

Cortical Atrophy is Associated with Accelerated Cognitive Decline in Mild Cognitive Impairment with Subsyndromal Depression

Mitzi M. Gonzales, Ph.D., Philip S. Insel, M.S., Craig Nelson, M.D., Duygu Tosun, Ph.D., Niklas Mattsson, M.D., Ph.D., Susanne G. Mueller, M.D., Simona Sacuiu, M.D., Ph.D., David Bickford, B.A., Michael W. Weiner, M.D., R. Scott Mackin, Ph.D. and the Alzheimer's Disease Neuroimaging Initiative¹

Objectives: To investigate the association between cognitive decline and cortical atrophy in individuals with mild cognitive impairment (MCI) and chronic subsyndromal symptoms of depression (SSD) over a 4-year period. **Design:** Prospective cohort study. **Setting:** Multicenter, clinic-based. **Participants:** Within the Alzheimer's Disease Neuroimaging Initiative repository, the Neuropsychiatric Inventory was used to identify individuals with MCI and stable endorsement (SSD group $N = 32$) or no endorsement (non-SSD group $N = 69$) of depressive symptoms across time points. **Measurements:** Repeated measures of cognitive outcomes, cortical atrophy, and their associations were evaluated with mixed effects models adjusting for age, education, sex, and APOE genotype. **Results:** The SSD group demonstrated accelerated decline on measures of global cognition (Alzheimer Disease Assessment Scale; $df = 421$, $t = 2.242$, $p = 0.025$), memory (Wechsler Memory Scale-Revised Logical Memory II; $df = 244$, $t = -2.525$, $p = 0.011$), information processing speed (Trail Making Test Parts A [$df = 421$, $t = 2.376$, $p = 0.018$] and B [$df = 421$, $t = 2.533$, $p = 0.012$]), and semantic fluency (Category Fluency; $df = 424$, $t = -2.418$, $p = 0.016$), as well as accelerated frontal lobe ($df = 341$, $t = -2.648$, $p = 0.008$) and anterior cingulate ($df = 341$, $t = -3.786$, $p < 0.001$) atrophy. No group differences

¹Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.usc.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. The complete list of ADNI investigators is available at <http://adni.loni.usc.edu/study-design/ongoing-investigations/>.

Received September 2, 2016; revised March 10, 2017; accepted April 18, 2017.

From the Department of Mental Health (MMG), V.A. Northern California Health Care System, Martinez, CA; Center for Imaging of Neurodegenerative Diseases (PSI, DT, SGM, MWW, RSM), Veterans Administration Medical Center, San Francisco, CA; Departments of Psychiatry (CN, DB, MWW, RSM); Department of Radiology (DT, SGM, MWW); Department of Medicine (MWW), University of California, San Francisco, CA; Clinical Memory Research Unit, Faculty of Medicine (NM), Lund University, Lund, Sweden; Department of Neurology (NM), Skane University Hospital, Lund, Sweden; and the Institute of Neuroscience, Physiology, Sahlgrenska Academy (SS), University of Gothenburg, Sweden. Send correspondence and reprint requests to R. Scott Mackin, 401 Parnassus Ave, Box 0984-LLD, San Francisco, CA 94143. e-mail: Scott.Mackin@ucsf.edu

Published by Elsevier Inc. on behalf of American Association for Geriatric Psychiatry.

<http://dx.doi.org/10.1016/j.jagp.2017.04.011>

were observed for rate of decline on measures of attention, learning, and confrontation naming or for rate of atrophy in any other regions. Accelerated frontal lobe and anterior cingulate atrophy was associated with cognitive decline on measures of global cognition, information processing speed, and semantic fluency (all $p < 0.05$), but not memory. **Conclusions:** Individuals with chronic SSD may represent an MCI subgroup that is highly vulnerable to accelerated cognitive decline, an effect that may be governed by frontal lobe and anterior cingulate atrophy. (*Am J Geriatr Psychiatry* 2017; 25:980–991)

Key Words: Depressive symptoms, mild cognitive impairment, cortical atrophy, cognitive decline, frontal lobe, anterior cingulate

Mild cognitive impairment (MCI) has been conceptualized as an antecedent to dementia onset.¹ However, only 10% to 15% of those with MCI convert to dementia each year, posing challenges to accurate prediction of individual long-term outcomes within this population. Of note, subsyndromal symptoms of depression (SSD)—depressive symptomatology below the frequency and severity for a diagnosis of major or mild depression²—has been associated with more rapid conversion from MCI to Alzheimer disease (AD) dementia,³ suggesting that SSD may be an etiological risk factor or prodromal manifestation of dementia neuropathology.⁴ Efforts to disentangle the directionality and temporal association between SSD and dementia within MCI, however, have been limited by the relapse and remitting course of SSD. Within comorbid SSD and MCI populations, 35% of individuals' depressive symptomatology remits, whereas 65% display a stable or worsening course over a 3-year period.⁵ Those with stable or progressive depressive symptomatology may accumulate increased neuropathologic burden over time, heightening the risk for dementia conversion. Thus, longitudinal evaluations of chronic SSD in MCI may provide an optimal framework for assessing the neurobiological correlates of depressive symptomatology on cognitive decline.

In accordance with the hypothesis that chronic SSD may confer risk for neuropathology, individuals with MCI and chronic SSD have been found to display more rapid deterioration in global cognitive functioning as well as accelerated progression to AD dementia.^{6,7} Lee et al.⁸ found that SSD at baseline was associated with accelerated cognitive decline on measures of global cognition, language, processing speed, and executive function across a 2-year period. Although the results indicate that SSD may independently accelerate cognitive

decline, little is known about the underlying etiological processes.

Neuroimaging assessments of cortical atrophy may hold particular promise to elucidate the neurobiological mechanisms of SSD-related accelerated cognitive decline in MCI populations. Cortical atrophy in the hippocampus and entorhinal cortex has been consistently reported in MCI.⁹ Similarly, late-life depression has been associated with cortical atrophy, particularly within the anterior cingulate, prefrontal cortex, and orbitofrontal cortex.¹⁰ Nevertheless, few studies have evaluated the associations of chronic SSD with atrophy within MCI samples. The existent literature suggests that atrophy in the anterior cingulate and frontal lobe may be characteristic of chronic SSD in individuals with MCI,^{3,8} indicating that rate of cortical atrophy may be a mechanism linking accelerated cognitive decline and depressive symptomatology.

