Renata de Almeida Muniz

REPERCUSSÕES DO COMPROMETIMENTO COGNITIVO E DA DISFUNÇÃO EXECUTIVA NA FUNCIONALIDADE DE IDOSOS COM DOENÇA DE ALZHEIMER

Belo Horizonte
Escola de Educação Física, Fisioterapia e Terapia Ocupacional da UFMG
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Trabalho de Conclusão de Curso apresentado à Escola de Educação Física, Fisioterapia e Terapia Ocupacional da Universidade Federal de Minas Gerais, como requisito parcial à obtenção de título de Especialista Terapia Ocupacional aplicada a Gerontologia.

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LISTA DE ABRAVIATURAS

ABVD – Atividade Básica de Vida Diária

AIVD – Atividade Instrumental de Vida Diária

AVD – Atividade de Vida Diária

ADAS-Cog - Alzheimer's Disease Assessment Scale Cognitive portion

BRDRS - Blessed Roth Dementia Rating Scale

BRSD - Behavior Rating Scale for Dementia

CAMCOG – Cambridge Cognitive Test

CAMDEX - Cambridge Examination for Mental Disorders in the Elderly

CCL – Comprometimento Cognitivo Leve

CDR - Clinical Dementia Rating Scale

CDR SB - Clinical Dementia Rating Scale Sum of Boxes

CIRS-G - Cumulative Index Rating Scale for Geriatrics

CMAI - Cohen-Mansfield Agitation Inventory

DA – Doença de Alzheimer

DAFS-R – Direct Assessment of Functional Status

DP – Desvio Padrão

DV – Demência Vascular

EXIT 25 – Executive Interview

FAQ - Functional Assessment Questionnaire

FrSBe - Frontal Systems Behavioral Scale

GDS-S - Scale-Shot Form

MDRS - Mattis Dementia Rating Scale

MEM - Measure Episodic Memory

MMSE - Mini-Mental State Examination

NPI - Neuropsychiatric Inventory

NRS - Neurobehavioral Rating Scale

PODS - Pfeffer Outpatient Disabilities Scale

PSMS - Physical Self-Maintenance Scale

TMSE - Thai Mental State Examination

WCST - Wisconsin Card Sorting Test

RESUMO

Introdução: O envelhecimento populacional promove um aumento significativo da prevalência de doenças crônico-degenerativas e incapacitantes, repercutindo e comprometendo a independência e a autonomia dos indivíduos. **Objetivo:** Entender as repercussões do comprometimento cognitivo e da disfunção executiva no desempenho funcional de indivíduos com doença de Alzheimer. **Metodologia:** Foi realizada uma revisão crítica da literatura. A pesquisa foi realizada por meio de buscas nas bases de dados eletrônicas Lilacs e Medline, utilizando-se as palavras-chave: "executive dysfunction", "dementia", "daily activities", "Alzheimer's disease" e "executive function", no período de 1990 a 2010. **Resultados:** A disfunção executiva estava associada a menor capacidade para realizar AIVD. Os indivíduos com Doença de Alzheimer apresentaram pior desempenho funcional nas AVD quando comparados a outros grupos. Os escores apresentados nas avaliações de funções executivas e cognitivas sofreram influência da gravidade da demência. **Conclusões:** Existem poucas investigações comprometidas a avaliar as repercussões de déficits cognitivos e comprometimento das funções executivas no desempenho funcional de idosos com demência. Há necessidade de mais estudos metodologicamente qualificados, com enfoque no desempenho ocupacional, para análise criteriosa. Torna-se fundamental o conhecimento relativo às perdas da capacidade funcional em atividades do cotidiano e suas relações com a cognição e funções executivas, para que se possam promover intervenções pontuais.

ABSTRACT

Introduction: population ageing leads to a significant raise of prevalence of chronic and disabling diseases, affecting and reflecting into the independence and autonomy of individuals. **Aim:** Understand the reflexions of cognitive commitment and executive dysfunction in individuals suffering from Alzheimer. **Methodology:** A critical review of the literature was executed. The research was carried out between 1990 and 2000 by means of Lilacs and Medline electronic data base search, employing key-words as for instance “executive dysfunction”, “dementia”, “daily activities”, “Alzheimer’s disease” and “executive function”. **Results:** The executive dysfunction was closely associated with a minor capacity of performing AIVD. The individuals suffering from the Alzheimer disease demonstrated worse functional performance in AVD when compared to the other groups. The scores presented in the assessment of executive and cognitive functions were influenced by the severity of dementia. **Conclusions:** There are only a few studies committed in assessing the reflections of cognitive deficits and the endangerment of executive functions into the functional performance of elderly with dementia. More methodologically qualified studies focusing on occupational performance are necessary to produce more cautious analyses. The knowledge concerning the loss of functional ability in daily activities and its relation with cognition and executive functions become fundamental so one can carry out punctual interventions.

SUMÁRIO

1 INTRODUÇÃO

O envelhecimento populacional é uma realidade e levanta crescentes questões sobre as condições de saúde e a prevalência de morbidades entre os idosos (PEREIRA, 2009). Há um aumento significativo da prevalência de doenças crônico-degenerativas e incapacitantes, especialmente de doenças neurológicas e psiquiátricas (WAGNER, 2006) e de quadros demenciais (MACHADO, 2006), que repercutem e comprometem a independência e a autonomia dos indivíduos (RAMOS, 2003).

Para se manter engajado e envolvido em atividades significativas do cotidiano, o idoso necessita ser independente para desempenhar ativamente tarefas físicas e mentais, tais como, a capacidade de cuidar de si mesmo, realizar sua higiene pessoal, preparar refeições e alimentar-se, transferir-se de um local para outro, arrumar a casa, controlar suas finanças, manejar adequadamente suas medicações, ser responsável pelos compromissos firmados, fazer compras e usar meios de comunicação (PEREIRA, 2009).

Neste panorama devemos abordar o conceito de capacidade funcional, sendo este o novo paradigma de saúde do idoso, vinculado a uma vida independente e com autonomia, estando menos articulado a especificidades clínicas ou número de doenças crônicas, e mais à capacidade de realizar atividades do cotidiano numa abordagem integrada à saúde física, saúde mental, independência na vida diária, integração social, suporte familiar e independência econômica (RAMOS, 2003; CALDAS, 2003). Portanto, a capacidade funcional é, geralmente, mensurada utilizando-se escalas que avaliam atividades básicas e instrumentais de vida diária (CASSIANO, 2008).

Ao considerarmos o conceito de capacidade funcional do idoso, atenção deve ser focada na habilidade executiva como mediadora do desempenho dos indivíduos em atividades cotidianas. As funções executivas correspondem às habilidades cognitivas e princípios de organização indispensáveis para lidar com situações instáveis e diversificadas do contexto social, contribuindo para um comportamento apropriado do sujeito (NITRINI, *et al*., 2005). Portanto, as funções executivas são habilidades essenciais para o desempenho de comportamentos complexos (YASSUDA; ABREU, 2006). As porções pré-frontais dos lobos frontais são as estruturas responsáveis pelas funções executivas, sendo importante destacar que estas habilidades exercem influência no funcionamento cognitivo global e nas AVD

(MAGILA; CARAMELLI, 2000). A capacidade para solucionar problemas, direcionar comportamentos a objetivos específicos, planejar estratégias eficazes e inibir atos ineficazes correspondem a um conjunto de habilidades interligadas das funções executivas (MALLOY-DINIZ, et al., 2008). Para tanto, as habilidades executivas dependem da integridade das estruturas pré-frontais e de suas conexões estriatais (TEIXEIRA-JR e CARAMELLI, 2006).

Dentre as demências, a Doença de Alzheimer (DA) é a mais frequente no idoso (PITELLA, 2006). A DA é caracterizada por um comprometimento significativo da capacidade funcional e do envolvimento social de um indivíduo, associadas à degeneração progressiva das estruturas cerebrais. O comprometimento caracteriza-se por início gradual e declínio contínuo das funções cognitivas, sendo importante considerar o déficit de memória e de pelo menos mais uma função cognitiva (ÁVILA E BOTTINO, 2008).

Além disso, uma intervenção direcionada a indivíduos com DA é complexa considerando que o funcionamento cognitivo está fortemente associado ao desempenho das atividades cotidianas (FERRARI, 2007). Segundo Njegovan et al. (2001), as alterações no desempenho das atividades de vida diária (AVD) podem ocorrer desde os estágios iniciais da demência, sendo que, nos danos cognitivos leves, as perdas são detectadas prioritariamente nas atividades instrumentais de vida diária (AIVD), estando a realização das atividades básicas de vida diária (ABVD) prejudicada somente nos estágios demenciais mais avançados. A DA também afeta o comportamento dos indivíduos, com diferentes manifestações ao longo do curso da doença (ÁVILA E BOTTINO, 2008).

Nesta perspectiva, essa revisão de literatura justifica-se pela necessidade de entender as repercussões do comprometimento cognitivo e da disfunção executiva no desempenho funcional de indivíduos com doença de Alzheimer. A proposta do estudo visa corroborar para o embasamento da prática clínica e buscar reflexões para a implementação de ações efetivas de prevenção e reabilitação.

2 METODOLOGIA

Este estudo trata-se de uma revisão crítica da literatura. A pesquisa foi realizada por meio de buscas nas bases de dados eletrônicas Lilacs e Medline, utilizando-se as palavras-chave: *"executive dysfunction", "dementia", "daily activities", "Alzheimer's disease" e "executive function*".

Os critérios de inclusão estabelecidos foram os seguintes:

- Artigos científicos que investigaram a relação entre desempenho executivo, cognição e funcionalidade de idosos com demência;
- Publicados no período de janeiro de 1990 a setembro de 2010;

Todos os estudos obtidos foram avaliados em uma primeira fase por meio dos títulos e resumos. Assim, foi possível verificar se eles eram relacionados com a temática da presente investigação. Foi realizada a leitura na íntegra dos artigos pré-selecionados, com o propósito de definir pela inclusão e/ou exclusão dos mesmos do estudo. Foram excluídos artigos após análise criteriosa da metodologia.

Foram encontrados 128 artigos e destes 7 foram selecionados para este estudo por estarem de acordo com os critérios de inclusão.

3 RESULTADOS

Os resultados serão apresentados no quadro a seguir.

Autor principal, título do trabalho e ano de publicação	Periódico	Objetivo	Tipo de estudo	Amostra	Instrumentos de Avaliação e procedimentos	Resultados
CHEN, Stephen T. et al. Executive dysfunction in Alzheimer's disease: association with neuropsychiatric symptoms and functional impairment, 1998	The Journal of Neuropsychiatry and Clinical Neurosciences	Avaliar a presença e a extensão de disfunção executiva em pacientes com DA, além testar a hipótese de que o comprometimento executivo está associado a maior sintomatologia neuropsiquiátrica e incapacidade funcional. Este estudo também buscou explorar a relação entre disfunção executiva e tipos específicos de sintomatologia neuropsiquiátrica.	Estudo Observacional: transversal	Uma amostra de conveniência de 31 homens foi incluída neste estudo, recrutados de clínicas e um centro médico. A idade média foi de 69.9 anos, o escore médio para o Mini-Mental State Examination (MMSE) foi de 17,6, a duração média da doença foi de 4,1 e a média de escolaridade foi de 13,9 anos.	Para testar o funcionamento executive foram utilizados o Controlled Oral Word Association Test FAS subtest que avalia fluência verbal; a escala Mattis Dementia Rating Scale (MDRS) Conceptualization que avalia categorização e abstração; MDRS Initiation que avalia sequências verbais e motoras, padrões e iniciação; Stroop Interference que testa o controle inibitório; o Trail Making Parte B que testa atenção dividida e sequenciamento; o Wisconsin Card Sorting	Observou-se forte correlação entre a capacidade de abstração e categorização e capacidade funcional –0.82 ($p< 0.005$) independente do escore no MMSE. Disfunção executiva foi significativamente associada com incapacidade para desempenhar atividades diárias no grupo de pacientes com DA. O estudo inferiu que para desempenhar AVD, como cuidar de si é necessário flexibilidade cognitiva e resistência a interferências e distrações que são independentes do nível de cognição global. A disfunção executiva foi amplamente correlacionada com a agitação/desinibição e no escore total neuropsiquiátrico da NRS. Na análise estatística observa-se

					Test (WCST) Categories que avalia resolução de problemas; e oWCST Perseverative Errors que testa a flexibilidade cognitiva. Também foi utilizado o MMSE para avaliar o comprometimento cognitivo global; o Neurobehavioral Rating Scale (NRS) que analisa comprometimentos do comportamento como agitação/desinibição, ansiedade/depressão, comportamento lentificado e psicoses; o NRS Total Neuropsychiatric; e a subescala de atividades da Blessed de Demência para mensurar a habilidade dos sujeitos para desempenhar atividades do cotidiano como, alimentar, vestir, manejar dinheiro e realizar tarefas domésticas.	uma variação de -0.31 para -0.55 para os valores de correlação, atingindo significância estatística de $p<0.01$ em todos os níveis de análise. Após covariância para o MMSE, 8 de 11 correlações entre disfunção executiva e sintomas neuropsicológicos permaneceram estatisticamente significativos (tau-b variou de -0.32 para -0.45, com $p<0.05$), indicando que a maioria destas correlações foram independentes dos escores apresentados no MMSE. Relações relevantes foram encontradas entre déficit executivo e incapacidade funcional (tau-b apresentou variação de -0.33 para -0.70, com $p<0.005$). Houve manutenção da significância estatística após a covariância entre os escores apresentados no MMSE ($p<0.05$).

BOYLE, Patrícia A. et al. Executive Dysfunction and Apathy predict functional impairment in Alzheimer Disease, 2003	American Journal of Geriatric Psychiatry	Examinar as contribuições independentes do prejuízo cognitivo global, disfunção executiva e distúrbio comportamental, mediadas pelo córtex pré-frontal, no desempenho de AVD, ABVD e AIVD em indivíduos com DA leve a moderada.	Estudo Observacional: transversal	45 pacientes com DA (21 homens e 24 mulheres) e seus cuidadores foram recrutados de uma clínica. A amostra apresentou uma média de idade de 76,7 (DP: 7,7), pontuação média no MEEM de 22 (DP: 3,2), e uma média de escolaridade de 11,4 (DP: 2,8).	A escala MDRS foi utilizada como medida de avaliação global da cognição e gravidade da demência. A subescala MDRS avaliou atenção, iniciação/perseveração, construção, categorização e memória. Para avaliar os distúrbios do comportamento mediados pelos circuitos frontais foi utilizada a escala Frontal Systems Behavioral Scale (FrSBe). Para mensurar as habilidades funcionais foi utilizado o questionário de Lawton e Brody composto de 14 itens, sendo 8 questões referentes a AIVD e 6 para ABVD. Para avaliar a influência da gravidade de doenças clínicas sobre as variáveis do estudo foi	O escore médio na escala MDRS foi de 109 (DP=14.4), indicando demência. A pontuação média total obtida na avaliação das AVD foi de 19,7 indicando grau leve a moderado de comprometimento. Observou-se um grau moderado de comprometimento nas AIVD, com escore médio de 9 pontos no questionário de Lawton e Brody, assim como, pontuação média de 10.7, indicando prejuízo funcional leve nas ABVD. Na avaliação FrSBe os escores médios revelaram níveis globais moderados de apatia e disfunção executiva, além de grau leve de desinibição. Observaram-se correlações altamente significativas entre o MDRS total e avaliação de AVD Total ($r [43] = 0.52$; $p<0.001$), e entre o FrSBe total e o escore total para AVD ($r [43] = -0.57$; $p<0.001$). Considerando os escores totais da escala MDRS e a avaliação FrSBe como variáveis independentes, e o escore total da escala de AVD como variável dependente,

					utilizada a escala CIRS-G. Também foi aplicada a escala GDS-S contendo 15 itens.	verificou-se que houve contribuições independentes na funcionalidade: associações significativas entre a subescala de iniciação/perseveração do MDRS e AIVD (r [43] = 0.41; p<0.01) e entre a escala de apatia do FrSBe (r [43] = -0.63; p<0.001). Os pesquisadores apontaram que iniciação/perseveração e apatia, variáveis independentes, contribuem 17% e 27% respectivamente, para o comprometimento das AIVD (variável dependente). O estudo revelou associações negativas expressivas entre os escores do domínio da apatia FrSBe e ABVD (r [43] = -0.45; p<0.01) e entre o escores do domínio da disfunção executiva do FrSBe e ABVD (r [43] = -0.37; p<0.02). Somente a subescala inibição/perseveração do MDRS correlacionou-se com ABVD (r [43] = 0.31; p<0.04).

STOUT, Julie C. et al. Frontal Behavioral Syndromes and Functional Status in Probable Alzheimer Disease, 2003.	American Journal of Geriatric Psychiatry	Estudar os resultados encontrados no FrSBe (The Frontal Systems Behavioral Scale) em uma amostra ampliada de indivíduos com provável diagnóstico de DA, nas diferentes fases de gravidade da demência para caracterizar as classificações globais e tipos de síndromes do comportamento frontal. Além disso, a presente investigação visou descrever como estes distúrbios estão relacionados com habilidades funcionais do dia-a-dia em indivíduos com DA.	Estudo Observacional: Transversal	85 voluntários do centro de pesquisa da DA de uma Universidade participaram deste estudo. Destes, 73 foram diagnosticados clinicamente com hipótese de DA e 12 indivíduos saudáveis constituíram o grupo controle. A amostra foi dividida em três grupos: grupo controle (n=23); DA leve a moderada (n=49); DA severa (n=24). Foram recrutados mais 11 indivíduos saudáveis da Universidade da Indiana para compor o grupo controle. O	A escala FrSBe foi utilizada para avaliar o comportamento considerando os três domínios/circuitos frontais: apatia (escala A; 14 itens), desinibição/descontrole emocional (escala D; 15 itens) e disfunção executiva (escala E; 17 itens). A escala MDRS foi utilizada para mensurar o funcionamento cognitivo, incluindo uma pontuação global e escores da subescala para atenção, iniciação e perseveração, construção, conceituação e memória. Para avaliar as AVD foram utilizados a Physical Self-Maintenance Scale (PSMS-6) e a escala Pfeffer Outpatient Disabilities Scale (PODS). A escala PSMS-6 informa sobre o	Para todos os indivíduos com hipótese diagnóstica de DA, o escore obtido na escala MDRS foi menor, indicando maior grau de demência. Foram associados com maior escore na apatia, desinibição e disfunção executiva da subescala FrSbe ($r[73] = -0.48$, $p < 0.001$; $r[73] = -0.27$, $p < 0.05$; e $r[73] = -0.43$, $p < 0.001$, respectivamente). Comparado com o grupo DA leve a moderada e grupo controle, evidenciou-se significativamente que, o grupo DA severa apresentou maior distúrbio comportamental, como indicado pelo maior escore na FrSBe Total e nas subescalas Apatia e Disfunção Executiva. Observou-se similarmente maior pontuação na escala e subescalas acima citadas para o grupo DA leve a moderada quando comparado com o grupo controle. Para a subescala desinibição, somente o grupo DA severa apresentou escore significativamente mais elevado em relação ao grupo controle. Houve comprometimento para desempenhar as ABVD em 42

SWANBERG, M.M. et al. Executive Dysfunction in Alzheimer Disease, 2004	Archives of Neurology	Determinar a prevalência de disfunção executiva em uma amostra de sujeitos com DA de um centro de referência do idoso, e estudar sua relação com a cognição, funcionalidade, e sintomas neuropsiquiátri-cos.	Estudo de Coorte Retrospectivo	A amostra foi constituída por 137 (62% mulheres) sujeitos com diagnóstico provável de DA. A partir de avaliações realizadas em centros de referência terciária, análises retrospectivas foram desenvolvidas. Uma amostra de 64 voluntários (57% mulheres) cognitivamente normais foi incluída no grupo controle para comparações. A média de idade foi de 70.3 ± 8.8 para o grupo controle e 72.9 ± 8.4	Foram incluídas as informações e resultados obtidos dos testes na linha de base e follow-up de 12 meses. A função executiva foi avaliada utilizando a tarefa de cancelamento de cartas e o teste dos labirintos da escala Alzheimer's Disease Assessment Scale Cognitive portion (ADAS-Cog). A função cognitiva foi avaliada utilizando o MMSE e o CDR SB. As alterações comportamentais foram mensuradas com o Cohen-Mansfield Agitation Inventory (CMAI) e com a escala Blessed Roth Dementia Rating Scale (BRSD). A escala BRSD avalia comportamento desorganizado, depressão, apatia, irritabilidade/agressivi	Os resultados apresentados na avaliação inicial na tarefa de cancelamento de cartas foram usados para classificar a coorte de sujeitos com DA como tendo disfunção executiva e função executiva normal, estimando a prevalência, devido ao baixo grau de erros de classificação após os 12 meses de acompanhamento e sua distribuição normal. De acordo com o ponto de corte, 6% dos sujeitos do grupo controle e 64% dos pacientes com DA apresentaram disfunção executiva. Baseado na avaliação inicial para o teste de tempo para labirintos, 2% de sujeitos do grupo controle e 58% de pacientes com DA foram classificados com disfunção executiva. Os pacientes classificados como tendo disfunção executiva apresentaram demência severa baseado na CDR SB ($p<0.001$), pior funcionamento cognitivo segundo os escores do MMSE ($p<0.001$), piores escores para o desempenho de AVD ($p=0.01$) e mais frequentes sintomas de

				para pacientes com DA. A média de escolaridade foi de 13.8 ± 2.9 para o grupo controle e 13.3 ± 2.8 para os pacientes com DA.	dade, psicoses e sintomas vegetativos. Por meio do Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory, foram avaliadas ABVD como, capacidade para tomar banho, realizar higiene, vestir e locomover-se, bem como, AIVD incluindo capacidade para lidar com eletrodomésticos, discutir sobre eventos e utilizar o correio.	psicose na avaliação inicial. Estes indivíduos demonstraram também piora significativamente maior em termos de gravidade da demência e funcionamento cognitivo, 12 meses após a avaliação inicial. Observou-se forte correlação entre desempenho em AVD e funções executivas. Os indivíduos incapazes de desempenhar atividades de autocuidado e realizar tarefas em casa devido à disfunção executiva tiveram piores escores na escala em comparação com indivíduos com DA sem comprometimento das funções executivas. Observou-se que apenas 28% da variação no desempenho da função executiva foram explicados pelo escore inicial apresentado no MMSE e 18% pelo escore basal no CDR SB em pacientes com DA.
SENANARONG, V. et al. Neuropsychiatric symptoms, functional impairment and	International Psychogeriatrics	Investigar a relação entre distúrbios comportamentais, AVD e funções executivas.	Estudo Observacional transversal Correlacional Exploratório	73 pacientes tailandeses com DA, (20 homens – 27.4% - e 53 mulheres – 72.6%) de uma	A gravidade da demência foi avaliada utilizando o Thai Mental State Examination (TMSE) e o CDR SB. A escala CDR SB inclui	As avaliações das funções executivas (fluência verbal e teste do desenho do relógio) e todas as mensurações obtidas para AVD tinham correlações significativas. Além disso, as

executive ability in Thai patients with Alzheimer's Disease, 2005				clínica para distúrbios de memória foram recrutados e avaliados no período de Janeiro de 2000 a Outubro de 2001. A média de idade foi de 70.28 ± 8.10 anos. Quarenta e nove (68%) pacientes tinham 10 anos ou menos de escolaridade.	questões de memória, orientação, juízo crítico e resolução de problemas, atividades na comunidade, lar, lazer e cuidados pessoais. As AVD foram avaliadas usando o Functional Assessment Questionnaire (FAQ) e a Escala Tailandesa de AVD que consiste em 6 ABVD e 7 AIVD. O comportamento foi mensurado através do Neuropsychiatric Inventory (NPI), enfatizando agitação/agressividade, apatia e desinibição. Foi realizado também o teste de fluência verbal do Cambridge Examination for Mental Disorders in the Elderly (CAMDEX) modificado para incluir nomes de animais e letras e o teste do desenho do relógio para avaliar as funções executivas.	avaliações das funções executivas apresentaram também correlações fortes para medidas cognitivas globais obtidas através do TMSE e CDR SB. Na população deste estudo observou-se que o teste do desenho do relógio e fluência verbal refletem a gravidade da demência. Houve correlação estatisticamente significativa entre o teste do desenho do relógio e o comportamento frontal de agitação (r= -0.367), apatia (r = -0.273) e desinibição (r = -0.247). A fluência verbal correlacionou-se com agitação (r = -0.341). Houve correlações significativas entre os escores da Escala Tailandesa de AVD e agitação (r = 0.350), apatia (r = 0.441), e desinibição (r = 0,417). O FAQ mostrou correlações idênticas para os mesmos três comportamentos. Depois de controlar o TMSE, uma correlação significativa manteve-se entre os escores da Escala Tailandesa de AVD e agitação (r = 0.291) e apatia (r = 0.342).

