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Reduced cerebral white matter integrity assessed by DTI in cognitively normal H63D-HFE polymorphism carriers

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Abstract

Background and Purpose—The H63D-HFE single nucleotide polymorphism (SNP) has been associated with brain iron dysregulation; however, the emergent role of this missense variant in brain structure and function has yet to be determined. Previous work has demonstrated that HFE SNP carriers have reduced white matter MRI proton relaxation rates. The mechanism by which white matter alterations perturb MRI relaxation is unknown as is how these metrics are related to myelin integrity.

Methods—Fifteen subjects homozygous for the HFE-H63D SNP and 25 controls with wildtype HFE had diffusion-weighted, anatomical MRIs taken, and underwent cognitive assessment. Fractional anisotropy (FA), mean diffusion (MD), and mode of anisotropy (MO) were calculated from the diffusion dataset to investigate the relationship between the H63D-HFE SNP and myelin integrity.

Results—A decrease in FA, an increase in MD, and an increase in MO are demonstrated in multiple H63D-HFE polymorphism carrier white matter tracts. Regions with altered diffusion metrics are notably located in heavily myelinated white matter association fibers, such as the anterior corona radiata and longitudinal fasciculi.

Conclusions—The MRI data presented here demonstrate that H63D-HFE polymorphism carriers have diffusivity changes in white matter compared to wild-type subjects. The reduced integrity white matter tracts in H63D-HFE carriers is hypothesized to be related to increased susceptibility of these late-myelinating regions to cellular stress induced by oligodendrocyte iron dyshomeostasis.

Keywords

White Matter; HFE; H63D; DTI; MRI

Introduction

Prominent single nucleotide polymorphisms (SNPs) within the HFE gene sequence (H63D and C282Y) were initially characterized in individuals with hereditary hemochromatosis.¹ Each HFE SNP produces a functional conformation change which alters binding affinity to the transferrin receptor resulting in cellular iron dyshomeostasis, increased oxidative stress, and alterations in inflammatory response.² These SNPs are highly prevalent with global carrier penetrance rates of 15.6% and 3.8% for H63D and C282Y, respectively.^{3, 4} While the C282Y SNP is strongly implicated in systemic iron overload, the H63D SNP only modestly alters iron load in human carriers⁵, both have been indicated to interact with the development of neurodegenerative disease. Additionally, recent evidence suggests that the H63D polymorphism results in a change of the HFE ALK3 interaction in the bone morphogenic pathway; resulting in potential downstream oligodendrocyte maturation modification.⁶

The major structures that comprise white matter are oligodendrocyte cell bodies, neuronal axons, and myelin. Oligodendrocytes are responsible for the myelination of axons in white matter to increase action potential amplitude and improve conductivity. Water, total lipid, and cholesterol content of white matter change with age, such that lipid and cholesterol content increase during myelin maturation.⁷ Additionally, oligodendrocytes are the predominant iron containing cells in the human brain with remarkably high iron load due to the co-factor mediated redox reactions in cholesterol synthesis, lipid biosynthesis during myelination, and maintenance of metabolic processes.⁸ The accumulation of iron in the brain rapidly increases during childhood and plateaus during mid-adulthood, temporally coinciding with myelination of late forming white matter regions.⁹ Body iron homeostasis is tightly regulated at the proximal small intestine to govern the efflux of iron into plasma.¹⁰ Regulation of brain iron is further controlled at the level of the blood brain barrier via microvascular endothelial cells and astrocytes.¹¹ The loss of systemic and brain iron regulation, leading to neural iron overload, subsequent oxidative stress, and cell death, is observed in a number of neurological conditions.¹²

In a previous study, we demonstrated that H63D polymorphism carriers display decreased MRI relaxation rates in late-myelinating white matter regions such as the frontal fasciculi and anterior corona radiata of the frontal lobe.¹³ White matter proton relaxation is a factor of lipid/cholesterol content, axonal water restriction, iron content, and density of white matter myelination. The macromolecular proton changes suggest modifications in myelination within regions of the H63D-HFE carrier brain that myelinate later in life. While relaxation measures demonstrate an underlying change in white matter pathology, the metric does not provide a clear indication of white matter integrity. Conversely, diffusion MRI parametrics provide insight into the pathological characteristics of white matter. As such, diffusion

tensor metrics were utilized in this study to investigate more precisely the relationship between the H63D-HFE polymorphism and myelin integrity.

