Journal of Clinical and Experimental Neuropsychology

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ncen20

Regional differences in relationships between apparent white matter integrity, cognition and mood in patients with ischemic stroke

John Williamson [a], David Nyenhuis [b], Glenn T. Stebbins [c], Damon Lamb [d], Vaidas Simkus [b], Kumar Sripathirathan [c], Changsheng Wang [c], Leyla deToledo-Morrell [c] & Philip Gorelick [b]

[a] Department of Neurology, University of Florida, Gainesville, FL, USA

[b] Center for Stroke Research, Department of Neurology, University of Illinois at Chicago, Chicago, IL, USA

[c] Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA

[d] Department of Biology, Emory University, Atlanta, GA, USA

Available online: 10 Feb 2010

To cite this article: John Williamson, David Nyenhuis, Glenn T. Stebbins, Damon Lamb, Vaidas Simkus, Kumar Sripathirathan, Changsheng Wang, Leyla deToledo-Morrell & Philip Gorelick (2010): Regional differences in relationships between apparent white matter integrity, cognition and mood in patients with ischemic stroke, Journal of Clinical and Experimental Neuropsychology, 32:7, 673-681

To link to this article: http://dx.doi.org/10.1080/13803390903427406

JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY
2010, 32 (7), 673–681

Psychology Press
Taylor & Francis Group

Regional differences in relationships between apparent white matter integrity, cognition and mood in patients with ischemic stroke

John Williamson,[1] David Nyenhuis,[2] Glenn T. Stebbins,[3] Damon Lamb,[4] Vaidas Simkus,[2] Kumar Sripathirathan,[3] Changsheng Wang,[3] Leyla de Toledo-Morrell,[3] and Philip Gorelick[2]

[1]Department of Neurology, University of Florida, Gainesville, FL, USA
[2]Center for Stroke Research, Department of Neurology, University of Illinois at Chicago, Chicago, IL, USA
[3]Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA
[4]Department of Biology, Emory University, Atlanta, GA, USA

White matter changes are one potential etiology of behavioral changes in cerebrovascular disease. Whole brain diffusion tensor imaging–fractional anisotropy (DTI-FA) as a measure of apparent white matter integrity is related to cognitive function in cerebrovascular disease. However, white matter changes are not uniform, nor are their effects. We examine the relationship between regional differences in DTI-FA and cognition and mood in an ischemic-stroke sample. Participants were 108 patients, 3–6 months post stroke. Working memory, basic attention, recall, language, visuo-spatial, psychomotor, and encoding skills, and mood were assessed via neuropsychological evaluation. DTI scans were performed on a 1.5T GE magnetic resonance imaging (MRI) system. Fractional anisotropy (FA) was calculated for frontal, temporal, occipital, and parietal regions using automated masks. Frontal and parietal FAs were more strongly and consistently related to cognitive and mood scores than were FA values from whole brain or temporal or occipital regions. This research contributes to our understanding of the etiology of cognitive and mood deficits in cerebrovascular disease.

Keywords: Affect; Diffusion tensor imaging; Regions of interest; Stroke; White matter disease.

INTRODUCTION

Cerebrovascular disease is among the leading causes of late-life dementia and cognitive impairment in the United States and Western Europe (Gorelick et al., 1994a). There are multiple mechanisms of cognitive impairment in cerebrovascular disease including the lesion size, location, and number and type of damaged brain tissues (e.g., gray or white matter) involved. There are several subtypes of cognitive changes due to cerebrovascular disease, the most common of which may be driven by small-vessel ischemic disease and white matter changes (O'Brien, 2006).

Two common threads in the exploration of neuropsychological profiles in cerebrovascular disease are prominent deterioration of executive functions (Boyle et al., 2003; Desmond, 2004; Kramer et al., 2002; Pohjasvaara et al., 2002; Román & Royall, 1999) and behavioral disruption (e.g., vascular depression hypothesis; Alexopoulos et al., 1998). The reason for this may be the contribution of pathways involving frontal lobe connections. A recent neuroimaging study of white matter disease in vascular dementia (VaD) demonstrated preferential damage of frontal white matter (Gootjes et al., 2004), illustrating a potential direct explanation of disease–behavior interaction. Further, another study, using volumetric measures of magnetic resonance imaging (MRI) and regional positron emission tomography (PET) glucose metabolism in cerebral cortex, showed hypometabolism in the frontal

This work is supported by National Institute on Aging (NIA; R01 AG17934), Principal Investigator: PG (2000–2003) and DN (2003–2006).

Address correspondence to John Williamson, Department of Neurology, McKnight Brain Institute of the University of Florida Dept. of Neurology, PO Box 100236, Gainesville, FL 32610–0236, USA (E-mail: john.williamson@neurology.ufl.edu).

http://www.psypress.com/jcen
DOI: 10.1080/13803390903427406

cortex regardless of region of detected white matter hyperintensities and also reported significantly higher frequency of white matter hyperintensities in the prefrontal region than in other brain regions. No relationship was found between white matter hyperintensities in any region of the brain and altered metabolism in parietal or occipitotemporal regions (Tullberg et al., 2004).

Though the literature on cognitive deficits in cerebrovascular disease emphasizes executive functions, additional domains are affected. Nyenhuis at al. (2004) report immediate memory, psychomotor slowing, and depressed mood in a poststroke sample: $n = 41$, vascular cognitive impairment–no dementia (vascular CIND); $n = 62$, poststroke no cognitive impairment. Garrett et al. (2004) report changes in cognitive flexibility, verbal recall, and recognition as a function of cerebrovascular disease ($n = 18$, vascular CIND; $n = 25$, healthy; $n = 29$, high risk; and $n = 26$, VaD).

