Diffusion Tensor Imaging of Neuropsychiatric Symptoms in Mild Cognitive Impairment and Alzheimer's Dementia

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Neuropsychiatric symptoms (NPS) occur frequently in mild cognitive impairment (MCI) and Alzheimer's dementia (AD). The authors examined the relationship between NPS and white-matter integrity in these conditions. Twenty-two individuals with MCI and 23 with mild AD underwent clinical assessments including the Neuropsychiatric Inventory Questionnaire and 3.0-tesla magnetic resonance scans. Fractional anisotropy (FA) was measured in the following manually-drawn regions of interest (ROI): fornix, cingulum bundle, splenium, and cerebral peduncles (control region). The probability of having NPS by tertile of ROI FA was assessed by logistic regression. Because associations were similar within MCI and AD groups, the two groups were combined. Compared with those in the highest tertile, participants within the lowest anterior cingulum (AC) FA tertile were more likely to exhibit irritability, agitation, dysphoria, apathy, and nighttime behavioral disturbances. After adjusting for Mini-Mental State Exam status, participants in the lowest versus highest tertile of AC FA were more likely to report irritability. Using DTI, low AC FA was associated with increased odds of irritability in mild AD and MCI participants. Further imaging studies are necessary to elucidate the role of the AC in the pathophysiology of neuropsychiatric symptoms in AD and MCI.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2012; 24:484–488)

Neuropsychiatric symptoms (NPS), including dysphoria and irritability, are highly prevalent in patients with mild cognitive impairment (MCI) and Alzheimer's dementia (AD).[1] NPS are associated with serious consequences for patients, including accelerated cognitive and functional decline[2] and the transition from MCI to AD.[1] Although white-matter (WM) abnormalities are common in AD,[3] little is known about the relationship between these abnormalities and NPS. Diffusion tensor imaging (DTI), an imaging technique used to assess the integrity and connectivity of WM, has been used to study neuropsychiatric disorders. Only one study has examined DTI correlates of neuropsychiatric symptoms in AD.[4]

The present study is an exploratory analysis of the relationship between WM integrity, using DTI, and neuropsychiatric symptoms in MCI and AD patients. Earlier literature has implicated the anterior cingulate in the pathophysiology of NPS in AD.[5,6] Thus, we hypothesized that greater anterior cingulate WM alterations, characterized by lower fractional anisotropy (FA), would be associated with NPS in MCI and AD.

METHODS

Subjects

Study design and recruitment have been previously described;[3] only MCI and AD participants from the baseline assessment were included in this analysis. Briefly, participants were recruited from the Johns Hopkins Alzheimer's Disease Research Center and Memory Clinics. MCI participants had mild memory

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problems (Clinical Dementia Rating [CDR]=0.5),[7] and met criteria for amnestic MCI with single or multiple impaired domains.[8] AD patients had a CDR of 1 and met NINCDS/ADRDA criteria for probable AD.[9] Exclusion criteria included age <55 years, a neurological or major psychiatric illness other than AD, and a Geriatric Depression Scale >7.[10] We obtained informed consent, and the study was approved by a Johns Hopkins Institutional Review Board. A group of 25 MCI and 25 AD subjects completed the baseline examination.

Assessments

In-person evaluations consisted of medical, psychiatric, and neurologic histories; neuropsychological battery; neurological examinations; assessment of dementia severity using the CDR[7]; and magnetic resonance (MR) scan. The Neuropsychiatric Inventory Questionnaire (NPI-Q), which evaluates 12 NPS domains, including agitation, depression, and euphoria, was administered to informants to evaluate the type and severity of NPS in participants.[11]

MRI Acquisition and Processing

The methods used to acquire the MRI scans, process the imaging data, and define the regions of interest (ROI) have been previously described.[3] Briefly, MR images were conducted on a 3.0-tesla scanner (Philips Medical Systems; Best, The Netherlands) at the F.M. Kirby Research Center for Functional Brain Imaging of the Kennedy Krieger Institute. The DTI data were processed on a personal computer, using DtiStudio software (*www.DtiStudio.org*).[12] FA was calculated, and values ranged from 0 to 1, where higher values indicate a greater degree of WM integrity.

The ROI were manually drawn, with high reliability (mean interclass correlation: 0.87; range: 0.82–0.95) in MriStudio/RoiEditor (*www.MriStudio.org*). A priori-defined ROI included the fornix, inferior cingulum, posterior cingulum, anterior cingulum (AC), splenium, and cerebral peduncles, as shown in Figure 1 of the Mielke et al. article.[3] For the present analyses, we averaged the two adjacent fornix slices and averaged the two axial slices of the posterior portion of the cingulum bundle.