PEREIRA, F.S. et al. Executive disfunction correlates with impaired functional status in older adults with varying degrees of cognitive impairment, 2008	International Psychogeriatrics	Examinar a associação entre funções executivas e funcionalidade, por meio de avaliação objetiva, em uma amostra de idosos brasileiros com diferentes níveis de disfunção cognitiva: Comprometimento Cognitivo Leve (CCL) e DA leve, quando comparado com indivíduos saudáveis.	Estudo Observacional: transversal	89 pacientes foram recrutados pelo Instituto de Psiquiatria da Universidade de São Paulo, sendo 70% mulheres. Os sujeitos da amostra foram divididos em três grupos: grupo controle (n=32); Comprometimento Cognitivo Leve (CCL) (n=31); DA leve (n=26). A média de idade foi de 73,8 ± 6,7 anos, variando de 59 a 89 anos. A média de escolaridade foi de 10,3 ± 6,0 anos, com uma variação de 1 a 26 anos de educação formal.	O exame do estado mental foi realizado com Cambridge Cognitive Test (CAMCOG), que faz parte da entrevista semi-estruturada CAMDEX e MMSE. Avaliação objetiva da funcionalidade foi realizada através da Direct Assessment of Functional Status (DAFS-R), que envolve a competência para desempenhar AVD em sete domínios: orientação temporal, comunicação, habilidade para lidar com dinheiro, capacidade para fazer compras, competências para se vestir e higiene, competências em relação à alimentação e habilidades de transporte. As funções executivas foram avaliadas através da	Os escores obtidos nos testes de rastreio cognitivo MMSE e CAMCOG foram significativamente inferiores para o grupo DA ($p < 0.001$). Houve diferenças significativas entre os três grupos do estudo em relação aos escores totais para a DAFS-R, sendo que o grupo controle apresentou melhor desempenho do que o grupo com CCL e grupo com DA ($p= 0.009$ e $p<0.001$ respectivamente). Além disso, neste mesmo instrumento de avaliação o grupo com CCL apresentou melhor desempenho do que o grupo com DA ($p<0.001$). Os sujeitos do grupo com DA apresentaram desempenho significativamente inferior na EXIT 25 em comparação com indivíduos sem demência ($p<0.001$ para comparações com grupo controle e CCL, e não foram observadas diferenças relevantes entre os sujeitos do grupo controle e CCL ($p=0.29$). Observou-se forte correlação negativa entre os escores totais da DAFS-R e EXIT25 ($r= -0.87$,

					entrevista estruturada Executive Interview (EXIT 25), composta por 25 itens que avalia fluência verbal, fluência em desenhar, comportamento de imitação, controle motor/impulsivo e sinais de liberação frontal.	p<0.001). Os resultados do estudo sugerem uma associação quase três vezes mais forte entre EXIT25 e DAFS-R do que entre os escores do CAMCOG e DAFS-R. Neste estudo inferiu-se que a disfunção executiva e medidas gerais de funcionamento cognitivo estão associadas a uma menor capacidade para realizar AIVD.
FARIAS, Sarah Tomaszewski, et al. Longitudinal changes in memory and executive functioning are associated with longitudinal change in instrumental activities of daily living in older adults, 2009.	Clinical Neuropsychology	Examinar as contribuições relativas de mudanças longitudinais de memória e funcionamento executivo no desempenho cotidiano de adultos idosos.	Estudo de coorte - longitudinal	100 participantes de um estudo multicêntrico longitudinal do envelhecimento foram incluídos no estudo, 45 eram cognitivamente normais (grupo controle), 29 tinham o diagnóstico clínico de CCL, e 26 com diagnóstico de demência. Dos 26 participantes com diagnóstico de	O Measure Episodic Memory (MEM) foi utilizado para avaliar a memória episódica. As funções executivas foram avaliadas através da escala EXEC que inclui itens da escala Wechsler como a repetição de dígitos invertida e memória visual, a subescala iniciação/perseveração da MDRS, que inclui itens que avaliam raciocínio abstrato, e teste de fluência verbal. A escala BRDRS foi utilizada para avaliar	Houve diferenças na linha de base no MEM e EXEC para os grupos cognitivos (para F global, p's <0.0001, e todos os testes foram significativos, p<0.05, após comparações múltiplas). Observou-se um contínuo da patologia aliado a gravidade do comprometimento. A taxa de mudança anual no MEM e EXEC também apresentou diferenças (p's = 0.04 e 0.004, respectivamente; após comparações múltiplas verificou-se significância em associações pareadas somente entre o grupo normal e demência). A escala EXEC mostrou evidências de declínio anual no grupo normal, no entanto, o mesmo não foi

				demência, 15 preenchiam os critérios para DA, sete para Demência Vascular (DV) e quatro apresentaram diagnóstico misto (DA/DV). O grupo controle apresentou uma média de idade de 73,5 (DP: 7,7), pontuação média no MEEM de 29,0 (DP: 1,3), média de anos de escolaridade de 14,7 (DP: 2,9), sendo 47% do sexo feminino. O grupo com com CCL, apresentou uma média de idade de 73,0 (DP: 8,5), pontuação média no	as AIVD. A escala é composta de itens, tais como, capacidade para orientar-se em ruas conhecidas, desempenhar tarefas domésticas, lidar com pequenas quantias de dinheiro, lembrar-se de eventos recentes, recordar uma pequena lista de itens, orientação espacial. Quanto menor o escore obtido na escala, melhor é desempenho funcional do indivíduo.	observado no MEM. O grupo CCL e grupo com demência também apresentou maior queda na escala EXEC em comparação com o MEM. Constatou-se nos grupos, comprometimento progressivo nas AIVD ($p<0.001$). Os grupos apresentaram comprometimento das AIVD similarmente ao progressivo declínio cognitivo ($p < 0.001$). O grupo de demência na linha de base foi incapaz de realizar mais de dois dos oito itens avaliados de habilidades funcionais. Houve diferenças significativas entre os grupos em relação às mudanças anuais nas AIVD ($p< 0.001$; após ajuste de múltiplas comparações observou-se significância de $p < 0.05$ para CCL/dementes e grupo controle/dementes). O grupo com demência ganhou em média um ponto por ano na escala de AIVD, tornando cada vez mais depende. Observou-se na linha de base que os resultados da escala MEM associou-se com as medidas basais das AIVD ($p = 0.001$) e

				MEEM de 28,0 (DP: 1,9), média de anos de escolaridade de 14,1 (DP: 3,1), além de 24% ser do sexo feminino. A amostra de 26 participantes com diagnóstico de demência apresentou uma média de idade de 74,5 (DP: 8,7), escore médio no MEEM de 23,8 (DP:3,7), média de anos de escolaridade de 14,0 (DP: 3,5), sendo 31% do sexo feminino.		após mudanças longitudinais ($p< 0.001$). Portanto um declínio mais acentuado no MEM ao longo do tempo foi associado a um maior grau de declínio funcional. Notou-se também que, medidas basais na escala EXEC se correlacionaram com as medidas iniciais de AIVD, assim como, para as mudanças obtidas longitudinalmente ($p<0.001$ respectivamente). Observou-se que maior grau de declínio na escala EXEC estava associado a maior comprometimento funcional. A magnitude da correlação entre as alterações no MEM e mudanças no desempenho de AIVD foi -0.69 (<0,001); e a correlação entre as alterações na escala EXEC e AIVD foi -0.72 ($p < 0.001$).

4 DISCUSSÃO DOS RESULTADOS

O presente estudo traz informações sobre as repercussões do comprometimento cognitivo e da disfunção executiva no desempenho funcional de indivíduos com doença de Alzheimer.

Em relação aos objetivos dos estudos verificou-se que todos investigaram a relação entre funções executivas, comprometimento cognitivo e capacidade funcional de idosos (FARIAS *et al*., 2009; PEREIRA *et al.,* 2008; SENANARONG *et al*., 2005; SWANBERG *et al*., 2004; BOYLE *et al*., 2003; STOUT *et al*., 2003; CHEN *et al*., 1998). Cinco estudos retrataram a relação entre distúrbios comportamentais com o desempenho executivo e funcional (CHEN *et al*., 1998; BOYLE *et al*., 2003; STOUT *et al*., 2003; SWANBERG *et al*., 2004; SENANARONG *et al*., 2005) e apenas dois estudos analisaram longitudinalmente mudanças da cognição e funções executivas, discutindo suas implicações na capacidade para desempenhar AVD de idosos com DA (FARIAS, *et al*., 2009; SWANBERG *et al*., 2004).

Considerando a metodologia, os sete estudos selecionados eram observacionais, cinco eram transversais (PEREIRA *et al.,*2008; BOYLE *et al*.,2003; STOUT *et al*.,2003) e dois estudos eram de coorte (FARIAS, *et al*., 2009; SWANBERG *et al*., 2004). Os estudos transversais fornecem informações limitadas sobre o curso e declínio da cognição e da funcionalidade, além de não estabelecerem correlações entre as variáveis ao longo do tempo. Nesta perspectiva Newman *et al*. (2003) esclarecem que os estudos transversais são úteis quando se quer descrever e estudar relação entre as variáveis, no entanto, é difícil estabelecer relações causais a partir de dados oriundos de um corte transversal no tempo. Os pesquisadores Cummings, Newman e Hulley (2003) discorrem que os estudos de coorte/longitudinais visam estabelecer inferências a respeito de associações entre duas ou mais variáveis, ou seja, a sequência temporal fortalece a evidência de que uma variável pode ser a causa do desfecho. A partir do exposto deve-se considerar uma limitação na comparação da metodologia dos estudos.

Verificou-se uma heterogeneidade na amostra dos estudos incluídos nesta revisão: o tamanho da amostra variou de 45 (BOYLE *et al*., 2003) a 201 idosos (SWANBERG *et al*., 2004); quanto à origem três estudos avaliaram idosos vinculados a clínicas (SENANARONG *et al*., 2005; BOYLE *et al*., 2003; CHEN *et al*., 1998), um em centro de referência (SWANBERG *et al*., 2004) e três investigaram idosos recrutados para estudos desenvolvidos em centros

universitários (FARIAS, *et al*., 2009; PEREIRA *et al.,* 2008; STOUT *et al*., 2003). A origem da amostra pode ser uma possível explicação para as diferenças apresentadas. Deve-se considerar que nenhum estudo recrutou idosos da comunidade. Além disso, muitos idosos poderiam estar em atendimento em outras unidades de atendimento à saúde. Vale destacar também que, a amostra de sujeitos dos estudos é proveniente de países diferentes. É relevante abordar algumas peculiaridades demográficas dos estudos incluídos nesta revisão: três dos estudos apresentaram uma proporção superior de mulheres (PEREIRA *et al.,* 2008; SENANARONG *et al*., 2005; SWANBERG *et al*., 2004); um estudo analisou apenas idosos do sexo masculino (CHEN *et al*., 1998), e outro apresentou diferença irrisória quanto ao sexo (BOYLE *et al*., 2003); o sexo masculino predominou na amostra do estudo de Farias *et al*. (2009), e no grupo de DA severa do estudo de Stout *et al*. (2003); a idade média variou de 69,9 anos (CHEN *et al*., 1998) a 76,7 anos (BOYLE *et al*., 2003); a média de anos de escolaridade variou de 10,3 (PEREIRA *et al.,* 2008) a 14,6 anos (STOUT *et al*., 2003). Considerar os aspectos da idade e da escolaridade torna-se fundamental para a proposta desta revisão, pois segundo Ávila e Bottino (2008), a idade traz pouca alteração em testes que avaliam conhecimentos adquiridos durante toda a vida e hábitos, no entanto, o envelhecimento traz alterações na memória episódica, habilidades espaciais e funções executivas. Houve classificação e separação de grupos de idosos quanto grau de comprometimento cognitivo, porém três estudos não fizeram esta distinção, apresentando apenas idosos com DA (SENANARONG *et al*., 2005; BOYLE *et al*., 2003; CHEN *et al*., 1998). Na pesquisa de Swanberg *et al*. (2004), os idosos foram diferenciados em grupo de indivíduos com DA e um grupo controle de idosos saudáveis. Em outros estudos os indivíduos da amostra foram distintos quanto a gravidade da DA (STOUT *et al*., 2003), e quanto ao nível de desempenho cognitivo, ou seja, indivíduos classificados com Comprometimento Cognitivo Leve (CCL) e demência (FARIAS, *et al*., 2009; PEREIRA *et al.,*2008). É importante salientar que houve um estudo que alocou sujeitos com DA, Demência Vascular (DV) e comprometimento misto de DA/DV (FARIAS, *et al*., 2009).

Com relação aos instrumentos de avaliação nota-se que todos os estudos utilizaram escalas para avaliação das funções cognitivas globais, funções executivas, além da funcionalidade. Deve-se, portanto, considerar uma limitação na comparação dos estudos, tendo em vista os diferentes protocolos utilizados e os diferentes aspectos abordados dentro da dimensão da cognição e das funções executivas. Para avaliação do funcionamento cognitivo verificou-se que três estudos utilizaram o Mini-Mental State Examination (MMSE) (PEREIRA *et al.,*

2008; SWANBERG *et al*., 2004; CHEN *et al*., 1998), a escala Clinical Dementia Rating Scale (CDR) (SENANARONG *et al*., 2005; SWANBERG *et al*., 2004) e a Mattis Dementia Rating Scale (MDRS) (BOYLE *et al*., 2003; STOUT *et al*., 2003). A utilização de uma mesma escala favorece a comparação dos resultados encontrados, apesar das amostras distintas.

Quanto aos instrumentos utilizados para avaliar as funções executivas observou-se que quatro estudos utilizaram a subescala Mattis Dementia Rating Scale (MDRS) (FARIAS, *et al*., 2009; BOYLE *et al*., 2003; STOUT *et al*., 2003; CHEN *et al*., 1998). Ao analisar as avaliações de funcionalidade observou-se que foram utilizados instrumentos variados. Os estudos avaliaram as ABVD e AIVD (PEREIRA *et al.,* 2008; SENANARONG *et al*., 2005; SWANBERG *et al*., 2004; BOYLE *et al*., 2003; STOUT *et al*., 2003; CHEN *et al*., 1998), exceto um que avaliou apenas as AIVD (FARIAS, *et al*., 2009). É importante destacar os diferentes instrumentos utilizados nos estudos para mensurar a capacidade para desempenhar AVD: a subescala de atividades da Blessed Demência, Lawton e Brody, Activities of Daily Living Inventory, Functional Assessment Questionnaire (FAQ) e escala Tailandesa de AVD, e a escala Direct Assessment of Functional Status (DAFSR) (PEREIRA *et al.,* 2008; SENANARONG *et al*., 2005; SWANBERG *et al*., 2004; BOYLE *et al*., 2003; CHEN *et al*., 1998). Apenas um estudo considerou instrumentos distintos na avaliação da capacidade funcional, utilizando a escala Physical Self-Maintenance Scale (PSMS) para mensurar o desempenho em ABVD e a escala Pfeffer Outpatient Disabilities Scale (PODS) para AIVD (STOUT *et al*., 2003). O estudo que avaliou somente AIVD utilizou a escala Blessed Roth Dementia Rating Scale (BRDRS) (FARIAS, *et al*., 2009). Na literatura observam-se protocolos semelhantes na avaliação da funcionalidade. Em estudo longitudinal com 124 sujeitos para avaliar a associação de comprometimento de memória episódica e funções executivas com a capacidade para desempenhar AIVD, a escala BRDRS foi utilizada (CAHN-WEINER, *et al*., 2007). Em outro estudo um dos instrumentos utilizados para mensurar as AIVD foi o Índice de Lawton e Brody (MARRA *et al.*, 2007). Com a finalidade de avaliar objetivamente a funcionalidade de 89 idosos, o DAFSR foi traduzido e adaptado culturalmente para a população brasileira, possibilitando sua aplicação (PEREIRA, 2009). É importante considerar possíveis vieses ao analisar os resultados das escalas que avaliaram a funcionalidade, considerando a capacidade do informante de observar e relatar mudanças sutis nas atividades de vida diária dos pacientes.

Alguns estudos avaliaram os distúrbios de comportamento (SENANARONG *et al*., 2005; SWANBERG *et al*., 2004; BOYLE *et al*., 2003; STOUT *et al*., 2003; CHEN *et al*., 1998).

Notou-se que dois estudos utilizaram a escala Frontal Systems Behavioral Scale (FrSBe) para avaliação dos distúrbios do comportamento (BOYLE *et al*., 2003; STOUT *et al*.,2003), o que viabilizou uma comparação efetiva entre os resultados obtidos. No entanto, devem-se considerar diferenças socioculturais e classificação dos grupos pesquisados quanto à gravidade da demência. Os outros estudos utilizaram as escalas Cohen-Mansfield Agitation Inventory (CMAI) e Behavior Rating Scale for Dementia (BRSD), Neuropsychiatric Inventory (NPI) e Neurobehavioral Rating Scale (NRS) (SENANARONG *et al*., 2005; SWANBERG *et al*., 2004; CHEN *et al*., 1998).

Em relação aos resultados observou-se forte correlação entre os escores obtidos nas escalas de avaliação de AVD e das funções executivas (FARIAS, *et al*., 2009; PEREIRA *et al.,* 2008; SENANARONG *et al*., 2005; SWANBERG *et al*., 2004; BOYLE *et al*., 2003; CHEN *et al*., 1998). Os achados acima citados se articulam com resultados do estudo de Razani *et al*. (2007), onde o funcionamento executivo se correlacionou significativamente com os aspectos da capacidade funcional em pacientes com demência, sendo esta relação mais relevante para o teste de fluência verbal e o teste Wisconsin Card Sorting Test (WCST) que avalia flexibilidade cognitiva e capacidade de raciocínio. Em todos os estudos notou-se que a disfunção executiva estava associada à menor capacidade para realizar AIVD (FARIAS, *et al*., 2009; PEREIRA *et al.,* 2008; SENANARONG *et al*., 2005; SWANBERG *et al*., 2004; BOYLE *et al*., 2003; STOUT *et al*., 2003; CHEN *et al*., 1998).

É importante considerar também que alguns estudos destacaram correlações significativas entre avaliações de funções executivas e medidas de funcionamento cognitivo, ou seja, indivíduos com disfunção executiva tinham significativamente maior comprometimento das funções cognitivas (SENANARONG *et al*., 2005; STOUT *et al*., 2003). Wagner (2006) discutindo a existência de disfunções executivas durante o processo de envelhecimento cognitivo reforçou o fato de que, ao se mensurar funções executivas, é importante levar em consideração os processos cognitivos associados, tornando-se difícil isolar uma única habilidade executiva. Diferentemente, outro estudo evidenciou baixa correlação entre desempenho das funções cognitivas e escores obtidos nas escalas de funções executivas (SWANBERG *et al*., 2004).

Em alguns estudos foi possível considerar que indivíduos com DA apresentaram pior desempenho funcional nas AVD quando comparados a outros grupos (FARIAS, *et al*., 2009;

PEREIRA *et al.,* 2008; SWANBERG *et al*., 2004; STOUT *et al*., 2003). Nesta perspectiva, é importante considerar os dados reportados por Sauvaget *et al*. (2002), onde a demência é o mais forte preditor de incapacidade física e de declínio nas ABVD e AIVD. Além disso, a demência é um fator determinante para o desenvolvimento de incapacidade e declínio funcional, independentemente da presença de outras doenças crônicas (AGÜERO-TORRES, *et al*., 1998).

Vale destacar também em três estudos associação predominantemente mais forte entre AVD e funções executivas do que entre os escores de AVD e cognição (FARIAS, *et al*., 2009; PEREIRA *et al.,* 2008; CHEN *et al*., 1998). Esses achados estão de acordo com um estudo longitudinal desenvolvido, enfatizando que o comprometimento das funções executivas ao longo do tempo estão mais associadas ao rápido declínio das AIVD, quando comparado com a memória (CAHN-WEINER, et al., 2007).

Além disso, é relevante apontar que os escores apresentados nas avaliações de funções executivas, cognitivas e da capacidade funcional sofreram influência da gravidade da demência (FARIAS, *et al*., 2009; SENANARONG *et al*., 2005; SWANBERG *et al*., 2004; STOUT *et al*., 2003). A literatura reporta achados similares, como no estudo realizado por Marra *et al.* (2007) onde verificou-se que, quanto mais elevado o nível de gravidade de demência, pior o desempenho dos idosos em questionários que avaliaram as ABVD e AIVD. Também reportaram que nos estágios iniciais as AIVD são mais afetadas que as ABVD que permanecem praticamente inalteradas. Observou-se que à medida que o quadro demencial avança, o comprometimento em todas as atividades funcionais aumenta significativamente, ou seja, praticamente todas as AIVD avaliadas haviam sido comprometidas, enquanto que um terço das atividades básicas apresentavam alteração. Contribuição similar foi encontrada em estudo longitudinal realizado por Njegovan et al. (2001), em uma amostra de 5.874 idosos da comunidade, que considerou a relação entre gravidade das alterações cognitivas e o desempenho funcional nas atividades diárias. Os autores deste estudo verificaram que determinadas funções hierarquicamente superiores entre as AIVD, como fazer compras e cuidar das finanças são perdidas primeiro do que as funções básicas como alimentar-se, vestir-se e caminhar.

Quanto aos sintomas comportamentais apenas um estudo relatou associação entre disfunção executiva e sintomas de psicose (SWANBERG *et al*., 2004). Dois estudos apontaram

correlação significativa entre disfunção executiva e apatia (SENANARONG *et al*., 2005; STOUT *et al*., 2003). Na literatura verificou-se achado similar em estudo realizado por McPherson *et al.* (2002), que correlacionou uma bateria de testes neuropsicológicos com avaliação do comportamento em oitenta indivíduos com DA. Estes pesquisadores verificaram que, indivíduos com DA que apresentaram comportamento de apatia, demonstraram pior desempenho em testes de avaliação das funções executivas, quando comparado a indivíduos com DA sem apatia. É relevante apontar também que dois dos estudos verificaram correlação significativa entre os testes de função executiva e comportamento de agitação e desinibição (SENANARONG *et al*., 2005; CHEN *et al*., 1998). Um dos estudos inferiu que quanto maior o grau de demência maior o comprometimento do comportamento de desinibição e apatia (STOUT *et al*., 2003). Houve correlação importante entre os escores apresentados nas escalas de avaliação de AVD e apatia (SENANARONG *et al*., 2005; BOYLE *et al*., 2003; STOUT *et al*., 2003). A relação entre disfunção executiva com apatia está também associada a maior comprometimento em AIVD e ABVD (BOYLE *et al*., 2003).

5 CONCLUSÃO

A presente revisão de literatura investigou a relação entre funções executivas, cognição, e desempenho funcional em atividades diárias de indivíduos com doença de Alzheimer.

Existem poucas investigações que avaliam as repercussões de déficits cognitivos e o comprometimento das funções executivas no desempenho funcional de idosos com demência, limitando a comparação dos resultados do estudo. Cabe aos profissionais e aos pesquisadores análise crítica e o desenvolvimento de estudos direcionados à população, na detecção de comprometimentos específicos da cognição e das funções executivas.

Conhecer e entender o declínio funcional em idosos permite a detecção precoce de quadros degenerativos, favorecendo a implementação de ações efetivas de reabilitação, a manutenção da funcionalidade e a compensação das perdas. Diante da ocorrência de declínio funcional, torna-se fundamental o conhecimento relativo às perdas da capacidade funcional e sua relação com a cognição e com as funções executivas, para que se possa dinamizar intervenções pontuais e direcionadas com o intuito de desacelerar o processo de deterioração, reduzindo a dependência e favorecendo ao máximo a autonomia.

Nesta revisão concluiu-se que há necessidade de mais estudos metodologicamente qualificados, com enfoque no desempenho ocupacional, para análise criteriosa. A partir de análise dos estudos, considera-se a necessidade de descrição mais detalhada de atividades funcionais no ambiente do indivíduo, para evidenciar limitações específicas. Faz-se também necessária a ampliação das amostras, assim como torná-las mais homogêneas e representativas da população.

