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Grey Matter Atrophy in Mild Cognitive Impairment / Early Alzheimer Disease Associated with Delusions: A Voxel-Based Morphometry Study

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Abstract: Objectives: Grey matter atrophy in the right hemisphere has been shown to be more severe in dementia patients with delusions, suggesting a neuroanatomical localization that may be pertinent to impending neurodegeneration. Delusional symptoms may arise when atrophy in these areas reduces the regulatory functions of the right hemisphere, in tandem with asymmetric neuropathology in the left hemisphere. We hypothesized that delusional patients with either amnestic mild cognitive impairment (MCI) or early Alzheimer Disease (AD) would experience more pronounced grey matter atrophy in the right frontal lobe compared with matched patients without delusions. Methods: We used neuroimaging and clinical data obtained from the Alzheimer's Disease Neuroimaging Initiative. A comparison group of twenty-nine non-delusional MCI/early AD participants were compared with twenty-nine delusional participants using voxel-based morphometry, matched at baseline by age, sex, education, and Mini-Mental State Exam score. All included participants were diagnosed with amnestic MCI at study baseline. Results: Fifteen voxel clusters of decreased grey matter in participants with delusions were detected. Prominent grey matter decrease was observed in the right precentral gyrus, right inferior frontal gyrus, right insula, and left middle occipital gyrus, areas that may be involved in control of thought and emotions. Conclusion: Greater right fronto-temporal grey matter atrophy was observed in MCI or early AD participants with delusions compared to matched patients without delusions. Consistent with our predictions, asymmetric grey matter atrophy in the right hemisphere may contribute to development of delusions through loss of executive inhibition.

Keywords: Alzheimer disease, delusions, executive control, inhibition, mild cognitive impairment, voxel-based morphometry.

INTRODUCTION

Mild Cognitive Impairment (MCI), especially the amnestic form [1, 2] is considered a prodromal phase of Alzheimer Disease (AD) [3, 4]. The international health burden of AD and related dementias is increasing [5], and localization of the atrophy associated with neuropsychiatric symptoms is important for development of biomarkers for early neurodegeneration. Previous research has shown that there is distinct neuropathology associated with the development of delusions in dementia [6]. Neuropsychiatric symptoms collectively increase the level of caregiver burden in MCI [7], and our review has found that delusional symptoms significantly increase the level of functional impairment and caregiver burden in AD patients [8]. Previous research has shown there are significant neural correlates of conversion from MCI to AD, with degeneration in the temporal, hippocampal and cingulate cortices [9] and this has been analyzed in the Alzheimer's Disease Neuroimaging Initiative (ADNI) [10, 11]. Along these lines, persistent neuroanatomical changes may accompany the development of delusions in patients with

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[#]*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf*

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MCI at baseline as they transition to AD and is an important area for our understanding of MCI disease course and conversion to AD.

Executive control and inhibition processes are closely linked. Intrusive thoughts and emotions are cardinal characteristics of psychosis and delusions. Previous research has supported the idea that inhibition in the right fronto-temporal areas are involved in these intrusive thoughts. Specifically, the right inferior frontal cortex is involved in inhibition of the posterior cortical and subcortical areas [12-14]. In neurodegeneration, right fronto-temporal pathology has been linked to psychotic symptoms and delusions in Alzheimer Disease patients using measures of cortical metabolism [15, 16], linear measurements of computerized tomography scans [17], and regional cerebral blood flow and cerebral perfusion [18, 19]. There has been little work directly addressing the neurobiology of delusions in late MCI/early AD via voxel-based morphometry (VBM), beyond a study which compared groups based on their delusional outcome, which selected scans prior to delusional onset [20] and another looking at neuropsychiatric symptoms across the AD spectrum [21]. Further work exploring this relationship will help characterize the neurobiology of delusional presentation in the MCI/early AD phase.

We conducted a VBM analysis with data from the ADNI database in a group of MCI/early AD patients with delusions, compared with a baseline-matched group of MCI/early AD patients without delusions. We predicted more pronounced grey matter (GM) atrophy in the right frontal areas of the brain, based on the hypothesis that decreasing the capacity of the right frontal lobes to inhibit intrusive thoughts may contribute to the emergence of delusional symptomatology.