Thus, the overarching goal of the current study was to determine if accelerated cognitive decline in MCI participants with chronic SSD is associated with rate of cortical atrophy. Based on previous investigations,^{6–8} we predicted that MCI participants with chronic SSD would display accelerated cognitive decline across global cognition, memory, information processing speed, and semantic fluency domains. Additionally, it was hypothesized that MCI participants with SSD would display more rapid cortical atrophy in the frontal lobe and anterior cingulate, but not regions typically associated with MCI due to AD such as the posterior cingulate, temporal lobe, hippocampus, and entorhinal cortex.^{9,11} Finally, we hypothesized that SSD-related accelerated cognitive decline within the domains of global cognition, memory, information processing speed, and semantic fluency would be associated with rate of frontal lobe and anterior cingulate atrophy.

METHODS

Participants

Data for the current study were obtained from the September 24, 2015, version of the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI study is conducted in accordance with the Declaration of Helsinki and procedures were approved by the institutional review boards of all participating sites. All participants provided written informed consent at enrollment.

From the larger ADNI database, the present study included individuals with baseline magnetic resonance imaging (MRI) data who were diagnosed with MCI by a psychiatrist or neurologist at each study site and reviewed by a central review committee. Criteria for MCI diagnosis included 1) age between 55 and 90 years; 2) subjective memory complaint; 3) Mini-Mental Status Exam score greater than 24; 4) Global Clinical Dementia Rating Scale score = 0.5; 5) evidence of memory impairment on neuropsychological assessment Wechsler Memory Scale (WMS)–Revised Logical Memory II less than or equal to 8¹² (adjusted for age and education). Exclusion criteria at baseline included: 1) presence of major depressive disorder or significant symptoms of depression (Geriatric Depression Scale [GDS] > 6); 2) modified Hachinski ischemia score greater than 5; 3) significant neurological or psychiatric illness; 4) use of antidepressant drugs with anticholinergic side effects; and 5) high dose of neuroleptics or chronic sedatives or hypnotics, antiparkinsonian medication, and use of narcotic analgesics.

Participants were classified as SSD if at least one depressive symptom (i.e., depression/dysphoria, apathy/indifference, or loss of appetite) was endorsed at each timepoint on the informant-based Neuropsychiatric Inventory (NPI).¹³ Insomnia was not considered an inclusionary symptom of SSD, given that older adults have been reported to display significant variability in sleep quality over time.¹⁴ Participants were included in the non-SSD group if no depressive symptoms, as described earlier, were reported across all timepoints.

Procedures

Participants completed clinical, cognitive, laboratory, and neuroimaging assessments every 6 months

during the first 2 study years, followed by annual assessments thereafter.

Neuropsychiatric Assessment

Neuropsychiatric symptoms were evaluated using the informant-based NPI,¹³ which uses a semi-structured interview formant to assess 12 behavioral domains (delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep disturbance, and appetite/eating changes). If a behavior is endorsed, the informant is asked to assess the frequency on a 4-point scale (ranging 1–4) and the severity on a 3-point scale (ranging 1–3). For the current study, the number of endorsed depressive symptoms on the NPI was used to define the SSD and non-SSD groups.

Cognitive Assessment

As previously described, participants completed standard clinical neuropsychological instruments with established reliability and validity. The assessment included measures of 1) general cognitive functioning: The Alzheimer's Disease Assessment Scale–Cognitive Scale (ADAS-Cog) total score;¹⁵ 2) verbal learning: WMS Logical Memory I¹² and Rey Auditory Verbal Learning Test (RAVLT) Immediate Recall total scores; 3) memory: WMS Logical Memory II¹² and RAVLT Delayed Recall total scores; 4) information processing speed: Trail Making Test Parts A and B time to completion,¹⁶ Digit Symbol Substitution Test total correct response;¹⁷ 5) semantic fluency: Category fluency (animals) total correct responses;¹⁸ 6) attention: Wechsler Adult Intelligence Scale-Third Edition Digit Span subtest total correct forwards and backwards responses;¹⁷ and 7) confrontation naming: Boston Naming Test-30 item total correct responses.¹⁹

MRI Acquisition and Analysis

MRI acquisition and analysis has been previously described.³ Briefly, high-resolution T1 structural images were obtained using 1.5T General Electric (Fairfield, CT), Philips (Andover, MA), or Siemens (Washington, DC) scanners with standardized MRI protocol and acquisition parameters (adni.loni.usc.edu/methods/documents/mri-protocols/). ADNI MRI quality control was conducted at the Mayo Clinic.²⁰ Cortical thickness

quantification was conducted using the Freesurfer Version 4.4 longitudinal processing framework (<http://surfer.nmr.mgh.harvard.edu/>).^{21,22} Similar to prior literature,³ cortical thickness was derived from nine a priori regions of interest that have been associated with late-life depression and/or MCI:⁹⁻¹¹ frontal lobe (medial and lateral orbitofrontal, rostral and caudal middle frontal, and superior frontal), anterior cingulate (rostral and caudal regions), precuneus, cuneus, posterior cingulate, temporal lobe, parahippocampus, hippocampus, and entorhinal cortex. In exploratory analyses, we also examined five separate subregions of frontal lobe (medial and lateral orbitofrontal, rostral and caudal middle frontal, and superior frontal) and two subregions of the anterior cingulate (rostral and caudal regions). Thickness values in the left and right hemispheres were averaged to obtain one measure for each cortical region of interest.

Statistical Analyses

SSD and non-SSD group differences in demographic characteristics (age, sex, *APOE* status, years of education), NPI scores, and GDS scores were analyzed using Mann-Whitney U tests for continuous measures and Fisher's Exact test for categorical measures. The effects of missing data on demographics, *APOE* status, and chronic SSD were evaluated with a generalized linear mixed effects regression model using a binomial outcome and Wald test-derived p-values.