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Executive Dysfunction and Apathy Predict Functional Impairment in Alzheimer Disease

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Objective: *The purpose of this study was to examine the extent to which executive cognitive dysfunction and frontally-mediated behavioral disturbances are associated with functional impairment in patients with mild-to-moderate Alzheimer disease (AD).* **Methods:** *Patients with AD (N = 45) completed the Mattis Dementia Rating Scale, and patients' caregivers completed the Frontal Systems Behavioral Inventory and a modified form of the Lawton and Brody Activities of Daily Living (ADLs) Questionnaire.* **Results:** *Multiple-regression analyses revealed that executive cognitive dysfunction and apathy scores accounted for 44% of the variance in instrumental activities of daily living; executive cognitive dysfunction alone explained 17% of the variance in instrumental ADLs, and apathy scores explained an additional 27%. Executive dysfunction and frontal-behavioral impairment explained 28% of the variance in basic ADLs (BADLs), and, after accounting for executive dysfunction, apathy was the only symptom found to explain additional unique variance in BADLs.* **Conclusion:** *These findings suggest that specific cognitive and behavioral symptoms are associated with functional impairment in patients with AD.* (Am J Geriatr Psychiatry 2003; 11:214–221)

Alzheimer disease (AD) is associated with significant declines in cognitive and behavioral functioning[1] and is a leading cause of disability among elderly persons.[2–4] Much of the disability reported among patients with AD is a direct result of impairments in activities of daily living (ADLs).[4,5] ADLs include basic and instrumental activities (BADLs and IADLs, respectively), and independent living requires successful performance of both.[5] BADLs involve self-care behaviors such as grooming and bathing, and IADLs include more complex behaviors such as cooking, bill paying, and medication management. Performance of ADLs declines gradually in AD, resulting in increased patient and caregiver distress,[6] elevated healthcare costs,[7] and the need for institutionalization.[3,7]

Relatively little is known about the determinants of ADL dysfunction in patients with AD. Most investigations of functional abilities in AD have utilized only

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global cognitive screening instruments such as the Mini-Mental State Exam (MMSE).[8] Findings indicate an association between global cognition and ADL declines, such that patients with severely impaired cognition generally perform more poorly on functional assessments than do those with mildly impaired cognition.[9,10] However, few studies have investigated the extent to which specific cognitive deficits influence ADLs.

In addition to cognitive dysfunction, behavioral disturbances may also play an important role in the regulation of ADLs in patients with AD. Behavioral disturbances correlate significantly with dementia-related functional declines,[10,11] and several researchers have suggested that behavioral symptoms may affect ADLs independent of cognition in AD.[11] Previous studies have not examined the independent contributions made by cognitive and behavioral disturbances to ADLs in AD, however, nor have they examined associations between specific behavioral symptoms and ADLs in this population.

Investigations of ADLs in patients with neurologic disorders other than AD suggest an important association between frontal/executive dysfunction and functional deficits.[12–17] Executive cognitive dysfunction has emerged as a more reliable indicator of IADLs than global cognition in patients with vascular dementia (VaD),[16,17] and behavioral manifestations of frontal-systems pathology also are associated with functional disability in VaD.[18] Apathy is a syndrome of motivational loss,[19,20] believed to be frontally-mediated, and recent evidence suggests that apathy, in particular, may have significant negative functional consequences in VaD patients.[18] Whereas executive cognitive dysfunction has been found to relate to IADLs in VaD,[16] apathy has been found to relate to both IADLs and BADLs in VaD patients.[18] Such findings therefore suggest a link between frontally-mediated cognitive dysfunction, behavioral symptoms, and ADL impairment in VaD.

As in other neurologic populations, frontal/executive impairments may serve as important determinants of functional abilities among patients with AD. Executive cognitive dysfunction and apathy are common in AD[20,21] and can be more pronounced than are other cognitive and behavioral symptoms.[20–23] It has been suggested that these symptoms may be uniquely related to functional deficits in AD,[10,24] but studies have not directly examined such associations. Moreover, studies have not examined the independent effects of executive cognitive and frontal-behavioral symptoms on IADLs and BADLs, respectively, in patients with AD.

The current study was designed to examine the independent contributions made by global cognitive impairment, executive cognitive dysfunction, and frontally-mediated behavioral disturbances to total ADLs, IADLs, and BADLs in patients with mild-to-moderate AD. Specific hypotheses were the following:

1. Global cognitive dysfunction contributes significantly to the prediction of total ADLs in patients with AD, and frontal behavioral disturbance explains unique variance above and beyond cognition.
2. Executive cognitive dysfunction contributes significantly to the prediction of IADLs, and apathy explains unique variance above and beyond executive cognitive impairment.
3. Frontal behavioral symptoms contribute significantly to the prediction of BADLs, whereas executive cognitive dysfunction does not.

METHODS

Participants

Forty-five consecutively referred AD patients (21 men, 24 women) and their caregivers were recruited from Brown University-based Memory Clinics in Providence, RI. All patients met criteria for the diagnosis of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (NINCDS-ADRDA).[25] Other possible causes of dementia were excluded through comprehensive medical and laboratory testing and neuroimaging studies. Study inclusion criteria required that participants were 65 years of age or older and scored above 15 on the MMSE, so as to ensure that participants were able to comply with testing. The current sample had a mean of 76.7 years of age (standard deviation [SD]: 7.7), obtained a mean MMSE score of 22 (SD: 3.2), and had a mean of 11.4 (SD: 2.8) years of formal education. Exclusion criteria included preexisting neurologic and/or psychiatric disorders, unstable medical conditions, a history of significant head trauma, and the lack of a reliable caregiver willing to provide behavioral ratings. Written informed consent was obtained from both the

AD patients and their caregivers after they received a description of study procedures and potential risks and benefits.

Procedures

Cognitive assessment. All participants were administered the Mattis Dementia Rating Scale (DRS)[26] as part of a comprehensive neuropsychological assessment battery. The DRS is a psychometric instrument designed to evaluate the nature and severity of dementia, and it has been found to discriminate accurately AD from healthy elderly subjects with high sensitivity and specificity levels.[27] The DRS yields an index of global cognitive functioning, as well as subscale data for five specific cognitive skill areas: Attention (37 points), Initiation/Perseveration (37 points), Construction (6 points), Conceptualization (39 points), and Memory (25 points). The Initiation/Perseveration (IP) subscale of the DRS measures executive functions such as category fluency and complex sequencing abilities, and it has been shown to correlate significantly with other executive tests.[15,27] Scores from the IP subscale of the DRS were used as a measure of executive functioning in this study. Total DRS scores range from 0 to 144, with higher scores reflecting better performance. DRS Total and subscale scores were computed by summing relevant items, and raw scores were used in these analyses.

Frontal behavioral assessment. The frontal behavioral assessment was conducted on the same day as the neuropsychological evaluation and was done with the Frontal Systems Behavioral Inventory (FrSBe[28]). The FrSBe quantifies behavioral syndromes associated with frontal systems pathology, including apathy; it is a 46-item, caregiver-rated instrument that possesses high intrascale reliability and construct validity and has been shown to have validity for evaluating patients with frontal-systems lesions.[28,29] Using the FrBSe, caregivers rate a series of items designed to measure three frontal behavioral syndromes: Apathy (14 items), Disinhibition (15 items), and Executive Dysfunction (17 items). Individual items are rated for two time-points (pre- and post-disease onset) with a 5-point scale ranging from "Almost Never" to "Almost Always." This scale involves the use of retrospective accounts of behavior (caregivers rate pre- and post-illness behavior at a single time-point), and evidence suggests that caregivers are reliable reporters of premorbid personality functioning and are able to detect the onset of changes in personality after the patient's diagnosis of dementia.[28] FrSBe total and subscale difference scores (post-illness minus pre-illness) were calculated for use in the present analyses. Difference scores were used as estimates of current behavioral functioning because they adjust for premorbid personality functioning and therefore reduce the possibility of inflation of behavioral estimates.

ADL assessment. Caregivers completed the Lawton and Brody ADL Questionnaire,[5] an instrument designed to measure functional abilities in elderly patients with neurological disorders. This 14-item questionnaire consists of 8 questions pertaining to IADLs (e.g., ability to handle finances, manage medications; maximum score: 16) and 6 questions pertaining to BADLS (e.g., toileting, grooming; maximum score: 12). Item scores of 0 reflect complete dependence on others for task performance, 1: the need for some assistance, and 2: complete independence in task performance. Points obtained on each relevant subscale item were summed to calculate Total IADL and BADL scores, and the Total ADL score was computed by summing IADL and BADL scores for each patient. ADL scores served as the primary outcome variables in the present study.

Secondary outcome measures. In addition to the cognitive and behavioral assessments relevant to our specific hypotheses, we also assessed medical illness burden and depression in order to account for the potential impact of those factors on ADLs. Medical illness may result in functional declines independent of cognitive impairment,[30] although at least one study reported no association between medical burden and ADLs in patients with AD.[11] Medical illness burden was not expected to contribute significantly to the prediction of ADLs in this sample. We also measured depression to determine whether relationships between apathy and functional abilities were better accounted for by mood symptoms.

Medical illness burden was assessed with the Cumulative Index Rating Scale for Geriatrics (CIRS-G),[31] a clinician-rated tool designed to rate the presence and severity of illness in elderly subjects that has been shown to be valid when measured against postmortem pathology. Illness is rated on a severity scale from 0 to 4 (0: no illness; 4: very severe) across systems, including vascular, cardiac, hematopoietic, respiratory, renal, genitourinary, musculoskeletal, neurological (other than

dementia), endocrine, gastrointestinal, and ear-nose-throat-larynx. The total score is the sum of scores for each organ system, and total scores were used in the statistical analyses.

To assess depression, patients were administered the Geriatric Depression Scale-Short Form (GDS-S).[32] The GDS-S is a 15 item, self-report scale specifically designed to assess the presence of depression in elderly patients. This scale has been shown to have good reliability and validity for use even in populations with some cognitive impairment.[32] Individual items are read to the patient and the patient responds using a yes/no response, indicating the presence/absence of depressive symptoms. Total scores are calculated by summing the number of items endorsed that indicate the presence of depressive symptoms. Total GDS-S scores were used in the present analyses.

Statistical Methods

Pearson correlations were run to examine bivariate associations between the independent and dependent variables. Hierarchical multiple-regression analyses were used to test Hypotheses 1 and 2 examining the independent contributions made by global cognition and frontal behavioral functioning to ADLs and executive cognitive dysfunction and apathy to IADLs, respectively. Similarly, a hierarchical-regression analysis was used to examine hypothesis 3, and a second regression analysis incorporating an exploratory stepwise procedure was used to examine the relative contributions made by specific FrSBe subscale scores to BADLs. Secondary hierarchical-regression models were then run to examine possible effects of depression and medical illness burden on our primary outcome variables, with depression and medical illness burden entered as primary predictor variables before cognitive and behavioral predictors.

RESULTS

Mean performances on the DRS, FrSBe, and ADL measures are reported in Table 1. The mean DRS Total for this group was 109 (standard deviation [SD]: 14.4), which falls 15 points below the recommended cutoff for impairment, consistent with dementia. The mean ADL total score was 19.7 out of a possible 28 points, indicating a mild-to-moderate overall level of ADL impairment in this sample. The mean IADL score was 9 out of a possible 16 points (range: 3–16), indicating a moderate degree of IADL impairment, and the mean BADL score was 10.7 out of a possible 12 points (range: 5–12), indicating only a mild level of BADL impairment. The mean FrSBe scores indicated moderate overall levels of Apathy and Executive Dysfunction and a mild level of Disinhibition.

Prediction of Total ADLs

Bivariate correlations revealed highly significant correlations between the DRS Total and ADL Total scores ($r_{[43]} = 0.52$; $p<0.001$) and between the FrSBe Total and ADL Total scores ($r_{[43]} = -0.57$; $p<0.001$). A hierarchical multiple regression was then conducted to examine the independent contributions made by global cognitive and frontal behavioral measures to ADL Total scores, with DRS and FrSBe Total Scores as independent variables and ADL Total Scores as the dependent variable. As predicted, both contributed significantly to ADLs, with the overall model accounting for 40% of the variance in ADLs ($F_{[2, 42]} = 13.6$; $p < 0.001$). At Step 1, DRS Total explained 28% of the variance; at Step 2, FrSBe Total explained an additional 12% of the variance, thereby significantly increasing the variance accounted for by the entire model.

Prediction of Instrumental ADLs

Bivariate correlational analyses revealed significant associations between the IP subscale of the DRS and IADLs ($r_{[43]} = 0.41$; $p<0.01$) and FrSBe Apathy and

TABLE 1. Performance on the DRS, FrSBe, and ADL measures

Test	Mean score and standard deviation
DRS Total	109 (14.4)
DRS Attention	34 (1.8)
DRS Initiation/Perseveration	25.7 (7.4)
DRS Construction	5 (1.0)
DRS Conceptualization	29 (5.4)
DRS Memory	14 (4.4)
FrSBe Apathy (change score)	18.8 (11.9)
FrSBe Executive (change score)	23.6 (15.1)
FrSBe Disinhibition (change score)	9.2 (9.9)
IADL	9 (4.0)
BADL	10.7 (1.6)
Total ADL	19.7 (5.2)

Note: DRS: Mattis Dementia Rating Scale; FrSBe: Frontal Systems Behavioral Inventory; IADL: Instrumental Activities of Daily Living; BADL: Basic Activities of Daily Living; ADL: Activities of Daily Living.

IADLs ($r_{[43]} = -0.63$; $p<0.001$). Of note, no other DRS subtest correlated significantly with IADL performance; also, intercorrelations between all predictor variables were examined and consistently fell below 0.40. To examine the hypothesis that executive cognitive functioning and apathy contribute significantly to IADLs, a planned hierarchical multiple regression was conducted with IP and Apathy as the independent variables and IADLs as the dependent variable. The total model accounted for 44% of the variance in IADLs ($F_{[2, 41]} = 16.29$; $p < 0.001$). At Step 1, IP accounted for 17% in IADLs; at Step 2, Apathy explained an additional 27%, thereby significantly increasing the variance explained by the model.

Prediction of Basic ADLs

Bivariate correlations revealed significant negative associations between FrSBe Apathy scores and BADLs ($r_{[43]} = -0.45$; $p<0.01$) and FrSBe Executive scores and BADLs ($r_{[43]} = -0.37$; $p<0.02$), but FrSBe Disinhibition was not significantly associated with BADLs. IP was the only DRS subscale that correlated significantly with BADLs ($r_{[43]} = 0.31$; $p<0.04$). To examine the hypothesis that FrSBe subscales, but not IP, would contribute significantly to the prediction of BADLs, a planned hierarchical regression was conducted with IP entered at Step 1 as an independent variable (thus allowing IP to account for its unique variance before other factors) and FrSBe subscales entered at Step 2. The total model accounted for 28% of the variance in BADLs ($F_{[2, 40]} = 3.51$; $p = 0.017$) with both IP and FrSBe subscales contributing significantly to BADLs. At Step 1, IP explained 9% of the variance; at Step 2, the FrSBe subscales explained an additional 19%, thereby significantly increasing the total variance explained.

To further explore the contributions made by specific FrSBe subscales, a second regression was run, with IP entered at Step 1 and the three FrSBe subscales entered at Step 2, using an exploratory, stepwise regression procedure (entry criteria: $p<0.05$ for FrSBe subscales). After accounting for IP, only the Apathy subscale emerged as a significant predictor of BADLs; Apathy explained an additional 15% of the variance over and above IP ($F_{[1, 43]} = 6.22$; $p = 0.004$). The other FrSBe subscales (Executive Dysfunction, Disinhibition) and did not contribute significantly to the prediction of BADLs by use of this approach.

Secondary analyses. Age, medical illness burden, and depression did not correlate significantly with ADLs in bivariate analyses. However, to ensure that predictive relationships between cognitive and behavioral variables and ADLs were independent of such factors, we re-ran the same hierarchical regressions reported above with age, medical status, and depression entered as independent variables before relevant cognitive and behavioral variables. Results revealed no significant predictive association between age, medical status, or depression and total ADLs, IADLs, or BADLs.

Discriminant function analysis. A post-hoc discriminant function analysis was conducted to determine how accurately the IP subscale of the DRS and FrSBe Apathy scores could classify AD patients into "high" and "low" ADL groups. High and low ADLs were determined with a median split on ADL Total scores. The median Total ADL score was 20.5 (out of a possible 28 points); therefore, for this analysis, scores of 21 or greater were considered high, and scores of 20 or lower were considered low. Using the IP and Apathy subscale scores, an overall classification accuracy of 88.6% (canonical correlation: $r = 0.67$; $p<0.001$) was obtained, with 82% of the low ADL group correctly classified and 95.5% of the high ADL group correctly classified.

DISCUSSION

The present results demonstrate that executive cognitive and frontal behavioral impairments contribute independently to functional deficits in patients with mild-to-moderate AD. These findings are the first that we are aware of that demonstrate the role of specific frontal/executive deficits in determining ADL impairment and are the first to demonstrate the independent effect of frontally-mediated behavioral symptoms, above and beyond cognitive status. Frontally-mediated behavioral disturbances such as apathy are associated with significant patient and caregiver distress and increased healthcare utilization,[6,15] and our findings reflect the direct effect of apathy on ADLs.

Importantly, apathy, in this sample, was the only frontally-mediated behavioral symptom found to be significantly associated with both IADL and BADL impairment. Previous studies have suggested that behavioral disturbances may play an important role in determining

functional outcomes for dementia patients,[11,15,18,22] but previous research has not examined the role of specific behavioral symptoms by means of a hypothesis-driven approach. In our sample, apathy accounted for 27% of the variance in IADLs, even after accounting for executive cognitive dysfunction. This finding demonstrates a strong association between motivational loss and performance of IADLs. Moreover, when compared with the other frontal behavioral syndromes, apathy emerged as the only significant behavioral predictor of basic self-care activities in our sample, accounting for 15% of the variance in BADLs over and above executive dysfunction. That apathy affected simple self-care abilities in even mild-to-moderately impaired individuals confirms a strong association between apathy and functional abilities in patients with AD.

The finding that executive dysfunction and apathy were uniquely associated with ADLs, after accounting for depression and cognitive impairment, also has important implications for the assessment and treatment of patients with AD. Our data indicated only a modest correlation between the FrSBe Apathy score and the GDS score ($r = 0.24$), supporting the idea that apathy is distinct from depression[33] and providing new evidence that apathy is uniquely associated with functional deficits. Such findings underscore the need for the careful assessment of apathy as a potentially debilitating symptom of AD. Apathy may also represent a specific target for treatment interventions aimed at reducing disability among patients with AD.

Our finding that executive cognitive dysfunction was an important determinant of self-care abilities is consistent with findings from patients with other neurologic disorders[12,16,17] and indicates a similar relationship between executive cognitive dysfunction and independent living skills in AD. Executive cognitive functions include complex thinking abilities, mental flexibility/set shifting, and goal-directedness.[34] Individuals with executive cognitive dysfunction likely have difficulty organizing and carrying out complex IADLs, such as medication management, that require the initiation of a goal-directed behavior, organization of action, and persistence. Although executive dysfunction also was associated with performance of BADLs, it is important to acknowledge that the magnitude of this effect was smaller than for IADLs. The need for intact executive cognitive abilities may be considerably less for BADLs, as behaviors such as feeding and grooming are more routine and overlearned.

Both executive cognitive dysfunction and frontal behavioral syndromes are associated with frontal-systems pathology.[34,35] and our results emphasize the importance of the careful assessment of frontal/executive functions in AD. Apathy is believed to be mediated by mesial-frontal neural networks,[33] whereas executive cognitive dysfunction is associated with dorsolateral-frontal dysfunction.[34] Therefore, evaluations of only one aspect of frontal/executive functioning (e.g., cognitive but not behavioral) may omit important information for the estimation of a patient's functional capabilities. Our data indicate that frontal behavioral and executive cognitive deficits are independently associated with ADL failures, and AD patients who present clinically with prominent frontal/executive deficits may benefit from formal evaluations of functional status.

We did not find a significant association between medical illness burden and ADLs. Previous findings have been equivocal, but our results support those of Tekin and colleagues[11] and suggest that medical illness burden does not affect functional impairment in AD among patients in the mild-to-moderate stages of the disease. However, it is noteworthy that patients in the current study were community-dwelling and had relatively low levels of medical illness. Medical problems may play a more critical role in determining ADLs as illness burden increases in severity and affects mobility.

Some methodological limitations of the current study warrant discussion. First, this study involved the analysis of cross-sectional data. Although we were able to investigate statistical predictors of functional impairment with this design, true predictors are best identified with a longitudinal design. This study therefore identified potential predictors of future functional impairment that warrant further investigation with longitudinal designs. Second, this study involved a relatively small sample of AD patients, with only mild-to-moderate cognitive impairment and relatively mild BADL impairment. Although significant results were found, the small sample size limits our ability to determine the absolute magnitude of estimates of the proportion of variance accounted for by the independent variables (particularly with respect to BADLs, as our range of BADL scores also was restricted). Finally, we utilized only one measure of executive cognitive dysfunction. Although the IP subtest of the DRS is recognized as an appropriate test of executive impairment in dementia, the analysis of other executive tasks may yield important informa-

tion regarding the usefulness of such tests for detecting functional deficits in patients with AD. Future studies investigating the predictors of ADL dysfunction in AD should include longitudinal designs and use multiple tests of executive cognitive functions.

The identification of possible predictors of functional declines in patients with AD has significant healthcare implications. An improved understanding of the factors associated with functional disability may enable early identification of patients likely to need assistance and may facilitate the development of techniques to prolong independence even among individuals already experiencing cognitive decline. Strategies aimed at improving executive cognitive functioning and reducing frontally-mediated behavioral disturbances such as apathy may greatly improve daily functioning and quality of life of AD patients and their caregivers. We need future studies using longitudinal designs that investigate the predictors of functional disability in dementia patients.

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ORIGINAL CONTRIBUTION

Executive Dysfunction in Alzheimer Disease

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Background: Executive dysfunction (EDF) is common in Alzheimer disease (AD); however, its relationship to other symptoms is difficult to assess in patients with AD.

Objectives: To determine the prevalence of EDF and study its relationship to cognitive, functional, and neuropsychiatric symptoms in patients with AD.

Design, Setting, and Patients: A retrospective analysis of data from participants in the English Instruments Protocol of the Alzheimer's Disease Cooperative Study. Subjects were drawn from a sample of patients evaluated at tertiary referral centers.

Results: A total of 64% of AD patients were classified as having EDF. Patients with EDF performed worse on tests of cognition ($P<.001$), dementia severity ($P<.001$), and activities of daily living ($P=.01$) and had more frequent symptoms of psychosis ($P=.03$) with greater emergence during the 12-month interval ($P=.03$) compared with patients with normal executive function. Less than 30% of the variance in executive function performance was explained by cognitive measures.

Conclusion: These findings support the assessment of executive function in persons with AD and the importance of frontal lobe dysfunction in AD.

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ALZHEIMER DISEASE (AD) affects an estimated 4 million people in the United States and is the leading cause of late-onset dementia worldwide. Its core features include impairments in memory, visuospatial functions, language, executive functions (EFs), and neuropsychiatric symptoms.[1] Defined as the ability to abstract, plan, organize, shift set, and adapt current and past knowledge to future behavior, EF occurs in AD, but its prevalence and relationship to other clinical and demographic features of the disease are unknown. Recent studies[2-4] suggest that executive dysfunction (EDF) is a common manifestation of AD and occurs in all stages of the illness, although it is more mild than in the frontotemporal lobar degenerations. There also is evidence to support a frontal variant of AD. Johnson et al[5] conducted a clinicopathologic study on a sample of 16 patients with AD and found that there was a subset that had early and prominent impairment on tests of EF; other test scores were similar across the groups. Autopsy studies of the frontal variant patients revealed significant increases in the number of neurofibrillary tangles in the frontal cortex compared with patients with more typical AD. Several studies[6,7] using standard neuropsychological tests of EF have demonstrated links among EDF and functional decline measured by poor performance on activities of daily living (ADL) scales. Using functional imaging and neuropathologic data, a link has been found between frontal involvement and psychosis in AD[8-10] and between agitation and frontal dysfunction, suggesting that EDF might be linked to behavioral disorders.[11-16]

In routine clinical settings, standardized tests of EF that were not specifically designed to test EF in patients with AD, such as the Stroop color word interference test,[17] the Wisconsin Card Sorting Test,[18] and the Controlled Oral Word Association Test,[19] result in floor effects for many AD patients, suggesting that better measures of assessing EF in patients with dementia are needed. The original Alzheimer's Disease Assessment Scale–Cognitive portion (ADAS-Cog) was recently modified to include 2 tests of EF—letter cancellation and mazes—that are easy to administer and can be performed by AD patients in mild and moderate stages of the disease.[20] The prevalence of abnor-

malities of EF as measured by these tests and the association between the executive measures behavior and function have not been systematically evaluated.

