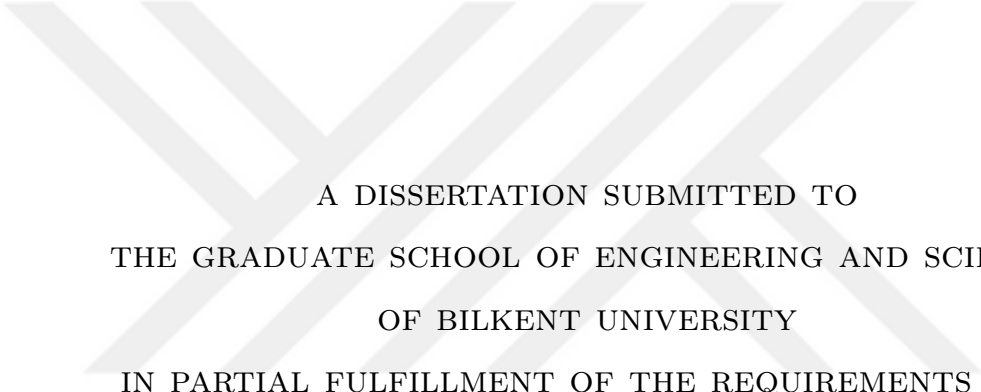


GENETIC INFLUENCES ON CORTICAL STRUCTURE AND FUNCTION



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By
Pınar Demirayak
July 2018

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FUNCTION

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We certify that we have read this dissertation and that in our opinion it is fully adequate, in scope and in quality, as a dissertation for the degree of Doctor of Philosophy.

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ABSTRACT

GENETIC INFLUENCES ON CORTICAL STRUCTURE AND FUNCTION

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Structure and function of the human central nervous system is determined by both genetic and environmental influences. One of the fundamental quests in neuroscience studies is to determine to what degree each of these two factors influence the development and function of the nervous system and, ultimately, human behavior. However, this is an inherently difficult problem to tackle as it is nearly impossible to tease apart the individual contributions of genes and environment, since they interact heavily throughout an organism's life. Recently, our understanding about the role that specific genes play in the development of brain structure and function, has been greatly advanced by studies that combine genetic and neuroimaging methods to investigate congenital neurodevelopmental disorders. These studies of patients, that are homozygous for a specific mutation, allow to single out contributions of individual genes in the neurodevelopmental process and have the potential to reveal gene-based alterations in cortical structure and function that can not be compensated by mechanisms of cortical plasticity or mitigating environmental effects. In this thesis I pursue this promising approach further and investigate the effects of three different single gene mutations on brain structure and function - namely *RAD51*, *LAMC3* and *HTRA2*. Each of these genes is highly expressed during neurodevelopment, and each influences cortical structure and function differently. Overall, I find that these genes are all highly associated with abnormal structural and functional connectivity patterns, however, and surprisingly, highly abnormal structure does not necessarily predict highly abnormal behavior.

Keywords: Congenital Mirror Movements Disorder, RAD51, Pachygyria, LAMC3, Essential Tremor, HTRA2, connectivity.

ÖZET

GENETİĞİN KORTİKAL YAPI VE FONKSİYONA ETKİSİ

Pınar Demirayak

Nörobilim, Doktora

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İnsan merkezi sinir sisteminin yapısı ve işlevi hem genetik hem de çevresel etkiler tarafından belirlenir. Nörobilim çalışmalarının temel amaçlarından biri, bu iki faktörün her birinin sinir sisteminin gelişimini ve işlevini ve nihayetinde insan davranışını ne derece etkilediğini belirlemektir. Bununla birlikte, bir organizmanın yaşamı boyunca büyük ölçüde etkileşime girdiği için genlerin ve çevrenin bireysel katkılarını birbirinden ayırmanın neredeyse imkânsız olması nedeyle baş edilmesi zor bir problemidir. Son zamanlarda spesifik genlerin beyin yapısının ve fonksiyonunun gelişiminde oynadığı rol hakkındaki bilgi birikimi, doğumsal nörogelişimsel bozuklukları araştırmak için genetik ve nörogörüntüleme yöntemlerini birleştiren çalışmalarla büyük ölçüde ilerlemiştir. Belirli bir mutasyon için homozigot olan hastalar üzerinde yapılan bu çalışmalar, nörogelişimsel süreçte bireysel genlerin tek başına katkılarının anlaşılmasına izin verir ve kortikal plastisite mekanizmaları veya çevresel etkilerin hafifletilmesi ile telafi edilemeyen kortikal yapı ve fonksiyondaki gen temelli değişiklikleri ortaya çıkarma potansiyeline sahiptir. Bu tez çalışmasında, bu umut verici yaklaşımı daha ileriye götürecek üç farklı tek gen mutasyonunun- textit RAD51, textit LAMC3 ve textit HTRA2 - beyin yapısı ve işlevi üzerindeki etkileri araştırılmıştır. Bu genlerin her biri nörogelişim sırasında yüksek oranda ifade edilir, her biri kortikal yapıyı etkiler ve farklı işlev görür. Genel olarak, bu genlerin anormal yapısal ve fonksiyonel bağlantı modelleri ile çok ilişkili olduğunu ancak şaşırtıcı bir şekilde, oldukça anormal yapının yüksek derecede anormal davranışı öngörmediği saptanmıştır.

Anahtar sözcükler: Doğumsal Ayna Hareket Bozukluğu, RAD51, Pakigiri, LAMC3, Esansiyel Tremor, HTRA2, bağlantısallık.



To my beloved family

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Contents

1	Introduction	1
1.1	Neurodevelopment of Human Brain	1
1.1.1	Gray Matter Development	4
1.1.2	White Matter Development	5
1.1.3	Neurobiological Circuits of Sensory and Cognitive Processes in Neurodevelopmental Disorders	7
1.1.4	Genetic Mechanisms of Abnormal Cortical Architecture	9
1.1.5	Methodological comparisons for MRI analysis software packages	12
2	Bilateral Occipital Pachygyria	15
2.1	Background	15
2.2	Materials and Methods	17
2.2.1	Participants	17
2.2.2	Data Acquisition	18
2.2.3	Functional Localizer	19
2.2.4	Analysis	20
2.3	Results	23
2.3.1	Microstructural Integrity along Major White Matter Pathways	24
2.3.2	Functional Connectivity	31
2.4	Discussion	35
2.4.1	By what mechanism are object and face perception spared?	36
2.4.2	Evidence for compromised visuo-spatial attention.	37
2.4.3	Agreement of structural and functional indeces.	38

2.4.4	Gray matter or white matter – the LAMC3 chicken and egg question.	39
2.4.5	Limitations	40
2.5	Conclusion	42
3	Essential Tremor	43
3.1	Background	43
3.2	Materials and Methods	45
3.2.1	Participants	45
3.2.2	Data Acquisition	46
3.2.3	Morphometry Analysis	46
3.2.4	DTI Analysis	47
3.3	Results	48
3.3.1	Clinical Assessment of Essential Tremor	48
3.3.2	Morphological Assessment	49
3.3.3	WM Microstructural Integrity Assessment	52
3.4	Discussion	52
3.4.1	Essential Tremor related to a structural neural anomaly along cerebellar-thalamic-cortical pathway	55
3.4.2	Increment of superior temporal gyrus could be a compensatory mechanism for ET?	56
3.4.3	Malformations in microstructural architecture effects local connections in ET	57
3.4.4	How the genetic component of the ET is effective on structural architecture?	58
3.5	Conclusion	59
4	Congenital Mirror Movement	60
4.1	Background	60
4.2	Materials and Methods	64
4.2.1	Participants	64
4.2.2	Data Acquisition	64
4.2.3	Task-based fMRI Experimental Procedures & Analyses . .	65
4.2.4	Resting State Analysis Procedures	67

4.2.5	DTI Analysis Procedures	68
4.2.6	Nonparametric Analysis Procedures	69
4.3	Results	69
4.3.1	Task-related fMRI Activity	69
4.3.2	Structural Connections	71
4.3.3	Functional Connectivity	76
4.4	Discussion	80
4.5	Conclusion	84
5	General Discussion and Conclusion	85
5.1	Genetic Influences on Neurodevelopment	85
5.2	Genetic Influences on White Matter Integrity	87
5.3	Genetic Influences on Functional Connectivity	88
5.4	Genetic Influences on Brain Morphometry	88
5.5	Overall Conclusion	89
A	White Matter Connections in Bilateral Occipital Pachygyria Case	122
B	Functional Connectivity in Bilateral Occipital Pachygyria Case	126
C	Demographic Information of Essential Tremor	136
D	Corticospinal fibers reconstruction in CMMD patient	139
E	2D Reconstruction of Dentate Rubro Thalamic and Cortico Ponto Cerebellar Pathways	142
F	Functional Connectivity among motor areas in CMMD	146

List of Figures

2.1	T1-weighted images of the patient's brain and the MNI 2 mm standard template (from 152 participants' brains). Shown are a sagittal, coronal and transversal views (from left to right). Red arrows point to pachygyric regions in the occipital lobes.	16
2.2	White matter tract atlas of the patient and a matched healthy control participant. This figure depicts tracts of the brain stem, projection and association fibers. While fiber volume appears to be reduced in bilateral IFOF, ILF, SLF and posterior corona radiata, we also note an increased fiber volume in anterior corona radiata in the patient. Images are labelled color FA maps co-registered onto T1 weighted anatomical images (following radiological convention). Label Glossary:ac-anterior commissure, acr-anterior region of corona radiata, alic-anterior limb of internal capsule, cbt-corticobulbar tract, cg-cingulum, cst-corticospinal tract, dscp-decussation of superior cerebral peduncle, icp-inferior cerebral peduncle, ifo-inferior fronto-occipital fasciculus, ilf-inferior longitudinal fasciculus, pcr-posterior region of corona radiata, plic-posterior limb of internal capsule, scr-superior region of internal capsule, sfo-superior fronto-occipital fasciculus, slf-superior longitudinal fasciculus, unc-uncinate fasciculus	26
2.3	White matter tract atlas of the patient and a matched healthy control participant. For the label glossary please see Figure 2.2. .	27
2.4	White matter tract atlas of the patient and a matched healthy control participant in sagittal slices. For the label glossary please see Figure 2.2	28

2.5 Graphical overview of statistical outcomes comparing intrahemispheric (a) and interhemispheric (b) white matter integrity between patient and control group along major white matter tracts. Colors correspond to values of the t-statistics: blue indicates that the patient’s values were lower than those of the controls, red indicates that the patient’s values were higher than those of the controls. Light gray corresponds to statistically non-significant differences between patient and control. LH: left hemisphere, RH: right hemisphere, IFOF: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus, FA: fractional anisotropy, MD: mean diffusivity, RD: radial diffusivity, AD: axial diffusivity. See Table 2.1 and 2.2 for corresponding numerical results. 29

2.6 Graphical overview of functional connectivity differences between patient and controls. Colors correspond to t-statistics: blue indicates that the patient’s connectivity values were significantly lower than those of the controls, red indicates that the patient’s connectivity values were significantly higher than those of the controls. Connectivity was computed for each hemisphere between 24 ROIs. Here we consider only ROI connections (226 in total) relevant to the white matter tracts of interest, i.e. IFOF, SLF, ILF, calcarine and cingulate. ROI pairs from converging areas are included in both converging tracts to provide full overview. All 576 connectivity scores can be found in Supplementary Figure B.1. LH: left hemisphere, RH: right hemisphere, IFOF: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus, FA: fractional anisotropy, MD: mean diffusivity, RD: radial diffusivity, AD: axial diffusivity. 34

2.7 Functional localization of place, face and object cortical areas. Shown are a sagittal, coronal and two transversal views (from left to right) with the corresponding MNI152 2mm standard space coordinates. Color scale represent GLM analysis results based on z-statistics between 4 and 7.8. 35

3.1 Volumetric comparisons between (a.) early onset essential tremor patients (EOET) vs younger healthy controls (y-HC) and (b.) late onset essential tremor patients (LOET) vs older healthy controls (o-HC). Labeled inflated images in the left panels indicate significant gray matter volumetric differences whereas labeled white matter images in the right panels indicate significant white matter volumetric difference 50

3.2 TBSS (family-wise error-corrected threshold-cluster extend voxel P maps) reveal regions of significantly reduced FA (red) and increased MD (blue) in early-onset essential tremor (EOET) patients compared with age-matched young healthy controls (y-HC) (A), Late-onset essential tremor (LOET) patients compared with age-matched old healthy controls (o-HC) (B), EOET compared with LOET (C), y-HC compared with o-HC (D). 53

4.1 Top row: Statistical parametric maps for a representative control and a patient during finger tapping. Bar plots: fMRI responses in pre-defined regions of interest (ROIs). (A) right hand, (B) left hand, (C) bimanual finger movements. Abnormal lateralization in M1 in patients is clearly seen in the statistical parametric maps. Abnormal activity pattern was also observed in SMA in patients: in controls left SMA activity was always larger than right SMA activity, but not in patients. M1: primary motor cortex hand area, SMA: supplementary Motor Area. Error bars show ± 1 standard deviation. Color bar for the statistical parametric map indicates the t-score ranging from -8 (blue) to 2.98 (yellow). Maps are thresholded at an α level of 0.05. 72

4.2	Top row: Statistical parametric maps for a representative control and a patient during finger tapping. Bar plots: fMRI responses in pre-defined regions of interest (ROIs). (A) right hand, (B) left hand, (C) bimanual finger movements. Abnormal activity was observed in THA, GP and STR (PUT+CAU) in patients. THA: Thalamus, GP: Globus Pallidus, STR: Striatum, PUT: Putamen, CAU: Caudate. Error bars show ± 1 standard deviation. Color bar for the statistical parametric map indicates the t-score ranging from -8 (blue) to 2.98 (yellow). Maps are thresholded at an α level of 0.05.	73
4.3	Difference in functional connectivity between the patient and the control group. Colors represent t-statistics. Blue: control group's values lower than the patient's, red: control group's values higher than patient's	79
A.1	ROI locations that were used in probabilistic tractography A. Left anterior part of ILF, B. Right anterior part of ILF, C. Left superior lateral part of ILF, D. Right superior lateral part of ILF, E. Left and right temporal part of ILF, F. Left and right occipital part of IFOF, left and right posterior part of ILF, G. Left optic radiation part of IFOF, left and right tapetum, left calcarine, H. right optic radiation part of IFOF, left and right tapetum, I. Right calcarine, J. Splenium, left and right frontal part of IFOF, K. Left and right cingulate, L. Right SLF, M. Left SLF. IFOF: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus.	123
A.2	2D probabilistic tracktography of bilateral calcarine, cingulate, IFOF in the occipital pachygyria patient and a representative control.	124
A.3	2D probabilistic tracktography of bilateral ILF, SLF, tapetum and splenium in the occipital pachygyria patient and a representative control.	125

B.1	2D probabilistic tractography of bilateral ILF, SLF, tapetum and splenium in the occipital pachygyria patient and a representative control.	129
D.1	Region of interests from (1) pontine, (2) anterior pyramid of upper medulla, (3) lateral funiculus of the cervical cord levels of medulla that were used in reconstruction of corticospinal fibers. Yellow and red lines represent crossed fibers, light blue and dark blue lines show uncrossed fibers in corticospinal tract	140
D.2	Representative reconstruction of corticospinal fibers in a CMMD patient. Yellow and Red show crossed fibers, Light and Dark Blue show uncrossed fibers	141
E.1	Schematic representation of afferent (red line) and efferent (yellow line) cerebellocerebral loop pathways. DRTC: Dentate-Rubro-Thalamo-Cortical pathway, CPC: Cortico-Ponto-Cerebellar Pathway, THA: Thalamus, DN: Dentate Nucleus, RN: Red Nucleus, CH: Cerebellar Hemisphere, SCP: Superior Cerebellar Peduncle, MCP: Middle Cerebellar Peduncle	143
E.2	2D probabilistic tractography of bilateral DRTC and SCP in the CMMD patient and a representative control.	144
E.3	2D probabilistic tractography of bilateral DRTC and SCP in the CMMD patient and a representative control.	145

List of Tables

2.1	White matter diffusion indices in bilateral calcarine, cingulate, inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF) probabilistic tracts. (*p<0.05, **p<0.01, ***p<0.001, all FDR corrected, $\wedge$ inside the range of control group. L: Left, R: Right, FA: fractional anisotropy, MD: mean diffusivity, RD: radial Diffusivity, AD: axial diffusivity, IFOF: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus. . . .	30
2.2	White matter diffusion indices in tapetum and splenium probabilistic tracts suggest a disruption of interhemispheric connectivity in the patient. (*p<0.05, **p<0.01, ***p<0.001, all FDR corrected)L: Left, R: Right, FA: fractional anisotropy, MD: mean diffusivity, RD: radial Diffusivity, AD: axial diffusivity	32
3.1	Demographic information of individuals with ET classified by age at onset and age, sex matched healthy controls. Values are mean $\pm$ standard deviations or N (%). *p values refer to the Mann-Whitney U or two-sample t-test between *each ET group and matched healthy controls, and **EOET and LOET patients. . . .	46
3.2	Results of independent sample t test analysis in white matter (WM) and gray matter (GM) morphometry,. *FDR corrected p<0.05, **FDR corrected p<0.01	51

3.3	The mean FA and MD ($\times 10^{-3}$ mm ² /s) values of significant clusters in early-onset (EOET), late-onset (LOET) patients, younger (y-HC) and older (o-HC) control groups. Tracts were identified according to Johns Hopkins University WM tractography atlas and the International Consortium for Brain Mapping DTI-81 WM atlas.	54
4.1	MNI coordinates of the center of the spherical ROIs that were used in task-based fMRI comparisons	67
4.2	Demographic characteristics and summary of the unimanual task-based fMRI comparisons. N:number of participants, m: male, f: female, y: years, ns: not significant, M1: primary motor cortex, SMA: supplementary motor area, THA: thalamus, GP: globus pallidus, STR: striatum, L: Left, R: Right, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$	74
4.3	Diffusion indices for healthy controls and the CMMD patient in crossed and uncrossed corticospinal tracts (CSTs). 95% confidence intervals for the control group is computed by a non-parametric bootstrap procedure (see Methods). Conventional null-hypothesis significance (p value) is computed using one-sample t-test (* $p < 0.05$, ** $p < 0.01$, all FDR-corrected. +: patient value outside of 95% CI).	75
4.4	White matter diffusion indices in cortico-cerebellar pathways. 95% confidence intervals for the control group are computed by using a non-parametric bootstrap procedure. Conventional null hypothesis testing is used to obtain the p values. DRTC: Dentato-rubro-thalamo-cortical, FPC: Frontoponto-cerebellar, TPC: Temporo-ponto-cerebellar, PPC: Parietoponto-cerebellar, OPC: Occipito-ponto-cerebellar, R: Right, L: Left. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, all FDR corrected. +: patient value outside of 95% CI.)	77

B.1	MNI coordinates of the center of the spherical ROIs that were used in resting state fMRI comparisons. IFOF: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, CALC: calcarine sulcus, SLF: Superior longitudinal fasciculus, CIN: cingulate cortex, TAP: tepetum	127
B.2	Resting state fMRI connectivity comparison between the ROIs along Inferior Fronto-Occipital Fasciculus (IFOF) by using standard null hypothesis testing (one-sample t-test) and nonparametric bootstrap procedure. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, all FDR corrected)	130
B.3	Resting state fMRI connectivity comparison between the ROIs along Superior Longitudinal Fasciculus (SLF) by using standard null hypothesis testing (one-sample t-test) and nonparametric bootstrap procedure. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, all FDR corrected)	131
B.4	Resting state fMRI connectivity comparison between the ROIs along Inferior Longitudinal Fasciculus (ILF) by using standard null hypothesis testing (one-sample t-test) and nonparametric bootstrap procedure. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, all FDR corrected)	133
B.5	Resting state fMRI connectivity comparison between the ROIs along calcarine tract by using standard null hypothesis testing (one-sample t-test) and nonparametric bootstrap procedure. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, all FDR corrected)	134
B.6	Resting state fMRI connectivity comparison between the ROIs along cingulate tract by using standard null hypothesis testing (one-sample t-test) and nonparametric bootstrap procedure. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, all FDR corrected)	135
C.1	For tremor +, low amplitude or barely perceivable tremor; ++, moderate amplitude tremor (1-2 cm); +++, large amplitude, severe tremor (>2 cm) (1). For Archimedes spiral test, bradykinesia, rigidity, postural instability and hypomimia: +, mild; ++, moderate; +++, severe. L, left hand; R, right hand	137

C.2 Diffusion indices for early-onset essential tremor (EOET) and late-onset essential tremor (LOET) patients versus age-matched healthy controls (HC) in bilateral dentate-rubro-thalamo-cortical tracts (DRTCs). Conventional null-hypothesis significance ($p^*<0.05$) is computed using independent-sample t-test. FA: Fractional anisotropy, MD: mean diffusivity, RD: radial diffusivity, AD: axial diffusivity, L: Left, R: Right 138

F.1 Resting state fMRI connectivity between the ROIs located in dentate nucleus (cerebellum), red nucleus, primary MC (hand area), SMA, thalamus, caudate nucleus and globus pallidus. Statistically significant connections are shown. 95 % confidence intervals for the healthy control group are computed using a non-parametric bootstrap procedure. Statistical significance (p values) are computed using standard null hypothesis testing (one-sample t-test). Results of non-parametric bootstrap for Pearson’s correlation coefficient r scores in resting-state fMRI data (* $p<0.05$, ** $p<0.01$, *** $p<0.001$, all FDR corrected) 147

Chapter 1

Introduction

1.1 Neurodevelopment of Human Brain

Brain development is a well-organized, systematic, predetermined and highly dynamic process that begins with the conception and continues well into the post-natal period, even until adolescence in humans. To understand the processes that underlie functions and organization of the adult brain, investigations upon specialization of brain during neurodevelopment and maintaining complex information processing system are required. To be able to understand the complexity of the neural development that leads eventually to the adult brain abilities, reviewing the major steps of the neural development is critical.

