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Psychological Well-Being and Regional Brain Amyloid and Tau in Mild Cognitive Impairment

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Abstract

Objectives—To determine whether psychological well-being in people with mild cognitive impairment (MCI), a risk state for Alzheimer disease (AD), is associated with in vivo measures of brain pathology.

Methods—Cross-sectional clinical assessments and positron emission tomography (PET) scans after intravenous injections of 2-(1-{6-[(2-[F18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene) malononitrile (FDDNP), a molecule that binds to plaques and tangles, were performed on middle-aged and older adults at a university research institute. Volunteers were aged 40–85 years with MCI (N = 35) or normal cognition (N = 29) without depression or anxiety. Statistical analyses included general linear models, using regional FDDNP-PET binding values as dependent variables and the Vigor-Activity subscale of the Profile of Mood States (POMS) as the independent variable, covarying for age. The POMS is a self-rated inventory of 65 adjectives that describe positive and negative feelings.

Results—Scores on the POMS Vigor-Activity subscale were inversely associated with degree of FDDNP binding in the posterior cingulate cortex (r = −0.35, p = 0.04) in the MCI group but not in the control group.

Conclusion—Psychological well-being, as indicated by self-reports of greater vigor and activity, is associated with lower FDDNP-PET binding in the posterior cingulate cortex, a region involved in emotional regulation, in individuals with MCI but not in those with normal cognition. These findings are consistent with previous work indicating that deposition of brain amyloid plaques and tau tangles may result in noncognitive and cognitive symptoms in persons at risk for AD.

Keywords

Aging; FDDNP; positron emission tomography; POMS; well-being

Introduction

Although psychopathology associated with cognitive disorders has been studied extensively, self-perception of health and well-being is receiving greater attention, particularly in individuals who are at risk for Alzheimer disease (AD) and other dementias. Depression and anxiety are known risk factors for AD and are associated with neuro-psychological deficits, higher rates of progression to dementia, and neuropathologic changes found in AD.[1–4] However, clinically significant depressive or anxiety symptoms are not present in most individuals who are at risk for AD[5] and are common exclusion criteria in studies on cognitive impairment. Psychological well-being, which can be reported by nearly all individuals, may be a more applicable measure in such nondemented populations.

Perhaps the most well-studied cohort at risk for developing AD is composed of individuals with mild cognitive impairment (MCI), which is characterized by cognitive decline intermediate between normal aging and dementia.[6,7] Approximately 14%–18% of individuals aged 70 years and older have MCI, 10%–15% of whom will progress to dementia each year.[8]

In subjects with MCI, our group found self-reported depression, anxiety, and memory complaints are associated with a biomarker for MCI and AD,[9,10] specifically the small molecule 2-(1-{6-[(2-[F18]fluo-roethyl)(methyl)amino]-2-naphthyl}ethylidene)malo-nonitrile (FDDNP), an in vivo probe that binds to cerebral aggregates of amyloid-beta plaques and tau neurofibrillary tangles,[11] the neuropathologic hallmarks of AD. FDDNP visualized via positron emission tomography (PET) differentiates individuals with MCI, AD, and normal cognition, wherein global FDDNP-PET binding is highest in patients with AD, intermediate in those with MCI, and lowest in normal comparison subjects.[11]

Previous studies have demonstrated the predictive value of positive self-perception of health and emotions in stroke, dementia, and delirium.[12–14] Such measures may provide insight and predictive value in patients with MCI who are at risk for dementia. Furthermore, one's sense of well-being may reflect and even influence neurobiologic changes in memory disorders. In this cross-sectional study, we hypothesized that psychological well-being in MCI patients is associated with decreased FDDNP-PET binding, a marker for amyloid and tau proteins and an early detection tool for MCI and AD.