Materials & Methods

HFE H63D and Control Study Participants

Study participants were consented and enrolled within an ongoing memory and aging study approved by The Pennsylvania State University – College of Medicine Institutional Review Board (IRB). All participants were administered a battery of cognitive tests by a neuropsychologist and subjects selected for this study were determined to be within a cognitively normal range^{14, 15} based on these results (Table 1) and reported no neurological or medical complications. A total of forty healthy cognitively normal subjects (twenty-one male) were included in this study design. Blood samples from each subject were drawn and genotyped for the HFE-H63D single nucleotide variations via conventional multiplex polymerase chain reaction amplification and primer/probe binding.^{16, 17} A total of 15 participants (six male) were heterozygous for the H63D/+ minor G allele (rs1799945), no homozygous H63D participants were identified. All subjects identified as having the H63D SNP were stratified into an H63D-HFE positive group. Twenty-five participants (fifteen male) were identified as having wild-type alleles for HFE and were stratified as WT-HFE controls (Table 2). No statistical bias in gender difference was determined in the study cohorts ($p=0.220$). No subjects in the study, either HFE-WT or HFE-H63D, presented with hemochromatosis.

MRI Protocols

All subjects were scanned on a 3.0 T Siemens Tim Trio system. A 3D T₁-weighted scan was obtained with the following parameters: TR = 2300 ms, TE = 2.98 ms, FOV = 25.6 x 25.6 x 16 cm, matrix = 256 x 256 x 160, for a final isotropic resolution of 1 x 1 x 1 mm. A multi-echo T₂-weighted spin-echo protocol was used with the following parameters: average = 1, TR = 6000 ms, 9 echoes with TE = 11 – 99 ms with an echo spacing of 11 ms, FOV = 17.6 x 25.6 x 14 cm, matrix = 176 x 256 x 56, for a final resolution of 1 x 1 x 2.5 mm. Diffusion tensor imaging parameters were 1 average, TR = 8300, TE = 87, FOV = 256 x 256 x 130 mm, matrix dimension = 128 x 128 x 65, 65 slices, 2mm isotropic voxel size, and B-values of 0 and 1000 with 10 A0 and 60 B1000 directions.

Diffusion MRI Statistical Parametric Analysis

Diffusion imaging data were eddy- and motion-corrected with the FSL toolbox (FMRIB Software Library v5.0, Oxford, UK.).¹⁸ Fractional anisotropy (FA), mode of anisotropy (MO), and mean diffusivity (MD) parametric maps were then calculated using the DTIFIT FSL module. All diffusion maps (FA, MO, and MD) were spatially aligned to the 3D-T₁ image using a rigid-body transformation, realigned to the MNI152 atlas standard space¹⁹, normalized to the Johns Hopkins University (JHU) FA template²⁰ using the individual subject FA map at a spatial resolution of 1 x 1 x 1 mm, and smoothed with a 2.5 mm isotropic Gaussian kernel using SPM 8 (Wellcome Trust Centre for Neuroimaging, UK).

For diffusion MRI statistical parametric analyses, the subjects were stratified based on their H63D carrier status. A group based statistical parametric two-sample T-test was performed between the H63D-HFE vs WT-HFE subject groups using age and gender as covariates in the design matrix. These tests were performed within SPM 8 using the normalized diffusion parametric maps with a regional white matter inclusive mask, a p value = 0.0025, and an absolute voxel cluster extent threshold size = 50; on par with recommended conservative thresholds for genetic neuroimaging studies.^{21–23}

For regional analysis of diffusion data the JHU-MNI-SS “Eve” template^{20, 24} was normalized to the MNI152 template brain. The regions of interest from this atlas were individually parcellated and normalized to the MNI152 atlas along with the template brain, consisting of 176 individual white and gray matter ROIs. As the hypothesis for this work focused on white matter diffusion differences specifically, 98 ROIs containing white matter were selected from the JHU atlas (Table 4).²⁴ The individual regions were imported into the MarsBaR toolbox for SPM²⁵ and FA, MD, and MO measures were output for each subjects’ normalized diffusion parametric map.

