Are there neuroimaging signatures for MBI? A review of the 5 domains

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Objectives

1. Discuss the prevalence in a pre-dementia population of the 5 MBI domains: motivation/drive, affective/emotional regulation, impulse control, social appropriateness, and psychosis
2. Review the imaging findings in each domain
3. Explore gaps in knowledge, and future directions for neuroimaging studies of Neuropsychiatric Symptoms in pre-dementia

There is plenty of evidence for neural signatures of NPS in AD

Brain Imaging and Behavior
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ORIGINAL RESEARCH

Identify a shared neural circuit linking multiple neuropsychiatric symptoms with Alzheimer's pathology

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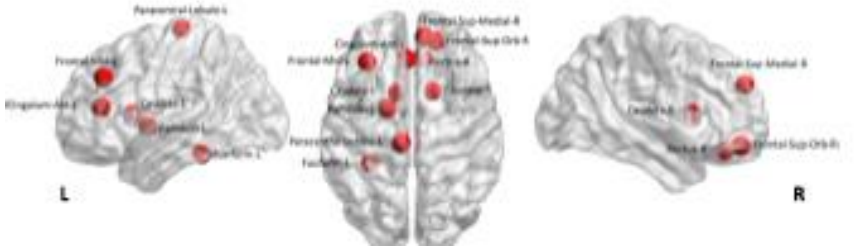
Abstract Neuropsychiatric symptoms (NPS) are common in Alzheimer's disease (AD)-associated neurodegeneration. However, NPS lack a consistent relationship with AD pathology. It is unknown whether any common neural circuits can link these clinically disparate while mechanistically similar features with AD pathology. Here, we explored the neural circuits of NPS in AD-associated neurodegeneration using multivariate pattern analysis (MVPA) of resting-state functional MRI data. Data from 98 subjects (70 amnestic mild cognitive impairment and 28 AD subjects) were obtained. The top 10 regions differentiating symptom presence across NPS were identified, which were mostly the fronto-limbic regions (medial prefrontal cortex, caudate, etc.). These 10 regions' functional connectivity classified symptomatic subjects across individual NPS at 69.46–81.27%, and predicted multiple NPS (indexed by Neuropsychiatric Symptom Questionnaire-Inventory) and AD pathology (indexed by baseline and change of beta-amyloid/pTau ratio) all above 70%. Our findings suggest a fronto-limbic dominated neural circuit that links multiple NPS and AD pathology. With further examination of the structural and pathological changes within the circuit, the circuit may shed light on linking behavioral disturbances with AD-associated neurodegeneration.

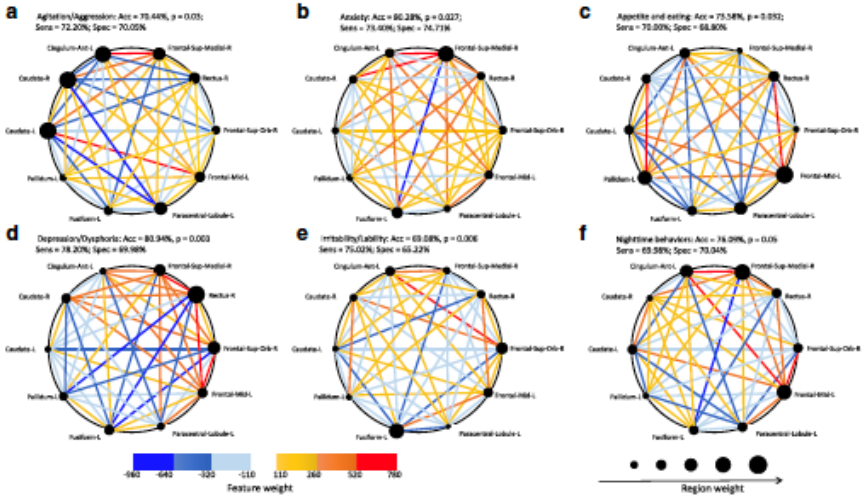
Keywords Alzheimer's disease · Functional magnetic resonance imaging · Mild cognitive impairment · Multivariate pattern analysis · Neuropsychiatric symptoms

Xixi Wang and Ping Ren contributed equally to this work.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). 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. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu.

Introduction





PATH Study (Community Sample): NPS/MBI increase in frequency with time proximal to dementia

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Neuropsychiatric Symptoms and Cognitive Impairment: Understanding the Importance of Co-Morbid Symptoms

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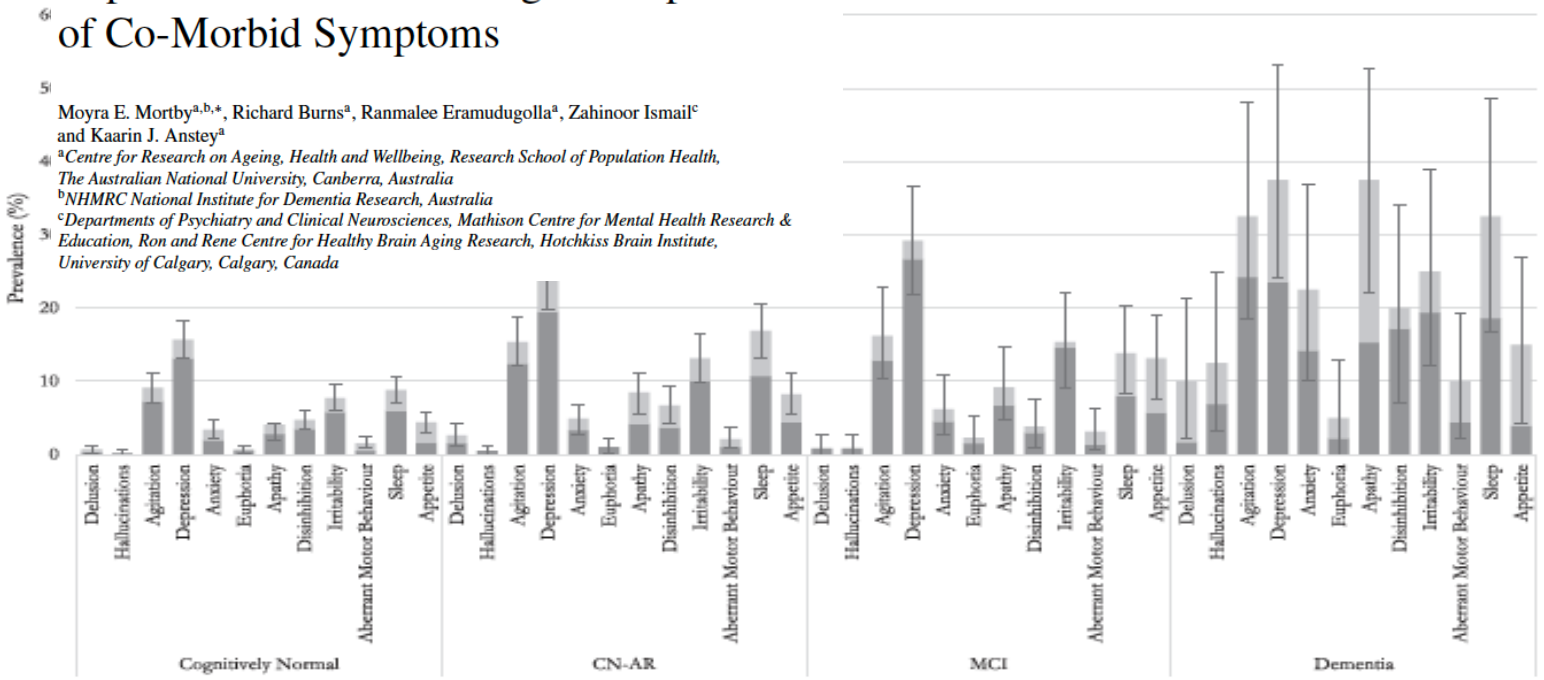

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Prevalence estimates of mild behavioral impairment in a population-based sample of pre-dementia states and cognitively healthy older adults

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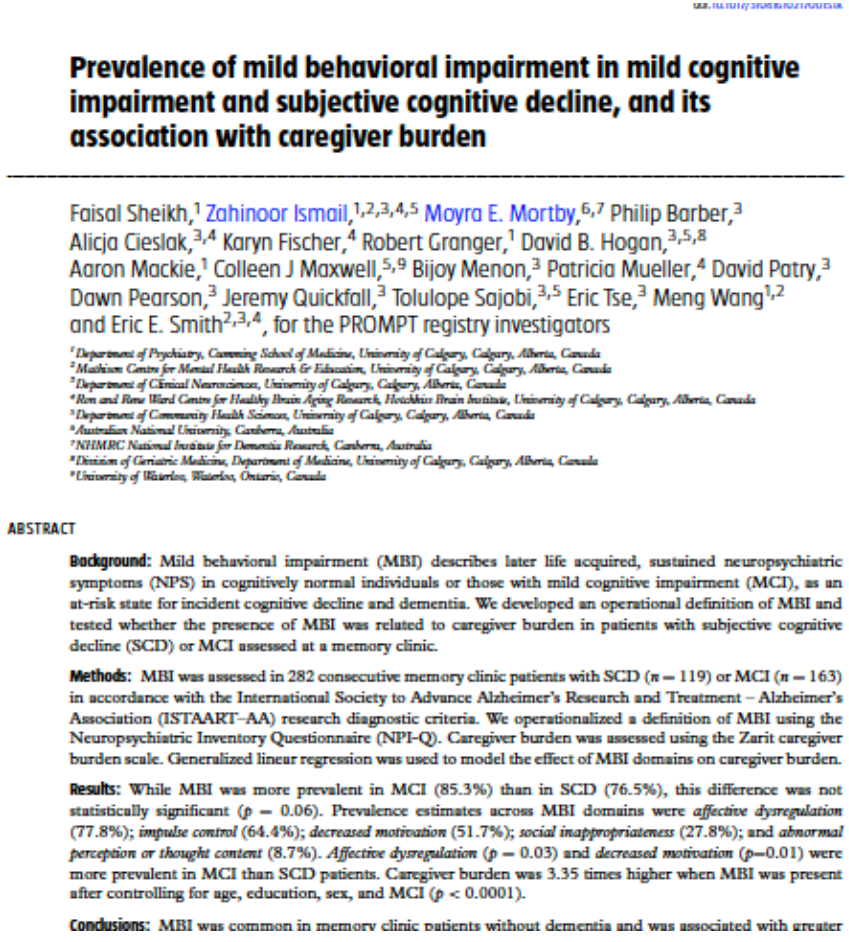
Table 3. Prevalence of mild behavioral impairment in the PATH through life study