Neural development begins during the first week after conception, cell division of fertilized egg become a multicellular blastocyst. During the following two weeks, the blastocyst differentiates into main three germ layers, namely ectoderm (outer layer), mesoderm (middle layer) and endoderm (internal layer). The established structure of these three germ layers is called gastrula, central and peripheral nervous system derive from the outer layer, ectodermal component of the gastrula.

Central nervous system develops from the outer most layer, ectoderm. Ectodermal cells bring different stem cells that will give rise to different cell types depending on the position along the dorso-ventral axis of the embryo [1].

As early as twentieth day of embryogenesis, neural system begins to develop by the emergence of neural plate that is formed from the dorsal most ectoderm and that process is called neurulation. By the three to four weeks of gestation inducing signals from notochord is critical to neural tube formation which eventually becomes brain and the spinal cord.

Neural plate grooves to form neural tube until the fourth week of development. After the neural plate folds and closes, neural crest cells detach from their margins and migrate away and these cells form the majority of peripheral nervous system [1]. The constituent cells that form the neural tube are called neural precursor cells. The neural precursor cells could divide to produce more precursor cells or specialized neuroblasts that give rise to differentiate into neurons or glial cells. During the sixth and eighth weeks after gestation over 100 billion neurons and several time more glial cell are produced from these neuroblasts [2].

During the neural development, anterior part of the neural tube gives rise to primary anatomical regions such as forebrain, midbrain and hindbrain. Rapid cell proliferation occurs at the inner surface of the neural tube which is called ventricular zone, then these neural precursor cells migrate through the surface of the neural tube. After the differentiation of these neural precursor cells to neurons, those neurons that belong to the CNS begin to migrate. Neurons that are differentiated earlier located in the deepest layers of the brain whereas lastly differentiated neurons migrate to the outermost layers of the neocortex.

Emergence of this laminar structure of the human neocortex depends on the neurogenesis, migration of the postmitotic neurons [3], formation of the transverse zones (preplate, cortical plate, marginal zone and subplate) and construction of six-layer neocortical laminar organization [1]. Progenitor of neurons and glial cells settle in the ventricular zone (VZ). Early polymorphic neurons emerge and

establish the preplate (PP) and their axons with the growing axons from thalamus establish the intermediate zone (IZ). Latter generated neurons establish the cortical plate (CP). It splits PP into marginal zone (MZ) and subplate (SP).

Neocortex has six cellular layers or laminae whereas other brain structures such as subcortical areas may have fewer laminae. Each lamina contains distinct cell populations that are different in neuronal type (such as size, shape) and; input and outputs characteristics. Specifically, layer 6 and 5 contain pyramidal neurons whose axons leave the cortex, layer 4 typically includes stellate neurons that have many synapses enable horizontal connections. Layer 3 and 2 also contain smaller pyramidal neurons and these neurons connect other cortical regions. The outer most superficial layer, layer 1 includes fewer amounts of axons and dendrites as well as neuron bodies.

The intact columnar organization of human neocortex is highly depend on intact circuitry of molecular mechanisms of neuronal migration. The migration-promoting signals induce the polarization of the neuron and protrusion extensions [4]. Lamellipodia or filopodia like protrusions are stabilized by adhering to the extracellular matrix during radial cell driven migrations. Rakic and Sidman showed that radial glia guide the newly generated neurons from the VZ to the most superficial layers [5].

Soma of radial glial cells are located in the VZ and their axons extend throughout the wall of neural tube while their dendrites attaching the basement membrane [6]. Postmitotic neurons that are newly generated in VZ migrate through the axons of these radial glial cell toward their final position in CP [7].

The basement membrane is a thin layer of extracellular matrix composed of collagen, proteoglycans, nidogen and the neural growth promoting ligand laminin. Expression of laminin proteins at the pial surface of the brain is critical since the laminin family proteins are fundamental components to maintain integrity of basement membrane. The laminin as being a cell adhesive glycoprotein involved in adhesion interactions also regulate the neuronal migration and differentiation [8, 9].

Although there are few exceptions, the most of the neurons located in the human neocortex are produced by the end of these processes in very early stage of the neuronal development. Although they share some common features white and gray matter development also follows specific development phases.

1.1.1 Gray Matter Development

As human brain development is structurally and functionally non-linear process, imaging studies also showed non-linear alterations in region specific gray matter volumes with preadolescent increase followed by a postadolescent decrease [10, 11, 12, 13]. Findings from large scale longitudinal pediatric neuroimaging studies suggest that gray matter volume follow an inverted U-shaped trajectory in frontal, temporal, parietal and occipital lobes [10, 14]. Gray matter development peak around the age of 12 for the frontal and the parietal lobes while peak about age of 16 for temporal and increment continues around age of 20 for the occipital lobe [10].

These findings of heterochronous development of gray matter volume of cerebral cortex are also consistent with histological evidence in humans from Rakic's studies in terms of increased synaptic pruning during adolescence and early adulthood [15, 16]. However, gray matter volumetric decline are greater than only synaptic pruning would explain. Paus (2005) explain the phenomena by considering the effect of intra-cortical myelination in MRI signals [17]. Approximately 1/3 of the imaged voxels give white matter signals due to the lipids in the content of the myelin sheath structure. Thus, unmyelinated white matter structure could bias the classification of gray matter/white matter brain tissue and continuing intra-cortical myelination could explain the progressive reduction in adolescence [17].

Given the heterochronous development of gray matter volume in cortex is critical for the structure-function interaction of these regions. When maturation related loss of gray matter volume is applied to longitudinal samples maturation hierarchy is revealed among cortical regions. According to Gogtay and Thompson

(2010) [18], primary sensory motor areas, frontal and occipital poles mature first, the maturation continues in a parietal to frontal direction. The findings could be interpreted as primary functions such as motor control, sensory systems develop first and this process followed by temporal and parietal cortices associated with language and spatial attention. Last regions to mature involving prefrontal and lateral temporal cortices that are associated with integration of sensorimotor processes as well as modulation of attention, language and some critical aspects of decision making [2].

1.1.2 White Matter Development

White matter development continues after gray matter has reached its peak volume [19, 20]. The directionality of the myelination process in white matter maturation could be summarized from caudal to rostral in general. The order of the myelination occurs as follows: it begins with the myelination of the brainstem then myelination of cerebellum and basal ganglia takes place and lastly the cerebral hemispheres myelination progress is completed [1]. In addition to its order, there are regional specific differences in timing of the white matter connections' development. Motor and sensory systems mature within the first two years in the post-natal period. Moreover thalamic radiation connections remain to develop until 5 or 7 years old whereas intracortical fibers still develop until the early adulthood. A lot of studies showed that myelination of the corpus callosum continues during the first ten years of age. Although it is thin in the first month, the genu part and then the splenium parts of corpus callosum rapidly develop during the next 5 months.

Extent of maturation of white matter tracts is controversial, while some cross-sectional diffusion tensor imaging (DTI) studies suggest that it finishes before the twenties [21, 22], others show that it continues until twenties, especially in major long-range association fibers including the inferior and superior longitudinal and fronto-occipital fasciculi [23, 24].

Organization of fibers into fascicles during white matter maturation passes

into three phases. The first phase includes progressive fascicle formation that is characterized by increased fractional anisotropy (FA), and axial diffusivity (AD) and reduction of radial diffusivity (RD) with no changes in mean diffusivity values during the late prenatal period. In the second phase of the development oligodendrocytes lineage precursors proliferate together with neurofilaments and microtubules so increase in membrane density occurs during this phase. As it is expected, membrane density sensitive white matter microstructural indices namely AD, RD and mean diffusivity (MD) reduce in the second phase whereas there is no significant change in FA values. In the third phase, fiber myelination rapidly progresses and in parallel with this there is a progressive increase in FA values whereas there is a reduction in RD and MD values with no changes in AD values.

1.1.2.1 Development of Commissural and Projection Fibers

Development of all parts of corpus callosum (genu, body, splenium) as well as corticospinal tract is associated with increase in FA scores and decrease in MD scores in young population [23]. However, other parameters does not change as FA and MD. These alterations in FA and MD are coherent with elderly aging that shows changes in these parameters in the opposite direction. In development studies commissural fiber tacking often more consistent across subjects whereas corticospinal tract shows more variations in terms of length. Nevertheless, the extend and the shape of it is still considered as coherent between scans within an individual [23]. On the other hand the development of the corpus callosum showed differences in terms of its parts in the prenatal period. Its formation is more advanced in the frontal lobe-namely in genu- than the occipital lobe-in splenium. In other words, enlargement of forceps major is more advanced than forceps minor. However, both splenium and forceps major become identifiable at birth [25]. However, callosal connections to parietal lobe are not as identifiable as the splenium. The main reason behind this is superior regions of the corona radiata mostly have low diffusion anisotropy between the birth and 1 months of age (approximate FA is between 0.1 and 0.2) [26]. Interestingly, relatively low

anisotropy in healthy adults are commonly seen (approximate FA is between 0.3 and 0.4) and the existence of the three prominent tracts with different orientations namely corpus callosum, SLF and projection fibers) could cause the lower anisotropy in these areas [27, 28].

1.1.2.2 Development of Association Fibers

While subtle changes occur in commissural and projection fibers in young population, more substantial alterations in association fibers are found in 1 to 6 years intervals [23]. Coherently, the majority of the association fibers including superior longitudinal and inferior fronto-occipital and the left inferior longitudinal fasciculi showed significantly increasing FA and decreasing RD scores during the development [29]. The IFOF and ILF- two major white matter pathways can be identified as early as in one-month old toddler, however their projections to frontal, temporal and occipital lobes are not well-established [25]. Strikingly identification of SLF is not possible even at birth but it become visible at the age of five [25].

1.1.3 Neurobiological Circuits of Sensory and Cognitive Processes in Neurodevelopmental Disorders

Movements whether they are voluntary or involuntary emerge as a result of spatial and temporal patterns of muscular contradictions orchestrated by the brain and spinal cord. Investigations on the precise involvement of each motor unit in the motor system are fundamental to figure out both normal behavior and the etiology of the motor system neurodevelopmental disorders. Congenital abnormalities on the motor system point out the abnormal structure or function of the components of motor system as well as connectivity defects among motor units. These abnormalities often emerge during childhood and persist during the adulthood.

Development of motor system continues through both by maturation of the neural circuitry and exposure to different motor activities in the first 15 years of life [1]. The neural circuitry in motor system organization can be grouped into four categories: lower motor circuitry, upper motor circuitry, cerebellum and basal ganglia motor movement control circuitries. The generation of the all body movements begins with stimulation of the skeletal muscle by lower motor neurons that are located in brain stem and spinal cord. Lower motor neurons' activation is coordinated by local circuits that are critical for the complex reflexes and rhythmic locomotor movements [2]. Local circuits could generate the simple movements but they are controlled by the descending projections of 'upper' motor neurons for high-order control. Descending projections from primary motor cortex, supplementary motor cortex and premotor cortex are fundamental for the preparation, initiation and coordination of the voluntary movements. These 'upper' motor neurons could regulate the activity in the local circuits by enabling and coordinating the complex movement sequences. Basal ganglia and cerebellum circuits serve as feedback and control mechanisms of the complex movements. Their involvements are critical for the regulation of upper motor areas for the spatial and temporal precision of the fine motor movements. Congenital motor disorders could emerge as a result of the abnormalities in any of those or combinations of the circuits. Especially congenital disorders related to initiation, termination or controlling the voluntary movements mainly affect basic motor pathways. Two main motor pathways- direct and indirect pathways- signal through the basal ganglia and they have either excitatory or inhibitory affect the activity on cortical motor areas. Excitation of the direct pathway creates excitatory thalamic input to cortical areas whereas excitation of the indirect pathway produces inhibitory thalamic input to higher cortical motor areas. Normal functioning basal ganglia balance these two pathways properly in terms of the intention.

Motor system provide initial inputs to organisms for further processing by higher cognitive processes and regulating the behavioral output based on the cognitive functions. Animal studies show dissociation of fronto-striato-cerebellar

circuitries that mediate higher cognitive functions including attention, motivation and emotion [30]. Progressive development of fronto-cortical and fronto-subcortical networks highly affects the cognitive control and children with neurodevelopmental disorders show deficits in these late developing circuits. Association cortices involve attentional processing [31]. Particularly activation in intraparietal cortex and superior frontal cortex that are the components of the "top-down attention network" is associated with preparation and application goal-directed selection of the stimuli [32]. On the other hand, high order sensory cortices contribute "bottom-up attention network" based on the salience of the stimulus [32]. The inferior temporal cortices process the sensory features such as object perception, place perception and face recognition [30]. These findings were also supported with lesion studies that showed lesion in inferior temporal cortices cause agnosia [33]. Some cortical areas such as dorsolateral prefrontal cortex mediate the inhibition of the irrelevant stimuli hence contribute to sustained attention [30]. Both common neurodevelopmental disorders such as attention deficit hyperactivity disorder and rare genetically rooted neurodevelopmental disorders might have effective by unbalancing the precise interaction between areas in attention networks.

1.1.4 Genetic Mechanisms of Abnormal Cortical Architecture

Gene expression during the neurodevelopment regulates the structure and function of the human brain. At each stage of neurodevelopment common multiple expressions of transcription factors are important for both determining the properties of a cell and their interaction with biochemical environment. Longitudinal neuroimaging studies showed that prolonged alterations in brain structure is closely related with acquisition of high level cognitive abilities such as executive functions, memory etc [34]. Signaling cascade of the intracellular regulators are sensitive the genetic expressions in turn modulate transcription actors. Both transcription factors and downstream genes regulate the cellular function and also contribute cell surface receptors and adhesion based cell to cell signaling

molecules. If some of these processes go wrong, associated neurodevelopmental disorder may appear.

Neurodevelopmental disorders are a heterogeneous spectrum of features that emerge during the childhood and may or may not continue to exist during adulthood. In its large heterogeneous spectrum, classification of the neurodevelopmental disorders is mainly based on variety of clinical symptoms. Through technological advances genetic backgrounds of neurodevelopmental disorders are identified and the identification specific mutations are used to clarify diagnoses. Genetic data provides that expressivity variability (same mutation may lead different clinical symptoms) and locus heterogeneity (similar clinical symptoms may occur due to different genetic loci) are commonly seen in the population and blurred the classification of the diagnosis [35]. Thus, not only genetic mechanisms but also their effects of brain structure and function, and identification of possible behavioral outcomes are scientifically significant.

Major steps of the neurodevelopment from the neurogenesis, differentiation, neuronal migration to organization of neural networks require a complex interactions of multiple genetic mechanisms. Since these major steps overlap in time and space establishment of the proper signaling pathway including turning on the expression of the proper genes in a specific time is extremely important. In the present study, effects of three specific gene mutations, namely LAMC3, HTRA2 and RAD51 on the brain architecture were investigated. A brief description of each gene mechanism is provided below.

LAMC3. Cortical development highly depends on the timing of the expression of specific genes and migration of the neurons from their production zone to their mature positions. Especially extracellular matrix molecules containing gamma 3 chain have been linked with cortical malformation abnormalities [36]. An In-vivo study on LAMC3 gene expression in mouse model showed that its expression enriched in the cortical plate where the post migratory pyramidal neurons were located and different layers of the neocortex [37]. LAMC3 proteins were highly detected in soma and dendrites of pyramidal neurons and rarely along or the near the axons [37].

These localization sites were also critical for the radial glial cells' organization. When the cortical layers were established radial glial cells attach the cortical wall for neuronal migration [36]. Gamma 3 chain of the laminin protein localizes at the pial surface hence they provide attachment sites for radial glial cells [36]. Mutation in this precise system results cortical gyration malformations specifically pachy/polymicrogyria.

Effects of gamma 3 chain mutation in brain morphology were studied by conducting a study with LAMC3 knocked-out mouse model. Radner and his colleagues' study (2013) showed increased thickness in layer 1 in mouse with homozygous LAMC3 mutation, compressed layers through 2 to 6 and fusion of the pial surface [36]. Overall in vivo studies on LAMC3 genetic mutation indicated c3 containing laminins play an important role in the neurodevelopment of the cortical basement membrane that serves as an attachment site for radial glial cells, hence guiding neural development.

HTRA2. HTRA2 gene encodes serine protease that is on the intermembrane space of mitochondria [38]. When there is an apoptotic stimulus HTRA2 protein is released from the intermembrane of the mitochondria into the cytosol and binds to inhibitor proteins to apoptotic process to start the cascade of apoptosis. In-vivo mouse model study indicated that mutation in HTRA2 gene cause to loss of protease activity, motor neuron degeneration and eventually repetitive movements [39]. Similarly HTRA2 knocked-out mice showed parkinsonian symptoms that were associated with loss of neurons in striatum [40]. Another in-vivo study on mouse model showed that since one of the alleles is dysfunctional, overexpression of the functioning allele might be linked with motor impairments [41].

Three rare missense alleles were reported as linked with parkinsonian symptoms, namely HTRA2 p.R36W, p.P143A, and p.R404W [42]. HTRA2 p.A141S and p.P143A locates in close proximity to serine at residue 142 that is phosphorylated upon the activity of p38, dependent on PTEN induced PINK1 [43]. The other mutation allele p.R404W locates in close proximity to serine at residue 400 that is phosphorylated upon activation of CDK5 [43]. PINK1 and CDK5 kinases are both known to be associated with Parkinson disease [44].

Previous report investigating the genetic backgrounds of our patient and control samples suggested that HTRA2 p.G399S may be responsible for hereditary essential tremor and homozygous allele of the mutation linked with parkinsonian symptoms.

RAD51. Molecular mechanism of RAD51 protein in congenital motor disorders is still unclear. In-vivo mouse model study on RAD51 gene expression peaked at E12 and declined afterwards [45]. Expression of RAD51 was mostly detected in the cortical ventricular zone in the cortex of newborn mice whereas it was found in a subpopulation of corticospinal axons at the pyramidal decussation in 2-day-old mice. Thus, it can be concluded that RAD51 gene is effective during neurodevelopmental process as well as correct establishment of corticospinal tract.

An alternative mechanism for the motor disorders regarding to its involvement in well known role in DNA double stranded break repair was suggested [45]. Its involvement in DNA repair process could also be applied to congenital disorders. Insufficient DNA repair due to the mutation during early neurodevelopment may cause excessive apoptosis and altered central nervous system development [45].

Effects of these genetic mutations were investigated by using different methodologies to provide a multi-perspective understanding of each of the neurodevelopmental disorders.

1.1.5 Methodological comparisons for MRI analysis software packages

There are different software packages that are most widely used in neuroimaging studies for structural and functional brain imaging studies. These packages are Freesurfer (<https://surfer.nmr.mgh.harvard.edu/>), SPM (<https://www.fil.ion.ucl.ac.uk/spm/>) and FSL (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>).

Freesurfer is one of the most prominent software package that is designed to use

automated pipeline for T1-weighted analysis to create hemispheric white and pial surfaces as well as estimation of cortical thickness [46]. Results of postmortem cortical thickness measurements were compared with Freesurfer volumetric thickness estimations indicated a good agreement [47, 48, 49, 50].

On the other hand, SPM is also one of the widely used analysis tool for multi-purpose. Its standard preprocessing procedure includes correction for slice-timing differences, realignment, normalization to MNI space and spatial smoothing. Sensitive parameters for SPM preprocessing is important to distinguish true activations from false positives [51]. FSL software package also follows similar preprocessing steps. By using both preprocessing procedures output files are provided in nifti formats. The nifti format could be used in different software packages for the post-processing step. Main difference between SPM and FSL packages in the preprocessing is the registration step especially registration of functional data to anatomical data and eventually in standard template. Magnetic resonance image analysis experience provided an insight that preprocessing in SPM is more convenient due to its automatically saving option during each step.