Statistical Analysis of Demographic, Cognitive Tests, and regional Diffusion MRI

For statistical data analysis, the SPSS 24 program package was utilized (IBM Corporation, Armonk, New York). An analysis of co-variance (ANCOVA) was performed using the general linear model with Bonferroni correction in the design. Subject age and gender were used as covariates for all cognitive tests. Two-tailed T-tests using the general linear model with Bonferroni correction were used to test for significance between H63D carrier and non-carrier subjects for age. A chi-square test of independence was used to test for significance between groups for gender bias, gene frequency, and allele frequency between the samples. Regional FA, MD, and MO parametric outputs from the 98 white matter ROIs in the JHU atlas were statistically compared using a one-way ANOVA with Tukey multiple comparison correction and a p value threshold of 0.05.

Results

Participant demographic and neurocognitive testing determined that there was no difference between H63D-HFE and WT-HFE subjects in age, gender distribution, and on all cognitive measures except the dementia rating scale ($p = 0.044$, Table 1). The H63D (rs1799945) minor G allele and genotype frequencies were determined to be similar to reported population demographics ($\chi^2 = 0.483$ & 0.269, respectively).^{3, 4, 26} The genotype of the study population was not significantly different from expected values for SNPs as determined by the Hardy-Weinberg genetic equilibrium ($\chi^2 = 0.910$).

Voxel-based comparison between genetically stratified cognitively normal subjects demonstrates a reduction in fractional anisotropy within white matter regions of H63D-HFE subjects (Fig. 1a and b). Regions with reduced FA include the right anterior corona radiata, right orbitofrontal tract, left superior longitudinal fasciculus, and left subcallosal fasciculus (Fig. 1b). Mean diffusion parametric analysis demonstrates focal increases in white matter regions in the H63D-HFE subject group (Fig. 2a and b). Regions with increased mean diffusion include the anterior corona radiata, superior corona radiata, superior occipital-

frontal fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, forceps minor, and the subcallosal fasciculus. H63D subjects further demonstrate an increase in anisotropy mode in the superior posterior limb of the left internal capsule (retrolenticular) (Fig. 3a and b).

FA, MD, and MO parameters of white matter regions of interest from the 'Eve' atlas can be found in Table 3 (ROIs in Fig. 4 with complete list in table 4). A number of white matter tracts in the H63D subjects have altered diffusion parametrics on regional analysis that overlap with voxel based differences outlined in Figs. 1–3. An overlap between voxel-wise and ROI differences is not expected due to the regional averaging of parametric measures in the ROI analysis. Region on interest with decreased FA include the right anterior portion of the corona radiata, the left occipitofrontal fasciculus, bilateral white matter of the lateral orbitofrontal cortex, bilateral middle temporal gyrus white matter, bilateral superior frontal gyrus white matter, and bilateral superior temporal gyrus white matter. An increase in H63D white matter mean diffusion is found bilaterally in the anterior portion of the corona radiata, left external capsule, left gyrus rectus white matter, and right superior temporal gyrus white matter. An increase in white matter mode of anisotropy was found bilaterally in the retrolenticular internal capsule of H63D patients.

Discussion

The interaction of HFE gene sequence polymorphisms and white matter integrity largely remains unknown. The MRI data presented here demonstrate that cognitively normal H63D-HFE carriers have diffusivity changes in white matter compared to wild-type subjects. Numerous alterations are observed in white matter regions connecting associative and executive areas of the brain. The proton diffusion changes suggest axonal modifications within white matter regions known to myelinate later in development.

The frontal white matter reductions in FA and increase in MD are indicative of reduced integrity as the tissue becomes less structured with proton behavior approaching that of a cellular water compartment. The FA reduction in H63D subjects is found in frontal white matter communicating fibers between structures supporting high-level cognitive capabilities. Furthermore, the reduced FA and MD increase in H63D-HFE carriers' anterior corona radiata hemispherically connect those white matter regions outlined in the comparison. The frontal regions with increased MD overlap precisely with previous magnetic resonance imaging work which revealed proton relaxation rate reductions in late-myelinating frontal fascicular white matter of H63D-HFE genotype carriers.¹³ We hypothesize that the white matter alterations outlined with diffusion metrics are related to metabolic iron changes within late-myelinating oligodendrocytes of the frontal lobe white matter.