Statistical Analysis

Two AD participants who lacked DTI data, and three MCI participants with incomplete NPI-Q data were excluded, leaving 22 MCI and 23 AD participants for these analyses. Differences in demographic and medical characteristics were examined between the MCI and AD groups with Fisher's exact test for dichotomous variables and two-tailed Student's *t*-tests for continuous variables.

MCI and AD groups were initially examined separately. Because associations between the ROI and NPI-Q symptoms were similar, the groups were combined. Since NPS are more common in moderate-to-severe AD, where patients have lower FA,[2] we controlled for the Mini-Mental State Exam (MMSE).[13] Univariate and multivariate logistic-regression models were estimated to examine associations between individual NPS (presence vs. absence of each symptom) and tertiles of FA in each region. Tertiles were utilized to avoid odds ratios (OR) that approached infinity and because the relationship between NPS and DTI measures might not be linear. The a priori p value was <0.05, and all tests were two-tailed. Corrections for multiple comparisons were not performed in this pilot study. Data analyses were performed with STATA Version 9.2 (2007; StataCorp.; College Station, TX).

RESULTS

Subject Characteristics

There were no significant differences in age, sex, race, education, APOE genotype, or prevalence of cardiovascular conditions (e.g., hypertension, myocardial infarction, diabetes mellitus) between MCI and AD groups. AD participants had worse scores on CDR ($t[43] = -6.55$; $p<0.01$), MMSE ($t[43]=5.64$; $p<0.01$), and NPI-Q ($t[43] = -3.05$; $p<0.01$) than MCI participants. Among the combined group of MCI and AD patients, the most prevalent NPS were irritability (35.6%), apathy (33.3%), and dysphoria (31.1%).

Relationship Between NPS and DTI

Of the ROI examined, FA of the AC and fornix regions was most strongly associated with NPS. Therefore, logistic-regression models were estimated to examine the relative contribution of AC and fornix FA to the presence of the 12 NPS. Table 1 displays the regression model for the AC as measured by OR (95% confidence interval [CI]). On the basis of the univariate model, participants in the lowest FA tertile for AC were more likely to experience irritability (4.95 [1.02–24.10]), agitation (8.67 [1.39–53.85]), dysphoria (5.33 [1.02–27.76]),

TABLE 1. Association Between Tertiles of Anterior Cingulum Mean FA and the Presence of NPI-Q Symptoms Based on Univariate and Multivariate Logistic Regressions Where the Highest Tertile is the Comparison Group (N=45)

				Univariate Logistic Regression				Multivariate Logistic Regression[a]			
				Low Versus High		Middle Versus High		Low Versus High		Middle Versus High	
Presence of NPI-Q Symptom	N (lowest tertile)	N (middle tertile)	N (highest tertile)	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p
Agitation	8	2	2	8.67 (1.39–53.85)	**0.020**	0.93 (0.11–7.59)	NS	7.45 (1.00–55.50)	0.050	0.88 (0.11–7.37)	NS
Dysphoria	8	3	3	5.33 (1.02–27.76)	**0.047**	0.92 (0.16–5.49)	NS	3.94 (0.65–24.10)	NS	0.83 (0.13–5.09)	NS
Anxiety	7	0	5	2.00 (0.45–8.96)	NS	No events in this group		1.79 (0.31–10.39)	NS	No events in this group	
Apathy	9	2	4	4.95 (1.02–24.10)	**0.048**	0.39 (0.06–2.55)	NS	2.64 (0.45–15.43)	NS	0.29 (0.04–2.08)	NS
Irritability	9	3	4	4.95 (1.02–24.10)	**0.048**	0.63 (0.12–3.47)	NS	7.21 (1.09–47.85)	**0.041**	0.70 (0.13–3.94)	NS
Motor difficulties	5	1	1	7.78 (0.78–77.93)	0.081	0.93 (0.05–16.39)	NS	5.12 (0.42–62.30)	NS	0.80 (0.04–14.62)	NS
Nighttime behavioral disturbances	8	2	3	5.53 (1.02–27.76)	**0.047**	0.57 (0.08–4.01)	NS	3.50 (0.57–21.55)	NS	0.48 (0.07–3.56)	NS
Appetite disturbances	5	2	1	7.78 (0.78–77.93)	0.081	2.00 (0.16–24.66)	NS	4.31 (0.36–51.25)	NS	1.62 (0.12–21.07)	NS

[a]Multivariate analyses corrected for Mini-Mental State Exam.
CI: confidence interval; NPI-Q: Neuropsychiatric Inventory Questionnaire.

apathy (4.95 [1.02–24.10]), and nighttime behavioral disturbances (5.53 [1.02–27.76]) than those in the highest tertile. Only irritability remained significant in the multivariate model (7.21 [1.09–47.85]). There were no significant associations for the fornix.