MILD BEHAVIORAL IMPAIRMENT	COGNITIVELY NORMAL ($N = 847$)			CN-AR ($N = 397$)			MCI ($N = 133$)			χ^2	GROUP DIFFERENCES
	N	(%)	(95% CI)	*N*	(%)	(95% CI)	*N*	(%)	(95% CI)		
Any MBI	234	(27.6)	(24.9, 30.7)	171	(43.1)	(38.6, 47.9)	65	(48.9)	(40.8, 57.1)	χ^2 (2) = 42.9, $p < 0.001$	MCI > CN
Decreased motivation	26	(3.1)	(2, 4.3)	33	(8.3)	(5.7, 11.1)	12	(9.0)	(4.2, 13.9)	χ^2 (2) = 19.7, $p < 0.001$	CN-AR > CN MCI > CN
Affective dysregulation	146	(17.2)	(14.8, 19.8)	104	(26.2)	(22.3, 30.7)	43	(32.3)	(24.3, 40.9)	χ^2 (2) = 23.7, $p < 0.001$	CN-AR > CN MCI > CN
Impulse dyscontrol	138	(16.3)	(13.9, 19)	114	(28.7)	(24.1, 33.2)	45	(33.8)	(25.7, 41.5)	χ^2 (2) = 37.8, $p < 0.001$	CN-AR > CN MCI > CN
Social inappropriateness	40	(4.7)	(3.3, 6.2)	28	(7.1)	(4.6, 9.6)	5	(3.8)	(0.8, 7.2)	χ^2 (2) = 3.62, $p = 0.164$	CN-AR > CN
Abnormal perception or through content	8	(0.9)	(0.4, 1.6)	11	(2.8)	(1.3, 4.6)	2	(1.5)	(0, 4)	χ^2 (2) = 6.00, $p = 0.050$	CN-AR > CN

Prevalence of MBI Criterion 1 in Clinical Sample of SCD (76.5%) and MCI (85.3%)



Prevalence of mild behavioral impairment in mild cognitive impairment and subjective cognitive decline, and its association with caregiver burden

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ABSTRACT

Background: Mild behavioral impairment (MBI) describes later life acquired, sustained neuropsychiatric symptoms (NPS) in cognitively normal individuals or those with mild cognitive impairment (MCI), as an at-risk state for incident cognitive decline and dementia. We developed an operational definition of MBI and tested whether the presence of MBI was related to caregiver burden in patients with subjective cognitive decline (SCD) or MCI assessed at a memory clinic.

Methods: MBI was assessed in 282 consecutive memory clinic patients with SCD ($n = 119$) or MCI ($n = 163$) in accordance with the International Society to Advance Alzheimer's Research and Treatment – Alzheimer's Association (ISTAART–AA) research diagnostic criteria. We operationalized a definition of MBI using the Neuropsychiatric Inventory Questionnaire (NPI-Q). Caregiver burden was assessed using the Zarit caregiver burden scale. Generalized linear regression was used to model the effect of MBI domains on caregiver burden.

Results: While MBI was more prevalent in MCI (85.3%) than in SCD (76.5%), this difference was not statistically significant ($p = 0.06$). Prevalence estimates across MBI domains were *affective dysregulation* (77.8%); *impulse control* (64.4%); *decreased motivation* (51.7%); *social inappropriateness* (27.8%); and *abnormal perception or thought content* (8.7%). *Affective dysregulation* ($p = 0.03$) and *decreased motivation* ($p=0.01$) were more prevalent in MCI than SCD patients. Caregiver burden was 3.35 times higher when MBI was present after controlling for age, education, sex, and MCI ($p < 0.0001$).

Conclusions: MBI was common in memory clinic patients without dementia and was associated with greater

- SCD n=94
  - Affect 56.3%
  - Agitation 47.9%
  - Apathy 32.8%
  - Social 21.8%
  - Psychosis 4.2%
- MCI n=147
  - Affect 68.7%
  - Agitation 55.8%
  - Apathy 49.1%
  - Social 23.3%
  - Psychosis 9.2%

Domain 1:
Drive / Motivation (i.e. apathy)

Pre-MCI and MCI: Neuropsychological, Clinical, and Imaging Features and Progression Rates

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Objective: *To compare clinical, imaging, and neuropsychological characteristics and longitudinal course of subjects with pre-mild cognitive impairment (pre-MCI), who exhibit features of MCI on clinical examination but lack impairment on neuropsychological examination, to subjects with no cognitive impairment (NCI), nonamnestic MCI (naMCI), amnestic MCI (aMCI), and mild dementia.* **Methods:** *For 369 subjects, clinical dementia rating sum of boxes (CDR-SB), ApoE genotyping, cardiovascular risk factors, parkinsonism (UPDRS) scores, structural brain MRIs, and neuropsychological testing were obtained at baseline, whereas 275 of these subjects received an annual follow-up for 2–3 years.* **Results:** *At baseline, pre-MCI subjects showed impairment on tests of executive function and language, higher apathy scores, and lower left hippocampal volumes (HPCV) in comparison to NCI subjects. Pre-MCI subjects showed less impairment on at least one memory measure, CDR-SB and UPDRS scores, in comparison to naMCI, aMCI and mild dementia subjects. Follow-up over 2–3 years showed 28.6% of pre-MCI subjects, but less than 5% of NCI subjects progressed to MCI or dementia. Progression rates to dementia were equivalent between naMCI (22.2%) and aMCI (34.5%) groups, but greater than for the pre-MCI group (2.4%). Progression to dementia was best predicted by the CDR-SB, a list learning and executive function test.* **Conclusion:** *This study demonstrates that clinically defined pre-MCI has cognitive, functional, motor, behavioral and imaging features that are intermediate between NCI and MCI states at baseline. Pre-MCI subjects showed*

- N=369
- Baseline
  - Pre-MCI had higher apathy scores and smaller l. hippocampal volumes compared to NC
- Follow-up 2-3 years progression to MCI/dementia
  - Pre-MCI: 28.6%
  - NC: <5%

ADNI: "apathy belongs to the spectrum of prodromal AD symptoms"

- MCI +/- apathy; n=65
- No cognitive differences between groups
- Apathy: decreased glucose metabolism in PCC

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Apathy as a feature of prodromal Alzheimer's disease: an FDG-PET ADNI study

Julien Delrieu[1], Thomas Desmidt[2], Vincent Camus[2], Sandrine Sourdet[1], Claire Boutoleau-Bretonnière[3], Emmanuel Mullin[4], Bruno Vellas[1,5], Pierre Payoux[6,7], Thibaud Lebouvier[3] and Alzheimer's Disease Neuroimaging Initiative †

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†Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). 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. A complete listing of ADNI investigators can be found at http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Objective: The goal of this study is to evaluate brain metabolism in mild cognitive impairment (MCI) patients with and without apathy (as determined by the Neuropsychiatric Inventory Questionnaire).

Methods: Baseline data from 65 MCI participants (11 with apathy and 54 without) from the Alzheimer's Disease (AD) Neuroimaging Initiative study were analyzed. All participants underwent a comprehensive cognitive and neuropsychiatric assessment, volumetric MRI and measures of cerebral glucose metabolism applying ^{18}F-fluorodeoxyglucose positron emission tomography at baseline. The presence of apathy at baseline was determined by the Neuropsychiatric Inventory Questionnaire.

Results: There was no difference between apathy and apathy-free MCI patients regarding cognitive assessment and neuropsychiatric measures when apathy-specific items were removed. Cerebrovascular disease load and cerebral atrophy were equivalent in both groups. Compared with the apathy-free MCI patients, MCI patients with apathy had significantly decreased metabolism in the posterior cingulate cortex.

Conclusion: The presence of apathy in MCI patients is associated with AD-specific pattern of brain metabolic defect. These results could suggest that apathy belongs to the spectrum of prodromal AD symptoms.

Key words: apathy; FDG-PET; biomarker; Alzheimer's disease; mild cognitive impairment; Alzheimer's disease neuroimaging initiative (ADNI)
History: Received 18 April 2013; Accepted 28 May 2014; Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI: 10.1002/gps.4161

Anatomical region	Coordinates x	y	z	p-value Uncorrected	Z score
Left cerebrum, limbic lobe, cingulate gyrus, Brodmann area 31	−10	−36	40	<0.001	4.56
Right cerebrum, limbic lobe, cingulate gyrus, Brodmann area 31	2	−26	32	<0.001	3.96
Left cerebrum, limbic lobe, cingulate gyrus, Brodmann area 31	14	−34	42	<0.001	3.93

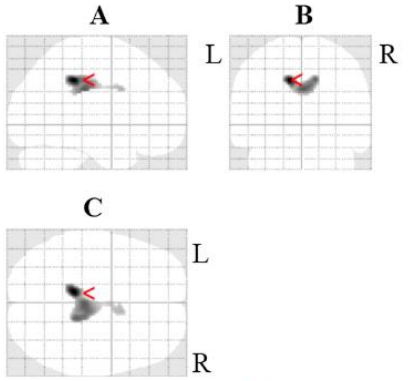


Figure 2 Statistical parametric mapping eight projections showing corrected areas with reduced glucose cerebral metabolism in MCI subjects apathy+ compared with MCI subjects apathy−.