Oligodendrocytes contain the majority of brain iron, as it is required for myelinogenesis, and disruption of white-matter iron homeostasis results in myelination alteration and cognitive impairment.^{27, 28} Changes in myelin are discernable by their effects on proton diffusivity within a voxel, measurable by DTI metrics. The observation that these alterations are located in late-myelinating frontal areas is hypothesized to be related to increased cellular susceptibility within this region in HFE polymorphism carriers. The H63D SNP has been

associated with iron dyshomeostasis resulting in increased oxidative stress and inflammatory response.²⁹ Iron accumulation in the brain, oxidative stress, and reduction in myelin integrity are observed in a number of neurological conditions.

Diffusion based measures of white matter integrity are well known to correlate to alterations in cognition. Increased executive function is positively correlated with FA and negatively with MD in frontal white matter tracts, anterior internal capsule, and the genu of corpus callosum.^{30, 31} Reductions in language and attention processing correlate with diffusion parameters (reduced FA and increased MD) in the frontal lobe of Parkinson's patients.³⁰ Fractional anisotropy of the corpus callosum genu is negatively associated with increased apathy in schizophrenia patients indicative of executive function disruption.³¹ Additionally, white matter microstructure and integrity have been associated with a number of genetic variants such as *CLU*³², *COMT*³³, *NTRK1/3*^{34, 35}, and *ErbB4*.³⁶ While the H63D-HFE participants did not show a reduction in apparent clinical cognitive ability, there was a slight reduction in H63D carrier dementia rating scale score. The cognitive measures used in this study were designed to identify subjects with gross cognitive declines associated with neurodegeneration. All participants were within standard cognitive normal range, with H63D-HFE carriers placing within the 60th – 71st percentile and WT-HFE in the 72nd – 81st percentile.¹⁴ The significance of these white matter MRI diffusion alterations and how they relate to detailed cognitive performance remain unidentified. The sensitivity of the diffusion metrics compared to cognitive measures is hard to determine with the limited number of subjects in this study cohort. Finer measures of cognition are required to delineate if there are subtle changes in cognitive ability within the HFE polymorphism carriers.

A decrease in FA with an increase in both MO and MD are indicative of general loss of axonal integrity. Crossing fiber integrity was determined with the calculation of the mode of anisotropy which describes the anisotropy type as planar or linear in the voxel of interest.³⁷ Voxels with predominant planar orientation indicate crossing fibers in those regions while those with linear orientation indicate less regional crossing fibers. A change of MO denotes an alteration in the number of crossing fibers in each voxel, such that an increase signifies a decrease in the number of axonal crossing fibers and general decrease in track integrity. The MO increase in the retrolenticular portion of the internal capsule has the occipitopontine, occipitotectal, and optic radiations crossing through the region. The increase in anisotropy mode is indicative of a decrease in crossing fiber planarity, however it does not relay information on which axis (primary, secondary, or tertiary) has reduced fiber integrity. While motor or visual skills were not specifically examined, no subject deficiencies were noted in the study cohort. As such, it is hard to determine if the increase in diffusion mode represents reduced fiber integrity along longitudinal (visual) or descending (motor) tracts. However, the overlapped increase in MD and diffusion mode strengthens the hypothesis for reduced fiber integrity in H63D carriers within this region (Figs. 2 and 3).

A left-right asymmetry is observed in the FA, MD, and MO parametric maps. The reduction in H63D-HFE FA is most noted on the right while the H63D increase in MD and MO are noted in left portions of the brain. There is an observed bilateral distribution of a white matter MD increase in H63D-HFE subjects throughout the brain. While an overlap in all diffusion parametrics is not expected, as they represent different aspects of white matter

proton diffusion, an overlap between the three diffusion metrics in observed within left retrolenticular white matter lateral to the corpus callosum. This overlap highlights this region as having microstructural white matter changes, potentially related to demyelination and change in proton cellular compartmentalization.

