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Fiber tracking functionally distinct components of the internal capsule

Edith V. Sullivan, Ph.D.[1], **Natalie M. Zahr, Ph.D.**[1,2], **Torsten Rohlfing, Ph.D.**[2], and **Adolf Pfefferbaum, M.D.**[1,2]

[1] Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine

[2] Neuroscience Program, SRI International

Abstract

The internal capsule conveys information from primary and supplementary motor areas, frontopontine and thalamic peduncles to brain stem and cerebellar regions, and from thalamus to prefrontal cortex. Neurological accidents involving the internal capsule indicate differential functional correlates with its sectors. To examine the microstructural condition of this fiber system and to test functional correlates of its sectors in health and aging, 12 younger and 12 older adults were examined with diffusion tensor imaging (DTI) fiber tracking and neuropsychological tests. Greater age-related degradation was evident in the anterior than posterior limb and in the superior than inferior division of the internal capsule. The superior division age effect was especially notable in axial and radial diffusivity. Fractional anisotropy (FA) across the three (anterior, genu, posterior) fiber bundles of the inferior division accounted for 27–73% of the variance for each neuropsychological domain. Identification of a triple dissociation indicated selective correlations between anterior FA and Set Shifting, genu FA and Motor Skills, and posterior FA and Fluency. Quantitative fiber tracking combined with assessment of cognitive and motor functions enabled the identification of selective brain structure-function relations in healthy adults without lesions that were previously observed only in patients with lesions of the internal capsule.

Keywords

DTI; internal capsule; white matter; fiber tracking; fluency; speed; dexterity

INTRODUCTION

The internal capsule is a heterogeneous fiber system, coursing between the supratentorium and brain stem, and forming the centrum semiovale in the supratentorium and the corticospinal tract in the infratentorium. This extensive fiber system conveys information from primary and supplementary motor areas, frontopontine and thalamic peduncles to brain stem and cerebellar regions, and from thalamus to prefrontal cortex (Schmahmann, Rosene, & Pandya, 2004). Thus, the internal capsule provides connectivity between sites supporting multiple, diverse, and dissociable functions. Consistent with this depiction of its structure

Corresponding author: Edith V. Sullivan, Ph.D., Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences, 401 Quarry Road, Stanford, CA 94305-5723, 650-498-7328 (phone), 650-859-2743 (FAX), edie@stanford.edu.

and function are accounts of neurological accidents involving the internal capsule that indicate differential functional correlates with its three recognized sectors: anterior limb damage can result in arm and facial weakness; genu damage can produce frontal lobe and memory impairment; and posterior limb damage can produce ataxia (for review, Schmahmann, Rosene, & Pandya, 2004). Its twisting trajectory, however, complicates localization of fiber projections and functional ramifications (in vivo study: Holodny, Gor, Watts, Gutin, & Ulug, 2005; postmortem study:Kretschmann, 1988; Ross, 1980).

Diffusion tensor imaging (DTI) provides a method for examination of the microstructural condition of white matter fiber systems and for testing functional correlates of their sectors in health, normal aging, and neuropsychiatric disorders. Principal DTI metrics are fractional anisotropy (FA), a measure of the degree to which water diffusion in an image voxel exhibits a predominant orientation, and mean diffusivity, a measure of the magnitude of freely diffusing water molecules in interstitial and intracellular spaces contained in the voxel. The orientational components of diffusivity provide additional information about axonal integrity with longitudinal or axial diffusivity (λL) and myelination and myelin integrity with transverse or radial diffusivity (λT) (Song, et al., 2002; Song, et al., 2005; Sun, et al., 2006a; Sun, et al., 2006b). DTI studies of normal adult aging, for example, have consistently observed an anterior-to-posterior gradient, where commissural and association fiber systems of frontal regions, such as the genu of the corpus callosum and frontal forceps are characterized by lower FA or higher diffusivity in older than younger adults (Ardekani, Kumar, Bartzokis, & Sinha, 2007; Bhagat & Beaulieu, 2004; Bucur, et al., 2008; Head, et al., 2004; Kennedy & Raz, 2009; Madden, Bennett, & Song, 2009; e.g., Pfefferbaum, Adalsteinsson, & Sullivan, 2005; Salat, et al., 2005; Sullivan, Adalsteinsson, & Pfefferbaum, 2006; Sullivan & Pfefferbaum, 2010; Takahashi, et al., 2004; Yoon, Shim, Lee, Shon, & Yang, 2008; for reviews, Zahr, Pfefferbaum, & Sullivan, 2010). Typically, the age effect is similar for men and women and is greater in diffusivity, especially λT, than FA (Kennedy & Raz, 2009; Sullivan, Rohlfing, & Pfefferbaum, 2010).

Using these metrics, DTI studies tracking the internal capsule of healthy adults have commonly focused on the effects of normal aging on fiber integrity. These studies have identified lower FA and higher diffusivity in older than younger healthy adults (e.g., Bennett, Madden, Vaidya, Howard, & Howard, 2010; Stadlbauer, Salomonowitz, Strunk, Hammen, & Ganslandt, 2008; Sullivan, Rohlfing, & Pfefferbaum, 2010; Westlye, et al., 2009). Functional correlates of this age-related variance indicated that faster hand and finger movement were related to higher FA and lower diffusivity in samples of tracked fibers of the internal capsule; in contrast to upper limb coordinated and speeded movement, lower limb and truncal stability (standing on one foot) did not relate to local DTI metrics, providing limited evidence for selectivity of the observed relationships (Sullivan, Rohlfing, & Pfefferbaum, 2010). As part of a multiple dissociation of local white matter regions of interest and components of attention without respect to age effects, variance of FA in the anterior limb of the internal capsule was selectively predictive of alerting, whereas splenial FA predicted orienting and FA of the anterior coronal radiata predicted conflict processing (Niogi, Mukherjee, Ghajar, & McCandliss, 2010).

Examination of multiple, selective fiber samples throughout the brain and brain stem has also yielded a superior-to-inferior gradient in DTI metrics (Sullivan, Rohlfing, & Pfefferbaum, 2010). Supratentorial fiber systems (e.g., fornix and external capsule) showed age-related effects, whereas infratentorial ones (e.g., pontocerebellar tract) did not. Even within the supratentorium, fiber systems located superiorly were more vulnerable to age effects than those located inferiorly, notably, the superior vs. the inferior cingulate bundle and the superior vs. the inferior longitudinal fasciculus (Stadlbauer, Salomonowitz, Strunk, Hammen, & Ganslandt, 2008). Given the far-reaching fiber fan and stem of the internal

capsule, it is reasonable to pose the hypothesis that the internal capsule itself would obey a superior-inferior gradient along with an anterior-posterior one, a depiction with an anatomical basis (Kretschmann, 1988; Morecraft, et al., 2002; Schmahmann, Ko, & MacMore, 2004). Identification of selective functional correlates of these gradients would provide validation for parsing of the internal capsule.