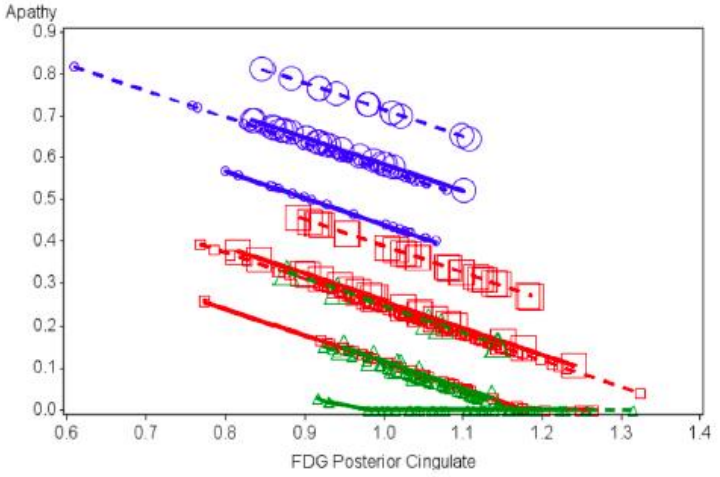
ADNI: "cross-sectional relationship between posterior cingulate hypometabolism and higher apathy scores"

- CN/ MCI/ early AD; n=405
- PCC more important in early stages, in contrast to ACC/ OFC in later stages

Regional 18F-Fluorodeoxyglucose Hypometabolism is Associated with Higher Apathy Scores Over Time in Early Alzheimer Disease

Jennifer R. Gatchel, M.D., Ph.D., Nancy J. Donovan, M.D., Joseph J. Locascio, Ph.D., J. Alex Becker, Ph.D., Dorene M. Rentz, Psy.D., Reisa A. Sperling, M.D., Keith A. Johnson, M.D., Gad A. Marshall, M.D., for the Alzheimer's Disease Neuroimaging Initiative[1]

Objectives: *Apathy is among the earliest and most pervasive neuropsychiatric symptoms in prodromal and mild Alzheimer disease (AD) dementia that correlates with functional impairment and disease progression. We investigated the association of apathy with regional 18F-fluorodeoxyglucose (FDG) metabolism in cognitively normal, mild cognitive impairment, and AD dementia subjects from the Alzheimer's Disease Neuroimaging Initiative database.* **Design:** *Cross-sectional and longitudinal studies.* **Setting:** *57 North American research sites.* **Participants:** *402 community dwelling elders.* **Measurements:** *Apathy was assessed using the Neuropsychiatric Inventory Questionnaire. Baseline FDG metabolism in five regions implicated in the neurobiology of apathy and AD was investigated in relationship to apathy at baseline (cross-sectional general linear model) and longitudinally (mixed random/fixed effect model). Covariates included age, sex, diagnosis, apolipoprotein E genotype, premorbid intelligence, cognition, and antidepressant use.* **Results:** *Cross-sectional analysis revealed that posterior cingulate hypometabolism, diagnosis, male sex, and antidepressant use were associated*



Domain 2: Emotional / Affective regulation (i.e. depression and anxiety)

Harvard Aging Brain

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Depressive symptoms and biomarkers of Alzheimer's disease in cognitively normal older adults

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Abstract

Even low levels of depressive symptoms are associated with an increased risk of cognitive decline in older adults without overt cognitive impairment (CN). Our objective was to examine whether very low, "subthreshold symptoms of depression" (SSD) are associated with Alzheimer's disease (AD) biomarkers of neurodegeneration in CN adults and whether these associations are specific to particular depressive symptoms. We analyzed data from 248 community-dwelling CN older adults, including measurements of cortical amyloid burden, neurodegeneration markers of hippocampal volume (HV) and cerebral 18F-fluorodeoxyglucose (FDG) metabolism in a composite of AD-related regions and the 30-item Geriatric Depression Scale (GDS). Participants with GDS>10 were excluded. General linear regression models evaluated the cross-sectional

- CN; n=248
- Depressive sx (GDS)
- GDS score inversely correlated with hippocampal volume and FDG metabolism in AD metaROI

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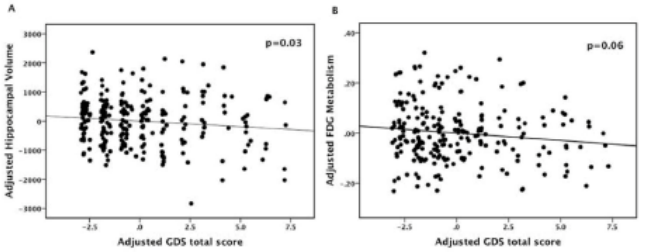

Figure 2. The relation of GDS to Hippocampal Volume (A) and FDG Metabolism (B)
Multiple regression models with backward elimination were employed. In each model the pool of predictors included GDS, age, sex, premorbid intelligence, prior depression, antidepressant medication use, amyloid status and the interaction of GDS with amyloid. Hippocampal volume was adjusted for intracranial volume. Abbreviation: GDS (Geriatric Depression Scale-30 item) FDG (18F-fluorodeoxyglucose)

“NPS can be an important additional tool to the biomarker-based investigation of presymptomatic AD”

Mayo Clinic Study of Aging

- CN > 70 yrs; n=668
- Outcome: SUVR <1.32 in AD regions
- OR for low SUVR=2.12 with depression; OR= 2.59 in Apoε4 carriers

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FDG-PET and Neuropsychiatric Symptoms among Cognitively Normal Elderly Persons: The Mayo Clinic Study of Aging

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Abstract. One of the key research agenda of the field of aging is investigation of presymptomatic Alzheimer's disease (AD). Furthermore, abnormalities in brain glucose metabolism (as measured by FDG-PET) have been reported among cognitively normal elderly persons. However, little is known about the association of FDG-PET abnormalities with neuropsychiatric symptoms (NPS) in a population-based setting. Thus, we conducted a cross-sectional study derived from the ongoing population-based Mayo Clinic Study of Aging in order to examine the association between brain glucose metabolism and NPS among cognitively normal (CN) persons aged>70 years. Participants underwent FDG-PET and completed the Neuropsychiatric Inventory Questionnaire (NPI-Q), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI). Cognitive classification was made by an expert consensus panel. We conducted multivariable logistic regression analyses to compute odds ratios (OR) and 95% confidence intervals after adjusting for age, sex, and education. For continuous variables, we used linear regression and Spearman rank-order correlations. Of 668 CN participants (median 78.1 years, 55.4% males), 205 had an abnormal FDG-PET (i.e., standardized uptake value ratio< 1.32 in AD-related regions). Abnormal FDG-PET was associated with depression as measured by NPI-Q (OR = 2.12; 1.23–3.64); the point estimate was further elevated for APOE ε4 carriers (OR = 2.59; 1.00–6.69), though marginally significant. Additionally, we observed a significant association between abnormal FDG-PET and depressive and anxiety symptoms when treated as continuous measures. These findings indicate that NPS, even in community-based samples, can be an important additional tool to the biomarker-based investigation of presymptomatic AD.

Keywords: Agitation, Alzheimer's disease, anxiety, apathy, cognitively normal persons, depression, FDG-PET, neuroimaging, neuropsychiatric symptoms

Table 2
NPS and FDG-PET

NPS	Abnormal FDG-PET ($N=204$) n (%)	Normal FDG-PET ($N=454$) n (%)	OR (95% CI)
Agitation	5 (2.5)	9 (2.0)	1.21 (0.38–3.79)
Depression	31 (15.2)	33 (7.3)	**2.12 (1.23–3.64)***
Anxiety	13 (6.4)	19 (4.2)	1.61 (0.76–3.42)
Apathy/Indifference	9 (4.4)	20 (4.4)	0.86 (0.37–1.97)

*$p \leq 0.05$. Note: Neuropsychiatric data were missing for 1 participant with an abnormal FDG-PET and 9 participants with a normal FDG-PET. In this analysis, we only included participants in which NPS (agitation, depression, anxiety, and apathy as measured by NPI-Q) were present.

Table 3
Depression, anxiety, and regions of interest

ROI	BDI ($N=655$)	p	BAI ($N=655$)	p
Anterior Cingulate	–0.0014 (–0.0033, 0.0005)	0.14	–0.0015 (–0.0038, 0.0008)	0.20
Prefrontal	–0.0015 (–0.0040, 0.0011)	0.26	–0.0013 (–0.0044, 0.0018)	0.41
Temporal	–0.0006 (–0.0026, 0.0013)	0.52	–0.0000 (–0.0023, 0.0023)	0.99
Caudate	–0.0015 (–0.0036, 0.006)	0.15	–0.0019 (–0.0044, 0.0006)	0.13
Insula	–0.0011 (–0.0028, 0.0006)	0.21	–0.0009 (–0.0029, 0.0012)	0.40
Medial Temporal	–0.0001 (–0.0013, 0.0011)	0.86	–0.0000 (–0.0014, 0.0014)	1.00
Parietal	–0.0012 (–0.0041, 0.0017)	0.42	–0.0008 (–0.0042, 0.0027)	0.67
Thalamus	–0.0004 (–0.0024, 0.0015)	0.66	–0.0009 (–0.0033, 0.0014)	0.44

functional disruption of the frontal region, known to be associated with primary or other secondary depression, underlies depression in preclinical AD

Frontal Dysfunction Underlies Depression in Mild Cognitive Impairment: A FDG-PET Study

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Objective Depression is a very common symptom in people with mild cognitive impairment (MCI), a preclinical stage of Alzheimer's disease (AD), and in those with clinically evident AD. Moreover, MCI individuals with depression show a higher conversion rate to clinical AD than those without depression. This study aimed to elucidate the functional neuroanatomical substrate of depression in MCI.