MATERIALS AND METHODS

The ADNI data collection protocol was approved with Institutional Review Boards at participating centers [22]. Study protocol was approved by the Institutional Review Board at St. Michael's Hospital. With 1.5 Tesla T1 structural MR images from ADNI, we conducted a cross-sectional analysis on a total of 58 patients. Twenty-nine MCI/early AD patients with delusions were compared with twenty-nine MCI/early AD patients who were matched to delusional patients on age, sex, years of education, baseline global cognitive functioning score (Mini-Mental State Examination, MMSE), baseline clinical diagnosis of MCI, and time in months since study entry. Data on presence/absence of delusions were obtained from informant report on the Neuropsychiatric Inventory Questionnaire (NPI-Q). We conducted our analysis using images at timepoints when participants first reported to have delusions, matched with patients with no reported delusions during 48 months of follow-up.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is an international multi-center collaboration [23] which has set the precedent for providing access to curated data for secondary neuroimaging analyses, without embargo, for research purposes [23]. All ADNI data is quality-checked by neuroimaging experts when submitted to the central server, and is pre-processed to enhance standardization between scanning hardware and protocols [23]. This resource presents an invaluable opportunity to study the neuroanatomical correlates of delusions in MCI/early AD in cross-sectional fashion since ADNI participants are continually enrolled from participating institutions around the globe, and the longevity of the study [22] has ensured a large sample size as a primary source.

Our source pool of participant data was from ADNI 1 (inclusion/exclusion criteria and other relevant details for ADNI are available on their website [22]), enrolled in the U.S.A. and Canada. Participants were included if they had a baseline diagnosis of amnestic MCI (single- or multiple-domain) according to revised Petersen Criteria [2, 24]. All MCI participants had a Clinical Dementia Rating (CDR) score of 0.5 at baseline. Selected participants needed to have an MRI scan from the first visit at which delusions were reported. Participants were excluded if they presented with hallucinations at any point during ADNI 1 (up to month 48) to prevent confounding neuropsychiatric symptoms. No patients in our analysis sample had delusions at the baseline assessment, although in the larger ADNI database, about 1.3% of informants reported delusions at baseline [25]. Matched non-delusional MCI participants were selected for each delusional participant based on sex, age within two years, education level within two years, time (in months) since study entry, and baseline MMSE score within 2 points to match for global cognitive functioning. During the pre-processing, two participants were excluded because their timepoint-matched MR images were not available on the server. All pre-processed scans were reviewed for gross acquisition errors as an additional quality check after those conducted at ADNI MR imaging headquarters.

VBM creates statistical parametric maps identifying voxel clusters of significant morphological difference between the groups [26]. The pre-processed magnetic resonance images in ADNI were the best suited for subsequent VBM analyses because the pipeline reduces geometric distortion, image intensity non-uniformity due to radio-frequency pulses, and the wave/dielectric effect [27]. As the ADNI is an international collaboration, these steps, in addition to scaling with the use of MRI phantoms, help reduce the level of variation between scanners and scanning protocols [27] and help to address concerns regarding multi-center VBM studies [28].

Voxel-based morphometry is a method of comparing homologous voxels between two groups of brains [26]. We used the VBM- Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) processing pipeline to analyze our images, methodologically described in detail by Ashburner [29]. VBM-DARTEL analyses were conducted in Statistical Parametric Mapping (SPM) Software Version 8 (http://www.fil.ion.ucl.ac.uk /spm/software/spm8/), running on MatLAB_R2010b (1994-2010, Mathworks, Inc.). Briefly, this process involved an approximate registration of MRI images to an average Montreal Neurological Institute (MNI) template, segmentation of the images into grey matter, white matter and cerebrospinal fluid (CSF) images using tissue prior probability maps, registration through DARTEL [30], which iteratively aligned each image to generate a study-specific template, and normalization of each individual image to MNI space to fit the study-specific template.

GM images were smoothed by convolving with an isotropic Gaussian kernel of 5mm full-width half maximum (FWHM). Image voxels were modulated with the Jacobian determinants of their deformation fields to account for tissue volumes and not concentration. Grouped images were entered into a General Linear Model (GLM) for an independent two-sample t-test with unequal variance. Total intracranial volume (TIV) was calculated using a separate script posted on the SPM Mailing List Archives (https://www.jiscmail.ac.uk/cgi-bin/webadmin?A0=spm) (spm_get_volumes.m), which arithmetically summed the numerical volumes of the white matter, grey matter, and CSF (in L) from images after initial segmentation. TIV was entered into the GLM for proportional scaling normalization, to account for systematic differences in the global brain size due to age effects.