This project sought to define EDF using ADAS-Cog measures and to estimate the prevalence of EDF in a sample of AD patients drawn from specialty referral centers. We hypothesized that patients with EDF as identified by ADAS-Cog tasks would have (1) worse general cognitive function, (2) greater progression of cognitive impairment measure 12 months after baseline, (3) more impairment of ADL, and (4) more abnormal behaviors.

METHODS

SUBJECTS

We retrospectively analyzed responses from cognitively normal, elderly controls (NECs) and a subset of patients who had participated in the English Instruments Protocol of the Alzheimer's Disease Cooperative Study[21] but were not participants in the treatment of agitation protocol.[22] The English Instruments Protocol was specifically designed to test new measures that might be used in clinical trials and to determine their psychometric properties. Patients did not receive experimental treatment in the case of this study. A total of 137 subjects (62% female) with probable AD diagnosed using the National Institutes of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria[23] and with Mini-Mental State Examination (MMSE)[24] scores higher than 10 were identified for inclusion in these analyses. A control sample of 64 cognitively normal volunteers (57% female) was included for comparison. All subjects were older than 45 years (mean±SD age, 70.3±8.8 years for controls and 72.9±8.4 for AD patients), with a minimum of 6 years of education (mean±SD years of education, 13.8±2.9 for controls and 13.3±2.8 for AD patients), and had reliable caregivers. Subjects were free of preexisting psychiatric illness, including schizophrenia, recurrent depression, and substance abuse. Those requiring use of psychoactive agents, with a history of significant medical problems, or with a history of significant head trauma were excluded. A complete description of inclusion and exclusion criteria used in this protocol is found elsewhere.[21]

PROCEDURES

All subjects were evaluated at baseline and again at scheduled intervals during the next 12 months. Information and test results obtained at baseline and 12 months were included in this study. Six participants in the AD cohort did not have valid EF test data at baseline and were therefore not included, so our sample size was 131.

EXECUTIVE FUNCTION

Executive function was tested using the most complex of a series of 6 cancellation tasks and the time to complete the first 3 mazes from the expanded ADAS-Cog.[20] The letter cancellation task tests the subject's ability to concentrate and use appropriate search strategies. During this "either of 2 numbers" task, the patient is asked to cross out either of 2 numbers (eg, 3 or 7) that were randomly mixed in with other numbers on a sheet of paper. The score is obtained by subtracting the number of incorrectly crossed off items and the number of reminders given from the number of correctly crossed off items, with a minimum score imposed as 0. A maximum score is 40; lower scores indicate worse performance.

The maze task assesses impulse resistance, planning, reasoning, and foresight. During the maze task, subjects are given a series (up to 7) of increasingly difficult mazes to complete as quickly as possible. Mohs et al[20] recommended that the first 3 mazes be used in future studies because these could be completed by most AD patients, thus limiting floor effects. One incorrect decision is allowed, after the second "dead end" the maze was discontinued, and the maximum time per maze was assigned. The maximum time allowed to complete each maze is 240 seconds, yielding a total maximum time of 720 seconds. Higher scores indicate worst performance.

We defined EDF as scores more than 1.5 SDs below the mean scores obtained by the NECs. To establish the validity of this approach, we defined cutoff values for both the cancellation task and the maze times based on NEC performance at both the baseline and 12-month visits.

OTHER MEASURES

The cognitive function of patients was measured by the MMSE, a 30-point test that assesses the domains of attention, orientation, calculation, memory, language, and visuospatial functioning, and with the Clinical Dementia Rating Scale sum of boxes (CDR SB).[25] The CDR SB has a range of 0 to 18, representing the sum of 6 individual domains in the instrument; higher scores indicate worse dementia. Behavioral disturbances were assessed using the Cohen-Mansfield Agitation Inventory (CMAI),[26] a 36-item, informant-based scale that rates behaviors observed in the past 2 weeks, and the Behavior Rating Scale for Dementia (BRSD),[27] a 48-item, informant-based scale that rates behaviors that have occurred in the last month. The BRSD has been subjected to a factor analysis, with 6 factors being identified: behavioral dysregulation, depression, inertia, irritability/aggression, psychosis, and vegetative symptoms. The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory,[28] which assesses both basic ADLs, such as bathing, grooming, walking, and dressing, and instrumental ADLs, such as handling mail, discussing current events, and using household appliances, was administered to measure functional impairment. The range of scores is 0 to 78, with higher score indicating better function.

STATISTICAL ANALYSIS

The distribution of the control scores on each task at baseline and 12 months was evaluated to determine if establishing cutoff values based on the mean and standard deviation was appropriate. We used Shapiro-Wilk tests of normality and examined skew, kurtosis, and quantile-quantile plots of the control scores.[29] Means and standard deviations for the 2 EF measures in NECs were calculated at baseline and 12 months so that 4 cutoffs were established to evaluate the validity of classifications of AD patients as EDF. However, only cutoffs based on normally distributed control scores at baseline were used in the exploration of the relationships between EF and cognitive, functional, and behavioral variables.

After determining the most appropriate way of identifying AD patients as having EDF or normal EF (NEF), unpaired *t* tests were used to explore the association between EDF and the CDR SB, MMSE, ADL Inventory, CMAI, and BRSD at baseline and 12 months. Holm adjustment[30] for multiple comparisons was used, and adjusted *P* values less than .05 were considered statistically significant.

Emergence of BRSD subscores was calculated as the number of items in that subscore that emerged divided by the number of items in that subscore that were eligible to emerge. Eligibility for emergence was defined as the proportion of BRSD items given a frequency rating of 0 or 1 (symptoms present 2 or fewer days in the previous month) at the baseline visit and

Association Between EDF and NEF and Other Domains in 137 Patients With AD*

Variable	AD Patients With EDF	AD Patients With NEF	*P* Value
Education, y	12.9 ± 2.7	14.2 ± 3.0	.14
Duration of AD, y	4.8 ± 3.3	4.5 ± 1.9	.52
Age, y	72.4 ± 8.4	74.0 ± 8.5	.62
CDR SB, baseline	8.5 ± 2.6	6.8 ± 2.3	<.001
CDR SB, change†	–2.9 ± 2.4	–1.4 ± 2.0	.01
MMSE, baseline	17.2 ± 4.2	21.4 ± 4.0	<.001
MMSE, change†	–5.5 ± 4.4	–2.6 ± 4.6	.02
Cancellation task, baseline, No. of hits†	8.2 ± 4.7	22.4 ± 5.1	<.001
3 Maze times, baseline, s†	243.0 ± 157.5	100.3 ± 106.1	<.001
ADL, baseline†	48.3 ± 14.3	57.1 ± 14.2	.01
CMAI, baseline	22.9 ± 19.3	17.4 ± 13.8	.54
BRSD-t, baseline	26.3 ± 16.5	20.7 ± 15.0	.46
BRSD-dep, baseline	4.8 ± 5.0	3.0 ± 3.3	.14
BRSD-psych, baseline	1.8 ± 3.1	0.5 ± 1.3	.01

Abbreviations: AD, Alzheimer disease; ADL, activities of daily living; BRSD-dep, BRSD depression score; BRSD-psych, BRSD psychosis score; BRSD-t, Behavorial Rating Scale for Dementia total score; CDR SB, Clinical Dementia Rating Scale sum of boxes; CMAI, Cohen-Mansfield Agitation Inventory; EDF, executive dysfunction (by baseline visit cancellation task); MMSE, Mini-Mental State Examination; NEF, normal executive function.
*Data are presented as mean ± SD.
†Change during 12 months.

that were given a frequency rating higher than 2 (symptoms present at least 3 days in the month before the 12-month visit) at the 12-month visit. Nonparametric *t* tests were used to compare emergence rates for patients characterized as EDF or NEF.

Finally, the 2 cognitive severity scores were univariately regressed on the baseline score on which the EDF classification was based. Using this approach, we estimated the proportion of variance in EDF task performance that could be explained by cognitive functioning.

RESULTS

DEFINITION OF EDF BASED ON NEC SCORES

Distribution of NEC scores for maze times was not normally distributed, but distribution of NEC scores for letter cancellation was, making cancellation task scores more appropriate for defining EDF, estimating prevalence, and exploring relationships between EDF and other domains. The cutoff scores for the cancellation tasks were 37.2/40 for the baseline visit and 37/40 for the12-month visit. Any person with scores at or better than these levels was classified as having NEF for that visit. For the maze times, the cutoff scores were 88.2/720 seconds for the baseline visit and 69.4/720 seconds for the 12-month visit. Any person with a sum of maze times at or faster than this was classified as having NEF at that visit.

Using the cutoff scores at baseline for letter cancellation, 6% of NECs and 64% of AD patients were classified as having EDF. Based on maze times at baseline, 2% of NECs and 58% of AD patients were classified as having EDF. Neither floor nor ceiling effects were present.

Misclassification, defined as an EDF label at baseline and an NEF label at 12 months, was minimal using the cancellation task: 3 of the 64 controls were labeled as having EDF at baseline; only 1 was misclassified (scored as having NEF) based on 12-month results. Two (3%) of 64 AD patients labeled as having EDF at baseline were labeled as having NEF at 12 months. However, using the maze times criteria, 13 (22%) of 58 AD patients labeled as having EDF at baseline were labeled as having NEF at 12 months; no controls were misclassified based on maze times.

ASSOCIATION BETWEEN EDF AND OTHER DOMAINS

The cancellation task at baseline was used to classify the AD cohort as having EDF or NEF because of the low degree of misclassification and its normal distribution. We therefore explored the association between EDF or NEF status and scores from tests of other domains in this cohort.

The **Table** presents the means and standard deviations of the scores across the AD cohort grouped as EDF or NEF, as well as the results of independent-sample *t* tests performed to compare scores on the CDR SB and MMSE at baseline and change during the 12-month study and baseline scores of the ADL, CMAI, and BRSD total and subscores. Age, years of education, and duration of dementia were not different between subjects in the EDF and NEF categories.

Patients classified as having EDF had significantly more severe dementia (based on CDR SB), worse cognitive functioning (MMSE score), poorer ADL scores, and more frequent symptoms of psychosis at baseline. These individuals also demonstrated significantly greater worsening in terms of dementia and cognitive functioning 12 months after baseline. Similar results were seen when EDF and NEF were based on the sum of maze times.

The emergence of psychosis during 12 months in those patients with EDF at both baseline and 12 months (n=61) measured by cancellation task scores was 5 times (7.2%) the rate observed in those with NEF at both baseline and 12 months ($P=.03$). Only 12 of the 34 patients classified as having NEF at baseline continued to have NEF at the follow-up visit. Psychosis emergence in those with EDF at baseline was nearly double the rate observed in those with NEF at baseline; however, this was not statistically significant ($P=.20$).

INDEPENDENCE OF EF AND OVERALL COGNITIVE STATUS/DEMENTIA SEVERITY

Univariate regression for each of the instrument scores on the baseline cancellation task scores for the AD cohort revealed significant association with baseline values on CDR SB ($F_{1,129}=28.1$, $P<.001$), MMSE ($F_{1,129}=48.8$, $P<.001$), and ADL ($F_{1,129}=26.7$, $P<.001$). These analyses showed that with no other variables in the model, 28% of the variance in cancellation task performance at baseline was explained by baseline MMSE score and 18% was explained by baseline CDR SB score in the AD patients.

COMMENT

Executive dysfunction was common in this sample of AD patients, with an estimated prevalence of 64%. Executive dysfunction was significantly associated with MMSE, CDR SB, and ADL scores and frequency of psychosis at baseline and with worsening demonstrated by change in MMSE and CDR SB scores during the 12 months. Psychosis symptom emergence also was significantly associated with the presence of EDF at the baseline and 12-month visits. The association with CDR SB and ADL scores indicates that the sample with EDF had poorer everyday and community function.

The finding that less than 30% of the variance in the EF task performance could be attributed to overall dementia severity or global cognitive status suggests that the cancellation task recommended by Mohs et al[20] is an appropriate measure of EF in this particular patient population and is not simply a measure of general cognitive decline. These data, derived from a subset of patients tested by Mohs et al,[20] suggest that the letter cancellation test may have predictive value, with poorer performance indicating greater neuropsychiatric impairment at baseline and in the future.

Several reports in the literature have examined the association between ADL performance and cognitive status. A few have specifically evaluated the association between EF and ADL. Tekin et al[6] assessed the relationship of ADL with neuropsychiatric symptoms, cognition, and medical illness burden. They found a correlation between instrumental ADL performance measured using the Functional Activities Questionnaire[31] and MMSE score. However, they found that neuropsychiatric symptoms were more strongly correlated with Functional Activities Questionnaire score than MMSE performance. Other investigators have identified correlations between impaired functional abilities and EDF.[32,33] When studies examined ADL performance and cognition, they showed ADL performance declined with increasing dementia severity; however, when studies examined individual cognitive domains, executive abilities accounted for most of the variance.[34] Similarly, we found a strong correlation between ADL performance and EF. Patients who are unable to perform many of their hobbies, chores at home, and personal grooming (items rated in both the CDR and the ADL Inventory) because of EDF would have worse scores for these items compared with AD patients without EDF.

We found a relationship between psychotic symptoms and executive impairment in the present study, and this has been reported previously.[16,35-38] In the few studies[32,39] that looked specifically at the executive domain, it was found that patients with psychosis perform more poorly on executive tasks compared with their performance on tests of other cognitive functions. Our results show that patients with EDF at baseline have a greater risk of developing psychosis at the 12-month visit. This suggests that EDF may have predictive value. Functional imaging data also suggest that there is a greater degree of frontal hypometabolism and perfusion in patients with psychotic symptoms.[8,14]

Limitations of this study should be considered when interpreting its results. Our sample population was drawn from specialty referral centers, and findings may not be generalizable to a broader community sample of patients with AD. Sampling patients who came into referral centers may have introduced bias (ie, patients with greater EDF and more functional impairment may have been less willing to participate in this study). This bias would lead us to underestimate the prevalence of EDF in the general community. Alternatively, it is possible that patients with more impairment were recruited because physicians are more likely to refer problematic and challenging patients to referral centers. Our measures of EF are not standard measures given in neuropsychological test batteries. These measures were, however, adapted from paradigms used in cognitive and clinical neuropsychology[38,40] to test EF. No concurrent validity assessment was performed, and we cannot draw conclusions about the prevalence or correlates of EDF as measured by other EF tests. Finally, some aspects of behavior mediated by the frontal lobes such as apathy are not well assessed by the BRSD or CMAI. Therefore, our behavioral measures may not have been sufficiently sensitive to the symptoms most likely to be associated with EDF and/or frontal lobe impairment.

In summary, this study has demonstrated that EDF is present in approximately 60% of a community-dwelling cohort of AD patients and is associated with greater dementia severity, worse overall cognitive status and functional impairment, and more frequent and higher emergence rates for symptoms of psychosis. Although the cancellation task was better for establishing a cutoff at which EDF could be defined, both the mazes and the cancellation task may be valuable in the clinical assessment of patients because poor performance correlates with functional decline and neuropsychiatric symptoms. These 2 brief measures of EF may be helpful to clinicians when more extensive standardized tests of EF are too difficult to be performed by AD patients. The association of EDF and psychosis emergence may help physicians and caregivers in the monitoring and treatment of these symptoms. Finally, the ADAS-Cog with the addition of letter cancellation and mazes is increasingly used in drug trials to monitor clinical response. The association we found between EDF as measured by these tests and performance on the ADL may provide additional means of assessing relationships among cognitive, functional, and behavioral changes in response to therapy.

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quisition of data (Dr Mohs and Thal); *analysis and interpretation of data* (Drs Swanberg, Tractenberg, Mohs, and Cummings); *drafting of the manuscript* (Drs Swanberg and Tractenberg); *critical revision of the manuscript for important intellectual content* (Drs Tractenberg, Mohs, Thal, and Cummings); *statistical expertise* (Dr Tractenberg); *administrative, technical, and material support* (Drs Tractenberg and Mohs); *study supervision* (Dr Thal and Cummings).

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Executive Dysfunction in Alzheimer's Disease: Association With Neuropsychiatric Symptoms and Functional Impairment

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Relationships between measures of executive skills and neuropsychiatric and functional status were examined in a group of 31 patients with Alzheimer's disease. Deficits in four executive skills tests were significantly associated with the Agitation/Disinhibition factor score and Total Neuropsychiatric score on the Neurobehavioral Rating Scale, as well as the Activities subscore on the Blessed Dementia Scale. The majority of these associations remained significant after covariance for Mini-Mental State Examination scores. Executive dysfunction is associated with clinically relevant neuropsychiatric symptoms and functional impairment in Alzheimer's disease. These associations may be independent of other cognitive deficits such as memory, language, and visuospatial skills, and may not be appreciated on routine clinical evaluations. Executive skills deficits, neuropsychiatric symptoms, and functional disability may emerge from shared neurobiological mechanisms.

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Alzheimer's disease (AD) is characterized by impairment in multiple cognitive domains, including memory, language, visuospatial skills, and executive functions. Executive functions are those cognitive processes that orchestrate the performance of complex, goal-oriented tasks and behaviors.[1] These abilities include motivation, strategy development and adjustment, response control, and abstraction, and they are mediated primarily by prefrontal brain regions.[2,3] Impairment of executive functions occurs in multiple neuropsychiatric disorders, including dementias, schizophrenia, and major depression.[4–6] The effect of AD on executive functions is poorly understood. Limited data suggest that executive dysfunction is common in AD[2] and is associated with delusions,[7] rapid progression of dementia,[8] and a need for a high level of care.[5]

Agitation, psychosis, depression, and apathy are common neuropsychiatric disturbances in patients with AD. Such neuropsychiatric symptoms may result in increased caregiver distress,[9] a higher rate of nursing home placement,[10] and more rapid disease progression.[11,12] Neuroimaging and neuropathologic studies indicate that neuropsychiatric symptoms are associated with dysfunction in specific brain regions and that dysfunction of the frontal cortex may be particularly relevant to noncognitive expressions of the illness.[13–16]

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There is little consensus on the relationship between cognitive deficits and the neuropsychiatric symptoms that occur in patients with AD; different studies have found no association,[17] a positive correlation,[18] weak positive associations,[19,20] a negative association,[21] and mixed relationships.[22] Studies of cognitive deficits and mood symptoms have also revealed mixed results.[23–27] The relationship between cognitive impairment and functional disability is better supported.[28,29] Most of these studies used measures of global cognition such as the Mini-Mental State Examination (MMSE),[30] which contains memory, language, and visuospatial items, but not tests of executive function. The relationship between executive dysfunction and neuropsychiatric or functional status remains unclear.

We evaluated the presence and the extent of executive dysfunction in patients with AD. Neuropsychiatric symptoms and overall functional ability were also measured. The goals of this study were to 1) test the hypothesis that executive dysfunction is associated with greater neuropsychiatric symptomatology and functional impairment, and 2) explore relationships between executive dysfunction and specific types of neuropsychiatric symptoms.

METHODS

Participants

Participants were recruited from the Dementia Clinic, Neurobehavior Inpatient Unit, and Geropsychiatry Inpatient Unit of the West Los Angeles Veterans Affairs Medical Center, and from the UCLA Memory Disorders Clinic and Alzheimer's Disease Clinic. A convenience sample of 31 patients was included in the study. Each patient and his or her closest relative consented to participate in the study after the procedure had been fully explained.

Each patient had undergone a thorough clinical evaluation that included complete blood count, chemistry panel, serum thyroid-stimulating hormone and vitamin B_{12} levels, and structural neuroimaging study with magnetic resonance imaging (MRI) or computed tomography (CT). Cerebrospinal fluid analysis, electroencephalogram, urine heavy metal screen, and serum human immunodeficiency virus antibody assay were performed when clinically indicated. Final diagnosis was determined by a clinical research investigator.

Patients met the criteria for probable AD established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[31] Structural neuroimaging results for all patients with AD were normal, demonstrated cerebral atrophy, or showed only thin periventricular lucency (on CT) or hyperintensity (on MRI). Patients were excluded from the study if there was a history of a psychotic disorder unrelated to dementia, a history of head trauma resulting in loss of consciousness, a psychoactive substance use disorder, or a systemic illness or other neurological condition that could account for the cognitive impairment. The severity of noncognitive symptoms was not an inclusion or exclusion criterion. All patients were free of psychoactive medications for at least 3 weeks prior to the research assessment. No patient had been treated with a cholinesterase inhibitor.

Clinical Assessment

The neuropsychological assessment was completed by a subspecialty-trained neuropsychologist. We selected seven tests of executive function that we felt represented different aspects of executive functioning (shown in parentheses):

1. Controlled Oral Word Association Test[32] FAS subtest (verbal fluency, initiation).
2. Mattis Dementia Rating Scale (MDRS)[33] Conceptualization (similarities, abstraction).
3. MDRS Initiation (verbal and motor sequences, patterns, initiation).
4. Stroop[34] Interference (response inhibition).
5. Trail Making[35] Part B (divided attention, sequencing).
6. Wisconsin Card Sorting Test (WCST)[36] Categories (problem solving).
7. WCST Perseverative Errors (set shifting and flexibility).

The assessment of neuropsychiatric symptoms and functional ability was performed by one investigator (D.L.S.) within 2 weeks of the neuropsychological assessment and included the following instruments:

1. The MMSE, a measure of overall cognitive impairment.
2. The Neurobehavioral Rating Scale (NRS), a 28-item observer-rated assessment of cognitive and noncognitive symptoms in dementia. Principal components analysis has revealed six NRS factors: Agitation/Disinhibition, Anxiety/Depression, Behavioral Retardation, Psychosis, Cognition/Insight, and Verbal Output Disturbance.[27,37] The NRS Total Neuropsychiatric score represents the sum of 20 items measuring noncognitive symptoms. Each NRS item is scored on a scale of 0 (not present) to 6 (extremely severe).

3. The Blessed Dementia Scale–Activities subscale (BDS-A),[38] an 11-item caregiver-rated measure of the patient's ability to perform daily activities, including eating, dressing, managing money, and performing household tasks.

Statistical Analysis

We used Kendall's tau-b and Kendall's partial tau[39] correlation analyses to examine the associations of executive dysfunction with neuropsychiatric symptomatology and with functional disability. Correlations independent of global cognitive impairment were examined by covarying for MMSE scores.

RESULTS

Patient Characteristics

Thirty-one men participated in this study; the majority of patients were recruited from VA treatment sites as described above. Mean age was 69.9 years, mean MMSE score was 17.6, mean duration of illness was 4.1 years, and mean educational background was 13.9 years.

Measures of Executive Function, Neuropsychiatric Symptoms, and Functional Ability

Scores on tests of executive function and scales of neuropsychiatric symptoms or functional ability are shown in Table 1. A broad range of scores was present on all measures. Moderate floor effects were observed on three executive skills tests: 13 patients (42%) were unable to perform the Stroop Interference Test (maximum time 500 seconds), 17 (55%) were unable to perform the Trail Making Test Part B (maximum time 500 seconds), and 10 (32%) committed the maximum 47 perseverative errors on the WCST. Data from these tests were excluded from further analysis. Higher scores on the remaining four tests of executive function indicate better performance. Higher scores on the NRS and the BDS-A indicate more severe neuropsychiatric symptoms or functional disability.

TABLE 1. Scores on executive skills tests, Neurobehavioral Rating Scale, and Blessed Dementia Scale–Activities subscale (BDS-A)

Variable	Mean ± SD	Range
Executive skills tests		
FAS (words/min)	17.0 ± 12.2	0–47
MDRS Conceptualization	26.8 ± 9.0	4–39
MDRS Initiation	22.2 ± 8.5	5–36
WCST Categories	1.38 ± 1.4	0–5
Neurobehavioral Rating Scale		
Agitation/Disinhibition	5.9 ± 3.1	1–14
Anxiety/Depression	3.4 ± 2.7	0–9
Behavioral Retardation	2.1 ± 3.1	−2–10
Psychosis	3.4 ± 3.3	0–13
Total neuropsychiatric	13.6 ± 5.1	5–24
Functional ability		
Blessed Dementia Scale–Activities	5.3 ± 2.7	1–13

Note: FAS = Controlled Oral Word Association subtest; MDRS = Mattis Dementia Rating Scale; WCST = Wisconsin Card Sorting Test.

