Published in final edited form as:

J Neuropsychiatry Clin Neurosci. 2012 September 1; 24(4): 484–488. doi:10.1176/appi.neuropsych.11120375.

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

Sarah K. Tighe, M.D., Kenichi Oishi, M.D., Ph.D., Susumu Mori, Ph.D., Gwenn S. Smith, Ph.D., Marilyn Albert, Ph.D., Constantine G. Lyke, M.D., M.H.S., and Michelle M. Mielke, Ph.D.

The Johns Hopkins University School of Medicine, Departments of Psychiatry and Behavioral Sciences, Neurology, Radiology, Baltimore, MD, USA and the Kennedy Krieger Institute, Baltimore, MD, USA

Abstract

Neuropsychiatric symptoms (NPS) occur frequently in mild cognitive impairment (MCI) and Alzheimer's dementia (AD). We 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 using logistic regression. Because associations were similar within MCI and AD groups, the two groups were combined. Compared to 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 ($p < 0.05$). After adjusting for MMSE, participants in the lowest vs. highest tertile of AC FA were more likely to report irritability (OR: 7.21, $p = 0.041$). 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 NPS in AD and MCI.

Keywords

Diffusion tensor imaging; Alzheimer's disease; Mild cognitive impairment; Neuropsychiatric symptoms

OBJECTIVE

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}. While 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

Corresponding Author: Sarah Tighe, **Telephone:** 410-550-2204, stighe1@jhmi.edu.

Address for Reprints: Sarah K. Tighe, Department of Psychiatry and Behavioral Sciences, Division of Geriatric Psychiatry and Neuropsychiatry, Alpha Commons Building, 4th Floor, 5300 Alpha Commons Drive, Baltimore, MD 21224

Previous Presentation: 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 remaining authors have reported no biomedical financial interests or potential conflicts of interest.

assess the integrity and connectivity of WM, has been employed to study neuropsychiatric disorders. Only one study has examined DTI correlates of NPS in AD {4}.

The present study is an exploratory analysis of the relationship between WM integrity, using DTI, and NPS in MCI and AD patients. Prior 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.

Research Design and Statistics

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 problems, Clinical Dementia Rating (CDR)=0.5 {7}, and met criteria for amnesic MCI with single or multiple impaired domains {8}. AD patients had a CDR=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}. Informed consent was obtained, and the study was approved by a Johns Hopkins Institutional Review Board. Twenty five 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}.

MR Acquisition and Processing—The methods used to acquire the MR 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 (www.DtiStudio.org) {12}. FA was calculated and values ranged from zero to one 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 demonstrated in Figure 1 of Mielke et al {3}. For the present analysis, 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 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 using 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 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 $p < 0.05$, and all tests were two-tailed. Corrections for multiple comparisons were not performed in this pilot study. Data analyses were performed using STATA Version 9.2 (2007, StataCorp, College Station, TX).

RESULTS

Subject Characteristics

There were no significant differences in age ($t=0.05, df=43, p=0.96$), sex ($p=0.72$), race ($p=0.14$), education ($t=1.11, df=43, p=0.28$), APOE genotype ($p=0.33$), or the prevalence of cardiovascular conditions (e.g., hypertension, myocardial infarction, and diabetes mellitus) between MCI and AD groups. AD participants had worse scores on CDR ($t=-6.55, df=43, p<0.01$), MMSE ($t=5.64, df=43, p<0.01$) and NPI-Q ($t=-3.05, df=43, p<0.01$) compared to 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% CI). Based on 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]), apathy (4.95 [1.02–24.10]), and nighttime behavioral disturbances (5.53 [1.02–27.76]) compared to 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 using 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. Prior 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}. While 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 compared to non-apatetic 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. Further, 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 the analysis, we did not perform corrections for multiple comparisons. Thus, the results of this analysis 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 compared to normal tissue {15}. Further, the administration of pharmacologic agents, including antidepressants, neuroleptics, and cholinesterase inhibitors, is common in these patients and may obscure imaging correlates of brain-behavior relationships. 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 with irritability to AD patients with this symptom is also expected to yield valuable information about the neurobiological underpinnings of NPS in cognitively impaired elderly.

Acknowledgments

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 Astra-Zeneca, GlaxoSmithKline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Pfizer, Genentech, Elan, NFL Players Association, NFL Benefits Office, and Avanir. Dr. Lyketsos has received honorarium or travel support from Pfizer, Forest, GlaxoSmithKline, and Health Monitor.

This research was funded in part by grants from GlaxoSmithKline, the National Institute on Aging (P50-AG005146, P50-AG 021334, R21AG033774), and the National Center for Research Resources (P41-RR15241). The authors would like to thank research assistants Sarah Forrester and Clifford Workman for their assistance with this manuscript.