Accordingly, quantitative fiber tracking provided assessment of local white matter microstructural integrity of components of the internal capsule. We expected that FA would be lower and diffusivity would be higher in older than younger adults and that, as predicted from lesion studies, DTI metrics of each sector would correlate differentially with measures of problem solving, set shifting, fluency, working memory, and finger speed and dexterity.

METHODS

Subjects

The participants were 24 healthy, right-handed, non-smoking men and women; 12 (6 men, 6 women) were in the younger group (mean±SD=25.5±4.34, range=20–33 years) and 12 (6 men, 6 women) were in the older group (mean±SD=77.7±4.94, range=67–85 years). DTI data of fiber systems (exclusive of the internal capsule) and neuropsychological test data were presented elsewhere (Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009); the data on components of the internal capsule and their relationships with selective functions have been presented in abstract form only (Sullivan, Zahr, Rohlfing, & Pfefferbaum, 2008, November). As previously described (Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009), all participants provided signed, informed consent for study participation, as approved by the Institutional Review Boards of SRI International and Stanford University. The Structured Clinical Interview for the Diagnostic and Statistical Manual (DSM) IV-TR, administered by a trained research psychologist, was used to detect DSM-IV diagnoses or medical conditions that can affect brain functioning (e.g., diabetes, head injury, epilepsy, uncontrolled hypertension, radiation, chemotherapy) or preclude MR study (e.g., pacemakers).

Using t-tests to examine group differences, the two age groups did not differ significantly in education (younger=16.3±2.18 years; older=17.1±1.98 years, p=.337) or estimated general intelligence (NART IQ: younger=141.4±2.57; older=118.2±5.59, p=.063). The older group had a higher socioeconomic status (SES, Hollingshead, 1975), indicated by lower scores (SES: younger=26.1±10.11; older=18.3±6.24, p=.034), but scored lower than the younger group on the Dementia Rating Scale (DRS, cutoff for dementia <124 out of 144, Mattis, 2004) (DRS: younger 141.4±2.57; older=137.2±4.71, p=.013), although well-within the normal range of published values for healthy elderly individuals living in the community (e.g., 137.48 ± 5.18, Vitaliano, Breen, Albert, Russo, & Prinz, 1984). The significantly greater body mass index (BMI; slightly overweight, i.e., BMI between 25 and 29.9 kg/m^2) of the older (26.6±4.55) than the younger group (23.1±2.98, p=.034) was close to the mean BMI calculated from 5,200 subjects participating in the cardiovascular health study (26.3 ± 3.9 kg/m2, Janssen, Katzmarzyk, & Ross, 2005). Although the older group had significantly higher systolic blood pressure (135.9±21.84) than the younger group (114.0±16.16, p=.011), they were all in the pre-hypertensive range (i.e., between 120 and 139 mmHg, Chobanian, et al., 2003), and only one man and two women were taking hypertension medication. Diastolic blood pressure did not differ significantly between the younger (68.6±8.46) and older (75.4±11.65, p=.114) groups.

Image Acquisition and Fiber Tracking Quantification

The internal capsule was assessed with DTI fiber tracking measured as fractional anisotropy (FA) and mean diffusivity (MD), quantified separately for longitudinal (λL) diffusivity, indexing axonal integrity, and transverse (λT) diffusivity, indexing myelin integrity.

Diffusion and Structural MRI Acquisition—Data were acquired with an 8-channel head coil at 3T after higher-order (nonlinear) shimming (Kim, Adalsteinsson, Glover, & Spielman, 2002). Diffusion and structural fast spin-echo (FSE) data were collected with the same slice locations: DTI (2D echo-planar, TR=7300ms, TE=86.6ms, thickness=2.5mm, skip=0mm, locations=62, b=0 (5 NEX)+15 noncollinear diffusion directions b=860s/mm^2 (2 NEX)+15 opposite polarity noncollinear diffusion directions b=860s/mm^2 (2 NEX), FOV=240mm, x-dim=96, y-dim=96, reconstructed to 128×128, 4030 total images); FSE (2D axial, TR=7850ms, TE=17/102ms, thickness=2.5mm, skip=0mm, locations=62). T1-weighted SPoiled Gradient Recalled (SPGR; 3D axial IR-prep, TR=6.5ms, TE=1.6ms, thick=1.25mm, skip=0mm, locations=124) images were aligned, such that two 1.25mm SPGR slices subtended each 2.5mm thick FSE/DTI slice. A field map was generated from a gradient recalled echo sequence pair (TR=460ms, TE=3/5ms, thickness=2.5mm, skip=0mm, locations=62).

DTI Analysis—DTI quantification was preceded by eddy-current correction on a slice-by-slice basis using within-slice registration, which took advantage of the symmetry of the opposing polarity acquisition (Bodammer, Kaufmann, Kanowski, & Tempelmann, 2004) and also allowed for compensation of the diffusion effect created by the imaging gradients (Neeman, Freyer, & Sillerud, 1991). Using the field maps, B_0-field inhomogeneity-induced geometric distortion in the eddy current-corrected images was corrected with PRELUDE (Phase Region Expanding Labeller for Unwrapping Discrete Estimates, Jenkinson, 2003) and FUGUE (FMRIB's Utility for Geometrically Unwarping EPIs, Jenkinson, 2001).

DTI models water diffusion within each voxel as a zero-mean multivariate Gaussian distribution, which is parameterized by its symmetric 3×3 covariance matrix, the diffusion tensor. The diffusion-weighted data measured with respect to each of the diffusion gradient directions exhibits a signal attenuation relative to *b*=0 data acquired without diffusion gradients. The logarithm of this signal attenuation is a linear combination of the six unique elements of the diffusion tensor, their weights determined by the direction of the diffusion gradients. Computing a least-squares solution for this over-determined system of linear equations independently at each voxel yielded the elements of the diffusion tensor for that voxel. The diffusion tensor was then diagonalized, yielding eigenvalues λ_1, λ_2, λ_3, and corresponding eigenvectors. From the eigenvalues, fractional anisotropy (FA), mean diffusivity (MD) and two orientational diffusivity measures, λL and λT, were calculated on a voxel-by-voxel basis (Pierpaoli and Basser, 1996; Basser and Pierpaoli, 1998; Basser and Jones, 2002).

Fiber Tracking—To establish common anatomical coordinates across subjects, SPGR data for each subject were aligned (Rohlfing & Maurer, 2003) (http://nitrc.org/projects/cmtk/) with a brain made from these 24 subjects with group-wise nonrigid registration (SRI24 atlas, Rohlfing, Zahr, Sullivan, & Pfefferbaum, 2010) (http://nitrc.org/projects/sri24/). Each subject's FA data were reformatted into atlas space using the transformation computed between the atlas and that subject's SPGR data, concatenated with a second transformation registering subject SPGR to subject DTI space. From the reformatted FA maps from all subjects, a group average FA image was then created.