Methods

Participants

Volunteers were part of a larger longitudinal study of AD and age-associated cognitive decline[11] and were recruited through advertisements, media coverage, and referrals by physicians and families. Members of the research staff screened potential volunteers via telephone interviews. All participants provided written informed consent, in accordance with procedures of the Human Research Protection Program of the University of California, Los Angeles, and received clinical assessments, magnetic resonance imaging (MRI), and FDDNP-PET scans. Individuals with a diagnosis of dementia, major depressive disorder, or an anxiety disorder or ra-diographic evidence of stroke were excluded. Of the 1,617 individuals screened for the larger AD and memory study, 289 (17.9%) were excluded because of depression or anxiety. Cumulative radiation dosim-etry for all scans was below the mandated maximum annual dose and in compliance with state and federal regulations.

Clinical Assessment

All volunteers received a psychiatric and medical history and mental status exam, comprehensive neuropsychological evaluation by a licensed neuro-psychologist, and several

self-rated and clinician-rated measurements of psychological symptoms. We used modified diagnostic criteria for MCI,[6,7] which included (1) patient awareness of memory decline, preferably confirmed by another person; (2) measurable, greater-than-normal cognitive impairment detected with standard assessment tests; (3) preservation of daily activities functioning; and (4) an absence of dementia.

Our clinical assessment included the Profile of Mood States (POMS), developed by McNair et al.[15] in 1971, that consists of 65 self-rated adjectives on a five-point scale from 0 (not at all) to 4 (extremely). Multiple-factor analytic studies have confirmed six factors or subscales: Tension-Anxiety, Depression, Anger-Hostility, Fatigue, Confusion, and Vigor-Activity. The Vigor-Activity subscale was used to assess an individual's psychological well-being and consists of eight items (Lively, Active, Energetic, Relaxed, Cheerful, Alert, Carefree, and Vigorous) with a possible total score of 0–32 points. Psychometric properties of the POMS include internal consistency of subscales, concurrent validity with scales and diagnostic instruments, discriminate validity, and test–retest reliability in younger and older adults.[15,16]

Imaging

The method of FDDNP-PET imaging is described in detail elsewhere.[11] In brief, FDDNP was prepared at very high specific activities (>37 GBq/mol).[11] All scans were performed with the ECAT HR or EXACT HR+ tomograph (Siemens-CTI, Knoxville, TN) with subjects supine and the imaging plane parallel to the orbitomeatal line. A bolus of FDDNP (320–550 MBq) was administered intravenously, and consecutive dynamic PET scans were performed for 2 hours. Scans were decay corrected and reconstructed using filtered back-projection (Hann filter, 5.5 mm full width at half maximum) with scatter and measured attenuation correction. The resulting images contained 47 contiguous slices with plane separation of 3.37 mm (ECAT HR) or 63 contiguous slices with plane separation of 2.42 mm (EXACT HR+).

To quantify FDDNP binding, we performed Logan graphic analysis with cerebellum as the reference region for time points between 30 and 125 minutes.[17] The slope of the linear portion of the Logan plot is the relative distribution volume, which is equal to the distribution volume of the tracer in a region of interest divided by that in the reference region. We generated relative distribution volume parametric images and analyzed them using regions of interest drawn manually on the coregistered MRI scans or on an image obtained in the first 5 minutes after injection (perfusion image) bilaterally on parietal, medial temporal (limbic regions, including hippocampus, parahippocampal areas, and entorhinal cortex), lateral temporal, posterior cingulate, parietal, and frontal regions, as previously described.[18] Each regional relative distribution volume or binding value was expressed as an average of left and right regions. Rules for region of interest drawing were based on the standard identification of gyral and sulcal landmarks with respect to the atlas of Talairach and Tournoux.[19] The atlas provided a visual guide and reference for identifying the important landmarks needed in delineating the regions of interest. Region of interest determinations were performed by individuals blind to the clinical assessments.