Methods Thirty-six patients were recruited from a University Hospital-based cohort; 18 of these subjects had MCI with depression (MCI_D); the remaining 18 subjects were age- and gender-matched, and had MCI with no depression (MCI_ND). For comparison, 16 cognitively normal (CN) elderly individuals were also included. All subjects underwent Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scanning and regional cerebral glucose metabolism was compared among the three groups by a voxel-based method. The relationship between severity of depression, as measured by Hamilton Rating Scale for Depression (HRSD) scores, and glucose metabolism was also investigated.

Results MCI_D showed lower glucose metabolism in the right superior frontal gyrus than MCI_ND. There was a significant negative correlation between HRSD score and glucose metabolism at the same frontal region for overall MCI subjects. When compared with CN, both MCI_D and MCI_ND showed decreased glucose metabolism in the precuneus, while MCI_D had, in addition, reduced metabolism in other diffuse brain regions.

Conclusion Given previous observations on depression in AD, our results suggest that functional disruption of the frontal region, known to be associated with primary or other secondary depression, underlies depression in preclinical AD as well as clinically evident AD.

Psychiatry Investig 2010;7:208-214

Key Words Mild cognitive impairment, Depression, Frontal, Fluorodeoxyglucose Positron Emission Tomography.

- **aMCI +/- Depression (major/minor, HAMD for severity) n=36**
- **BA 6 (Right superior frontal gyrus) hypometabolism in MCI_D vs. MCI_ND**

INTRODUCTION

Depression is a very common and significant psychiatric complication that affects 30 to 50% of Alzheimer's disease (AD) patients.[1,2] Depression increases the suffering of AD patients and their families, and compounds consequent disability. While other psychiatric symptoms, such as delusion, hallucination, agitation, and apathy, occur mainly in the later stages of AD, depression is common even in the very early stage of the disease. Patients with mild cognitive impairment (MCI), a preclinical stage of AD, also frequently experience depression. The prevalence of depression in MCI has been reported to be 16-20%.[3,4] MCI with depression has more than a two-fold higher AD conversion rate, compared to MCI with no depression.[5,6]

A couple of functional neuroimaging studies revealed that functional impairment of frontal cortical regions was associated with depression in AD.[7-9] A previous report by our study group has indicated that depressive AD patients have lower glucose metabolism in the right superior frontal gyrus than non-depressive AD patients.[7] Other [^{18}F] Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) studies have also reported that superior frontal hypometabolism is associated with depression in AD.[8,9] Hirono et al.[8] reported that de-

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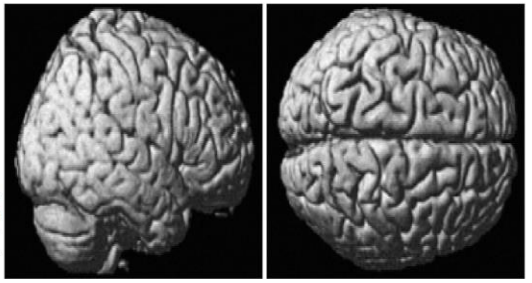

Figure 1. Statistical parametric maps showing decreased glucose metabolism in mild cognitive impairment (MCI) with depression compared with MCI without depression at $p < 0.001$ (uncorrected).

"Those whose depressive symptoms persisted over 2 years also had higher conversion to AD and more decline on measures of global cognition, language, and executive functioning"

ADNI

Depressive Symptoms in Mild Cognitive Impairment Predict Greater Atrophy in Alzheimer's Disease-Related Regions

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Background: Depression has been associated with higher conversion rates from mild cognitive impairment (MCI) to Alzheimer's disease (AD) and may be a marker of prodromal AD that can be used to identify individuals with MCI who are most likely to progress to AD. Thus, we examined the neuroanatomical changes associated with depressive symptoms in MCI.

Methods: Two-hundred forty-three MCI subjects from the Alzheimer's Disease Neuroimaging Initiative who had brain magnetic resonance imaging scans at baseline and 2-year follow-up were classified into depressed ($n = 44$), nondepressed with other neuropsychiatric symptoms ($n = 93$), and no-symptom (NOSYMP; $n = 106$) groups based on the Neuropsychiatric Inventory Questionnaire. Tensor-based morphometry was used to create individual three-dimensional maps of 2-year brain changes that were compared between groups.

Results: Depressed subjects had more frontal ($p = .024$), parietal ($p = .030$), and temporal ($p = .038$) white matter atrophy than NOSYMP subjects. Those whose depressive symptoms persisted over 2 years also had higher conversion to AD and more decline on measures of global cognition, language, and executive functioning compared with stable NOSYMP subjects. Nondepressed with other neuropsychiatric symptoms and NOSYMP groups exhibited no differences in rates of atrophy.

Conclusions: Depressive symptoms were associated with greater atrophy in AD-affected regions, increased cognitive decline, and higher rates of conversion to AD. Depression in individuals with MCI may be associated with underlying neuropathological changes, including prodromal AD, and may be a potentially useful clinical marker in identifying MCI patients who are most likely to progress to AD.

Key Words: Alzheimer's disease, depression, mild cognitive impairment, neuropsychiatric symptoms, tensor-based morphometry, white matter

Mild cognitive impairment (MCI) (1) is conceptualized as a transitional state between normal aging and early Alzheimer's disease (AD). In longitudinal studies, individuals meeting criteria for MCI are at increased risk for progressing to AD compared with age-matched control subjects (1,2). However, rates of conversion from MCI to AD are highly variable (3) because the cognitive deficits exhibited by these individuals may be related to a number of different pathologies. In an effort to detect AD in prodromal stages, there have been attempts to identify subgroups of MCI patients who are at highest risk for progression to AD. Many approaches focus on identifying early biological markers in structural (4) and functional (5) neuroimaging and cerebrospinal fluid (6), but clinical tools, such as neuropsychological testing (7), have also been useful.

Another potential clinical marker for identifying MCI individuals at high risk of developing AD is the presence of neuropsychiatric symptoms. Depression, in particular, has been associated with increased risk of dementia (8,9). We previously demonstrated that depressive symptoms predicted progression to AD in MCI patients (10,11), but the neurobiological mechanism underlying this association is not yet fully understood. In several cross-sectional studies, depressed elderly appear to have underlying brain changes associated with AD, including reduced temporal lobe (12), hippocampal, and amygdala volume (13,14). As depressive symptoms may be a clinical marker of prodromal AD, we wanted to extend the findings in the existing literature and demonstrate that depressive symptoms would be associated with AD-related neuroanatomical changes, particularly in white matter regions.

Tensor-based morphometry (TBM) is a relatively novel computational approach that can compare longitudinally acquired images and visualize the spatial profile of brain atrophy over time, including estimates of tissue volume loss at each voxel in the brain (15). This approach has been successfully used to track longitudinal changes associated with normal brain aging and neurodegenerative disorders (16,17). Also, it may be more sensitive in detecting changes in white matter volume, as it does not require a segmentation step, thus avoiding potential errors in accurate tissue classification. We applied TBM to compare patterns of brain atrophy in MCI patients with and without depressive symptoms. Specifically, we hypothesized that MCI patients with depressive symptoms would demonstrate greater brain atrophy over 2 years compared with those without depressive symptoms in regions specifically associated with AD pathology.

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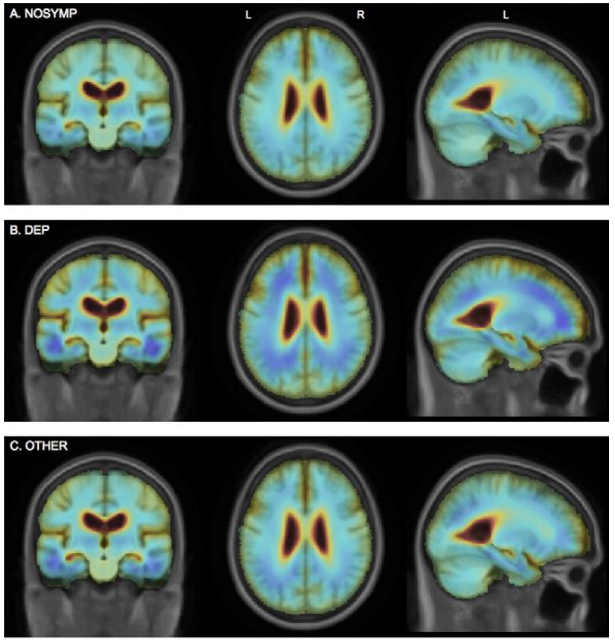
- MCI: D, no-D, no-symp; n=243
- Tensor based morphometry 2 yr.
- Frontal, Parietal and Temporal WM Atrophy in depressed vs. asymptomatic participants



“co-existence of these clinical phenotypes is a potential marker for higher risk of AD”

Medical College of Wisconsin Study

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Research report

The co-existence of geriatric depression and amnestic mild cognitive impairment detrimentally affect gray matter volumes: Voxel-based morphometry study☆

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HIGHLIGHTS

- Geriatric depression is related to mood-regulating regional gray matter (GM) loss.
- MCI is related to GM volume loss in brain regions involved in cognitive functions.
- Depression- MCI interactions are related to widespread cortical/subcortical GM loss.
- Depressive symptom–memory interactions detrimentally affect frontal and insula GM.
- Co-existence of late-life depression and MCI may be a potential marker of early AD.

