Characterizing dementia with Lewy bodies by means of diffusion tensor imaging

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ABSTRACT

Objective: To investigate patterns of in vivo white matter tract change using diffusion tensor imaging (DTI), we conducted a cross-sectional study of dementia with Lewy bodies (DLB) in comparison with Alzheimer disease (AD) and normal aging.

Methods: The study included 106 subjects (35 with DLB, 36 with AD, and 35 elderly controls) who underwent clinical and neuropsychological assessment and diffusion tensor MRI. We used tract-based spatial statistics to investigate patterns of reduced fractional anisotropy (FA) and increased mean diffusivity (MD) across the entire white matter tract skeleton and also investigated correlations with clinical features.

Results: Areas of reduced FA in subjects with DLB vs controls were found primarily in parieto-occipital white matter tracts; in AD, the changes were much more diffuse. DLB was also associated with reduced FA in the pons and left thalamus, in comparison with AD. The pattern of MD increase was diffuse in AD and DLB. We found an association between DTI parameters and impaired episodic memory, letter fluency, and severity of motor parkinsonism in DLB.

Conclusions: Despite a similar level of dementia severity, patterns of DTI changes in AD and DLB differed significantly. The selective involvement of the visual association areas and subcortical structures and the significant clinical correlations highlight the potential importance of white matter tract change in the pathogenesis of DLB. DTI may be a useful technique to investigate early and possible preclinical changes in DLB and warrants further investigation. *Neurology*® 2012;79:906-914

GLOSSARY

AD = Alzheimer disease; **BVMT** = Brief Visual Memory Task-Revised; **CAMCOG** = Cambridge Cognitive Examination; **DLB** = dementia with Lewy bodies; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FWE** = familywise error; **HVLT** = Hopkins Verbal Learning Test; **ILF** = inferior longitudinal fasciculus; **MD** = mean diffusivity; **MMSE** = Mini-Mental State Examination; **NPI** = Neuropsychiatric Inventory; **ROI** = region of interest; **TBSS** = tract-based spatial statistics; **TFCE** = threshold-free cluster enhancement algorithm; **UPDRS-III** = Unified Parkinson's Disease Rating Scale Part III; **VBM** = voxel-based morphometry.

Dementia with Lewy bodies (DLB) is a common form of neurodegenerative dementia in older people, second to Alzheimer disease (AD). The separation between AD and DLB clinically remains a challenge. We therefore need to establish in vivo biomarkers that can distinguish the differing pathologies and their contribution to the clinical features of the conditions.

Diffusion tensor imaging (DTI) utilizes the anisotropic nature of diffusion in neuronal white matter tracts.¹ With neuronal degeneration, the mean diffusivity (MD) increases with the loss of structural barriers that normally restrict diffusion, and diffusion becomes less directionally oriented, which is associated with a reduction in fractional anisotropy (FA).²

Previous studies investigating the DTI changes in DLB have used conventional region of interest (ROI) or voxel-based morphometry (VBM) methods.³⁻⁸ Some studies found widespread FA changes in comparison with healthy controls,^{3,7} whereas others have found very little

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Supplemental Data

From the Institute for Ageing and Health, Campus for Ageing and Vitality (R.W., S.J.C., R.B., J.T.O.), and Institute of Cellular Medicine & Newcastle Magnetic Resonance Centre (A.M.B., J.S.W., J.H.), Newcastle University, Newcastle upon Tyne, UK.

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change.^{5,6} The most consistent finding has been of reduced FA in the region of the inferior longitudinal fasciculus (ILF),^{3,6–8} and FA reductions have also been reported to occur in the posterior cingulate and precuneal areas.^{3–5,7} DTI therefore shows promise as a useful imaging technique to provide important pathologic insights into the disease process.

Tract-based spatial statistics (TBSS) is a relatively novel methodologic algorithm designed to combine the benefits of an operator-independent VBM style of analysis with the tract-based information gained from tractography. This method has recently been shown to be a reliable means of measuring FA changes in older adults. By contrast, partial volume effects remain problematic in measures of MD (and radial and axial diffusivity) in areas of atrophy.⁹

We used TBSS to investigate the pattern of white matter tract change in subjects with DLB, in comparison with subjects with AD and age-matched controls. We hypothesized that there would be significant FA reduction affecting predominantly the posterior white matter tracts in DLB and that in AD, the changes would be more diffuse. By correlating the DTI changes with clinical features, we also aimed to provide further insights into the potential pathologic features underpinning the characteristic clinical and cognitive features observed.