To visualize the results, the GLM was used to create a statistical parametric map (SPM) with an implicit absolute masking threshold of 0.2. The specified direction of our one-tailed t-contrast was group 1 (D-) > group 2 (D+), in line with our hypothesis that the D+ group would have less grey matter than the matched D- group (supplementary detailed methods, T1 of Henley, Ridgway, Scahill *et al.* (2010) explains the t-contrast for grey matter volumes between groups [31]). A statistical parametric map was generated without masking with other contrasts, selecting an exploratory significance threshold of $p < 0.001$ uncorrected, one-tailed. We reported this significance threshold since our sample size was relatively small, the FWE (Family-Wise Error) and FDR (False Discovery Rate) corrections are still considered to be conservative for small sample sizes, and the pathology expected in MCI/early AD is expected to be lower than that observed in more advanced AD (especially between MCI D- and MCI D+ groups). We repeated the statistical parametric mapping with FWHM at 10mm, and we also repeated the thresholding using a FWE correction (utilizing Random Field Theory) [32] at $p < 0.05$ and FDR correction at $p < 0.05$.

Results were visualized using xjView 8.1 running on MatLAB_R2010b, which overlaid the positive t-test statistical parametric map onto an average MRI template image of 152 T1 brains from the ICBM (International Consortium for Brain Mapping). xjView automatically set a color scheme based on the statistical parametric map for the significant positive t-test results in the specified contrast. Voxel cluster coordinates in MNI space produced by SPM8 were converted to Talairach space using Brain Map GingerALE 2.3 (2003-2013, Research Imaging Institute, UTHSCSA) and neuroanatomical location was identified using the Talairach Atlas (2003-2013, Research Imaging Institute, UTHSCSA).

RESULTS

Demographic Data

Baseline demographic characteristics of our ADNI participant groups are included in (Table **1**). There were no significant differences between groups in age, sex, years of education, and baseline MMSE/CDR scores. The number of ApoE alleles were also not significantly different between D- and D+ groups. There was a significant relationship between delusional group and diagnosis at scan timepoint X^2 (1) = 5.61, $p = 0.018$. The clinical dementia rating (CDR) at delusions/matched visit was increased in those with delusions compared to those without ($p = 0.005$)). The MMSE score at delusions/matched visit was significantly lower in those with delusions than those without ($p = 0.039$). Finally, there was a significant difference in the proportion of MCI to AD diagnoses between the D- and D+ groups at delusions/matched visit, with 69% of the D- group having a diagnosis of MCI compared to only 38% of the D+ group having a diagnosis of MCI. In the D+ group when they first reported delusions, 62% (18 out of 29) of our participants had mild delusions, ten had moderate delusions, and one had severe delusions. Full demographic data for all subjects are available from ADNI.

Voxel-Based Morphometry

Fig. (**1**) shows a 3-dimensional rendering of the brain, with the significant areas of grey matter decrease at the uncorrected $p < 0.001$ threshold projected on the cortical surface. Table **2** lists all the voxel clusters that had significant grey matter decrease in the D+ group compared to the D- group. All coordinates are in Talairach space. To reduce interpretation of false positives, we considered for discussion voxel clusters from this table with a size greater than or equal to ten. The top three most significant areas of GM decrease were in the right insula, right precentral gyrus, and right inferior frontal gyrus (RIFG). One voxel cluster with a size of 19 was identified in the left middle occipital gyrus. Fig. (**2**) shows a glass-brain projection of the results. The majority of our significant voxel clusters were located on the right side of the brain (3A), and in the frontal areas (3B, 3C). Conducting the analysis with FWE and FDR corrections at $p < 0.05$ did not produce any suprathreshold voxel clusters; neither did conducting the analysis with a larger smoothing kernel with a Gaussian FWHM of 10mm.

DISCUSSION

We conducted a voxel-based morphometry analysis between two groups of MCI/early AD participants from the ADNI collaboration, one group with clinically active delusional presentation, matched with a comparison group who did not present with delusions. While these findings need to be interpreted with caution given the small sample size and limited strength of the results, consistent with our hypothesis, we observed significant areas of grey matter atrophy in the delusional group compared to the non-delusional group in the right fronto-temporal areas of the brain. In these patients, it is possible delusional symptoms may surface when this increased atrophy leads to removal of the inhibitory/executive monitoring function of the right fronto-temporal areas of the brain.

The largest cluster of grey matter difference was observed in the right insula (cluster 1). The right insular cortex has been implicated in the presence of delusions in psychotic illnesses such as schizophrenia. Recent work has found that the grey matter volume of the right insular cortex was inversely correlated with the severity of delusions in schizophrenia patients [33]. In addition, the right insula is involved in perceptions of self-generated stimuli as opposed to external stimuli [34], and emotions [35]. A recent review found

Table 1. Demographic Characteristics of Mild Cognitive Impairment (MCI)/Early Alzheimer Disease (AD) Comparison Groups.