Fiber tracking was performed in each subject's native DTI space with the software by Gerig et al. (Gerig, Corouge, Vachet, Krishnan, & MacFall, 2005) based on the method of Mori and colleagues (Mori & van Zijl, 2002; Xu, Mori, Solaiyappan, van Zijl, & Davatzikos, 2002; Xue, van Zijl, Crain, Solaiyappan, & Mori, 1999). This approach uses the target-source concept with fibers arising in a source and passing through a target. On the atlas FA image, 7mm-thick axial sources were defined bilaterally as the internal capsule, divided into anterior, genu and posterior limbs at the level of the superior reaches of the thalamus, and 5mm-thick axial targets were defined bilaterally as the cerebral peduncles at the level of the mammillary bodies. Target and sources were then mapped to the corresponding locations on the native space basis images for each subject with a numerical inversion of the transformation previously used to reformat the individual FA maps into SRI24 space. For each subject, the tensor field, targets, and sources were passed to the fiber tracking routine in that subject's native DTI space. Fiber tracking parameters included white matter extraction threshold (minimum FA) of .17, minimum fiber length of 37.5 mm, maximum fiber length of 187.5 mm, fiber tracking threshold of .125 (terminates a fiber if the vector field in the local neighborhood is too noisy), and maximum voxel-to-voxel coherence minimum transition smoothness threshold of .80 (~37° maximum deviation between fiber segments from neighboring voxels).

The output of the fiber tracking routine was a 3D graphical representation of the fiber paths comprising a table of all point locations along each fiber with local DTI metrics (FA; MD; $\lambda L = \lambda_1$; $\lambda T = [\lambda_2 + \lambda_3]/2$). For each fiber, mean FA, mean MD, mean λL, and mean λT were computed. Fibers arising from the same source and target were combined into a fiber tract, and the averaged DTI measures over all fibers in each tract were the units of subsequent analysis.

Cognitive and Motor Tests

Tests assessed problem solving [CANTAB Stockings of Cambridge [http://www.camcog.com)], working memory [blocks forward (Wechsler, 1997), Sternberg paradigm (Desmond, et al., 2003)], set shifting [CANTAB Intra-Extra Dimensional Shift task, Comprehensive Trail Making Test (Smith, et al., 2008)], verbal and nonverbal fluency [semantic (Newcombe, 1969) and figural (Ruff, 1988) fluency], upper limb motor function [Grooved Pegboard (Trites, 1977), fine finger movement (Corkin, Growdon, Sullivan, Nissen, & Huff, 1986), and CANTAB Motor and Big/Little Circle].

Each test score was standardized by z-transformation to produce a mean score of 0 and a standard deviation of 1 over all subjects; scores were multiplied by -1 for tests in which high raw scores were indicative of worse performance (e.g., Grooved Pegboard completion time). Composite scores for each functional domain were calculated as the mean of the standardized z-scores of the tests identified within a domain.

Statistical Analysis

An initial omnibus analysis of variance (ANOVA) was conducted for each of the four DTI metrics (FA, MD, λL, and λT). Primary analyses were based on group-by-fiber tract and group-by-factor analysis of variance (ANOVA); where appropriate, Greenhouse-Geiser (GG) correction was applied, and only group effects and interactions involving group effects were of interest to this analysis. Follow-up group differences were determined by t-tests and confirmed by Mann-Whitney U tests with the prediction that the older group would have lower FA, higher diffusivity, and poorer test performance than the younger group. In another set of analyses using simple linear regressions, we examined whether individual fiber tract DTI metrics were predictive of composite test scores. Family-wise Bonferroni correction for 36 comparisons (3 anterior-posterior limbs by 3 superior-to-inferior divisions by 4 DTI

metrics) for two-tailed tests required a p-value ≤ 0.0014 to be considered significant and used in further analysis. Multiple regression assessed the selectivity of observed correlations.

RESULTS

Age Effects on Fiber Tracking Metrics in Regions of the Internal Capsule

A series of 2-group (younger, older) by 3-limb (anterior, genu, posterior) by 2-hemisphere (left, right) ANOVAs conducted for each DTI metric sought interaction effects involving group irrespective of superior-inferior division. Only the 3-way interaction for FA was significant ($F(2,44)=3.999$, $p=.0401$, G-G corrected), where the older group had lower FA than the younger group, modestly more so in the right hemisphere of the anterior limb. For MD, only the group ($F(1,22)=180.01$, $p=.0003$) and group-by-region ($F(2,44)=6.29$, $p=.0079$, G-G corrected) effects were significant. ANOVA failed to identify group-by-hemisphere interactions for λL or λT. Because the one hemisphere difference identified as significant was trivial, we derived mean DTI scores for the left and right hemisphere of each division and limb for the remaining analyses.

The next set of ANOVAs used the bilateral measures and examined group differences in the anterior-genu-posterior fibers by the superior-central-inferior divisions with an omnibus test for each of the four DTI metrics. Bar graphs of the mean±SE by group for each of these 9 measures for each metric are presented in Figure 1, and statistics for the four omnibus ANOVAs are presented in Table 1.

FA—For FA (Figure 1), the ANOVA revealed these significant effects: the older group had lower FA than the younger group, and FA was lower in the superior and anterior than inferior and posterior divisions. In no case, however, were interactions involving group significant.

MD—In contrast with FA effects, diffusivity metrics revealed interactions with group. For MD (Figure 1), in addition to a significant group effect, with the older having higher MD than the younger group, the group interactions with the superior-inferior divisions and with the anterior-posterior limbs were significant. Here, the older group showed a superior-inferior gradient not present in the younger group, where MD was highest in the superior divisions and lowest and at the same levels as the younger group in the inferior divisions. Three follow-up ANOVAs for MD examining 2-group by 3-anterior/genu/posterior limbs for each superior-inferior division revealed interactions with group for the superior ($F(2,44)=3.34$, $p=.0446$) and central ($F(2,44)=3.77$, $p=.0308$) but not inferior ($F(2,44)=1.33$, $p=.2749$) divisions.

λL—The ANOVA for λL indicated no significant group differences but identified a significant group interaction with superior-inferior segments, attributable to higher diffusivity in the older group in the superior sector but the opposite pattern in the inferior division (Figure 1). The only follow-up ANOVA yielding an interaction with group was for the superior division, indicating that λL was disproportionately greater in the anterior than posterior fibers of the older relative to the younger group ($F(2,44)=4.53$, $p=.0162$).