METHODS Subject recruitment and assessment.

Seventy-one individuals over the age of 60 (36 subjects with probable AD¹⁰ and 35 with probable DLB¹¹) were recruited between November 2008 and September 2010 from a community-dwelling population of patients referred to local old age psychiatry, geriatric medicine, or neurology services. All subjects underwent clinical and neuropsychological evaluations with diagnostic procedures previously employed by our group.¹² Thirty-five control subjects were recruited from among relatives and friends of subjects with dementia or volunteered via advertisements in local community newsletters.

Assessment of global cognitive measures in all subjects (those with AD or DLB and controls) involved use of the Cambridge Cognitive Examination (CAMCOG), which incorporates the Mini-Mental State Examination (MMSE).¹³ Verbal episodic memory and visual episodic memory were assessed with the Hopkins Verbal Learning Test (HVLT) and Brief Visual Memory Task–Revised (BVMTR), respectively,^{14,15} and verbal fluency was assessed with the Delis Kaplan letter fluency task (FAS).¹⁶ Motor parkinsonism was assessed with the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III).¹⁷ For subjects with dementia, neuropsychiatric features were assessed with the Neu-

ropsychiatric Inventory (NPI),¹⁸ and function was assessed with the Bristol Activities of Daily Living.¹⁹

Standard protocol approvals, registrations, and patient consents. The research was approved by the local ethics committee. All subjects (or, where appropriate, their nearest relative) provided written informed consent.

MRI data acquisition. Subjects underwent MRI scanning on a 3T MRI system (Intera Achieva scanner, Philips Medical Systems, Eindhoven, Netherlands) with an 8-channel receiver head coil within 2 months of the study assessment. The MRI data for 3 subjects (one each in the AD, DLB, and control groups) were excluded because of motion artifact. For details on the DTI acquisition and preprocessing, see appendix e-1 on the *Neurology*[®] Web site at www.neurology.org.

TBSS. Voxelwise statistical analysis of the FA data were carried out with TBSS.²⁰ The steps involved are represented in figure e-1. All subjects' FA data were aligned to a 1-mm isotropic FA template in standard space. A mean FA skeleton representing the centers of all tracts common to the group was created by averaging the FA images and thresholding at FA >0.2 to exclude skeleton voxels, which may contain gray matter or CSF. Each subject's aligned FA data were then projected onto the mean FA skeleton. Resulting data were fed into voxelwise cross-subject statistics. Data for MD were also projected onto the mean skeleton by using nonlinear registration and projection vectors from the FA images.

Statistics. Demographic, clinical, and cognitive measures.

Group characteristics were evaluated with the Statistical Package for Social Sciences (SPSS, version 17). Differences in demographic and clinical data were assessed with use of either *t* tests or analysis of variance (ANOVA) for continuous variables and χ^2 tests for categorical measures. For each test statistic, a probability value of <0.05 was regarded as significant.

A composite score of episodic memory (verbal and visual) was derived to incorporate all aspects of the memory task. Normalized scores for each task component (total recall, delayed recall, and recognition) were derived with use of the control group as a reference, creating a *Z* score:

$$Z(\text{task component}) = (x_i - \mu_{\text{control}}) / S_{\text{control}}$$

where x_i = study participant's individual score, μ = control group mean, S = control group SD. The episodic memory composite was then calculated by adding the normalized *Z* scores of the 6 components (equal weighting).

DTI. Differences in DTI indices in the DLB and AD groups were compared with data for controls by means of a permutation-based, nonparametric, 2-sample, unpaired *t* test in the FSL randomize program. Age was included in the design matrix as a covariate (nuisance variable) in all analyses. Regression analysis was used to investigate the effects of clinical and neuropsychological measures on DTI parameters, with both age and MMSE included as nuisance variables. We generated 5,000 permutations of the data, producing statistical maps uncorrected and familywise error (FWE) corrected for multiple comparisons, which controls the rate of type 1 errors for all voxels collectively. Statistical maps were represented with use of either uncorrected ($p < 0.05$) or corrected ($p < 0.05$ or $p < 0.005$) thresholds. Cluster-like structures were enhanced with the threshold-free cluster enhancement algorithm (TFCE).²¹ The regions showing significant differences between groups were located and labeled anatomically by mapping the statistical map to the JHU DTI WM atlas in MNI space and Talairach atlas within the FSL atlas