In order to assess group differences in the rate of cognitive change, we used linear mixed effects regression for repeated measures of the 12 cognitive outcomes with each model separately fit with both a random intercept and slope and an unstructured covariance matrix for the random effects. Independent variables in the model included age, sex, years of education, *APOE* status (at least one *APOE* $\epsilon 4$ allele versus $\epsilon 4$ non-carrier), depression group (chronic SSD versus non-SSD), time since the initial observation, and an interaction between depression group and time since the initial observation.

To examine group differences in rate of cortical atrophy, we modeled repeated measures of cortical thickness in nine a priori regions of interest with linear mixed effects regression with random intercept and slope with covariates for age, sex, *APOE* status, depression group, time since the initial observation, and an interaction

between depression group and time since the initial observation. In exploratory analyses, we re-ran the models for the five subregions of the frontal lobe and two subregions of the anterior cingulate cortex. It should be noted that the analyses and sample are similar to previous work by our group,³ but include a slightly larger sample size.

Finally, we evaluated whether change in cortical atrophy over time in two regions, the frontal lobe and anterior cingulate (selected based on previous literature³), was associated with the rate of cognitive decline in measures with a significant SSD group effect. This analysis was done in two steps. In step 1, subject-specific rates of cognition and atrophy were estimated separately using mixed effects regression. In step 2, rates of cognitive decline were then regressed on atrophy rates, adjusting for age, sex, and *APOE* genotype. Steps 1 and 2 were repeated in 500 bootstrap samples to estimate the variance of the association between atrophy and cognitive decline and test for its significance. In exploratory analyses, we also tested the interaction term between atrophy and SSD to predict changes in cognition. Additionally, we assessed the correlation between baseline cortical thickness and cognitive measures to evaluate for potential confounds in our models.

Model fits were assessed by examination of the residuals. All p values were two-tailed and cognitive and cortical atrophy outcomes were adjusted for multiple comparisons using a false discovery rate (FDR) correction. Statistical analyses were conducted with the R Package (version 2.8.1, The R Foundation for Statistical Computing, <http://www.r-project.org/>).

RESULTS

Demographic Factors

The baseline study sample included 32 participants in the SSD group and 69 participants in the non-SSD group. Median follow-up time was 3 years, with a median of six neuropsychological assessments (with the exception of the WMS [median: 4]) and five MRI scans. As seen in [Table 1](#), there were no baseline differences between SSD and non-SSD groups with regard to sociodemographics (age, sex, years of education), *APOE* status, or baseline MMSE score. The SSD group had significantly higher scores on the GDS and NPI than the non-SSD group.

TABLE 1. Demographic and Clinical Characteristics of SSD Groups at Baseline (N = 101, df = 99)

	Non-SSD (N = 69)	SSD (N = 32)	Mann-Whitney U or Fisher's
			Exact P
Age, years	73.71 ± 7.99	75.84 ± 7.59	0.278
Sex (M:F)	47:22	24:8	0.640
APOE status (ε4:non-ε4)	35:34	19:13	0.521
Education, years	15.93 ± 3.01	15.62 ± 2.86	0.547
MMSE	27.19 ± 1.90	27.09 ± 1.69	0.742
GDS Total Score	1.28 ± 1.24	2.19 ± 1.51	0.004
NPI Total Score	0.43 ± 0.83	5.41 ± 4.05	<0.001

Notes: Group differences were analyzed using Mann-Whitney U tests for continuous measures and Fisher's Exact test for categorical measures. All values represent mean ± standard deviation unless otherwise noted. GDS: Geriatric Depression Scale; MCI: mild cognitive impairment; MMSE: Mini Mental Status Exam; NPI: Neuropsychiatric Inventory; SSD: subsyndromal depression.

Baseline Cognitive Performance

There were no baseline differences in cognitive performance between SSD and non-SSD groups with the exception of poorer performance of the SSD group on one measure, RAVLT Immediate Recall (Table 2).

Rate of Cognitive Decline in SSD

As compared with the non-SSD group, the SSD group displayed significantly accelerated cognitive

decline on 5 out of the 12 cognitive measures in the fully adjusted models (Table 3): ADAS-Cog, Trail Making Test Parts A and B, WMS Logical Memory Delayed Recall, and Category Fluency. With FDR correction, the results for the Trail Making Test Parts A and B, WMS Logical Memory Delayed Recall, and Category Fluency were at the p = 0.05 level.

Baseline Cortical Thickness

At baseline, the SSD group demonstrated lower temporal lobe and entorhinal cortex cortical thickness (Table 4). No other significant differences were observed.

Rate of Cortical Atrophy in SSD

In the fully adjusted models, the SSD group demonstrated accelerated atrophy in the frontal and anterior cingulate relative to the non-SSD group (Table 5). Significant findings were also observed in the majority of subregions of the anterior cingulate and frontal lobe including the rostral anterior cingulate (df = 341, β = -0.029, SE = 0.011, t = -2.782, p = 0.006); caudal anterior cingulate (df = 341, β = -0.042, SE = 0.011, t = -3.652, p < 0.001), medial orbitofrontal (df = 341, β = -0.023, SE = 0.008, t = -2.780, p = 0.006), rostral middle frontal (df = 341, β = -0.018, SE = 0.007, t = -2.459, p = 0.014), and superior frontal (df = 341,

TABLE 2. Linear Mixed Effects Regression Results of the Relationship Between SSD in MCI and Cognitive Performance Baseline (df = 95)

