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Mood changes in cognitively normal older adults are linked to Alzheimer's disease biomarker levels

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Abstract

Objectives—To evaluate whether cerebrospinal fluid (CSF) and PET Pittsburgh Compound B (PiB) biomarkers of underlying Alzheimer disease (AD) pathology (β-amyloid$_{42}$ [Aβ_{42}], tau, phosphorylated tau$_{181}$ [ptau$_{181}$], tau/Aβ_{42}, ptau$_{181}$/Aβ_{42} and mean cortical binding potential [MCBP] for PET-PiB) predict changes in mood in cognitively normal older adults.

Setting—Knight Alzheimer's Disease Research Center (ADRC) at Washington University (WU).

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Author Contributions:

GMB: Study concept and design, data analysis and interpretation, drafting and critical revision of manuscript.
NG: Data interpretation, drafting and critical revision of manuscript.
DH: Data interpretation, critical revision of manuscript.
EKV: Data interpretation, critical revision of manuscript.
DMH: Data acquisition and interpretation, critical revision of manuscript.
TLSB: Data acquisition, and interpretation, critical revision of manuscript.
AMF: Data acquisition, and interpretation, critical revision of manuscript.
JCM: Data acquisition, and interpretation, critical revision of manuscript.
CMR: Study concept and design, data analysis and interpretation, drafting and critical revision of manuscript.

Participants—Participants, 65 year of age or older, were enrolled from longitudinal studies at the WU Knight ADRC.

Measurements—CSF, PET-PiB biomarkers, Clinical Dementia Rating (CDR), Mini-Mental State Examination (MMSE), Profile of Mood States-Short Form (POMS-SF), the Geriatric Depression Scale (GDS) and Neuropsychiatric Inventory Questionnaire (NPI-Q).

Results—Data from 118 participants at baseline and 66 participants at one-year follow-up were analyzed. CSF and PET biomarkers were not associated cross-sectionally with any mood disturbances at baseline (p >0.05). Changes in mood as indicated by the total mood disturbance score on the POMS-SF, selected POMS-SF subscales, GDS, and NPI-Q scores from baseline to one-year follow-up were associated with ($p < .05$) CSF and PET-PiB biomarkers. There was no statistically significant decline in cognitive functioning

Conclusion—Generally, higher values of CSF and PET-PiB biomarkers are associated with more changes in mood in cognitively normal older adults. Further work is needed to understand the temporal development of mood changes over several years during the phase of preclinical AD. Evaluating mood as a noncognitive outcome may provide further insight into the development of preclinical AD in cognitively normal older adults.

Keywords

Alzheimer disease; Older adults; Mood; Depression; Biomarkers

Introduction

Mood disturbances, alternatively termed behavioral disturbances or neuropsychiatric symptoms, are common concomitant conditions of symptomatic Alzheimer's disease (AD).[1] Depressive symptoms in particular, have been found to predict the development of symptomatic AD for persons who are cognitively normal and persons with mild cognitive impairment (MCI).[2, 3] Other mood disturbances such as apathy and anxiety are associated with decreased cognitive functioning, increased functional impairment, poorer prognosis, and faster rate of decline leading to institutionalization.[4] Research efforts have recently shifted from symptomatic AD to preclinical AD, which is defined as cognitive normality with biomarker evidence (cerebrospinal fluid (CSF), imaging) that the pathological process of AD has begun.[5] Experts recommend examining neurobehavioral outcomes (e.g. mood, social interaction) to link the pathological process to clinical symptoms, delineate a time course and understand the impact of neurobehavioral outcomes on functional decline prior to overt symptom onset.[5]

Studies using biomarkers suggest that the natural history of changes in mood and depressive symptoms in particular, begin during the preclinical period.[6–8] However, the current literature on mood in preclinical AD is skewed to the evaluation of singular, negative dimensions of mood (e.g. depression, anxiety). There is a critical need to more comprehensively assess mood disturbances in preclinical AD with global measures of mood to further understand its role and progression in AD. We evaluated the relationship between changes in mood states (positive and negative), changes in cognitive functioning and AD

biomarker values (CSF, Positron Emission Technology (PET) amyloid imaging) in a sample of cognitively normal older adults.

Methods

Standard protocol approvals, registrations, and patient consents

All study protocols, consent documents and questionnaires were approved by Washington University Human Research Protection Office. Written informed consent was obtained from all participants and their informants. Study data were collected and managed using REDCap electronic data capture tools[12] hosted at Washington University.

Participants

We used available data from participants enrolled in a longitudinal study assessing preclinical AD and driving performance (R01 AG043434) at the Knight Alzheimer's Disease Research Center (ADRC) at Washington University School of Medicine in St. Louis. The study population was a subset of those enrolled in the affiliated R01 AG043434 study. Participants were part of a rolling enrollment process that occurred from years one to three.