Table 1 Demographic, clinical, and cognitive measures^a

Characteristic	DLB (n = 35)	AD (n = 36)	Controls (n = 35)	Statistical analysis
M:F (% female)	27:8 (23)	21:15 (42)	20:15 (43)	$\chi^2 = 3.85, p = 0.146^b$
Age, y	78.4 ± 6.9	78.3 ± 5.8	76.7 ± 5.2	$F_{2,105} = 0.80, p = 0.450^h$
Education, y	10.8 ± 2.6 ^c	11.1 ± 3.5	11.7 ± 2.6	$F_{2,104} = 0.98, p = 0.379^h$
MMSE	20.3 ± 5.3	19.5 ± 4.4	29.1 ± 1.0	$t_{69} = 0.71, p = 0.48^d$ (AD vs DLB)
CAMCOG total	67.7 ± 15.3	65.8 ± 12.1	97.3 ± 3.8	$t_{69} = 0.58, p = 0.566^d$ (AD vs DLB)
Episodic Memory Composite Score	-12.9 ± 5.6 ^e	-18.2 ± 2.8 ^e	0.0 ± 4.1	$t_{64} = 4.85, p < 0.001^{d,f}$ (AD vs DLB)
Letter fluency	20.8 ± 13.0	27.5 ± 14.3	41.0 ± 11.1	$t_{67} = 2.00, p = 0.049^{d,f}$ (AD vs DLB)
Bristol ADL	18.2 ± 9.6 ^e	14.1 ± 7.2 ^g	NA	$t_{66} = 2.02, p = 0.042^{d,f}$ (AD vs DLB)
NPI total	21.5 ± 17.1 ^e	16.8 ± 11.9 ^g	NA	$t_{66} = 1.30, p = 0.197^d$ (AD vs DLB)
UPDRS III	26.0 ± 10.7	5.4 ± 4.3	2.0 ± 1.9	$t_{69} = 10.6, p < 0.001^{d,f}$ (AD vs DLB)

Abbreviations: AD = Alzheimer disease; Bristol ADL = Bristol Activities of Daily Living; CAMCOG = Cambridge Cognitive Examination; DLB = dementia with Lewy bodies; NA = not applicable; NPI = Neuropsychiatric Inventory; MMSE = Mini-Mental State Examination; UPDRS III = Unified Parkinson's Disease Rating Scale, Part III.

^a Values are expressed as mean ± 1 SD.

^b χ^2 = DLB, AD, controls.

^c No. = 34.

^d Student t test = AD and DLB.

^e No. = 33.

^f Significant.

^g No. = 35.

^h Analysis of variance = DLB, AD, controls.

toolbox. The figures show DTI results overlaid onto the MNI template image and mean FA skeleton.

RESULTS Subject demographics. The demographic data for patients and control subjects are summarized in table 1. Subject groups were well matched for age and educational level, and the AD and DLB group mean CAMCOG and MMSE scores were comparable. The DLB group's episodic memory composite score was higher than that of the AD group, whereas the letter fluency score in DLB was significantly lower than in AD. The DLB group had slightly more functional impairment and significantly higher UPDRS-III scores than the subjects with AD.

Fractional anisotropy. Areas of significantly reduced FA in DLB and AD vs controls are represented in figure 1, A and B, respectively. In DLB, change was identified predominantly in the parieto-occipital white matter tracts, with relative sparing of the frontal areas. In AD, however, areas of reduced FA (vs controls) were more widespread and included involvement of the white matter tracts of the frontal lobes. To highlight the differing patterns further, we reviewed the ratio of suprathreshold voxels in the anterior vs posterior regions of the white matter tract skeleton, as defined by the central sulcus. The proportion of significant voxels affecting posterior regions was 21.0% in DLB and 38.5% in AD, and that affecting frontal regions was 3.2% in DLB and

33.6% in AD. Therefore, the posterior-to-anterior (% posterior to % anterior) ratio of affected voxels was 6.5 in DLB and 1.1 in AD (table 2).