	MCI/Early AD D-	MCI/Early AD D+	Significance (p, two-tailed)
N	29	29	NA
Age	74.345 (6.62)	74.379 (6.33)	.984
Sex (Male/Female)	17/12	17/12	NA
Education (Years)	15.862 (2.89)	15.655 (2.73)	.780
MMSE Score at Baseline	27.31 (1.80)	26.59 (1.88)	.139
MMSE at Delusions / Matched Visit	24.93 (4.30)	22.28 (5.20)	.039
Global CDR at Delusions / Matched Visit (CDR:number of participants)	0: 2 0.5: 20 1: 6 2: 1	0: 0 0.5: 11 1: 14 2: 4	.013
CDR Sum of Boxes at Baseline	1.62 (.96)	1.83 (.69)	.349
CDR Sum of Boxes at Delusions / Matched Visit	2.76 (2.09)	4.86 (3.24)	.005
Diagnosis at Baseline	MCI n=29	MCI n=29	NA
Diagnosis at Delusions / Matched Visit	MCI n=20 (69.0%) AD n=9 (31.0%)	MCI n=11 (37.9%) AD n=18 (62.1%)	$X^2 = 5.61, .018$
Number of ApoE Alleles	None: n=12 One: n=11 Two: n=6	None: n=12 One: n=14 Two: n=3	$X^2 = 1.36, .507$
Mean Follow-up Time (Months)	38.07 (12.96)	38.28 (13.74)	NA (Range: 6-48)

Demographic characteristics of the MCI/Early AD comparison groups. Unless otherwise specified, p-values are from a two-sample independent t-test at $p < 0.05$. MMSE = Mini-Mental State Exam; CDR = Clinical Dementia Rating; NA = Not Applicable

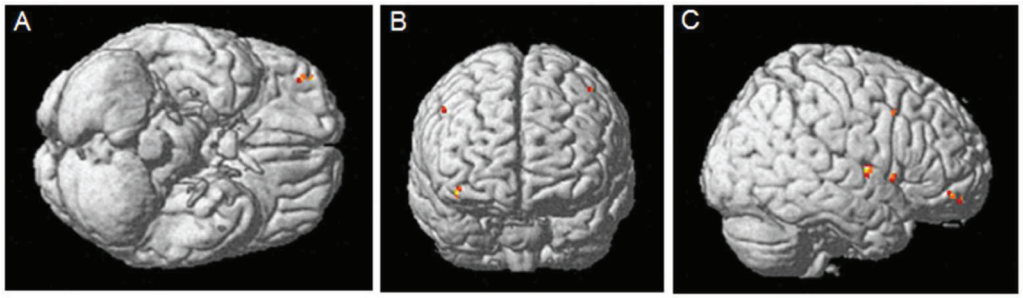

Fig. (1). Three-Dimensional Rendering of Voxel-Based Morphometry Results. VBM results in **A**: ventral, **B**: frontal, and **C**: right sagittal views, $p < 0.001$ uncorrected. The 3D projection was generated in xjView 8.1, which overlaid the significant voxel clusters from the statistical parametric map onto the cortical surface and exterior skull base.

that the insular cortex plays a significant role in awareness of self and rigidly held beliefs characteristic of delusions, and in mediating and perpetuating these thoughts [35]. By the same token, degeneration of the grey matter in this area of the brain may lead to greater susceptibility to delusional onset, but we must be mindful that the neuropsychology and pharmacology of delusions in schizophrenia are likely very different from that of dementia.

We also found a significantly decreased GM voxel cluster in the right precentral gyrus (cluster 2) and the left middle occipital gyrus (cluster 5). The precentral gyrus is generally responsible for motor control. More research is needed to investigate this region and whether it plays a role in delusional formation in MCI/Early AD patients. The occipital cortex has been implicated in the development of visual hallucinations in AD [36]. The hallucinations item from the NPI-Q mainly reflects auditory hallucinations, so it is possible that some patients may have had visual hallucinations. Recent analyses have reported cortical thinning in the inferior temporal and parietal areas of patients with hallucinations in the ADNI cohort along the MCI – AD spectrum [37].

Table 2. Suprathreshold Voxel Clusters from VBM-DARTEL.