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ABSTRACT

While late-life depression (LLD) and amnestic mild cognitive impairment (aMCI), alone and in combination, is associated with an increased risk of incident Alzheimer's disease (AD), the neurobiological mechanisms of this link are unclear. We examined the main and interactive effects of LLD and aMCI on the gray matter (GM) volumes in 72 physically healthy participants aged 60 and older. Participants were separated into normal controls, cognitively normal depressed, non-depressed aMCI, and depressed aMCI groups. Optimized voxel-based morphometry estimated GM volumes. The main and interactive effects of LLD and aMCI, and of depressive symptoms and episodic memory deficits on the GM volumes were analyzed. While decreased GM volumes in the mood regulating circuitry structures were associated with depression, GM atrophy in regions essential for various cognitive performance were related to aMCI. LLD- aMCI interactions were associated with widespread subcortical and cortical GM volume loss of brain structures implicated in AD. The interactions between episodic memory deficits and depressive symptom severity are associated with volume loss in right inferior frontal gyrus/anterior insula and left medial frontal gyrus clusters. Our findings suggest that the co-existence of these clinical phenotypes is a potential marker for higher risk of AD.

1. Introduction

An estimated 35 million people worldwide are living with Alzheimer's disease (AD) today, and this number is anticipated to rise to 113 million by year 2050 [1]. While AD-modifying agents are currently in various phases of clinical trials, several of these have failed to show benefit. Modification of vascular, lifestyle, and psychosocial factors may prevent or reduce the incidence of AD in a significant proportion of individuals [2]. Late-life depression (LLD), one such modifiable risk factor, affects a significant proportion of older adults, and is associated with poorer outcomes of co-morbid medical disorders, increased mortality risk and incident cognitive decline [3].

LLD is associated with increased risk of developing mild cognitive impairment (MCI) and AD [2,4,5]. In LLD, volume declines in the brain regions earliest affected by AD, including the frontal and medial temporal lobe (MTL) structures are seen, although these findings are not universal [6–15]. Circumscribed hippocampal abnormalities are reported in LLD, and depressed elderly with

☆ This work was presented as a poster at the Alzheimer's Imaging Consortium session of the Alzheimer's Association International Conference, Vancouver, British Columbia, Canada, July 14–19, 2012.

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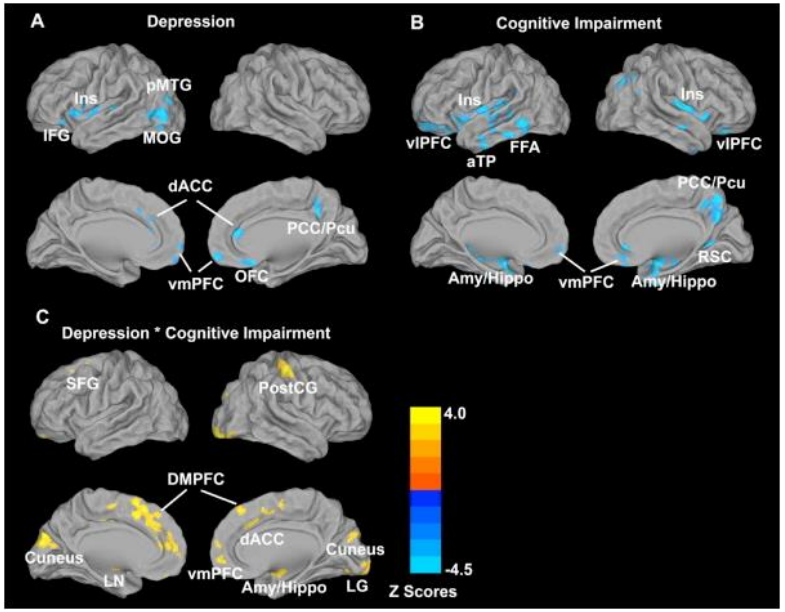
- LLD+/- and aMCI+/-
- n=72; age>60
- Depression-Cognition interactions assoc w volume loss in RIFG/ Ant Ins/ LMFG



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

ADNI

- MCI +/- SSD (chronic); n=101
- 4 year follow up
- Depression had accelerated decline in cognition
- Depression had accelerated atrophy in frontal lobe and ACC

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

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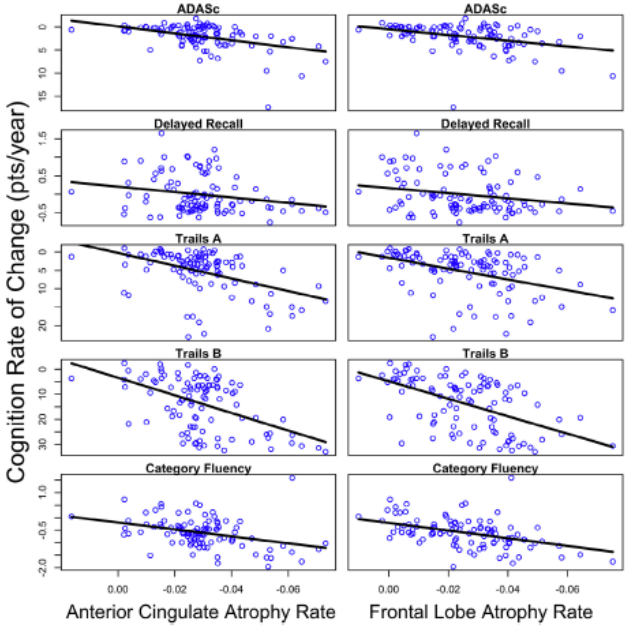
Objectives: *To investigate the association between cognitive decline and cortical atrophy in individuals with mild cognitive impairment (MCI) and chronic subsyndromal symptoms of depression (SSD) over a 4-year period.* **Design:** *Prospective cohort study.* **Setting:** *Multicenter, clinic-based.* **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*



Chronic D: “additional risk factor for conversion to dementia in MCI as opposite to representing typical prodromal AD symptomatology”.

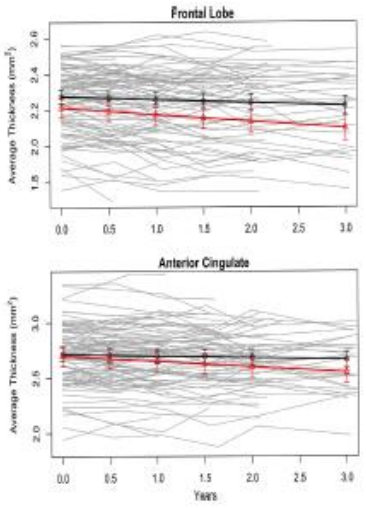
ADNI

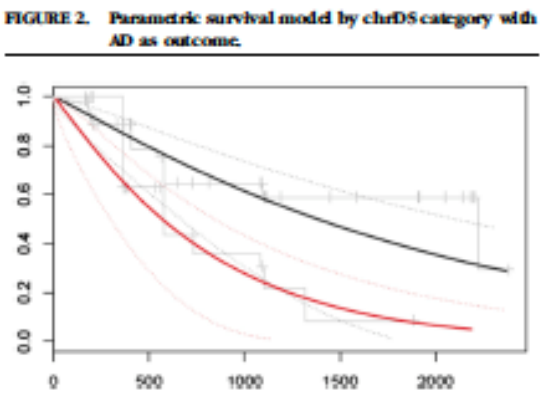
- aMCI +/- chronic D; n=95
- 3-year f/u
- D: accelerated atrophy in frontal and ACC regions
- D had 60% shorter conversion time to AD than no-D participants

Chronic Depressive Symptomatology in Mild Cognitive Impairment Is Associated with Frontal Atrophy Rate which Hastens Conversion to Alzheimer Dementia

Simona Sacuiu, M.D., Ph.D., Philip S. Insel, M.S., Susanne Mueller, M.D., Duygu Tosun, Ph.D., Niklas Mattsson, M.D., Ph.D., Clifford R. Jack Jr., M.D., Charles DeCarli, M.D., Ronald Petersen, M.D., Ph.D., Paul S. Aisen, M.D., Michael W. Weiner, M.D., R. Scott Mackin, Ph.D., for the Alzheimer's Disease Neuroimaging Initiative

Objective: *Investigate the association of chronic depressive symptomatology (chrDS) with cortical atrophy rates and conversion to Alzheimer dementia (AD) over 3 years in mild cognitive impairment (MCI).* **Methods:** *In a multicenter, clinic-based study, MCI elderly participants were selected from the Alzheimer's Disease Neuroimaging Initiative repository, based on availability of both serial structural magnetic resonance imaging and chrDS endorsed on three depression-related items from the Neuropsychiatric Inventory Questionnaire (chrDS N = 32 or no depressive symptoms N = 62) throughout follow-up. Clinical and laboratory investigations were performed every 6 months during the first 2 years and yearly thereafter (median follow-up: 3 years; interquartile range: 1.5—4.0 years). Cortical atrophy rates in 16 predefined frontotemporoparietal regions affected in major depression and AD and the rate of incident AD at follow-up.* **Results:** *ChrDS in a single domain amnestic MCI sample were associated with accelerated cortical atrophy in the frontal lobe and anterior cingulate but not with atrophy rates in temporomedial or other AD-affected regions. During follow-up, 38 participants (42.7%) developed AD. Participants with chrDS had 60% shorter conversion time to AD than those without depressive symptoms. This association remained significant in survival models adjusted for temporomedial atrophy rates and showed the same trend in models adjusted for frontal cortical atrophy rate, which all increased the risk of AD.* **Conclusion:** *Our results suggest that chrDS associated with progressive atrophy of frontal regions may represent an*





“Age-related demyelination is associated with memory impairment (especially in prodromal dementia states) and sx of depression in an anatomically specific manner”

University of Crete

Myelin Content Changes in Probable Alzheimer’s Disease and Mild Cognitive Impairment: Associations With Age and Severity of Neuropsychiatric Impairment