FSL (the FMRIB Software Library) is a comprehensive library of analysis tools for functional, structural and diffusion magnetic resonance imaging [52]. Since it is open source software, has simple interface, flexibility and detailed documentation FSL is one of the most preferable brain analysis software in neuroscience area. For the DTI analysis, probabilistic tractography method is widely used for estimating local probability density functions on parameters of interest in a diffusion model [53]. Method that is implemented in FSL software package enables automatic relevance determination to perform online selection of the number of fiber orientations supported by the data at each voxel, simplifying the problem of tracking in a multi-orientation field [54]. Latest version of FSL offers multi-fiber tractography offers significant advantages in sensitivity when tracking non-dominant fiber populations [54]. Another software pipeline Tract-Based Spatial Statistics (TBSS) perform voxel-wise comparisons based on diffusion model [55].

These MRI analysis tools were used to investigate the effects of the LAMC3,

HTRA2 and RAD51 gene mutations by giving a detailed results from both structural and functional comparisons.



Chapter 2

Bilateral Occipital Pachygyria

2.1 Background

Patient NG 367-1, [37] is homozygous for a single mutation in the LAMC3 gene and shows severe bilateral smoothening and thickening (>8 mm) of the lateral occipital lobes (Figure 2.1). In previous work, we found that the cortical structural changes in this patient’s brain also involve regions beyond the occipital lobes, and primarily those that play a role in visual attention [56]. Consistent with this, the patient showed pronounced behavioral deficits in visuo-spatial attention. Strikingly, however, her object- and face recognition remain intact, despite significant gray matter structural changes in lateral occipital cortices, inferior temporal gyri, and fusiform gyri [57, 58, 56].

Given that these perceptual sparing is mediated by widely distributed networks comprising functionally specific brain regions in fusiform face area (FFA), lateral occipital cortex (LOC) and it is conceivable that gray matter structural abnormality in these regions might possibly contribute to abnormal functioning of these areas. However, behavioral results indicated intact face and object recognition but disrupted visuo-spatial attention in the patient. A plausible alternative hypothesis could be that alterations in structural and functional connectivity

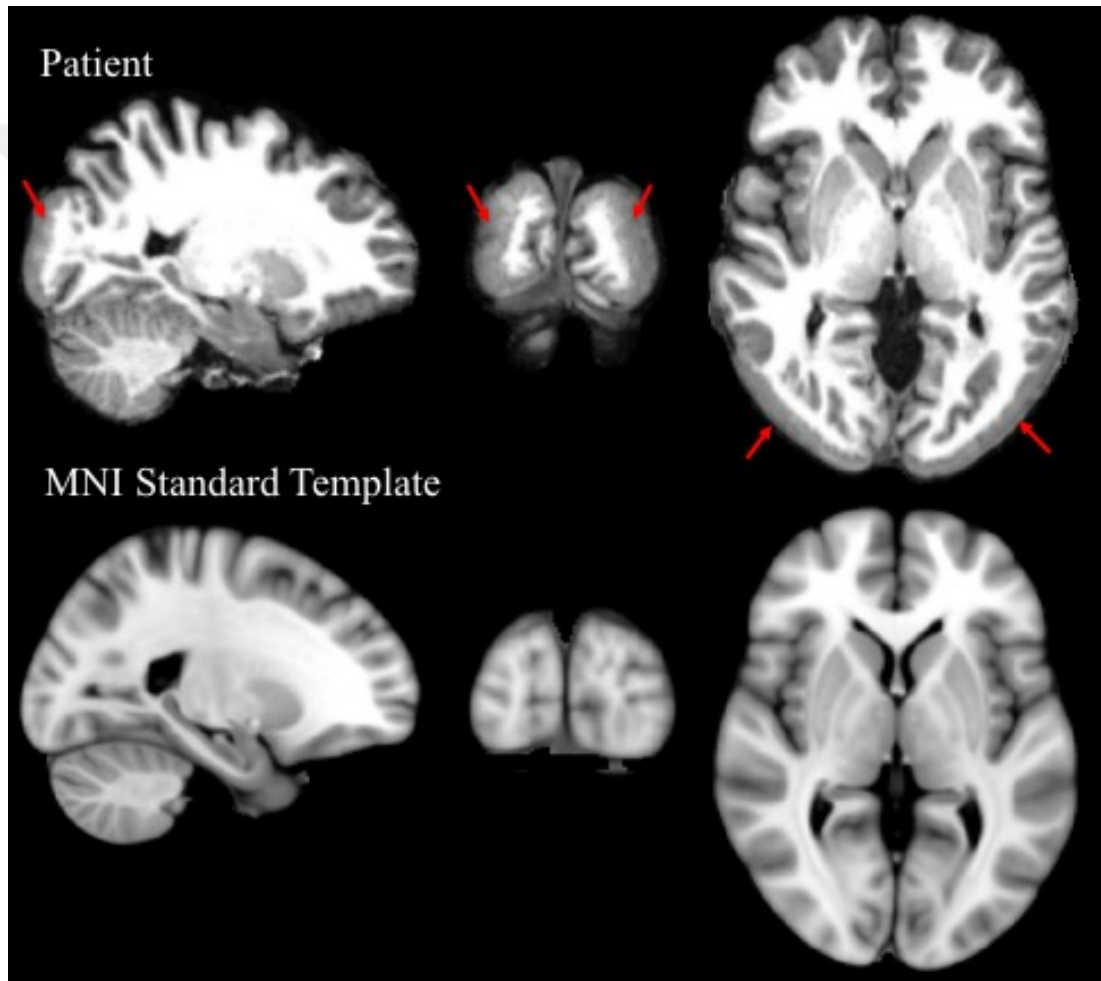


Figure 2.1: T1-weighted images of the patient's brain and the MNI 2 mm standard template (from 152 participants' brains). Shown are a sagittal, coronal and transversal views (from left to right). Red arrows point to pachygyric regions in the occipital lobes.

between brain regions in the patient could predict her spared perceptual abilities. Intact (in the same range of healthy controls) or even strengthened intra and/or interhemispheric connectivity would also be consistent with higher white matter volume in several cortical regions, including the inferior temporal and right lateral occipital cortex [56] findings. Initial structural connectivity results of Barak et al. (2011) [37] indicated that white matter microstructural integrity in pachygyric regions were affected by showing decreases in fractional and radial anisotropy in white matter pathways and a total lack of short U- fibers in the lateral occipital region. However, the extend of compromised structural connectivity and its effect on functional connectivity are not yet known. While the quality of structural connections can have a direct influence on functional connectivity [59, 60, 61, 62], it has also been shown that functional connectivity can persist despite dramatic cortical structural changes (e.g. for resting state connectivity see [63] or [64]). Thus, possibly intact functional connectivity may serve as a compensating mechanism for structural changes in our patient [65, 66]. To investigate these two possibilities, we quantitatively assess microstructural integrity and functional connectivity in major visual structural pathways in NG 367-1 and a matched control group. We assess intra-, and interhemispheric connectivity explicitly since both are critical in cognitive functioning [67].

2.2 Materials and Methods

2.2.1 Participants

Case The patient, a 37-year-old (at the time of study) female, has prominent bilateral smoothing and thickening of the lateral occipital cortex, a structural abnormality that has been tied to a mutation in the laminin $\gamma 3$ gene: LAMC3 [37]. Beyond the occipital area, Urgen et al., (2018) found significant structural changes in gray matter morphometric indices throughout the brain [56]. The patient is neurologically intact with average intelligence, and has completed 12 years of schooling. She has been prescribed valproic acid, levetiracetam, pregabalin and

topiramate due to staring and blinking spells. Further patient details can be found in Urgen et al. (2018) [56]. The patient’s perceptual abilities had been assessed by us previously in a separate study [56] and found – with the exception of spatial attention – to be largely intact. The study was in accordance with the declaration of Helsinki and was approved by the Research Ethics Committee at Bilkent University (Approval Number:2010_08_31_2). The patient gave written consent prior to participating in this study and was compensated for her time of participation.

Healthy controls Nine age (mean age = 36.58, standard deviation = 3.68) and sex matched healthy participants were included as a control group to the study. Data from one of the controls (age = 38) was also used for a white matter atlas, and one additional control (age =33) participated in the functional localizer scan. All participants gave informed consent prior to participating in the study and were paid for their participation.

2.2.2 Data Acquisition

Data were acquired in a 3T MR scanner (Magnetom Trio, Siemens AG, Germany) in National Magnetic Resonance Research Center (UMRAM), Bilkent University, Ankara, Turkey. 32-channel phase array head coil was used for the scans. For anatomical scans, high resolution, three dimensional, MPRAGE, T1 weighted images were acquired (single shot turbo flash; voxel size = $1 \times 1 \times 1 \text{ mm}^3$; repetition time, TR = 2600 ms; echo time, TE = 3.02 ms; flip angle = 8 degrees; field of view, FOV = $256 \times 224 \text{ mm}^2$; slice orientation = sagittal; phase encode direction = anterior-posterior; number of slices = 176; acceleration factor (GRAPPA) = 2).

For DTI scans multiband (MB) diffusion-weighted echo-planar imaging (EPI) sequence (voxel size = $1.8 \times 1.8 \times 1.8 \text{ mm}^3$; TR= 3802 ms; TE = 86.6 ms; flip angle = 78 degrees; MB = 2; FOV = $210 \times 181 \text{ mm}^2$; slice orientation = axial; phase encode direction = anterior-posterior; number of slices = 81; b=0, 1000 s/mm², diffusion directions = 64) that parameters were optimized by our group

for whole brain coverage was used.

Functional data were acquired with a multiband gradient-echo (GE) -planar imaging (EPI) sequence (voxel size = $1.8 \times 1.8 \times 1.8 \text{ mm}^3$; TR= 1005 ms; TE = 27.4 ms; flip angle = 42 degrees; FOV = $208 \times 186 \text{ mm}^2$; slice orientation = parallel to calcarine sulcus; phase encode direction = anterior-posterior; number of slices = 72) was used. The resting state scans took about 10 minutes. Each participant took part in only one scanning session, and started with the structural scan, followed by MB-EPI DTI and a MB-EPI resting state fMRI scans. The patient also participated in one additional scanning session where we aimed to functionally localize the fusiform face area (FFA), the parahippocampal place area (PPA), face place localizer, as well as the lateral occipital complex (LOC).

2.2.3 Functional Localizer

The patient and a matched healthy individual also participated in a functional localizer scan, intended to identify the fusiform face area (FFA), the parahippocampal place area (PPA), as well as the lateral occipital complex (LOC). These areas were localized using standard procedures [57, 68, 58]. For the face-place localizer, blocks of unfamiliar faces and places were alternated with blocks of uniform gray background ('blank' condition). For the object localizer, blocks of objects and scrambled objects images were alternated with 'blank' blocks. In a block 20 randomly chosen images were presented for 300ms followed by 200ms blank, resulting in a stimulus presentation rate of 2Hz. Each run consisted of 18 blocks (3 conditions repeated 6 times) à 8TRs as well as 5TRs 'blank' at the beginning and end of the run, resulting in a total 154 TRs (TR=2s). Each localizer scan (faces-places-blank; objects-scrambled objects-blank) was repeated twice. Each run took about 5 min. The patient was told to carefully look at each image as questions may be asked about the images later. We decided against a classic fixation task during the scan, since this type of task proved to be too stressful for the patient.

2.2.4 Analysis

2.2.4.1 Tract-based Atlasing

Diffusion weighted images were analyzed with FSL 5.0 (FMRIB Image Analysis Group, Oxford, UK). We first performed automatic segmentation and eddy current correction, after which fractional anisotropy (FA) maps were calculated using the FSL Diffusion Toolbox (FDT 2.0). Maps of the patient and one control participant were co-registered with corresponding T1- weighted images, and major white matter tracts were labeled by hand after careful visual inspection.

2.2.4.2 White matter micro-structural integrity

FA, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps were calculated using the FSL Diffusion Toolbox (FDT 2.0). FA is a measure of directionality of the diffusion, whereas MD is a measure of overall diffusivity [69]. AD and RD index the diffusivity in the longitudinal direction (approximately parallel to the main axon bundle) and transversal direction (perpendicular to the main axon bundle) respectively [70]. All indices are computed from the same eigenvalues of the diffusion tensors, and their values often correlate. While FA is very sensitive to microstructural changes it is less specific as to the type of change, high and low FA values can be associated with abnormal structure and function [71, 72], though increases in FA can also correlate with increases in functional connectivity [73] or cognitive abilities. Increases in FA often co-occur with decreases in MD and RD and increases in AD. Elevated MD values have been associated with atrophy in tissue density or damage, whereas increases in RD might be due to de-myelination, or lesser membrane density [74, 75, 76], changes in the axonal diameters or density. Decreases in AD can be associated with axonal injury [77]. While an increase in AD could be due to more fiber coherence [76], it could also indicate a destruction of neurofibrils or axonal degeneration [78]. In general, maturing white matter is highly associated with increased anisotropy due to the structure of the axonal cell membranes [70].

In order to calculate the fiber-tracking maps we used FSL’s Probabilistic Tracking Tool, FDT version 5.0. Here, we first registered each participant’s data to the MNI 2mm standard space. Then, using FSL View, we defined ROI masks and performed seed-based tractography and eliminated those fibers that do not pass through these masks.

We selected ROIs in order to investigate the major white matter pathways between the occipital and temporal region and other parts of the brain as well as interhemispheric connections. Supplementary Figure 1 shows ROI locations and Supplementary Table 1 provides corresponding MNI coordinates. These major pathways- namely ILF, SLF and IFOF influence the hierarchical processing in higher-level vision [79].

Since ILF, SLF and IFOF contain both long fibers as well as short connections, we placed ROIs as waypoint seeds in the frontal-, optic radiation and occipital parts of the inferior fronto-occipital fasciculus (IFOF), and the anterior-, superior-, inferior-, temporal- and posterior parts of the inferior longitudinal fasciculus (ILF) (Supplementary Figure A.1. In addition, ROIs on the bilateral calcarine sulcus, cingulate cortex, superior longitudinal fasciculus (SLF), splenium and tapetum were created to investigate structural integrity in tracts that emanate from the cortical areas close to the pachygyric occipital regions. In all probabilistic tract calculations (except for the splenium) a binary midline mask was used as an exclusion mask to restrict computations to the target hemisphere (Supplementary Figure A.2 & A.3). This restriction was essential for interhemispheric comparisons. We computed FA, MD, RD and AD values for each tract and compared values between patient and healthy controls using nonparametric bootstrapping.

2.2.4.3 Resting State Analysis

Preprocessing of functional data was performed on Statistical Parametric Mapping software (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) implemented in MATLAB (Mathworks Inc, SherbornMA, USA). Preprocessing in

SPM8 includes image realignment, slice acquisition-time correction, functional and anatomical images coregistration. Functional images normalized to Montreal Neurological Institute (MNI) by fitting mean functional images to single reference EPI standard SPM template and smoothed with 6 mm Gaussian kernel to reduce spatial noise.

ROI-based Connectivity. We next created spherical ROIs on each participant’s cortex in the bilateral lateral orbitofrontal, rostral middle frontal, superior frontal areas, pericalcarine sulcus, lateral occipital gyrus, lingual gyrus, parahippocampal gyrus, entorhinal area, fusiform gyrus, middle temporal gyrus, superior temporal gyrus, cuneus, precuneus, precentral gyrus, postcentral gyrus, caudal middle frontal gyrus, isthmus of cingulate gyrus, rostral anterior cingulate cortex and caudal anterior cingulate gyrus that were connected via cerebral white matter tracts namely IFOF, ILF, calcarine sulcus, SLF, cingulate cortex and tapetum of corpus callosum. Each ROI was smoothed with a 6mm-radius Gaussian kernel. Supplementary Table B.1 provides an overview of all ROIs used in the functional connectivity analysis.

FMRI time series were extracted and coherence scores were calculated between pairs of ROIs for each individual using the Welch’s periodogram method (with a 64-time point discrete Fourier transform, Hanning window - to reduce leakage - and a 32-point overlap). Coherence, $\text{Coh}_{xy}(\lambda)$, between two time series, x and y at frequency λ was measured by using formula:

$$\text{Coh}_{xy}(\lambda) = \frac{|\text{R}_{xy}(\lambda)|^2}{\text{f}_{xx}(\lambda)\text{f}_{yy}(\lambda)} \quad (1)$$

where $\text{R}_{xy}(\lambda)$ is the complex valued coherency of x and y, $\text{f}_{xy}(\lambda)$ is the cross-spectrum of x and y, and $\text{f}_{xx}(\lambda)$ is the power spectrum of x [80]. Mean frequency scores between 0 and 0.15 range were computed for each coherence calculation [81]. The calculations were performed in Python programming platform using the SciPy library. Coherence values thus obtained were compared between groups via both a one-sample t-test and a non-parametric bootstrapping technique.

Functional Localizer Analysis Preprocessing and General Linear Model

(GLM) analysis were performed with FEAT (FSL 5.0, FMRIB Image Analysis Group, Oxford, UK). Preprocessing steps include image realignment, slice acquisition-time correction, functional and MNI 2mm standard space co-registration. The GLM was created from two runs for each localizer (face vs place and object vs scrambled object). Results were projected onto the co-registered T1-weighted anatomical structure.

2.2.4.4 Nonparametric Analysis Procedures

Since values of a single case were compared to a group of healthy controls, the assumption of normality of the sample (from the patient) was violated and classical statistical techniques cannot be applied. Thus, for each track and ROI we determined the 99% confidence intervals (CI) for control group mean diffusion indices and coherence scores (resting state fMRI) using sampling with replacement in a nonparametric bootstrapping procedure [82].

We also conducted one sample t-tests comparing patient and control group mean diffusion indices and coherence scores. To correct for a false-positive inflation at multiple comparisons we employed the FDR procedure by Benjamini and Hochberg (1995) [83]. If the patient’s mean score lies outside the corresponding estimated control group confidence interval, outside the range of the control group raw scores, and the one sample t-test comparing patient score and controls is significant at the P FDR criterion of at least $P \text{ FDR} \leq 0.05$, we report a given region to be significantly different between patient and controls.

2.3 Results

We conjectured that the sparing of object and face perception in patient NG 367-1 could be due to increases in microstructural integrity along white matter pathways and/or due to increases in functional connectivity between cortical areas connected by these pathways. In order to examine the two possibilities,

we compare microstructural integrity and functional connectivity in major visual structural pathways between the patient and a matched control group.

2.3.1 Microstructural Integrity along Major White Matter Pathways

Figure 2.2, 2.3 and 2.4 depict color-coded fractional anisotropy (FA) values along major white matter pathways in the patient (left column) and a matched healthy participant (right column).

Brain Stem Fibers Regarding the brain stem structures cerebellar peduncle, superior cerebellar peduncle and decussation of the superior cerebellar peduncle were identified at midbrain level (Figure 2.2, A and B).

Projection Fibers and Callosal Fibers The best plain to represent and identify fibers that lie in the superior-inferior axis was the transverse plane (Figure 2.2). At the level of internal capsule (Figure 2.2, C-D and E-F) anterior and posterior thalamic radiations became a part of corticobulbar and corticospinal tracts [84]. Anterior limb of internal capsule includes anterior thalamic radiation whereas posterior limb contains superior projection of thalamic radiations. In addition several projection, association and callosal fibers joined the projection fibers which were extended to the corona radiata [84]. Anterior, posterior and superior regions of these projection fibers were identified in Figure 2.2 E-H) and compared in Figure 2.2, 2.3 and 2.4. In Figure 2.3 A-B, C-D, E-F, G-H and in Figure 2.4 A-B superior part of corona radiata was abundant and spread in patients in contrast to the healthy control. Also in C-D images increased anterior coronal radiata fibers could be seen in patient.

Association Fibers To be able to identify association fibers which were lie along anterior-posterior axis, coronal 2D images were used (Figure 2.3). In anterior cross section it could be seen that association fibers joined thalamic, projection fibers and callosal fibers. Moreover in more posterior regions association fibers such as inferior-fronto occipital, uncinate and longitudinal fasciculi

project through the external capsule whereas projection fibers such as corticobulbar and thalamic fibers joined in the anterior limb of internal capsule (Figure 2.3, A-B) [84]. In Figure 2.3 A-B it could be seen that anterior part of inferior fronto-occipital, uncinate and superior lateral fasciculi merged in external capsule whereas projection fibers merged in anterior limb of internal capsule in the same cross section. In addition reduced superior longitudinal fasciculus was seen in patient's data compared to healthy control in Figure 2.3 C-D and E-F and in Figure 2.4 E-F and G-H images. In Figure 2.3 C-D it could be clearly seen that inferior longitudinal fasciculus starts to merge with fronto-occipital fasciculus to connect posterior part of cerebral cortex to more anterior areas. However in Figure 2.2 A-B, and C-D reduced inferior longitudinal fasciculus fibers and posterior part of merged inferior longitudinal and inferior fronto-occipital fasciculi were identified in the patient's data.