λT—The pattern of group differences revealed by ANOVA for λT (Figure 1) was similar but not identical to those of MD. Like MD, λT was greater in the older than younger group, especially in the superior and anterior regions. Further, λT was significantly greater in the older group than the younger group ($F(1,22)=26.65$, $p=.0001$).

Age Effects on Cognitive and Motor Performance

A group-by-test composite score ANOVA indicated a significant group effect ($F(1,22)=25.18$, $p=.0001$) but no interaction ($F(4,88)=.66$, $p=.62$). Follow-up t-tests showed that the older group achieved significantly lower scores than the younger group on all five test composites, with p-values ranging from .0172 to .0001. Bonferroni correction of α for five directional tests of significance requires $p=.02$; therefore, all differences were considered significant.

Relations between Regional Fiber Tracking of the Internal Capsule and Performance

Bivariate correlation coefficients and p-values for tests between each regional DTI metric and each cognitive and motor composite score across the entire group of 24 subjects are presented in the table provided in the appendix. Family-wise Bonferroni adjustment for 36 comparisons and $\alpha=.05$ required that $p\leq.0014$. Significant correlations involving FA and diffusivity emerged for performance measures of Fluency, Problem Solving, and Motor Speed and Dexterity, fewer for Set Shifting, and none for Working Memory.

Multiple regression analysis indicated that FA across the three anterior-to-posterior fiber bundles of the inferior division accounted for a substantial amount of the variance for each functional domain: 73% for Fluency, 64% for Set Shifting, 51% for Motor Skills, 32% for Problem Solving, and 27% for Working Memory.

A series of hierarchical regression analyses tested for selectivity of regional DTI metrics as predictors of performance. Each model tested one of the four DTI metrics (FA, MD, λL, and λT). Thus, the DTI metric of the anterior, genu, and posterior fibers served as the simultaneous predictor of each of the five performance composite scores. In no case was any metric of anterior-posterior limbs of the superior or central divisions a significant and unique predictor of performance. Only hierarchical regression using the inferior DTI regional metrics identified unique predictors of performance and a triple dissociation. In particular, FA of the inferior division of the anterior fibers was uniquely predictive of Set Shifting; FA of the inferior genu fibers was uniquely predictive of Motor Skills; and FA of the inferior posterior fibers was uniquely predictive of Fluency (Figure 2). A second set of hierarchical regressions entered age as a fourth predictor. The initial relations held with age adding insignificantly to Fluency or Set Shifting; however, adding age to the analysis changes the variance distribution, such that age contributed significantly along with inferior genu FA for Motor Skills.

DISCUSSION

The fiber systems of the internal capsule comprise much of the centrum semiovale and are far-reaching in three dimensions, coursing from cortex to brain stem. Cortical sites connecting inferiorly through the corticospinal and corticopontine tracts include frontal and parietal regions (Kretschmann, 1988; Morecraft, et al., 2002; Schmahmann, Ko, & MacMore, 2004). Given these extensive connections, it seemed reasonable to consider that the microstructure of its fiber systems, assessed by superior-to-inferior divisions as well as the traditional anterior-to-posterior systems, would be heterogeneous with respect to the effects of age and relationship with function (Holodny, Gor, Watts, Gutin, & Ulug, 2005; Kennedy & Raz, 2009). Accordingly, fiber tracking revealed greater age-related degradation in the anterior than posterior limb, evident with measures of diffusivity but not FA. Yet, even for diffusivity, which is commonly more sensitive to age-related differences than anisotropy (for review, Sullivan & Pfefferbaum, 2010), a significant age effect was present only in the superior and central but not inferior divisions of the internal capsule.

Transverse diffusivity (λT) showed the expected age effects in all three superior-to-inferior divisions, being higher in the older than younger participants. One interpretation of greater than normal transverse diffusivity in older age or degenerative diseases is as a sign of myelin damage (Song, et al., 2002; Song, et al., 2005). This pattern also held for axial diffusivity (λL) but only in the superior division, whereas the opposite (younger greater than older) held for the inferior division, therefore accounting for the lack of an apparent age effect in mean diffusivity, MD, of the inferior division of the internal capsule. The underlying causes of changes in axial diffusivity are more controversial than those of transverse diffusivity. Among the interpretations of age- or disease-related increases of axial diffusivity are that it is a reflection of damage to the axon (Song, et al., 2002). Higher λL in the younger than older group could also reflect the higher anisotropy detected and an elongation of the ellipsoid describing the local diffusion (cf., Bennett, Madden, Vaidya, Howard, & Howard, 2010).

The observed brain microstructure-performance correlations provide functional support for the anterior-to-genu-to-posterior limb segmentation of the internal capsule. The most consistent relationships were present in the inferior division, possibly because the average FA was higher and coefficient of variation (CV) lower there (average FA=.68, CV=8.9%) than in either of the two more superior divisions (superior FA=.44, CV=19.6%; central FA=.61, CV=15.2%). Other DTI studies report that these inferior fiber bundles are largely unaffected by age (Holodny, Gor, Watts, Gutin, & Ulug, 2005; Kennedy & Raz, 2009; Stadlbauer, Salomonowitz, Strunk, Hammen, & Ganslandt, 2008; Sullivan, Rohlfing, & Pfefferbaum, 2010), alcoholism (Pfefferbaum, Rosenbloom, Rohlfing, & Sullivan, 2009), or Alzheimer's disease (Bozzali, et al., 2002; Takahashi, et al., 2002), yet are affected in other degenerative diseases affecting motor systems, such as progressive supranuclear palsy and multiple system atrophy (Blain, et al., 2006; Nilsson, et al., 2007).

FA across the three anterior-to-posterior fiber bundles of the inferior division accounted for 27% to 73% of the variance for each functional domain, with the highest for Fluency. The strongest evidence for brain microstructure-function relationships was the identification of a triple dissociation, with selective correlations between anterior FA and Set Shifting, genu FA and Motor Skills, and posterior FA and Fluency, discussed next.

Set shifting ability, a reflection of cognitive flexibility and known to be affected by lesions of dorsolateral prefrontal cortex in monkeys (e.g., Moore, Schettler, Killiany, Rosene, & Moss, 2009) and humans (e.g., Milner, 1963), was related to FA in the inferior anterior limb of the internal capsule. Anatomical tracing studies in nonhuman primates have revealed connections of the anterior limb of the internal capsule with dorsolateral and ventrolateral prefrontal cortex that vary with rostral-caudal position (for review, Haber & Knutson, 2009) and are consistent with human studies using electrical stimulation (Machado, et al., 2009). In humans, DTI connectivity analysis using the anterior limb as a mapping seed revealed connectivity with regions including the frontal pole and cerebellum among other sites (Gutman, Holtzheimer, Behrens, Johansen-Berg, & Mayberg, 2009). Given these connections, one can speculate that degradation of fibers of the anterior limb of the internal capsule could result in a subtle disconnection syndrome affecting functions, including set shifting, reliant on their prefrontal (Konishi, et al., 1998; Milner, 1963) and cerebellar projection sites (Courchesne, et al., 1994; Lie, Specht, Marshall, & Fink, 2006). It is tempting to speculate that these pathways, which are affected in obsessive-compulsive disorder (Gutman, Holtzheimer, Behrens, Johansen-Berg, & Mayberg, 2009), would also be relevant to mental flexibility required for shifting set.