We were unable to include hallucinations, delusions, elation, and disinhibition in regression models because no one in the reference (highest tertile) group reported these NPS. Instead, Fisher's exact tests were performed to examine the relationship between FA of these regions and symptoms. Only disinhibition was associated with low FA in the AC (p=0.033) and fornix (p=0.008).

DISCUSSION

We examined WM correlates of NPS in a combined group of MCI and AD patients by use of DTI. Lower AC FA, indicative of worse WM integrity in this area, was associated with higher odds of irritability. This study provides additional evidence that the anterior cingulate is important to the pathophysiology of NPS in the earliest stages of Alzheimer's disease. Previous neuropathology work reported an association between the burden of neurofibrillary tangles in the left anterior cingulate and two NPS, apathy and agitation, in patients with AD.[5] Although associations between affective NPS and reduced metabolism or perfusion in the anterior cingulate have been observed with functional imaging,[6] only one other DTI study has examined NPS in AD.[4] Kim et al. observed lower FA in the left AC of apathetic participants than in nonapathetic subjects.[4]

Our findings suggest that compromised WM integrity within the AC and dysfunction of its associated neuroanatomical circuits may be involved in the pathophysiology of irritability in patients with AD or MCI. Furthermore, these data suggest that decreased AC FA occurs in the early stages of AD and may be associated with a vulnerability to developing NPS. Originating with the neurons of the anterior cingulate cortex with projections to the limbic striatum, the anterior cingulate-subcortical circuit regulates motivated behavior.[14] Findings from basic and translational research have implicated dopaminergic and cholinergic neurotransmission in this system.[14]

Limitations of this study warrant consideration. Given the exploratory nature of these analyses, we did not perform corrections for multiple comparisons. Thus, these results are preliminary and require future

replication. The presence of white-matter hyperintensities (WMH) was not considered in the exclusion criteria. Patients with a known history of stroke and/or cerebrovascular disease were excluded from this study, and the prevalence of vascular factors such as hypertension, hypercholesterolemia, diabetes mellitus, and myocardial infarction did not differ between the MCI and AD groups. Nevertheless, the presence of WMH could confound these findings, given previous literature that demonstrated reduced anisotropy in WMH as compared with normal tissue.[15] Furthermore, the administration of pharmacologic agents, including antidepressants, neuroleptics, and cholinesterase inhibitors, is common in these patients and may obscure imaging correlates of the brain–behavior relationship. However, there is limited evidence of the effects of psychotropic medications on FA measures from within-subject studies.[16] One paper that examined SSRIs in late-life depression did not show a systematic change in FA with SSRI use.[16] Another limitation is the cross-sectional nature of the study design. Consequently, we are unable to draw any causal inferences regarding the relationship between WM irregularities in the AC and the presence of irritability. Finally, the sample size was small. To increase the power of this analysis, the AD and MCI groups were combined for the regression analyses because the relationships between FA and NPS were similar between the groups.

In conclusion, our exploratory analysis revealed initial insights into the relationship between WM pathology and NPS in a combination of MCI and AD patients. These data suggest that NPS in MCI and AD are linked to WM abnormalities in the AC. In light of the preliminary nature of these results, replication with a larger cohort of patients is warranted. A DTI comparison of WM abnormalities in MCI patients versus AD patients with irritability would be expected to yield valuable information about the neurobiological underpinnings of NPS in cognitively impaired elderly persons.

The results of this study were presented in the form of a Poster on May 12, 2011 at the 2011 Society of Biological Psychiatry Conference held in San Francisco, CA, May 12–14, 2011.

The authors thank research assistants Sarah Forrester and Clifford Workman for their assistance with this manuscript.

The images acquired from patients with Alzheimer's dementia and mild cognitive impairment were supported by a methods development grant from GlaxoSmithKline awarded to Drs. Lyketsos and Albert. Dr. Lyketsos has received grant support (research or CME) from the following organizations: NIMH, NIA, Associated Jewish Federation of Baltimore, Weinberg Foundation, Forest, GlaxoSmithKline, Eisai, Pfizer, Astra-Zeneca, Lilly, Ortho-McNeil, Bristol-Myers, Novartis, National Football League, and Elan. Dr. Lyketsos has served as a consultant/advisor for AstraZeneca, GlaxoSmithKline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Pfizer, Genentech, Elan, the NFL Players Association, NFL Benefits Office, and Avanir. Dr. Lyketsos has received honorarium or travel support from Pfizer, Forest, GlaxoSmithKline, and Health Monitor. The remaining authors have reported no biomedical financial interests or potential conflicts of interest. This research was funded in part by grants from GlaxoSmithKline, the National Institute on Aging (P50 AG005146, P50 AG021334, R21 AG033774), and the National Center for Research Resources (P41 RR15241).

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