Limbic Fibers Cingulum projections in the color coded FA maps might contain cingulate gyrus and some corpus callosum projections. Cingulum projections turned towards to temporal lobe and lies along the hippocampus until it arrives to the amygdala [84]. In Figure 2.4 E-F, projection of fornix and the striata terminalis found in the dorsal surface and cingulum projections lied through ventral surface in temporal lobe.

White matter atlas showed a reduction in white matter connectivity in association fibers including superior longitudinal fasciculus (SLF) and posterior association fibers including ILF and IFOF and increased projection fibers including anterior and superior corona radiata in patient's brain. To be able to reveal these possible alterations and compare with the healthy controls identified some main tracts and calculated FA, MD, RD and AD scores to assess WM microstructural integrity.

Intra- and Interhemispheric Microstructural Integrity. Overall, in the patient intrahemispheric white matter integrity in the tracts we investigated appeared to be compromised. FA values were significantly lower, except for the left and right cingulate and ILF. MD, RD values were significantly elevated in all tracts except for MD in the in the right and left ILF. AD values were elevated

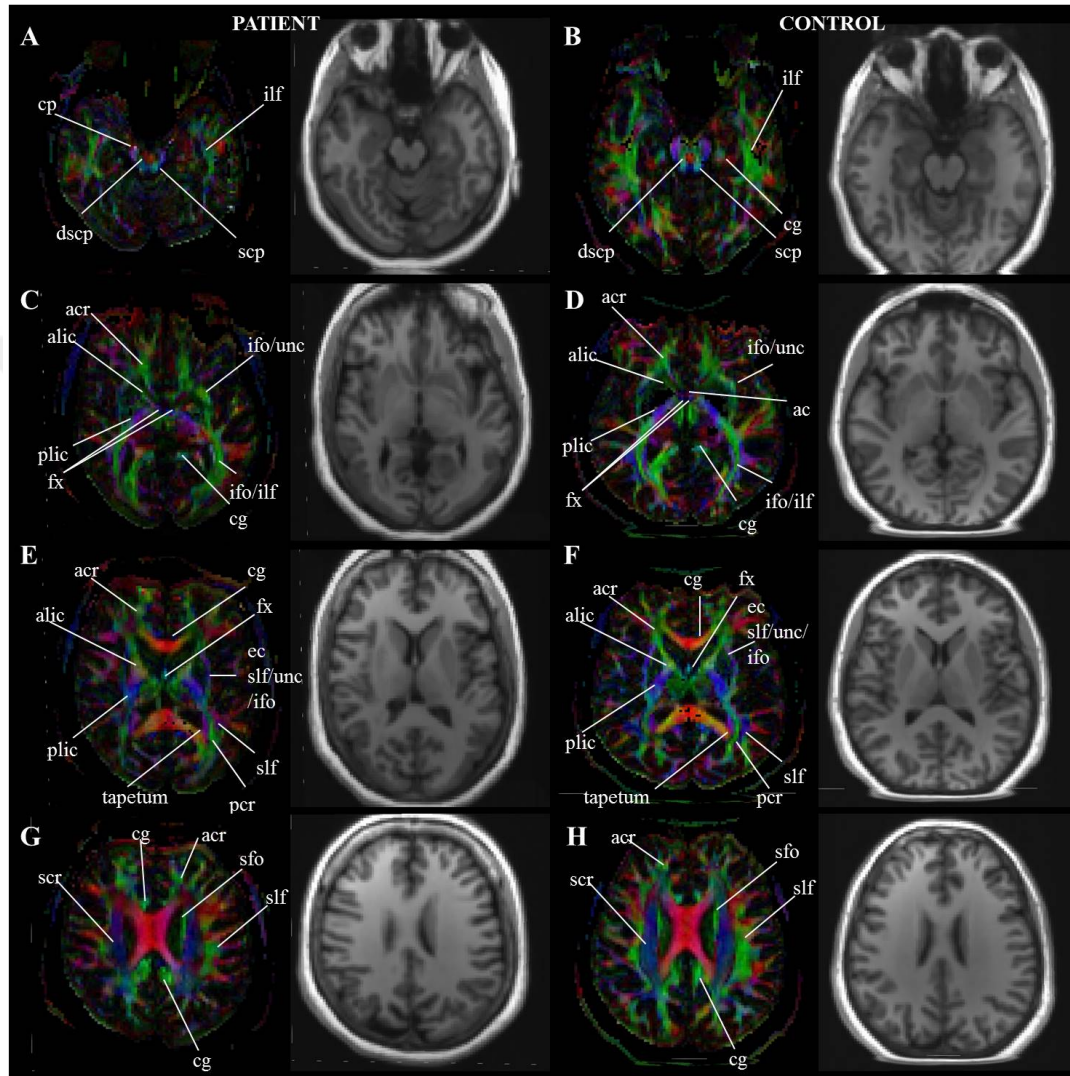


Figure 2.2: White matter tract atlas of the patient and a matched healthy control participant. This figure depicts tracts of the brain stem, projection and association fibers. While fiber volume appears to be reduced in bilateral IFOF, ILF, SLF and posterior corona radiata, we also note an increased fiber volume in anterior corona radiata in the patient. Images are labelled color FA maps co-registered onto T1 weighted anatomical images (following radiological convention). Label Glossary:ac-anterior commissure, acr-anterior region of corona radiata, alic-anterior limb of internal capsule, cbt-corticobulbar tract, cg-cingulum, cst-corticospinal tract, dscp-decussation of superior cerebral peduncle, icp-inferior cerebral peduncle, ifo-inferior fronto-occipital fasciculus, ilf-inferior longitudinal fasciculus, pcr-posterior region of corona radiata, plic-posterior limb of internal capsule, scr-superior region of internal capsule, sfo-superior fronto-occipital fasciculus, slf-superior longitudinal fasciculus, unc-uncinate fasciculus

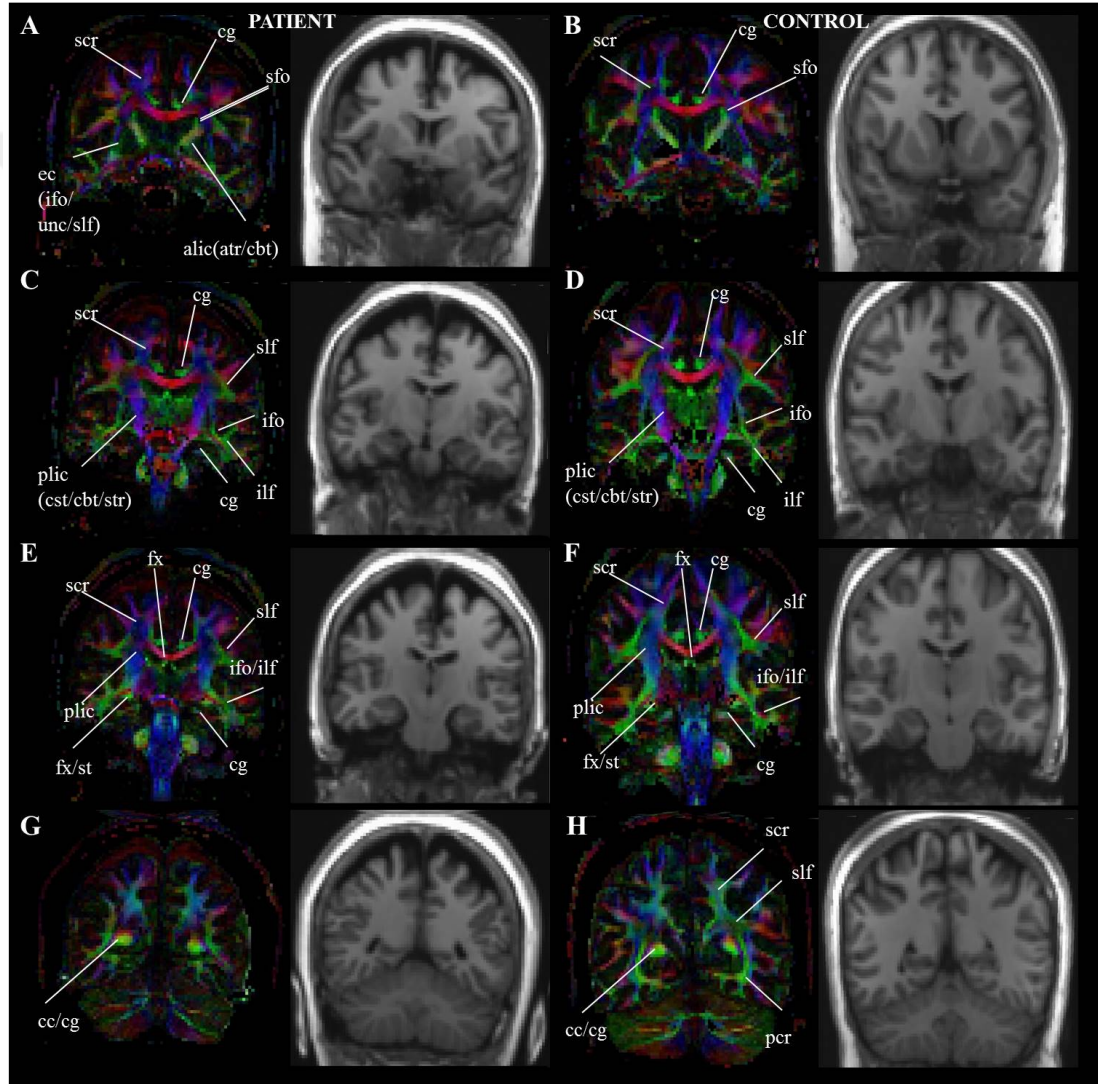


Figure 2.3: White matter tract atlas of the patient and a matched healthy control participant. For the label glossary please see Figure 2.2.

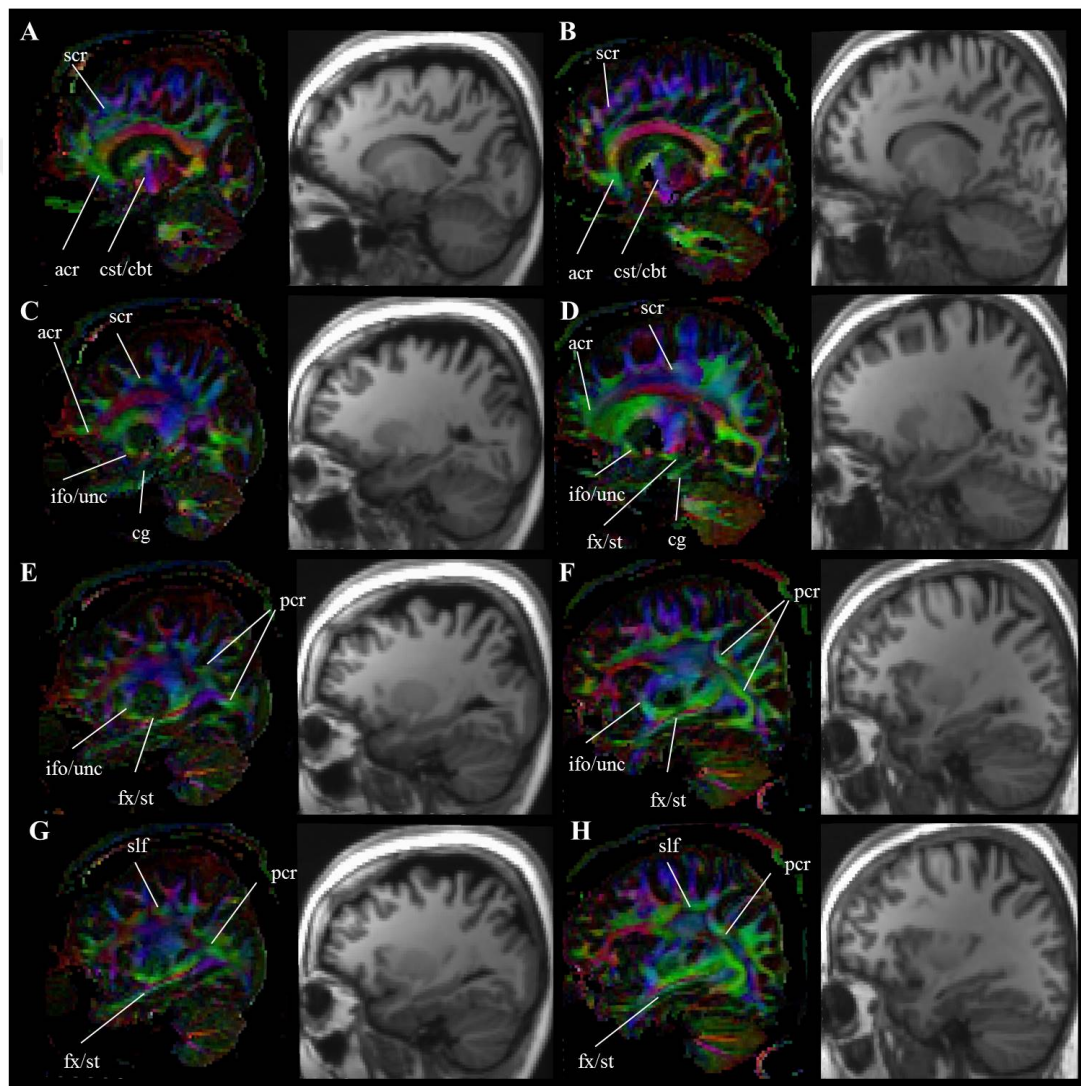


Figure 2.4: White matter tract atlas of the patient and a matched healthy control participant in sagittal slices. For the label glossary please see Figure 2.2

a. Intrahemispheric White Matter Microstructural Integrity

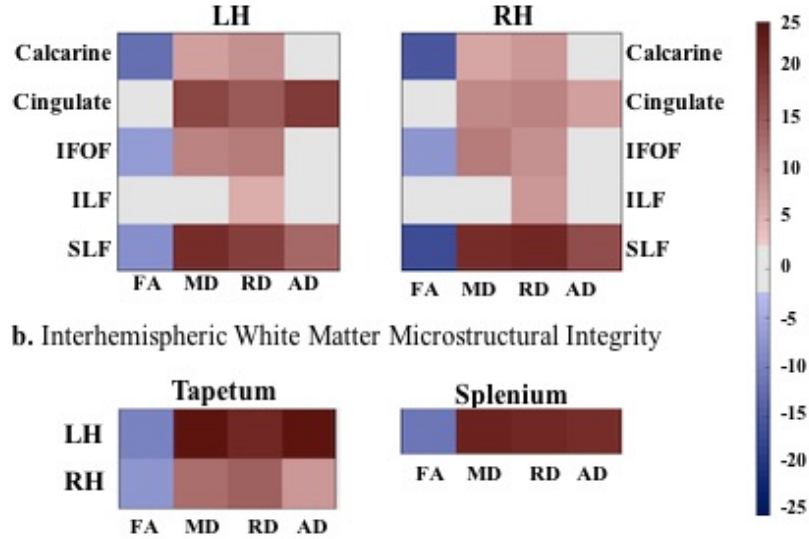


Figure 2.5: Graphical overview of statistical outcomes comparing intrahemispheric (a) and interhemispheric (b) white matter integrity between patient and control group along major white matter tracts. Colors correspond to values of the t-statistics: blue indicates that the patient's values were lower than those of the controls, red indicates that the patient's values were higher than those of the controls. Light gray corresponds to statistically non-significant differences between patient and control. LH: left hemisphere, RH: right hemisphere, IFOF: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus, FA: fractional anisotropy, MD: mean diffusivity, RD: radial diffusivity, AD: axial diffusivity. See Table 2.1 and 2.2 for corresponding numerical results.

in the patient's cingulate, and SLF. Interhemispheric microstructural integrity appeared to be largely abnormal in the patient. Her FA values in tapetum and splenium were significantly lower compared to the healthy control group, while MD, RD and AD values were significantly elevated. Figure 2.5 provides a graphical overview of these results and Table 2.1 and Table 2.2 provide corresponding numerical values and results of all statistical tests for intra- and interhemispheric microstructural integrity, respectively.

Table 2.1: White matter diffusion indices in bilateral calcarine, cingulate, inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF) probabilistic tracts. (*p<0.05, **p<0.01, ***p<0.001, all FDR corrected, $\wedge$ inside the range of control group. L: Left, R: Right, FA: fractional anisotropy, MD: mean diffusivity, RD: radial Diffusivity, AD: axial diffusivity, IFOF: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus.

Tracts		Control Group 99% CI	Patient	t test(df=11)	p values
Calcarine	FA	L: 0.2911-0.3118	0.2442	-11.8691	<0.0001***
		R: 0.2809-0.2985	0.2286	-15.0230	<0.0001***
	MD($\times 10^3$)	L: 0.8079-0.8524	0.903	7.3116	<0.0001***
		R: 0.8011-0.8440	0.887	6.6975	<0.0001***
	RD($\times 10^3$)	L: 0.6791-0.7180	0.780	9.0384	<0.0001***
		R: 0.6748-0.7164	0.776	8.4796	<0.0001***
	AD($\times 10^3$)	L:1.1000-1.1000	1.155	4.4022	0.0023
		R:1.1000-1.2000	1.110	3.0602	0.0156 $\wedge$
	Cingulate	L:0.2891-0.3141	0.2965	-1.1341	0.2896
		R:0.2838-0.3081	0.2606	-6.2907	<0.0001 $\wedge$
		L:0.8292-0.8668	0.998	17.3605	<0.0001***
		R:0.8472-0.8958	0.983	10.0094	<0.0001***
		L:0.6953-0.7361	0.860	15.2595	<0.0001***
		R:0.7135-0.7653	0.867	10.7653	<0.0001***
IFOF	FA	L:1.1000-1.2000	1.275	18.7984	<0.0001***
		R:1.1000-1.2000	1.212	7.7484	<0.0001***
	MD($\times 10^3$)	L:0.3319-0.4338	0.2232	-6.7399	<0.0001***
		R:0.3276-0.4107	0.2278	-7.4275	<0.0001***
	RD($\times 10^3$)	L:0.7812-0.8668	1.029	10.7715	<0.0001***
		R:0.8078-0.8540	0.951	11.5250	<0.0001***
	AD($\times 10^3$)	L:0.5908-0.7011	0.929	11.1335	<0.0001***
		R:0.6238-0.7063	0.837	9.2239	<0.0001***
	AD($\times 10^3$)	L:1.1000-1.2000	1.233	2.0515	0.0743

ILF		R:1.1000-1.2000	1.180	0.8884	0.4002
	FA	L:0.3025-0.3385	0.3048	-1.7141	0.3048
		R:0.2845-0.3379	0.2411	-5.9750	<0.0001^
	MD($\times 10^3$)	L:0.8030-0.8442	0.872	5.3366	0.0007^
		R:0.8033-0.8436	0.918	10.3327	<0.0001^
	RD ($\times 10^3$)	L:0.6593-0.6908	0.717	5.7877	0.0004**
		R:0.6563-0.7109	0.792	8.5232	<0.0001***
	AD($\times 10^3$)	L:1.1000-1.2000	1.185	3.9356	0.0043^
R:1.1000-1.1000		1.164	4.9557	0.0011^	
SLF	FA	L:0.2730-0.3133	0.2164	-8.5442	<0.0001***
		R:0.3053-0.3249	0.2368	-16.9594	<0.0001***
	MD($\times 10^3$)	L:0.8397-0.8812	1.062	20.8271	<0.0001***
		R:0.8498-0.9167	1.199	20.5553	<0.0001***
	RD($\times 10^3$)	L:0.7098-0.7597	0.949	18.5844	<0.0001***
		R:0.7150-0.7794	1.070	21.5479	<0.0001***
	AD($\times 10^3$)	L:1.1000-1.2000	1.277	13.8128	<0.0001***
		R:1.1000-1.3000	1.450	16.8246	<0.0001***

2.3.2 Functional Connectivity

We next wanted to test whether the observed changes in white matter structural integrity would directly affect communication between cortical areas. To do so we estimated functional connectivity (from resting state data) for white matter tracts by computing the coherence score of the BOLD response between 24 ROIs in each hemisphere and compared these scores between patient and controls. In this study we focus only on those ROI connections (226 in total) that are relevant for the respective white matter tracts of interest. All 2304 connectivity (576 for each hemisphere) difference scores can be found in Supplementary Figure B.1. Note that in this presentation of the data it is possible that the same ROI occurs in several tracts. For example, for the precuneus as part of the SLF, we consider

Table 2.2: White matter diffusion indices in tapetum and splenium probabilistic tracts suggest a disruption of interhemispheric connectivity in the patient. (*p<0.05, **p<0.01, ***p<0.001, all FDR corrected)L: Left, R: Right, FA: fractional anisotropy, MD: mean diffusivity, RD: radial Diffusivity, AD: axial diffusivity

Tracts		Control Group 99% CI	Patient	t test(df=11)	p values
Tapetum	FA	L: 0.2843-0.2987	0.2591	-9.6872	<0.0001***
		R:0.2817-0.3012	0.2551	-7.8058	<0.0001***
	MD($\times 10^3$)	L:0.8472-0.8722	1.002	24.9157	<0.0001***
		R:0.8427-0.8792	0.971	13.1798	<0.0001***
	RD($\times 10^3$)	L:0.7176-0.7464	0.873	21.4350	<0.0001***
		R:0.7152-0.7508	0.852	14.6869	<0.0001***
Splenium	AD($\times 10^3$)	L:1.1000-1.2000	1.258	25.8092	<0.0001***
		R:1.1000-1.2000	1.205	8.5079	<0.0001***
	FA	0.2993-0.3110	0.2756	-10.9923	<0.0001***
		0.8494-0.8887	1.063	22.0751	<0.0001***
		0.7116-0.7491	0.918	21.5889	<0.0001***
		1.1000-1.2000	1.351	20.8674	<0.0001***

its connectivity with precentral gyrus and pars opercularis, however when it is considered part of the the ILF, we report its connectivity with fusiform gyrus and parahippocampus. Figure 2.6 shows the resulting connectivity difference plots. Supplementary Tables B.2-B.6 provides corresponding numerical values and highlights the significant differences.