Relationships Between Executive Dysfunction and Neuropsychiatric Symptoms

Relationships between low scores on executive skills tests and greater neuropsychiatric symptoms emerged (Table 2). Executive dysfunction correlated most robustly with NRS Agitation/Disinhibition and Total Neuropsychiatric scores. Kendall's tau-b ranged from –0.31 to –0.55, reaching statistical significance at the $P<0.01$ level in all analyses. Statistically significant relationships also emerged between poor performance on some of the executive skills tests and scores on NRS Psychosis and Anxiety/Depression factors. There was no significant correlation between scores on executive skills tests and the NRS Behavioral Retardation score.

After covariance for MMSE using partial correlations, 8 of 11 correlations between executive dysfunction and neuropsychiatric symptoms remained statistically significant (tau-b range –0.32 to –0.45, $P<0.05$), indicating that the majority of these relationships were independent of the effects of MMSE scores (Table 3). MMSE scores did not correlate significantly with neuropsychiatric symptoms, with the exception of NRS Total Neuropsychiatric scores (tau-b = –0.32, $P<0.01$).

Relationships Between Executive Dysfunction and Functional Ability

Relationships were found between executive deficits and functional disability (tau-b range –0.33 to –0.70, $P<0.005$; Table 2). Correlations between functional impairment and three of four tests—MDRS Conceptualization, MDRS Initiation, and WCST Categories—maintained statistical significance after covariance for MMSE scores ($P<0.05$), despite a relatively high degree of correlation between MMSE and BDS-A scores (tau-b = –0.52, $P<0.005$).

DISCUSSION

In this study of patients with AD we found significant relationships between executive dysfunction and neuropsychiatric symptoms. Poor performance on four tests of executive functioning was significantly associated with greater degrees of agitated and disinhibited behaviors, as well as overall neuropsychiatric disturbance.

Spearman correlation coefficients for these relationships ranged from –0.58 to –0.68, indicating that scores on executive skills tests accounted for 34% to 46% of the variance of the NRS Total Neuropsychiatric scores. Low scores on tests of executive function were also associated with psychosis and with anxiety and depression, although not for all tests and not as strongly. There was no association between executive dysfunction and scores reflecting apathy, blunted affect, and psychomotor retardation.

The majority of these relationships between executive dysfunction and neuropsychiatric symptoms were independent of MMSE scores, suggesting that there is greater specificity for executive deficits that extends beyond global cognitive abilities. Previous studies that examined the relationships between cognition and behavior in patients with AD did not focus on specific areas of cognition.[17–19,21–26] Two studies compared the neuropsychological profiles of dementia patients with and without delusions. Jeste et al.[7] reported that AD patients with delusions performed more poorly on tests of memory, conceptualization, and verbal fluency than those without delusions. Flynn et al.[20] found that the delusional group had more difficulty with abstraction. Neither study controlled for degree of dementia or examined other types of neuropsychiatric symptoms. Our study demonstrates that a focused area of cognitive impairment, loss of executive skills, is accompanied by, and is a possible marker for, neuropsychiatric symptoms in AD, beyond the effects of global cognitive impairment.

Executive dysfunction was also significantly associated with inability to perform daily activities in this group of patients with AD. The relationship between WCST Categories scores and functional ability was particularly strong, and remained statistically significant after covariance with MMSE. The Spearman correlation and Spearman partial correlation coefficients for this relationship were –0.82 ($P<0.005$) and –0.58 ($P<0.005$), respectively, indicating that scores on this test accounted for more than 67% of the variance in scores of functional ability without controlling for MMSE, and 34% of the variance after controlling for MMSE. The ability to perform daily living activities to care for oneself may thus require a cognitive flexibility and a resistance to interference or distraction that are independent of overall level of cognition. The presence of executive skills deficits in a patient with AD therefore has important clinical implications for the level of care that the patient requires. Previous studies on AD, using other measures, have found relationships between cognition and functional impairment,[28,29] although none, to our knowl-

TABLE 2. Kendall's tau-b values for correlations of Neurobehavioral Rating Scale scores and Blessed Dementia Scale–Activities subscale (BDS-A) scores with measures of executive skills

	Neurobehavioral Rating Scale					
Executive Skills Test	Agitation/ Disinhibition	Anxiety/ Depression	Behavioral Retardation	Psychosis	Total Neuropsychiatric	BDS-A
FAS	−0.31**	−0.20	−0.01	−0.34**	−0.45***	−0.33***
MDRS Concept.	−0.40**	−0.23	−0.09	−0.22	−0.55***	−0.49***
MDRS Initiation	−0.42***	−0.36**	0.04	−0.23	−0.47***	−0.48***
WCST Categories	−0.41***	−0.16	0.01	−0.31*	−0.50***	−0.70***

Note: FAS = Controlled Oral Word Association subtest; MDRS = Mattis Dementia Rating Scale; Concept. = Conceptualization; WCST = Wisconsin Card Sorting Test.
*$P<0.05$; **$P<0.01$; ***$P<0.005$.

TABLE 3. Kendall's partial tau values for correlations, after covariance for MMSE scores, of Neurobehavioral Rating Scale scores and Blessed Dementia Scale–Activities subscale (BDS-A) scores with measures of executive skills

	Neurobehavioral Rating Scale					
Executive Skills Test	Agitation/ Disinhibition	Anxiety/ Depression	Behavioral Retardation	Psychosis	Total Neuropsychiatric	BDS-A
FAS	−0.21	−0.11	−0.002	−0.22	−0.32*	−0.06
MDRS Concept.	−0.32*	−0.16	−0.13	−0.06	−0.45***	−0.27*
MDRS Initiation	−0.34**	−0.32*	0.03	−0.08	−0.35**	−0.27*
WCST Categories	−0.34*	−0.06	−0.01	−0.17	−0.38***	−0.58***

Note: FAS = Controlled Oral Word Association subtest; MDRS = Mattis Dementia Rating Scale; Concept. = Conceptualization; WCST = Wisconsin Card Sorting Test.
*$P<0.05$; **$P<0.01$; ***$P<0.005$.

edge, has investigated specific areas of cognition in this regard. In a study of young, chronically ill schizophrenic inpatients and elderly residents in a retirement community, Royall et al.[5] found that a measure of executive function was better correlated than MMSE scores with functional status in each group, suggesting that executive dysfunction has a substantial role in determining patients' level of functioning that is perhaps more important than global cognitive impairment, age, or disease.

Low executive skills scores were not associated with severity of all neuropsychiatric symptoms. Significant independent relationships were observed with agitated and disinhibited behaviors but did not appear with symptoms such as blunted affect and emotional withdrawal. These contrasting results suggest that executive deficits are not a proxy for generalized, overall morbidity, but that there is a specific connection between difficulty organizing and planning and the active, agitated, and disinhibited behaviors of AD. Such executive difficulties may have particular relevance to the ability to conform behaviors to socially appropriate norms. It is noteworthy that scores on the MDRS Conceptualization subtest, which measures the ability to recognize group similarities and differences and to appreciate metaphoric meaning, were associated with agitated behaviors and functional deficits. This finding suggests that difficulty with such "higher order" skills of abstract, inductive reasoning, which extend beyond the "organizational" executive skills such as fluency, planning, and strategy formation, is relevant to behavioral symptoms in patients with AD.

Underlying neurobiologic correlates may provide the basis for the relationships between executive dysfunction and specific neuropsychiatric symptoms. Both executive functioning and many neuropsychiatric disturbances are mediated through frontal-subcortical circuits.[40] The dorsolateral prefrontal circuit facilitates executive functioning, and neuroimaging and neuropathologic studies implicate frontal cortical involvement in psychosis associated with AD.[14–16] Our previous results demonstrated a relationship between global frontal cortical hypometabolism and NRS total score, NRS Agitation/Disinhibition factor score, and Psychosis factor score in patients with AD, and a lack of association between frontal metabolic rate and the NRS Anxiety/Depression or Behavioral Retardation factor scores.[16] Thus, deficits in executive skills, agitated behaviors, and functional disability in AD may share pathophysiologic processes in the frontal cortex, whereas apathy and blunted affect may not be associated with executive skills deficits and may be due to dysfunction outside the frontal lobe or to dysfunction in discrete subregions of the frontal cortex.

Other factors may be involved in the observed relationships between executive dysfunction and neuropsychiatric symptoms. Executive dysfunction may therefore be a marker of frontal lobe dysfunction but not etiologically related to neuropsychiatric phenomenology. The presence of neuropsychiatric disturbances could interfere with performance on executive skills tests. However, one would then expect behavioral retardation to be associated with initiation and cognitive flexibility. No such association was found. Nor was speed of performance relevant; the FAS test, which is timed, was the least associated of the tests with agitation, total neuropsychiatric symptomatology, and functional disability.

Other methodologic issues should be considered in interpreting the results of the study. The presence of small periventricular hyperintensities on MRI, which was not an exclusion criterion, may affect executive function.[41] The neuropsychological tests selected depend on cognitive domains other than executive functioning, and therefore may not be "clean" measures of executive skills. (The WCST requires motor and visuospatial abilities; the FAS and MDRS tests call on language skills.) Conversely, the MMSE has been associated with executive functioning in AD[42] and therefore may not be an ideal covariate to account for the effects of global cognitive impairment.

The results of this study suggest that agitated, disinhibited behaviors and deficits in self-care activities are associated with executive dysfunction in AD. In relation to noncognitive disturbances in AD, measurement of executive skills may be at least as important as measurement of global cognitive status. These findings have important clinical implications. Executive skills are not routinely assessed in patients with AD, although such assessment may assist the clinician in determining the patient's need for assisted living or psychiatric intervention. That three of the seven proposed executive skills tests could not be performed by 32% to 55% of a moderately impaired AD group suggests a need for better measures of executive skills in this population, as well as the possible utility of such measures in earlier detection of AD. Known neuroanatomic circuits and pathophysiologic observations support the relationships among frontal lobe dysfunction, deficits in executive skills, and certain neuropsychiatric symptoms. These data support the further study of executive dysfunction in AD, including the longitudinal course of deficits, associated neuropsychiatric disturbances, efficacy of treatment, and more precise elucidation of neurobiologic mechanisms.

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Executive dysfunction correlates with impaired functional status in older adults with varying degrees of cognitive impairment

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ABSTRACT

Background: Previous studies have reported an association between executive dysfunction and the ability to perform activities of daily living (ADL)s among older adults. This study aims to examine the association between executive functions and functional status in a cross-section of older adults with varying degrees of cognitive impairment.

Methods: 89 individuals (mean age 73.8 years) were recruited at a memory clinic in São Paulo, Brazil. Subjects underwent evaluation, and were allocated into three diagnostic groups according to cognitive status: normal controls (NC, n = 32), mild cognitive impairment (MCI, n = 31) and mild Alzheimer's disease (AD, n = 26). Executive functions were assessed with the 25-item Executive Interview (EXIT25), and functional status was measured with the Direct Assessment of Functional Status test (DAFS-R).

Results: Significantly different total DAFS-R scores were observed across the three diagnostic groups. Patients with AD performed significantly worse in EXIT25 compared with subjects without dementia, and no significant differences were detected between NC and MCI patients. We found a robust negative correlation between the DAFS-R and the EXIT25 scores ($r = -0.872$, $p < 0.001$). Linear regression analyses suggested a significant influence of the EXIT-25 and the CAMCOG on the DAFS-R scores.

Conclusion: Executive dysfunction and decline in general measures of cognitive functioning are associated with a lower ability to undertake instrumental ADLs. MCI patients showed worse functional status than NC subjects. MCI patients may show subtle changes in functional status that may only be captured by objective measures of ADLs.

Key words: executive function, functional status, DAFS-R, EXIT25, mild cognitive impairment, Alzheimer's disease

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Introduction

Cognitive impairment has been implicated as a risk factor for loss of autonomy and dependence, and the magnitude of this risk may vary depending on how well and how quickly the subject can perform simple everyday tasks (Gill *et al.*, 1995). To date, the concept of mild cognitive impairment (MCI) is the best attempt to characterize the transitional phase between healthy cognitive aging and the initial stages of dementia (Petersen and Negash, 2008), in spite of the unquestionable etiological and prognostic heterogeneity of this categorization. According to the current diagnostic criteria (Petersen and Negash, 2008), patients with MCI, as opposed to those with dementia, have normal global cognitive functioning, which renders the ability to perform activities of daily living (ADL) unimpaired. Nevertheless, subtle difficulties illustrated by slowing and hesitation in the management of complex ADL tasks may indicate some degree of dysfunction that might be detected by sensitive screening.

The relationship between cognitive impairment and functional competence has been documented by several studies (Teri *et al.*, 1988; Perry and Hodges, 2000). The functional assessment of older subjects is usually based on their ability to perform basic (BADL) and instrumental (IADL) activities of daily living. The former category refers to the ability to complete simple functions such as eating, bathing, grooming and getting dressed, whereas the term IADL comprises more complex activities required for independent living, such as the preparation of meals, shopping, managing finances and using the telephone or public transportation (Lindeboom *et al.*, 2003). Even mild degrees of cognitive deterioration may have negative effects on the ability to perform complex IADL (Perneczky *et al.*, 2006; Farias *et al.*, 2006). This observation has encouraged some authors to propose the inclusion of IADL deficits in the diagnostic criteria for MCI, in order to improve the prediction of the risk of conversion to dementia (Peres *et al.*, 2006).

Although the completion of IADL requires competent memory, it involves executive functions (EF) as well. EF are complex cognitive abilities that enable an individual to perform tasks that includes planning, problem solving, anticipation of possible outcomes, and inhibition of irrelevant processing (Lezak *et al.*, 2004). A few studies have proposed that the impairment on EF is a key factor that underlies poor functional achievement (Cahn-Weiner *et al.*, 2000; van Hooren *et al.*, 2005; Royall *et al.*, 2005). Disturbances in EF are also associated with the higher needs for care and a more rapid progression to dementia (Mann *et al.*, 1992). Executive dysfunction may be even more strongly associated with functional impairment than are deficits in memory, language, visuospatial skills, and psychomotor speed (Bell-McGinty *et al.*, 2002; Cahn-Weiner *et al.*, 2002) and may, at least for some AD patients, precede overt memory decline (Binetti *et al.*, 1996). Royall *et al.* (2005) further suggested that the conversion from amnestic MCI to dementia subsumes a concurrent impairment in EF. This observation is in agreement with Rozzini *et al.* (2007), who provided evidence that the conversion from MCI to AD upon a follow-up of one year is associated with worsening scores on EF and functional status (FS), which is independent of memory deterioration. In a recent review by the Committee on Research

of the American Neuropsychiatry Association, an expert panel suggested that measures of executive functions are strong correlates of functional capacities, particularly involving medical or financial decision-making (Royall *et al.*, 2007).

The objective assessment of FS is not a routine procedure in the evaluation of cognitive impairment and dementia. The assessment of functionality usually relies on the subjective appraisal of a relative or caregiver, or even on the patient's judgment about him or herself. For this reason, most instruments designed to assess the FS indirectly may be influenced by the informant's personality, mood and cognitive state, yielding biased information that can both minimize or maximize the actual deficits (Loewenstein *et al.*, 2001). The purpose of the present study is to examine the association between EF and FS by means of an objective assessment schedule in a sample of Brazilian older adults with different levels of cognitive impairment (MCI and mild AD), as compared to healthy controls.

Methods

Patients and controls were recruited from community sources, including patients with spontaneous demand for assessment due to memory complaints, invitation of community-dwelling elderly through radio advertisements, health lectures for seniors, and referral from other clinics for the assessment of suspected cognitive decline at a university-based memory clinic (Institute of Psychiatry, University of São Paulo). Eighty-nine subjects (70% women) were enrolled for the current sub-study. Mean age was 73.8 ± 6.7 years, ranging from 59 to 89 years, and mean education was 10.3 ± 6.0 years of education, ranging from 1 to 26 years of formal education.

Patients were examined by clinicians specialized in the evaluation of dementing disorders, including geriatric psychiatrists, neurologists, geriatricians and neuropsychologists. Mental state examination was performed with the Brazilian version of the Cambridge Examination for Mental Disorders in the Elderly (CAMDEX) semi-structured interview which yields scores for the Cambridge Cognitive Test (CAMCOG) (Roth *et al.*, 1986); the Mini-mental State Examination (MMSE) (Folstein *et al.*, 1975) and the Hachinski Ischemic Score (Hachinski *et al.*, 1975). The Clock Drawing Test, which is part of the CAMCOG schedule, was additionally scored accordingly to Sunderland's guidelines (Sunderland *et al.*, 1989). The Brazilian version of the CAMCOG has shown adequate psychometric and diagnostic properties (Bottino *et al.*, 1999; Nunes *et al.*, 2008). The 21-item Hamilton Depression Scale (HAM-D) was administered to rule out depressive symptomatology (Hamilton, 1960). Neuropsychological examinations were conducted by trained psychologists and included the Rivermead Behavioural Memory Test (RBMT) (Wilson *et al.*, 1985; Oliveira and Schmidt, 1999; Yassuda *et al.*, 2006), the Fuld Object-Memory Evaluation (FOME) (Fuld, 1980; Diniz *et al.*, 2007), Verbal Fluency (category: fruit; Diniz *et al.*, 2007), the Trail-Making Test (TMT) A and B (Army Individual Test Battery, 1944; Diniz *et al.*, 2007), the Short Cognitive Test

(SKT) (Erzigkeit, 1991; Flaks *et al.*, 2006) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Vocabulary and Block Design tests (Wechsler, 1981). The following scores were of interest in the clinical evaluation of patients: for the RBMT, profile and screening scores; for the FOME, the sum of the five consecutive immediate recalls of 10 objects, and the 30-minute delayed recall; for verbal fluency, the total number of generated fruits; for the TMT, the seconds required to complete each trail; for the SKT the total and the attention and memory scores.

Evidence of functional decline was based on the scores of the Informant Questionnaire of Cognitive Disorders of the Elderly (IQCODE) (Jorm and Jacomb, 1989) and on the Blessed Dementia Scale (BDS) (Blessed *et al.*, 1968). Clinicians also took into account caregivers' and patients' reports on ADL limitations. Laboratory tests were carried out for every patient to rule out potentially reversible causes of cognitive impairment, including: thyroid function, complete blood count, blood chemistry, folic acid and vitamin B12, blood lipid profile, syphilis tests). Neuroimaging studies (CT scans or MRI) were completed according to clinical judgment.

Consensus diagnoses were reached by the expert multidisciplinary team, taking into account clinical, neuropsychological, and laboratorial and neuroimaging data. Dementia was diagnosed according to DSM-IV criteria (American Psychiatric Association, 1994). AD was diagnosed according to the NINCDS–ADRDA criteria (McKhann *et al.*, 1994). Diagnosis of MCI was made according to the Petersen's (2004) criteria: (1) subjective cognitive complaint, preferably corroborated by an informant; (2) objective impairment in the performance on the cognitive tests of the assessment battery, but not severe enough to reach dementia diagnosis; (3) preserved global intellectual function; and (4) preserved or minimal impairments in activities of daily living. In Brazil, some cognitive instruments suitable for dementia diagnosis have had their applicability and psychometric properties evaluated; however, almost none has normative data for older adults. Therefore, evaluating criterion 2 was particularly challenging, due to the lack of Brazilian norms for the selected instruments. Objective test results were compared with international norms; however, clinical judgment taking into account patients' educational and occupational backgrounds and our extensive experience with the instruments were used to determine whether performance was below normal parameters.

The MCI patients were classified into three different sub-types according to the pattern of cognitive impairment: (1) amnestic (aMCI) if there was only objective impairment in one or more of the memory tests (e.g. RBMT or FULD); (2) non-amnestic (naMCI) if there was objective impairment on one cognitive domain, except memory; and (3) multiple domain (mdMCI) if there was objective impairment in two or more cognitive domains. Subjects without evidence of cognitive impairment were regarded as normal controls (NC), although some reported memory complaints.

In the studied sample 32 subjects were cognitively unimpaired (NC), 26 had AD, and 31 had evidence of MCI. Of these, 22% had a neuropsychological

profile compatible with the diagnosis of single-domain amnestic MCI, 62.5% multiple-domain amnestic MCI, and 15.5% non-amnestic MCI. To test if the sample size of each diagnostic group (NC, AD, MCI) was adequate to provide reliable comparisons, power analysis was performed for each diagnostic group pair assuming $p = 0.05$, and revealed power ($1\text{-}\beta$) of at least 74%, i.e. a probability of type II error of 26%.

To assess FS, participants completed the revised version of Direct Assessment of Functional Status Scale (DAFS-R) (Loewenstein *et al*., 1989). The DAFS-R schedule evaluates the behavioral competence in tasks that simulate ADL. Seven ADL domains are objectively tested: time orientation, communication skills, ability to deal with finances, shopping, grooming, eating and transportation. Each DAFS-R domain or sub-domains have different score ranges (higher scores indicating better performance), and cut-off scores separating normal from impaired functioning have been established by Loewenstein and Bates (2006). Time orientation includes "telling time" (score ranging from 0 to 8; cut-off: 4) and "orientation to date" (range: 0–8; cut-off: 4). Communication skills include "using the telephone" (range: 0–9; cut-off: 6) and "writing a letter" (range: 0–6; cut-off: 4). The ability to deal with finances is assessed by "identification of currency" (range: 0–7; cut-off: 6), "counting currency" (range: 0–4; cut-off: 2), "writing a check" (range: 0–5; cut-off: 3), "balancing a check-book" (range: 0–8; cut-off: 2) and "finding change for a purchase" (range: 0–8; cut-off: 0). Shopping skills are tested by the ability to "recall a shopping list from memory" (range: 0–6; cut-off: 2), to "recognize shopping list items from memory" (range: 0–6; cut-off: 3), to "choose shopping items with the aid of a written list" (range: 0–8; cut-off: 8). Grooming skills are scored from 0 to 13 (cut-off: 10) and eating skills from 0 to 10 (cut-off: 8). Transportation skills are assessed by the ability to name and respond to road signs (range:0–13; cut-off: 12). For the current study, the latter item was not included in the analysis, because a large proportion of subjects were non-drivers and would thus have more difficulty interpreting road signs.

To assess EF, patients were submitted to the Executive Interview (EXIT25), which is a bedside, structured, clinical assessment that incorporates multiple tasks that address executive functions. It comprises 25 items that assess verbal fluency, design fluency, frontal release signs, motor/impulsive control and imitation behavior. The total score ranges from 0 to 50, higher scores being indicative of greater impairment. Scores of 15 or higher suggest a clinically significant impairment of EF (Royall *et al*., 1992).

For cognitively unimpaired patients, the examination of EF and FS took approximately 45 minutes, whereas patients with cognitive impairment required 60 to 75 minutes to complete the assessment using both scales.

The SPSS 14.0 was used to compile and analyze the database for this study. One-way analyses of variance were carried out to compare means from three diagnostic groups for EXIT25 and DAFS-R scores, because scores followed a normal distribution. The confounding effect of age and education level was controlled for by analyses of co-variance (ANCOVA). Pair-wise comparisons were carried out with Bonferroni post-hoc tests. Pearson correlation scores were calculated to assess the relation between EF and FS, and the relation

between these instruments and age and education. Regression analysis was performed in order to identify which variables were most predictive of everyday functional changes. DAFS-R was used as the dependent variable, while age, education, gender, EXIT25 and CAMCOG scores, were included in the model as independent variables.

Results

Demographic characteristics of patients in the sample are presented in Table 1, along with the total scores on the MMSE and the CAMCOG. The proportion of men and women in each diagnostic group was statistically equivalent ($p = 0.29$). There were significant differences between NC, MCI and AD with respect to age ($p = 0.001$) and years of schooling ($p = 0.002$), AD patients being older than MCI and NC, and NC more educated than AD and MCI. As expected, the scores on cognitive screening tests (MMSE and CAMCOG) were significantly lower in the AD group ($p < 0.001$), and the latter test further differentiated MCI from NC ($p < 0.001$).