Both executive dysfunction and emotional changes in cerebrovascular disease likely are related to multiple processes including subcortical white matter damage, presumably caused by small-vessel ischemic disease (Pantoni & Garcia, 1997), and specific subcortical and cortical infarcts (e.g., Annoni et al., 2003, demonstrated executive dysfunction with right laterothalamic dysfunction, hypothesizing disruption of fronto-thalamic connections). Moser et al. (2001) point out that vascular pathologies show a preference for frontal-subcortical regions.

Structural MRI techniques are sensitive to cognitive impairment and mood in cerebrovascular disease. There is an increased prevalence of white matter hyperintensities in depression (Jorm et al., 2005). To explore the hypothesis that white matter damage is a potential etiology of depression rather than a proxy for overall cerebrovascular disease, the Leukoaraiosis and Disability Study (LADIS) examined the impact of lacunes and regional white matter hyperintensities (O'Brien et al., 2006). The investigators found that frontal and temporal white matter hyperintensities were most strongly related with depression scores (Geriatric Depression Inventory) and independent of lacunar infarction.

In a study of 46 postlacunar stroke patients, McMurtray, Liao, Haider, Licht, and Mendez (2007) demonstrated decreased cognitive performance across several domains, including overall function, language fluency, and both verbal and nonverbal memory as a function of severity of leukoaraiosis (visually identified). In another study, only frontal/executive functions were found to be influenced by severity of white matter disease (Wen et al., 2004).

Diffusion tensor imaging is increasingly used in studies of cerebrovascular disease and aging, and preliminary results are promising. Head et al. (2004) demonstrated differential vulnerability of frontal lobe white matter in nondemented aging using diffusion tensor imaging–fractional anisotropy (DTI-FA). DTI-FA correlated positively with gray matter thickness and negatively with hyperintensity volumes, with late myelinating tracts more strongly associated (Kochunov et al., 2007), demonstrating expected relationships with accepted measures of general cerebral health. Significant correlations between DTI-FA values and cognitive impairment in cerebral small-vessel disease have also been demonstrated. O'Sullivan et al. (2004) present evidence that diffusion tensor MRI is more sensitive to cognitive changes than are traditional MRI approaches. Though no DTI studies exist specifically examining stroke and mood relationships, differences in apparent white matter integrity (DTI-FA) in frontal and temporal regions of healthy elderly participants have been related to depression (Yang, Xuebing, Hong, & Yu, 2007).

There is a relative dearth of DTI studies of cognition and mood in the same sample of patients with cerebrovascular disease. In addition to studying the impact of regional changes in fractional anisotropy on measures of cognition and mood in cerebrovascular disease, our study aims to address the utility of automated region of interest DTI-FA maps. Imaging methods are commonly used in epidemiological studies of cerebrovascular disease. However, manually based region of interest analyses can be cost prohibitive due to time and implementation issues. Automated regions of interest offer a compromise that may allow for greater sensitivity and application of imaging technologies in these populations without a significant time cost.

We ask the following questions. First, can large regions of interest (lobar masks) functionally discriminate between cognitive and emotion data? Given previous research on vascular cognitive impairment and vascular depression, along with imaging data showing preferential damage of fronto-subcortical white matter in cerebrovascular disease, it is important to understand the relationship of regional white matter integrity deterioration to cognitive and emotion functions in this population. Second, do region of interest analyses offer additional qualitative data to whole brain approaches in this population? It is possible that relying on whole brain white matter integrity in epidemiological studies of vascular based cognitive and mood changes may mask relationships and may be potentially misleading. Further, understanding regional relationships as a function of disease processes may yield further insight into how functional systems in complex cognitive and mood behaviors are impacted.

METHOD

Participants

Study participants were selected from the Risk Markers for Dementia after Stroke (RMDAS) sample. RMDAS is a longitudinal study of 116 ischemic stroke patients with baseline and annual neuropsychological and imaging examinations (Nyenhuis et al., 2004; Wang et al., 2006). A total of 108 had complete DTI-FA datasets and were used for analyses in this study. Participants were consecutive patients with ischemic strokes within three to six months of enrollment seen at Rush University. RMDAS exclusion criteria included severe aphasia (≤50% on the Boston Diagnostic Aphasia Examination

Commands subtest) or severe dementia (Mini-Mental State Examination, MMSE score < 10); prior dementing or degenerative neurological disease other than stroke; epilepsy; current psychiatric illness; or an inability to complete brain MRI. Patients with temporal lobe strokes were also excluded to increase our ability to compare results against Alzheimer's disease data. The Institutional Review Boards (IRBs) at Rush University Medical Center and at the University of Illinois approved all study procedures, and written informed consent was obtained from all patients.

Clinical and epidemiological evaluation

Participants were rated for stroke severity (National Institute of Neurological Disorders and Stroke, NINDS, Stroke Data Bank Stroke Severity Scale; National Institutes of Health, NIH, Stroke Scale: Brott et al., 1989; Foulkes et al., 1988) and underwent structured and unstructured interviews to assess prior stroke history and history and symptoms of cognitive dysfunction. The Epidemiological Risk Factor Questionnaire (Gorelick et al., 1994) was used to assess demographic factors and known and potential risk factors for ischemic stroke and dementia.

Neuropsychological evaluation

A 60–90-min neuropsychological examination (Table 1) was administered to each participant. Cognitive tests were grouped into the following domains based on test content: basic attention, working memory, language, visuospatial skills, psychomotor skills, immediate memory, delayed memory, and recognition memory. Correlational analyses showed higher intradomain than interdomain test correlations, supporting the test classification method (Nyenhuis et al., 2004).

To allow for interdomain comparison, a principal component (PC) score was calculated for each domain, based on all participants' test scores in that domain. PC scores were set to have a mean of zero and a standard deviation of one. For domains with a single variable, the score was simply that variable standardized. For domains with two variables, both variables were first standardized and then weighted equally to form a *z* score. For domains with more than two variables, the first principal component score provided optimal weights with each succeeding component accounting for the remaining variability to produce a score that captured the most variation possible (see Nyenhuis et al., 2004, for an example application).