Intra- and Interhemispheric Functional Connections. The intrahemispheric functional connectivity between ROIs along IFOF, SLF, ILF, calcarine and cingulate, appeared to be largely preserved in the patient compared to the control group. However, 33.33% of the connections in the calcarine, 17.5% in the SLF, 16.07% in IFOF, 14.29% in the ILF and 12.5% in the cingulate, showed reduced functional connectivity in the patient, as indicated by the blue hues in Figure 2.6. Interestingly, these reductions in connectivity were rarely symmetric in the two hemispheres, except for the connection between the superior-parietal gyrus and the postcentral sulcus (SLF), between the cuneus and precuneus (IFOF & calcarine) and cuneus and enthorinal cortex. Most frequent reductions in connectivity were found for connections with pre-and postcentral sulcus (SLF, IFOF), precuneus (SLF, IFOF, calcarine), cuneus (ILF, IFOF, calcarine) and enthorinal cortex (ILF). Interestingly, results also indicate a statistically significant functional hyperconnectivity in left IFOF (Figure 2.6, reddish hue) between rostral middle frontal and lateral orbitofrontal gyrus.

There were no statistically significant differences in interhemispheric functional connectivity for tapetum between patient and control group.

Functional Localization of Face, Place and Object Areas The patient had no problems in object and face perception despite pronounced morphometric changes in lateral occipital and inferior temporal cortex [56]. Because the visual behavior was intact, we expected functional localization of the visual face and object areas to be successful, but also expected some differences as to where these areas would be localized compared to healthy controls. Figure 2.7 confirms that functional localization of parahippocampal place area (PPA), fusiform face area (FFA) and lateral occipital cortex (LOC) was possible. As expected, however, these activation patterns in the patient’s brain were localized in, what appears

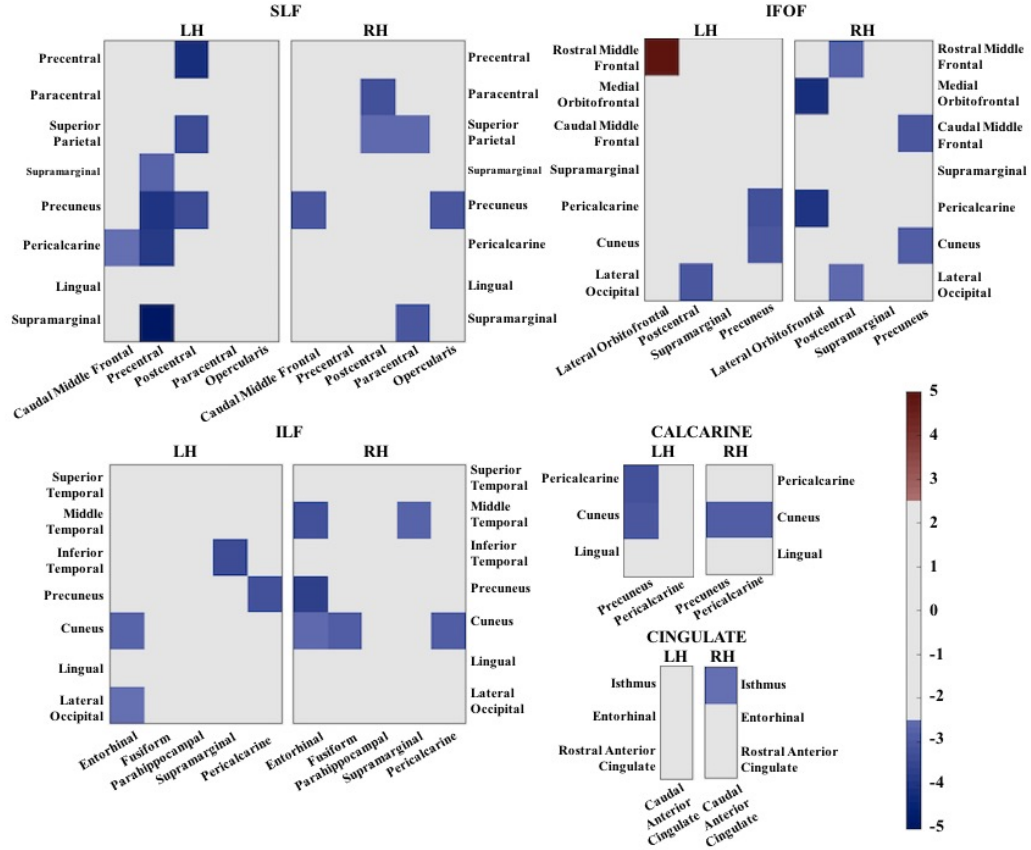


Figure 2.6: Graphical overview of functional connectivity differences between patient and controls. Colors correspond to t-statistics: blue indicates that the patient's connectivity values were significantly lower than those of the controls, red indicates that the patient's connectivity values were significantly higher than those of the controls. Connectivity was computed for each hemisphere between 24 ROIs. Here we consider only ROI connections (226 in total) relevant to the white matter tracts of interest, i.e. IFOF, SLF, ILF, calcarine and cingulate. ROI pairs from converging areas are included in both converging tracts to provide full overview. All 576 connectivity scores can be found in Supplementary Figure B.1. LH: left hemisphere, RH: right hemisphere, IFOF: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus, FA: fractional anisotropy, MD: mean diffusivity, RD: radial diffusivity, AD: axial diffusivity.

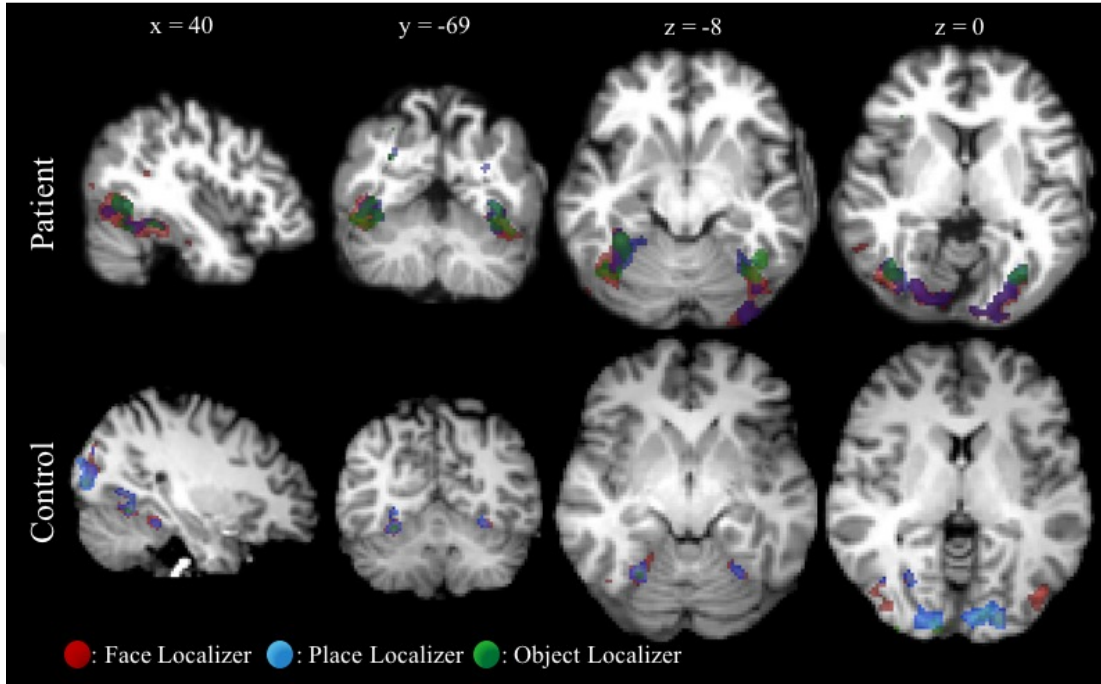


Figure 2.7: Functional localization of place, face and object cortical areas. Shown are a sagittal, coronal and two transversal views (from left to right) with the corresponding MNI152 2mm standard space coordinates. Color scale represent GLM analysis results based on z-statistics between 4 and 7.8.

to be, an additional 'inner cortical surface', located beneath the thick pacygyric cortical surface in the occipital lobe. Overall, activation patterns in the patient seemed to be more inferior and more overlapping in the patient than in the control.

2.4 Discussion

The aim of this study was to discover the neural basis of the remarkably intact object and face perception abilities of a patient with a homozygous LAMC3 gene mutation. The patient had severe bilateral smoothing and thickening of the lateral occipital cortex [37] and further significant structural changes in gray matter, e.g. in the inferior temporal lobe [56]. Both, LO and IT are cortical

regions that are critically involved in face and object perception [57, 68, 58]. Thus, it is a puzzle, how this patient’s brain accomplishes normal function despite these congenital structural changes.

To achieve our aim, we investigated the microstructural integrity of major structural pathways involved in visual processes and functional connectivity along these pathways in the patient and a matched control group. Taken together, our results indicate a change of microstructural white matter integrity to various degrees in all investigated pathways – intra and interhemispheric - , with most changes in SLF and fewest changes in ILF. In contrast, functional connectivity appeared to be largely intact. Nevertheless, there were several reductions in functional connectivity in all pathways, most notably in the SLF.

On the one hand, the microstructural integrity -, and functional findings are consistent with morphometry results of Urgen et al. (2018) [56], which point to deficits in visuo-spatial attention. On the other hand they can also provide an explanation for the spared object and face perception in the patient, as will be discussed next. Taken together, we find only moderate links between indices of white matter structural integrity and resting state functional connectivity.

2.4.1 By what mechanism are object and face perception spared?

ILF. Microstructural integrity was most preserved in the ILF. This pathway projects along the temporal lobe with fibers terminating in occipital cortex, and is thought to subserve hierarchical processing in the ventral stream, which plays a role in object recognition [85, 79]. Specifically, it is involved in mediating the fast transfer of visual signals to anterior temporal areas and neuromodulatory reverse projections from the amygdala to early visual areas which are critical for connecting visual areas to the amygdala and hippocampus [85]. This pathway is also directly involved in face recognition [86, 87, 88], scene perception [89, 90] and object recognition [91, 92, 93, 85, 86]. For example, lower FA values in the ILF

have been associated with age-related decline in face discrimination performance [94]. In our study, FA, MD and AD of the ILF were not statistically different between patient and controls. Even though radial diffusivity was increased in this pathway in the patient, it appears not to have had major effects on the functional connectivity between most interconnected regions, and in particular those, directly involved in face, place and/or object recognition e.g. the fusiform gyrus, the inferior temporal cortex, or lateral occipital cortex.

IFOF. Also the IFOF, which connects occipito-temporal areas with ventro-medial frontal cortex, has been associated with face recognition [95, 96], visual recognition and conceptualization [97] visual attention [98, 99], but also plays a role in determining the appropriate course of action [100] and is part of reward pathway [101, 102, 103]. While the IFOF in the patient showed several changes in microstructural integrity, i.e. lower FA, as well as increased MD, and RD, a decrease in functional connectivity occurred only for a few more connections than in the ILF, and primarily for those cortical regions that play a role in visual attention, e.g. precuneus, postcentral sulcus [99], both also connected to other cortical regions via the SLF), or caudal middle frontal gyrus [104].

Thus, given that the major structural and functional neural paths subserving face and object recognition were intact in the patient, it is perhaps no surprise that we see rather ‘normal’ cortical activation in response to faces, places and objects and find intact object-, face recognition behavior. What is perhaps surprising though, is that this outcome could have not been ‘predicted’ from the gray matter morphometry results. Morphometry results in Urgen et al. (2018) [56] were, however, consistent with the patient’s problems in visuo-spatial attention, and the microstructural and functional connectivity findings of this study are en par with this, as discussed next.

2.4.2 Evidence for compromised visuo-spatial attention.

SLF. The SLF, connecting the superior parietal lobule/intraparietal sulcus with

the superior frontal gyrus/frontal eye field, has been primarily associated spatial attention [71], and top-down modulation of visual processes [105] via dorsal fronto-parietal - [32, 106, 107] and ventral attention networks [108]. All diffusion indices differed significantly in the SLF between patient and controls, indicating a compromised microstructural integrity in this pathway. Even though this tract also showed the highest occurrence of changes in functional connectivity it was still below 20% of the total number of connections. However, all changes involved connectivity decreases between cortical areas involved in spatial attention, such as pre-and postcentral sulcus and superior parietal gyrus (nodes in the dorsal attention network, [109, 99, 32], pars opercularis, caudal middle frontal gyrus, precuneus or supramarginal gyrus (nodes in the ventral network,[32].

Functional significance of lower FA along SLF on attention is shown that FA correlates with poorer performance in orienting to attention with increased saccadic latency and poorer performance [110]. Also, a balance of mutual inhibition between bihemispheric posterior parietal areas is important in visuospatial attention[111]. The corpus callosum is largest fiber bundle which mediates interhemispheric communication among cortical areas has an important role in balancing in higher level cognitive functioning [112]. Our results indicated that both microstructural integrity along SLF and balance mechanism between bilateral SLF pathways were affected in our patient. Taken together, these findings are consistent with the patient’s problems in visuospatial attention and changes in gray matter morphometric indices reported by Urgen et al. (2018) [56].

2.4.3 Agreement of structural and functional indices.

We postulated that the increases in white matter volume in the patient’s inferior temporal cortex [56] might be a mechanism to compensate the adverse effects of gray matter changes, and might translate to changes in microstructural integrity or increases in functional connectivity in pathways connecting this area. While we do not find direct evidence for this, white matter structure and functional connectivity in the ILF were largely intact.

Overall, white matter volume changes ([56], their Supplementary Table 6) tended to be associated with intact functional connectivity results rather than with microstructural integrity changes. For example, increases in white matter volume in cuneous, lingual gyrus, lateral orbitofrontal cortex or lateral occipital cortex were consistent with intact or even hyper-connectivity of these areas (lateral orbitofrontal cortex with rostral middle frontal gyrus), but not with the overall decrease in FA in the IFOF, calcarine or tapetum. However, in the SLF - and connected cortical areas that play a role in visual attention - decreases in white matter volume tended to co-occur with decreases in functional connectivity and decreases in microstructural integrity. In fact, it appears that only in the context of explaining the patient’s deficits, e.g. in visual attention, that these measures (and morphometric indices) yielded consistent outcomes. Intact visual behavior, such as object or face perception in our patient, appears to be best accounted for by functional connectivity, and appears to be only moderately related to microstructural integrity, or voxel-based morphometry outcomes. The observation, that the link between structure and function can at best be moderate, would be consistent with previous work showing that white matter structural connectivity is not correlated to resting state functional connectivity [113], or that normal resting state functional connectivity is possible despite missing or severed corpus callosum (see [63] or [64] but also see [62] for an alternative view).

2.4.4 Gray matter or white matter – the LAMC3 chicken and egg question.

Alterations in white matter structure can have profound effects on gray matter by affecting large ensembles of neurons [114, 115], conversely changes in gray matter structure can influence the structure and integrity of axons [116, 117]. Also, white matter fascicles comprise almost a quarter of the white matter volume in human brain [28, 118]. Although there is no consistent evidence that shows the direction of the effect between white and gray matter structures, intact microstructural integrity could provide a consistent insight with higher white matter volume in associated areas as it is reported in Urgen et al. (2018) [56].

With the new possibilities of whole genome sequencing, and novel genomic analysis tools, several studies have started to tie individual genes to brain structure and function (gray matter: [119, 120] white matter: [37, 121, 122]). Yet, the specific genetic influence on human brain architecture remains poorly understood, including LAMC3’s direct effects on white and gray matter development.

LAMC3 transcription appears to peak at the interval between late development to late infancy during which the migration of postmitotic neurons to the cortical plate and the myelination of axons takes place [37]. This process is one of the most prolonged developmental periods that continues to the twenties [123, 124]. Thus, any changes (e.g. in expression levels of LAMC3) during this period of development could lead to alterations in white matter structure. However, LAMC3 could also affect gray matter development directly. Laminin expression is effective in both neuronal migration and final laminar positioning of neurons in neocortex [125]. Find some things to say here by what mechanism this might be. Thus, one cannot distinguish whether LAMC3 affected white matter structure which in turn affected gray matter structure or vice versa.

Why alterations in gray or white matter brought on by the homozygous LAMC3 mutation would lead to only impairments of visual attention but not in basic visual perception, or face, and object recognition – as we found in our patient - , remains an open question. It might be possible that the human brain, when faced with widespread congenital structural changes, is capable of maintaining basic and and highly localized or specialized perceptual mechanisms, but cannot fully achieve higher cognitive functions which require systematic excitation and suppression of complex networks [126].

2.4.5 Limitations

The biggest limitation of any single case study is to draw conclusions comparing an individual to a control group. We have here an absolutely unique individual and thus no alternative to this approach. In order to guard against false positives we apply a very conservative criterium for statistical significance: 1) the patient’s

score had to lie outside the 99% bootstrapped confidence interval, 2) it had to be outside the range of the control group raw scores and 3) FDR-corrected t-values had to be smaller than 0.

Effects of Hemodynamic Response Function Latency and Shape on Functional Connectivity. Functional connectivity is defined by Friston et al. (1993) [127] as the temporal correlation of spatially remote neurophysiological events. However, this correlation method at zero lag is very sensitive to the shape of the Hemodynamic Response Function (HRF) [81]. Even in the same scan and subject, the shape of the HRF may be different in different parts of the brain [128], which may render correlations spuriously low. To be able to overcome this, we used coherence comparison in the frequency domain in order to measure how two distinct areas are coherently active during the resting state scan.

Effects of Medication. The patient’s seizures are being controlled with a combination of valproic acid, levetiracetam, pregabalin and topiramate. While she has no reported side effects and has been able to successfully perform the tasks in her private and professional life, these drugs may affect cortical structure and functional. For example, it has been shown that valproic acid treatment contributes to white matter repair and neurogenesis in the ischemic brain [129]. Similarly, topiramate treatment provided dose-dependent and long-lasting protection of developing white matter in the rodent model [130]. Although there is no direct evidence on pregabalin effects on white matter, it has been linked to decreases in functional connectivity between components of DMN network [131]. Even though our patient has been on medication for several years, her dosage has been much lower compared to these studies, which might have rendered the possible positive and negative effects of these mediations, or their interactions, on white matter microstructure and functional connectivity negligible.

2.5 Conclusion

We conclude that the neural basis of the remarkably intact object and face recognition abilities of a patient with a homozygous LAMC3 gene mutation can be best explained by the largely intact white matter structural integrity and functional connectivity in the pathways involved in these perceptual tasks, most notably the ILF. Our results provide further support that the link between cortical structure and function is - more often than not - not a direct one. This is perhaps not entirely surprising given the complex structural and functional architecture of the brain. However, why indices of structural integrity and functional connectivity sometimes do and sometimes do not yield consistent outcomes when explaining a given behavior or cognitive function remains a question for future research.

Chapter 3

Essential Tremor

3.1 Background

Essential tremor (ET) is typically characterized with postural and kinetic tremor with different frequencies generally in upper distal limbs and rarely in head, voice and legs [132]. Growing evidence for the contribution of genetic factors in the cause of ET has come from familial aggregation studies [133], analysis of the mode of inheritance [134], twin studies [135, 136] and linkage studies but the importance of early versus late-onset ET comparison has received little attention.

