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Structural Correlates of Apathy in Alzheimer's Disease

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Key Words
Apathy · Alzheimer's disease · Neuropsychiatric Inventory · Cingulate gyrus · Atrophy

Abstract
Background: Apathy is the most common noncognitive symptom in Alzheimer's disease (AD). The structural correlates of apathy in AD have not yet been described. ***Methods:*** We analyzed magnetic resonance imaging data of 35 AD patients with and without apathy. ***Results:*** There was a significant linear association between apathy severity and cortical gray matter atrophy in the bilateral anterior cingulate [Brodmann area (BA) 24; $r = 0.39–0.42$, $p = 0.01$] and left medial frontal cortex (BA 8 and 9; $r = 0.4$, $p < 0.02$). Left mean cingulate cortical thinning predicted the presence/absence of apathy at the trend level of significance. ***Conclusion:*** Our study demonstrates a strong association between apathy and the integrity of medial frontal regions in AD.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder in the elderly. Cognitive and functional decline are frequently accompanied by neuropsychiatric symptoms in AD. These behaviors are distressing to the patients and their caregivers. Apathy is the most pervasive behavioral symptom in AD. It manifests as loss of interest, motivation, volition, enjoyment, spontaneity and emotional behavior [1]. Apathy is a prominent symptom in the intermediate cognitive state of mild cognitive impairment. The prevalence of apathy is positively correlated with disease duration and severity [2]. Although apathy and depression co-occur [3], the literature suggests that they can be reliably distinguished [4–6]. One study using factor analysis to group the Neuropsychiatric Inventory (NPI) symptoms into behavioral syndromes reported that while depression and anxiety loaded onto the 'mood' factor, hallucinations, delusions, irritability and agitation loaded onto the 'psychosis' factor and disinhibition and euphoria loaded onto the 'frontal' factor, apathy and aberrant motor behavior failed to group with any other NPI symptoms [7]. Apathy has been

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postulated to result from disruption of the connections between the anterior cingulate gyrus and other cortical and subcortical areas, and leads to greater functional dependence and caregiver burden [8, 9].

Only a few neuroimaging studies have investigated the structural/functional correlations of apathy in dementia. Using 18-fluorodeoxyglucose positron emission tomography or single photon emission computerized tomography, investigators have shown that hypometabolism of or reduced blood flow to the medial frontal, lateral frontal, orbitofrontal, anterior and posterior temporal areas associate with apathy in AD [10–13]. One large voxel-based morphometry study examined the brain-behavior correlates of neuropsychiatric symptoms measured with the NPI. The study included 75 patients with the frontal or temporal variant of frontotemporal dementia (FTD), 52 patients with AD, 12 with corticobasal ganglionic degeneration and 9 with progressive supranuclear palsy. The study demonstrated associations between apathy and atrophy of the right ventral anterior cingulate and the adjacent ventromedial superior frontal gyrus in the frontotemporal/semantic dementia group only. The authors posited that the apparent lack of association of apathy and the cingulate and mesial frontal cortex in AD were likely due to the small sample size [14]. Differences in the localization of effects in these studies may reflect variations in the method of measuring apathy, differences in the threshold for identifying apathy, low power due to small sample sizes, variability among patient populations, and differences in imaging modalities. The pathologic correlates of apathy in AD have been studied in two postmortem analyses [15, 16]. Both studies report neuropathologic correlations between apathy and anterior cingulate neurofibrillary tangle counts. However, the relationship of apathy to cortical gray matter (GM) thinning – a common hallmark of neurodegeneration in AD – has not been established in vivo.