SUPRATHRESHOLD VOXEL CLUSTERS, *p < 0.001* uncorrected								
Cluster No.	**Coordinates (Talairach)**			**Cluster Size**	**Location (Nearest Grey Matter)**	**T**	**P_{uncorr} (Peak)**	**P_{uncorr} (Cluster)**
	X	**Y**	**Z**	**K_E**				
1	**42**	**-7**	**7**	**39**	**Right Insula**	**3.92**	**1.2218 e-04**	**0.179**
2	**50**	**9**	**6**	**10**	**Right Precentral Gyrus**	**3.77**	**1.9556 e-04**	**0.500**
3	**36**	**44**	**0**	**13**	**Right Inferior Frontal Gyrus**	**3.71**	**2.4264 e-04**	**0.438**
4	-42	0	51	6	Left Middle Frontal Gyrus	3.60	3.3653 e-04	0.611
5	**-37**	**-63**	**5**	**19**	**Left Middle Occipital Gyrus**	**3.59**	**3.5269 e-04**	**0.345**
6	36	49	-2	7	Right Middle Frontal Gyrus	3.51	4.4142 e-04	0.579
7	33	18	-8	2	Right Inferior Frontal Gyrus	3.50	4.5499 e-04	0.789
8	-24	-47	35	4	Left Cingulate Gyrus	3.46	5.2531e-04	0.686
9	44	6	42	7	Right Middle Frontal Gyrus	3.41	6.0327e-04	0.579
10	50	-2	12	4	Right Precentral Gyrus	3.37	6.7328e-04	0.686
11	49	25	16	1	Right Inferior Frontal Gyrus	3.32	7.9620e-04	0.861
12	15	21	61	2	Right Superior Frontal Gyrus	3.31	8.1487e-04	0.789
13	23	-65	-11	1	Right Cerebellar Declive	3.30	8.5317e-04	0.861
14	-48	-27	41	1	Left Postcentral Gyrus	3.28	8.9365e-04	0.861
15	-36	39	-4	1	Left Middle Frontal Gyrus	3.25	9.9064e-04	0.861

List of suprathreshold voxel clusters observed at the uncorrected p < 0.001 threshold, between Mild Cognitive Impairment (MCI)/Early Alzheimer Disease (AD) patients without delusions (D-) and MCI/Early AD patients with delusions (D+) via independent two-sample t-test. All coordinates in Talairach space. Peak-level significance values are included. Clusters with $K_E \geq 10$ are in bold.

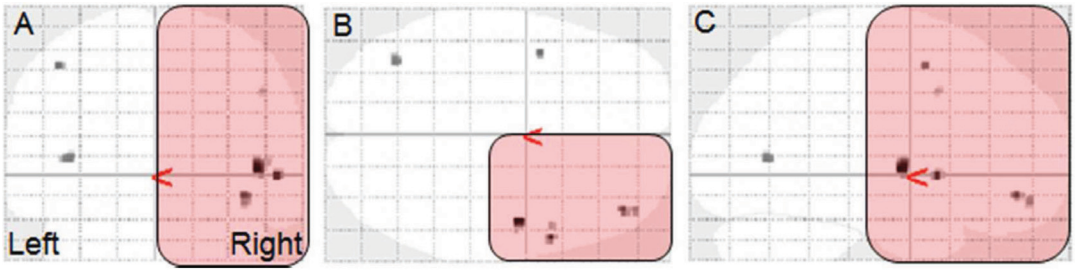

Fig. (2). Glass-Brain Projection of the VBM Results. **A**: Coronal view in neurological convention; **B**: Axial View; **C**: Right Sagittal View. An average model brain has been made transparent, illustrating the significant voxel clusters of decreased grey matter in the delusional (D+) group relative to the non-delusional (D-) group shown as black spots. The majority of the significant voxel clusters are located in the right (**A**) and frontal (**B** and **C**) areas of the brain.

The right inferior frontal gyrus (RIFG) (cluster 3) was involved. The RIFG may be involved in the inhibition of impulsive thoughts and inappropriate behaviors [12]. In measures of functional activation of the brain during the go/no-go task, in which participants press a button when presented with a 'go' visual stimulus but must inhibit themselves from carrying out the action when a 'no-go' visual stimulus is presented, the RIFG is significantly activated when the inhibitory signal is presented [12]. Recent research has found significant involvement of the right inferior frontal gyrus in delusions post-stroke [38]. As we observed significant decreases in the grey matter in the D+ group compared to the D- group in the RIFG, the results lend support to our hypothesis that more pronounced grey matter atrophy in the right frontal areas may contribute towards intrusive thoughts in these patients.