	Non-SSD (N = 69)	SSD (N = 32)	B Estimate	Standard Error	t	p	FDR p
Alzheimer's Disease Assessment Scale	10.72 ± 4.31	12.47 ± 3.71	1.277	0.802	1.592	0.115	0.614
WMS Logical Memory I	7.57 ± 3.16	6.75 ± 3.34	-0.676	0.649	-1.042	0.300	0.614
RAVLT Immediate Recall	36.54 ± 11.17	28.72 ± 8.07	-5.669	1.979	-2.864	0.005 ^a	0.067
WMS Logical Memory II	4.30 ± 3.01	3.47 ± 2.29	-0.768	0.632	-1.216	0.227	0.614
RAVLT Delayed Recall	2.94 ± 3.52	2.19 ± 1.96	0.309	0.593	0.521	0.603	0.784
Trail Making Test A	41.91 ± 24.09	45.09 ± 20.16	1.638	4.291	0.382	0.703	0.831
Trail Making Test B	117.17 ± 68.22	151.91 ± 84.69	16.753	14.731	1.372	0.258	0.614
Digit Symbol Substitution Test	39.99 ± 10.46	35.88 ± 9.98	-3.401	2.331	-1.459	0.148	0.614
Category Fluency (animals)	16.00 ± 5.32	15.69 ± 4.43	-0.124	1.056	-0.118	0.907	0.929
WAIS-III Digit Span Forwards	8.67 ± 1.98	8.06 ± 2.14	-0.334	0.398	-0.840	0.403	0.655
WAIS-III Digit Span Backwards	6.10 ± 2.10	6.22 ± 2.21	-0.034	0.383	-0.089	0.929	0.929
Boston Naming Test	26.07 ± 3.41	24.44 ± 4.33	-0.778	0.795	-0.978	0.331	0.614

Notes: Longitudinal cognitive data was regressed on age, sex, years of education, APOE status, SSD group, time interval from baseline, and the interaction between SSD group and time interval from baseline using linear mixed models. MCI: mild cognitive impairment; RAVLT: Rey Auditory Verbal Learning Test; SSD: subsyndromal depression; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition; WMS: Wechsler Memory Scale.

^ap < 0.05.

TABLE 3. Linear Mixed Effects Regression Results of the Relationship Between SSD in MCI and Change in Cognitive Performance Across the 4-Year Interval

	Interaction Between SSD and Time					
	df	β Estimate	Standard Error	t	p	FDR p
Alzheimer's Disease Assessment Scale	421	1.580	0.705	2.242	0.025 ^a	0.061
WMS Logical Memory I	245	-0.300	0.287	-1.046	0.297	0.445
RAVLT Immediate Recall	423	0.290	0.719	0.403	0.687	0.687
WMS Logical Memory II	244	-0.698	0.274	-2.525	0.011 ^a	0.054
RAVLT Delayed Recall	421	0.116	0.248	0.466	0.641	0.687
Trail Making Test A	421	4.681	1.970	2.376	0.018 ^a	0.054
Trail Making Test B	411	12.150	4.796	2.533	0.012 ^a	0.054
Digit Symbol Substitution Test	391	-0.782	0.895	-0.874	0.383	0.503
Category Fluency (animals)	424	-0.855	0.354	-2.418	0.016 ^a	0.054
WAIS-III Digit Span Forwards	392	-0.190	0.154	-1.233	0.218	0.374
WAIS-III Digit Span Backwards	390	-0.133	0.164	-0.809	0.419	0.503
Boston Naming Test	423	-0.466	0.375	-1.242	0.215	0.374

Notes: Longitudinal cognitive data was regressed on age, sex, years of education, *APOE* status, SSD group, time interval from baseline, and the interaction between SSD group and time interval from baseline using linear mixed models. MCI: mild cognitive impairment; RAVLT: Rey Auditory Verbal Learning Test; SSD: subsyndromal depression; WAIS-III: Wechsler Adult Intelligence Scale-Third Edition; WMS: Wechsler Memory Scale.

^ap ≤ 0.05.

TABLE 4. Linear Mixed Effects Regression Results of the Relationship Between SSD in MCI and Cortical Thickness in A Priori Regions of Interest at Baseline (df = 95)

	β Estimate	Standard Error	t	p	FDR p
Frontal lobe	-0.050	0.034	-1.460	0.148	0.542
Anterior cingulate	-0.001	0.551	0.017	0.987	0.987
Precuneus	-0.038	0.040	-0.947	0.832	0.659
Cuneus	0.006	0.026	0.212	0.532	0.915
Posterior cingulate	-0.051	0.044	-1.164	0.247	0.659
Temporal lobe	-0.119	0.045	-2.655	0.009 ^a	0.051
Parahippocampus	-0.030	0.067	-0.451	0.653	0.896
Hippocampus	-98.919	107.474	-0.920	0.356	0.659
Entorhinal cortex	-0.279	0.102	-2.729	0.008 ^a	0.051

Notes: Longitudinal cortical atrophy was regressed on age, sex, *APOE* status, SSD group, time interval from baseline, and the interaction between SSD group and time interval from baseline using linear mixed models. MCI: mild cognitive impairment; SSD: subsyndromal depression.

^ap < 0.05.

$\beta = -0.021$, SE = 0.009, $t = -2.269$, $p = 0.024$). No significant group differences were observed in the lateral orbitofrontal (df = 341, $\beta = -0.019$, SE = 0.010, $t = -1.897$, $p = 0.059$) or caudal middle frontal gyri (df = 341, $\beta = -0.017$, SE = 0.009, $t = -1.855$, $p = 0.064$). All significant results persisted with multiple comparisons correction (FDR $p < 0.05$).

Relation between Rate of Change in Cognition and Cortical Thickness

Accelerated frontal lobe atrophy was associated with more rapid decline on the ADAS-Cog, Trail Making

Test Part B, and Category Fluency (Table 6, Figure 1). Accelerated anterior cingulate lobe atrophy was associated with faster decline on the ADAS-Cog, Trail Making Test Part A and B, and Category Fluency (Table 6, Figure 1). No significant interactions between rate of atrophy and SSD group were observed across cognitive measures (all $p > 0.05$). There were significant baseline correlations between frontal lobe cortical thickness and Trail Making Test Parts A and B (Table 6), so these models were re-analyzed statistically adjusting for this association. The association between rate of frontal lobe atrophy and decline in Trail Making Test Part A remained nonsignificant ($\beta = -0.430$,

TABLE 5. Linear Mixed Effects Regression Results of the Relationship Between SSD in MCI and Change in Cortical Thickness in A Priori Regions of Interest Over the 4-Year Study Interval (df = 341)

	Interaction Between SSD and Time				
	β Estimate	Standard Error	t	p	FDR p
Frontal lobe	-0.020	0.007	-2.648	0.008 ^a	0.040
Anterior cingulate	-0.036	0.009	-3.786	<0.001 ^a	<0.001
Precuneus	-0.009	0.007	-1.238	0.217	0.380
Cuneus	-0.003	0.005	-0.626	0.532	0.760
Posterior cingulate	-0.015	0.010	-1.518	0.130	0.320
Temporal lobe	-0.018	0.010	-1.706	0.089	0.300
Parahippocampus	-0.012	0.010	-1.212	0.226	0.380
Hippocampus	-5.924	14.530	-0.408	0.684	0.860
Entorhinal cortex	0.001	0.019	0.042	0.967	0.970

Notes: Longitudinal cortical atrophy was regressed on age, sex, APOE status, SSD group, time interval from baseline, and the interaction between SSD group and time interval from baseline using linear mixed models. MCI: mild cognitive impairment; SSD: subsyndromal depression.
^ap < 0.05.