Fine finger movement speed was related to the integrity of fibers of the inferior internal capsule genu, known to interconnect striatal and motor cortical regions subserving motor

control. This relation provides further support to the possibility that the fibers measured are projections from (or at least connected with) the supplementary motor area (Morecraft, et al., 2002), possibly at the level of the hand region, given the somatotopic organization of the internal capsule with respect to the primary and supplementary motor areas.

The most robust correlation occurred between FA in the inferior posterior limb of the internal capsule and Fluency, comprising semantic and figural fluency measures. Subcortical lesions including those in the internal capsule can result in aphasia (Alexander & LoVerme, 1980; Damasio & Geschwind, 1984). Using path analysis of multifactorial data from computed tomography, glucose metabolic positron emission tomography, and neuropsychological testing, Metter and colleagues (Metter, et al., 1988) identified direct, selective relations between verbal fluency and imaging measures of the posterior limb of the internal capsule and indirect relations with frontal sites. This pattern comports with an observation by Taylor (Taylor, 1969), who noted that post-surgical epilepsy patients whose excisions included the motor face area, which projects through the internal capsule, had the greatest deficits in verbal and nonverbal fluency. Further, consistent with the medial pontine/face area projection described by Schmahmann et al. (Schmahmann, Rosene, & Pandya, 2004), longer MRI transverse relaxation time (T2, an index of free water content in tissue) in central pons of uncomplicated alcoholics correlated with lower output on phonemic, semantic, and nonverbal fluency measures (Sullivan & Pfefferbaum, 2001). Another DTI study of the internal capsule and its functions failed to find structure-function correlations possibly because fluency was not tested (Kennedy & Raz, 2009).

Despite the power of a triple dissociation, this study has limitations. The most obvious is the small sample size on which regression analysis was based, presenting the possibility that the observed brain structure-function relations were chance events. The small sample combined with the large number of correlations conducted also restricted criteria for determining which relations were significant; thus, we may have discounted modest relations that would have endured correction for multiple comparisons with a larger sample. In addition, studies based on small, relatively homogeneous samples restrict generalizability of findings. Considering these limitations, it is essential that the relations identified be replicated in larger samples of healthy adults.

In summary, these patterns of diffusivity differences in the internal capsule comport with neurological outcome in human lesion studies, suggesting mechanisms of functional degradation, attributed at least in part to regionally selective, compromised fiber microstructure affecting myelin and axonal morphology. Quantitative fiber tracking combined with assessment of selective cognitive and motor functions enabled the identification of selective brain structure-function relations in the form of a triple dissociation, thus supporting the differential functional composition of the internal capsule detectable in healthy adults without lesions and previously observed only in patients with lesions of the internal capsule.

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References

Alexander MP, LoVerme SR Jr. Aphasia after left hemispheric intracerebral hemorrhage. Neurology 1980;30:1193–202. [PubMed: 6158714]

Ardekani S, Kumar A, Bartzokis G, Sinha U. Exploratory voxel-based analysis of diffusion indices and hemispheric asymmetry in normal aging. Magnetic Resonance Imaging 2007;25:154–167. [PubMed: 17275609]

Bennett IJ, Madden DJ, Vaidya CJ, Howard DV, Howard JH Jr. Age-related differences in multiple measures of white matter integrity: A diffusion tensor imaging study of healthy aging. Hum Brain Mapp 2010;31:378–90. [PubMed: 19662658]

Bhagat YA, Beaulieu C. Diffusion anisotropy in subcortical white matter and cortical gray matter: changes with aging and the role of CSF-suppression. J Magn Reson Imaging 2004;20:216–27. [PubMed: 15269946]

Blain CR, Barker GJ, Jarosz JM, Coyle NA, Landau S, Brown RG, Chaudhuri KR, Simmons A, Jones DK, Williams SC, Leigh PN. Measuring brain stem and cerebellar damage in parkinsonian syndromes using diffusion tensor MRI. Neurology 2006;67:2199–205. [PubMed: 17190944]

Bodammer N, Kaufmann J, Kanowski M, Tempelmann C. Eddy current correction in diffusion-weighted imaging using pairs of images acquired with opposite diffusion gradient polarity. Magn Reson Med 2004;51:188–93. [PubMed: 14705060]

Bozzali M, Falini A, Franceschi M, Cercignani M, Zuffi M, Scotti G, Comi G, Filippi M. White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. Journal of Neurology Neurosurgery & Psychiatry 2002;72:742–6.

Bucur B, Madden DJ, Spaniol J, Provenzale JM, Cabeza R, White LE, Huettel SA. Age-related slowing of memory retrieval: Contributions of perceptual speed and cerebral white matter integrity. Neurobiol Aging 2008;29:1070–1079. [PubMed: 17383774]

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–52. [PubMed: 14656957]

Corkin, S.; Growdon, JH.; Sullivan, EV.; Nissen, MJ.; Huff, FJ. Assessing treatment effects from a neuropsychological perspective. In: Poon, L., editor. Handbook of Clinical Memory Assessment in Older Adults. Washington DC: American Psychological Association; 1986. p. 156-167.

Courchesne E, Townsend J, Akshoomoff NA, Saitoh O, Yeung-Courchesne R, Lincoln AJ, James HE, Haas RH, Schreibman L, Lau L. Impairment in shifting attention in autistic and cerebellar patients. Behavioral Neuroscience 1994;108:848–865. [PubMed: 7826509]

Damasio A, Geschwind N. The neural basis of language. Annual Review of Neuroscience 1984;7:127–47.

Desmond JE, Chen SH, De Rosa E, Pryor MR, Pfefferbaum A, Sullivan EV. Increased fronto-cerebellar activation in alcoholics during verbal working memory: An fMRI study. NeuroImage 2003;19:1510–1520. [PubMed: 12948707]

Gerig, G.; Corouge, I.; Vachet, C.; Krishnan, KR.; MacFall, JR. Quantitative analysis of diffusion properties of white matter fiber tracts: a validation study; Paper presented at the 13th Proceedings of the International Society for Magnetic Resonance in Medicine; Miami, FL. 2005.