Inclusion criteria

Participants were required to be English-speaking adults, age 65 years or older, willing to take part in PET Pittsburgh Compound B (PiB) amyloid imaging and lumbar puncture for collection of CSF, and be cognitively normal (i.e. no dementia symptoms) as defined by a score of 0 on the Clinical Dementia Rating (CDR).[9, 10] Experienced clinicians integrate information from a neurological exam and interviews with the participant and an informant (a family member or close acquaintance) to derive a CDR. The participant serves as their own control where intraindividual changes over time indicate whether symptomatic AD encompassing both MCI due to AD, and AD dementia, is present and if so, its severity.[11, 12] A standard scoring algorithm is used to generate the overall CDR (0 cognitively normal, 0.5 very mild impairment, 1 mild, 2 moderate, and 3 severe dementia). More information for CDR scoring may be found at (http://www.biostat.wustl.edu/~adrc/cdrpgm/). The CDR-Sum of Boxes is the sum of the scores from the six CDR domains, ranges from 0–18, and provides a more detailed, continuous measure used to interpret progression of dementia.[13] At baseline, participants take part in clinical and psychometric assessments including the Mini-Mental State Examination.[14] Biomarkers (PET-PiB amyloid imaging and CSF) are also obtained at baseline. At yearly follow-up, participants repeat the clinical and psychometric assessments.

Pittsburgh Compound B uptake measurement

Participants take part in PET-PiB imaging to determine presence and burden of brain amyloid.[15] A binding potential (BP) value reflecting the region of interest (ROI) binding value proportional to the number of binding sites for each ROI is calculated. Dynamic PET imaging was conducted with a Siemens Biograph PET-CT scanner in three-dimensional mode after intravenous administration of approximately 12mCi of PiB. The images were reconstructed on a 128×128×63 matrix (2.12×2.12×2.43 mm) using filtered back-projection.

Participants also underwent a structural magnetic resonance imaging (MRI) exam at 3 Tesla, which was segmented using FreeSurfer 5.1 (Martinos Center, Boston, MA). Visual inspection of the automated segmentation results was performed for quality assurance purposes in all datasets. Correction was done when necessary according to the FreeSurfer manual (http://surfer.nmr.mgh.harvard.edu/fswiki/). Regions were combined as described by Su et al.[16] The mean cortical binding potential (MCBP) is obtained by taking the mean of the binding potentials from brain regions (prefrontal cortex, gyrus rectus, lateral temporal cortex, and precuneus) known to have high uptake of PiB among participants with AD, as previously described.[17, 18]

CSF measurement

Following an overnight fast, experienced neurologists use a 22-gauge Sprotte spinal needle to collect 20–30 mL of CSF via standard lumbar puncture (LP) into a polypropylene tube at 8:00 AM. After brief centrifugation, CSF samples were aliquoted and stored at −84°C.[19] All biomarker assays include a common reference standard, within-plate sample randomization and strict standardized protocol adherence. β-amyloid$_{42}$ (Aβ_{42}), total tau, and phosphorylated tau$_{181}$ (ptau$_{181}$) levels were measured using enzyme linked immunosorbant assay (ELISA) (INNOTEST; Fujiebio [formerly Innogenetics], Ghent, Belgium). Lower levels of Aβ_{42} are indicative of amyloid plagues while higher levels of tau and ptau$_{181}$ indicate neuronal degeneration; ratios of tau/Aβ_{42} and ptau$_{181}$/Aβ_{42} predict cognitive decline.[20]

Outcome measures

Three outcome measures were evaluated. The Profile of Mood States -Short Form (POMS-SF) is a 30-item questionnaire that assesses different mood states (both positive and negative) and total mood disturbance (TMD).[21] There are six subscales with individual t-scores (30–80) to detect impairment in anxiety, depression, anger, vigor, fatigue and confusion. Higher scores on the vigor subscale indicate more positive mood, and higher scores on the remaining subscales indicate more negative mood. The TMD score is calculated by summing scores on the anxiety, depression, anger, fatigue, and confusion subscales, and then subtracting the vigor subscale score. The TMD scale ranges from −20 to 100 with higher scores indicating greater mood disturbance. The Geriatric Depression Scale short form (GDS) is a 15-item screen for depression in older adults.[22] Respondents answer “yes” or “no” for each item, with higher scores (range: 0–15) indicating greater depression. The Neuropsychiatric Inventory Questionnaire (NPI-Q) consists of 12 items, each assessing 12 behavioral domains.[23] The informant indicates whether each symptom is present (“yes” or “no”). For each “yes” response, the informant is then asked to rate the severity of the symptom (mild, moderate, or severe). Higher scores (range: 0–36) on the NPI-Q indicate greater neuropsychiatric symptoms.