Previous voxel-based morphometry studies investigating the neuroanatomical correlates of delusions in MCI patients with neuroimages at baseline, prior to delusional onset, have found significant grey matter volume reduction in the left and right parahippocampal gyri, right posterior cingulate gyrus, right orbitofrontal cortex, right inferior frontal gyrus, right medial frontal gyrus, and right anterior cingulate, among others [20]. Nakaaki *et al.* observed significant decreases in grey matter volume in the frontal areas of the

brain, and hypothesized that greater degeneration in these areas may be responsible for development of delusions [20]. A VBM study across the AD spectrum found significant associations between GM volume in the right hippocampal areas with delusions, and between the anterior cingulate with disinhibition [21]. Our finding that the right inferior frontal gyrus had more atrophy in the delusional group relative to the comparison group supports previous work in some respects, although our conclusions must be tempered given the small patient sample and the uncorrected nature of our results.

We did not address subtypes of delusions in our analysis as these data were not readily available from ADNI (the NPI-Q delusions item reflects delusions of theft and threat of harm from others). Future studies should explore this issue since certain delusional subtypes of MCI/AD may differentially affect frontal executive faculties, and unique impairment between subtypes may correspond to greater atrophy observed in different areas. We have previously explored the link between impairment of function reflecting degeneration in certain brain areas and the development of psychotic symptoms [39]. A pilot study found significant asymmetric left hand side decreases in fractional anisotropy (FA) in several white matter tracts connecting the occipital lobes to frontal and temporal lobes [40]. One may use a similar experimental design to determine if there is any significant loss of tract integrity as a factor of atrophy in these areas.

Our findings should be interpreted with due caution and are preliminary, as there were several limitations. Our findings were significant only at the $p < 0.001$ uncorrected level and the clusters were small. The areas of atrophy need to be replicated with a larger sample size with multiple comparison correction. However, our significance criterion of $p < 0.001$ is in line with a comparable cross-sectional voxel-based morphometry study investigating delusions in bipolar depression [41], among other literature with similar sample sizes [42-44]. Future work could further explore our identified neuroanatomical areas and conduct a small-volume corrected ROI-based analysis to verify our findings of decreased grey matter atrophy in those areas.

In addition, we only looked at images in a cross-sectional design. Although we can identify the neuroanatomical correlates of delusional presentation at the selected timepoint, we cannot determine the grey matter changes longitudinally associated with the development of delusions over time in the same participant, though they all had amnestic MCI at baseline. It is possible that a small minority of patients with amnestic MCI at baseline converted to a form of dementia other than AD and this may confound the results. Furthermore, a significant number of the MCI patients at baseline had already converted to Alzheimer Disease at the timepoint for which we selected their scan if delusions were present (see Table **1**). It will be crucial to identify longitudinally the time points at which these grey matter differences first occur to effectively characterize delusions in early Alzheimer Disease.

CONCLUSION

We conducted a VBM study to determine the neuroanatomical correlates of delusions in patients with MCI/early AD. We found significant decreases in the grey matter in several voxel clusters predominantly in the right fronto-temporal areas of the brain, suggesting that greater atrophy here may contribute to the development of delusions. However, our results need to be interpreted with due caution given the relatively small sample size and the cluster sizes involved. To our knowledge, these pilot results provide one of the first pieces of evidence that there are distinct neuroanatomical correlates specific to delusional presentation in MCI/early AD, akin to a recently published study investigating the neural basis of hallucinations using the ADNI cohort [37]. Future studies should focus on biomarker development in these areas, identify methods of preventing degeneration, or explore the characteristics of these areas that make them susceptible to degeneration.

CONFLICT OF INTEREST AND SOURCE OF FUNDING

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Dr. Chow reports no disclosures.

Dr. Schweizer reports no other disclosures.

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AUTHOR CONTRIBUTIONS

Study conceptualization and design: WT, CF, CM, ZI, TC, TS. Data collection: WT, CM. Data analysis: WT, CM. Analysis interpretation: WT, CF, CM, TS. First draft of manuscript: WT. Subsequent revisions to manuscript for important intellectual content: CF, CM, ZI, TC, TS. Approved final version of manuscript for submission: WT, CF, CM, ZI, TC, TS. Study supervision: CF, CM, TS.

PREVIOUS PRESENTATION

This work was presented as an oral poster presentation at the 7th Canadian Conference on Dementia in Vancouver, Canada: Oct 4-6, 2013. The abstract from the conference has been published in the Canadian Geriatrics Journal, 16(4), 2013, pp. 196-199.