TABLE 6. Associations Between Change in Cortical Thickness and Change in Cognition Over Time

Cognitive Measure	Cortical Thickness Region	Baseline Cognition and Thickness Correlation	Association Between Change in Cortical Thickness and Change in Cognition			
			Rho (p value)	β Estimate	Standard Error	t
Alzheimer's Disease Assessment Scale	Frontal lobe	-0.156 (0.120)	-0.993	0.362	-2.743	0.007 ^a
WMS Logical Memory II	Frontal lobe	0.033 (0.886)	0.114	-1.803	1.390	0.168
Trail Making Test A	Frontal lobe	-0.277 (0.005 ^b)	-2.376	1.318	2.376	0.075
Trail Making Test B	Frontal lobe	-0.303 (0.002 ^a)	-5.639	1.795	-3.142	0.002 ^a
Category Fluency (animals)	Frontal lobe	0.187 (0.062)	0.247	0.111	2.225	0.028 ^a
Alzheimer's Disease Assessment Scale	Anterior cingulate	-0.149 (0.139)	-1.119	0.378	-2.960	0.004 ^a
WMS Logical Memory II	Anterior cingulate	-0.078 (0.439)	0.110	0.073	1.507	0.134
Trail Making Test A	Anterior cingulate	0.003 (0.977)	-2.581	1.127	-2.290	0.024 ^a
Trail Making Test B	Anterior cingulate	-0.100 (0.321)	-5.253	1.528	-3.438	0.001 ^a
Category Fluency (animals)	Anterior cingulate	0.108 (0.286)	0.207	0.103	2.010	0.046 ^a

Notes: This analysis was done in two steps. In step 1, subject-specific rates of cognition and atrophy were estimated separately using mixed effects regression. In step 2, rates of cognitive decline were then regressed on atrophy rates, adjusting for age, sex, and APOE genotype. Steps 1 and 2 were repeated in 500 bootstrap samples to estimate the variance of the association between atrophy and cognitive decline and test for its significance. Refer to Tables 3 and 5 for degrees of freedom in each of the models for cognitive and cortical atrophy analyses, respectively. WMS: Wechsler Memory Scale.
^ap ≤ 0.05.
^bp < 0.05.

SE = 1.519, t = -0.283, p = 0.777) and Trail Making Test Part B was no longer statistically significant after this adjustment (β = -1.406, SE = 1.037, t = -1.356, p = 0.179).

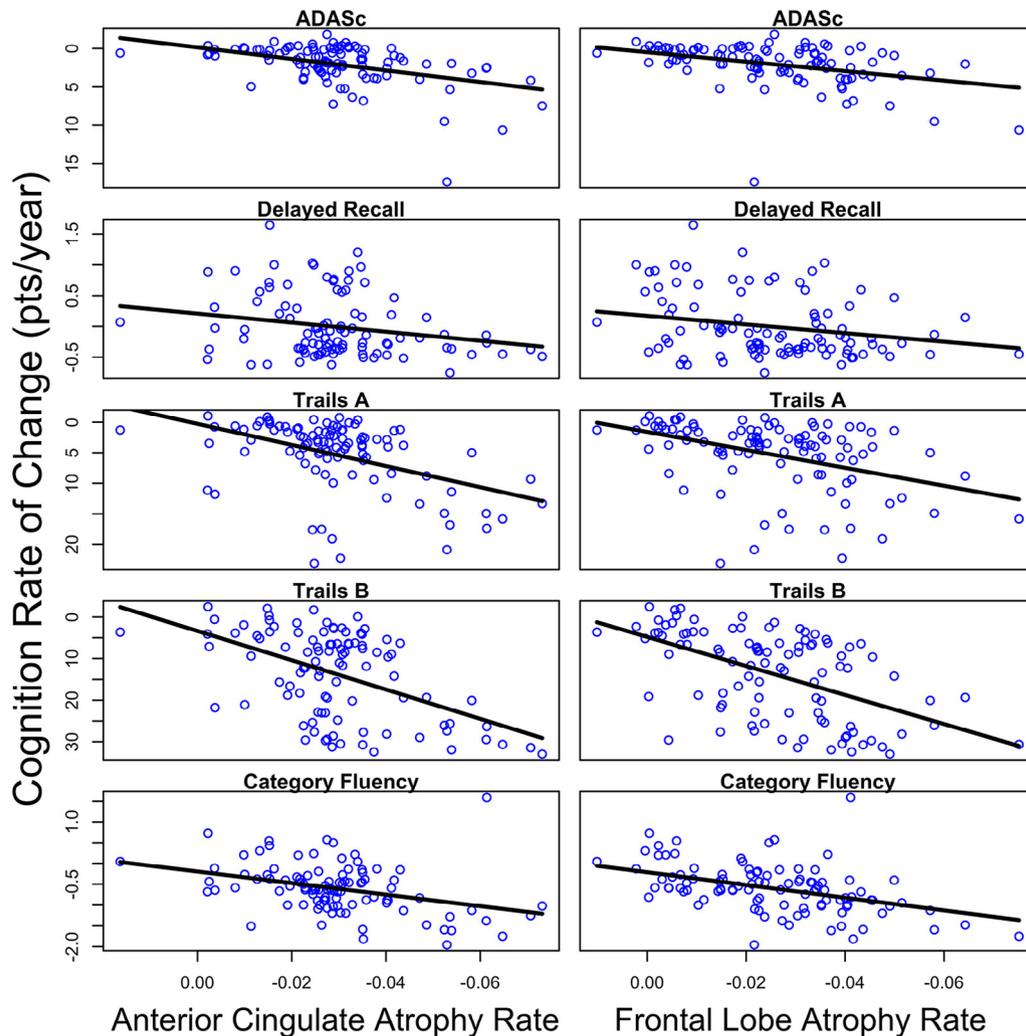
DISCUSSION

This study evaluated the association between rate of cortical atrophy and cognitive decline in participants with MCI and chronic SSD over an extended 4-year period. Our results demonstrate that MCI participants