Direct statistical comparison of the FA data between groups is presented in figure 1, C and D.

Mean diffusivity. Results for increased MD in the dementia groups vs controls were more extensive and statistically significant than observed for reduced FA in both groups (figure 2). In comparison with controls, areas of significant MD increase in DLB were global and included areas of the brainstem, thalamus, cingulate, and temporal, parieto-occipital, and frontal lobes. These areas were also affected in the AD group in comparison with controls.

Correlations with clinical features. Episodic memory. A significant correlation between impaired episodic memory and increased MD was regionally similar in both AD and DLB and included clusters in the bilateral parahippocampal gyri (hippocampal cingulum) and left cingulate gyrus (frontal) (figure 3, A and B). We did not find a correlation between FA and episodic memory in AD or DLB.

Letter fluency. The relationship between FA and letter fluency in DLB ($p < 0.05$, corrected) was significant and involved predominantly bilateral frontal, parietal, and subcortical structures (figure 3C) and was not found in AD. A relationship between MD and letter fluency was also observed in DLB

Figure 1 Tract-based spatial statistics maps indicating areas of reduced fractional anisotropy (FA) (blue) in dementia with Lewy bodies (DLB) and Alzheimer disease (AD) (blue), overlaid onto the Montreal Neurological Institute template image and mean FA skeleton (green)

(A) DLB vs controls: change was identified mainly in the parieto-occipital areas (precuneal and cingulate gyri). Reduced FA in the temporal lobes was in a region of the posterior thalamic radiation that included the optic radiation ($p < 0.05$, corrected). (B) AD vs controls: change was more widespread than in DLB and included clusters in the temporal, parieto-occipital, and frontal lobes ($p < 0.05$, corrected). (C) DLB vs AD: reduced FA in the pons and left thalamus ($p < 0.05$). (D) AD vs DLB: small clusters of reduced FA in the parahippocampal gyri, frontal lobes, and fornix ($p < 0.05$).

(figure 3D) in subcortical structures, including areas of the brainstem, striatum, and white matter tracts of the precuneus (parietal), precentral gyrus (frontal), and corpus callosum (parietal).

Motor parkinsonism (UPDRS-III). We found a correlation ($p < 0.05$, uncorrected) between higher UPDRS-III scores and reduced FA in subcortical structures, including the thalami, pons, and medulla, as well as the precentral gyrus (figure 3E). Other small clusters were found in the occipital, parietal, and temporal lobes, which included the precuneus and postcentral gyrus.

DISCUSSION DLB was characterized by a pattern of posterior predominance in FA change, with involvement of the parieto-occipital and temporal white matter tracts and relative sparing of the frontal lobes. Although these areas were also involved in AD, they were part of a more generalized pattern of change rather than preferential involvement, as highlighted by the much greater ratio of posterior-to-anterior suprathreshold voxels in DLB. These areas are important for visual information processing, and given that characteristic features of DLB are recurrent

Table 2 No. (%) of suprathreshold voxels ($p < 0.05$, familywise error corrected) in DLB and AD, compared with controls

	No. of voxels		
	Anterior tract skeleton (total = 24,723)	Posterior tract skeleton (total = 32,031)	Posterior: anterior ratio
DLB	802 (3.24)	6,732 (21.02)	6.5
AD	8,298 (33.56)	12,338 (38.52)	1.1

Abbreviations: AD = Alzheimer disease; DLB = dementia with Lewy bodies.

^a The anterior and posterior regions of the tract-based spatial statistics white matter tract skeleton were defined by the central sulcus in order to obtain a posterior:anterior (% posterior to % anterior) ratio of suprathreshold voxels in each group.

visual hallucinations as well as early visuo-perceptual deficits, it was of great interest that these areas were affected.¹¹ Previous DTI studies using ROI methods have found reductions of FA in the precuneus occipital areas and ILF in DLB.^{3,5,7} SPECT studies have also revealed precuneal and occipital hypoperfusion,²² and PET studies have revealed occipital hypometabolism,²³ without associated structural gray matter loss of sufficient magnitude to explain this.²⁴ Therefore, it is possible that the functional imaging changes reflect damage to the microstructural white matter connections, supporting the notion that DLB is a disease predominantly caused by neuronal synaptic dysfunction rather than loss.