Mood and behavior variables were assessed with two self/observer report scales; the Chicago Multiscale Depression Inventory (CMDI; Nyenhuis et al., 1998) and the Frontal Systems Behavior Scale, Informant Version (FrSBe; Grace and Malloy, 2001). The CMDI is a depression symptom measure developed to parse out mood from physiological symptoms that may confound the measurement of depression in neurological patient groups. The FrSBe examines neurobehavioral changes in the areas of disinhibition, dysexecutive function, and apathy.

Imaging

All participants underwent magnetic resonance imaging (MRI) examination according to the following protocol:

TABLE 1
Neuropsychological assessment instruments listed by domain

Domain	*Instrument*	*Reference*
Basic attention	Digits Forward	Wechsler, 1997
	Wechsler Memory Scale Mental Control	Wechsler, 1945
Working memory	Self-Ordered Pointing Test Total Score	Shimamura & Jurica, 1994
	Digit Span Backward	Wechsler, 1997
	Behavioral Dyscontrol Scale	Grisby & Kaye, 1996
Language	Boston Diagnostic Aphasia Examination, Commands subtest	Goodglass & Kaplan 1989
	Boston Naming Test	Goodglass & Kaplan 1989
	Semantic Fluency, Animal Naming	Morris et al., 1989
Spatial	Figure Recognition Test	Scherr et al., 1988
	Ravens Progressive Matrices	Raven 1995
Psychomotor	Grooved Pegboard	Russell & Starkey, 1993
	Symbol Digit Modalities Test, Oral subtest	Smith, 1991
Memory: immediate	Controlled Learning and Enhanced Recall Total	Buschke & Grober, 1986
	Wechsler Memory Scale–III, Logical Memory Immediate, paragraph 1	Wechsler, 1997
Memory: delayed	Controlled Learning and Enhanced Recall Delayed Recall	Buschke & Grober, 1986
	Wechsler Memory Scale–III Logical Memory Delayed Recall, para 1	Wechsler, 1997
Memory: recognition	Controlled Learning and Enhanced Recall Delayed Recognition	Buschke & Grober, 1986
Behavior: depression, executive function, disinhibition, and apathy	Chicago Multiscale Depression Inventory	Nyenhuis et al., 1998
	Frontal Systems Behavioral Scale; Informant Version	Grace & Malloy, 2001

Image acquisition

Axial scout images using a short time to repetition (TR); short echo time (TE; T1-weighted) gradient-echo pulse sequence; T1 weighted 3D spoiled gradient recalled (SPGR; 124 slices, coronal acquisition, in-plane acquisition matrix = 256 × 192, slice thickness = 1.6 mm, gap = 0, field of view, FOV = 22 × 22, TR/TE = 34/7, flip angle = 35 degrees, 1 NEX); and T2 weighted 3D SPGR (coronal acquisition, in-plane acquisition matrix = 256 × 144, slice thickness = 1.5 mm, gap = 0, FOV = 26 × 19.5, TR/TE = 2,625/110, echo train length, ETL = 32, bandwidth = 62.5 kHz, flip angle = 35 degrees, 2 NEX) were acquired on a GE 1.5 Tesla imaging system (Signa, General Electric Medical Systems, Milwaukee, WI) with XL high-speed gradients (Rev 10) in a single session.

Diffusion tensor weighted imaging scans included an axial diffusion weighted single shot spin echo, echo planar scan (FOV = 24 cm, 128 × 128, zero filled to 256 × 256, 19 slices, 6 mm thick, 0 gap) acquired at the same locations as the in-plane structural images. Two *b*-values were used, $b = 0$ s/mm^2 and a high b-value ($b = 800$ s/mm^2). The high *b*-value was obtained by applying gradients along two axes simultaneously according to the following pattern that yields measurements along six noncollinear directions: (x, y, z) = [(1, 1, 0), (0, 1, 1), (1, 0, 1), (–1, 1, 0), (0, –1, 1), (1, 0, –1)]. This was repeated four times for each slice, with the sign of all of the gradients inverted for two of the repetitions. The magnitude images were averaged prior to calculation of the apparent diffusion coefficients (ADCs); this approach eliminates cross-terms with imaging gradients. An additional set of inversion recovery images with cerebrospinal fluid nulling (TI ~ 2,100 ms) was acquired for each slice with $b = 0$ s/mm^2. These images were used to unwrap the eddy current effect of the diffusion gradients in the diffusion weighted images prior to ADC calculations. From the averaged and unwarped diffusion weighted images, six ADCs were calculated, from which the six independent elements of the diffusion tensor were determined for each voxel. As an estimate of white matter integrity, a fractional anisotropy (FA) value was calculated as follows: From the diffusion tensor in each voxel, three eigenvectors were derived, defining the direction of the diffusion system, with the corresponding eigenvalues. Based on the three eigenvalues and the mean eigenvalue, the anisotropy was measured as FA, yielding values between 0 and 1.

Region of interest derivation

Region of interest (ROI) masks were generated for frontal, parietal, temporal, and occipital regions using the Wake Forest University Pick Atlas plugin for SPM2 (Statistical Parametric Mapping). The Wake Forest Pick Atlas (Maldjian, Laurienti, Kraft, & Burdette, 2003) is a tool for creating ROI masks using normalized brain template regions. The atlas has been successfully used in a diverse range of ROI studies (e.g., Newman, Trivedi, Bendlin, Ries, & Johnson, 2007; Woolley et al., 2007). These masks were then applied to each image using an automated MatLab script to overlay the ROIs and extract the FA volumes.