with chronic SSD 1) display accelerated cognitive decline longitudinally on measures of global cognition, memory, information processing speed, and semantic fluency; 2) display accelerated rate of frontal lobe and anterior cingulate atrophy over time; and 3) show cognitive decline on measures of global cognition, information processing speed, and semantic fluency associated with frontal lobe and anterior cingulate atrophy independent of SSD.

Consistent with the literature indicating that depression is a risk factor for dementia,^{6,7} within this MCI sample chronic SSD was associated with accelerated

FIGURE 1. Linear mixed effects regression results of the relationship between change in cortical thickness (column 1: anterior cingulate; column 2: frontal lobe) and cognitive decline across the 4-year study interval. All $p < 0.05$. ADASc: Alzheimer's Disease Assessment Scale–Cognitive Scale.



decline on measures of global cognition, memory, information processing speed, and semantic fluency. The findings persisted over and above adjustment for other well-established cognitive decline risk factors including age, education, and *APOE* status,²³ indicating that the association of chronic SSD with cognition is independent of these factors. The current results support the literature suggesting that late life depressive symptomatology is associated with executive dysfunction and cognitive slowing.²⁴ Moreover, our data demonstrate that chronic SSD is also associated with cognitive decline in the broader domains of global cognition,

memory, and semantic fluency, which have been less commonly assessed. Finally, by examining an MCI sample, the findings indicate that chronic SSD may accelerate cognitive decline within an already cognitively vulnerable population and may serve as a useful predictor for future cognitive deterioration with this population.

In addition to accelerated cognitive decline, chronic SSD in MCI participants was also associated with more rapid frontal lobe and anterior cingulate atrophy independent of age, education, and *APOE* status. Late-life depression has been consistently associated with

structural and functional abnormalities in these two regions including lower task-related activation,²⁵ cortical thickness,²⁶ white matter integrity,²⁷ and cerebral perfusion.²⁸ The current results confirm previous findings³ by demonstrating that even depressive symptomatology below the threshold for clinical diagnosis may be associated with accelerated atrophy. Thus, chronic SSD may represent an etiological risk factor or biomarker for accelerated frontal lobe and anterior cingulate atrophy within MCI populations.

In the current study, no significant group differences in rate of atrophy were observed in the regions most commonly associated with MCI and AD including the posterior cingulate, precuneus, temporal lobe, parahippocampus, hippocampus, and entorhinal cortex.^{9,11} Atrophy in these regions may be consistent across the sample because all participants had a diagnosis of MCI. In contrast, accelerated degradation in the frontal lobe and anterior cingulate was uniquely associated with chronic SSD, indicating that depressive symptomatology may reflect cerebral pathology distinct from typical AD pathology.^{9,11}

Finally, our results demonstrated that accelerated cognitive decline in global cognition, information processing speed, and semantic fluency was associated with rate of frontal lobe and anterior cingulate atrophy. The frontal lobe and anterior cingulate act in concert with one another and subcortical regions to govern attentional regulation, task switching, and response sequencing,^{29,30} processes fundamental to performance in the affected cognitive domains. Our results suggest that more rapid frontal lobe and anterior cingulate atrophy may be an underlying mechanism of SSD-related accelerated cognitive decline in MCI.

In contrast to global cognition, information processing speed, and semantic fluency, decline in memory performance was not significantly associated with cortical atrophy in either the frontal lobe or the anterior cingulate. Successful memory retrieval is governed by concurrent activation of the frontal and medial temporal lobes.³¹ Within MCI populations, there is evidence to suggest that in addition to temporal atrophy, disconnection between the entorhinal cortex and higher cortical regions may underlie impaired memory recall.³² Thus, joint examinations of structural neuroimaging with functional connectivity may distinguish neural networks that can be targeted to prevent or attenuate memory decline in comorbid chronic SSD and MCI populations.

Although the etiology of advanced atrophy in chronic SSD has yet to be fully defined, several potential mechanisms have been proposed. In particular, white matter damage, which has been commonly reported in late-life depression,²⁷ has been linked with secondary gray matter degeneration, hypometabolism, and conversion from MCI to dementia.³³ Additionally, depressive symptomatology in geriatric populations has been associated with reduced cerebral blood within the frontal lobe and anterior cingulate.²⁸ Hypoperfusion in these regions may induce neuronal degeneration,³⁴ resulting in cortical atrophy. Depressive symptomatology and chronic stress have been associated with hypercortisolemia,³⁵ which may diminish neurotrophin levels and accelerate atrophy in vulnerable brain regions.³⁶ Of note, a prior postmortem study detected higher levels of inflammation in the frontal lobe and anterior cingulate within depressed individuals.³⁷ Finally, it has been proposed that depressive symptomatology may contribute to neurodegeneration by increasing β amyloid and tau-protein accumulation,³⁸ which may extend damage to regions typically preserved in MCI such as the frontal lobe and anterior cingulate.

The results of the current study must be considered within the strengths and limitations of the study design. The strengths of the study include the relatively large sample size with repeated neuropsychological and neuroimaging data over a 4-year period. Furthermore, the ADNI data set provides a well-characterized sample and includes strong adherence to clinical MCI diagnosis guidelines and thorough quality control for neuroimaging data. The ADNI cohort is limited to amnesic MCI, however, and it is possible that effects related to SSD may be different in a more heterogeneous MCI sample. Another limitation of the current sample is the relatively high educational attainment of the subjects, which limits the generalizability of the results. Also, the current study was restricted to subsyndromal symptoms of depression because more significant depressive symptomatology is an exclusion criterion for the ADNI study. It is possible that the cognitive and neuropathologic profiles of individuals with major and minor depression may differ from those in the current study. Additionally, at baseline, the SSD group displayed poorer performance on one measure of learning and reduced entorhinal and temporal lobe cortical thickness in comparison with the non-SSD group, indicating that they may have more advanced disease severity in some brain regions.