Age of onset in essential tremor may be associated with a different set of risk factors, pathophysiological mechanisms and clinical course between early-onset (EOET) and late-onset essential tremors (LOET). Specifically, unlike EOET, individuals with LOET are less likely to have a family history of tremor [137]. Besides, the EOET patients have more hand involvement and more associated with dystonia than LOET patients [135, 138]. On the other hand, Deuschl and Elble [139] reported some neurologic abnormalities in LOET patients including increased prevalence and incidence of Lewy bodies, dementia and cerebellar atrophy. As it is indicated by various studies different pathophysiological mechanisms based on different associated gene expression could be effective on ET. In this

sense, restricting the genetic background by recruiting individuals from the same families to investigate the effect of age-of-onset of ET is critical to exclude the differences that may arise from different gene-disease phenotypes.

Pathophysiology of the ET is still poorly understood. Although there is a high inconsistency about the pathophysiological abnormalities, consistent evidence from the morphological analyses in ET showed cerebral and cerebellar atrophy, mainly in bilateral frontal, occipital lobes, left middle temporal gyrus, right superior parietal lobule, insula and cingulum [140, 141, 142]. Additionally, diffusion tensor imaging (DTI) studies contribute to the understanding of the pathophysiology by showing reduced fractional anisotropy in the cerebellum, brain stem and cerebral hemispheres in patients with ET [143]. Also, more recent studies reported microstructural impairment in the frontoparietal region and superior cerebellar peduncle [144, 145]. Quantitative assessments of white matter structure from the diffusion tensor imaging have been shown to correlate with the severity and with progression rates of degenerative disease of the brain [146]. In this sense, white matter measurements in both early- and late onset patients with ET are critical to reveal the effect of onset of the disease.

Previously, Gulsuner et al. [147] showed that HTRA2 could be a responsible gene for ET both in homozygous and heterozygous forms. Here, we recruited early- and late-onset familial ET patients who were homozygous and heterozygous for the HTRA2 p.G399S gene mutation, respectively. In the present study, we examined the effects of the HTRA2 gene mutation linked age-of-onset in ET on structural architecture of the human brain to reveal phenotype-specific patterns of gene. Our study provides morphometrical comparison of gray matter and white matter as well as the whole brain white matter integrity including tract-based spatial statistics. Our goal is to provide a detailed structural assessment to map the effects of HTRA2 mutation linked age-of-onset in ET onto specific brain architectures and mechanisms.

3.2 Materials and Methods

3.2.1 Participants

Five LOET patients exhibiting tremor on the distal upper limbs participated in the present study. Four EOET patients were also recruited to match LOET cases for clinical symptoms, gender and disease duration (i.e., time from disease onset to MRI scan) (Table 3.2.1, see Results for clinical assessment of the patients). Family members of LOET patients heterozygous for HTRA2 p.G399S allele whereas EOET patients homozygous for the same allele. Diagnosis of ET was based on a detailed neurological evaluation including neurological history and examination. Twenty-five healthy controls (HC) were enrolled to the study and they were divided into two groups as younger (y-HC) and older (o-HC) HC. Table 3.2.1 shows demographic information of the participants. The difference between the age at examination of ET patients and their matched healthy controls were not statistically significant ($p=0.42$ for EOET and y-HC comparison, $p=0.18$ for LOET and o-HC comparisons). However, the difference between age at MRI examination was statistically significant between early-onset and late-onset ET patients ($p=0.014$). The sex distributions were similar between ET patients and their age-matched controls (Table 3.2.1). Besides, although disease duration between early- and late-onset patients was not different ($p=0.99$), difference between patient groups in terms of age at onset was statistically significant ($p=0.002$) (Table 3.2.1).

All subjects participated in T1 weighted structural imaging and diffusion tensor imaging (DTI) components of the study. Informed written consent was obtained in accordance with the procedures and protocols approved by the Human Subjects Ethics Committee of Bilkent University (Approval Number:2011_07_25.01).

Table 3.1: Demographic information of individuals with ET classified by age at onset and age, sex matched healthy controls. Values are mean $\pm$ standard deviations or N (%). *p values refer to the Mann-Whitney U or two-sample t-test between *each ET group and matched healthy controls, and **EOET and LOET patients.

	LOET Patients	Older HC	p*	EOET Patients	Younger HC	p*	p**
N	5	11		4	14		
Age at MRI [y]	64 $\pm$ 19.58	51.1 $\pm$ 15.95	0.183	22.75 $\pm$ 18.21	29.79 $\pm$ 14.1	0.419	0.014
Gender [female]	2 (40%)	3 (27.3%)	0.622	1 (25%)	4 (28.6%)	0.891	0.655
Age at onset [y]	50.2 $\pm$ 15.88			9.25 $\pm$ 7.93			0.002
Disease duration [y]	14 $\pm$ 27.4			13.75 $\pm$ 12.69			0.987

3.2.2 Data Acquisition

Data were acquired in a 3 Tesla MR scanner (Magnetom Trio, Siemens AG, Germany) in National Magnetic Resonance Research Center (UMRAM), Ankara, Turkey. A 32-channel phase array head coil was used for all scans. High resolution T1-weighted three-dimensional magnetization-prepared rapid gradient-echo (MPRAGE) images were acquired in each session (single shot turbo flash; voxel size = $1 \times 1 \times 1$ mm³; repetition time, TR = 2600 ms; echo time, TE = 3.02 ms; flip angle = 8 degrees; field of view, FOV = 256×224 mm²; slice orientation = sagittal; phase encode direction = anterior-posterior; number of slices = 176; acceleration factor (GRAPPA) = 2). For the DTI scan a diffusion-weighted echo-planar imaging (EPI) sequence (voxel size = $2 \times 2 \times 2$ mm³; TR= 12584 ms; TE = 102 ms; FOV = 256×256 mm²; phase encode direction = anterior-posterior; number of slices = 75; b=0, 1000 s/mm², diffusion directions = 30, acquisition time = 8.37 min.) was used. Total acquisition time of MRI was 30 minutes. All subjects participated in all components of the study in a single session.

3.2.3 Morphometry Analysis

Structural analyses were performed using Freesurfer image analysis package (<http://surfer.nmr.mgh.harvard.edu/>) version 5.3. Preprocessing steps included

removal of non-brain tissue, subcortical segmentation [148] and identification of white matter/gray matter boundary based on cortical reconstruction and volumetric parcellation. Once these steps were completed, cortex was registered to Desikan Killiany Atlas and parceled into volumetric units according to gyral and sulcal structure. Then we computed WM volume for each parceled unit and each participant's volumetric measurements were normalized with their total intracranial volume. All statistical analyses were performed using SPSS v.20 (SPSS Inc., Chicago, IL). White matter and GM volumes were compared between EOET-young control, LOET-old control, EOET and LOET and young control-old control pairs via two sample t test. Multiple comparisons were controlled via false discovery rate (FDR) method using Benjamini–Hochberg approach [83].

3.2.4 DTI Analysis

Diffusion weighted images were analyzed using FSL 5.0 (FMRIB Image Analysis Group, Oxford, UK). Firstly, automatic segmentation of the brain from the non-brain tissue and eddy currents correction were performed by using FDT 2.0 (FMRIB's Diffusion Toolbox) which is the part of FSL 5.0 (FMRIB Image Analysis Group, Oxford, UK). Next, fractional anisotropy (FA), mean diffusivity (MD) maps were obtained from the DTI data.

Tract-based spatial statistics (TBSS) (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS>) was used to perform the multi-subject diffusion tensor (DT) MRI analysis [149]. Fractional anisotropy volumes were aligned to a target image as follows: (1) the FSL FA template was selected as the target image, (2) the non-linear transformation that mapped each participant's FA image to the target image was computed using FMRIB's Non-Linear Image Registration Tool (FNIRT), (3) the transformation information was used to align each subject's FA to the standard space. A mean FA image was created by averaging the aligned individual FA images and thinned to create FA skeleton representing common WM tracts of all participants. Furthermore, individual MD and FA maps were projected onto the mean skeleton.

DT MRI voxelwise statistics were performed using a permutation-based inference tool for nonparametric statistical thresholding (Randomise [150]). The number of permutations was set to 5000. FA and MD values within the mean skeleton were compared between EOET and LOET patient groups with the corresponding controls. Also, two patient groups and two control groups were compared with each other. For the between-group comparisons cluster-based threshold corrected for multiple comparisons were used [151]. Next, the total number of voxels with significantly low FA and high MD were calculated. Hemispheric binary masks were used to calculate total number of significant voxels in each hemisphere. The corresponding WM structures which were specified according to Johns Hopkins University WM Tractography International Consortium for Brain Mapping DTI-81 WM atlas.

3.3 Results

3.3.1 Clinical Assessment of Essential Tremor

Members of three families (ET-1, ET-5 and ET-59 families), who are of Turkish origin with positive ET clinical symptoms were examined. ET-1 family showed high rates of consanguineous marriage and it is known that ET has been segregating in the family for generations [147]. Demographic data of the individuals are summarized in Supplementary Table C.1. The consanguineous members of three ET families were clinically examined for ET by expert neurologists based on criteria of both the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) and the consensus statement of the Movement Disorder Society on Tremor (MDS) [152, 153]. Based on these criteria, nine individuals from these families were diagnosed with ET (Supplementary Table C.1). The participants with ET who reported age of onset before 30 years old ($n=4$), were considered as early-onset and others were grouped as late-onset ($n=5$) patients. In these families, ages of onset of tremor varied from approximately 1 to 63 years. All individuals had at one type of tremor as resting, postural, kinetic and intentional

tremors. The clinical features of ET individuals 10-026 (ET-1), 15-462 (ET-1), 13-018 (ET-5) and 14-282 (ET- 59) were particularly more severe than other affected individuals which is also seen in their Archimedes spiral test score with highest score amplitude. To separate ET symptoms from Parkinson Disease, bradykinesia with at least either muscular rigidity or postural instability were also evaluated according to the diagnostic criteria of the UK Parkinson Disease Society Brain Bank [154]. Individual 10-026 from ET-1 family is illustrating both ET and Parkinson’s disease symptoms including highest score bradykinesia and rigidity among the patient group.

3.3.2 Morphological Assessment

The segmented white-matter and gray-matter structure in the left and right hemispheres were compared according to their volumes available in Freesurfer package.

Gray Matter Compared to healthy younger controls, EOET patients had higher GM volume in the left lateral occipito-temporal sulcus, right superior temporal G-T transverse, right inferior occipital sulcus and gyrus regions (Figure 3.1, Table 3.3.2). Moreover, LOET patients had less GM volume in the left occipito-temporal and medial lingual gyrus, right precuneus gyrus, left inferior occipital gyrus and sulcus regions, bilateral middle occipital gyri, bilateral middle-lunatus occipital sulci, right superior-transversal occipital sulcus, bilateral putamen, left accumbens and left ventral diencephalon than age-matched older healthy controls (Figure 3.1, Table 3.3.2).

When two groups of patients were compared LOET patients had lower GM volumes in the right superior temporal G-T transverse, bilateral inferior occipital gyrus and sulcus regions, right middle occipital gyrus, right superior-transversal occipital sulcus, bilateral putamen and left ventral diencephalon than EOET patients. Furthermore, the regions that showed statistically significant difference between patient groups and patients’ age-matched healthy controls were also compared to rule out the effect of age and no significant difference was found in these comparisons (Figure 3.1, Table 3.3.2).

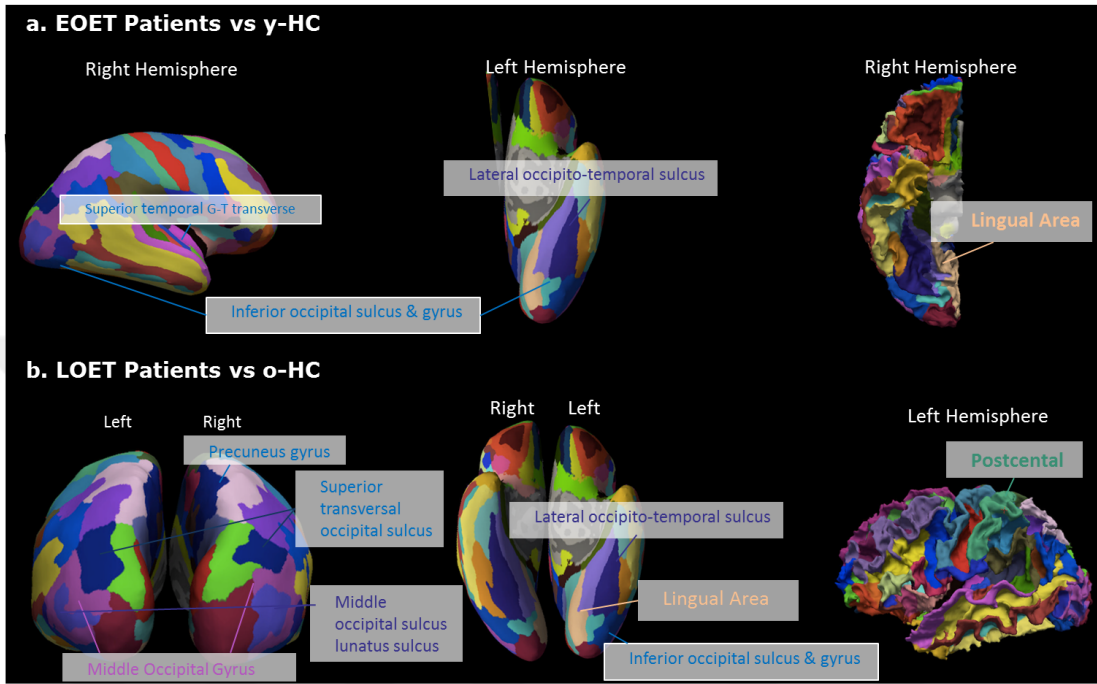


Figure 3.1: Volumetric comparisons between (a.) early onset essential tremor patients (EOET) vs younger healthy controls (y-HC) and (b.) late onset essential tremor patients (LOET) vs older healthy controls (o-HC). Labeled inflated images in the left panels indicate significant gray matter volumetric differences whereas labeled white matter images in the right panels indicate significant white matter volumetric difference

White Matter In WM comparisons, EOET patients had less WM volume than the corresponding healthy young controls only in the right lingual area (Table 3.3.2). In addition, LOET patients had smaller WM volume in the left inferior parietal areas relatively to the older healthy controls. On the contrary, LOET patients had higher WM volume in the left postcentral region compared to old healthy controls (Figure 3.1, Table 3.3.2). However, no significant change was found in WM volumes in comparison of whole patient and control groups.

Table 3.2: Results of independent sample t test analysis in white matter (WM) and gray matter (GM) morphometry, .
*FDR corrected $p < 0.05$, **FDR corrected $p < 0.01$

Segmented Brain Regions		EOET vs y-HC df=16	LOET vs o-HC df=14	EOET vs LOET df=7	y-HC vs o-HC df=23
Frontal	WM Postcentral, L	-0.274	2.197*	-1.824	0.509
	GM Lateral Occipito-Temporal(S), L	3.521**	0.973	1.607	2.127
	GM Superior Temporal G-T Transverse (G), R	2.308*	-0.56	5.513***	0.05
	GM Occipito-Temporal & Medial Lingual (G), L	0.602	-2.659*	2.015	2.068
Parietal	WM Inferior Parietal, L	-0.718	-3.395***	1.358	-0.014
	GM Precuneus (G), R	-0.078	-2.304*	1.967	1.122
Occipital	WM Lingual, R	-2.183*	-0.564	-1.176	0.664
	GM Inferior Occipital (G&S), R	3.174**	-1.252	4.722**	-0.547
	GM Inferior Occipital (G&S), L	1.277	-2.204*	2.534*	-0.395
	GM Middle Occipital (G), R	-0.111	-3.644**	3.121*	0.245
	GM Middle Occipital (G), L	0.511	-2.783*	2.288	0.061
	GM Middle-Lunatus Occipital (S), R	0.51	-2.212*	2.371	0.647
	GM Middle-Lunatus Occipital (S), L	0.445	-2.82*	1.402	-0.954
	GM Superior-Transversal Occipital (S), R	0.719	-2.307*	8.773***	1.926
Subcortical	GM Putamen, L	0.452	-2.645*	3.545*	1.638
	GM Putamen, R	0.945	-2.999*	5.623**	1.559
	GM Accumbens, L	0.609	-3.619**	3.855**	0.113
	GM Ventral DC, L	-0.164	-3.076**	2.048	1.026

3.3.3 WM Microstructural Integrity Assessment

In TBSS analysis, mean fractional anisotropy (FA) and mean diffusivity (MD) values of statistically significant clusters were summarized in Table 3.3.3. In EOET patient and age-matched young healthy control comparisons, FA reduction was identified in the genu, body and splenium parts of corpus callosum, bilateral inferior fronto-occipital fasciculus (IFOF), bilateral inferior longitudinal fasciculus (ILF), right anterior limb of internal capsule (ALIC), bilateral posterior limb of internal capsule (PLIC), bilateral external capsules, right premotor and left postcentral regions. In all of these regions significantly elevated MD values were also obtained (Figure 3.2.1A & Table 3.3.3). In addition, in LOET patients vs older healthy control comparison FA values of the patient group were lower in genu, body and splenium parts of corpus callosum, bilateral IFOF, bilateral ILF, bilateral superior longitudinal fasciculus (SLF), right ALIC, left premotor and left thalamus regions. MD values in LOET patients were also significantly higher in these regions except right ALIC and left premotor than age-matched healthy controls (Figure 3.2.1B & Table 3.3.3). Additionally, elevated MD scores were obtained in bilateral PLIC, right postcentral gyrus in LOET patients.

When two patient groups were compared FA values in LOET patients were significantly higher along the right corticospinal tract compared to EOET patients. However, MD values in EOET patients were higher along bilateral anterior corona radiata, left PLIC and bilateral parieto-occipital tracts compared to LOET patients (Figure 3.2.1C & Table 3.3.3). In addition, age effect on MD values were mainly in motor related areas including the left premotor, left postcentral and right thalamus regions between healthy controls (Figure 3.2.1D & Table 3.3.3).

3.4 Discussion

As predicted, here we found different morphological abnormality patterns between EOET and LOET patients. Reduced GM volumes in LOET patients mainly include bilateral middle occipital gyri, bilateral putamen areas, right precuneus

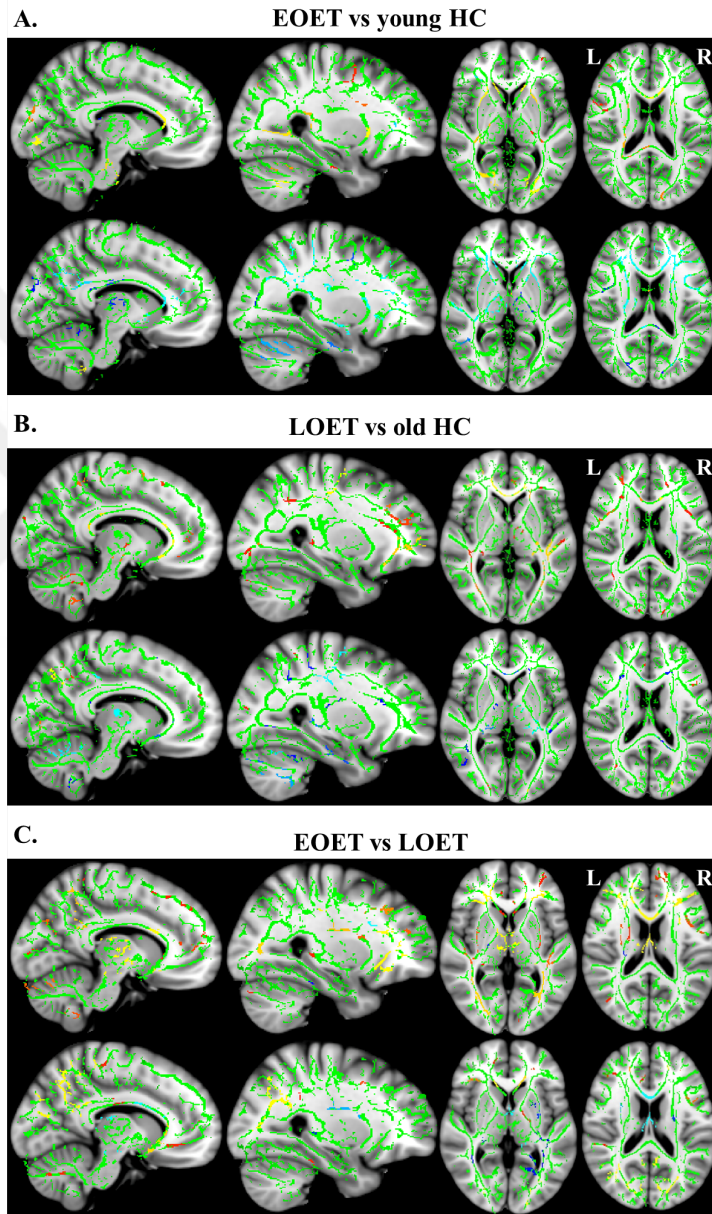


Figure 3.2: TBSS (family-wise error-corrected threshold-cluster extend voxel P maps) reveal regions of significantly reduced FA (red) and increased MD (blue) in early-onset essential tremor (EOET) patients compared with age-matched young healthy controls (y-HC) (A), Late-onset essential tremor (LOET) patients compared with age-matched old healthy controls (o-HC) (B), EOET compared with LOET (C), y-HC compared with o-HC (D).