Lesion identification

Ischemic strokes were identified by the study neuroradiologist and a neuroradiological fellow working under her supervision, consistent with the Cardiovascular Health Study (Manolio et al., 1994) criteria for image analysis. Images consisted of T1- and T2-weighted images reformatted to 6-mm slices reconstructed in the axial plane and standardized to the anterior commissure–posterior commissure (AC–PC) axis. Strokes were defined as lesions greater than 3 mm in maximum antero-posterior or lateral dimension. Clear boundaries as indicated by hyperintensities on T2-weighted images when involving the cortex or deep nuclear regions (basal ganglia and thalamus) and by hypointensities on T1-weighted images when involving the white matter, and with no mass effect while also presenting in a definable vascular distribution, were required. Further, lesions were coded for location (cortical, subcortical white matter, deep gray structures, infratentorial), side (right, left, bilateral, midline), and size.

Stroke volumes

Ischemic strokes were outlined based on involvement in T2-weighted images (anatomical determination referenced to T1-weighted images). Areas were calculated, multiplied by slice thickness, and summed over consecutive involved slices, to yield a volume measurement for each identified lesion. Lesion volumes were then summed to arrive at a total stroke volume for each patient. The Analyze software package (Mayo Clinic; http://www.mayo.edu/bir/Software/Analyze/Analyze.html) was used to do tracings and generate volumes.

Statistical methods

Two sets of multivariate stepwise linear regressions were calculated for each mask and the cognitive principal component scores as well as the subscales of the FrSBe and CMDI. In the first model, to account for the impact of stroke factors on the relationship of regional white matter integrity to cognition and emotion, stroke volume, total number of strokes, any left hemisphere strokes, and ventricle to brain ratio were entered in the first step (forced), and the five white matter masks were entered in the second step (stepwise). The second model was designed to account for changes in the relationship of white matter to cognition and emotion as a function of age. Age was entered (forced) into the first stage, and the white matter regions were entered into the second step (stepwise). These models were run separately for purposes of interpretation.

RESULTS

Patient characteristics and demographics

Measures of functional impairment (e.g., Stroke Severity Score), demographic data (e.g., age, education, sex), and mental status (MMSE) are summarized in Table 2. Stroke characteristics of the sample including total number of strokes, stroke volumes, and stroke locations

TABLE 2
Descriptive statistics, stroke severity, and mental status

Characteristic	*Mean*
Age (years)	65.04 ± 9.006
Education (years)	13.93 ± 3.779
Gender: % male	50.9
Stroke Severity Scale	1.67 ± 1.970
MMSE	27.23 ± 2.965

Note. MMSE = Mini-Mental State Examination. Means and standard deviations are shown, except for gender, for which percentage male is shown.

TABLE 3
Stroke characteristics

Demographics	*Mean ± SD*
Stroke volume	9,148.62 ± 1,744.291
No. of strokes	1.74 ± 1.978
No. of cortical strokes	0.48 ± 0.872
No. of subcortical strokes	0.46 ± 0.501

are reported in Table 3. It should be noted that some participants did not have complete neuroimaging protocols, and therefore only 107 participants were used in this analysis.

ROI FA scores, neuropsychological PC scores, and mood data

Zero-order correlations between the cognitive and mood scores, the whole brain FA score, and each of the regional FA scores are listed in Table 4. The whole brain FA score is significantly correlated with 6 of the 7 cognitive domain scores and 3 of the 6 mood measures. Of the 13 cognitive and behavioral domains, whole brain FA is the most highly correlated FA score with only 1: the CMDI vegetative subscore.

Correlations of the ROIs to the cognitive and mood data reveal generally greater sensitivity of the parietal and frontal masks. The parietal FA score is significantly correlated with all seven cognitive domain scores and with three of the six mood/behavior measures. It shares the highest correlation with cognitive scores in six of the seven cognitive domains. The frontal FA score is significantly correlated with six of the seven cognitive domain scores and four of the six mood measures. It has the highest correlation with one of the cognitive domains, psychomotor speed, and three of the six mood measures. The temporal ROI FA scores are significantly correlated with six of the seven cognitive domain measures and none of the mood measures, while the occipital ROI FA score correlated only with the psychomotor domain score and none of the mood measures.

Multivariate stepwise linear regressions controlling for stroke factors, stroke volume, total number of strokes, and ventricle to brain ratio, reveal significant additional variance accounted for by the region of interest masks. Specifically, the parietal FA mask is a significant predictor, when accounting for stroke variables, for basic attention ($B = .259$, $p < .05$), working memory ($B = .367$, $p < .05$), language ($B = .393$, $p < .05$), spatial ($B = .433$, $p < .05$), psychomotor ($B = .386$, $p < .05$), encoding ($B = .446$, $p < .05$), and recall ($B = .517$, $p < .05$) skills. The frontal FA mask is a significant predictor for FrSBe apathy ($B = –.258$, $p < .05$), CMDI vegetative ($B = –.333$, $p < .05$), CMDI evaluative ($B = –.355$, $p < .05$), and CMDI mood ($B = –.359$, $p < .05$) symptoms. Partial correlations

TABLE 4
Bivariate correlations of FA masks and cognitive and behavioral performance

	Mask				
Cognitive/behavioral domain	*Whole brain*	*Frontal*	*Temporal*	*Parietal*	*Occipital*
Basic attention	*ns*	*ns*	*ns*	.203*	*ns*
Working memory	.314*	.339*	.317*	.342*	*ns*
Language	.257*	.328*	.272*	.387*	*ns*
Spatial	.353*	.399*	.332*	.433*	*ns*
Psychomotor	.356*	.444*	.352*	.395*	.249*
Encoding memory	.263*	.204*	.319*	.325*	*ns*
Recall memory	.251*	*ns*	.309*	.340*	*ns*
FrSBe: Disinhibition	*ns*	*ns*	*ns*	*ns*	*ns*
FrSBe: Disexecutive	*ns*	*ns*	*ns*	*ns*	*ns*
FrSBe: Apathy	*ns*	–.210*	*ns*	*ns*	*ns*
CMDI: Mood	–.288*	–.297*	*ns*	–.226*	*ns*
CMDI: Evaluative	–.291*	–.304*	*ns*	–.245*	*ns*
CMDI: Vegetative	–.309*	–.299*	*ns*	–.225*	*ns*

Note. FA = fractional anisotropy. FrSBe = Frontal Systems Behavior Scale, Informant Version. CMDI = Chicago Multiscale Depression Inventory.
*<.05, only significant correlations reported, *ns* = not significant.