Thus, future studies with longer follow-up periods should examine individuals without depressive symptoms at baseline to determine if they display a similar pattern of cortical atrophy over time. There was also a significant association between baseline frontal lobe thickness and Trail Making Test Parts A and B. Inclusion of this significant baseline correlation changed the pattern of results for Trail Making Test Part B, indicating that baseline associations between cognition and cortical thickness may exert an influence on longitudinal decline for some measures of cognition. Finally, prior studies have reported reductions in white matter integrity and cerebral perfusion in older adults with depressive symptomatology.^{27,28} Thus, future studies may benefit from incorporation of multi-modal neuroimaging techniques, including indices of white matter integrity, cerebral blood flow, and amyloid beta accumulation, in effort to more fully elucidate the neurobiological mechanisms underlying cognitive decline in MCI patient with chronic SSD.

Overall, the current study indicates that chronic SSD was associated with accelerated cognitive decline and cortical atrophy within a sample of individuals carrying an MCI diagnosis. Moreover, SSD-related accelerated decline in global cognition, information processing speed, and semantic fluency domains was associated with rate of frontal lobe and anterior cingulate atrophy. Our results suggest that individuals with chronic SSD may represent an MCI subgroup with elevated risk for cognitive deterioration and potential conversion to dementia. Thus, monitoring depressive symptoms over time, rather than at a single occurrence, may be efficacious for identifying cognitively vulnerable individuals.³⁹ Our results also indicate that frontal lobe and anterior cingulate atrophy may be viable biomarkers for predicting further cognitive decline, underscoring the potential importance of treating SSD in effort to preserve cognition.

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott, AstraZeneca AB, Bayer Schering Pharma AG, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corporation, Genentech, GE Healthcare, GlaxoSmithKline, Innogenetics, Johnson and Johnson, Eli Lilly and Co,

Medpace, Inc, Merck and Co, Inc, Novartis AG, Pfizer, Inc, F. Hoffman-La Roche, Schering-Plough, Synarc, Inc, as well as nonprofit partners the Alzheimer's Association and Alzheimer's Drug Discovery Foundation, with participation from the U.S. Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuroimaging at the University of California, Los Angeles. This research was also supported by National Institutes of Health grants P30 AG010129, K01 AG030514, and the Dana Foundation. Data analysis was supported in part by the following grant from the National Institutes of Health: R01 MH098062 and R01 MH101472.

Dr. Gonzales, Mr. Insel, Dr. Mattsson, Dr. Mueller, Dr. Sacuiu, and Mr. Bickford reported no biomedical financial interests or potential conflicts of interest.

During the past 2 years, Dr. Nelson has received lecture honoraria from Bristol Myers Squibb (Canada), Otsuka (Asia); he has been an advisor or consultant to Corcept, Genentech, Janssen, Lundbeck, Otsuka, and Sunovion; and has received research support from Avid Radiopharmaceuticals, Inc and NIMH (R01MH098062, R01MH101472).

Dr. Tosun has received research support from the National Institute of Mental Health (R01MH098062, R01MH101472), Avid Radiopharmaceuticals, Inc, Michael J Fox Foundation, Alzheimer's Association, and California Department of Public Health.

Dr. Weiner receives grant funding from the National Institutes of Health, the Department of Defense, the Alzheimer's Association, the Veterans Administration, and the California Department of Public Health. Dr. Weiner has served on the Scientific Advisory Boards for Pfizer, BOLT International, Neurotrope Bioscience, Alzheon, Inc., Alzheimer's Therapeutic Research Institute (ATRI), Eli Lilly, University of Pennsylvania's Neuroscience of Behavior Initiative, National Brain Research Centre (NBRC) (India), Dolby Family Ventures, LP, and ADNI. Dr. Weiner has provided consulting to Synarc, Pfizer, Janssen, Alzheimer's Drug Discovery Foundation (ADDF), Neurotrope Bioscience, Avid Radiopharmaceuticals, Inc, Clearview Healthcare Partners, Perceptive Informatics, Smartfish AS, Araclon, Merck, Biogen Idec, BioClinica, and Genentech. He holds stock options with Alzheon, Inc. The following entities have provided funding for Dr. Weiner's

Subsyndromal Depression, Cognition, and Atrophy

academic travel; Pfizer, Neuroscience School of Advanced Studies (NSAS), Kenes, Intl., ADRC, UCLA, UCSD; ADCS, Sanofi-Aventis Groupe, University Center Hospital, Toulouse, Araclon, AC Immune, Nutricia, Eli Lilly, New York Academy of Sciences (NYAS), National Brain Research Center, India for Johns Hopkins Medicine, Consortium for Multiple Sclerosis Centers (CMSC), Northwestern University, Fidelity Biosciences Research Initiative, University

of Pennsylvania, The Alzheimer's Association, Merck, ADPD, Alzheimer's Drug Discovery Foundation (ADDF), Tokyo University, Kyoto University, Weill-Cornell University, Rockefeller University, Memorial Sloan-Kettering Cancer Center, and Biogen Idec.

During the past 2 years, Dr. Mackin has received research support from The National Institute of Mental Health, Johnson and Johnson, and Avid Radiopharmaceuticals, Inc.