We have previously reported the patterns of gray matter atrophy in this group¹² and found very few areas of significant volume loss in DLB when compared to controls. Interestingly, there was a trend toward a posterior pattern of atrophy in DLB, although this did not reach statistical significance. It is unlikely that such an effect size would account for the highly significant pattern of parieto-occipital FA change.¹² Therefore, white matter tract degeneration may be a more sensitive marker and a more prominent feature of DLB, and longitudinal studies are needed to help address this.

It is also important to note that TBSS is biased toward the central white matter tracts and less sensitive to peripheral white matter tracts. This may have also contributed to the less prominent FA changes in the temporal regions in DLB as compared with the parieto-occipital regions in DLB, but it is unlikely to significantly influence frontal white matter tract change.²⁵

In contrast to the regional FA changes, the average diffusion was increased in white matter tracts in both anterior and posterior regions in DLB. Although MD and FA are related parameters, they describe differing diffusion processes. MD represents

the total or average diffusivity of the component eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) and therefore provides a generalized measure (scalar quantity) of diffusion in a voxel and is nonspecific regarding the directionality of the diffusion process. However, FA can be regarded as a weighted average of the component eigenvalues, dominated by the largest component, and largely depends on the anisotropic nature of the diffusion process. Therefore, our results suggest that in DLB, total diffusivity is a global effect, whereas diffusion in the posterior white matter tracts is more isotropic (less directional), possibly indicating more severe tract abnormalities in these regions. In the frontal areas, diffusion is less isotropic (more directional), possibly indicating less severe tract abnormality. It is possible that changes in FA may become more generalized as disease progresses, in a similar pattern to the MD changes observed. Longitudinal studies are needed to monitor disease progression, and pathologic correlational studies may assist in our understanding of the mechanisms of DTI change.

TBSS represents a significant methodologic improvement in voxelwise analysis of DTI data; however, partial volume effects of CSF on MD (and associated eigenvalues) remain problematic. Recently, it has been shown that in atrophy-prone areas (particularly in older adults), the FA data are a more reliable measure and not as prone to the partial volume effects.⁹ Improvements in methods to better control for the effects of CSF contamination (on a voxelwise level) are needed and will help us to better understand these discrepancies. Interpretation of these changes must therefore be with the important caveat that atrophy may also be contributing to more extensive MD change.

We found reduced FA in the white matter in the region of the left thalamus in DLB when compared with AD. Structural imaging studies have not found significant change in the thalamus in DLB,²⁶ whereas functional imaging studies using SPECT have revealed increased thalamic perfusion and a pattern of covariance with occipital hypoperfusion in DLB.²⁷ It is possible that microstructural change causes an alteration in the neurotransmitter or receptor status, with resultant perfusion changes, in DLB.

More extensive microstructural change in the temporal lobes was found in AD, particularly in the medial temporal lobe structures. This is consistent with the known pathologic change in the area and the early and characteristic impairment of episodic memory.²⁸ This differs from DLB, in which episodic memory is usually not as profoundly affected and relative preservation of the medial temporal lobe in structural imaging has been well-established.¹¹ However, partial volume effects of CSF in atrophic areas

Figure 2 Tract-based spatial statistics maps indicating areas of increased mean diffusivity (red) in (A) dementia with Lewy bodies (DLB) and (B) Alzheimer disease (AD), overlaid onto the Montreal Neurological Institute template image and mean fractional anisotropy (FA) skeleton (green)

In DLB, changes were global and included areas of the brainstem, thalamus, cingulate, temporal, parieto-occipital, and frontal lobes ($p < 0.005$, corrected). These areas were also affected in AD compared with controls with more extensive involvement of the temporal lobes ($p < 0.005$, corrected).

may also explain the differences observed, with less prominent change seen in DLB.

We found that the episodic memory composite score and medial temporal white matter tract change appear to be associated in both AD and DLB. Additional analysis (data not reported), including measures of hippocampal volume as a covariate, did not change this correlation, suggesting that this finding is related to white matter change rather than to gray matter atrophy. Given that the DLB group performed better than the AD group on tests of episodic memory and showed less DTI change in the medial temporal lobe structures, and that the medial temporal lobe change correlated with episodic memory in both groups, it is possible that microstructural change in this region may be related to Alzheimer pathology.