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Background: Existing indices of white matter integrity such as fractional anisotropy and magnetization transfer ratio may not provide optimal specificity to myelin content. In contrast, myelin water fraction (MWF) derived from the multi-echo T_2 relaxation time technique may serve as a more direct measure of myelin content.
Purpose/Hypothesis: The goal of the present study was to identify markers of regional demyelination in patients with probable Alzheimer’s disease (AD) and mild cognitive impairment (MCI) in relation to age and severity of neuropsychiatric impairment.
Population: The sample included patients diagnosed with probable AD ($n = 25$) or MCI ($n = 43$), and cognitively intact elderly controls ($n = 33$).
Field Strength/Sequence Assessment: Long T_2, short T_2, and MWF values were measured with a 1.5T scanner in periventricular and deep normal-appearing white matter (NAWM), serving as indices of intra/extracellular water content and myelin content. A comprehensive neuropsychological and neuropsychiatric assessment was administered to all participants.
Statistical Tests, Results: AD patients displayed higher age-adjusted long and short T_2 values and reduced MWF values in left temporal/parietal and bilateral periventricular NAWM than controls and MCI patients ($P < 0.004$; one-way analysis of covariance [ANCOVA] tests). Short T_2/MWF values in temporal, frontal, and periventricular NAWM of controls and/or MCI patients were significantly associated with episodic and semantic memory performance and depressive symptomatology ($P < 0.004$; partial correlation indices). The impact of age on memory performance was significantly ($P < 0.01$; mediated linear regression analyses) mediated by age-related changes in short T_2 and MWF values in these regions.
Data Conclusion: Age-related demyelination is associated with memory impairment (especially in prodromal dementia states) and symptoms of depression in an anatomically specific manner.
Level of Evidence: 1
Technical Efficacy: Stage 3

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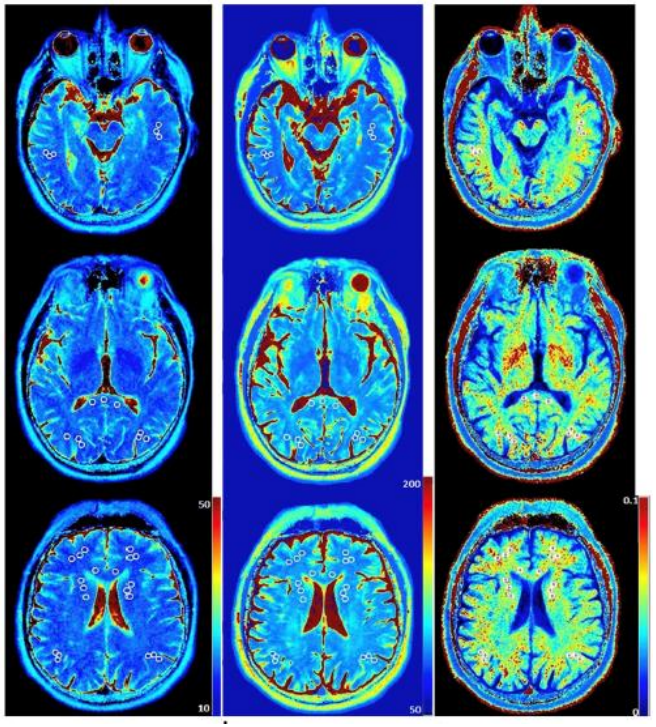
- NC, MCI, AD; n=101; age >60 yrs
- CESD



“anxiety is not a prodromal noncognitive feature of AD but may accelerate decline toward AD through direct or indirect effects on EC”

ADNI

Anxiety Symptoms in Amnestic Mild Cognitive Impairment Are Associated with Medial Temporal Atrophy and Predict Conversion to Alzheimer Disease

*Linda Mah, M.D., M.H.Sc., F.R.C.P.C., Malcolm A. Binns, Ph.D., David C. Steffens, M.D., M.H.Sc., for the Alzheimer's Disease Neuroimaging Initiative**

Objective: *To test the hypothesis that anxiety in amnestic mild cognitive impairment (aMCI) increases rates of conversion to Alzheimer disease (AD) and to identify potential neural mechanisms underlying such an association.* **Methods:** *Participants (N = 376) with aMCI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were studied over a median period of 36 months. A Cox proportional-hazards model was used to assess the association between anxiety severity ratings on the Neuropsychiatric Inventory Questionnaire and AD risk. Other variables were depression, memory loss, and MRI-derived AD-related regions of interest (ROIs), including hippocampal, amygdalar, entorhinal cortical (EC) volumes, and EC thickness. In addition, a linear regression model was used to determine the effect of anxiety in aMCI on rates of atrophy within ROIs.* **Results:** *Anxiety severity increased rate of aMCI conversion to AD, after controlling for depression and cognitive decline. The association between anxiety and AD remained significant even with inclusion of ROI baseline values or atrophy rates as explanatory variables. Further, anxiety status predicted greater rates of decrease in EC volume. An association between anxiety and EC thickness missed significance.* **Conclusion:** *Anxiety symptoms in aMCI predict conversion to AD, over and beyond the effects of depression, memory loss, or atrophy within AD neuroimaging biomarkers. These findings, together with the greater EC atrophy rate predicted by anxiety, are compatible with the hypothesis that anxiety is not a prodromal noncognitive feature of AD but may accelerate decline toward AD through direct or indirect effects on EC.* (Am J Geriatr Psychiatry 2015; 23:466–476)

Key Words: Alzheimer disease, anxiety, depression, mild cognitive impairment, neuropsychiatric symptoms, amygdala, entorhinal cortex, MRI biomarker

- aMCI +/- anxiety; n=376
- Median 3 year f/u
- Anxiety severity increased conversion rate to AD
- Anxiety predicted greater rate of EC volume decline

TABLE 4. Effect of Change in ROI (ΔROI)[a] at Each Visit from Baseline on Hazard of AD and on Hazard Ratio (HR_p) for Anxiety

ROI	HR_p	Wald z Value	p	HR_p for Anxiety with Inclusion of ΔROI in the Model[b]
ΔICV,[c] mL	1.01	+1.57	0.12	1.27
ΔHC, mL	0.33	−1.09	0.28	1.27
ΔAmygdala, mL	0.27	−0.98	0.33	1.28
ΔEC volume, mL	0.08	−2.23	0.03	1.29
ΔEC thickness (mm)	0.12	−3.28	0.001	1.29
ΔEC surface area (cm^2)	0.74	−0.78	0.43	1.27

[a] See text for calculation of ΔROI.
[b] Cox proportional-hazards models (130 events, N = 332) additionally included sex, education, baseline memory, and baseline executive function (see text).
[c] Included in all models.

Domain 3: impulse control (i.e. agitation and reward salience)

"These findings support an emerging conceptual framework in which NPS constitute an early clinical manifestation of AD pathophysiology"

ADNI

Neuropsychiatric symptoms predict hypometabolism in preclinical Alzheimer disease

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ABSTRACT

Objective: To identify regional brain metabolic dysfunctions associated with neuropsyc symptoms (NPS) in preclinical Alzheimer disease (AD).

Methods: We stratified 115 cognitively normal individuals into preclinical AD (both amylo tau pathologies present), asymptomatic at risk for AD (either amyloid or tau pathology pr or healthy controls (no amyloid or tau pathology present) using [18F]florbetapir PET an phosphorylated tau biomarkers. Regression and voxel-based regression models evaluat relationships between baseline NPS measured by the Neuropsychiatric Inventory (NPI) and line and 2-year change in metabolism measured by [18F]fluorodeoxyglucose (FDG) PET.

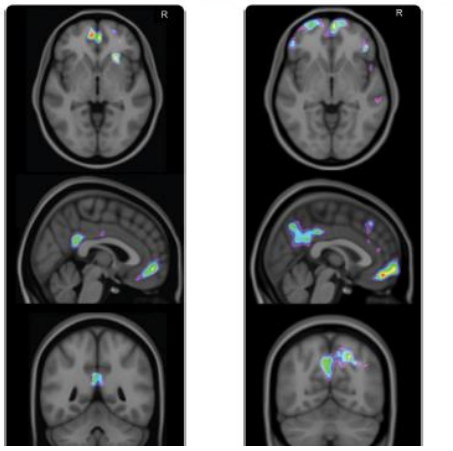
Results: Individuals with preclinical AD with higher NPI scores had higher [18F]FDG uptake posterior cingulate cortex (PCC), ventromedial prefrontal cortex, and right anterior insula at line. High NPI scores predicted subsequent hypometabolism in the PCC over 2 years individuals with preclinical AD. Sleep/nighttime behavior disorders and irritability and lability the components of the NPI that drove this metabolic dysfunction.

Conclusions: The magnitude of NPS in preclinical cases, driven by sleep behavior and irrit domains, is linked to transitory metabolic dysfunctions within limbic networks vulnerable AD process and predicts subsequent PCC hypometabolism. These findings support an em conceptual framework in which NPS constitute an early clinical manifestation pathophysiology. *Neurology*® 2017;88:1814–1821

GLOSSARY

AD = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **ADNI-mem** = Alzheimer's Disease imaging Initiative memory composite score; **AI** = anterior insula; **AR-AD** = asymptomatic at risk for Alzheimer disease Clinical Dementia Rating; **[18F]FDG** = [18F]fluorodeoxyglucose; **MCI** = mild cognitive impairment; **NPI** = Neurops Inventory; **NPS** = neuropsychiatric symptoms; **PCC** = posterior cingulate cortex; **p-tau** = phosphorylated tau; **SN** = network; **SUVR** = standardized uptake value ratio; **vmPFC** = ventromedial prefrontal cortex.