While the outcome of this work demonstrates a relationship between white matter integrity and HFE polymorphisms, the data should be interpreted in the context of the study design and limitations. The limited number of subjects, geographic localization, and gender distribution within the study cohort should be noted, as these can be determinant factors in outcomes from genome wide imaging studies. However, comparison to the genetic and gender makeup of similar consortium cohorts demonstrates that the study population in this work did not deviate from expected genetic penetrance and gender bias. The examination of the dependent and independent interaction of the H63D and C282Y polymorphisms to each other was not possible with the number of study carriers identified with the C282Y SNP. When considered in the context of the wider literature base, the data and outcomes in this study are congruent with prior research illustrating brain MRI alterations within HFE polymorphism carriers.^{38, 39} It is of interest that HFE is involved in the bone morphogenic pathway through its interaction with ALK3 (BMPRIa), such that the H63D-HFE polymorphism limits cell surface expression.⁶ This interaction represents a plausible link between HFE polymorphisms and the associated reduction in white matter integrity demonstrated in this study.^{40, 41}

There is a limited amount of work on the associative interaction between HFE genetics and MRI metrics^{13, 42, 43}, especially those related to white matter integrity.³⁸ Our data provide evidence that there are alterations in frontal lobe white matter integrity in the fasciculi and corona radiata that are hemispherically connected with frontal and orbitofrontal regions associated with higher executive function. The apparent decrease in white matter integrity in the outlined regions is hypothesized to relate to increased axonal susceptibility in these regions to cellular stress. Future study will be required to further delineate how the H63D-HFE polymorphism interplays with white matter integrity histologically and if axonal alterations are linked to subtle behavioral changes.

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Figure 1.

Decrease in white matter fractional anisotropy in H63D-HFE polymorphism compared to wild-type (WT) carriers visualized in three-axes (a) and along a posterior to anterior progression with atlas coordinate notation (b). Parametric group analyses demonstrates a fractional anisotropy decrease in the right anterior corona radiata (yellow arrow), right orbitofrontal tract (purple arrow), left superior longitudinal fasciculus (blue arrow), and left subcallosal fasciculus (green arrow) white matter of H63D carriers. Voxel threshold of $p < 0.0025$ with a minimal cluster size of 50.

Figure 2.

Increase in white matter mean diffusivity in H63D-HFE polymorphism compared to wild-type (WT) carriers visualized in three-axes (a) and along a posterior to anterior progression with atlas coordinate notation (b). Regions with increased mean diffusion (MD) in the H63D-HFE polymorphism carriers were found in the superior corona radiata (cyan arrow), anterior corona radiata (yellow arrow), superior occipito-frontal fasciculus (purple arrow), inferior longitudinal fasciculus (orange arrow), superior longitudinal fasciculus (blue arrow), forceps minor (red arrow), and subcallosal fasciculus (green arrow). It is notable that the frontal lobe white matter regions with reduced fractional anisotropy outlined in Fig. 1 overlap with frontal lobe regions with increased MD. Furthermore, frontal regions outlined here overlap with previous data showing a decrease in proton relaxation rate. Voxel threshold of $p < 0.0025$ with a minimal cluster size of 50.

Figure 3.

Regions with increased mode of anisotropy in the H63D-HFE polymorphism compared to wild-type (WT) carriers visualized in three-axes (a) and along a posterior to anterior progression with atlas coordinate notation (b). An increase in anisotropy mode is demonstrated in H63D-HFE polymorphism carriers in the superior-posterior limb of the internal capsule (retrolenticular) as it extends into the superior corona radiata (white arrow). Furthermore, the regional increase in mode overlaps with regions with increased mean diffusion in the H63D-HFE carriers. Voxel threshold of $p < 0.0025$ with a minimal cluster size of 50.

Figure 4.