Anatomic brain MRI scans were obtained using a 3-Tesla magnet (General Electric-Signa, Milwaukee, WI) scanner. Fifty-four transverse planes were collected throughout the brain, superior to the cerebellum, using a double-echo, fast-spin echo series with a 24-cm field of view and 256 × 256 matrix with 3 mm/0 gap (TR = 6,000 [3 Tesla] and 2,000 [1.5 Tesla]; TE = 17/85 [3 Tesla] and 30/90 [1.5 Tesla]). MRI scans were coregistered to PET scans for the following brain regions: medial and lateral temporal, posterior cingulate, parietal, and frontal regions.

Data Analysis

Data were screened for outliers and normality assumptions. Because scores on the POMS Vigor-Activity subscale did not follow a normal distribution pattern, log-transformed scores were used in the analyses. A mixed model was estimated to determine whether psychological well-being was related to cerebral amyloid plaque and tangle binding for each diagnostic group. Regional FDDNP-PET binding values were used as dependent variables, with the Vigor-Activity subscale as the independent (between-subject) variable and region as the within-subject factor. A Vigor-Activity subscale by region interaction term was also included in the model to determine whether region-specific associations were present, and post-hoc analyses were conducted if this interaction term was significant. Age was used as a covariate, because it was previously found to be associated with FDDNP-PET binding in non-demented older adults.[20] Although the primary hypothesis was to test the relationship between the Vigor-Activity subscale and regional brain FDDNP-PET binding values in MCI subjects, we also examined this relationship in the cognitively normal individuals using a similar general linear model. A significance level of 0.05 was used for all inferences.

Results

Demographic and clinical characteristics of both diagnostic groups are shown in Table 1. The MCI and control groups did not differ in any of the variables except the Mini Mental State Examination score, the means differing only by 1.3 points. Because this study excluded volunteers with clinically significant psychiatric conditions, subjects did not display high levels of anxiety or depression.

The mean scores for the POMS Vigor-Activity subscale and the regional FDDNP-PET binding levels for each diagnostic group are shown in Table 2. Vigor-Activity scores were similar between the MCI and control groups. The regional FDDNP-PET binding levels for MCI subjects were significantly higher than in the control group, consistent with our previous results,[10] with the exception of the posterior cingulate region. The Vigor-Activity subscale was significantly associated with FDDNP-PET binding ($F_{(1,32)} = 5.52$, $p = 0.025$) in the MCI group but not in the control group. A significant Vigor-Activity subscale by brain region interaction term ($F_{(4, 132)} = 2.49$, $p = 0.05$) indicated region-specific correlations in subjects with MCI. Post-hoc analyses revealed that decreased FDDNP-PET binding in the posterior cingulate cortex (PCC) correlated with increased Vigor-Activity subscale scores ($r = -0.35$, $t_{(32)} = -2.15$, $p = 0.04$; Fig. 1). No other brain region was significantly correlated with the Vigor-Activity subscale. Similar analyses in the control group did not yield a significant Vigor-Activity by brain region interaction term or a significant main effect for the Vigor-Activity subscale.

Discussion

This study is the first to demonstrate a relationship between psychological well-being and in vivo measures of brain marker for amyloid and tau proteins. We found in middle-aged and older adults with MCI that psychological well-being, as measured by the POMS Vigor-Activity subscale, is correlated with less amyloid and tau protein in the PCC. This relationship was not present in the control group and may therefore reflect a phenomenon limited to MCI. Previous studies reported relationships between subjective measures of psychopathology and biomarkers for AD but focused primarily on depressive and anxiety symptoms,[9,21] which are common in MCI and AD but not present in most individuals studied, which may reflect subject sampling and exclusion of subjects with mood and behavioral symptoms. Because psychological well-being is a variable that can be measured in nearly all participants, regardless of presence of other mental symptoms, it may provide a

more useful domain to assess in volunteers without psychological symptoms than measures of negative symptoms, such as anxiety or depression.