Table 3.3: The mean FA and MD ($\times 10^{-3} \text{ mm}^2/\text{s}$) values of significant clusters in early-onset (EOET), late-onset (LOET) patients, younger (y-HC) and older (o-HC) control groups. Tracts were identified according to Johns Hopkins University WM tractography atlas and the International Consortium for Brain Mapping DTI-81 WM atlas.

Brain Region	EOET vs y-HC		LOET vs o-HC		EOET vs LOET		y-HC vs o-HC	
	FAp/FAc	MDp/MDc	FAp/FAc	MDp/MDc	FAe/FAI	MDe/MDI	FAY/FAo	MDy/MDo
CC genu	0.53/0.75	0.95/0.77	0.52/0.59	0.98/0.88	-	0.97/1.16	-	-
CC body	0.74/0.77	1.03/0.87	0.48/0.7	1.55/0.84	-	0.89/2.27	-	-
CC splenium	0.77/0.85	0.83/0.72	0.21/0.83	2.63/0.73	-	-	-	-
L IFOF	0.23/0.35	0.89/0.8	0.26/0.43	1.12/0.9	-	0.87/0.91	-	-
R IFOF	0.27/0.37	0.89/0.8	0.35/0.43	0.96/0.8	-	0.85/1.05	-	-
L ILF	0.5/0.54	0.95/0.82	0.32/0.39	1.12/0.8	-	0.89/0.85	-	0.99/0.99
R ILF	0.34/0.45	0.83/0.77	0.35/0.42	0.87/0.78	-	-	-	-
L SLF	-	-	0.4/0.51	0.79/0.68	-	-	-	-
R SLF	-	-	0.43/0.52	0.76/0.69	-	-	-	-
L ALIC	0.62/0.57	0.75/0.75	-	-	-	-	-	-
R ALIC	0.51/0.59	0.79/0.76	0.64/0.67	-	-	-	-	-
L PLIC	0.65/0.74	0.73/0.66	-	0.75/0.72	-	0.79/0.71	-	-
R PLIC	0.7/0.74	0.74/0.67	-	0.76/0.7	0.69/0.67	-	-	-
L external capsule	0.27/0.49	0.78/0.77	0.36/0.21	0.92/0.78	-	-	-	-
R external capsule	0.34/0.49	0.85/0.78	-	-	-	-	-	-
L premotor	-	-	0.26/0.46	-	-	1.05/1.06	-	0.88/0.86
R premotor	0.32/0.45	0.98/0.78	-	-	-	-	-	-
L postcentral	0.22/0.37	0.9/0.83	-	-	-	0.98/1.15	-	1.02/0.83
R postcentral	-	1.18/0.91	-	1.47/0.98	-	0.96/1.11	-	-
L thalamus	-	0.77/0.72	0.33/0.36	1.15/0.83	-	-	-	-
R thalamus	-	0.77/0.71	-	0.86/0.86	-	-	-	0.73/0.69

CC:corpus callosum, IFOF:inferior fronto-occipital fasciculus, ILF:inferior longitudinal fasciculus, SLF:superior longitudinal fasciculus, ALIC:anterior limb of internal capsule, PLIC:posterior limb of internal capsule, FAp/FAc: fractional anisotropy of patients/fractional anisotropy of controls, FAe/FAI:fractional anisotropy of EOET patients/fractional anisotropy of LOET patients, FAY/FAo:fractional anisotropy of y-HC/fractional anisotropy of o-HC, MDp/MDc:mean diffusivity of patients/mean diffusivity of controls, MDe/MDI:mean diffusivity of EOET patients/mean diffusivity of LOET patients, MDy/MDo:mean diffusivity of o-HC. WM:white matter, L:Left, R:Right.

(gyrus part), right middle-lunate occipital sulcus, right superior-transverse occipital sulcus, right calcarine sulcus, left inferior occipital gyrus and sulcus and left nucleus accumbens compared to their age and sex matched healthy controls. Besides, EOET patients had less GM volume in the right subcentral gyrus and sulcus and right inferior occipital gyrus and sulcus regions as well as reduced WM volume in the right lingual area compared to controls. Also, TBSS analysis revealed coherent reduced microstructural integrity with morphological assessment, in forceps minor, left thalamus, right frontal part of IFOF, right posterior limb of internal capsule, bilateral SLF in LOET patients compared to controls. On the other hand, microstructural integrity was affected (reduced) more in EOET patients in corticospinal tract, forceps minor, splenium, left external capsule, right anterior and posterior limb of internal capsule, bilateral hippocampus, bilateral superior corona radiata, bilateral caudate, bilateral putamen and bilateral thalamus areas compared to controls.

Although number of patients was limited due to their specific genetic background, the present findings are novel in that our multi-perspective approach allows us to conclude that the structural abnormality exists in spinal-subcortical-cerebral connections. This abnormality is likely related to age of onset of ET that in turn affects microstructural integrity as will be discussed below.

3.4.1 Essential Tremor related to a structural neural anomaly along cerebellar-thalamic-cortical pathway

Electrophysiological and functional neuroimaging studies' results provide confirmatory evidence that abnormal activation among cerebellum, thalamus and medulla is possibly associated with essential tremor [155, 156, 157]. Furthermore lesion studies suggest that tremor could be abolished by a stereotaxic lesion on contralateral ventral intermedialis thalamus nuclei or a vascular lesion on thalamus, cerebellum, pons, corona radiata or frontal lobe [158, 159, 160, 161, 162]. More recent evidence from a case study showed that a patient with essential tremor who had sensorimotor stroke and eventually a cortical infarct neighboring

the left central sulcus improved bilaterally after the stroke [77]. These findings together support the presence of the linkage between cerebellar-thalamic-cortical pathways and essential tremor.

A case study showed that unilateral cortical lesion on the neighboring of the left precentral sulcus resulted in a bilateral improvement of the tremor [77]. The converging evidence from an EEG-EMG study showed that bilateral activation of the essential tremor also lead to interhemispheric coupling by indicating the essential role of the corpus callosum in ET [163]. Corpus callosum is an essential structure for the unimanual control. The possible explanation based on the findings is that when a subject prepares to execute a specific task movement, temporary inhibition in the ipsilateral M1 area arose [164]. Thus, facilitation of TMS-induced MEP responses in the contralateral M1 and inhibition in homologous M1 basically linked to existence of interhemispheric inhibition in healthy individuals during a unimanual movement [165]. Our data showed reduced microstructural integrity in the forceps minor that connects lateral and medial surfaces of frontal lobes. Also, morphometrical comparison showed higher GM volume on the left middle frontal sulcus whereas lower WM volume in the post central area in LOET patients compared to healthy controls.

The cortical activation might be the result of altered structural connectivity in cerebellar-thalamo-cortical circuit [166, 167]. The activation in this circuit may lead to the generation of thalamic oscillation at the tremor frequency [168, 169].

3.4.2 Increment of superior temporal gyrus could be a compensatory mechanism for ET?

Bilateral increase in gray matter volume in the superior temporal gyrus in ET cases was reported in the previous studies. Also, the recent functional imaging studies showed that superior temporal gyrus is activated during the temporal and

ordinal control of the learned movement sequences, which indicates temporal control of polyrhythmic movements and movement sequences, goal-directed preparatory activity and sensory coordination [170, 171, 172]. In addition, since visuo-motor areas in tremor patients are activated to compensate ataxia and tremor, gray matter volumetric increment in superior temporal cortex may reflect the long-term consequence of neuronal activity in this region [173]. However, the volumetric increments in bilateral superior temporal sulci were identified in EOET patients when compared to LOET patients. Our patients did not exhibit statistically significant volumetric difference when compared to healthy controls. Hence the increment could be due to the normal age-dependent atrophy.

3.4.3 Malformations in microstructural architecture effects local connections in ET

Our findings suggest that both intra-hemispheric connections, such as fronto-occipital, inferior longitudinal (ILF), superior longitudinal (SLF) fascicles, and intra hemispheric connections, such as forceps minor and splenium fiber bundles, were affected by ET in both age-of-onset patient groups. Microstructural integrity reduction was found in frontal and occipital parts of the WM fibers in these major WM pathways and subcortical structures including basal ganglia and thalamus. In addition to these, microstructural integrity disruption was also found along CST in both patient groups. Defects in this pathway are directly related to motor control weakness [174] which may lead to the tremor phenotype. Furthermore, inferior fronto-occipital fasciculus (IFOF) connects the frontal, temporal and occipital lobes which is important for integration of auditory, visual coordination on motor functioning [175]. Reduced microstructural integrity in frontal and occipital lobes in our patients indicates abnormality of visuo-auditory integration in fine motor coordination. Also, lesion studies in ILF and SLF revealed visual, emotional and cognitive impairments in patients [176, 177]. Additional studies about SLF also provided evidence that SLF is an important pathway for controlling movement integrity, gait functions and early gait disturbances [178, 179]. Disrupted microstructural integrity of bilateral ILF and SLF fiber bundles may

contribute to the loss of motor control in ET patients. Also, the underlying reason of reduced microstructural integrity in ILF pathway might be related to our patients' medication. Some tremor effective drugs such as dideral might affect cognitive skills of the patients as a side effect. Since one patient from each group was under medication, probable side effects of drugs should be considered.

3.4.4 How the genetic component of the ET is effective on structural architecture?

Previous findings revealed that HTRA2 p.G399S is the potential gene for essential tremor and homozygous allele is associated with earlier age onset of ET [147]. The family that was investigated by whole exome sequencing technique consists all our LOET patient group in the present study. On the other hand, our LOET patients had wild-type allele for the gene. As it was indicated in our previous work [147], age of onset of ET shows variations due to genetic or environmental effects [180]. Similarly, genetic is one of the contributing factors to difference between age of onset groups in the present study in terms of the structural architecture of the brain.

HTRA2 gene encodes a serine protease that localize in to intermembrane of the mitochondria [38]. When apoptotic stimulus present it is released to cytosol to bind apoptotic cycle inhibitor proteins and initiate the apoptosis [38]. Also, in-vivo studies showed that HtrA2 knockout mice lose neurons in striatum and showed parkinson-associated features [181]. More specifically, HTRA2 p.G399S is associated with the mitochondrial dysfunction, altered mitochondrial morphology, decrease protease activity and increased sensitivity to toxicity [182]. Parallel with these, morphometrical analyses revealed that LOET patients showed volumetric loss in bilateral putamen areas compared to both age-matched controls and EOET patients.

Putamen is a part of basal ganglia which is a part of nigrostriatal dopamine-containing pathway. Neuronal loss in this pathway is one of the key feature of

Parkinsonian tremor that lead to increase of the activity of GABAergic neurons on thalamus activity resulting in inhibition of thalamo-cortical network [183, 184]. As an underlying mechanism, expression of HTRA2 p.G399S gene might be effective on volumetric decrease as well as disrupted microstructural integrity in putamen which is important for motor control and tremor phenotype.

3.5 Conclusion

The effect of age-of-onset of essential tremor on structural brain connectivity was investigated in detail. Our work was critical to identify different patterns of structural disruptions based on the age of onset of essential tremor with potential benefits to both diagnosis and research. Our findings suggest that early-onset of age closely associated with sparse microstructural disruption including corticospinal tract, interhemispheric and subcortical connections whereas late-onset of the essential tremor is more associated with intrahemispheric connections such as superior longitudinal fasciculus, inferior longitudinal fasciculus and fronto-occipital fasciculus.

Chapter 4

Congenital Mirror Movement

4.1 Background

”We have a brain for one reason and one reason only – that’s to produce adaptable and complex movements. Movement is the only way we have affecting the world around us...” Neuroscientist Daniel Wolpert

The quote underlies the basic fact that the interactions of a human being with the surrounding world are through the intact functionality of the motor system. Mirror movements are involuntary, non-suppressible, mirroring movements of extremities on one side of the body along with the intentional movements of the homologous ones on the other side. In the developmental stage mirror movements may appear as a transient phenomenon. With the completion of myelination of the corpus callosum and neurologic development in motor pathways, motor activity in the ipsilateral side disappears [185, 186, 187]. Persisting mirror movements in adulthood is considered as abnormal [188]. The etiology of abnormal mirror movement is diverse, including central nervous system disorders such as Klippel-Feil Syndrome [189, 190, 191], X-linked Kallman’s Syndrome [192, 193, 194], ischemic stroke [195], hemiplegic cerebral palsy [196]. Unlike central nervous system disorders, congenital mirror movement disorder (CMMD) is characterized by

persistent mirror movements with no other neurological abnormalities [197].

Likewise its etiology, genetic origin of CMMD is diverse, it may be familial or sporadic. Familial CMMD usually has an autosomal dominant inheritance pattern [197, 198, 199, 200]. Results of studies on affected human individuals suggest that heterozygous mutations in the deleted in colorectal carcinoma (DCC) gene might be responsible for congenital form of mirror movement [201]. The DCC gene is a receptor protein for netrin, which is involved in axonal migration of neurons across the body's midline during the developmental stage [198, 201]. Abnormalities in axon guidance and the corticospinal tract are observed in the absence of ephrin or DCC genes in knock-out animal studies [202, 203]. In addition to ephrin and DCC genes, critical role of the RAD51 gene is shown during the neurodevelopmental stages. Focal expression of RAD51 gene at the pyramidal decussation during these critical stages reveals its critical role in a healthy motor system establishment. A recent study provided more detailed effects of RAD51 mutation motor control by showing abnormal corticospinal tract, reduced interhemispheric inhibition and abnormal involvement of secondary motor areas in CMMD [204]. In addition to corticospinal tract and cortical communications, functional and structural effects of RAD51 gene on other elements of CNS involved in motor control remain unknown.

Regions of cortical hyper activation or disinhibition in CMMD cases may reflect a combination of local myelin loss and/or deafferentation from subcortical sites as a result of extensive critical involvement of subcortical nuclei. Hence, affected areas include not only cortical areas such as primary motor cortex or secondary motor areas but also subcortical nuclei. Two groups of subcortical nuclei –basal ganglia and cerebellum have been considered as effective control mechanism in the motor system. Information from variety of cortical areas is thought to be integrated in those subcortical nuclei and funneled information is transmitted to primary motor cortex [205]. Rather, motor information flows reciprocally between these subcortical nuclei and many cortical areas including frontal, prefrontal, inferotemporal and posterior parietal cortex [206]. Thalamus is a key player for the information flow by receiving projections from the subcortical nuclei and projecting back upon the cerebral cortex [207]. Despite their intersecting target

regions on the cortex, basal ganglia and cerebellum have unique local circuit connections including thalamus based on unique properties of projection neurons.

Basal ganglia consist of a set of nuclei located in cerebrum and unlike the cortex which has excitatory glutamatergic projection neurons basal ganglia has inhibitory GABAergic projection neurons [208]. When striatal projections are activated by the cortex, due to their neurochemical properties they tend to suppress by creating phasic decrease of discharge in pallidal output projections to thalamus. Phasic decrease of neurons in pallidum enables thalamocortical neurons to excite and vice versa connections contribute to further inhibition and suppression of antagonistic movements.

In addition to basal ganglia, by integrating sensory and motor information, cerebellum has an important functional role in coordinating fine movements [209]. The cerebrocerebellar connections includes feedback and feedforward information transformation via an afferent- superior cerebellar peduncle- and efferent middle cerebellar peduncle which are critical for fine-tuning motor control [210]. Dentate-rubro-thalamo-cortical (DRTC) pathway is a major pathway that passes through the superior cerebellar peduncle provides information flow among cerebellum, red nucleus, thalamus and cortical motor areas such as primary motor cortex and premotor cortex [211]. Moreover middle cerebellar peduncle is the largest efferent fiber bundle that originating from the different parts of the cerebral cortex and ends in the cerebellum [211]. Investigation of these two major -both afferent and efferent- pathways is critical to understand involvement of cerebellum in the motor system.

Studying the contributions of both cortical areas and subcortical nuclei in motor control, case studies with identified genetic bases provide a valuable connection between fine motor control and its genotype. CMMD is a unique phenomena to investigate effects of RAD51 gene expression deficiency on motor control by considering both cortical and subcortical components. A variety of possible mechanisms of CMMD have been investigated. According to one of possible mechanisms, CMMD was found to be related with abnormally uncrossed corticospinal fibers originating in M1s [212, 213]. The hypothesis is supported with

the results of delayed reaction time and EMG activity bilaterally during the unilateral motor area activation [214, 193]. In addition, some studies showed that another mechanism effecting bilateral cortical activation could occur due to the lack of interhemispheric inhibition [215]. Assuming that bilateral M1 areas have separate contralateral and ipsilateral projections to cortices, over excitatory communication or lack of inhibitory communications between bilateral M1 areas might explain the phenomena [216, 217, 204]. Another possible mechanism is that other secondary motor areas -such as supplementary motor area (SMA)- could regulate the activity of the M1 area for lateralized brain activation; thus, bilateral activation of secondary motor areas could contribute to the bilateral M1 activity [212]. These possible mechanisms were studied with unknown genetic background, DCC mutation and one study with RAD51 mutation on humans. Due to the CMMD's heterogeneous nature and the limited number of affected individuals, more multidimensional studies with specific genetic mutations contribute new information to general knowledge of motor system organization. We suggest that our study will provide a valuable contribution to the literature by providing not only cortical interplay between motor areas but also detailed information for cortico-subcortical nuclei circuit on CMMD patients with RAD51 mutation.

In a recent study Gallea et al. (2013) [204] investigated CMMD patients with RAD51 haploinsufficiency by using single-pulse TMS, DTI, and fMRI techniques. Gallea et al. (2013)[204] found abnormal decussation of CST, bilateral M1 activity during intended unimanual movements, and abnormal interhemispheric inhibition. Effective connectivity analyses of fMRI data revealed abnormal interaction between supplementary motor area (SMA) and M1 during unimanual and bimanual movements [204]. However, as discussed earlier, coordinated movements require not only the delicate interplay of cortical areas. Subcortical areas such as the basal ganglia are also critical to initiate, gate and terminate motor movements, but their roles in mirror movements arising from RAD51 gene mutations remain unknown. To address this question, using MRI, we investigated white matter anatomy, microstructural integrity and functional connectivity of CSTs, cortico-thalamic, cortico-cerebellar and cortico-basal ganglia loops, as well

as task-related brain activity in two CMMD patients and matched healthy participants.

4.2 Materials and Methods

4.2.1 Participants

Two right handed brothers (ages = 29 & 30) exhibiting familial CMMD on the distal upper limbs with no other neurological abnormalities were studied in task-based fMRI scans. Ten age and sex matched right handed healthy subjects (mean age: = 30.9, standard deviation = 5.04) were included as a control group in task-based fMRI scans. At a later date, one of the patients (age = 34, M) and eight age (mean age = 31.25, standard deviation = 5.5) and sex-matched healthy controls participated in DTI and resting state fMRI components of the study. Informed written consent was obtained from all participants in accordance with the declaration of Helsinki and; procedures and protocols were approved by the Bilkent Human Subjects Ethics Committee (Approval Number:2010_08_32_2)

4.2.2 Data Acquisition

Data were acquired in a 3T MR scanner (Magnetom Trio, Siemens AG, Germany) in the National Magnetic Resonance Research Center (UMRAM) at Bilkent University, Ankara, Turkey. A twelve-channel phase-array head coil was used for task-based fMRI scans and a 32-channel phase array head coil was used for DTI and resting state scans. High resolution T1-weighted three dimensional MPRAGE images were acquired in each session (single shot turbo flash; voxel size = $1 \times 1 \times 1$ mm³; repetition time, TR = 2600 ms; echo time, TE = 3.02 ms; flip angle = 8 degrees; field of view, FOV = 256×224 mm²; slice orientation = sagittal; phase encode direction = anterior-posterior; number of slices = 176; acceleration factor (GRAPPA) = 2). Next, for the task-based functional scans an echo-planar

imaging (EPI) sequence was used (voxel size = $3 \times 3 \times 3$ mm³; TR= 2000 ms; TE = 40 ms; flip angle = 71 degrees; FOV = 192×192 mm²; slice orientation = transverse; phase encode direction = anterior-posterior; number of slices = 26; matrix = 64×64).