Gutman DA, Holtzheimer PE, Behrens TE, Johansen-Berg H, Mayberg HS. A tractography analysis of two deep brain stimulation white matter targets for depression. Biol Psychiatry 2009;65:276–82. [PubMed: 19013554]

Haber SN, Knutson B. The Reward Circuit: Linking Primate Anatomy and Human Imaging. Neuropsychopharmacology. 2009

Head D, Buckner RL, Shimony JS, Williams LE, Akbudak E, Conturo TE, McAvoy M, Morris JC, Snyder AZ. 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 2004;14:410–423. [PubMed: 15028645]

Hollingshead, A. Four-Factor Index of Social Status. New Haven, CT: Yale University, Department of Sociology; 1975.

Holodny AI, Gor DM, Watts R, Gutin PH, Ulug AM. Diffusion-tensor MR tractography of somatotopic organization of corticospinal tracts in the internal capsule: initial anatomic results in contradistinction to prior reports. Radiology 2005;234:649–53. [PubMed: 15665224]

Janssen I, Katzmarzyk PT, Ross R. Body mass index is inversely related to mortality in older people after adjustment for waist circumference. J Am Geriatr Soc 2005;53:2112–8. [PubMed: 16398895]

Jenkinson M. Improved unwarping of EPI volumes using regularised B_0 Maps (abs). Human Brain Mapping - HBM200. 2001

Jenkinson M. A fast, automated, N-dimensional phase unwrapping algorithm. Magnetic Resonance in Medicine 2003;49:193–197. [PubMed: 12509838]

Kennedy KM, Raz N. Aging white matter and cognition: differential effects of regional variations in diffusion properties on memory, executive functions, and speed. Neuropsychologia 2009;47:916–27. [PubMed: 19166865]

Kim DH, Adalsteinsson E, Glover GH, Spielman DM. Regularized higher-order in vivo shimming. Magnetic Resonance in Medicine 2002;48:715–722. [PubMed: 12353290]

Konishi S, Nakajima K, Uchida I, Kameyama M, Nakahara K, Sekihara K, Miyashita Y. Transient activation of inferior prefrontal cortex during cognitive set shifting. Nat Neurosci 1998;1:80–4. [PubMed: 10195114]

Kretschmann HJ. Localisation of the corticospinal fibers in the internal capsule in man. Journal of Anatomy 1988;160:219–225. [PubMed: 3253257]

Lie CH, Specht K, Marshall JC, Fink GR. Using fMRI to decompose the neural processes underlying the Wisconsin Card Sorting Test. NeuroImage 2006;30:1038–1049. [PubMed: 16414280]

Machado A, Haber S, Sears N, Greenberg B, Malone D, Rezai A. Functional topography of the ventral striatum and anterior limb of the internal capsule determined by electrical stimulation of awake patients. Clin Neurophysiol 2009;120:1941–8. [PubMed: 19781987]

Madden DJ, Bennett IJ, Song AW. Cerebral white matter integrity and cognitive aging: Contributions from diffusion tensor imaging. Neuropsychology Review 2009;19:415–435. [PubMed: 19705281]

Mattis, S. Dementia Rating Scale (DRS) Professional Manual. Odessa, FL: Psychological Assessment Resources, Inc; 2004.

Metter EJ, Riege WH, Hanson WR, Jackson CA, Kempler D, van Lancker D. Subcortical structures in aphasia. An analysis based on (F-18)-fluorodeoxyglucose, positron emission tomography, and computed tomography. Arch Neurol 1988;45:1229–34. [PubMed: 3263849]

Milner B. Effects of different brain lesions on card sorting. Archives of Neurology 1963;9:90–100.

Moore TL, Schettler SP, Killiany RJ, Rosene DL, Moss MB. Effects on executive function following damage to the prefrontal cortex in the rhesus monkey (Macaca mulatta). Behav Neurosci 2009;123:231–41. [PubMed: 19331446]

Morecraft RJ, Herrick JL, Stilwell-Morecraft KS, Louie JL, Schroeder CM, Ottenbacher JG, Schoolfield MW. Localization of arm representation in the corona radiata and internal capsule in the non-human primate. Brain 2002;125:176–98. [PubMed: 11834603]

Mori S, van Zijl PC. Fiber tracking: principles and strategies - a technical review. NMR Biomed 2002;15:468–80. [PubMed: 12489096]

Neeman M, Freyer JP, Sillerud LO. A simple method for obtaining cross-term-free images for diffusion anisotropy studies in NMR microimaging. Magn Reson Med 1991;21:138–43. [PubMed: 1943671]

Newcombe, F. Missile Wounds of the Brain: A Study of Psychological Deficits. London: Oxford University Press; 1969.

Nilsson C, Markenroth Bloch K, Brockstedt S, Latt J, Widner H, Larsson EM. Tracking the neurodegeneration of parkinsonian disorders--a pilot study. Neuroradiology 2007;49:111–9. [PubMed: 17200869]

Niogi S, Mukherjee P, Ghajar J, McCandliss BD. Individual Differences in Distinct Components of Attention are Linked to Anatomical Variations in Distinct White Matter Tracts. Front Neuroanat 2010;4:2. [PubMed: 20204143]

Pfefferbaum A, Adalsteinsson E, Sullivan EV. Frontal circuitry degradation marks healthy adult aging: Evidence from diffusion tensor imaging. NeuroImage 2005;26:891–899. [PubMed: 15955499]

Pfefferbaum A, Rosenbloom MJ, Rohlfing T, Sullivan EV. Degradation of association and projection white matter systems in alcoholism detected with quantitative fiber tracking. Biological Psychiatry 2009;65:680–690. [PubMed: 19103436]

Rohlfing T, Maurer CR. Nonrigid image registration in shared-memory multiprocessor environments with application to brains, breasts, and bees. IEEE Transactions on Information Technology in Biomedicine 2003;7:16–25. [PubMed: 12670015]

Rohlfing T, Zahr NM, Sullivan EV, Pfefferbaum A. The SRI24 multichannel atlas of normal adult human brain structure. Human Brain Mapping 2010;31:798–819. [PubMed: 20017133]

Ross ED. Localization of the pyramidal tract in the internal capsule by whole brain dissection. Neurology 1980;30:59–64. [PubMed: 7188635]

Ruff, R. Ruff Figural Fluence Test: Administration Manual. San Diego, CA: Neuropsychological Resources; 1988.