Although advanced biomarkers for AD and other neurodegenerative disorders have made an indelible mark on this area of research, easily administered self-rated instruments also have proved to be important markers for disease. Subjective measures of health, memory, mood, and anxiety have been associated with conversion to dementia, biomarkers for AD, and more rapid cognitive decline in older adults.[3,9,10,14,22–26] Three large population studies of older adults showed poor self-rated health to be an independent risk factor for incident dementia.[14,25,26] Individuals with a greater sense of purpose in life were found to be at lower risk for developing MCI and AD,[27] whereas those with greater anxiety and vulnerability to stress were at higher risk for developing AD.[28] Subjective memory complaints in non-demented middle-aged and older adults have been associated with greater presence of tau and amyloid proteins,[10] global cerebral metabolic decline independent of baseline objective memory performance,[22] and the apolipoprotein E–4 allele,[24] a major genetic risk factor for AD. Although both anxiety and depressive symptoms have been associated with increased risk for AD,[3] studies suggest distinct neu-robiologic processes. First, whereas depression correlated with FDDNP-PET binding in the lateral temporal cortex in MCI, anxiety correlated with the amyloid and tau biomarker in the PCC.[9] Second, although a history of depression was associated with increased plaques and tangles in AD patients,[29] anxiety was not associated with neuropathologic lesions found in late-life dementia.[28] Our results suggest that psychological well-being may also be an important marker for disease in memory disorders.

To our knowledge, there is no widely accepted, valid measure of psychological well-being. A study defined psychological well-being as a composite of six scales, measuring positive affect, satisfaction with life, self-esteem, negative affect, depression, and anxiety, but acknowledged other instruments used to assess psychological well-being.[30] In this study, we used the POMS Vigor-Activity subscale as a measure of psychological well-being. Conceptually, one might argue that the Vigor-Activity subscale is merely a proxy for the converse of depression, anxiety, and other "negative" emotional states. The developers of the POMS may have conceptualized it as such, as the Vigor-Activity score weighted negatively against the total score on the POMS. However, data on normal elderly living in the community indicate no inverse relationship between scores on established measures of depression and anxiety and the POMS Vigor-Activity subscale.[16] Anxiety or depression may suggest poor psychological well-being, but poor psychological well-being does not necessarily indicate anxiety or depression. Perhaps the Vigor-Activity subscale measures the converse of apathy, which is clinically distinct from depression.[31] The Apathy Inventory, a validated scale to assess apathy in elderly individuals with and without dementia, consists of three dimensions—emotional blunting, loss of interest, and loss of initiative[32]—that could be argued to lie on the same continuum as items on the Vigor-Activity subscale. Regardless of any putative relationships with anxiety, depression, or apathy or how one defines psychological well-being, measures of "positive" self-perceptions may be a more useful construct than psychopathology in nondemented populations, given the lack of psychopathology in most of these individuals.

Our finding that the relationship between psychological well-being and FDDNP-PET binding was significant only in the PCC may be supported by other studies that have examined the psychological and biologic functions of the PCC. The PCC is believed to be part of a neural system that mediates self-reflection on one's abilities, traits, and thoughts.[33] Abnormalities in the PCC may produce apathy, which may be a converse of psychological well-being. Investigators have reported decreased perfusion, low gray matter density, and greater dopamine receptor density in the PCC among patients with neurode-generative

disorders and apathy.[34–36] Further studies suggest that apathy is not only clinically but neuro-biologically distinct from depression. Whereas apathy has been associated with greater levels of tau protein and not amyloid beta 1–42 ($A\beta42$) in the cerebrospinal fluid of patients with AD,[37] depression has been associated with elevated plasma $A\beta42$ but not tau levels.[38] Imaging studies have found that apathy and depression involve distinct neural circuits in AD and Parkinson's disease.[34,39] Our own previous studies implicated the PCC in different neuropsychiatric conditions. Kumar et al.[21] reported higher PCC and lateral temporal cortical FDDNP binding in cognitively intact patients with late-life major depressive disorder than in healthy control subjects. Lavretsky et al.[9] reported a correlation between trait anxiety scores and FDDNP binding values in the PCC in MCI subjects. Together with the current findings, these studies suggest that we may be seeing different phenotypic expressions of a common neurobiologic mechanism.