Statistical analyses

For cross-sectional analyses, general linear models were used to determine whether MCBP values (treated as dichotomous using a median split) were associated with TMD scores at baseline (dependent variable treated as continuous), after adjustment for age, gender, and education. This analysis was repeated five times, once for each of the CSF variables at

baseline ($A\beta_{42}$, tau, $ptau_{181}$, tau/$A\beta_{42}$ and $ptau_{181}/A\beta_{42}$). Lower values of $A\beta_{42}$, and higher values of all other biomarkers, are associated with preclinical AD. When appropriate, given the distribution of scores, we then repeated the analyses using the biomarker variables listed above for the POMS-SF subscales, and the GDS and NPI-Q measures. As with the analyses of MCBP, all other analyses treated the biomarker variables as dichotomous, where the variables reflected lower and higher biomarker values constructed using median splits. For the longitudinal analyses, a change score from baseline to one-year follow-up was calculated, separately for TMD scores, POMS-SF subscales, GDS and NPI-Q measures. This score indicates the change from baseline to follow-up and can be either positive or negative. All analyses were repeated using the respective change scores in place of baseline scores. Finally, we examined changes in memory using the CDR, MMSE, Wechsler Memory Scales[24] task of Associate Learning and Delayed Logical Memory, and the free-recall portion of the Free and Cued Selective Reminding Test.[25]

Results

Data were available for 118 participants at baseline and 66 participants at a follow-up that took place approximately one-year later. Due to rolling enrollment into the study, only 66 participants had follow-up data available for longitudinal analyses. Compared to normative scores, baseline scores on all subscales of the POMS-SF[27], GDS[28] and NPI-Q[29] indicate little to no mood disturbances as self-reported by participants or informants (table 1). At baseline, all participants were cognitively normal as indicated by the CDR (all CDR 0) and MMSE scores (mean=29.34, SD=0.95). Additionally, 7.6% of participants had an active mood disorder while 15.3% reported use of an antidepressant. Because there was little variation (scores indicated little to no symptoms) on the GDS, NPI-Q, and depression, anger and fatigue subscales of the POMS-SF at baseline, analyses were not conducted for these measures. The values of each biomarker variable were not associated with the TMD or remaining subscales on the POMS-SF in the cross-sectional analyses (table 2). Additionally, we assessed the correlations between CSF $A\beta_{42}$ and MCBP for PET PiB at baseline since both biomarkers examine amyloid burden, but in different parts of the central nervous system. When treated as continuous variables, there was no correlation ($r = -0.07$, p = 0.45), however, there was moderate and statistically significant association when both biomarkers were treated dichotomously ($\chi^2 = 18.32$, p = < 0.001).

In the longitudinal analyses, cognitive decline was not statistically significant as indicated by the CDR-Sum of Boxes ($t = 1.09$, $p = .279$) or MMSE ($t = -1.78$, $p = .859$) from baseline to follow-up. One participant at follow-up had a CDR 0.5 but an MMSE score of 30. All other participants remained at CDR 0 at follow-up. We further examined change on neuropsychological tasks of memory, which may be more sensitive to early-related AD changes and cognitive decline. There was no statistically significant change on the Wechsler Memory Scales task of Associate Learning ($t = -1.81$, $p = .857$) and Delayed Logical Memory ($t = -0.05$, $p = .962$) or the free-recall score of the Free and Cued Selective Reminding Test ($t = -0.52$, $p = .606$). Additionally, there was no significant correlation between the change scores from the three memory tasks, CDR sum of boxes and MMSE and the TMD, NPIQ or GDS (table 3).

In the longitudinal analyses for mood changes, each of the change score outcomes was normally distributed and showed enough variation for statistical analysis. Participants with higher values of CSF tau/$A\beta_{42}$ had greater increases in total mood disturbance scores across the one-year follow-up period compared to participants with lower values (table 4). Higher values of CSF tau/$A\beta_{42}$ also predicted greater increases longitudinally in the negative emotions of anxiety, depression and confusion as measured by the POMS-SF subscales. MCBP for PET-PiB had a significant association with change in GDS scores, such that participants with greater increases in depressive affect across the follow-up period were in the MCBP group with higher values. Finally, CSF tau, $ptau_{181}$, tau/$A\beta_{42}$ and MCBP biomarkers also predicted change scores on the NPI-Q. Higher values of each of these biomarkers were associated with greater increases in neuropsychiatric symptoms across time.