Salat DH, Tuch DS, Hevelone ND, Fischl B, Corkin S, Rosas HD, Dale AM. Age-related changes in prefrontal white matter measured by diffusion tensor imaging. Ann N Y Acad Sci 2005;1064:37–49. [PubMed: 16394146]

Schmahmann JD, Ko R, MacMore J. The human basis pontis: motor syndromes and topographic organization. Brain 2004;127:1269–91. [PubMed: 15128614]

Schmahmann JD, Rosene DL, Pandya DN. Motor projections to the basis pontis in rhesus monkey. J Comp Neurol 2004;478:248–68. [PubMed: 15368534]

Smith SR, Servesco AM, Edwards JW, Rahban R, Barazani S, Nowinski LA, Little JA, Blazer AL, Green JG. Exploring the validity of the comprehensive trail making test. Clin Neuropsychol 2008;22:507–18. [PubMed: 17853128]

Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage 2002;17:1429–36. [PubMed: 12414282]

Song SK, Yoshino J, Le TQ, Lin SJ, Sun SW, Cross AH, Armstrong RC. Demyelination increases radial diffusivity in corpus callosum of mouse brain. Neuroimage 2005;26:132–140. [PubMed: 15862213]

Stadlbauer A, Salomonowitz E, Strunk G, Hammen T, Ganslandt O. Age-related degradation in the central nervous system: assessment with diffusion-tensor imaging and quantitative fiber tracking. Radiology 2008;247:179–88. [PubMed: 18292477]

Sullivan EV, Adalsteinsson E, Pfefferbaum A. Selective age-related degradation of anterior callosal fiber bundles quantified in vivo with fiber tracking. Cerebral Cortex 2006;16:1030–1039. [PubMed: 16207932]

Sullivan EV, Pfefferbaum A. Magnetic resonance relaxometry reveals central pontine abnormalities in clinically asymptomatic alcoholic men. Alcoholism: Clinical and Experimental Research 2001;25:1206–1212.

Sullivan, EV.; Pfefferbaum, A. Diffusion tensor imaging in aging and age-related disorders. In: Jones, DK., editor. Diffusion MRI: Theory, Methods and Applications. Oxford: Oxford University Press; 2010.

Sullivan EV, Rohlfing T, Pfefferbaum A. Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: Relations to timed performance. Neurobiology of Aging 2010;31:464–481. [PubMed: 18495300]

Sullivan, EV.; Zahr, NM.; Rohlfing, T.; Pfefferbaum, A. Fiber tracking internal capsule regions in normal aging: Cognitive and motor correlates (abs); Paper presented at the Annual Meeting of the Society for Neuroscience; November; Washington, D.C.. 2008 Nov.

Sun SW, Liang HF, Le TQ, Armstrong RC, Cross AH, Song SK. Differential sensitivity of in vivo and ex vivo diffusion tensor imaging to evolving optic nerve injury in mice with retinal ischemia. Neuroimage 2006a;32:1195–204. [PubMed: 16797189]

Sun SW, Liang HF, Trinkaus K, Cross AH, Armstrong RC, Song SK. Noninvasive detection of cuprizone induced axonal damage and demyelination in the mouse corpus callosum. Magn Reson Med 2006b;55:302–8. [PubMed: 16408263]

Takahashi S, Yonezawa H, Takahashi J, Kudo M, Inoue T, Tohgi H. Selective reduction of diffusion anisotropy in white matter of Alzheimer disease brains measured by 3.0 Tesla magnetic resonance imaging. Neuroscience Letters 2002;332:45–48. [PubMed: 12377381]

Takahashi T, Muruta T, Omori M, Kosaka H, Takahashi K, Yonekura Y, Wada Y. Quantitative evaluation of age-related white matter microsctuctural changes in MRI by multifractal analysis. Journal of the Neurological Sciences 2004;225:33–37. [PubMed: 15465083]

Taylor L. Localization of cerebral lesions by psychological testing. Clinical Neurosurgery 1969;16:269–287. [PubMed: 5811709]

Trites, RL. Neuropsychological Test Manual. Ottawa, Ontario, Canada: Royal Ottawa Hospital; 1977.

Vitaliano PP, Breen AR, Albert MS, Russo J, Prinz PN. Memory, attention, and functional status in community-residing Alzheimer type dementia patients and optimally healthy aged individuals. J Gerontol 1984;39:58–64. [PubMed: 6690588]

Wechsler, D. Wechsler Memory Scale - Third Edition. San Antonio, TX: The Psychological Corporation; 1997.

Westlye LT, Walhovd KB, Dale AM, Bjornerud A, Due-Tonnessen P, Engvig A, Grydeland H, Tamnes CK, Ostby Y, Fjell AM. Life-Span Changes of the Human Brain White Matter: Diffusion Tensor Imaging (DTI) and Volumetry. Cereb Cortex. 2009

Xu D, Mori S, Solaiyappan M, van Zijl PC, Davatzikos C. A framework for callosal fiber distribution analysis. Neuroimage 2002;17:1131–1143. [PubMed: 12414255]

Xue R, van Zijl PC, Crain BJ, Solaiyappan M, Mori S. In vivo three-dimensional reconstruction of rat brain axonal projections by diffusion tensor imaging. Magnetic Resonance in Medicine 1999;42:1123–1127. [PubMed: 10571934]

Yoon B, Shim YS, Lee KS, Shon YM, Yang DW. Region-specific changes of cerebral white matter during normal aging: a diffusion-tensor analysis. Arch Gerontol Geriatr 2008;47:129–38. [PubMed: 17764763]

Zahr, NM.; Pfefferbaum, A.; Sullivan, EV. Changes in macroscructure and microstructure of the aging brain. In: Abou-Saleh, M.; Katona, C.; Kumar, A., editors. Principles and Practice of Geriatric Psychiatry. 3. London: Wiley-Blackwell; 2010. in press

Zahr NM, Rohlfing T, Pfefferbaum A, Sullivan EV. Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: A quantitative fiber tracing study. NeuroImage 2009;44:1050–1062. [PubMed: 18977450]

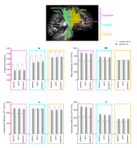

Figure 1.
Top: Midsagittal FA image displaying fiber tracking of the internal capsule divided into its anterior limb, genu, and posterior limb and into superior, central, and inferior divisions. Bar graphs: Mean±standard error FA, MD, λL, and λT of the bilateral anterior limb, genu, and posterior limb of the internal capsule for the younger and older groups. The results are color-coded by superior (magenta), central (turquoise), and inferior (mustard) boxes.

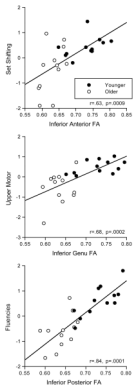

Figure 2.
Correlations between neuropsychological test composite scores and regional FA in the inferior division of the internal capsule across the 24 subjects. Young subjects are presented in closed circles, and older subjects are in open circles.