The total DAFS-R and EXIT25 scores for patients (AD and MCI) and controls (NC) are also displayed in Table 1. Analyses of covariance (ANCOVA) controlling for age and education indicated that the DAFS-R and EXIT25 scores were significantly different among the diagnostic groups ($p < 0.001$ and $p < 0.001$ respectively). Pair-wise comparisons indicated that the three diagnostic groups were significantly different for DAFS-R, with NC showing higher performance than MCI and AD ($p = 0.009$ and $p < 0.001$ respectively), and MCI higher than AD ($p < 0.001$). For EXIT25 there were no significant differences between NC and MCI ($p = 0.29$); however, AD patients had worse scores than patients with no dementia ($p < 0.001$ for comparisons with NC and MCI).

Pearson's correlations showed a robust negative association between the DAFS-R and the EXIT25 total scores ($r = -0.87$, $p < 0.001$) (Figure 1). Pearson's correlation coefficients further indicated that the scores on these scales

Table 1. Demographic characteristics, scores on cognitive screening tests (MMSE and CAMCOG), and total DAFS-R and EXIT25 scores of patients in the sample

	NC	MCI	AD	p
Gender (female/total)	24/32	23/31	15/26	0.28
Age, years (mean ± SD)	71.6 (5.6)	72.6 (7.0)	**77.9 (6.0)**	0.001*
Education, years (mean ± SD)	**13.2 (6.0)**	8.5 (5.5)	8.8 (5.5)	0.002*
MMSE (mean ± SD)	28.7 (1.6)	27.3 (2.4)	**20.4 (6.0)**	<0.001*
CAMCOG (mean ± SD)	**97.8 (5.5)**	**87.6 (9.2)**	**64.2 (17.5)**	<0.001*
DAFS-R (mean ± SD)	**98.0 (5.7)**	**87.6 (7.4)**	**61.4 (15.9)**	<0.001#
EXIT25 (mean ± SD)	7.0 (4.0)	10.1 (4.1)	**19.9 (5.2)**	<0.001#

NC = normal controls; MCI = mild cognitive impairment; AD Alzheimer's disease; MMSE = Mini-mental Status Examination; CAMCOG = Cambridge Cognitive Test; EXIT25 = 25-item Executive Interview; DAFS-R = Direct Assessment of Functional Status test* = one-way ANOVA; # = ANCOVA
Bold type indicates scores yielding significant differences compared to other diagnostic groups.

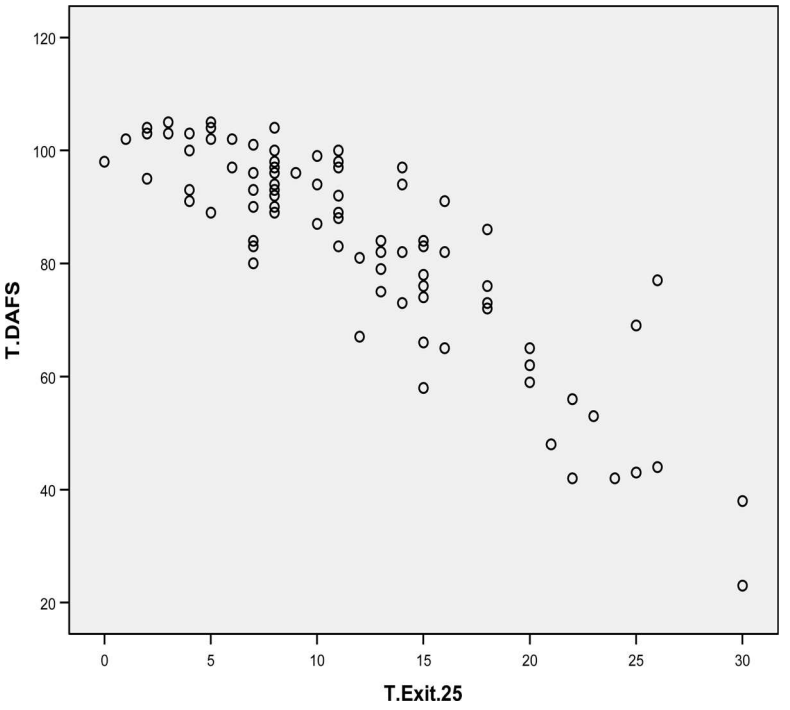

Figure 1. Pearson's correlation between the EXIT25 and the DAFS-R total score for patients in the sample, irrespective of diagnostic status

were moderately but significantly correlated with age (DAFS-R: $r = -0.47$, $p < 0.001$; EXIT25: $r = 0.49$, $p < 0.001$) and education (DAFS-R: $r = 0.36$ $p < 0.001$; EXIT25: $r = -0.39$, $p < 0.001$). Correlations between DAFS-R and EXIT25 scores were also significant in each diagnostic sub-group: for NC ($r = -0.707$; $p < 0.001$), MCI ($r = -0.513$; $p < 0.001$) and AD ($r = -0.744$; $p < 0.001$), although of smaller magnitude for the MCI group. This finding seems to reflect higher variance in scores for this group.

Table 2 presents results for the regression analysis, indicating that changes in CAMCOG and EXIT25 scores predict changes in DAFS-R scores. In addition, our results suggest the association between EXIT25 and DAFS-R is almost three times stronger than the association between the CAMCOG and DAFS-R.

Discussion

In the current study we examined the association between executive functions and functional status, as documented by the EXIT25 and the DAFS-R scores, in three groups of older adults with different levels of cognitive performance. Correlation and linear regression analysis showed that subjects who score higher in EXIT25 tend to have a worse performance in DAFS-R. Our data, in agreement with the available literature, suggest that executive dysfunction

Table 2. Results of regression analyses of DAFS-R as the dependent variable, and age, education, gender, EXIT25 and CAMCOG scores in the model as independent variables

	β	SE	p
Intercept	63.656	13.342	<0.001
Gender	1.232	1.839	0.06
Age, years	−0.064	0.139	0.64
Education, years	−0.305	0.159	0.060
EXIT25	−1.323	0.204	<0.001
CAMCOG	0.513	0.083	<0.001

DAFS-R = Direct Assessment of Functional Status test; β = standardized coefficient; SE = standardized error; EXIT25 = 25-item Executive Interview; CAMCOG = Cambridge Cognitive Test.

exerts a negative impact on the ability to perform activities of daily living, stronger than general cognitive deficits (Cahn-Weiner *et al.*, 2002; Bell-McGinty *et al.*, 2002; van Hooren *et al.*, 2006). To our knowledge, this is the first study to demonstrate this relation using an objective, performance-based assessment of ADLs. In agreement with a growing body of studies (Farias *et al.*, 2006; Perneczky *et al.*, 2006), our results also indicate that MCI patients (who do not meet FS impairment criteria based on subjective reports of FS) may reveal deficits in ADL when performance-based measures are used.

In the current sample, EXIT25 and DAFS-R scores were modestly influenced by age and education. Since age and education differences observed in the comparison groups were controlled for in the statistical analysis of variance as co-variables, and were included in the regression analysis model, we understand that the putative age and education biases do not jeopardize the actual indication of an important effect of impaired executive function on the performance on the DAFS-R.

Few studies have tried to differentiate healthy older adults from MCI and AD on the basis of the objective assessment of ADL and executive functions (Perneczy *et al.*, 2006). Most researchers have emphasized the importance of testing memory, language and visuospatial skills, overlooking the need for an objective assessment of functional impairment (De Bettignies *et al.*, 1990; Loewenstein *et al.*, 2001, Argüelles *et al.*, 2001). Loewenstein *et al.* (2006) examined the cognitive profiles of individuals with varying degrees of impairment, including patients clinically diagnosed as MCI, having neurobiological evidence of prodromal AD or vascular cognitive impairment, and patients with AD dementia, as compared to healthy controls. The authors found that both MCI groups had, in addition to poorer global cognitive performance, lower scores on measures of executive functions. These results are consistent with the notion that it is not only memory that is impaired in preclinical AD (Backman *et al.*, 2004).

In the current study, as expected, patients with AD were significantly more impaired than those with MCI and controls in cognitive and functional measures. EXIT25 raw scores suggest that MCI patients have worse executive abilities than

NC; however, when age and education effects are controlled for, MCI and NC scores do not reach statistical difference in this sample. These changes, although not within statistically significant limits, illustrate a similar tendency to that observed among patients with mild AD.

The present results suggest that the DAFS-R can differentiate patients with dementia, MCI and normal controls on the basis of functional impairment. Although the diagnostic criteria for MCI subsume functional preservation, the current findings suggest that MCI patients may already have difficulties performing ADLs. Interestingly, although the DAFS-R and the EXIT25 scores were strongly correlated, only the DAFS-R differentiated MCI from controls in this sample. This may be due to the fact that the DAFS-R "shopping skills" sub-domain is in fact a memory task, rendering the test more sensitive to the deficits presented by patients with amnestic MCI. In the current study, most of the MCI patients (84.5%) were classified as single- and multiple-domain amnestic MCI. We thus speculate that analysis of DAFS-R sub-domains across distinct MCI sub-types may reveal different patterns of functional impairment. For instance, multiple-domain MCI may be associated with a higher degree of executive dysfunctions with stronger impact on functional status (Tabert *et al.*, 2006).

The present study has some important limitations that need to be addressed. The study design was cross-sectional and the proposed hypothesis could be more appropriately tested in longitudinal designs. In addition, the studied sample was derived from a memory clinic which might introduce particular biases and yield results that may not be generalized to other populations. Although power analyses indicated adequate sample size, results should be replicated in larger samples. Future studies should also evaluate the independent contribution of other cognitive functions to FS impairment, such as memory, perception and motor control. A final limitation relates to the fact that executive dysfunction was documented by cognitive measures only, and corresponding frontal lobe atrophy was not confirmed by imaging data.

Despite these limitations, this study supports the notion that executive dysfunction is strongly associated with impairment in ADLs, that MCI patients may already show FS deficits which may be missed by subjective reports, and that performance-based measures of functional status may help identify patients at risk for cognitive decline beyond age-related changes. We hypothesize that a gradual reduction in DAFS-R illustrates the progressive functional changes that take place along the conversion from MCI to AD.

Conflict of interest

None.

Description of authors' roles

F. S. Pereira formulated the research questions and undertook data collection and the data analysis. M. S. Yassuda helped formulate the research questions and

the study design, and undertook data analyses. A. M. Oliveira was involved in the data collection, and O. V. Forlenza helped formulate the research questions and study design, and was involved in writing the paper.

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Frontal Behavioral Syndromes and Functional Status in Probable Alzheimer Disease

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Objective/Method: *The authors used the Frontal Systems Behavior Scale (FrSBe) to determine the frequency of frontal behavioral syndromes in 49 subjects with mild-to-moderate dementia and 23 subjects with severe dementia of Alzheimer disease (AD) and 23 healthy control (HC) participants.* **Results/Conclusions**: *Frontal behavior syndromes occurred with higher frequency in AD. Apathy and executive dysfunction were elevated both in mild-to-moderate and severe AD. Disinhibition was elevated only in severe AD. In AD, apathy was associated with difficulty in basic activities of daily living (ADL), whereas executive dysfunction was related to impairment in instrumental ADLs.* (Am J Geriatr Psychiatry 2003; 11:683–686)

Although memory impairment and other cognitive deficits are the hallmark symptoms of Alzheimer disease (AD), behavioral disturbances such as apathy, irritability, and aggressiveness are also recognized as distinct features of AD.[1,2] Many of the behavioral symptoms reported in AD overlap with those commonly described in individuals with prefrontal damage. Neuropathology in AD is known to involve the prefrontal circuits, providing a possible account for the presence of frontal-type behavioral disturbances. Behavioral disturbances in AD are associated with functional decline, a relationship that is independent of their association with cognitive (i.e., memory) impairment.[3] The importance of understanding the development and progression of these behavior disturbances in AD is highlighted by the frequent observations of these behavior disturbances, evidence for neural changes in the prefrontal cortex, and the reported role of these symptoms in functional decline.

A useful model for understanding how behavior disturbances in AD might relate to anatomical changes depicts several separate, but interacting, prefrontal-subcortical circuits, each related to a particular behavioral syndrome.[4] One syndrome consists of motivational disturbances such as apathy and akinesia and is linked to damage in mesial frontal-anterior cingulate circuits. In a second syndrome, linked to damage in an orbitofrontal circuit, emotional lability and disinhibited behavior are prominent. A third syndrome is associated with damage to a dorsolateral prefrontal circuit and is manifested as executive dysfunction, including problems with planning and judgment. The three frontal-behavioral syndromes are associated not only with damage in particular regions of the prefrontal cortex, but can also be caused by damage to the subcortical projections of these circuits.

The Frontal Systems Behavioral Scale (FrSBe; Psychological Assessment Resources, Inc., Lutz, FL) was developed to assess the frequency of these three frontal behavioral syndromes. The FrSBe has been shown to have excellent reliability in several clinical groups, including AD, and the validity of the scale for measuring behaviors associated with frontal lobe dysfunction has been established. Previous studies of AD using the FrSBe indicate clinical elevations on this measure, as well as an association between higher FrSBe scores and increased dementia severity.[5] The current study extends these findings in a larger sample of AD with a wide range of dementia severity by characterizing the overall rates and types of frontal behavior syndromes and by describing how these disturbances relate to day-to-day functional abilities in AD.

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METHODS

Participants

Eighty-five volunteers from the Alzheimer's Disease Research Center (ADRC) of the University of California, San Diego participated in the study, including 73 with clinical diagnoses of probable AD and 12 healthy comparison subjects (HC). Eleven additional comparison subjects were recruited at Indiana University, for a total of 23 HC participants. Diagnoses were made by two senior staff neurologists according to criteria for primary degenerative dementia outlined in the DSM-III-R and criteria for probable AD developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). The mean age and education level did not differ between the three groups (mild-to-moderate AD, severe AD, and HC; see Table 1). A primary caregiver for individuals with AD, typically a family member, completed the FrSBe during the annual visit at the ADRC. Comparison-group subjects that attended the study visit without an informant were asked to give the questionnaire to a family member or friend with whom they had at least weekly contact.

Measures

The Frontal Systems Behavioral Scale (FrSBe) is a 46-item behavior rating scale designed to measure the frequency of behaviors clinically and theoretically linked to three frontal-behavioral domains: apathy/akinesia (Scale A; 14 items), disinhibition/emotional dysregulation (Scale D; 15 items), and executive dysfunction (Scale E; 17 items). Behavior during the previous 2 weeks was rated on the following scale: 1 = Almost Never; 2 = Seldom; 3 = Sometimes; 4 = Frequently; 5 = Almost Always.

Additional measures. The Mattis Dementia Rating Scale (MDRS; Psychological Assessment Resources, Inc.; Lutz, FL) is a measure of global cognitive functioning, including an overall score and subscale scores for attention, initiation and perseveration, construction, conceptualization, and memory. A cutoff score of 95 on the MDRS was used to distinguish between mild-to-moderate (MDRS: 96–144) and severe (MDRS ≤95) AD.

The Lawton-Powell Physical Self-Maintenance Scale, 6-item version (PSMS–6)[6] is an informant rating of the participant on daily self-maintenance tasks, including toileting, feeding, dressing, grooming, locomotion, and bathing. The Pfeffer Outpatient Disabilities Scale (PODS),[7] also an informant rating of participant's functional abilities, focuses on higher-level or instrumental activities of daily living (IADL), such as handling finances.

RESULTS

For all AD participants, lower MDRS scores, indicating more severe dementia, were associated with

TABLE 1. Participant characteristics and Frontal Systems Behavior Scale (FrSBe) scores

	Healthy Comparison (N = 23)	Mild-to-Moderate AD (N = 49)	Severe AD (N = 24)
Age at visit, years	71.2 (5.1)	73.4 (5.6)	71.4 (5.5)
Education, years	14.4 (2.5)	14.6 (3.1)	13.8 (2.8)
Men, %[a]	47.8	44.9	70.8
MDRS Total	138.6 (3.7)[b]	114.3 (10.5)	63.6 (24.0)
FrSBe Total	70.1 (17.1)	105.2 (25.8)	127.2 (27.2)
% clinically elevated[c]	4%	59%	75%
Scale A	22.2 (6.5)	34.3 (9.8)	27.3 (7.3)
% clinically elevated	4%	53%	71%
Scale D	20.5 (4.0)	22.8 (7.4)	34.3 (9.8)
% clinically elevated	0%	18%	38%
Scale E	27.4 (8.5)	48.1 (11.9)	58.7 (12.5)
% clinically elevated	4%	76%	83%

Note: Values are mean (standard deviation [SD]) unless otherwise indicated; AD: Alzheimer disease; MDRS: Mattis Dementia Rating Scale.

[a] The severe-AD group had significantly more men than the mild-to-moderate–AD and Healthy Comparison groups.

[b] Seven Healthy Comparison subjects did not have an MDRS score available. Mean Healthy-Comparison MDRS score is based on 16 Healthy Comparison subjects.

[c] Consistent with conventional use of T-scores, clinical elevation was defined as a T-score >70 (mean T = 50; SD: 10).

higher scores on the Apathy, Disinhibition, and Executive Dysfunction subscales of the FrSBe ($r_{[73]}$ = –0.48, p <0.001; $r_{[73]}$ = –0.27, p <0.05; and $r_{[73]}$ = –0.43, p <0.001, respectively). The characteristics of the sample on demographic and FrSBe scores, and the rates of clinical elevation in FrSBe scores (defined by *T*-scores >70, that correspond to two standard deviations [SDs] above the mean) are shown in Table 1.

Group Comparisons of Frontal Syndromes

Multivariate analysis of variance on all four FrSBe scores indicated a significant overall *F*-statistic ($F_{[6, 182]}$ = 15.11; p <0.001). Subsequent one-way analyses of variance revealed significant overall *F*-statistics for FrSBe Total and all three subscales (FrSBe Total, $F_{[2, 93]}$ = 32.92, p = 0.001; Apathy, $F_{[2, 93]}$ = 24.0, p <0.001; Disinhibition, $F_{[2, 93]}$ = 6.27, p = 0.003; and Executive Dysfunction, $F_{[2, 93]}$ = 46.46, p <0.001). Bonferroni-corrected post-hoc *t*-tests (Tamhane's T2 test for Apathy and Disinhibition, for unequal variances) indicated that, compared with the mild-to-moderate AD and HC groups, the severe-AD group evidenced significantly higher rates of behavioral disturbance as indicated by higher FrSBe Total, Apathy, and Executive Dysfunction subscale scores. Similarly, the mild-to-moderate AD group scored higher than HCs on FrSBe Total, Apathy, and Executive Dysfunction subscales. For the Disinhibition subscale, only the severe-AD group was elevated over HC-group levels.

Relationship of Frontal Syndromes to Functional Measures

Of the 73 AD participants, 42 were classified as impaired on the PSMS–6 (mean: 9.8; SD: 3.5; range: 7–18), and 31 were rated as unimpaired. An "impaired" score was defined as 7 or greater, indicating the need for assistance with at least one daily self-maintenance task. A direct logistic regression revealed that only the MDRS and Apathy subscale of the FrSBe were independently associated with the presence of functional impairment (Wald criterion: $z_{[73]}$ = 6.85; p <0.01 and $z_{[73]}$ = 5.43, p <0.05, respectively).

Analysis of PODS scores, a measure of independent activities of daily living, included only the mild-to-moderate AD subgroup (N = 49), because most items were not applicable to individuals in the severe-AD group. PODS scores were computed as proportions by dividing each participant's sum total by the number of items endorsed (i.e., activities not performed premorbidly were excluded). Scores were then converted to ranks because of violations in the assumption of normality. Multiple-regression analysis, with the PODS as the dependent variable and the MDRS and FrSBe subscales as independent variables, indicated that the equation accounted for 39% of the variance in IADL performance (adjusted R^2 = 0.39; $F_{[4, 44]}$ = 8.62; p <0.001). The MDRS and the FrSBe Executive Dysfunction subscale showed independent associations with POD scores (t = –2.41, p <0.05, and t = 3.02, p <0.01, respectively).

DISCUSSION

Our findings indicate that frontal behavioral syndromes occur frequently in AD and are positively related to the extent of functional impairment. The Apathy subscale was associated with basic ADL performance, whereas the Executive Dysfunction subscale was associated with instrumental ADLs. Frontal behavioral syndromes were associated with basic and higher-level ADLs in AD, independently of cognitive impairment. Our results are generally consistent with previous studies that have reported significant contributions of apathy and executive functioning to ADL and IADL functioning in AD and other types of dementia (for example, Norton et al.[8]). Thus, frontal behavioral syndromes, in addition to cognition and major psychiatric symptoms, contribute uniquely to loss of independence in AD.

Our findings also indicate a strong association between dementia severity, as measured by the MDRS, and overall severity of frontal behavioral syndromes. More specifically, only severe AD was associated with elevation on the Disinhibition scale, whereas the Apathy and Executive Dysfunction subscales were elevated in both mild-to-moderate and severe AD. These results are particularly striking, given that our findings are likely a conservative estimate of the severity of frontal syndromes in clinical settings, where referrals are more likely to include extreme behavior problems. Although this cross-sectional study suggests that frontal behavioral syndromes get worse with disease progression, longitudinal studies are essential for defining the progressive nature of frontal behavioral syndromes in AD. Existing longitudinal studies

indicate complex relationships between AD severity, progression, and behavioral syndromes.[9]

Although we did not have access to neuroanatomical data for our sample, a possible implication of our results is that the underlying neural pathways associated with symptoms of apathy and executive dysfunction (e.g., mesial frontal-anterior cingulate and dorsolateral prefrontal cortex) may be affected early in the disease process. In contrast, the orbitofrontal region, associated with disinhibition, may be affected more in the later stages of AD. Improved characterization of the pattern of progression in frontal-type behavioral disturbances and related neuropathology will facilitate the development of pharmaceutical interventions targeted to intervene in particular neural systems. Previous research[1] has indicated improvement in symptoms such as apathy and in psychotic symptoms in AD with the use of various pharmacological agents.

Symptoms consistent with frontal behavioral syndromes are known to contribute to caregiver burden and stress.[10] As the pattern of behavioral symptoms in AD is clarified in longitudinal studies, family/caregiver education and care-planning programs can be developed to address these symptoms. Education may be particularly important in helping caregivers to more correctly attribute frontal-type behavioral symptoms to the disease rather than willful misbehavior by the AD patient.

In conclusion, this study shows increased frequency of frontal behavioral syndromes in AD, with more severe AD associated with higher rates of elevation in frontal behavior syndromes. The functional disability associated with frontal behavioral syndromes is independent of the cognitive decline in AD. Findings suggest that further characterization of frontal syndromes in AD will facilitate the development and evaluation of pharmacological interventions and caregiver education programs.

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Longitudinal Changes in Memory and Executive Functioning are Associated with Longitudinal Change in Instrumental Activities of Daily Living in older adults

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Abstract

Impaired everyday function is a diagnostic criterion for dementia, and a determinant of healthcare utilization and caregiver burden. Although many previous studies have demonstrated a cross-sectional relationships between cognition (particularly executive functions and memory) and everyday function in older adults, very little is known about longitudinal relationships between these domains. This study examined the association between longitudinal change in episodic memory (MEM) and executive functioning (EXEC) and change in everyday function. Participants were a cognitively heterogeneous group of 100 elderly persons including those with normal cognition, as well as those with mild cognitive impairment and dementia. They were followed for an average of five years. Random effects modeling showed that change in both MEM and EXEC were independently associated with rate of change in informant-rated instrumental activities of daily living (IADLs), even after controlling for age, education, and gender. Findings indicate that declines in MEM and EXEC over time make unique and independent contributions to declines in older adults' ability to function in daily life.

Keywords

Memory; Executive functioning; Everyday Function; dementia; Alzheimer's disease

Mild Cognitive Impairment (MCI) and dementias such as Alzheimer's disease (AD) become increasingly common with age. They are both associated with problems in everyday function that result in patient and caregiver distress, reduced quality of life, increased use of healthcare services, and nursing home placement (Hope, Keene, Gedling, Fairburn, & Jacob, 1998; Vetter et al., 1999). Given its associated burden, an improved understanding of the determinants of functional decline, including the nature of the relationship between the development of specific cognitive impairments and the development of functional impairments is paramount.

