculta). Ainda nesse exemplo, todas as unidades dos grupos “visual” e “verbal” estão conectadas bidirecionalmente com outro grupo, que não recebe informações diretas do meio, o grupo “semântico”. Ou seja, a atividade desse grupo é modificada apenas pela interação com os outros grupos com os quais está interconectada, no caso, “visual” e “verbal” (Rogers et al., 2004).

Segundo esse modelo, a abstração semântica surge através de mecanismos estatísticos de aprendizado realizados nas áreas cerebrais equivalentes ao grupo “semântico”, capazes de receber, processar e integrar *inputs* provenientes das diversas modalidades perceptivas oriundas da experiência sensorial. O conteúdo da memória

semântica, portanto, não estaria armazenado em alguma região cerebral mas sim, estaria representado nas mesmas regiões responsáveis pela percepção e ação, cuja integração dependeria de seus padrões de atividade em conjunto com um centro amodal. Os mecanismos de aprendizado implícitos nesse modelo são capazes de fazer inferências e generalizações quando é apresentada alguma informação nova, pela estrutura de similaridade abstrata capturada da integração de todas as modalidades sensoriais (Rogers e McClelland, 2004a).

Estes pesquisadores estudaram esse modelo de redes neurais simulando o desempenho em testes de nomeação de pacientes com demência semântica. Para isso, treinaram as redes neurais para a nomeação correta de figuras e, após isso, diminuíram as conexões entre as unidades e entre os grupos. O processo técnico de atribuição dos nomes às unidades e treino da rede está descrito no artigo de Rogers et al. (2004) e os detalhes fogem ao escopo dessa Tese.

Os autores dividiram o desempenho dos pacientes em graus de comprometimento e classificaram as respostas como: corretas, erros superordenados, erros semânticos (resposta incorreta, porém do mesmo domínio semântico da palavra-alvo), erros por omissão e erros por cruzamento de domínio (resposta incorreta e de domínio semântico diferente da palavra-alvo). O mesmo foi feito com as respostas dos modelos de rede neural, que também foram classificados de acordo com o grau de comprometimento, ou seja, da quantidade de lesões (diminuição das conexões) entre as unidades e os grupos. Os autores mostraram um padrão qualitativo de desempenho similar entre os pacientes e o modelo de rede neural: quanto maior o grau de comprometimento, maior a proporção de erros por omissão e, em menor grau, de erros superordenados (Rogers et al., 2004). Nossos resultados discutidos no **artigo 3** confirmam que até a fase leve, há proporcionalmente menos erros por omissão; confirmam também que os erros coordenados [equivalentes aos erros semânticos na classificação de Rogers et al., (2004)] inicialmente aumentam, mas tendem a cair com a progressão da severidade.

Esse modelo de PDP também oferece explicações para o achado do nosso estudo de padrão de acerto após as pistas fonêmicas nos pacientes mais comprometidos (grupo DA), pois essa pista significa uma via de informação que pode alterar o equilíbrio

do sistema, levando a uma nova configuração onde a integração da informação visual agora conta com um descritor verbal específico para a palavra-alvo.

Embora as duas teorias acima descritas encontrem respostas parcialmente satisfatórias para os achados clínicos, elas não oferecem necessariamente o correlato anatômico macroscópico para seus respectivos modelos. No **artigo 6**, buscamos justamente isso: correlacionar os padrões de erro de nomeação, principalmente os semânticos, com a anatomia cerebral, usando para isso um modelo lesional que baseia-se na idéia de que "quanto menos substância cinzenta, mais erros de nomeação".

Conforme discutido nesse artigo, correlacionamos os erros de nomeação semânticos (coordenado, superordenado e circunlóquios) com a densidade de substância cinzenta através do método de RM-MBV. Encontramos quatro principais regiões envolvidas no processo semântico de nomeação: tálamos e regiões temporais mediais (envolvidos em todos os tipos de erros e também nos acertos); regiões temporais anteriores, principalmente giros temporais superior e inferior (relacionadas majoritariamente com os erros coordenados e também circunlóquios) e córtices pré-frontais, o esquerdo mais intensamente que o direito (giro frontal inferior mais relacionado com circunlóquios e giro frontal superior com erros superordenados).

Em conclusão, propusemos um modelo integrativo da organização cerebral da memória léxico-semântica: as alterações anátomo-patológicas iniciais, tais como perda da função e da densidade sinápticas, deposição anormal de peptídeo βA, ENF e atrofia cortical, levam ao comprometimento da organização estrutural da memória semântica. Isso corre tanto pela perda das unidades processadoras de informação, os neurônios, como por interrupção na comunicação entre eles. As alterações nessas redes neurofuncionais, cujas conexões se dão em PDP, seriam as responsáveis pelas dificuldades em nomear e categorizar que encontramos em nossos estudos. Essas alterações ocorrem principalmente em áreas como tálamos, estruturas temporais mediais, córtices pré-frontais e pólos temporais. Sugerimos, conforme discutido no **artigo 6**, que as estruturas relacionadas a todos os tipos de erros semânticos têm um papel mediador: o tálamo, como sincronizador do ritmo elétrico necessário para co-ativação das várias regiões cerebrais, como proposto por Kraut et al. (2003), e as regiões temporais mediais como hipocampos e giros parahipocampais, com o papel essencial de recuperar os

aspectos específicos dos conteúdos mentais; os pólos temporais podem servir como área de convergência amodal, que teria o papel de integrar as informações de diferentes modalidades sensoriais, como sugerido por Patterson et al. (2007); o córtex pré-frontal esquerdo (mais que o direito), pode ser o responsável por selecionar o aspecto semântico mais relevante em determinada circunstância e, talvez, converter essa representação semântica no seu correspondente fonológico: a palavra mais apropriada para ser dita em determinado contexto.

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