The prospect that psychological well-being may reflect a healthier neurobiology in individuals at risk for AD presents the possibility that interventions that enhance psychological well-being may actually protect against further neuropathologic changes and cognitive decline associated with AD. Our studies and others of middle-aged and older adults have shown that memory self-perception is associated with biomarkers of AD and rate of cognitive decline,[10,22–24] and actual memory performance can be significantly improved through a brief course of cognitive, psychological, and physical training.[40,41]

Several factors limit interpretation of these findings. The POMS, although validated in several study populations, has not been validated in individuals with MCI or as a distinct measure of psychological well-being. Although the POMS has demonstrated test–retest reliability,[15,16] it has not been validated as a measure of either a state or trait. The relatively small sample size, narrow range of cognitive impairment in this sample, and exclusion of individuals with depression or anxiety also limit the generalizability of the results. Although our specific interest was in studying psychological well-being and a biomarker for AD, due to the lack of existing data, we explored multiple brain regions, which may have led to a Type I error.

Despite such limitations, our findings support further study of psychological well-being as a readily measured marker for neurobiologic and clinical changes associated with AD, including amyloid and tau deposition, metabolism, cognitive performance, level of functioning, and treatment response. Longitudinal studies might also examine psychological well-being and its potential predictive value in the natural course of memory disorders.

Acknowledgments

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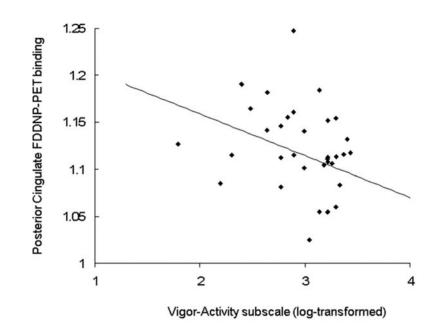
Figure 1. Plot of posterior cingulate (FDDNP-PET) binding with log-transformed POMS Vigor-Activity subscale scores

Table 1

Demographic and Clinical Characteristics

Variable	MCI (N = 35)	Control Subjects (N = 29)	$t(62)/\chi^2(1)$; p
Age, year	64.3 (11.5) (44–85)	63.2 (13.6) (40–85)	0.39; 0.70
Gender (women:men)	19:16	16:13	0.005; 0.94
Family history of AD (yes:no)	22:13	18:11	0.0042; 0.95
Education, year	16.77 (3.3) (12–24)	17.55 (2.7) (13–22)	−1.03; 0.31
MMSE score	28.2 (1.4) (25–30)	29.5 (0.7) (28–30)	−4.59; 0.0001
Hamilton Depression Scale	2.1 (2.8) (0–9)	2.1 (2.8) (0–13)	0.06; 0.95
Hamilton Anxiety Scale	4.6 (4.4) (0–17)	3.5 (4.1) (0–14)	1.06; 0.29

Notes: Values are means (SD) with ranges in parentheses below. MMSE: Mini Mental State Examination.

Table 2

POMS Vigor-Activity Subscale Scores and Regional FDDNP-PET Binding Values

Variable	MCI (N = 35)	Control Subjects (N = 29)	t(62)/χ^2(1); p
POMS Vigor-Activity subscale	20.0 (6.8) (5–32)	19.9 (5.5) (7–31)	−0.24; 0.81
FDDNP-PET cortical binding values			t(62)
Global	1.10 (0.03)	1.08 (0.02)	3.67; 0.0005
Medial temporal	1.14 (0.04)	1.11 (0.04)	3.00; 0.0039
Lateral temporal	1.11 (0.04)	1.08 (0.04)	3.28; 0.0017
Parietal	1.09 (0.04)	1.06 (0.03)	3.29; 0.0017
Posterior cingulate	1.12 (0.05)	1.10 (0.04)	1.43; 0.16
Frontal	1.06 (0.04)	1.04 (0.03)	2.25; 0.028

Notes: Values are means (SD) with ranges in parentheses below.