REFERENCES

[1] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC*, et al.* The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dementia 7(3): 270-9 (2011).

[2] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56(3): 303-8 (1999).

[3] Eckerstrom C, Olsson E, Bjerke M, Malmgren H, Edman A, Wallin A*, et al.* A combination of neuropsychological, neuroimaging, and cerebrospinal fluid markers predicts conversion from mild cognitive impairment to dementia. J Alzheimers Dis 36(3): 421-31 (2013).

[4] Levey A, Lah J, Goldstein F, Steenland K, Bliwise D. Mild cognitive impairment: an opportunity to identify patients at high risk for progression to Alzheimer's disease. Clin Therapeut 28(7): 991-1001 (2006).

[5] Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ. Epidemiology of dementias and Alzheimer's disease. Arch Med Res 43(8): 600-8 (2012).

[6] Ismail Z, Nguyen MQ, Fischer CE, Schweizer TA, Mulsant BH. Neuroimaging of delusions in Alzheimer's disease. Psychiat Res 202(2): 89-95 (2012).

[7] Trivedi SC, Subramanyam AA, Pinto C, Gambhire DD. Neuropsychiatric symptoms in mild cognitive impairment: An analysis and its impact on caregiving. Indian J Psychiat 55(2): 154-60 (2013).

[8] Fischer CE, Ismail Z, Schweizer TA. Delusions increase functional impairment in Alzheimer's disease. Dement Geriatric Cogn Disord 33(6): 393-9 (2012).

[9] Chetelat G, Landeau B, Eustache F, Mezenge F, Viader F, de la Sayette V*, et al.* Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: a longitudinal MRI study. NeuroImage 27(4): 934-46 (2005).

[10] Misra C, Fan Y, Davatzikos C. Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: results from ADNI. NeuroImage 44(4): 1415-22.(2009).

[11] Risacher SL, Saykin AJ, West JD, Shen L, Firpi HA, McDonald BC*, et al.* Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. Curr Alzheimer Res 6(4): 347-61 (2009).

[12] Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci 8(4): 170-7 (2004).

[13] Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: one decade on. Trends Cogn Sci 18(4): 177-85 (2014).

[14] Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM. The role of the right inferior frontal gyrus: inhibition and attentional control. NeuroImage 50(3): 1313-9 (2010).

[15] Sultzer DL, Brown CV, Mandelkern MA, Mahler ME, Mendez MF, Chen ST*, et al.* Delusional thoughts and regional frontal/temporal cortex metabolism in Alzheimer's disease. Am J Psychiat 160(2): 341-9 (2003).

[16] Sultzer DL, Leskin LP, Melrose RJ, Harwood DG, Narvaez TA, Ando TK*, et al.* Neurobiology of Delusions, Memory, and Insight in Alzheimer Disease. Am J Geriatr Psychiatry 22(11): 1346-55 (2014).

[17] Geroldi C, Bresciani L, Zanetti O, Frisoni GB. Regional brain atrophy in patients with mild Alzheimer's disease and delusions. International psychogeriatrics / IPA 14(4): 365-78 (2002).

[18] Matsuoka T, Narumoto J, Shibata K, Okamura A, Nakamura K, Okuyama C*, et al.* Insular hypoperfusion correlates with the severity of delusions in individuals with Alzheimer's disease. Dementia Geriatr Cogn Disord 29(4): 287-93 (2010).

[19] Nomura K, Kazui H, Wada T, Sugiyama H, Yamamoto D, Yoshiyama K*, et al.* Classification of delusions in Alzheimer's disease and their neural correlates. Psychogeriatrics 12(3): 200-10 (2012).

[20] Nakaaki S, Sato J, Torii K, Oka M, Negi A, Nakamae T*, et al.* Neuroanatomical abnormalities before onset of delusions in patients with Alzheimer's disease: a voxel-based morphometry study. Neuropsychiatric Dis Treatment 9: 1-8 (2013).

[21] Serra L, Perri R, Cercignani M, Spano B, Fadda L, Marra C*, et al.* Are the behavioral symptoms of Alzheimer's disease directly associated with neurodegeneration? J Alzheimers Dis 21(2): 627-39 (2010).

[22] ADNI Study Documents. http://adni.loni.usc.edu/ (2014).

[23] Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC*, et al.* The Alzheimer's Disease Neuroimaging Initiative: a review of papers published since its inception. Alzheimers Dementia 8(1): S1-68 (2012).

[24] Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO*, et al.* Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 256(3): 240-6 (2004).