- **Preclinical AD, asymptomatic at risk, NC (biomarker confirmed); n=115; 2 year f/u with pre/ post FDG PET**
- **Irritability predicted subsequent hypometabolism in the PCC over 2 years only in preclinical AD.**



Domain 4: Social appropriateness (i.e. social cognition)

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REVIEW

Social inappropriateness in neurodegenerative disorders

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ABSTRACT

Background: New onset of mood and behavioral changes in middle-aged patients are frequently the first manifestations of an unrecognized neurocognitive disorder. Impairment of social cognition, the cognitive ability to process social information coming from others, such as emotions, to attribute mental states to others, and to respond appropriately to them, is often at the origin of behavioral manifestations in neurodegenerative disorders.

Methods: This paper reviews the current literature on social cognition impairment in neurocognitive disorders, particularly in prodromal stages of behavioral-variant frontotemporal dementia (bvFTD), Alzheimer's disease (AD), idiopathic Parkinson's disease (IPD), and Lewy body dementia (LBD). The concepts of social cognition will be reviewed, including its impairment and neural basis, its clinical assessment, and the different therapeutic interventions available clinically.

Results: Socially inappropriate behaviors, such as loss of empathy, inappropriateness of affect, and disinhibition are frequently reported in prodromal bvFTD and in prodromal AD. Lack of self-control, reduced perception of social cues, such as recognition of facial emotions and sarcastic speech, and impaired Theory of Mind all contribute to the neuropsychiatric symptoms and are secondary to neurodegeneration in specific brain regions. In contrasts to bvFTD and AD, deficits in social cognition in IPD occur later in the course of the disease and are often multifactorial in origin.

Conclusions: Through various manifestations, social inappropriateness is frequently the first clinical sign of a neurodegenerative process, especially in AD and bvFTD, years before noticeable impairment on classical neuropsychological assessment and brain atrophy on imaging.

Key words: cognitive disorders, mild behavior impairment (MBI), Alzheimer's disease (AD), mild cognitive impairment (MCI), frontotemporal dementia (FTD)

Domain 5: Thoughts / perception (i.e. psychosis)

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Review article

Neuroimaging of delusions in Alzheimer's disease

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ABSTRACT

MEDLINE, Embase and PsycINFO were searched using the keywords "imaging", "neuroimaging", "CT", "MRI", "PET", "SPECT", "Alzheimer's", "dementia", "delusions" and "psychosis" to find studies specifically assessing or reporting on neuroimaging of delusions in Alzheimer's Dementia (AD), separate from hallucinations or psychosis in general in AD. Twenty-five studies were found meeting criteria and are included in this review which reports on structural, regional perfusion, metabolic and receptor binding imaging modalities assessing delusions as a whole, as well as persecutory and misidentification delusional subtypes. The majority of studies implicate right-sided pathology, primarily frontal lobe. Left-frontal predominance and release, secondary to right-sided pathology, may create a hyperinferential state resulting in the formation of delusions. This perturbation and imbalance of normal networks is associated with delusional phenomenology. Temporal lobe structures are also important in misidentification syndromes, which have a different natural history than paranoid delusions. Consistent with the neuropathological and genetic literature, neuroimaging has shown that paranoid versus misidentification delusions are associated with different phenomenology and different neural substrates. Delusional subtype is an important factor in understanding the neurobiological underpinnings of delusions in dementia. We also discuss methodological issues related to neuroimaging of delusions in AD.

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Neurobiology of Delusions in Alzheimer's Disease

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Abstract Alzheimer's disease (AD) is associated with cognitive and functional impairment as well as neuropsychiatric sequelae, including psychotic symptoms such as delusions and hallucinations. Strong evidence supports the need to study delusions separate from hallucinations. Integrating the epidemiology, clinical correlates, and neuropathological and genetic literature for delusions in AD allows us to speculate on etiology and mechanisms. Plaque and tangle deposition in individuals with susceptible alleles of serotonergic, muscarinic, nicotinic, or *Apoε4* genes appears to result in disruption of cortical circuitry, culminating in delusions. While delusions in AD correspond to a phenotype distinct from AD without delusions, subtypes of delusions may also define further distinct clinical entities. Persecutory delusions may occur earlier in the illness and have a more significant genetic component than misidentification delusions, which are associated with increased cognitive impairment and advanced dementia. Clearly distinguishing between these two syndromes is essential to making progress in the area of delusions in AD.

Keywords Alzheimer's · Dementia · Psychosis · Delusions · Persecutory delusions · Misidentifications · BPSD · Neuropsychiatry · Neuropsychiatric symptoms · NPS · Neuropathology · Genetics · Cognition · Paranoia · Suspiciousness · Confabulation

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Introduction

Despite being considered a disorder of cognition, Alzheimer's disease (AD) is associated with many neuropsychiatric symptoms (NPS) of clinical significance. NPS, also called behavioral and psychological symptoms of dementia (BPSD), are present in up to 97% of people diagnosed with dementia, resulting in suffering, caregiver distress, and extensive resource utilization [1]. These noncognitive manifestations of dementia are the primary reason for transfer of patients

Data is sparse as new onset psychotic patients go to psychiatry

ADNI

Gray matter atrophy in patients with mild cognitive impairment/Alzheimer's disease over the course of developing delusions

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[‡]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). 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. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.
This work was previously presented as a poster presentation at the 2014 American Association for Geriatric Psychiatry's Annual Meeting, in Orlando, Florida, USA. The abstract from the poster presentation is archived in Am J Geriatr Psychiatry, 22:3, Supplement 1, pp 132-133.

Objective: We conducted a neuroimaging analysis to understand the neuroanatomical correlates of gray matter loss in a group of mild cognitive impairment and early Alzheimer's disease patients who developed delusions.

Methods: With data collected as part of the Alzheimer's Disease Neuroimaging Initiative, we conducted voxel-based morphometry to determine areas of gray matter change in the same Alzheimer's Disease Neuroimaging Initiative participants, before and after they developed delusions.

Results: We identified 14 voxel clusters with significant gray matter decrease in patient scans post-delusional onset, correcting for multiple comparisons (false discovery rate, $p < 0.05$). Major areas of difference included the right and left insulae, left precuneus, the right and left cerebellar culmen, the left superior temporal gyrus, the right posterior cingulate, the right thalamus, and the left parahippocampal gyrus.

Conclusions: Although contrary to our initial predictions of enhanced right frontal atrophy, our preliminary work identifies several neuroanatomical areas, including the cerebellum and left posterior hemisphere, which may be involved in delusional development in these patients.

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Grey Matter Atrophy in Mild Cognitive Impairment / Early Alzheimer Disease Associated with Delusions: A Voxel-Based Morphometry Study

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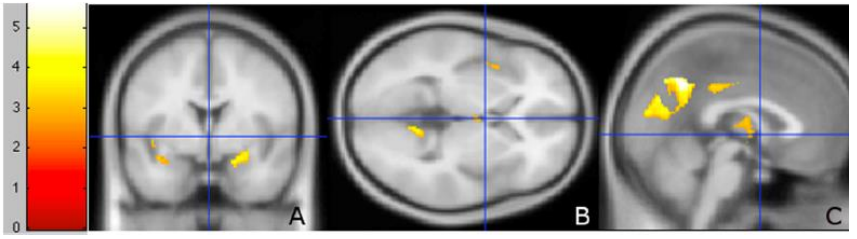
Tom A. Schweizer

Abstract: Objectives: Grey matter atrophy in the right hemisphere has been shown to be more severe in dementia patients with delusions, suggesting a neuroanatomical localization that may be pertinent to impending neurodegeneration. Delusional symptoms may arise when atrophy in these areas reduces the regulatory functions of the right hemisphere, in tandem with asymmetric neuropathology in the left hemisphere. We hypothesized that delusional patients with either amnestic mild cognitive impairment (MCI) or early Alzheimer Disease (AD) would experience more pronounced grey matter atrophy in the right frontal lobe compared with matched patients without delusions. Methods: We used neuroimaging and clinical data obtained from the Alzheimer's Disease Neuroimaging Initiative. A comparison group of twenty-nine non-delusional MCI/early AD participants were compared with twenty-nine delusional participants using voxel-based morphometry, matched at baseline by age, sex, education, and Mini-Mental State Exam score. All included participants were diagnosed with amnestic MCI at study baseline. Results: Fifteen voxel clusters of decreased grey matter in participants with delusions were detected. Prominent grey matter decrease was observed in the right precentral gyrus, right inferior frontal gyrus, right insula, and left middle occipital gyrus, areas that may be involved in control of thought and emotions. Conclusion: Greater right fronto-temporal grey matter atrophy was observed in MCI or early AD participants with delusions compared to matched patients without delusions. Consistent with our predictions, asymmetric grey matter atrophy in the right hemisphere may contribute to development of delusions through loss of executive inhibition.

Keywords: Alzheimer disease, delusions, executive control, inhibition, mild cognitive impairment, voxel-based morphometry.