Illustration of the JHU 'Eve' atlas regions of interest found to be different between H63D- and Wild-Type-HFE subjects (Table 3). The Corona Radiata Anterior (dark blue), Inferior Frontal Occipital Fasciculus (mid-blue), Lateral Fronto-Orbital White Matter (WM) (light blue), Middle Temporal WM (cyan), Superior Frontal WM (green), Superior Temporal WM (yellow), External Capsule (orange), Rectus WM (red), and Internal Capsule Retrolenticular (maroon) are illustrated in the same posterior to anterior progression with atlas coordinate notation as the other figures.

Table 1

Subject Demographics and Cognitive Scores

Demographic and Cognitive Test	Genotype		P Value
	H63D-HFE	WT-HFE	
Sex	6 Male; 9 Female	15 Male; 10 Female	$p = 0.220$
Age	73.93 ± 2.67	66.64 ± 1.73	$p = 0.110$
CDR	0.0 ± 0.0	0.042 ± 0.029	$p = 0.432$ [†]
MMSE	28.27 ± 0.44	28.80 ± 0.28	$p = 0.206$ [†]
DRS-2	139.6 ± 0.74	141.4 ± 0.39	$p = 0.044$ [†]
CVLT-II	58.87 ± 2.25	61.54 ± 3.07	$p = 0.715$ [†]
GDS	4.54 ± 0.86	2.38 ± 0.81	$p = 0.616$ [†]
BAI	4.07 ± 0.93	3.36 ± 0.83	$p = 0.436$ [†]
BEHAVE-AD	0.27 ± 0.15	0.16 ± 0.09	$p = 0.867$ [†]

WT = wild type, CDR = Clinical Dementia Rating, MMSE = Mini Mental State Examination, DRS-2 = Dementia Rating Scale-2, AMSS = Age-adjusted MOANS Scaled Score, AEMSS = Age and Education adjusted MOANS Scale Score, CVLT-II = California Verbal Learning Test Second Edition, GDS = Geriatric Depression Scale, BAI = Beck Anxiety Inventory, and BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease

[†] Gender, age, and multiple comparison corrected

Table 2

Subject HFE Genotype and Prevalence

Genotype	Total	Males	Females	% Incidence
H63D/+ (rs1799945)	15	6	9	37.5
Wild Type +/+	25	15	10	62.5

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Table 3

Regional Diffusion Measures

Region	Genotype		P Value
	H63D-HFE FA	WT-HFE FA	
Corona Radiata Anterior (R)	0.294 ± 0.008	0.323 ± 0.007	0.031
Inferior Frontal Occipital Fasciculus (L)	0.149 ± 0.003	0.158 ± 0.002	0.050
Lateral Fronto-Orbital WM (L)	0.168 ± 0.002	0.187 ± 0.004	0.001
Lateral Fronto-Orbital WM (R)	0.173 ± 0.003	0.191 ± 0.005	0.014
Middle Temporal WM (L)	0.161 ± 0.003	0.177 ± 0.004	0.003
Middle Temporal WM (R)	0.171 ± 0.003	0.183 ± 0.005	0.050
Superior Frontal WM (L)	0.257 ± 0.008	0.296 ± 0.013	0.036
Superior Frontal WM (R)	0.195 ± 0.006	0.237 ± 0.017	0.041
Superior Temporal WM (L)	0.139 ± 0.003	0.155 ± 0.005	0.006
Superior Temporal WM (R)	0.147 ± 0.003	0.161 ± 0.006	0.048
Region	H63D-HFE MD (x10 ⁻³)	WT-HFE MD (x10 ⁻³)	
Corona Radiata Anterior (L)	0.904 ± 0.012	0.845 ± 0.010	0.016
Corona Radiata Anterior (R)	0.935 ± 0.014	0.862 ± 0.013	0.048
External Capsule (L)	0.864 ± 0.014	0.802 ± 0.009	0.033
Rectus WM (L)	0.912 ± 0.012	0.862 ± 0.015	0.042
Superior Temporal WM (R)	1.408 ± 0.153	1.261 ± 0.035	0.033
Region	H63D-HFE Mode	WT-HFE Mode	
Internal Capsule Retrolenticular (L)	0.558 ± 0.012	0.506 ± 0.020	0.016
Internal Capsule Retrolenticular (R)	0.492 ± 0.011	0.442 ± 0.020	0.044

L = left, R = right, FA = fractional anisotropy, MD = mean diffusion, MO = mode of diffusion, WT = wild type, WM = white matter

All ROIs were multiple comparison corrected in the statistical model.