References

1. Lyketsos CG, Carrillo MC, Ryan JM. Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimers Dement*. 2011; 7:532–539. [PubMed: 21889116]
2. Mortimer JA, Ebbitt B, Jun SP. Predictors of cognitive and functional progression in patients with probable Alzheimer's disease. *Neurology*. 1992; 42:1689–1696. [PubMed: 1513455]

3. Mielke MM, Kozauer NA, Chan KC. Regionally-specific diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. *Neuroimage*. 2009; 46:47–55. [PubMed: 19457371]
4. Kim JW, Lee DY, Choo IH. Microstructural alteration of the anterior cingulum is associated with apathy in Alzheimer Disease. *Am J Geriatr Psychiatry*. 2011; 19:644–653. [PubMed: 21709610]
5. Tekin S, Mega MS, Masterman DM. Orbitofrontal and anterior cingulate cortex neurofibrillary tangle burden is associated with agitation in Alzheimer disease. *Ann Neurol*. 2001; 49:355–361. [PubMed: 11261510]
6. Marshall GA, Monserratt L, Harwood D. Positron emission tomography metabolic correlates of apathy in Alzheimer disease. *Arch Neurol*. 2007; 64:1015–1020. [PubMed: 17620493]
7. Hughes CP, Berg L, Danziger WL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982; 140:566–572. [PubMed: 7104545]
8. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004; 256:183–194. [PubMed: 15324362]
9. McKhann G, Drachman D, Folstein M. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34:939–944. [PubMed: 6610841]
10. Yesavage JA, Brink TL, Rose TL. Development and validation of a geriatric depression screening scale: a preliminary report. *Journal of psychiatric research*. 1982; 17:37–49. [PubMed: 7183759]
11. Cummings JL, Mega M, Gray K. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994; 44:2308–2314. [PubMed: 7991117]
12. Jiang H, van Zijl PC, Kim J. DtiStudio: resource program for diffusion tensor computation and fiber bundle tracking. *Comput Methods Programs Biomed*. 2006; 81:106–116. [PubMed: 16413083]
13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state" A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189–198. [PubMed: 1202204]
14. Bonelli RM, Cummings JL. Frontal-subcortical circuitry and behavior. *Dialogues Clin Neurosci*. 2007; 9:141–151. [PubMed: 17726913]
15. Taylor WD, Payne ME, Krishnan KR. Evidence of white matter tract disruption in MRI hyperintensities. *Biol Psychiatry*. 2001; 50:179–183. [PubMed: 11513816]
16. Taylor WD, Macfall JR, Boyd B. One-year change in anterior cingulate cortex white matter microstructure: relationship with late-life depression outcomes. *Am J Geriatr Psychiatry*. 2011; 19:43–52. [PubMed: 20808126]

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)

Presence of NPI-Q Symptom	n (low tert)	n (mid tert)	n (high tert)	Univariate Logistic Regression				Multivariate Logistic Regression ^a			
				Low vs. High		Middle vs. High		Low vs. High		Middle vs. High	
				Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Agitation	8	2	2	8.67 (1.39, 53.85)	0.020	0.93 (0.11, 7.59)	0.945	7.45 (1.00, 55.50)	0.050	0.88 (0.11, 7.37)	
Dysphoria	8	3	3	5.33 (1.02, 27.76)	0.047	0.92 (0.16, 5.49)	0.930	3.94 (0.65, 24.10)	0.137	0.83 (0.13, 5.09)	
Anxiety	7	0	5	2.00 (0.45, 8.96)	0.365	No events in this group		1.79 (0.31, 10.39)	0.517	No events in this group	
Apathy	9	2	4	4.95 (1.02, 24.10)	0.048	0.39 (0.06, 2.55)	0.328	2.64 (0.45, 15.43)	0.282	0.29 (0.04, 2.08)	
Irritability	9	3	4	4.95 (1.02, 24.10)	0.048	0.63 (0.12, 3.47)	0.600	7.21 (1.09, 47.85)	0.041	0.70 (0.13, 3.94)	
Motor difficulties	5	1	1	7.78 (0.78, 77.93)	0.081	0.93 (0.05, 16.39)	0.962	5.12 (0.42, 62.30)	0.200	0.80 (0.04, 14.62)	
NBD	8	2	3	5.53 (1.02, 27.76)	0.047	0.57 (0.08, 4.01)	0.573	3.50 (0.57, 21.55)	0.177	0.48 (0.07, 3.56)	
Appetite disturbances	5	2	1	7.78 (0.78, 77.93)	0.081	2.00 (0.16, 24.66)	0.589	4.31 (0.36, 51.25)	0.247	1.62 (0.12, 21.07)	

Key:

^a Multivariate analyses corrected for MMSE

CI: confidence interval

High: highest

Mid: middle

MMSE: Mini-Mental State Exam

NBD: nighttime behavioral disturbances

NPI-Q: Neuropsychiatric Inventory Questionnaire

Tert: tertile