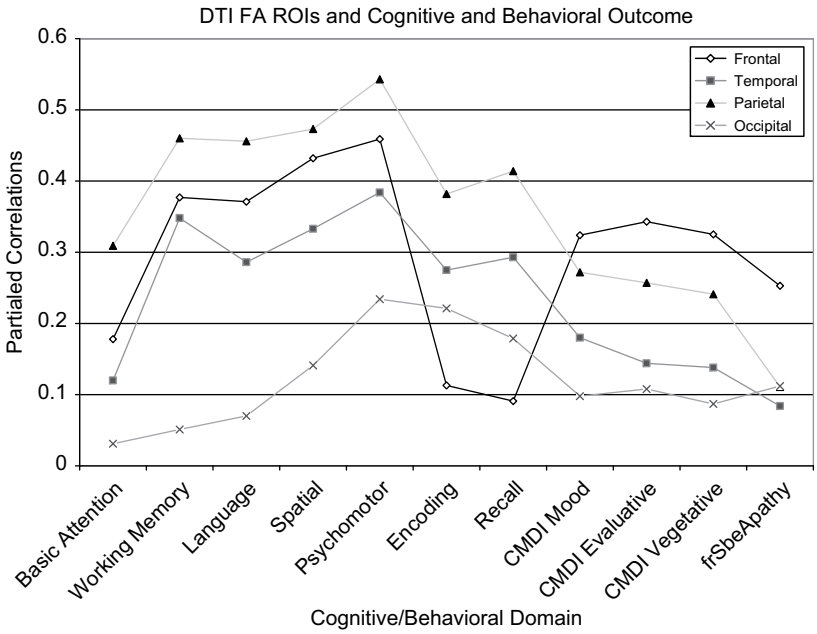

Figure 1. Partial correlations of diffusion tensor imaging–fractional anisotropy (DTI-FA) region of interest (ROI) masks and cognitive and mood measures (stroke volume, total no. of strokes, any left hemisphere strokes, and ventricle to brain ratio are controlled).

between ROIs and cognition/emotion are higher when compared with the bivariates. Partial correlations are graphically depicted in Figure 1.

Participant age is an important actor linked to both regional white matter changes (Raz et al., 2005) and also to cognitive and emotion changes, and it is thus highly pertinent to our variables of interest. When age is included in regression models, the relationships between white matter ROIs and cognition and emotion are altered. Controlling for age decreases, but does not eliminate, the relationship between white matter integrity and cognition. The parietal mask remains the strongest predictor for cognitive status with significant relationships to working memory ($B = .302$, $p < .05$), recall ($B = .312$, $p < .05$), encoding ($B = .287$, $p < .05$), psychomotor ($B = .301$, $p < .05$), spatial ($B = .423$, $p < .05$), language ($B = .380$, $p < .05$), and basic attention ($B = .197$, $p < .05$) skills. Within the emotion domain and controlling for age, there is an increase in the strength of the relationship of frontal lobe white matter integrity to FrSBe apathy ($B = –.218$, $p < .05$), CMDI mood ($B = –.400$, $p < .05$), CMDI vegetative ($B = –.407$, $p < .05$), and CMDI evaluative ($B = –.402$, $p < .05$) measures.

DISCUSSION

The primary findings of the study demonstrate regional sensitivity of DTI-FA to both cognition and emotion in cerebrovascular disease. While previous research has demonstrated greater sensitivity of whole brain DTI-FA to cognitive performance than visual white matter rating scales (e.g., O'Sullivan et al., 2004), the current study supports relatively greater sensitivity of automated regional masks than whole brain DTI-FA. The relationships of regional masks to cognition and emotion are consistent with our understanding of brain/behavior relationships. In our sample, the parietal mask is the strongest predictor of general cognitive status, and the frontal mask is the strongest predictor of emotional status.

In normal aging, DTI-FA has been shown to be sensitive to subtle microstructural changes. Yoon et al. (2007), in a cross-sectional design, demonstrated an anterior to posterior gradient acceleration of white matter changes in elderly participants, suggesting regional specific vulnerability to white matter deterioration in normal aging. As evidenced by behavioral presentations, this vulnerability may perhaps be amplified (or even caused) by cerebrovascular disease. Raz et al. (2005) present longitudinal data demonstrating regional brain volume changes as a function of age with particular vulnerabilities in older adults in the prefrontal white matter and temporal cortex. Interestingly, the parietal lobe did not change with aging. Raz et al. reported hypertension linkages to brain changes in their normal aging sample. Consistent with these data, in our sample, age is correlated with white matter and cognitive changes.

Age, as a variable, dilutes the relationships between white matter and cognition in our sample, though the parietal mask does remain the strongest predictor of cognitive performance. Interestingly, controlling for age increases the strength of the relationship of the frontal mask to emotional status. Perhaps this is an indictor of the independent contribution of significant cerebrovascular disease to fronto-subcortical white matter deterioration above and beyond normal aging. It is not entirely clear why age affects white matter relationships to cognition; it may

simply be longer exposure to common cerebrovascular disease risk factors. Age is a robust predictor of the presence of white matter hyperintensities, though the relationship of white matter hyperintensities to cognition is not entirely clear with conflicting results in the literature. Interestingly, consistent with our study, Grieve, Williams, Paul, Clark, and Gordon (2007) demonstrated a relationship between DTI-FA changes in frontal, parietal, and temporal lobes and healthy aging. Age was not associated with changes in the occipital lobe. FA declined the most in prefrontal cortex. Grieve et al. noted a particularly strong relationship between frontal and parietal FA and a cognitive switching task.