Methods

We analyzed structural magnetic resonance imaging (MRI) data from 17 probable AD patients with and 18 probable AD patients without apathy measured with the NPI [17]. Diagnosis of AD was reached by consensus decision among neurologists, psychiatrists and neuropsychologists and was based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [18] for probable AD, but did not meet core criteria for FTD [19]. The presence, frequency and severity of apathy were established with the NPI, a comprehensive structured caregiver-based interview for quantification of neuropsychiatric symptoms in patients with AD [17]. To minimize confounding effects of other neuropsychiatric behaviors, we selected our patient groups with sparse neuropsychiatric findings in all other NPI domains except for apathy. Thus, our apathy group consisted of probable AD patients who aside from apathy had few other neuropsychiatric abnormalities as measured by the NPI, and our nonapathy group consisted of probable AD patients who had no apathy and only few other NPI symptoms. All patients received a structural MRI scan with the following protocol: spoiled gradient echo, gapless coronal acquisition, TR 28 ms, TE 6 ms, field of view 220 mm, 256 × 192 matrix, slice thickness 1.5 mm. Subjects with significant cerebrovascular disease such as strokes and periventricular white matter changes were excluded from the study. The brain scans were spatially normalized to the ICBM53 average brain template. Image intensity nonuniformities were corrected. The scalp and soft tissues were removed, and three-dimensional hemispheric models were obtained from the images. Thirty-eight sulci per hemisphere were traced on each cortical model, and an average three-dimensional sulcal map unique to our study population was created. The individual cortical surfaces were flattened and warped so that the individual sulci were matched across individuals when correlating apathy scores with GM measures. Segmented GM was explicitly mapped onto the corresponding hemispheric model. Average three-dimensional GM density (GMD) maps were created for the groups with and without apathy. Statistical maps of the association between the product of the frequency and severity (FxS) apathy scores and GMD were created. For a detailed description of the techniques, see Apostolova et al. [20]. For each region showing a significant correlation with apathy, the mean GMD in that region, for each subject, was used for backward conditional linear and logistic regression analyses modeling apathy severity (i.e. FxS) and the presence or absence of apathy, respectively, while controlling for age, race, gender and education. Within the apathy group, the relationship between greater apathy and mean GMD in the cingulate regions was further examined using regression plots (fig. 2). We also conducted exploratory analyses to assess for potential correlations of any other NPI symptoms and mean GMD in our regions of interest.

Results

The demographic and clinical comparisons between the two groups are shown in table 1. The two groups differed significantly only for their mean FxS apathy scores. The FxS scores of all other NPI domains were not different between the two groups. No subjects in either group had a past medical history of head trauma, seizures, alcohol or substance abuse, psychosis, anxiety, depression or bipolar disorder. One subject from the apathy group had mild parkinsonism that did not require therapy and another had one episode of delirium after a major surgical procedure.

A significant correlation between the apathy score and GM atrophy was seen bilaterally in the supracallosal cin-

Table 1. Demographic and clinical variables

Variables	Apathy+ (n = 17)	Apathy– (n =18)	Statistics	p value
Age[1], years	73.9 ± 2.25	78.9 ± 1.97	t = –1.92	0.063
Education[1], years	13.8 ± 0.54	14.4 ± 0.57	$\chi^2 = 0.019$	0.25
Gender, M/F	7/10	7/10	$\chi^2 = 0.019$	0.89
MMSE score[1]	20.5 ± 1.58	21.4 ± 1.64	t = 0.5	0.16
Apathy FxS score[1]	5.73 ± 0.9	0	t = 6.74	<0.001
NPI 10[2]	9 (14.75)	8 (9.5)	N/A	N/A
Hypertension[3]	2 (11.8)	5 (27.8)	$\chi^2 = 0.24$	0.4
Coronary artery disease[3]	2 (11.8)	3 (16.7)	$\chi^2 = 0.68$	1
Stroke or TIA	0	0	N/A	N/A
Hypercholesterolemia[3]	3 (17.7)	1 (5.5)	$\chi^2 = 0.26$	0.34
Diabetes mellitus[3]	2 (11.8)	0	$\chi^2 = 0.13$	0.23
Hypothyroidism[3]	2 (17.7)	2 (11.1)	$\chi^2 = 0.95$	1
Antihypertensives[3]	4 (23.5)	4 (22.2)	$\chi^2 = 0.93$	1
Heart stimulants, antiarrhythmics[3]	2 (11.8)	2 (5.5)	$\chi^2 = 0.95$	1
Aspirin[3]	3 (17.7)	5 (27.8)	$\chi^2 = 0.48$	0.69
Thyroid supplements[3]	3 (17.7)	2 (11.1)	$\chi^2 = 0.58$	0.66
Sedative (h.s. p.r.n.)[3]	2 (11.8)	1 (5.5)	$\chi^2 = 0.51$	0.6
Antidepressants[3]	3 (17.7)	3 (16.7)	$\chi^2 = 0.94$	1
Antipsychotics[3]	0	2 (11.1)	$\chi^2 = 0.16$	0.49
Cholinesterase inhibitors[3]	13 (76.5)	10 (55.5)	$\chi^2 = 0.19$	0.29