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The assessment of everyday functioning in older adults typically focuses on an individual's ability to carry out activities of daily living (ADLs) because it is these activities that are critical to independent living. Basic ADLs (BADLs) include tasks such as grooming, feeding, and toileting, while instrumental ADLs (IADLs) involve complex behaviors including managing finances, handling medications, and housekeeping. BADLs are highly correlated with motor functioning and coordination (Bennett et al., 2002; Boyle, Cohen, Paul, Moser, & Gordon, 2002; Cahn & Sullican, 1998). In contrast, declines in IADLs have been shown to be more influenced by cognitive functioning, are affected relatively early in the course of dementia (Stern, Hesdorffer, Sano, & Mayeuz, 1990), and can even be present in preclinical dementia states such as mild cognitive impairment (MCI) (Griffith et al., 2003; Ritchie, Artero, & Touchon, 2001).

Previous studies have demonstrated *cross-sectional* relationships between neuropsychological performance and everyday function in older adult populations. Among these studies, the cognitive domains most consistently found to be associated with everyday function include executive functioning (Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002; Cahn-Weiner, Boyle, & Malloy, 2002; Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998; Royall, Palmer, Chiodo, & Polk, 2004) and memory (Farias, Mungas, Reed, Haan, & Jagust, 2004; Goldstein, McCue, Rogers, & Nussbaum, 1992; Jefferson et al., 2008). Cross-sectional studies, however, provide limited insight into the course of decline in cognition and function, and how change in one is related to change in the other. In fact, cross-sectional research designs investigating a developmental or progressive disease process may lead to erroneous conclusions or misleading results (Kraemer, Yesavage, Taylor, & Kupfer, 2000). Evidence that two variables change in tandem using prospective longitudinal research provides increased evidence (although does not prove) that there is a causal relationship between the two. At a minimum, understanding patterns of change in these two conceptually distinct domains provides better description of the course of dementia.

To date there is very little research examining longitudinal relationships between cognition and everyday function. Those longitudinal studies available have focused on global measures of cognition rather than specific neuropsychological domains. For example, population-based longitudinal studies have shown that global measures of baseline cognitive function are associated with a faster rate of functional decline and predict the development of future disabilities in IADLs (Barberger-Gateau & Fabrigoule, 1997; Lavery et al., 2005; Royall et al., 2004; Schmeidler, Mohs, & Aryan, 1998). A few recent studies have evaluated how specific cognitive functions *measured at baseline* predict future decline in functional status, although most have been limited to examining only a single cognitive domain (Royall 2004; Lavery 2005). Our group has previously shown that executive functioning at baseline is associated with future decline in functional abilities such that the greater degree of executive dysfunction at baseline, the fast functional abilities decline over time (Cahn 2007). Others studies have suggested that cognitive domains including memory may also influence functional trajectories (Bennett et al., 2002; Dodge, Du, Saxton, & Ganguli, 2006). In summary, there seems to be emerging evidence linking cognitive performance at baseline to longitudinal functional outcomes in older adults with and without dementia. What still remains unclear is how trajectories of change in cognition relate to longitudinal trajectories of change in everyday function. That is, how does the evolution of cognitive impairment relate to the evolution of functional impairment and are there differential relationships between change in specific cognitive domains and change in everyday function? The purpose of the present study was to examine the relative contributions of longitudinal changes in memory and executive functioning to longitudinal change in everyday function in older adults. Psychometrically matched measures of cognitive functions (i.e. measures with equivalent reliability and sensitivity) were used to facilitate unambiguous interpretation of any potential differential effects. Given the results of previous cross-sectional studies, we hypothesized that longitudinal

change in executive functioning would be associated with longitudinal change in IADLs. Additionally, because several previous cross-sectional studies also suggest memory dysfunction is associated with impairments in IADLs, we also hypothesized that longitudinal decline in memory over time would make an independent contribution to declines in everyday function.

Method

Participants

Participants were part of a multicenter collaborative longitudinal study of aging, described previously (Cahn-Weiner et al., 2007; Mungas et al., 2005). All participants received a thorough clinical evaluation including neurologic examination, appropriate laboratory tests, neuropsychological testing with a standardized battery, and neuroimaging, culminating in a clinical diagnosis made at a multidisciplinary consensus case conference. Exclusion criteria included 1) neurological illness other than AD or cerebrovascular disease (CVD), 2) cortical infarction on MRI, 3) head injury with loss of consciousness lasting longer than 30 minutes, and 4) alcohol abuse within 5 years. The institutional review boards at all participating institutions approved this study, and subjects or their legal representatives gave written informed consent.

Recruitment was targeted to ensure broad variability of cognitive function in order to capture the spectrum from normal aging, through mild cognitive impairment and dementia. Participants were selected for inclusion in this study if they had at least two evaluations that included functional assessment and neuropsychological testing performed within six months of each other. In this sample diagnosis is categorized both by syndrome (normal, MCI, demented) and by etiology (dementia type). Dementia is defined according to DSM-IV criteria (American Psychological Association, 1994) that stipulate the presence of multiple cognitive deficits sufficiently severe to impair daily function. Although no strict psychometric cut-off scores are used to define cognitive impairment, cognitive impairment is identified by clinicians when a participant's performance falls approximately 1.5 standard deviations below age-matched norms and in reference to their educational and socioeconomic background. If the participant is determined to be demented, the second step of the diagnostic evaluation is to assign a dementia type. Dementia types included AD, vascular dementia (VaD) or mixed AD/vascular dementia. A diagnosis of Possible or Probable AD was based on NINCDS-ADRDA criteria (McKhann et al., 1984); a diagnosis of Probable or Possible VaD was based on California ADDTC criteria (Chui et al., 1992). The syndrome of MCI is diagnosed when there is cognitive impairment but the criteria for dementia are not met. Based on the above criterion, 100 individuals were included in the study; 45 were cognitively normal, 29 had a clinical diagnosis of MCI, and 26 had dementia (15 diagnosed with AD, 7 with VaD and 4 with a mixed AD/VaD). These diagnoses are based on the baseline evaluation. Summary data on demographic characteristics and global cognitive function (Mini Mental State Examination) are presented in Table 1. In terms of the characteristics of the informants who rated the study participants' IADLs, 48% were spouses, 28% were an adult child of the participant or a son- or daughter-in-law, 5% were other relatives of the informant, 5% were a friend of the informant, 21% served as their own informant (limited to those that were cognitively normal), and 3% had someone else as the informant.

Neuropsychological Measures

All subjects received a standardized battery of neuropsychological tests. All personnel involved in test administration were trained in administration and scoring procedures and cross-center observation and cross-scoring of test protocols were done to monitor quality of data collection. Composite scales were developed to measure episodic memory (MEM) and executive function

(EXEC). Details of scale derivation and validation have been reported previously (Mungas, Reed, & Kramer, 2003). To summarize, item response theory (IRT) analytic methods (Hambleton, Swaminathan, & Rogers, 1991) were used to create psychometrically matched scales. Within the item response theory framework, scales are matched when they demonstrate equivalent reliability over all points in the ability continuum. The MEM scale was based on the MAS Word List Learning Test (Williams, 1991), which is similar in structure to other supra-span multiple trial list-learning tests. Donor items include the immediate recall trials (trials 1 and 3), delayed free recall, and delayed cued recall trials. Donor items for the EXEC scale included WMS-R (Wechsler, 1987) Digit Span backward and Spatial Span backward total scores, the entire Initiation/Perseveration subscale of the Mattis Dementia Rating Scale, which includes items assessing abstract reasoning, (Mattis, 1973) and letter fluency (Benton & Hamsher, 1976). These measures were converted to standard scores based upon the mean and standard deviation of a group of normal controls from a larger sample of 400 from this project (Mungas et al., 2003). The scales have a mean of 100 and SD of 15 in the sample of controls, and have high reliability ($r > .90$) from about -2.0 SD below the mean of the overall development sample to 2.0 SD above the mean. These measures do not have appreciable floor or ceiling effects for participants in this sample and have linear measurement properties across a broad ability range. They are near-normally distributed, which presents advantages for statistical analyses. In previous studies MEM has been shown to be associated with hippocampal volume, and EXEC is associated with cortical volume, and the presence of subcortical lacunes and abnormal white matter hyperintensities (Carey et al., 2008; Kramer et al., 2007; Mungas et al., 2005), the latter two of which have been implicated in disruption of frontal-subcortical circuits (Chui & Willis, 1997; Cummings 1994). EXEC (and MEM) have also been shown to correlate with metabolic rate in the dorsolateral frontal cortex, while activity in temporal regions is correlated with MEM but not EXEC (Reed et al, 2004).

Activities of Daily Living Measure

Everyday function was measured using the eight items from the Blessed Roth Dementia Rating Scale (BRDRS) that assess instrumental activities of daily living (items are shown in Table 2). Each item of the scale is rated by a clinician based on caregiver report of the patient's ability to complete the task using a scale of 1 = completely unable to perform task/dependent, 0.5 = has some difficulty performing the task/needs some assistance, and 0 = performs task normally. Thus, lower scores on this instrument indicate a higher level of everyday functioning; the total score could range from 0 to 8. The BDRS has been used extensively in large scale studies as a measure of functional status because of its demonstrated correlation with postmortem biochemical and neuropathological changes (Blessed, Roth, & Tomlinson, 1968).

Data Analysis

The goal of the study was to characterize the relationship between change in MEM and EXEC with change in IADLs, after adjusting for baseline level of cognitive function. We used a growth-curve approach, fitting random-effects regression models (Laird & Ware, 1982) to test the hypothesis that the rate of change in cognition is associated with rate of change in IADL. Rather than using only the first and last IADL assessment for each person to estimate change in IADL by a difference score, these models utilized all of the available data from each subject. They enabled us to estimate the mean trajectory of IADL over time and to characterize how change in cognition modified that average trajectory. The primary outcome variable was IADL measured over time. Baseline and longitudinal (time-varying) assessments of MEM and EXEC were used as the independent variables to predict baseline and change in IADLs. The time-varying MEM and EXEC variables were coded as change since baseline. When a MEM or EXEC assessment was not available to match the IADL assessment within six months, the values from the closest MEM or EXEC assessment were used. Models used for these analyses incorporated random-effects to allow for between person variability in IADL scores

summarized by a person's tendency to be above or below the predicted average level at a given time and to decline faster or slower than average. They, therefore, also adjusted for baseline IADL levels. They also allowed for different spacing between and number of assessments across subjects. Extensions to these models, called simultaneous models, were used to estimate correlations between change in MEM or change in EXEC and change in IADLs (Beckett, Tancredi, & Wilson, 2004; Harvey, Beckett, & Mungas, 2003).

Model building began with simple models assessing the association between baseline and change in one cognitive domain with level and change in IADLs. To assess associations between change in cognition with change in IADL, a time by change in cognition interaction was included in the model. Coefficients of this interaction may be interpreted as the average annual change in IADL associated with a one unit difference in the change in cognition. Examination of the correlation between the cognitive predictors revealed only a modest association (r = .48 between baseline MEM and EXEC and .44 between change in MEM and change in EXEC) and therefore was determined to be sufficiently low to include both domains in the same model. Thus, a final joint model assessed the independent associations of change in MEM and change in EXEC with change in IADL. All models were adjusted for the possible confounding effects of age, education, and gender. Model assumptions of normality, linearity, constant variance, and bivariate normality of the random effects were examined using graphical diagnostics, including residual plots and Q-Q plots. The IADL variable was not normally distributed, so the IADL rating was shifted by one and then transformed using the natural logarithm. This transformed variable as the outcome satisfied the assumptions of the models.

Multiple imputation methods, using a Markov Chain Monte Carlo approach, were used to impute missing IADL ratings. IADL ratings were only imputed for dates at which the functional measure was attempted but not completed either due to an insufficient caregiver available to evaluate the functional ability of the subject or an incomplete questionnaire. Only 7% of the IADL ratings were imputed and 62% of those imputed were for normal subjects. We imputed 10 data sets assuming an underlying distribution of the IADL ratings centered at the baseline mean of each diagnostic group and combined the results from each of the data sets to yield final estimates of the associations. Alternative assumptions including assuming an underlying distribution centered at no functional impairments and at the baseline mean of all subjects were also considered, and results from these analyses were similar to those presented.

Results

There were 483 IADL assessments for the 100 cases, all of whom had complete neuropsychological data. The modal number of annual assessments per participant was five, and ranged from 2 to 10. The average time from the initial to last assessment was 5.3 years (SD = 2.6, range = 0.9-10.3). Eighty-six percent of participants had at least three assessments including the baseline visit. If we treat number of visits as a categorical variable with 3 levels (2, 3, ≥4), there was no significant association between diagnosis and number of visits (p=0.3, Fisher's exact test). 91% of normals had more than 2 visits, 90% of MCI had more than 2 visits and 73% of demented subjects had more than 2 visits. The average lag between visits did differ by diagnostic group (F=9.5, p<0.001, ANOVA), with normals seen, on average every 1.2 years (SD=0.4), MCI seen on average every year (SD=0.2) and demented subjects seen every 0.9 years (SD=0.4). Although these time lags were statistically different, the practical significance of these small differences seem minimal.

Baseline and rates of change in the cognitive and functional variables

Table 3 presents baseline means and average annual rate of change on the functional and cognitive measures (both the composites and donor items) by diagnostic syndrome (cognitively normal, MCI, dementia). As expected baseline MEM and EXEC differed by cognitive groups

(for overall F, p's < .0001, all pairwise tests were also significant at p<.05 after adjusting for multiple comparisons) the cognitively normal group was average, the dementia group was clearly impaired, and the MCI group mean was intermediate. Thus, there was evidence of a continuum of underlying pathology and disease severity. The annual rate of change in MEM and EXEC also differed across groups (p's = .04 and .004, respectively; pairwise comparisons reached significance after adjustment for multiple comparisons only for the normal vs. dementia comparisons) in the same pattern (normals < MCI < dementia). Interestingly the EXEC scale showed evidence of annual decline in the normal group, whereas the MEM scale did not. The MCI and dementia groups also generally showed more decline on the EXEC scale in comparison to the MEM scale.

Similar to their progressive cognitive impairment, the groups also showed progressive impairment in IADLs (p <.001; all pairwise comparisons also significant at p<.05 level after adjusting for multiple comparisons). The dementia group at baseline was rated as unable to perform over two of the eight functional abilities assessed, and the MCI group mean IADL score was intermediate to normals and the demented participants. In terms of annual rate of change in IADLs there was a significant difference between the groups (p<0.001; MCI and demented and normals and demented were significant at p <.05 after adjusting for multiple comparisons). Normals at baseline showed essentially no change in everyday function over time. The MCI group gained about 0.2 points on the eight-point IADL scale per year (high scores indicate greater impairment). The dementia group gained, on average, about one point per year on the IADL scale, which roughly corresponds to becoming dependent in one more IADLs each year.

Change in cognitive associated with change in everyday function

Random effects models allowed us to investigate associations between longitudinal change in each of the cognitive variables and change in IADL ratings; however we also included terms to examine cross-sectional (baseline) relationships. First we examined the association between MEM and IADLs, independent of EXEC. In a model that included baseline MEM and MEM change (along with age, education, and gender) results showed that baseline MEM was associated with baseline IADLs (p=0.001) and longitudinal change in MEM was associated with longitudinal change in IADLs (p<0.001). Thus, a steeper decline in MEM over time was associated with a greater degree of functional decline. Age, education, and gender were not significantly associated with functional change.

In a separate model including baseline EXEC and change in EXEC (along with age, education, and gender), we found that baseline EXEC was associated with baseline IADLs, and change in EXEC was associated with change in IADLs (p's <0.001 for both). Thus again, a greater degree of decline in EXEC was associated with greater functional decline. Neither age, education nor gender were independently associated with functional change.

Finally, we examined a joint model that simultaneously included both MEM and EXEC variables (along with demographics). In this model, both baseline MEM and baseline EXEC were independently associated with baseline IADLs (p's = <.001 and .002, respectively). Additionally, longitudinal change in both MEM and EXEC were independently associated with IADL change (p's = 0.002 and .008, respectively), with declines in MEM and EXEC associated with greater functional decline. None of the demographic variables were associated with change in IADLs. These results are displayed in Table 4.

In order to obtain an estimate of the magnitude of the relationship between change in the cognitive variables and change in IADLs, we examined correlation coefficients between these domains. The correlation between change in MEM and change in IADLs was -.69 (<.001) and the correlation between change in EXEC and change in IADLs was -.72 (p <.001).

Discussion

The primary purpose of this study was to examine the association between longitudinal changes in domain-specific cognitive functions with longitudinal change in IADLs. A strength of this study was that it followed older adults whose cognitive functioning was well characterized by detailed neuropsychological testing over an average of five years. Results showed that declines in both MEM and EXEC confer unique and additive effects upon everyday function. Thus, an individual who experiences a decline over time in memory would also be expected to show a concomitant decline in everyday function. Similarly, an individual who shows a decline in executive function would likely also show a decline in everyday function. Since declines in each cognitive domain have independent associations with change in everyday function, individuals who show change in both memory and executive functioning would be expected to show an even greater decline in everyday function than individuals experiencing a decline in either one of the cognitive domains alone.

Very few previous studies have examined longitudinal relationships between cognition and everyday function and so this study represents an important extension of previous cross-sectional research. As previous cross-sectional studies (i.e. (Bell-McGinty et al., 2002; Cahn-Weiner et al., 2002) have suggested, the present study further confirms that executive dysfunction has important ramifications on an individual's functional capacities. Importantly, the present study suggests that *longitudinal decline* in executive functions is associated with declines in everyday abilities. In particular, the present study suggests that change in those executive functions related to working memory, behavioral initiation and regulation, strategy generation, and abstract thinking and concept formation are associated with changes in daily function.

Perhaps somewhat more controversial, but also supported by cross-sectional studies (i.e. (Farias et al., 2004; Jefferson et al., 2008), the current study also shows that memory abilities make important contributions to a person's functional capacities. Change in memory conferred its own effect on change in IADLs and this effect remained strong even when change in executive function was jointly included in the model. Such findings help to explain other recent findings that show individuals with MCI, many of whom have cognitive deficits confined to memory, demonstrate declines in everyday functioning (Tomaszewski Farias et al., In Press).

We are aware of only one prior study that examined concurrent change in specific cognitive domains and change in everyday function in older adults. Previously Royall and colleagues (Royall, Palmer, Chiodo, & Polk, 2005) found that change in executive function, but not change in memory, was independently associated with change in functional impairment. In contrast, the current study suggests that the effect of change in memory on change in IADLs is not entirely mediated by changes in executive function. The differences in results across the two studies may, in part, be the result of differences in the measurement properties of the different scales used in each study. In the present study we used measures of memory and executive function that were specifically designed to have similar measurement properties (i.e. similar reliability and sensitivity across a broad spectrum of ability level, and linear measurement properties such that neither scale has appreciable floor or ceiling effects (Mungas et al., 2003). The use of psychometrically matched measures in the current study allows us to draw more confident conclusions about domain-specific cognitive effects on everyday function. Another potential reason for the difference in results between the current study and that of Royall and colleagues is that participants in the latter study were largely cognitively normal at baseline, whereas the sample in the present study represented greater cognitive diversity, including those with cognitive impairment and frank dementia. Thus, certain cognitive changes may be selectively important depending on baseline status: change in executive function may be more important in predicting change in normal older adults, whereas memory change likely

becomes particularly important in predicting functional decline in MCI and dementia. In some support of this hypothesis, when we repeated the primary analysis using only those with cognitive impairment (MCI or dementia) only the association between change in MEM and change in IADLs reached statistical significance. Alternatively when analysis only included the normals, change in EXEC became associated with change in IADLs, although change in MEM was still also independently associated with change in IADLs (data not shown). Additionally, we observed that the EXEC scale showed more change in the normals than the MEM scale (see Table 3) suggesting that the EXEC domain is probably more sensitive to the effects of normal aging. This finding is consistent with other literature which suggests that declines in executive functioning are associated with normal aging, and may reflect some loss in the integrity of white matter connection which are vulnerable to cerebrovascular disease (Kramer et al., 2007).

In examining the magnitude of the relationship between the two cognitive domains and everyday function we found that the overlapping variance between MEM and EXEC with IADLs ranged from 48% to 52%. Such findings suggest fairly strong relationships between these domains. In a recent review article (N Chaytor & Schmitter-Edgecombe, 2003) the authors concluded that cross-sectional relationships between neuropsychological tests and measures of everyday functioning are primarily in the moderate range, often in the 18% to 20% range (N.Chaytor, Schmitter-Edgecombe, & Burr, 2006). Thus, longitudinal relationships among cognition and everyday function may be stronger than cross-sectional relationships. Further research is need to confirm this preliminary finding but if it proves to hold true it could have important clinical relevance and suggest serial neuropsychological testing maybe particularly useful.

In the current study we specifically selected a sample with broad variability of cognition and everyday function, ranging from fully cognitively normal to moderately impaired (at baseline). The assumption is that correspondingly broad variability of brain pathology will underlie this behavioral variability. We did not focus on separate analyses for normals, MCI, and demented cases because this inherently reduces variability and decreases sample size, and ultimately does not assess the continuous effects of pathology across its full range. Further, important for longitudinal studies like the present one, separate subgroup analyses also provides limited information about how functional limitations progress from normal cognition to severely impaired (Kraemer et al., 2000).

The current study does have a number of limitations that deserve mention. A degree of caution about the generalizability of the results is warranted. The participants of this longitudinal study were as a whole, well educated and comprised of a clinical sample, primarily recruited from memory disorders clinics where AD is the predominant disease (selection bias). As such, our results may differ from studies utilizing older adults out in the community who are not actively seeking treatment.

The current study focused on two cognitive domains, memory and executive function because prior studies had identified these domains as especially important to daily function. The particular executive function scale used in this study was derived primarily, although not exclusively, from working memory and verbal fluency tests. Both verbal fluency and working memory are commonly considered measures of select aspects of executive functioning, and both have been linked to frontal lobe functions (for recent reviews see (Cabeza & Nyberg, 2000; Henry & Crawford, 2004). However, other executive functions not covered by this composite are also likely to make important contributions to everyday function. For example, measures of novel problem solving and practical judgment are likely to be particularly relevant to everyday functioning but were not included in the current study. Further research on which aspects of executive functioning are particularly important to functional abilities will be

important. Other noncognitive/behavioral variables including depression can also play an important role in everyday function but were unfortunately not available in the current study. Additionally, while the BRDRS has advantages as a measure of everyday function (it has been correlated with postmortem pathological brain changes, and it is very simple to administer and time efficient), it is also has limitations because it is a fairly gross measure of everyday function. Also the use of informant-based ratings of everyday function offers both costs and benefits. Use of an informant or proxy to rate an individual's everyday functioning has been shown to be useful in differentiating individuals with dementia from healthy elders (DeBettignies, Mahurin, & Pirozzolo, 1990; Isella et al., 2006; A.F. Jorm & Jacomb, 1989; A.F. Jorm & Korten, 1988; Kemp, Brodaty, Pond, & Luscombe, 2002; Seltzer, Vasterling, Mathias, & Brennan, 2001), in predicting who will go on to show further decline (A. F. Jorm, Christensen, Jacomb, Korten, & Mackinnon, 2001), and in predicting incident dementia (Daly et al., 2000; Harwood, Hope, & Jacoby, 1997). A disadvantage of informant report is that it is subject to reporter bias.

Currently there is limited knowledge about the course and determinants of late life functional impairment, something which carries with it tremendous personal and social cost. This is the first study to show that longitudinal declines in both memory and executive functions are independently related to decline in everyday function in older adults. In conjunction with other findings, the current results provide further evidence that impairment and decline in memory and executive function play critical roles leading to functional disability in older adults.

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Table 1

Participant demographic characteristics and global cognitive status.

	Cognitively Normal (n=45)	MCI (n=29)	Dementia (n=26)
Age	73.5 (7.7)	73.0 (8.5)	74.5 (8.7)
Gender (% female)	47%	24%	31%
Education (years)	14.7 (2.9)	14.1 (3.1)	14.0 (3.5)
Ethnicity (% Caucasian)	82%	76%	88%
MMSE Score	29.0 (1.3)	28.0 (1.9)	23.8 (3.7)

Table 2

Blessed-Roth Dementia Rating Scale Instrumental Activities of Daily Living Items

a.	Ability to find way around familiar streets
b.	Perform household tasks
c.	Cope with small sums of money
d.	Remember short lists of items
e.	Find way about indoors
f.	Interpret surroundings (e.g., to recognize whether in hospital or at home)
g.	Recall recent events (e.g., recent outings, visits of relatives)
h.	Tendency to dwell in the past

* Each item was rated as either 0 = normal performance/no difficulty, .5 = some difficulty performing task, 1 = unable to perform task

Table 3

Mean baseline cognitive and functional scores (SD in parentheses) and annual rate of change (standard deviations in parentheses) by baseline cognitive status.