Controlling for stroke variables in our sample amplified the relationships between the ROI masks and cognitive and emotional performance, suggesting, at least in part, that the white matter damage is independent of stroke specific factors (e.g., stroke volume and total number of strokes). This amplified relationship suggests that the relationship may represent a physiological process outside the scope of stroke incidents, perhaps small-vessel ischemic disease. Further, atrophy, as measured by ventricle to brain ratio, does not impact the relationship between the ROIs and the outcome measures.

Though this is an early study of regional white matter integrity and both cognitive and emotional output in cerebrovascular disease, one similar study exists within the Alzheimer's disease literature. Huang, Friendland, and Auchus (2007) correlated neuropsychological performance (selected instruments from the Consortium to Establish a Registry for Alzheimer's disease, CERAD, neuropsychological battery including Word List Delayed Recall, Trail Making Test–B, and the Constructional Praxis component) to fractional anisotropy in frontal, temporal, parietal, and occipital regions of interest in 6 patients with probable Alzheimer's disease, 1 with mild cognitive impairment (MCI), and 8 participants with normal neuropsychological profiles. Though they acknowledge a small sample size and examined only selected a priori defined region–behavior relationships, their results suggest functionally relevant regional sensitivity to cognitive performance (e.g., statistical analyses were conducted on temporal lobe fractional anisotropy for Word List Delayed Recall and not Trail Making Test–B and the inverse with frontal lobe fractional anisotropy; ergo, the ROIs were never directly compared).

The strength of the parietal lobe regional FA in predicting cognitive performance across neuropsychological domains is somewhat surprising to us. Our a priori predictions were that frontal lobe FA would demonstrate a stronger relationship to working memory, basic attention, and psychomotor speed tasks (in addition to behavioral measures), temporal lobe FA would demonstrate a stronger relationship to recall and encoding, and parietal FA would demonstrate a stronger relationship to spatial and language tasks. The differences between this assumption and our results are apparently not due to statistical anomaly: The variance features across masks are not significantly different (i.e., range, standard deviations).

Anatomically, parietal lobe white matter does share large interconnections with frontal and temporal lobes. Functionally, the parietal lobe houses multimodal association cortex and has been associated with performance on a range of cognitive tasks in healthy participants. For example, Sylvester et al. (2003) explore two domains of executive functions: response inhibition and attention switching. They suggest that activation in the superior parietal cortex mediates the process of selective attention; the dorsal lateral prefrontal cortex maintains and manipulates the contents of working memory, while the anterior cingulate detects or responds to conflicting stimuli. Despite this possible specificity, congruence was found for attention shifts and interference resolution with activation in bilateral parietal cortex, left dorsolateral prefrontal cortex, premotor cortex, and medial frontal cortex. Further, Barcelo (1999) links set shifting to interactions between dorsolateral prefrontal cortex and temporoparietal interactions.

A recent study demonstrates that lesions of parietal white matter and tracts connecting parietal white matter to the frontal lobes impact performance on tasks that require processing speed (Turken et al., 2008). White matter hyperintensities in the parietal lobe have also been associated with decreased working memory performance (Lamar, Catani, Price, Heilman, & Libon, 2008). Given that normal aging impacts frontal lobe white matter, and, in order of progression, deterioration proceeds from anterior to posterior, it may be that small-vessel ischemic disease and the effects of stroke process on white matter deterioration of parietal connections is particularly impactful in the elderly. Of interest, gray matter volume in the temporal lobes is the strongest predictor of dementia status (Ikram et al., 2008).

This study has limitations. Our DTI protocol used six directions for defining the tensor and, as such, cannot be used to reliably determine the underlying tracts within regions (e.g., tractography). This limits our ability to look at specific regions beyond gross delineation. For example, it would be interesting to examine specific tracts as they relate to behavior, but we are limited in determining which specific tracts within a given region are related. For example, the lateral parietal lobe contains the posterior regions of the arcuate fasciculus, part of the superior and posterior thalamic peduncle, and aspects of the superior longitudinal fasciculus. We cannot separate these tracts using this low-resolution, low-angle scan.

Further, the sample is derived from a medical center population and may not generalize to other groups. Moreover, though our sample is relatively young, and we have taken precautions in our study to minimize the contribution of Alzheimer's disease by measuring hippocampal and entorhinal cortex volumes, we cannot definitely rule out Alzheimer's disease as a contributor in that we do not have pathological confirmation.

Future research may explore the sensitivity of regional white matter masks to cognitive and emotional functions over time in order to address whether these relationships are stable or malleable (e.g., whether improvement in fractional anisotropy relates to improved performance

across neuropsychological domains). Also, though we have preliminary research demonstrating changes in whole brain white matter integrity over time after stroke (e.g., Wang et al., 2006), it may be fruitful to explore regional improvements or decrements in white matter integrity independent of cognitive and emotional status. Increasing the specificity of DTI use in cerebrovascular disease may increase our prognostic accuracy and understanding of the effects of the disease process on functional systems underlying the neuropsychological and emotional changes observed in the vascular cognitive impairment literature.

In this study, we found evidence for functionally relevant changes in normal-appearing white matter integrity in cerebrovascular disease, demonstrating a potential double dissociation in associative strength between frontal and parietal regions in domain-specific emotional and cognitive functions. This is the first study to examine the relationships of regional white matter masks to both cognitive and emotional output in participants with cerebrovascular disease. The results support the view that the regional white matter application of DTI may be a useful in vivo tool for identifying differential impact of cerebrovascular disease on region-specific neurocognitive and emotional functions.

Original manuscript received 7 July 2009
Revised manuscript accepted 14 October 2009
First published online 10 February 2010

REFERENCES

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1998). "Vascular depression" hypothesis. *Archives of General Psychiatry*, *55*, 844–845.

Annoni, J. M., Khateb, A., Gramigna, S., Staub, F., Carota, A., Maeder, P., et al. (2003). Chronic cognitive impairment following laterothalamic infarcts: A study of 9 cases. *Archives of Neurology*, *60*, 1439–1443.