$p < 0.001$ is statistically significant. TIA = Transient ischemic attack; h.s. = before sleep; p.r.n. = when necessary.
[1] Mean ± SD.
[2] Median with interquartile range in parentheses.
[3] Number with percentage in parentheses.

gulate [Brodmann area (BA) 24] and the left medial frontal cortex (BA 8/9; fig. 1; table 2). The mean GMDs of the left and right cingulate regions that showed significant correlations on the three-dimensional maps were significant predictors of apathy severity after controlling for age, race, gender and education (backward stepwise linear regression with left cingulate mean GMD: $R^2 = 0.26$, $F = 3.23$, $p = 0.037$, left cingulate $t = –2.01$, $p = 0.05$; backward stepwise linear regression with the mean right cingulate GMD: $R^2 = 0.26$, $F = 3.28$, $p = 0.036$, right cingulate $t = –2.04$, $p = 0.05$). The only other significant predictor in both models was age ($t = –2.59$ to 2.78, $p = 0.01–0.02$). The regression plots in figure 2 show the linear inverse relationship between greater apathy (i.e., higher FxS scores) and GM atrophy (i.e., lower GMD) in the cingulate regions. In a backward stepwise logistic regression, the left cingulate mean GMD showed a trend for significance in predicting presence or absence of apathy (statistical model $R^2 = 0.21$, $p = 0.055$; left cingulate Wald = 2.74, $p = 0.098$).

The exploratory correlation analyses of mean GMDs in the bilateral cingulate and the left medial frontal cortex and the nonapathy NPI domain FxS scores revealed a trend significant correlation between the FxS irritability score and the right cingulate gyrus ($r = 0.345$, $p = 0.053$).

Discussion

Apathy is the most common neuropsychiatric symptom in AD – affecting 40% of those with mild, 80% of those with moderate and over 90% of those with severe AD [1]. Several functional neuroimaging studies have suggested a relationship between apathy and medial frontal dysfunction in AD [10, 12, 13], but the relationship to a structural measure of neurodegeneration, such as cortical atrophy for AD, has not previously been established.

The anterior cingulate is involved in sensory and emotional information processing and affective modulation of attention [21]. As hypothesized, AD patients with apa-