Discussion

Our findings suggest that CSF and PET-PiB biomarkers are able to predict increased mood disturbances longitudinally over one-year in a sample of cognitively normal older adults (CDR 0), but are unrelated to mood at baseline when assessed cross-sectionally. The lack of a relationship between measures of mood and the biomarkers at baseline together with the finding that participants with more abnormal biomarker values at baseline had higher change scores on mood measures (i.e., increasing mood disturbance) across a short follow-up period (one-year) suggests that the presence of abnormal AD biomarker levels are associated with a measurable impact on mood as the disease processes, although these changes are subtle and may not be recognized without formal testing. These findings extend our previous work[26] on the development of depressive and neuropsychiatric symptoms in participants with CDR > 0.

Traditional measures of mood in the AD literature have been useful in establishing the prevalence of mood disturbances and elucidating its relationship to cognitive decline. However, these scales are limited since assessment of mood is based upon a single mood state (e.g. GDS) or behavioral symptoms (NPI-Q). Mood states are commonly misinterpreted as being polar opposites (e.g. happy vs. sad, fatigue vs. energetic). However, this unilateral relationship is limited because mood states are multidimensional where an individual can experience multiple mood states at the same time. The POMS-SF has been used in samples of older adults to assess mood states; it provides a more comprehensive perspective of mood since it assesses negative mood states like anxiety and depression but also a positive mood state like vigor. All subscales are incorporated to give a total mood disturbance score. Changes in the POMS-SF TMD and anxiety, depression and confusion subscales were all associated with AD biomarker values. Vigor was not statistically different between the biomarker groups, suggesting that negative moods drive the shift in total disturbance score.

A recent study using a PET imaging FDDNP tracer found the POMS-SF vigor subscale to be associated with lower binding of amyloid and tau in participants with mild cognitive impairment, but not controls.[27] The vigor subscale was inversely correlated with FDDNP-PET binding in the posterior cingulate region. Since FDDNP labels amyloid plaques and neurofibrillary tangles, changes in vigor may be driven by tau, which is best known to

correlate with measures of cognitive decline.[28] Although that cross-sectional study had a modest sample size and only examined the POMS-SF vigor subscale, it suggests that positive moods like vigor may be related to biomarker values in early AD. Speculatively, changes in vigor may occur later in preclinical AD, whereas negative mood changes may occur earlier.

Previous work has examined the relationship between amyloid and either depressive symptomology or depressive disorder. One study found strong associations between CSF $A\beta_{42,}$ $A\beta_{40}$ and their ratios in cognitively normal populations with depressive symptoms and major depressive disorder.[29] Another study showed a relationship between abnormal CSF $A\beta_{42}$ and anxiety and agitation, but not depression and apathy in persons with MCI.[30] Others have found no relationship between depression scores and CSF $A\beta_{42}$, tau and $ptau_{181}$ for persons with AD and cognitively normal persons.[31] Studies using PET-PiB imaging have found increased PiB retention in persons with depression with and without cognitive impairment suggesting a shared biological mechanism between AD and depression.[32] See table 5 for other studies examining amyloid-depression relationships, including those that have examined plasma measures of amyloid. Many of these studies are cross-sectional analyses and may not have collected longitudinal data to examine change over time.

In our study, the relationship between the POMS and the biomarkers seemed to be stronger with tau compared to amyloid pathology. Changes in amyloid tend to occur first and before changes in tau within AD. However, neuropsychological measures of cognition have always been more closely correlated with tau pathology (burden and distribution) compared to amyloid pathology.[28, 33] The POMS assessment of mood seems to follow this paradigm. Additionally, higher values of CSF tau/$A\beta_{42}$ and MCBP for PET-PiB had more associations with changes in mood compared to other biomarkers. This relationship suggests that the ratio may be more sensitive to mood changes compared to either CSF $A\beta_{42}$ or tau alone.[19] Strikingly, studies looking at decline in cognition over a relatively short time period (a few years) among persons cognitively normal at baseline have indicated that the ratio of CSF tau/$A\beta_{42}$ is a better predictor of decline than either $A\beta_{42}$ or tau by themselves.[8, 34] Thus, like cognition, variables reflecting combinations of biomarkers may be better predictors of decline in noncognitive outcomes such as mood, compared to individual biomarkers.

GDS scores were associated with MCBP for PET-PiB but not CSF $A\beta_{42}$. Although both measures reflect amyloid levels, imaging of amyloid using PET-PiB assesses fibrillar amyloid in the form of plaques, whereas CSF reflects amyloid in a soluble state. The CSF and imaging amyloid measures are related to each other, but there is not a one-to-one correspondence.[35]

There are several limitations of the study. We found no cognitive decline over one-year on the MMSE and the CDR Sum of Boxes, which may have been due at least in part, to ceiling effects for the MMSE and floor effects for the CDR Sum of Boxes. However, this remained true even when we specifically examined measures of memory without floor and ceiling effects: delayed episodic memory, delayed free recall, and paired associates.