Barcelo, F. (1999). Electrophysiological evidence of two different types of error in the Wisconsin Card Sorting Test. *Neuroreport*, *10*, 1299–1303.

Boyle, P. A., Paul, R., Moser, D., Zawacki, T., Gordon, N., & Cohen, R. (2003). Cognitive and neurologic predictors of functional impairment in vascular dementia. *American Journal of Geriatric Psychiatry*, *11*, 103–106.

Brott, T., Marler, J. R., Olinger, C. P., Adams, H. P., Jr., Tomsick, T., Barsan, W. G., et al. (1989). Measurement of acute cerebral infarction: A clinical examination scale. *Stroke*, *20*, 864–870.

Buschke, H., & Grober, E. (1986). Genuine memory deficits in age-associated memory impairment. *Developmental Neuropsychology*, *2,* 287–307.

Desmond, D. W. (2004). The neuropsychology of vascular cognitive impairment: Is there a specific cognitive deficit? *Journal of the Neurological Sciences*, *226*, 3–7.

Foulkes, M. A., Wolf, P. A., Price, T. R., Mohr, J. P., & Hier, D. B. (1988). The stroke data bank: Design, methods, and characteristics. *Stroke*, *19*, 547–554.

Garrett, K. D., Browndyke, J. N., Whelihan, W., Paul, R. H., DiCarlo, M., Moser, D. J., et al. (2004). The neuropsychological profile of vascular cognitive impairment–no dementia: Comparisons to patients at risk for cerebrovascular disease and vascular dementia. *Archives of Clinical Neuropsychology*, *19*, 745–757.

Goodglass, H., & Kaplan, E. (1989). *The assessment of aphasia and related disorders* (2nd ed.). Philadelphia: Lea and Febiger.

Gootjes, L., Teipel, S. J., Zebuhr, Y., Schwarz, R., Leinsinger, G., Scheltens, P., et al. (2004). Regional distribution of white matter hyperintensities in vascular dementia, Alzheimer's disease and healthy aging. *Dementia and Geriatric Cognitive Disorders 18*, 180–188.

Gorelick, P. B., Freels, S., Harris, Y., Dollear, W., Billingsly, M., & Brown, N. (1994a). Epidemiology of vascular and Alzheimer's dementia among African-Americans in Chicago, IL: Baseline frequency and comparison of risk factors. *Neurology*, *44*, 1391–1396.

Gorelick, P. B., Román, G., & Mangone, C. A. (1994b). In P. B. Gorelick & M. A. Alter (Eds.), *Handbook of neuroepidemiology* (pp. 197–214). New York: Marcel Dekker.

Grace, J., & Malloy, P. F. (2001). *Frontal Systems Behavior Scale (FrSBe): Professional manual*. Lutz, FL: Psychological Assessment Resources.

Grieve, S. M., Williams, L. M., Paul, R. H., Clark, C. R., & Gordon, E. (2007). Cognitive aging, executive function, and fractional anisotropy: A diffusion tensor MR imaging study. *American Journal of Neuroradiology*, *28*, 226–235.

Grisby, J., & Kaye, K. (1996). *Behavior Dyscontrol Scale*: *Manual*. Denver, CO: Author.

Head, D., Buckner, R. L., Shimony, J. S., Williams, L. E., Akbudak, E., Conturo, T. E., et al. (2004). Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: Evidence from diffusion tensor imaging. *Cerebral Cortex*, *14*, 410–423.

Huang, J., Friendland, R. P., & Auchus, A. P. (2007). Diffusion tensor imaging of normal appearing white matter in mild cognitive impairment and early Alzheimer disease: Preliminary evidence of axonal degeneration in the temporal lobe. *American Journal of Neuroradiology*, *28*, 1943–1948.

Ikram, M. A., Vrooman, H. A., Vernooij, M. W., Heijer, T. D., Hofman, A., Niessen, W. J., et al. (2008). Brain tissue volumes in relation to cognitive function and risk of dementia. *Neurobiology of Aging.* Advance online publication. doi:10.1016/j.neurobiolaging.2008.04.008

Jorm, A. F., Anstey, K. J., Christensen, H., de Plater, G., Kumar, R., Wen, W., et al. (2005). MRI hyperintensities and depressive symptoms in a community sample of individuals 60–64 years old. *American Journal of Psychiatry*, *162*, 699–705.

Kochunov, P., Thompson, P. M., Lancaster, J. L., Bartzokis, G., Smith, S., Coyle, T., et al. (2007). Relationship between white matter fractional anisotropy and other indices of cerebral health in normal aging: Tract-based spatial statistics study of aging. *NeuroImage*, *35*, 478–487.

Kramer, J. H., Reed, B. R., Mungas, D., Weiner, M. W., & Chui, H. C. (2002). Executive dysfunction in subcortical ischaemic vascular disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *72*, 217–220.

Lamar, M., Catani, M., Price, C. C., Heilman, K. M., & Libon, D. J. (2008). The impact of region-specific leukoaraiosis on working memory deficits in dementia. *Neuropsychologia*, *46*, 2597–2601.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitechtonic atlas-based interrogation of fMRI data sets. *NeuroImage*, *19*, 1233–1239.

Manolio, T. A, Kronmal, R. A., Burke, G. L., Poirier, V., O'Leary, D. H., Gardin, J. M., et al. (1994). Magnetic resonance abnormalities and cardiovascular disease in older adults. The Cardiovascular Health Study. *Stroke*, *25*, 318–327.

McMurtray, A. M., Liao, A., Haider, J., Licht, E., & Mendez, M. (2007). Cognitive performance after lacunar stroke correlates with leukoaraiosis severity. *Cerebrovascular Diseases*, *24*, 271–276.

Morris, J. C., Heyman, A., Mohrs, R. C., Hughes, J. P., van Belle, G., Fillenbaum, G., et al. (1989). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part

1. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*, *39*, 1159–1165.