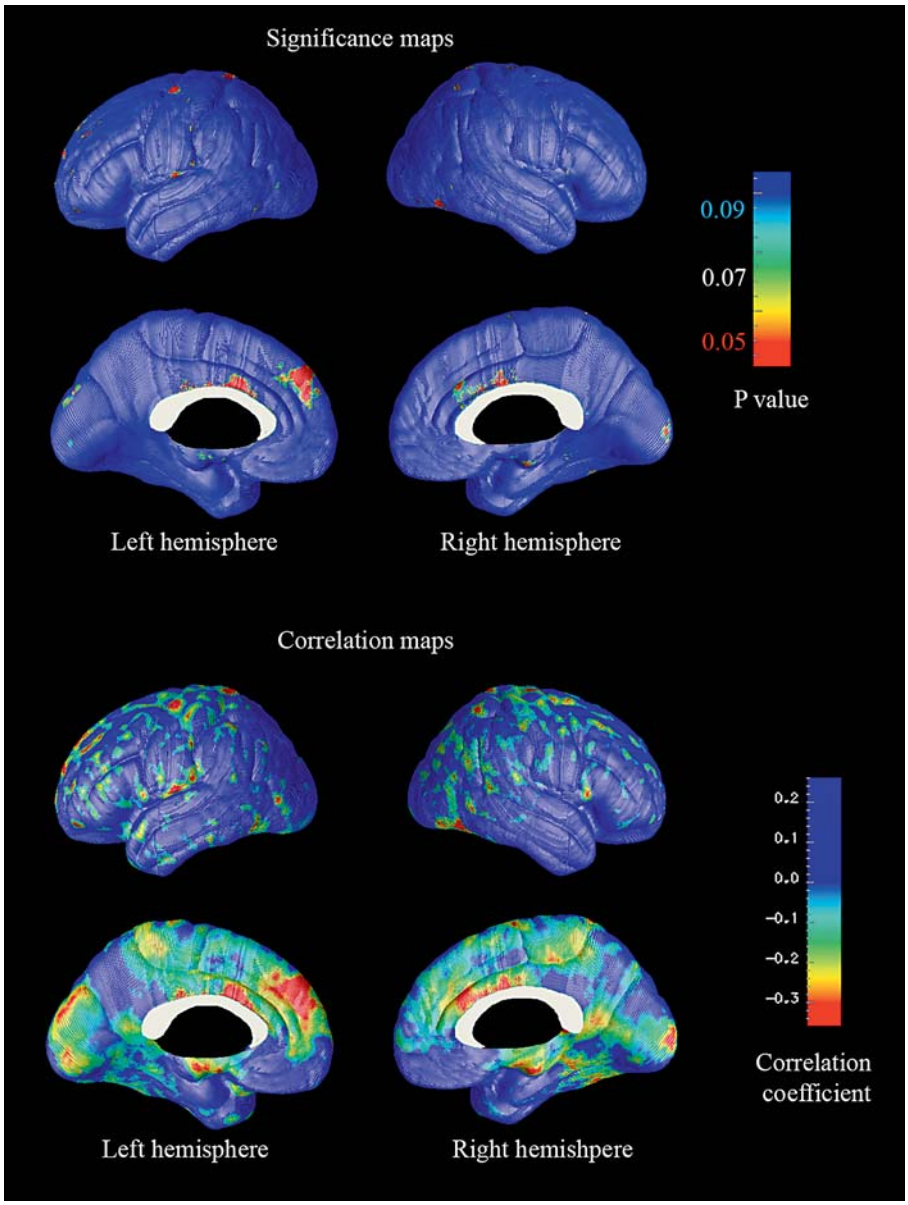

Fig. 1. Statistical (top) and correlation maps (bottom) showing the strength of the association between apathy severity and GMD among 17 probable AD patients with and 18 probable AD patients without apathy. As predicted, apathy severity correlated with bilateral anterior cingulate atrophy, as well as atrophy of the left supplementary motor area.

Table 2. Location, ICBM coordinates and statistical significance of the regions showing the strongest associations of apathy and GM atrophy

Region	BA	Coordinates, mm			r value	p value
		X	Y	Z		
Cingulate	left BA 24	−1	5.4	31.4	−0.42	<0.01
	right BA 24	3	4.4	31.9	−0.39	0.01
Supplementary motor area	left BA 9	−4	47.1	33.1	−0.40	<0.02

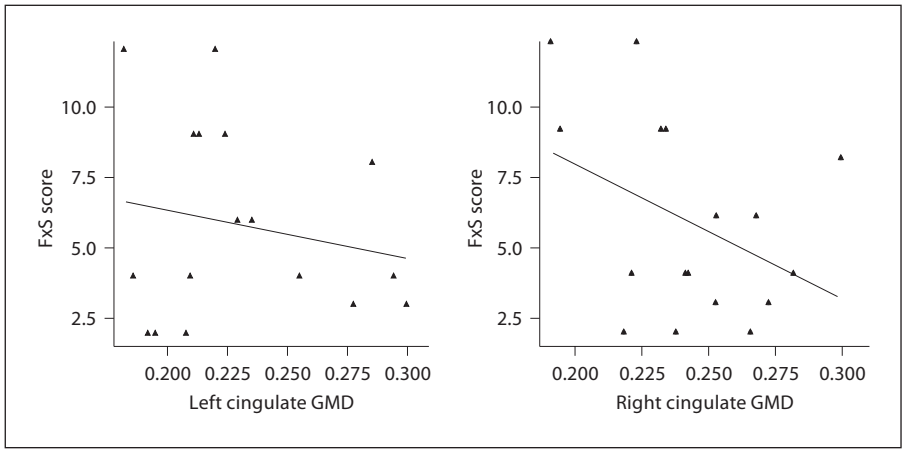

Fig. 2. Regression plots showing the inverse association between apathy (FxS score) and GM atrophy.