Due to rolling enrollment and testing in this study, data for change score analyses were only available for 66 participants at year one follow up. When comparing groups, statistical power is greatest when the groups have equal numbers of members. To maximize the statistical power of our analyses, we used a median split to divide the groups into those with "higher" and "lower" values of each biomarker. Thus, the groups were not representative of preclinical AD vs. no preclinical AD. In most studies, the cutoffs used for defining preclinical AD result in approximately 30% of cognitively normal participants being labeled as having preclinical AD. Indeed, in previous studies with larger samples, we used cutoffs of 459 pg/mL for $A\beta_{42}$, 339 pg/mL for tau, and 67 pg/mL for p-tau_{181} for CSF biomarkers[36] and a cutoff of .18 for MCBP for PiB[37] to define preclinical AD. As expected, assigning participants to groups based on the higher 50% and lower 50% of the specific biomarker distribution resulted in lower cutoffs. Specifically, cutoffs used here were 459 pg/mL for $A\beta_{42}$, 303 pg/mL for tau, and 54 pg/mL for p-tau_{181} for CSF biomarkers and .066 for MCBP for PiB.

Using an alpha of .05, as we did in this study, one would expect one out of 20 statistical tests to be significant by chance. Since we conducted N=54 tests in our change analyses (table 4), we would expect 54/20 = 2.7 of those tests might be significant by chance alone. However, we found N=11 (i.e., more than 4 times the expected number if due to chance) significant test results, and all change scores were in the expected direction (i.e., the direction of declining performance). The ultimate test of which of the results in this study, if any, are due to chance will be determined by future attempts at replication. However, in the meantime, we have indicated in Table 4 which 6 of the 11 tests are significant using the Benjamini-Hochberg procedure with a false discovery rate of 20%.[38, 39]

In this initial study that comprehensively assessed mood (positive and negative) in preclinical AD, we found that CSF and PET-PiB biomarkers predicted changes in mood over a one-year follow-up in a sample of adults ≥ 65 years and cognitively normal at baseline. Greater mood disturbances, including negative symptoms such as anxiety, depression and confusion were associated with biomarker values, despite no cognitive decline. These findings support the use of biomarkers in identifying changes in noncognitive outcomes such as mood in preclinical AD. Further work is needed to delineate the natural course of mood disturbances in preclinical AD and the resulting impact on functional activity.

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Dr. Fagan reports being on the scientific advisory boards of IBL International and Roche and is a consultant for AbbVie and Novartis.

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Table 1

Demographics.

	Total Sample (n = 118)*	
Age, y	72.5±4.7	
Education, y	16.1±2.6	
Women, N	61 (51.7%)	
Race, Caucasian, N	107 (90.7%)	
Diagnosis of active mood disorder, N	9 (7.6%)	
Diagnosis of remote mood disorder, N	5 (4.2%)	
Antidepressant use	18 (15.3%)	
Biomarkers		
CSF $A\beta_{42}$, pg/mL (N=118)	939.9±1376.7	
CSF tau, pg/mL (N=118)	349.6±199.5	
CSF $ptau_{181}$, pg/mL (N=117)	65.8±40.0	
CSF tau/$A\beta_{42}$ (N=118)	0.52±0.47	
CSF $ptau_{181}/A\beta_{42}$ (N=117)	0.09±0.07	
MCBP for PET PiB (N=116)	0.17±0.23	
	Baseline	Follow up
POMS-SF Total Mood Disturbance	−5.6±7.5	−5.3±7.1
Tension-Anxiety	33.0±4.0	32.7±3.6
Depression	32.3±1.3	32.7±1.8
Anger	36.3±1.1	36.4±1.4
Vigor	60.0±9.8	58.9±8.6
Fatigue	32.2±3.9	32.1±3.4
Confusion	37.6±3.0	37.7±2.8
GDS (N=91|50)	0.99±1.5	0.92±1.1
NPI-Q (N=93|50)	0.74±1.8	1.00±1.7

Abbreviations: POMS-SF = Profile of Mood States – Short Form; $A\beta_{42}$ = β-amyloid42; $ptau_{181}$ = phosphorylated tau_{181}; MCBP = Mean Cortical Binding Potential; PiB = Pittsburgh compound B; GDS = Geriatric Depression Scale; NPI-Q = Neuropsychiatric Inventory Questionnaire.