		Baseline Diagnostic Syndrome		
Cognitive Variable	**Assessment**	**Cognitively Normal (n=45)**	**MCI (n=29)**	**Dementia (n=26)**
Memory (MEM)	Baseline	104.6 (15.0)	89.5 (14.4)	68.1 (16.7)
	Annual Change	0.2 (3.6)	-0.9 (5.7)	-2.5 (3.8)
	Percent Change	0.4% (3%)	-1% (6%)	-3.7% (6.2%)
Immediate Recall, Trial 1	Baseline	6.3 (1.5)	4.8 (1.8)	3.3 (1.9)
	Annual Change	0.03 (0.56)	-0.04 (0.79)	-0.5 (1.1)
	Percent Change	1.7% (10%)	4.2% (22%)	-24% (32%)
Immediate Recall, Trial 2	Baseline	8.6 (2.1)	7.0 (1.9)	5.0 (1.6)
	Annual Change	0.02 (0.58)	-0.3 (0.7)	-0.6 (1.0)
	Percent Change	1.3% (8.4%)	-4.5% (13.9%)	-16% (27%)
Immediate Recall, Trial 3	Baseline	9.7 (1.7)	7.9 (1.8)	5.8 (2.1)
	Annual Change	0.1 (0.6)	-0.3 (1.1)	-0.6 (0.8)
	Percent Change	1.5% (6.9%)	-4.7% (15.5%)	-11 % (21%)
Delayed Free Recall	Baseline	10.2 (1.9)	8.0 (3.0)	3.5 (3.6)
	Annual Change	-0.1 (0.6)	-0.3 (1.6)	-0.9 (1.5)
	Percent Change	-0.4% (6.4%)	-7.7% (21.5%)	-27% (28%)
Delayed Cued Recall	Baseline	10.4 (1.6)	9.0 (2.0)	5.8 (3.0)
	Annual Change	-0.01 (0.53)	-0.2 (0.9)	-0.4 (1.2)
	Percent Change	0.3% (5.8%)	-1.0% (10.5%)	-6.9% (24%)
Executive (EXEC)	Baseline	101.1 (12.3)	84.4 (17.4)	73.4 (14.0)
	Annual Change	-0.7 (3.9)	-1.6 (3.0)	-3.7 (3.4)
	Percent Change	-0.7% (4%)	-1.7% (3.3%)	-5.3% (5.1%)
Digit Span Backward	Baseline	6.3 (1.9)	5.0 (2.1)	5.1 (1.8)
	Annual Change	0.05 (0.09)	0.07 (0.16)	0.05 (0.19)
	Percent Change	0.9% (1.9%)	1.6% (4.0%)	1.1% (4.6%(
Visual Memory Span Backward	Baseline	6.8 (1.7)	6.3 (2.0)	5.1 (1.6)
	Annual Change	-0.1 (0.6)	-0.3 (0.6)	-0.5 (1.1)
	Percent Change	-0.8% (9.8%)	-3.4% (7.7%)	-8.8% (18%)
Initiation/Perseveration DRS	Baseline	36.0 (1.8)	32.3 (4.9)	27.4 (6.0)
	Annual Change	-0.4 (0.8)	-0.7 (1.5)	-2.5 (2.5)
	Percent Change	-1.0% (2.4%)	-1.9% (4.7%)	-10% (10%)
Letter Fluency “A”	Baseline	12.6 (4.2)	9.3 (5.2)	7.0 (3.2)
	Annual Change	-0.1 (1.2)	-0.2 (1.2)	-0.7 (1.0)
	Percent Change	-0.1% (9.9%)	3.5% (25%)	-10% (20%)
Letter Fluency “F”	Baseline	14.0 (3.9)	11.3 (5.7)	9.4 (5.0)
	Annual Change	0.2 (1.0)	-0.5 (1.3)	-0.7 (0.9)
	Percent Change	1.8% (7.4%)	-3.6% (10.8%)	-10% (13%)
Letter Fluency “S”	Baseline	15.6 (4.2)	11.9 (6.5)	9.5 (3.8)

		Baseline Diagnostic Syndrome		
Cognitive Variable	**Assessment**	**Cognitively Normal (n=45)**	**MCI (n=29)**	**Dementia (n=26)**
	Annual Change	-0.3 (1.4)	-0.5 (1.3)	-1.7 (1.9)
	Percent Change	-1.4% (9.0%)	-4.3% (14.3%)	-18% (19%)
IADL	Baseline	0.28 (0.69)	0.65 (0.70)	2.6 (1.9)
	Annual Change	0.09 (0.34)	0.21 (0.33)	0.8 (0.8)

Baseline and annual change scores for the cognitive measures are in standard score points (mean = 100, SD = 15).

Baseline and annual change for the IADLs are in raw scores.

Table 4

Results of random effects modeling of baseline and longitudinal change in MEM and EXEC in association with baseline and longitudinal change in IADLs (adjusted for age, education and gender).

Baseline level of log-IADL			
Variable	**Estimate**	**Standard Error**	**p-value**
Age	0.002	0.005	0.6
Education	0.04	0.01	0.01
Male	-0.04	0.09	0.6
MEM	-0.02	0.002	<0.001
EXEC	-0.008	0.002	0.002
Change in log-IADL			
Variable	**Estimate**	**Standard Error**	**p-value**
Time	0.04	0.02	0.09
Age *time	0.001	0.001	0.29
Education*time	-0.005	0.003	0.17
Male*time	0.01	0.02	0.47
ΔMEM*time	-0.001	0.0003	0.002
ΔEXEC*time	-0.001	0.0005	0.008

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Neuropsychiatric symptoms, functional impairment and executive ability in Thai patients with Alzheimer's Disease

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ABSTRACT

Background: Instrumental activities of daily living (IADL) depend on executive planning and procedural memory mediated by the frontal lobes. Planning and judgment are involved in clock drawing. Neuropsychiatric symptoms are also mediated by frontal lobes, and a relationship between ADL, clock drawing and neuropsychiatric symptoms was hypothesized.

Objective: To investigate the relationship between behavioral disturbances, ADL, and executive function.

Methods: Seventy-three Thai patients with Alzheimer's disease (AD) were evaluated. Neuropsychiatric symptoms and behaviors were assessed with the Nevropsychiatric Inventory (NPI). The Thai version of the Mini-mental State Examination (TMSE) was utilized as a global cognitive assessment. A clock-drawing test (CDT) and both category (animals) and letter (ko, so in Thai) verbal fluency were used as executive measures. Thai ADL scale, Barthel Index (BI), and Functional Assessment Questionnaire (FAQ) were ADL measures used in this study.

Results: There were statistically significant correlations between CDT and the frontally-mediated behaviors of agitation ($r = -0.367$), apathy ($r = -0.273$) and disinhibition ($r = -0.247$). Verbal fluency correlated with agitation ($r = -0.341$). There were significant correlations between Thai ADL scores

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and agitation ($r = 0.350$), apathy ($r = 0.441$), and disinhibition ($r = 0.417$). FAQ correlated with the same three behaviors. After controlling for TMSE, a significant correlation remained between Thai ADL scores and agitation ($r = 0.291$) and apathy ($r = 0.342$).

Conclusions: We demonstrated correlations between ADL and behavioral changes in Thai elderly with AD. Our results emphasize the important relationships among behavioral changes and impaired ADL.

Key words: Neuropsychiatric symptoms, executive function, activities of daily living, Thailand, Alzheimer's disease, Neuropsychiatric Inventory

Introduction

Abnormalities of frontal lobe function give rise to executive neuropsychological disturbances and a variety of neuropsychiatric syndromes (Cummings and Mega, 2003). The frontal lobes control motor activity through the motor and pre-motor cortex and eye movements via the frontal eye fields. The prefrontal cortex mediates executive function, including planning, sequencing, organizing, strategy development and adjustment, abstraction, motivation and response control (Niedermeyer, 1998; Cummings and Coffey, 2000). Discrete brain regions are responsible for mediating specific categories of behavior: the dorsolateral prefrontal cortex mediates executive function, the medial prefrontal cortex and anterior cingulate region mediate motivational aspects of behavior, and the orbitofrontal cortex mediates inhibition, behavioral regulation, and social interaction (Cummings and Mega, 2003). Regions of the frontal cortex are integrated into complex frontal subcortical circuits devoted to specific categories of behavior (Cummings, 1993). Dysfunction of dorsolateral prefrontal sub-cortical circuits produces executive dysfunction; disruption of the medial frontal sub-cortical circuit produces apathy and diminished motivation; and damage to the orbitofrontal subcortical circuit produces disinhibition with tactless, impulsive behavior. Disturbances of frontal lobe function are reflected in impairment of Activities of Daily Living (ADL), as well as neuropsychiatric symptoms. Instrumental Activities of Daily Living (IADL) such as using transportation, managing financial matters, and organizing a household require the planning strategy and adjustment capacities of the dorsolateral prefrontal cortex (Nadler *et al.*, 1995; Cummings, 2003). Thus, disturbances of frontal lobe function result in a complex array of executive, ADL and behavioral disturbances.

Alzheimer's disease (AD) has its primary impact on medial temporal and posterior parietal regions (Cummings, 2003). However, mild executive function abnormalities are present early in the illness. The frontal lobes become

progressively more involved as the disease advances, and a subgroup of patients with AD manifest substantial frontal lobe impairment early in their disease course (Johnson *et al.*, 1999). Frontal lobe dysfunction in AD is anticipated to produce the triad of executive cognitive abnormalities, neuropsychiatric symptoms, and ADL impairment. Confirmation of this triad and identification of assessment techniques appropriate for characterizing these linked abnormalities would assist in patient prognosis and management.

Few studies have examined the relationship between neuropsychiatric symptoms and executive function or between neuropsychiatric symptoms and functional impairment. Studies of these disturbances have not been conducted previously in Thailand, and examining such relationships in Thai elderly will assist in understanding their transcultural validity. We evaluated the presence of neuropsychiatric symptoms in Thai patients with AD and explored the relationship between neuropsychiatric features, executive dysfunction and functional impairment. We hypothesized that there are relationships between certain neuropsychiatric symptoms that are frontally mediated and ADL, and between executive dysfunction and ADL performances.

Methods

Seventy-three Thai patients with AD from the Memory Disorders Clinic at Siriraj Hospital, Bangkok, Thailand were recruited in this study during January 2000 – October 2001. Dementia was diagnosed by Diagnostic and Statistic Manual of Mental Disorders, 4th edition (DSM IV) criteria (American Psychiatric Association, 1994). Exclusion criteria were (a) delirium; (b) a history of neuropsychiatric disorders before the onset of memory problems; (c) substance abuse or dependence; and (d) absence of an informant who could report reliably on the patient's behavior and neuropsychiatric symptoms. Blood tests including thyroid function test and serology for syphilis and computerized tomography (CT) of the brain were done in all patients. AD was diagnosed based on the criteria of the Joint Task Force of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) (McKhann *et al.*, 1984). Dementia severity was assessed by Thai Mental State Examination (TMSE) (Train the Brain Forum Committee, 1993), which is a translated and culturally modified Mini-mental State Examination (MMSE) (Folstein *et al.*, 1975), and the Clinical Dementia Rating scale – Sum of the Boxes (CDR-SB) (Morris, 1993; Hughes *et al.*, 1982). Individual items of CDR, including memory, orientation, judgment and problem-solving, community affairs, home, hobbies, and personal care are scored from 0 indicating no impairment to 3 indicating severe dementia; item scores are added to produce the CDR-SB.

Activities of daily living (ADL) were assessed using the Functional Assessment Questionnaire (FAQ) (Pfiffer *et al*., 1982), and the Thai ADL scale (Senanarong *et al*., 2003). The Thai ADL scale consists of 6 basic ADL items and 7 instrumental ADL items. The Thai ADL scale correlates well with Barthel Index and FAQ (Pfiffer *et al*., 1982). The scores of Thai ADL scale range from 0 (best performance) to 26 (most impaired).

Frontally-mediated behaviors were assessed with the Neuropsychiatric Inventory (NPI) (Cummings *et al*., 1994). The NPI measures 12 behavioral symptoms: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nighttime behavior and appetite changes. Each subscale score of the NPI is the product of its severity and frequency, (range 0–12). The Thai version of NPI has been used in other studies in Thailand (Senanarong *et al*., 2002). Agitation/aggression, apathy and disinhibition have been demonstrated by previous studies to be related to frontal pathology or functional abnormalities and they were the focus of this study (Cummings, 1993; Tekin *et al*., 2001a; Craig *et al*., 1996).

We used the verbal fluency (VF) test of the CAMDEX (Roth *et al*., 1986) modified to include animal naming and two letters, "ko" and "so" in Thai and the clock-drawing test (CDT) to assess executive function. The CDT used in this study employs a 10-point scoring system (Spreen and Strauss, 1991) modified from Sunderland and co-workers (1989) and Wolf-Klein and colleagues (1989). We asked patients to draw a clock face with a pre-drawn circle to point the time of 10 past 11. The score of this CDT ranges from 1 (most impaired) to 10 (normal). Scores (Spreen and Strauss, 1991) between 7 and 10 should be considered normal, a score of 6 is borderline (achieved by 13% of normal and 88% of AD patients). Scores of 5 or less are rare (0.8%) in normal patients but frequent in those with AD (83%). The VF and CDT require multiple aspects of executive function, including psychomotor speed and lexical search strategies (VF) as well as problem-solving and freedom from distraction (CDT).

Statistical analysis was performed using the SPSS 10.0 software program. Pearson correlation coefficients were used to assess correlation among measures. This was an exploratory study and no adjustments for multiple comparisons were applied. We accepted a more conservative p value of 0.01 as indicative of statistical significance. The study was approved by the hospital ethics committee.

Results

Seventy-three patients with AD were recruited: 20 men (27.4%) and 53 women (72.6%). The mean age was 70.28 years (SD = 8.10; range 54–90). Most caregivers (51) were female (20 male, 2 missing data). Forty nine (68%) patients

Table 1. Mean + standard deviation (SD) of assessments of subjects with AD ($N = 73$)

COGNITIVE AND BEHAVIORAL MEASURES	MEAN ± STANDARD DEVIATION (SD)
Thai Activities of Daily Living scale	10.07 ± 7.62 (N = 70)
Clinical Dementia Rating – sum of the boxes	6.46 ± 4.04 (N = 72)
Functional Assessment Questionnaire	18.20 ± 9.05 (N = 70)
Thai Mental State Examination	18.42 ± 6.60
Verbal fluency – animal	7.80 ± 5.70
Verbal Fluency – ko	3.09 ± 3.76
Verbal Fluency – so	2.87 ± 3.79
Verbal Fluency – sum (animal, ko, so)	13.68 ± 11.90
Clock-Drawing Test	4.39 ± 3.03
NPI agitation subscale score	0.59 ± 1.14
NPI apathy subscale score	1.66 ± 2.66
NPI disinhibition subscale score	1.08 ± 2.20
NPI total score	15.07 ± 14.55
NPI caregiver distress score	6.37 ± 6.61

NPI = Neuropsychiatric Inventory.

Table 2. Prevalence, mean + standard deviation (SD) of Neuropsychiatric Inventory (NPI) subscale scores ($N = 73$)

NPI SUBSCALE	PREVALENCE % (N)	NPI SUBSCALE SCORES
Delusions	27.4(20)	1.07 ± 2.42
Hallucinations	17.8(13)	0.55 ± 1.51
Agitation	35.6(26)	1.05 ± 1.86
Depression	30.1(22)	0.92 ± 2.28
Anxiety	42.5(31)	1.49 ± 2.19
Euphoria/elation	6.8(5)	0.23 ± 1.10
Apathy	45.2(33)	1.66 ± 2.66
Disinhibition	30.1(22)	1.08 ± 2.20
Irritability/lability	47.9(35)	1.63 ± 2.57
Aberrant motor behavior	42.5(31)	2.04 ± 3.37
Night time behavior	38.4(28)	2.03 ± 3.46
Appetite change	27.4(20)	1.32 ± 2.86

had 10 or fewer years of education. Table 1 shows mean Thai ADL, TMSE, verbal fluency (sum of category and letters) and NPI scores. NPI subscale scores are shown in table 2. Table 3 indicates that executive assessments (VF, CDT) and all ADL measures had significant correlations and that CDT and VF were highly correlated with the global cognitive measures TMSE and CDR-SB. After controlling for TMSE the relationship between executive and ADL measures was no longer significant, implying that in this population CDT and VF reflect dementia severity. Table 4 explores relationships between executive

Table 3. Pearson correlations (*r* and *p* value) between executive measures and ADL and global cognitive assessment

	THAI ADL	FAQ	TMSE	CDR – SB
CDT	−0.512(0.00)**	−0.584(0.00)**	0.620(0.00)**	−0.469(0.00)**
VF animals	−0.566(0.00)**	−0.611(0.00)**	0.651(0.00)**	−0.540(0.00)**
VF – ko	−0.409(0.00)**	−0.493(0.00)**	0.550(0.00)**	−0.312(0.01)*
VF – so	−0.472(0.00)**	−0.550(0.00)**	0.594(0.00)**	−0.338(0.00)**
VF – sum (animals, ko, so)	−0.550(0.00)**	−0.609(0.00)**	0.678(0.00)**	−0.459(0.00)**
TMSE	−0.670(0.00)**	−0.709(0.00)**	1	−0.751(0.00)**

CDT = Clock-drawing test; VF = Verbal Fluency; Thai ADL = Thai Activities of Daily Living; FAQ = Functional Assessment Questionnaire; TMSE = Thai Mental State Examination; CDR-SB = Clinical Dementia Rating – Sum of the Boxes.
* $p < 0.05$.
** $p < 0.01$.

Table 4. Pearson correlations (*r* and *p* value) between neuropsychiatric symptoms, executive assessment, ADL, and global cognitive assessment

MEASURES	NPI TOTAL SCORE	NPI AGITATION SCORE	NPI APATHY SCORE	NPI DISINHIBITION SCORE
CDT	−0.242(0.04)*	−0.367(0.00)**	−0.273(0.02)*	−0.247(0.04)*
VF animals	−0.226	−0.309(0.01)*	−0.196	−0.165
VF – ko	−0.150	−0.327(0.01)*	−0.103	−0.151
VF – so	−0.189	−0.291(0.01)*	−0.105	−0.194
VF – sum (animals, ko, so)	−0.172	−0.341(0.01)*	−0.154	−0.171
TMSE	−0.345(0.00)**	−0.433(0.00)**	−0.369(0.00)**	−0.373(0.00)**
Thai ADL	0.466(0.00)**	0.350(0.00)**	0.441(0.00)**	0.417(0.00)**
FAQ	0.440(0.00)**	0.332(0.01)*	0.298(0.01)*	0.387(0.00)**
CDR-SB	0.330(0.01)*	0.315(0.01)*	0.339(0.00)**	0.398(0.00)**

NPI = Neuropsychiatric Inventory; CDT = Clock Drawing Test; VF = Verbal Fluency; TMSE = Thai Mental State Examination; Thai ADL = Thai Activities of Daily Living; FAQ = Functional Assessment Questionnaire; CDR-SB = Clinical Dementia Rating – Sum of the Boxes.
* $p < 0.05$.
** $p < 0$.

measures (CDT, VF), global cognitive function (TMSE and CDR-SB) and overall function (Thai ADL, FAQ) with three frontally mediated behaviors measured by total, agitation, apathy and disinhibition NPI scores as well as with total NPI score. There were significant correlations between Thai ADL, NPI and the 3 NPI subscale scores and between FAQ and total and disinhibition NPI scores. Controlling for TMSE significant correlations remained between Thai ADL and NPI total ($r = 0.443$, $n = 46$, $p = 0.002$), agitation (0.291, 46, 0.045) and apathy (0.342, 46, 0.017) scores, and between FAQ and NPI total

(0.365, 46, 0.011) scores indicating that the general degree of cognitive decline does not account for the relationship between ADL and behavior. There were significant relationships between some of the executive and frontal behaviour measures (CDT with NPI and all 3 NPI subscale scores, and NPI agitation with all VF measures). TMSE correlated with agitation, apathy and disinhibition. At a conservative alpha level ($p < 0.01$) some significant correlations (agitation with CDT; TMSE with agitation, apathy and disinhibition) remained. However after controlling for TMSE significant relationships between NPI subscale scores and executive measures were lost, suggesting that in this population CDT and VF reflect severity of cognitive decline.

Discussion

This study explored the relationships among ADL, frontally-mediated neuropsychiatric symptoms and executive function measures. We found correlations between frontally-mediated behaviors and impaired ADL in Thai elderly with AD that were not attributable to general cognitive decline.

The prevalence of behavioral changes and neuropsychiatric symptoms in Thai patients with AD was similar to that found in Western countries except the prevalence of apathy in Thais in this study was low in comparison to the West (Mega *et al.*, 1996). Thai culture expects the elderly to be reserved and passive, without an active role in the family. This difference in cultural norms may explain the low prevalence of apathy.

The relationship between behavioral changes and ADL impairments in AD has been investigated in only a few studies. Tekin and colleagues (2001b) found that all sub-items of the NPI except depression correlated with impairment of instrumental ADL measured by the FAQ, and Norton and co-workers (2001) reported a relationship between ADL impairment and frontal dysfunction as measured by the Frontal System Behavior Scale.

Executive abilities are necessary for accomplishment of ADL. Barberger-Gateau and co-workers (1999) examined 1792 non-demented elderly people using neuropsychological batteries and an instrumental ADL assessment. They found a decline in neuropsychological performance, including an executive measure with increasing ADL dependency. Willis and co-workers (1998) demonstrated a significant relationship between cognitive function measured by MMSE in patients with AD and performance in IADL, and an association between this ADL performance and performance on executive function measures. Chen and colleagues (1998) also found relationships between executive deficits and functional disability ($r =$ between -0.33 and -0.70). Executive abilities are necessary for achievement of ADL.

Executive dysfunctions and neuropsychiatric symptoms have been found to be associated in past investigations, suggesting that both these types of behavioral change are mediated by frontal lobe mechanisms. Kuzis and co-workers (1999) investigated the association between apathy and depression and specific cognitive deficits in 72 patients with AD. They found that patients with apathy had significantly lower scores on tests of verbal memory, naming, set-shifting and verbal fluency compared with patients without apathy. Depression without apathy was not associated with more severe cognitive impairment, compared with the AD control group. They concluded that apathy but not depression was significantly associated with more severe cognitive deficits in AD. Recently, McPherson and co-workers (2002) confirmed the relationship between apathy and executive dysfunction in AD. Boyle and colleagues (2003) studied an association between frontally-mediated behavioral disturbances and functional impairment in patients with mild to moderate Alzheimer's disease. They found that executive cognitive dysfunction and apathy accounted for 44% of the variance in impaired instrumental activities of daily living. Cahn-Weiner and co-workers (2002) reported that verbal fluency performance and Trail-Making Test performance made significant independent contributions to predict instrumental activities of daily living in community dwelling older individuals as reported by a caregiver. Chen and co-workers (1998) also studied the relationship of neuropsychiatric symptoms in patients with AD. Executive function was measured by verbal fluency, Mattis Dementia Rating Scale (MDRS), Stroop Interference, Trail-Making Part B, and Wisconsin Card-Sorting Test (WCST). Functional impairment was assessed with the Blessed Dementia Scale-Activities subscale. They found that executive dysfunction correlated most with agitation/disinhibition and total neuropsychiatric symptom scores. After co-varying for MMSE, correlations between executive dysfunction and neuropsychiatric symptoms remained statistically significant, indicating the relationships were largely independent of cognitive decline. The failure of our study to identify relationships between executive function and behavior after adjustment for general cognitive decline may reflect the mixed nature of our executive function tests that require not only frontally mediated abilities but also rely on language, memory, and visuospatial skills.

This study demonstrated an association between impaired ADL and frontally-mediated neuropsychiatric symptoms in Thai elderly with AD. Neuropsychiatric symptoms that related to frontal dysfunction remained significantly correlated with ADL after covariance for MMSE scores. These results apply to Thai elderly with AD and have been observed in other cultural groups, establishing the transcultural and multi-ethnic validity of these relationships. These results emphasize the important relationship between apathy and impaired daily

activities; agitation and disinhibition were also associated with impaired ADL. Frontal lobe involvement in AD contributes importantly to some of the most disabling aspects of the dementia syndrome.

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