Patients with DLB usually have more difficulty than patients with AD with tasks involving executive function rather than memory, which may be due to the impairment in striatal function and dopaminergic deficiency. However, the functional connections involved in tasks of executive function are much more complex, and some studies have indicated that input from parietal, occipital, and temporal lobes is required, depending on the task demand.²⁹

We found a relationship between reduced FA and increased MD and the letter fluency task in DLB, which involved frontal (prefrontal cortex) and parietal lobes, the anterior cingulate, and subcortical structures. Given that both age and MMSE were included in the analysis design as covariates, these findings suggest that impaired verbal fluency may be associated with white matter tract degeneration and

Figure 3 Correlations of diffusion tensor imaging (DTI) parameters with clinical features

Relationship between episodic memory composite score and mean diffusivity in (A) Alzheimer disease (AD) (blue, $p < 0.05$, uncorrected) and (B) dementia with Lewy bodies (DLB) (pink, $p < 0.05$, uncorrected); (C, D), letter fluency and DTI indices (yellow, $p < 0.05$, corrected); (E) Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) and reduced fractional anisotropy (FA) (purple, $p < 0.05$, uncorrected). All results are overlaid onto the Montreal Neurological Institute template image and FA skeleton (green).

may not be driven by global cognitive impairment. In AD, although task performance was impaired, no correlation was found with reduced FA, which may suggest differing pathologic mechanisms underpinning executive dysfunction.

The UPDRS-III correlated with reduced FA in white matter tracts of the motor areas as well as subcortical structures in DLB. Motor parkinsonism in DLB is largely a result of abnormalities in the basal ganglia, with degeneration of dopaminergic neurons and striatal dopamine deficiency. The parietal and occipital areas have also been found to be activated during motor tasks in patients with parkinsonism, suggesting a compensatory mechanism.³⁰ PET studies in PD have demonstrated a positive correlation between UPDRS and metabolic change in the primary motor cortex and supplementary motor areas,³¹ and longitudinal studies have also revealed a progressive increase in the metabolic activity of subcortical structures and motor cortex.³² A SPECT study that compared patients with DLB with and without parkinsonism found that those with parkinsonism had reduced blood flow in the primary and supplementary motor areas.³³ A relatively small DTI study using VBM analysis techniques in PD reported significant FA reduction in the supplementary motor areas and anterior cingulate.³⁴ These findings highlight the importance of these areas in the pathogenesis of parkinsonism and, along with our findings, perhaps suggest a more complex mechanism for the motor symptoms in DLB, with disruption in the white matter in these compensatory (or secondary) regions leading to more prominent motor features.

This study included a large, well-characterized group of subjects with DLB. The groups were well matched for age, level of education, and dementia severity. However, there was a slight male predominance, as expected, in the DLB group. Although it is not yet clear what effect gender has on DTI changes in neurodegenerative disease, it is an important consideration in study design and is potentially a limitation of our study. All subjects met criteria for probable AD (1984 criteria)¹⁰ and probable AD dementia (2011 criteria).³⁵ The study subjects were recruited and assessed prior to the publication of the revised AD criteria,³⁵ so we are unable to adequately classify the groups based on "evidence of AD pathophysiological process." However, 33 of the AD group had MTA, as assessed by a visual rating scale,³⁶ indicating that 92% had evidence of the AD pathophysiological process.³⁵⁻³⁶ The reliance on the clinical diagnosis is also a limitation, as with all antemortem imaging studies.

AUTHOR CONTRIBUTIONS

R.W. designed the study, recruited and assessed study participants (including subject diagnostic rating), carried out the statistical analysis, and wrote the manuscript. A.M.B. codesigned the study, assisted with data interpretation, assisted with writing and revising of the manuscript, and obtained funding for the project. S.J.C. assisted in the study design and statistical analysis and reviewed the manuscript. J.S.W. assisted with assessment of study participants and reviewed the manuscript. R.B. participated in the subject diagnostic rating and reviewed the manuscript. J.H. was involved with design of the imaging protocol and reviewed the manuscript. J.T.O. codesigned the study, provided subject diagnostic rating, assisted with the development of the research question and with writing and revising of the manuscript, and obtained funding for the project.

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DISCLOSURE

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