*Mean±SD or percentage

Table 2

Cross-sectional baseline differences in mood after adjusting for age, gender and education.

	CSF $A\beta_{42}$			CSF tau			CSF $ptau_{181}$		
	Lower*	**Higher***	***p***	**Lower**	**Higher**	***p***	**Lower**	**Higher**	***p***
POMS TMD	−4.9 (−6.9 to −2.9)	−6.4 (−8.3 to −4.4)	0.29	−6.1 (−8.0 to −4.1)	−5.2 (−7.2 to −3.1)	0.51	−5.9 (−7.9 to −4.0)	−5.3 (−7.3 to −3.3)	0.66
Anxiety	33.1 (32.1 to 34.2)	32.9 (31.9 to 34.0)	0.80	32.0 (31.8 to 33.9)	33.2 (32.2 to 34.3)	0.64	32.6 (31.6 to 33.7)	33.5 (32.4 to 34.5)	0.27
Vigor	59.7 (57.1 to 62.3)	60.5 (57.9 to 63.0)	0.66	60.3 (57.7 to 62.8)	59.9 (57.3 to 62.5)	0.83	59.9 (57.3 to 62.4)	60.3 (57.7 to 63.0)	0.80
Confusion	38.2 (37.4 to 40.0)	37.1 (36.3 to 37.9)	0.06	37.8 (37.0 to 38.6)	37.5 (36.7 to 38.6)	0.62	37.8 (37.0 to 38.6)	37.5 (36.7 to 38.3)	0.57

	CSF tau/$A\beta_{42}$			CSF ptau/$A\beta_{42}$			MCBP for PET PIB		
	Lower	**Higher**	***p***	**Lower**	**Higher**	***p***	**Lower**	**Higher**	***p***
POMS TMD	−5.8 (−7.8 to −3.8)	−5.5 (−7.0 to −3.5)	0.86	−5.9 (−7.9 to −4.0)	−5.2 (−7.3 to −3.2)	0.63	−6.1 (−8.1 to −4.1)	−5.0 (−7.1 to −3.0)	0.45
Anxiety	33.1 (32.1 to 34.2)	32.8 (31.8 to 33.9)	0.69	32.8 (31.7 to 33.8)	33.4 (32.3 to 34.4)	0.43	32.7 (31.7 to 33.8)	33.5 (32.4 to 34.5)	0.33
Vigor	59.9 (57.3 to 62.5)	60.4 (57.8 to 63.1)	0.78	60.0 (57.4 to 62.5)	60.3 (57.6 to 63.9)	0.87	60.1 (57.6 to 62.7)	60.2 (57.5 to 62.9)	0.95
Confusion	37.3 (36.5 to 38.1)	37.9 (37.1 to 38.8)	0.28	37.4 (36.6 to 38.1)	38.0 (37.2 to 38.8)	0.28	37.4 (36.6 to 38.2)	38.1 (37.3 to 38.9)	0.23

Abbreviations: POMS-SF = Profile of Mood States – Short Form; TMD = Total Mood Disturbance; $A\beta_{42}$ = β-amyloid$_{42}$; $ptau_{181}$ = phosphorylated tau_{181}; MCBP = Mean Cortical Binding Potential; PiB = Pittsburgh compound B.

*Mean (95% Confidence Interval)

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Table 3

Correlation of change scores between measures of mood and neuropsychological memory tasks.

		POMS TMD	GDS	NPI-Q	WMS-AL	WMS-DLM	FCSRT	CDR-SOB	MMSE
POMS TMD	*r*	1							
GDS	*r*	−0.006	1						
NPI-Q	*r*	−0.038	0.345 *	1					
WMS-AL	*r*	−0.121	−0.139	−0.021	1				
WMS-DLM	*r*	−0.106	0.11	0.089	0.097	1			
FCSRT	*r*	0.039	0.024	0.004	0.117	0.192	1		
CDR-SOB	*r*	0.017	0.000	0.000	0.074	0.077	0.003	1	
MMSE	*r*	0.083	−0.164	0.027	−0.035	−0.065	−0.432 *	0.001	1

Abbreviations: POMS-SF = Profile of Mood States – Short Form; TMD = Total Mood Disturbance; GDS = Geriatric Depression Scale; NPI-Q = Neuropsychiatric Inventory Questionnaire; WMS-AL = Wechsler Memory Scales- Associate Learning; WMS-DLM = Wechsler Memory Scales-Delayed Logical Memory; FCSRT = Free and Cued Selective Reminding Test;

* = $p < .05$

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Table 4

Differences in mood change scores after adjusting for age, gender and education.