References

1. Albert MS, DeKosky ST, Dickson D, et al: The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; 7:270-279
2. Judd LL, Rapaport MH, Paulus MP, et al: Subsyndromal symptomatic depression: a new mood disorder? *J Clin Psychiatry* 1994; 55(suppl):18-28
3. Sacuiu S, Insel PS, Mueller S, et al: Chronic depressive symptomatology in mild cognitive impairment is associated with frontal atrophy rate which hastens conversion to Alzheimer dementia. *Am J Geriatr Psychiatry* 2016; 24:126-135
4. Steffens DC: Depressive symptoms and mild cognitive impairment in the elderly: an ominous combination. *Biol Psychiatry* 2012; 71:762-764
5. Mackin RS, Insel P, Aisen PS, et al: Longitudinal stability of subsyndromal symptoms of depression in individuals with mild cognitive impairment: relationship to conversion to dementia after 3 years. *Int J Geriatr Psychiatry* 2012; 27:355-363
6. Gabryelewicz T, Styczynska M, Luczywek E, et al: The rate of conversion of mild cognitive impairment to dementia: predictive role of depression. *Int J Geriatr Psychiatry* 2007; 22:563-567
7. Royall DR, Palmer RF: Alzheimer's disease pathology does not mediate the association between depressive symptoms and subsequent cognitive decline. *Alzheimers Dement* 2013; 9:318-325
8. Lee GJ, Lu PH, Hua X, et al: Depressive symptoms in mild cognitive impairment predict greater atrophy in Alzheimer's disease-related regions. *Biol Psychiatry* 2012; 71:814-821
9. Petersen RC, Jack CR Jr: Imaging and biomarkers in early Alzheimer's disease and mild cognitive impairment. *Clin Pharmacol Ther* 2009; 86:438-441
10. Bora E, Harrison BJ, Davey CG, et al: Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in major depressive disorder. *Psychol Med* 2012; 42:671-681
11. Apostolova LG, Thompson PM: Mapping progressive brain structural changes in early Alzheimer's disease and mild cognitive impairment. *Neuropsychologia* 2008; 46:1597-1612
12. Wechsler D: Manual for the Wechsler Memory Scale-Revised. San Antonio, TX: The Psychological Corporation, 1987
13. Kaufer DI, Cummings JL, Ketchel P, et al: Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuro-psychiatry Clin Neurosci* 2000; 12:233-239
14. Buysse DJ, Cheng Y, Germain A, et al: Night-to-night sleep variability in older adults with and without chronic insomnia. *Sleep Med* 2010; 11:56-64
15. Rosen WG, Mohs RC, Davis KL: A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984; 141:1356-1364
16. Reitan RM, Wolfson D: The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. 2nd ed. Tucson, AZ: Neuropsychology Press, 1983
17. Wechsler D: Wechsler Adult Intelligence Scale-Revised. San Antonio, TX: Psychological Corporation, 1981
18. Morris J, Heyman A, Mohs R, et al: The consortium to establish a registry for Alzheimer's disease (CERAD): I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* 1989; 39:1159-1165
19. Kaplan E, Goodglass H, Weintraub S: Boston Naming Test-Revised. Philadelphia, PA: Lea & Febiger, 1983
20. Jack CR, Bernstein MA, Fox NC, et al: The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. *J Magn Reson Imaging* 2008; 27:685-691
21. Fischl B, Salat DH, Busa E, et al: Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 2002; 33:341-355
22. Reuter M, Schmansky NJ, Rosas HD, et al: Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage* 2012; 61:1402-1418
23. McCullagh CD, Craig D, McIlroy SP, et al: Risk factors for dementia. *Adv Psychiatr Treat* 2001; 7:24-31
24. Herrmann LL, Goodwin GM, Ebmeier KP: The cognitive neuropsychology of depression in the elderly. *Psychol Med* 2007; 37:1693-1702
25. Aizenstein HJ, Butters MA, Wu M, et al: Altered functioning of the executive control circuit in late-life depression: episodic and persistent phenomena. *Am J Geriatr Psychiatry* 2009; 17:30-42
26. Mackin RS, Tosun D, Mueller SG, et al: Patterns of reduced cortical thickness in late-life depression and relationship to psychotherapeutic response. *Am J Geriatr Psychiatry* 2013; 21:794-802
27. Bae JN, MacFall JR, Krishnan KRR, et al: Dorsolateral prefrontal cortex and anterior cingulate cortex white matter alterations in late-life depression. *Biol Psychiatry* 2006; 60:1356-1363
28. Ishizaki J, Yamamoto H, Takahashi T, et al: Changes in regional cerebral blood flow following antidepressant treatment in late-life depression. *Int J Geriatr Psychiatry* 2008; 23:805-811
29. Badre D: Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends Cogn Sci* 2008; 12:193-200
30. Botvinick MM, Braver TS, Barch DM, et al: Conflict monitoring and cognitive control. *Psychol Rev* 2001; 108:624-652
31. Cabeza R, Nyberg L: Neural bases of learning and memory: functional neuroimaging evidence. *Curr Opin Neurol* 2000; 13:415-421
32. Stoub TR, Stebbins GT, Leurgans S, et al: Hippocampal disconnection contributes to memory dysfunction in individuals at risk for Alzheimer's disease. *Proc Natl Acad Sci USA* 2006; 103:10041-10045

33. Agosta F, Pievani M, Sala S, et al: White matter damage in Alzheimer disease and its relationship to gray matter atrophy. *Radiology* 2011; 258:853-863
34. Bennett SA, Tenniswood M, Chen J-H, et al: Chronic cerebral hypoperfusion elicits neuronal apoptosis and behavioral impairment. *Neuroreport* 1998; 9:161-166
35. Checkley S: The neuroendocrinology of depression and chronic stress. *Br Med Bull* 1996; 52:597-617
36. Dwivedi Y: Involvement of brain-derived neurotrophic factor in late-life depression. *Am J Geriatr Psychiatry* 2013; 21:433-449
37. Thomas A, Ferrier IN, Kalaria RN, et al: Cell adhesion molecule expression in the dorsolateral prefrontal cortex and anterior cingulate cortex in major depression in the elderly. *Br J Psychiatry* 2002; 181:129-134
38. Rapp MA, Schnaider-Beeri M, Purohit DP, et al: Increased neurofibrillary tangles in patients with Alzheimer disease with comorbid depression. *Am J Geriatr Psychiatry* 2008; 16:168-174
39. David ND, Lin F, Porsteinsson AP: Trajectories of neuropsychiatric symptoms and cognitive decline in mild cognitive impairment. *Am J Geriatr Psychiatry* 2016; 24:70-80