Summary of what the evidence is suggesting so far

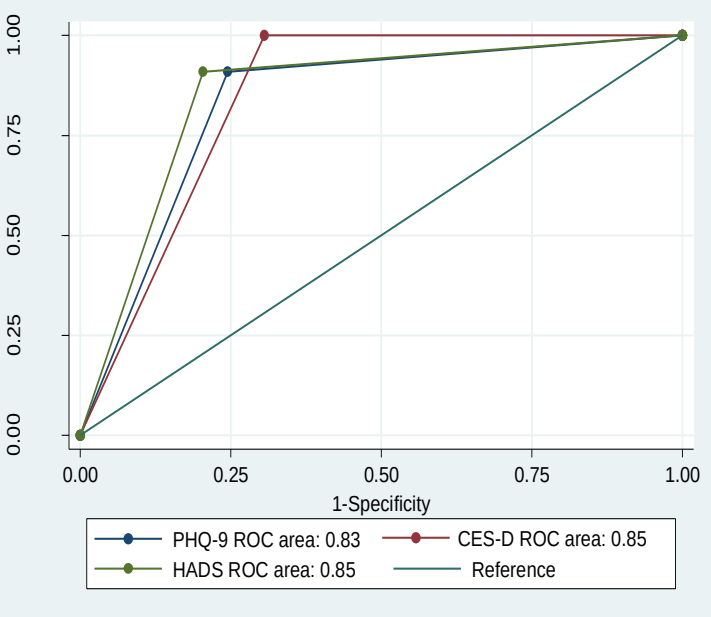
Risk factor

- Affective/ Emotional Regulation
  - Risk factor **and** prodrome
  - Time frame/ natural history is important

Prodrome

- Motivation/ Drive
- Agitation/ Impulse Control/ Reward
- Social Cognition
- Psychosis

Caveat: Measurement.
NEEDS Study - depression in cognitive clinic



ROC curve for the PHQ-9, CES-D, and HADS at traditional cut-points

- Cognitive Neurology Clinic; n=202
- SCID prevalence 12.4%
- PHQ-9 performed better with lowered cutpoint
- CES-D performed best
- **But is the SCID an actual gold standard?**
- **Are cross sectional assessments adequate?**

Measurement: MBI checklist

Mild Behavioral Impairment Checklist (MBI-C)

Date: _____

Rated by: ☐ Clinician ☐ Informant ☐ Subject

Location: ☐ Clinic ☐ Research

Label

Circle "Yes" **only** if the behavior has been present for at least **6 months** (continuously, or on and off) and is a **change** from her/his longstanding pattern of behavior. Otherwise, circle "No".

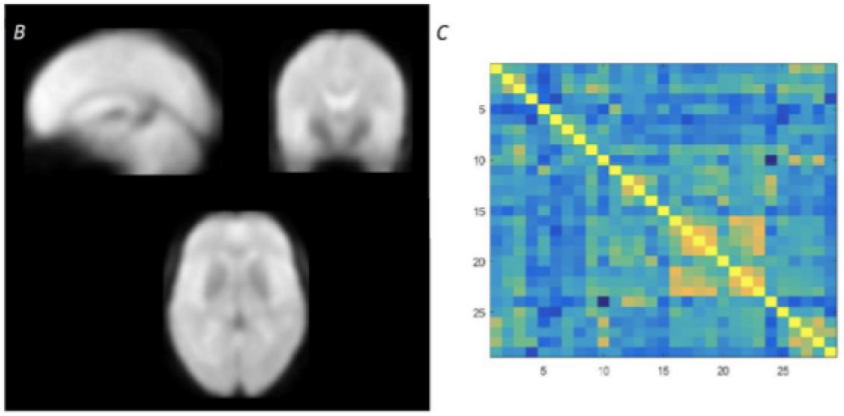
Please rate severity: **1 = Mild** (noticeable, but not a significant change); **2 = Moderate** (significant, but not a dramatic change); **3 = Severe** (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe.

	YES	NO	SEVERITY
This domain describes interest, motivation, and drive			
Has the person lost interest in friends, family, or home activities?	Yes	No	1 2 3
Does the person lack curiosity in topics that would usually have attracted her/his interest?	Yes	No	1 2 3
Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?	Yes	No	1 2 3
Has the person lost motivation to act on her/his obligations or interests?	Yes	No	1 2 3
Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?	Yes	No	1 2 3
Does she/he no longer care about anything?	Yes	No	1 2 3
This domain describes mood or anxiety symptoms			
Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?	Yes	No	1 2 3
Has the person become less able to experience pleasure?	Yes	No	1 2 3
Has the person become discouraged about their future or feel that she/he is a failure?	Yes	No	1 2 3
Does the person view herself/himself as a burden to family?	Yes	No	1 2 3
Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?	Yes	No	1 2 3
Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?	Yes	No	1 2 3
This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward			
Has the person become agitated, aggressive, irritable, or temperamental?	Yes	No	1 2 3
Has she/he become unreasonably or uncharacteristically argumentative?	Yes	No	1 2 3
Has the person become more impulsive, seeming to act without considering things?	Yes	No	1 2 3
Does the person display sexually disinhibited or intrusive behaviour, such as touching (themselves/others), hugging, groping, etc., in a manner that is out of character or may cause offence?	Yes	No	1 2 3
Has the person become more easily frustrated or impatient? Does she/he have troubles coping with delays, or waiting for events or for their turn?	Yes	No	1 2 3
Does the person display a new recklessness or lack of judgement when driving (e.g. speeding, erratic swerving, abrupt lane changes, etc.)?	Yes	No	1 2 3
Has the person become more stubborn or rigid, i.e., uncharacteristically insistent on having their way, or unwilling/unable to see/hear other views?	Yes	No	1 2 3
Is there a change in eating behaviors (e.g., overeating, cramming the mouth, insistent on eating only specific foods, or eating the food in exactly the same order)?	Yes	No	1 2 3
Does the person no longer find food tasteful or enjoyable? Are they eating less?	Yes	No	1 2 3
Does the person hoard objects when she/he did not do so before?	Yes	No	1 2 3
Has the person developed simple repetitive behaviors or compulsions?	Yes	No	1 2 3
Has the person recently developed trouble regulating smoking, alcohol, drug intake or gambling, or started shoplifting?	Yes	No	1 2 3
This domain describes following societal norms and having social graces, tact, and empathy			
Has the person become less concerned about how her/his words or actions affect others? Has she/he become insensitive to others' feelings?	Yes	No	1 2 3
Has the person started talking openly about very personal or private matters not usually discussed in public?	Yes	No	1 2 3
Does the person say rude or crude things or make lewd sexual remarks that she/he would not have said before?	Yes	No	1 2 3
Does the person seem to lack the social judgement she/he previously had about what to say or how to behave in public or private?	Yes	No	1 2 3
Does the person now talk to strangers as if familiar, or intrude on their activities?	Yes	No	1 2 3
This domain describes strongly held beliefs and sensory experiences			
Has the person developed beliefs that they are in danger, or that others are planning to harm them or steal their belongings?	Yes	No	1 2 3
Has the person developed suspiciousness about the intentions or motives of other people?	Yes	No	1 2 3
Does she/he have unrealistic beliefs about her/his power, wealth or skills?	Yes	No	1 2 3
Does the person describe hearing voices or does she/he talk to imaginary people or "spirits"?	Yes	No	1 2 3
Does the person report or complain about, or act as if seeing things (e.g. people, animals or insects) that are not there, i.e., that are imaginary to others?	Yes	No	1 2 3

www.MBItest.org

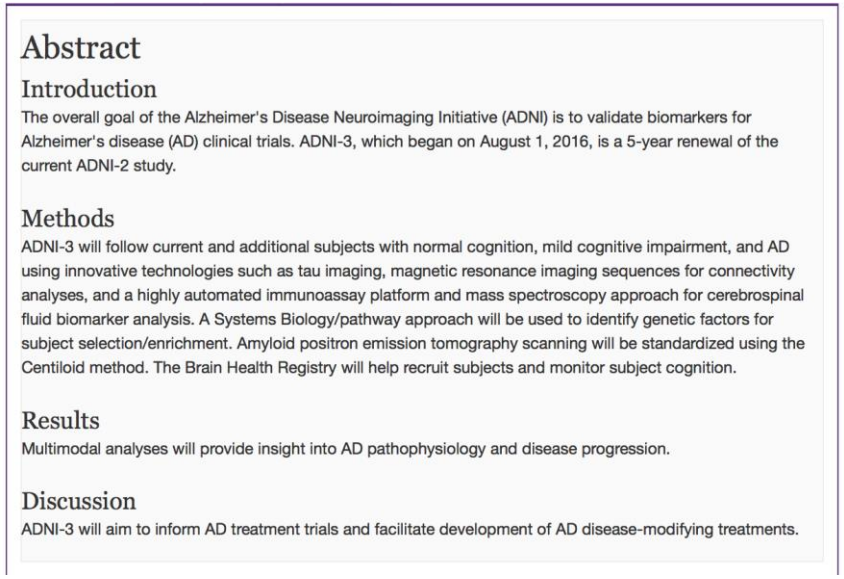
PARADIGM Pre-dementia at-risk states: a longitudinal study of cognition and neuroimaging biomarkers in Mild Behavioural Impairment

- MBI +/- using MBI-C and ISTAART-AA MBI criteria
- MCI +/-
- 2 year longitudinal observational study
- Cognitive outcomes
- Structural and functional MRI
- Genetics/ CSF



Future directions:

ADNI



Abstract

Introduction

The overall goal of the Alzheimer's Disease Neuroimaging Initiative (ADNI) is to validate biomarkers for Alzheimer's disease (AD) clinical trials. ADNI-3, which began on August 1, 2016, is a 5-year renewal of the current ADNI-2 study.

Methods

ADNI-3 will follow current and additional subjects with normal cognition, mild cognitive impairment, and AD using innovative technologies such as tau imaging, magnetic resonance imaging sequences for connectivity analyses, and a highly automated immunoassay platform and mass spectroscopy approach for cerebrospinal fluid biomarker analysis. A Systems Biology/pathway approach will be used to identify genetic factors for subject selection/enrichment. Amyloid positron emission tomography scanning will be standardized using the Centiloid method. The Brain Health Registry will help recruit subjects and monitor subject cognition.

Results

Multimodal analyses will provide insight into AD pathophysiology and disease progression.

Discussion

ADNI-3 will aim to inform AD treatment trials and facilitate development of AD disease-modifying treatments.

COMPASS-ND Study

- Canada's ADNI
- NC; MCI; dementia
- MBI-C included as NPS instrument (in addition to NPI-Q)
- 5 year observational study
- Imaging, biomarkers