	CSF $A\beta_{42}$			CSF tau		
	Lower*	**Higher***	***p***	**Lower**	**Higher**	***p***
POMS TMD	1.26 (−0.85 to 3.38)	−1.09 (−3.17 to 0.99)	0.12	−0.89 (−3.04 to 1.25)	1.08 (−1.07 to 3.23)	0.20
Anxiety	0.83 (−0.14 to 1.81)	0.56 (−0.40 to 1.52)	0.69	0.12 (−0.83 to 1.10)	1.27 (0.31 to 2.23)	0.10
Depression	−0.51 (−1.44 to 0.13)	−0.17 (−0.80 to 0.46)	0.46	−0.76 (−1.39 to −0.13)	0.07 (−0.55 to 0.70)	0.07
Anger	−0.00 (−0.50 to 0.50)	−0.36 (−0.85 to 0.13)	0.32	−0.32 (−0.82 to 0.19)	−0.06 (−.56 to 0.45)	0.47
Vigor	−1.09 (−4.14 to 1.95)	1.79 (−1.21 to 4.79)	0.18	0.43 (−2.69 to 3.55)	0.29 (−2.87 to 3.41)	0.95
Fatigue	0.67 (−0.48 to 1.82)	−0.83 (−1.96 to 0.30)	0.67	−0.63 (−1.80 to 0.54)	0.51 (−0.66 to 1.68)	0.17
Confusion	0.44 (−0.55 to 1.43)	0.26 (−0.72 to 1.23)	0.79	0.07 (−0.93 to 1.06)	0.65 (−0.34 to 1.65)	0.41
GDS	−0.06 (−0.50 to 0.39)	−0.44 (−0.87 to −0.01)	0.22	−0.27 (−0.76 to 0.21)	−0.25 (−0.68 to 0.17)	0.95
NPI−Q	−0.27 (−0.89 to 0.36)	−0.68 (−1.30 to −0.07)	0.34	−1.33 (−1.95 to −0.71)	0.14 (−0.40 to 0.68)	**0.001**†

	CSF $ptau_{181}$			CSF tau/$A\beta_{42}$		
	Lower	**Higher**	***p***	**Lower**	**Higher**	***p***
POMS TMD	−0.74 (−2.90 to 1.41)	0.81 (−1.35 to 2.96)	0.32	−1.97 (−4.02 to 0.07)	2.21 (0.17 to 4.24)	**0.005**†
Anxiety	0.20 (−0.77 to 1.17)	1.21 (0.24 to 2.18)	0.15	−0.15 (−1.09 to 0.79)	1.50 (0.56 to 2.43)	**0.02**†
Depression	−0.76 (−1.39 to −0.13)	0.07 (−0.55 to 0.70)	0.07	−0.81 (−1.44 to −0.19)	0.13 (−0.50 to 0.75)	**0.04**
Anger	−0.32 (−0.83 to 0.18)	−0.05 (−0.56 to 0.45)	0.45	−0.44 (−0.95 to 0.06)	0.07 (−0.43 to 0.57)	0.15
Vigor	0.43 (−2.69 to 3.54)	0.42 (−2.70 to 3.53)	1.00	1.67 (−1.42 to 4.76)	−1.00 (−4.08 to 2.08)	0.23
Fatigue	−0.40 (−1.59 to 0.79)	0.21 (−0.97 to 1.40)	0.47	−0.82 (−1.97 to 0.33)	0.75 (−0.40 to 1.90)	0.59
Confusion	0.13 (−0.86 to 1.13)	0.52 (−0.48 to 1.52)	0.59	−0.33 (−1.28 to 0.63)	1.12 (0.16 to 2.07)	**0.04**
GDS	−0.32 (−0.77 to 0.13)	−0.21 (−0.66 to 0.25)	0.73	−0.40 (−0.90 to 0.10)	−0.16 (−0.57 to 0.25)	0.47
NPI-Q	−0.93 (−1.53 to −0.34)	−0.05 (−0.67 to 0.57)	**0.05**	−1.30 (−1.95 to −0.64)	0.05 (−0.49 to 0.59	**0.003**†

	CSF ptau/$A\beta_{42}$			MCBP for PET PIB		
	Lower	**Higher**	***p***	**Lower**	**Higher**	***p***
POMS TMD	−1.30 (−3.42 to 0.82)	1.36 (−0.75 to 3.48)	0.08	−1.20 (−3.47 to 1.06)	0.84 (−1.44 to 3.13)	0.21
Anxiety	−0.22 (−1.15 to 0.71)	1.63 (0.70 to 2.55)	**0.007**†	0.23 (−0.81 to 1.27)	1.23 (0.18 to 2.28)	0.19