thy have greater GM atrophy of the anterior cingulate relative to those without apathy but with comparable Mini Mental State Examination scores. Additionally, apathy correlated with cortical atrophy of the left BAs 8 and 9. BAs 8 and 9 have been implicated in emotional processing in several functional imaging studies [22–24]. Our findings provide additional evidence for a cause-effect relationship between disruption of the anterior cingulate circuitry and the lack of interest and motivation commonly seen in AD.

The study by Rosen et al. [14] reported an association between apathy and atrophy of the right ventral anterior cingulate and adjacent medial frontal cortex in a group of frontotemporal/semantic dementia patients. The NINCDS-ADRDA criteria, when applied to dementia, can potentially overdiagnose AD in subjects with other forms of dementia including FTD if they are the sole set of criteria applied to the population under study. However, such misclassification occurs only rarely if standardized clinical and neuropsychological records and classic diagnostic criteria for the various dementias are concomitantly used [25] as is the case in tertiary memory disorders clinics such as ours.

Anterior cingulate atrophy is commonly associated with FTD as opposed to the posterior cingulate predominant pattern seen in AD. However, the anterior cingulate gyrus is not spared even in mild AD. Our group has recently demonstrated that relative to amnestic mild cognitive impairment, mild AD subjects demonstrate on average 10% more atrophy in the dorsal anterior cingulate gyrus – a difference that was highly statistically significant ($p < 0.002$) [26]. A recent study by Barnes et al. [27] compared the annual rates of atrophy seen in AD and FTD in the caudal anterior and posterior cingulate gyrus and reported no significant differences in the atrophy rates between the two groups [dorsal anterior cingulate: AD annual atrophy rate = 6.4% (SD 3.7%), FTD annual atrophy rate = 7.4% (SD 4.2%); posterior cingulate: AD annual atrophy rate = 7.7% (SD 5.8%), FTD annual atrophy rate = 7.6% (SD 4.6%)]. A preliminary study by another group used a cortical methodology similar to ours and compared the cortical atrophy pattern in AD and FTD [28]. The only area where FTD subjects had significantly more atrophy than AD subjects was the right orbitofrontal cortex.

As we have introduced a selection bias for all nonapathy domains in our study, the observed positive correlation between the FxS irritability score and the right anterior cingulate GM cannot be fully justified. A follow-up study with a similar design focusing on irritability or an exploratory study examining all NPI behaviors simultaneously would be two reasonable approaches to validate this observation.

Although our findings cannot be generalized to neurodegenerative disorders other than AD, taken together with the evidence from the lesion-based studies and more recently the study by Rosen et al. [14], we could posit that an injury to the frontosubcortical anterior cingulate circuit regardless of its etiology produces symptoms of apathy [29–31].

Several limitations of our study should be recognized. Apathy is commonly seen in many other neurodegenerative disorders, but no conclusions about the structural correlates of apathy in patients without AD can be drawn from this study. Our results cannot be generalized to personality traits seen in normal individuals. Additionally,

we lack postmortem tissue confirmation of the observed relationships (such as postmortem regional atrophy estimates, plaque and tangle counts). However, two studies have already reported a positive correlation between neurofibrillary tangle burden in the anterior cingulate and apathy in AD [15, 16]. The sample size of our study is one of the largest to date among studies of apathy in AD, but it is nevertheless still modest. The NPI was the only measure of apathy used and other measures may have provided additional insight.

Conclusions

This is the first structural MRI study in AD demonstrating a strong association between apathy and the integrity of medial frontal regions. This provides additional evidence that medial frontosubcortical circuits are important for volition, motivation and emotional behavior.

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