Moser, D. J., Cohen, R. A., Paul, R. H., Paulsen, J. S., Ott, B. R., Gordon, N. M., et al. (2001). Executive function and magnetic resonance imaging subcortical hyperintensities in vascular dementia. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, *14*, 89–92.

Newman, L. M., Trivedi, M. A., Bendlin, B. B., Ries, M. L., & Johnson, S. C. (2007). The relationship between gray matter morphometry and neuropsychological performance in a large sample of cognitively healthy adults. *Brain Imaging and Behavior*, *1*, 3–10.

Nyenhuis, D. L., Gorelick, P. B., Geenen, E. J., Smith, C. A., Gencheva, E., Freels, S., et al. (2004). The pattern of neuropsychological deficits in vascular cognitive impairment–no dementia (vascular CIND). *The Clinical Neuropsychologist*, *18*, 41–49.

Nyenhuis, D. L., Luchetta, T., Yamamoto, C., Terrien, A., Bernardin, L., Rao, S. M., et al. (1998). The development, standardization, and initial validation of the Chicago Multiscale Depression Inventory. *Journal of Personality Assessment*, *70*, 386–401.

O'Brien, J. T. (2006). Vascular cognitive impairment. *American Journal of Geriatric Psychiatry*, *14*, 724–733.

O'Brien, J. T., Firbank, M. J., Krishnan, M. S., van Straaten, E. C. W., van der Flier, W. M., Petrovic, K., et al. (2006). White matter hyperintensities rather than lacunar infarcts are associated with depressive symptoms in older people: The LADIS Study. *American Journal of Geriatric Psychiatry*, *14*, 834–840.

O'Sullivan, M., Morris, R. G., Huckstep, B., Jones, D. K., Williams, S. C. R., & Markus, H. S. (2004). Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis. *Journal of Neurology, Neurosurgery and Psychiatry*, *75*, 441–447.

Pantoni, L., & Garcia, J. H. (1997). Pathogenesis of leukoaraiosis: A review. *Stroke*, *28*, 652–659.

Pohjasvaara, T., Leskelä, M., Vataja, R., Kalska, H., Ylikoski, R., Hietanen, M., et al. (2002). Post-stroke depression, executive dysfunction and functional outcome. *European Journal of Neurology*, *9*, 269–275.

Raven, J. C. (1995). *Colored Progressive Matrices Sets A, AB, B*. Oxford, UK: University Press.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., et al. (2005). Regional brain changes in healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex*, *15*, 1676–1689.

Román, G. C., & Royall, D. R. (1999). Executive control function: A rational basis for the diagnosis of vascular dementia. *Alzheimer Disease and Associated Disorders*, *13*(Suppl. 3), S69–S80.

Russell, E., & Starkey, R. (1993). *Halstead–Russell Neuropsychological Evaluation System (HRNES)*. Los Angeles: Western Psychological Services.

Scherr, P. A., Albert, M. S., Funkenstein, H. H., Cook, N. R., Hennekens, C. H., Branch, L. G., et al. (1988). Correlates of cognitive function in an elderly community population. *American Journal of Epidemiology*, *128*, 1084–1101.

Shimamura, A., & Jurica, P. (1994). Memory interference effects and aging: Findings from a test of frontal lobe function. *Neuropsychology*, *1*, 408–412.

Shirley et al., 2007.

Smith, A. (1991). *Symbol Digit Modalities Test*. Los Angeles: Western Psychological Services.

Sylvester, C. C., Wager, T. D., Lacey, S. C., Hernandez, L., Nichools, T. E., Smith, E. E., et al. (2003). Switching attention and resolving interference: fMRI measures of executive functions. *Neuropsychologia*, *41*, 357–370.

Tullberg, M., Fletcher, E., DeCarli, C., Mungas, D., Reed, B. R., Harvey, D. J., et al. (2004). White matter lesions impair frontal lobe function regardless of their location. *Neurology*, *63*, 246–253.

Turken, A. U., Whitfield-Gabrieli, S., Bammer, R., Baldo, J. V., Dronkers, N. F., & Gabrieli, J. D. (2008). Cognitive processing speed and the structure of white matter pathways: Convergent evidence from normal variation and lesion studies. *NeuroImage*, *42*, 1032–1044.

Wang, C., Stebbins, G. T., Nyenhuis, D. L., de Toledo-Morrell, L., Freels, S., Gencheva, E., et al. (2006). Longitudinal changes in white matter following ischemic stroke: A three-year follow-up study. *Neurobiology of Aging*, *27*, 1827–1833.

Wechsler, D. (1945). A standardized memory scale for clinical use. *Journal of Psychology*, *19*, 87–95.

Wechsler, D. (1997). *WMS–III administration and scoring manual*. San Antonio, TX: The Psychological Corporation, Harcourt Brace Jovanovich.

Wen, H. M., Mok, V. C. T., Fan, Y. H., Lam, W. W. M., Tang, W. K., Wong, A., et al. (2004). Effect of white matter changes on cognitive impairment in patients with lacunar infarcts. *Stroke*, *35*, 1826–1830.

Woolley, J. D., Gorno-Tempinin, M. L., Seeley, W. W., Rankin, K., Lee, S. S., Matthews, B. R., et al. (2007). Binge eating is associated with right orbitofrontal-insular-striatal atrophy in frontotemporal dementia. *Neurology*, *69*, 1424–1433.

Yang, Q., Xuebing, H., Hong, N., & Yu, X. (2007). White matter microstructural abnormalities in late-life depression. *International Psychogeriatrics*, *19*, 757–766.

Yoon, B., Yong-Soo, S., Kwang-Soo, L., Young-Min, S., & Dong-Won, Y. (2007). Region-specific changes of cerebral white matter during normal aging: A diffusion-tensor analysis. *Archives of Gerontology and Geriatrics*, *47*, 129–138.