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	CSF ptau/Aβ$_{42}$			MCBP for PET PIB		
	Lower	**Higher**	***p***	**Lower**	**Higher**	***p***
Depression	−0.70 (−1.34 to −0.07)	0.02 (−0.62 to 0.65)	0.12	−0.45 (−1.11 to 0.22)	−0.16 (−0.83 to 0.51)	0.54
Anger	−0.31 (−0.82 to 0.20)	−0.06 (−0.57 to 0.44)	0.50	−0.56 (−1.08 to −0.04)	0.23 (−0.29 to 0.75)	**0.04**
Vigor	0.87 (−2.25 to 3.98)	− 0.02 (−3.13 to 3.09)	0.69	1.13 (−2.08 to 4.33)	0.66 (−2.57 to 3.89)	0.84
Fatigue	−0.55 (−1.73 to 0.63)	0.37 (−0.82 to 1.55)	0.28	−0.72 (−1.96 to 0.52)	0.26 (−0.99 to 1.51)	0.27
Confusion	−0.01 (−0.10 to 0.99)	0.66 (−0.33 to 1.65)	0.35	0.12 (−0.92 to 1.16)	0.73 (−0.32 to 1.79)	0.41
GDS	−0.40 (−0.88 to 0.07)	−0.16 (−0.59 to 0.28)	0.44	−0.73 (−1.20 to −0.26)	0.08 (−0.33 to 0.49)	**0.01**[†]
NPI−Q	−0.94 (−1.60 to −0.29)	−0.18 (−0.78 to 0.42)	0.09	−1.07 (−1.74 to −0.39)	−0.13 (−0.70 to 0.45)	**0.04**

Abbreviations: POMS-SF = Profile of Mood States – Short Form; TMD = Total Mood Disturbance; Aβ$_{42}$ = β-amyloid$_{42}$; ptau$_{181}$ = phosphorylated tau$_{181}$; MCBP = Mean Cortical Binding Potential; PiB = Pittsburgh compound B; GDS = Geriatric Depression Scale; NPI-Q = Neuropsychiatric Inventory Questionnaire.

[*] Mean (95% Confidence Interval)

[†] Also significant using the Benjamini-Hochberg procedure

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Table 5

Representative studies examining relationships between amyloid and depression using CSF, imaging and plasma

Biomarker type	Study	Sample(s)	Results	Biomarker relationship to depression found?
CSF	Pomara, N et al. 2012 American Journal of Psychiatry. 169(5), 523–530.	28 with MDD 19 no depression	Elderly individuals with depression had lower levels of CSF $A\beta_{42}$ compared to those without depression	Yes
	Diniz, BS et al. 2014. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 69(6), 845–851.	25 antidepressant-free patients with late life depression. 25 HC	No significant differences in AD related biomarkers between groups	No
Amyloid Imaging	Tateno, A et al. 2015. International journal of geriatric psychiatry, 30(7), 720–728.	33 MCI patients with a history of GD 22 HC	In depression and MCI groups, amyloid uptake was significantly associated with depression onset.	Yes
	Wu, KY et al. 2014. European journal of nuclear medicine and molecular imaging, 41(4), 714–722.	25 depressed patients 11 non-depressed patients	Depressed patients had greater amyloid uptake in parietal, precuneus, frontal, temporal, and occipital regions.	Yes
	Yasuno, F et al. (2016). International journal of geriatric psychiatry.	29 cognitively normal older participants	More depressive symptoms were associated with greater amyloid uptake	Yes
	Kumar A et al. (2011). Archives of general psychiatry, 68(11), 1143–1150.	20 patients with MDD 19 healthy controls	[^{18}F]FDDNP uptake was higher in posterior cingulate and lateral temporal regions in MDD group compared to healthy controls	Yes
Plasma	Pomara N et al. (2006). Neurochem Res, 31(3), 341–349.	47 with late life MDD 35 controls	Higher $A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$ were found in depressed individuals compared to healthy controls	Yes
	Kita Y et al. (2009). Psychogeriatrics, 9(4), 180–185.	30 patients with MDD 30 controls	$A\beta_{40}$ and $A\beta_{42}$ alone did not differ by groups. The $A\beta_{40}/A\beta_{42}$ ratio was higher in MDD group compared to controls	Mixed
	Blasko, I et al. (2010). Am. J. Geriat. Psychiatry, 18(11), 973–982.	331 HC	$A\beta_{42}$predicted future first depressive episode	Yes

Abbreviations: CSF = Cerebrospinal Fluid; MDD = Major Depressive Disorder; GD = Geriatric Depression; $A\beta_{42}$ = β-amyloid$_{42}$; $A\beta_{40}$ = β-amyloid$_{40}$; MCI = Mild Cognitive Impairment; HC = Healthy Controls;