Table 4

White matter regions in the ROI analysis

White Matter Regions from JHU 'Eve' Atlas	
Angular WM (L)	
Angular WM (R)	
Cerebellum WM (L)	
Cerebellum WM (R)	
Cerebral Peduncle (L)	
Cerebral Peduncle (R)	
Cingulum WM (L)	
Cingulum WM (R)	
Corona Radiata Anterior (L)	
Corona Radiata Anterior (R)	
Corona Radiata Posterior (L)	
Corona Radiata Posterior (R)	
Corona Radiata Superior (L)	
Corona Radiata Superior (R)	
Corpus Callosum Body (L)	
Corpus Callosum Body (R)	
Corpus Callosum Genu (L)	
Corpus Callosum Genu (R)	
Corpus Callosum Splenium (L)	
Corpus Callosum Splenium (R)	
Corticospinal Tract (L)	
Corticospinal Tract (R)	
Cuneus WM (L)	
Cuneus WM (R)	
External Capsule (L)	
External Capsule (R)	
Fornix (L)	
Fornix (R)	
Fornix Stria Terminalis (L)	
Fornix Stria Terminalis (R)	
Fusiform WM (L)	
Fusiform WM (R)	
Inferior Cerebellar Peduncle (L)	
Inferior Cerebellar Peduncle (R)	
Inferior Frontal Occipital Fasciculus (L)	
Inferior Frontal Occipital Fasciculus (R)	
Inferior Frontal WM (L)	
Inferior Frontal WM (R)	
Inferior Occipital WM (L)	

White Matter Regions from JHU ‘Eve’ Atlas

Inferior Occipital WM (R)
 Inferior Temporal WM (L)
 Inferior Temporal WM (R)
 Internal Capsule Anterior (L)
 Internal Capsule Anterior (R)
 Internal Capsule Posterior (L)
 Internal Capsule Posterior (R)
 Internal Capsule Retrolenticular (L)
 Internal Capsule Retrolenticular (R)
 Lateral Fronto-Orbital WM (L)
 Lateral Fronto-Orbital WM (R)
 Lingual WM (L)
 Lingual WM (R)
 Medial Lemniscus (L)
 Medial Lemniscus (R)
 Middle Cerebellar Peduncle (L)
 Middle Cerebellar Peduncle (R)
 Middle Frontal Orbital WM (L)
 Middle Frontal Orbital WM (R)
 Middle Frontal WM (L)
 Middle Frontal WM (R)
 Middle Occipital WM (L)
 Middle Occipital WM (R)
 Middle Temporal WM (L)
 Middle Temporal WM (R)
 Pontine Crossing Tract (L)
 Pontine Crossing Tract (R)
 Postcentral WM (L)
 Postcentral WM (R)
 Precentral WM (L)
 Precentral WM (R)
 Pre-Cuneus WM (L)
 Pre-Cuneus WM (R)
 Rectus WM (L)
 Rectus WM (R)
 Sagittal Stratum (L)
 Sagittal Stratum (R)
 Superior Cerebellar Peduncle (L)
 Superior Cerebellar Peduncle (R)
 Superior Frontal Occipital Fasciculus (L)
 Superior Frontal Occipital Fasciculus (R)
 Superior Frontal WM (L)

White Matter Regions from JHU ‘Eve’ Atlas	
Superior Frontal WM (R)	
Superior Longitudinal Fasciculus (L)	
Superior Longitudinal Fasciculus (R)	
Superior Occipital WM (L)	
Superior Occipital WM (R)	
Superior Parietal WM (L)	
Superior Parietal WM (R)	
Superior Temporal WM (L)	
Superior Temporal WM (R)	
Supramarginal WM (L)	
Supramarginal WM (R)	
Tapatum (L)	
Tapatum (R)	
Thalamic Radiation (L)	
Thalamic Radiation (R)	
Uncinate Fasciculus (L)	
Uncinate Fasciculus (R)	

L = left, R = Right, WM = White Matter

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