[25] Wadsworth LP, Lorius N, Donovan NJ, Locascio JJ, Rentz DM, Johnson KA*, et al.* Neuropsychiatric symptoms and global functional impairment along the Alzheimer's continuum. Dementia Geriatric Cogn Disord 34(2): 96-111 (2012).

[26] Ashburner J, Friston KJ. Voxel-based morphometry--the methods. NeuroImage 11(6 Pt 1): 805-21 (2000).

[27] Jack CR, Jr., Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D*, et al.* The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. J Magn Reson Imaging 27(4): 685-91 (2008).

[28] Focke NK, Helms G, Kaspar S, Diederich C, Toth V, Dechent P*, et al.* Multi-site voxel-based morphometry--not quite there yet. NeuroImage 56(3): 1164-70 (2011).

[29] Ashburner J. VBM Tutorial. University College London (2010).

[30] Ashburner J. A fast diffeomorphic image registration algorithm. NeuroImage 38(1): 95-113 (2007).

[31] Henley SM, Ridgway GR, Scahill RI, Kloppel S, Tabrizi SJ, Fox NC*, et al.* Pitfalls in the use of voxel-based morphometry as a biomarker: examples from huntington disease. Am J Neuroradiol 31(4): 711-9 (2010).

[32] Ashburner J. Computational anatomy with the SPM software. Mag Reson Imag 27(8): 1163-74 (2009).

[33] Cascella NG, Gerner GJ, Fieldstone SC, Sawa A, Schretlen DJ. The insula-claustrum region and delusions in schizophrenia. Schizophrenia Res 133(1-3): 77-81 (2011).

[34] Moran ME, Weisinger B, Ludovici K, McAdams H, Greenstein D, Gochman P*, et al.* At the boundary of the self: The insular cortex in patients with childhood-onset schizophrenia, their healthy siblings, and normal volunteers. Int J Dev Neurosci 32: 58-63 (2014).

[35] Paulus MP, Stein MB. Interoception in anxiety and depression. Brain Struct Func 214(5-6): 451-63 (2010).

[36] Holroyd S, Shepherd ML, Downs JH, 3rd. Occipital atrophy is associated with visual hallucinations in Alzheimer's disease. J Neuropsychiat Clin Neurosci 12(1): 25-8 (2000).

[37] Donovan NJ, Wadsworth LP, Lorius N, Locascio JJ, Rentz DM, Johnson KA*, et al.* Regional Cortical Thinning Predicts Worsening Apathy and Hallucinations Across the Alzheimer Disease Spectrum. Am J Geriatr Psychiatry 22(11): 1168-79 (2014).

[38] Devine MJ, Bentley P, Jones B, Hotton G, Greenwood RJ, Jenkins IH*, et al.* The role of the right inferior frontal gyrus in the pathogenesis of post-stroke psychosis. J Neurol 261(3): 600-3 (2014).

[39] Ismail Z, Nguyen MQ, Fischer CE, Schweizer TA, Mulsant BH, Mamo D. Neurobiology of delusions in Alzheimer's disease. Curr Psychiat Rep 13(3): 211-8 (2011).

[40] Nakaaki S, Sato J, Torii K, Oka M, Negi A, Nakamae T*, et al.* Decreased white matter integrity before the onset of delusions in patients with Alzheimer's disease: diffusion tensor imaging. Neuropsychiatr Dis Treat 9: 25-9 (2013).

[41] Radaelli D, Poletti S, Gorni I, Locatelli C, Smeraldi E, Colombo C*, et al.* Neural correlates of delusion in bipolar depression. Psychiatry Res 221(1): 1-5 (2014).

[42] Lv XF, Zheng XL, Zhang WD, Liu LZ, Zhang YM, Chen MY*, et al.* Radiation-induced changes in normal-appearing gray matter in patients with nasopharyngeal carcinoma: a magnetic resonance imaging voxel-based morphometry study. Neuroradiology 56(5): 423-30 (2014).

[43] Morris JK, Vidoni ED, Perea RD, Rada R, Johnson DK, Lyons K*, et al.* Insulin resistance and gray matter volume in neurodegenerative disease. Neuroscience 270: 139-47 (2014).

[44] Pickut BA, Van Hecke W, Kerckhofs E, Marien P, Vanneste S, Cras P*, et al.* Mindfulness based intervention in Parkinson's disease leads to structural brain changes on MRI: a randomized controlled longitudinal trial. Clin Neurol Neurosurg 115(12): 2419-25 (2013).

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