Table 1

Group by anterior-genu-posterior (AGP) limb by superior-central-inferior (SCI) internal capsule division ANOVA

DTI Metric and Effects	F-value	df	p-value*
FA			
Group	33.168	1,22	**.0001**
Group-by-AGP	0.177	2,44	.838
Group-by-SCI	1.037	2,44	.358
Group-by-AGP-by-SCI	0.409	4,88	.628
MD			
Group	27.546	1,22	**.0001**
Group-by-AGP	6.581	2,44	**.010**
Group-by-SCI	16.039	2,44	**.0001**
Group-by-AGP-by-SCI	1.157	4,88	.324
λL			
Group	1.642	1,22	.213
Group-by-AGP	3.221	2,44	.077
Group-by-SCI	24.076	2,44	**.0001**
Group-by-AGP-by-SCI	1.217	4,88	.307
λT			
Group	40.722	1,22	**.0001**
Group-by-AGP	2.726	2,44	.099
Group-by-SCI	8.429	2,44	**.003**
Group-by-AGP-by-SCI	0.85	4,88	.442

*Greenhouse-Geiser corrected where appropriate; bold=significant effect

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Appendix Table

Correlations between DTI metrics and neuropsychological scores

Regional DTI Metrics		Fluency	Working Memory	Problem Solving	Set Shifting	Upper Limb
Superior						
Anterior						
FA	**r=**	.52	.02	.42	.22	.39
	p=	0.009	0.91	0.039	0.30	0.063
ADC	**r=**	**−.62**	−.18	−.51	−.40	−.59
	p=	**0.0013**	0.4	0.0107	0.0553	0.0024
λL	**r=**	−.60	−.27	−.48	−.44	**−.62**
	p=	0.0021	0.21	0.0176	0.0297	**0.0012**
λT	**r=**	−.60	−.13	−.50	−.36	−.55
	p=	0.0018	0.54	0.012	0.0861	0.0051
Genu						
FA	**r=**	.51	.04	.41	.22	.45
	p=	0.0112	0.84	0.0451	0.30	0.026
ADC	**r=**	−.60	−.19	−.50	−.38	−.60
	p=	0.0017	0.37	0.0119	0.0683	0.0018
λL	**r=**	−.60	−.28	−.49	−.43	−.60
	p=	0.002	0.19	0.0158	0.0382	0.0015
λT	**r=**	−.59	−.14	−.49	−.34	−.58
	p=	0.0026	0.51	0.0141	0.1015	0.0032
Posterior						
FA	**r=**	.50	.08	.44	.22	.48
	p=	0.0135	0.7	0.0314	0.30	0.0178
ADC	**r=**	−.59	−.19	−.53	−.36	−.60
	p=	0.0022	0.37	0.0072	0.0861	0.0018
λL	**r=**	−.59	−.25	−.51	−.39	−.60
	p=	0.0026	0.23	0.0118	0.0581	0.0019
λT	**r=**	−.57	−.15	−.53	−.33	−.58

Regional DTI Metrics		Fluency	Working Memory	Problem Solving	Set Shifting	Upper Limb
	p=	0.0033	0.47	0.0083	0.1175	0.0028
Central						
Anterior						
FA	**r=**	**.75**	.42	.56	.52	.43
	p=	**0.0001**	0.0423	0.0046	0.009	0.0378
ADC	**r=**	−.59	−.40	**−.74**	−.50	**−.61**
	p=	0.0026	0.0528	**0.0001**	0.0126	**0.0014**
λL	**r=**	−.07	−.17	−.49	−.19	−0.42
	p=	0.74	0.44	0.0145	0.38	0.0405
λT	**r=**	**−.72**	−.43	**−.72**	−.55	−.58
	p=	**0.0001**	0.0341	**0.0001**	0.0051	0.0027
Genu						
FA	**r=**	**.77**	.44	.55	.50	.52
	p=	**0.0001**	0.0296	0.0055	0.0136	0.0096
ADC	**r=**	−.60	−.44	**−.75**	−.50	**−.63**
	p=	0.0018	0.0316	**0.0001**	0.0121	**0.0009**
λL	**r=**	−.11	−.22	−.55	−.24	−.40
	p=	0.61	0.34	0.0054	0.26	0.0529
λT	**r=**	**−.73**	−.46	**−.71**	−.54	**−.63**
	p=	**0.0001**	0.0223	**0.0001**	0.0069	**0.001**
Posterior						
FA	**r=**	**.77**	.45	.58	.50	.53
	p=	**0.0001**	0.0291	0.0029	0.0119	0.0075
ADC	**r=**	**−.62**	−.43	**−.75**	−.51	**−.63**
	p=	**0.0011**	0.0373	**0.0001**	0.0104	**0.0009**
λL	**r=**	−.15	−.22	−.57	−.26	−.42
	p=	0.47	0.31	0.0038	0.21	0.041
λT	**r=**	**−.73**	−.45	**−.71**	−.54	**−.63**
	p=	**0.0001**	0.0273	**0.0001**	0.0066	**0.001**

Regional DTI Metrics		Fluency	Working Memory	Problem Solving	Set Shifting	Upper Limb
Inferior						
Anterior						
FA	**r=**	**.82**	.50	.41	**.63**	**.64**
	p=	**0.0001**	0.0137	0.0486	**0.0009**	**0.0008**
ADC	**r=**	−.01	−.29	−.09	−.18	.08
	p=	0.97	0.17	0.69	0.41	0.72
λL	**r=**	**.67**	.21	.26	.40	.58
	p=	**0.0004**	0.31	0.23	0.0527	0.0031
λT	**r=**	**−.74**	−.55	−.37	**−.63**	−.55
	p=	**0.0001**	0.0053	0.0746	**0.0009**	0.0057
Genu						
FA	**r=**	**.82**	.48	.46	.61	**.68**
	p=	**0.0001**	0.0188	0.0235	0.0015	**0.0002**
ADC	**r=**	−.09	−.32	−.19	−.22	−.01
	p=	0.68	0.1255	0.39	0.31	0.95
λL	**r=**	**.67**	.22	.26	.41	.60
	p=	**0.0004**	0.30	0.22	0.0451	0.0018
λT	**r=**	**−.76**	−.54	−.44	**−.63**	**−.62**
	p=	**0.0001**	0.0067	0.0298	**0.0009**	**0.0011**
Posterior						
FA	**r=**	**.84**	.48	.51	.60	**.67**
	p=	**0.0001**	0.0179	0.0118	0.0019	**0.0004**
ADC	**r=**	−.09	−.31	−.21	−.16	.07
	p=	0.66	0.1387	0.32	0.46	0.75
λL	**r=**	**.70**	.25	.30	.45	**.66**
	p=	**0.0001**	0.24	0.16	0.0271	**0.0004**
λT	**r=**	**−.80**	.54	−.50	−.60	−.61
	p=	**0.0001**	0.0062	0.0131	0.0019	0.0017

family-wise Bonferroni correction for 36 comparisons, α =.05, p≤.0014

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bold=significant