For DTI scans, a multi-band (MB) diffusion-tensor EPI [218] sequence (voxel size = $2 \times 2 \times 2$ mm³; TR= 8283 ms; TE = 85.8 ms; MB = 2; FOV = 230×197 mm²; phase encode direction = anterior-posterior; number of slices = 120; b=0, 1000 s/mm², diffusion directions = 64) with whole brain coverage was used. Lastly, for the resting state functional scan echo-planar imaging (EPI) sequence (voxel size = $2 \times 2 \times 2$ mm³; TR= 1577 ms; TE = 27.4 ms; MB=6; flip angle = 42 degrees; FOV = 230×205 mm²; slice orientation = transverse; phase encode direction = anterior-posterior; number of slices = 120) was used.

In the task-based fMRI, subjects participated in two scanning sessions; each started with the structural scan, followed by the task-based functional runs. There were two task-based functional runs to choose the optimal run (i.e. less head motion, less noise, etc.) for the further analysis. DTI and resting state scans were conducted after task-based functional scans in a single session at a later date. This later session started with a T1-weighted structural scan and a MB-EPI DTI and a MB-EPI resting-state fMRI scans. Only one of the patients and eight healthy controls from the previous sessions participated in this session.

4.2.3 Task-based fMRI Experimental Procedures & Analyses

In a blocked-design protocol participants performed index finger tapping movement following visually presented cues during 12-second active block. Active blocks were repeated for five times interspersed with 12-second rest blocks. Visual stimuli were composed of a green arrow which pointed to the side of movement (left, right and both) for the active conditions as well as a closed-end green line for the rest condition. Order of the stimulus was fixed within a run. Stimulus

presentation program was written by us in Java programming platform.

Task-based fMRI data were preprocessed using Statistical Parametric Mapping software (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) implemented in MATLAB (Mathworks, Inc., SherbornMA, USA). Preprocessing steps included image realignment, slice acquisition-time correction, and functional and anatomical image coregistration. Functional images were normalized to Montreal Neurological Institute's (MNI) template by fitting mean functional images to the single reference EPI standard SPM template, and smoothed with a 6 mm Gaussian kernel to reduce spatial noise. First level statistical parameters were computed for each participant using the GLM procedure implemented in FSL fMRI Expert Analysis Tool FEAT, version 5.6.3. Contrasts of right finger movement versus rest, left finger movement versus rest and bimanual finger movement versus rest were defined to obtain Z-score maps over the whole brain. To compare control and patient groups, spherical regions of interest (ROIs) were created by using FSL in the bilateral M1s (hand area), SMA, thalamus, globus pallidus, putamen and caudate with 6-mm Gaussian kernel radius on each participants' functional data (Table 4.1). Putamen and caudate ROIs were combined and analyzed as striatum since they are histologically identical and both are composed of similar projection fibers [219]. Since our field of view did not fully cover cerebellum, it was not included as a part of ROIs for task-based fMRI comparisons.

Then these ROIs were binarized and applied onto the Z-score maps of individuals for each contrast. The mean Z-score were analyzed by conducting a mixed design 3-way ANOVA (Group x Task side x Hemisphere) to compare activations in unimanual movements. Bilateral movements were analyzed through a mixed design 2-way ANOVA (Group x Hemisphere). ANOVA comparisons were performed by using SPSS v.20 (SPSS Inc., Chicago, IL). Statistical parametric maps were projected onto 3D morphed brain surface to visualize the cortex activation, and onto 2D T1-weighted images to visualize activation in subcortical structures by using BrainVoyager QX 2.8.

Table 4.1: MNI coordinates of the center of the spherical ROIs that were used in task-based fMRI comparisons

Region	MNI Coordinates (x y z)
Left Primary Motor Cortex	-42 -16 52
Right Primary Motor Cortex	39 -22 52
Left Supplementary Motor Area	-9 -16 67
Right Supplementary Motor Area	12 -16 67
Left Thalamus	-12 -19 4
Right Thalamus	12 -19 4
Left Putamen	-21 8 -5
Right Putamen	24 8 -5
Left Caudate	-15 14 10
Right Caudate	15 14 10
Left Globus Pallidus	-15 -4 -5
Right Globus Pallidus	18 -4 -5

4.2.4 Resting State Analysis Procedures

The same preprocessing steps that were applied to task-based fMRI data were applied to resting state fMRI data. Spherical ROIs were created in FSL bilaterally on primary motor cortex (hand area), SMA, thalamus, globus pallidus, caudate, subthalamic nucleus, red nucleus and cerebellum (dentate) with 6-mm Gaussian kernel radius. fMRI time series were extracted and coherence scores were calculated between pairs of ROIs for each individual using the Welch's periodogram method (with a 64-time point discrete Fourier transform, Hanning window - to reduce leakage - and a 32-point overlap). Coherence, $Coh_{xy}(\lambda)$, between two time series, x and y at frequency λ was measured by using formula:

$$Coh_{xy}(\lambda) = \frac{|R_{xy}(\lambda)|^2}{f_{xx}(\lambda)f_{yy}(\lambda)}$$

where $R_{xy}(\lambda)$ is the complex valued coherency of x and y, $f_{xy}(\lambda)$ is the cross-spectrum of x and y, and $f_{xx}(\lambda)$ is the power spectrum of x [80]. Mean frequency scores between 0 and 0.15 range were computed for each coherence calculation [81]. The calculations were performed in Python programming platform using the

SciPy library. Coherence values thus obtained were compared between groups via both a one-sample t-test and a non-parametric bootstrapping technique.

4.2.5 DTI Analysis Procedures

Diffusion tensor images were analyzed using FSL 5.0 (FMRIB Image Analysis Group, Oxford, UK) (Supplementary Information). BEDPOSTX was used to model 5000 iterations within each voxel with a curvature threshold of 0.2. Crossed CST fibers were tracked by using the ROIs in pontine, anterior pyramid of upper medulla and lateral funiculus of the cervical cord (Supplementary Figure D.1). Uncrossed CST fibers were identified as those that pass through lateral funiculus of the upper spinal cord and discarding the fibers that pass through the anterior medial funiculus (Supplementary Figure D.2). FA, MD, RD, AD and a laterality index (LI) were computed for the CSTs. LI was defined as the difference of mean volumes of crossed and uncrossed fibers, divided by their sum. Calculations in both crossed and uncrossed CST tracts are restricted on a section between low pontine and upper medulla. Next, two main peduncles, superior and middle cerebellar peduncles (SCP and MCP respectively), were constructed to examine cortico-cerebellar connections. Tracts were determined as in Keser et al. (2015) [209]. Dentate-rubro-thalamo-cortical (DRTC) tract within the SCP was determined using ROIs in dentate nucleus and ipsilateral red nucleus (supplementary Figure E.1). Fronto-ponto-cerebellar (FPC), temporo-ponto-cerebellar (TPC), parieto-ponto-cerebellar (PPC), and occipito-ponto-cerebellar (OPC) tracts within the MCP were determined using ROIs in contralateral frontal, ipsilateral temporal, parietal and occipital lobes respectively (Supplementary Figures E.2 & E.3). All diffusion indices were compared between the patient and the control group using both a non-parametric procedure and conventional null-hypothesis testing methods, described next.

4.2.6 Nonparametric Analysis Procedures

Since single patient's data were compared to a group of healthy controls, the assumption of normality of the sample (from the patient) was violated and classical statistical techniques could not be applied. For statistical group comparisons of DTI and resting state fMRI data a nonparametric bootstrapping procedure was employed. The data of controls were sub-sampled by drawing randomly with substitution from their data set 10000 times. The mean of each sample was estimated and the 95% confidence interval on the resulting distribution was computed. Then the patients' mean diffusion indices, and coherence scores (resting state fMRI) were checked to determine if they were outside the 95% confidence interval. Further, a one-sample t-test, a more conventional null-hypothesis testing method, was applied to compare patients' scores with those of the controls. Multiple comparisons were controlled via false discovery rate (FDR) method using Benjamini–Hochberg approach [83]. These procedures were performed on Matlab 2015a.

4.3 Results

4.3.1 Task-related fMRI Activity

In the task-based fMRI component of our study, we measured the activity in thalamus (THA), striatum (STR), globus pallidus (GP), SMA and the hand area of M1 during a finger tapping task (left, right, bimanual) (Figure 4.1). Cerebellum was not included as an ROI due to our field-of-view (FOV) properties. Figure 4.2 shows the statistical parametric maps on inflated cortices as well as average fMRI responses in some of the pre-defined ROIs. FMRI responses, more specifically the Z-scores, in the ROIs were compared by using two mixed-design ANOVAs. A 3-way ANOVA (Group x Task side x Hemisphere) was used for comparing responses during unimanual movements whereas a 2-way ANOVA (Group x Hemisphere) was used for comparing responses during bimanual movements.

For the bimanual movement we found no main effect of group or hemisphere in any of the areas tested. For the unimanual movements, activations of M1, THA and STR showed group main effect (M1: $F(1, 10)=10.761$, $p=0.008$, THA: $F(1, 10)=8.686$, $p=0.015$, STR: $F(1,10)=7.069$, $p=0.024$). Activity in M1, THA and STR was statistically different between patient group and the healthy controls during the unimanual movement execution. However, the activity in GP showed a marginal trend toward significance between patient group and healthy controls. In GP, group main effect during unimanual movements was observed with marginal statistical significance (GP: $F(1,10)=4.893$, $p=0.051$). There was an interaction between hemisphere and task side in M1, THA and SMA (M1: $F(1, 10)=20.235$, $p=0.001$, THA: $F(1, 10)=10.028$, $p=0.010$, SMA: $F(1, 10)=5.666$, $p=0.039$). The interaction showed that ipsilateral motor activity was greater in the patients compared to controls in M1, THA and SMA areas, whereas there was less or no intergroup difference in the contralateral side during both right and left unimanual finger movements. In SMA we also found a main effect of hemisphere ($F(1, 10)=6.884$, $p=0.025$) and interaction between hemisphere and group ($F(1, 10)=9.225$, $p=0.013$). The activity in SMA was statistically different between left and right hemispheres during the unimanual right and left finger movements in both patient and control groups. Also, motor activity was statistically different in the left SMA between patients and control groups -i.e. mean z score of the left SMA was always larger in controls-, whereas the difference was smaller during the right finger movement or non-significant during the left finger movement in the right SMA.

Further group comparisons between statistically significant differences during right finger movement between groups in M1 and THA bilaterally (Left M1: $t(10)=-2.686$, $p=0.023$, Right M1: $t(10)=-4.014$, $p=0.002$; Left THA: $t(10)=-2.935$, $p=0.015$, Right THA: $t(10)=-2.495$, $p=0.032$). Critically, in M1 there was a significant difference between left and right finger movements in controls (Right M1: $t(9)=-7.779$, $p<0.001$, Left M1: $t(9)=9.976$, $p=0.003$) but not in patients (Right M1: $t(1)=-2.021$, $p=0.293$, Left M1: $t(1)=2.992$, $p=0.205$). These results were summarized in Table 4.2. Responses obtained from THA during unimanual movements were significantly higher in patients. In GP (subdivision of basal

ganglia) a similar trend was observed with marginal statistical significance (GP: $F(1,10)=4.893$, $p=0.051$).

In summary, we found abnormal lateralization in M1 and SMA during uni-manual movements, which is consistent with previous findings in literature [204]. We also found previously unknown abnormal activation in thalamus and basal ganglia, which have critical roles in motor computations and control, thus abnormal activations in these structures might be leading/contributing to mirror movements [220]. Given these possibilities we next investigated structural and functional connectivities between cortex and subcortical nuclei.

4.3.2 Structural Connections

Using DTI and probabilistic tractography, we investigated possible abnormalities in white matter connections by computing diffusion indices. Fractional anisotropy (FA) is a measure of directionality of the diffusion, whereas mean diffusivity (MD) is a measure of overall diffusivity [69]. Furthermore, axial and radial diffusivity (AD, RD) index the diffusivity in the longitudinal direction (approximately parallel to the main axon bundle) and transversal direction (perpendicular to the main axon bundle) respectively [70]. Those four indices are often used as indicators for white matter integrity. For statistical comparisons we used a non-parametric bootstrap method as well as conventional null-hypothesis significance tests. To correct for multiple comparisons we used the FDR procedure.

Corticospinal tracts Crossed and uncrossed CSTs were identified and examined for each participant. We first computed the ratio of contralateral and ipsilateral CST volumes. This computation revealed that controls (laterality index, $LI=0.065$) have more crossed fibers than the CMMD patient ($LI=-0.371$). Next FA, MD, RD and AD scores were extracted from these tracts. Table 1 shows the scores for controls and the patient. We found that the FA scores were lower, MD scores were higher along both the crossed and uncrossed corticospinal fibers in the patient. Both AD and RD scores closely covaried with increased MD scores. Reduced FA and elevated MD, RD and AD scores indicate possible

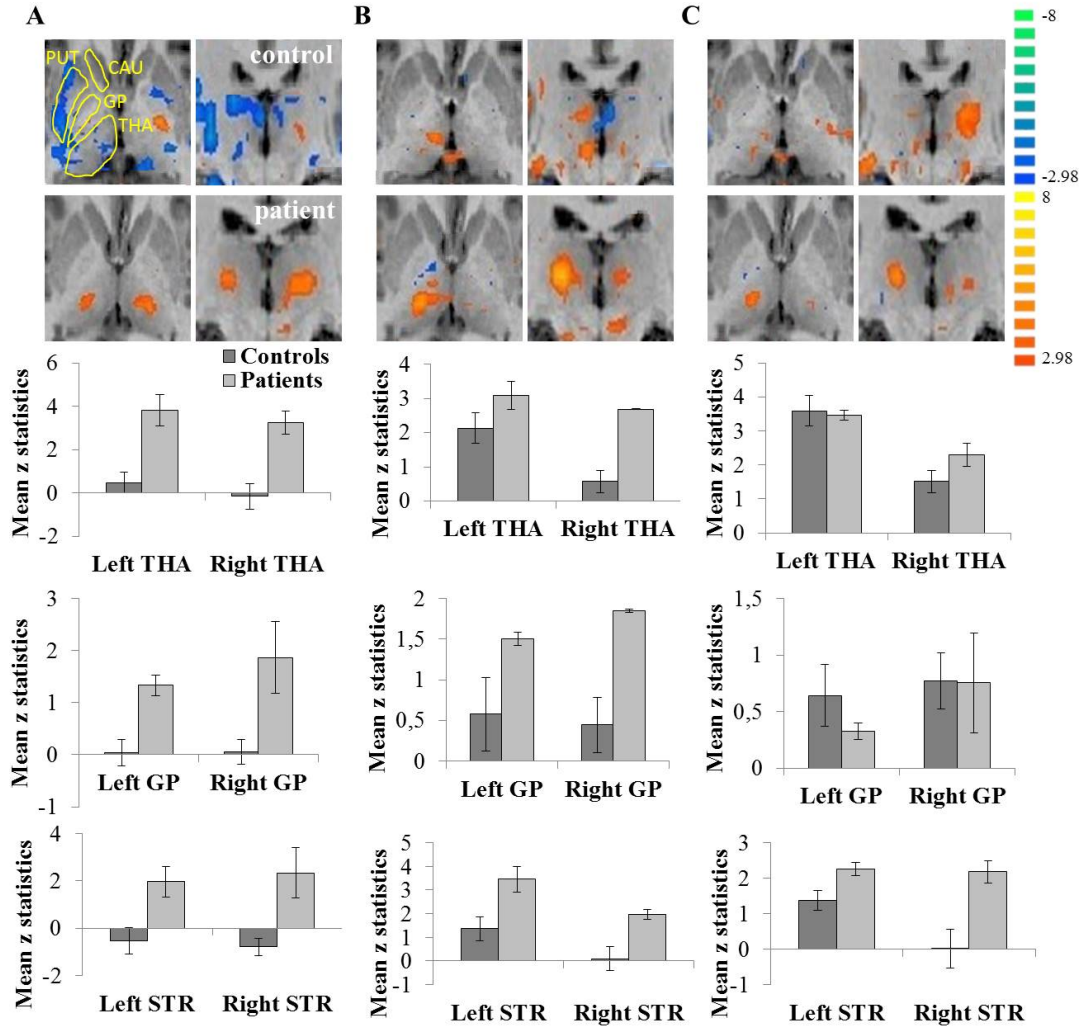


Figure 4.1: Top row: Statistical parametric maps for a representative control and a patient during finger tapping. Bar plots: fMRI responses in pre-defined regions of interest (ROIs). (A) right hand, (B) left hand, (C) bimanual finger movements. Abnormal lateralization in M1 in patients is clearly seen in the statistical parametric maps. Abnormal activity pattern was also observed in SMA in patients: in controls left SMA activity was always larger than right SMA activity, but not in patients. M1: primary motor cortex hand area, SMA: supplementary Motor Area. Error bars show ± 1 standard deviation. Color bar for the statistical parametric map indicates the t-score ranging from -8 (blue) to 2.98 (yellow). Maps are thresholded at an α level of 0.05.

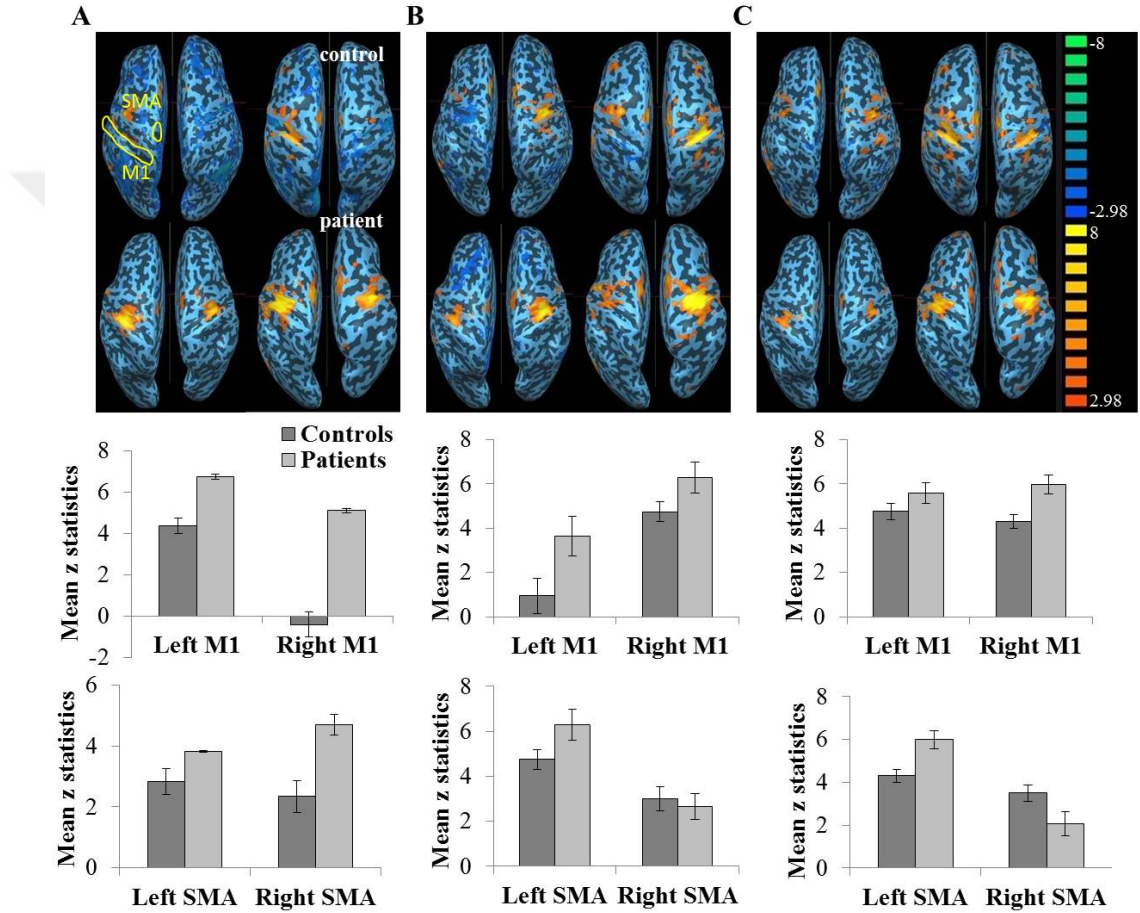


Figure 4.2: Top row: Statistical parametric maps for a representative control and a patient during finger tapping. Bar plots: fMRI responses in pre-defined regions of interest (ROIs). (A) right hand, (B) left hand, (C) bimanual finger movements. Abnormal activity was observed in THA, GP and STR (PUT+CAU) in patients. THA: Thalamus, GP: Globus Pallidus, STR: Striatum, PUT: Putamen, CAU: Caudate. Error bars show ± 1 standard deviation. Color bar for the statistical parametric map indicates the t-score ranging from -8 (blue) to 2.98 (yellow). Maps are thresholded at an α level of 0.05.

Table 4.2: Demographic characteristics and summary of the unimanual task-based fMRI comparisons. N: number of participants, m: male, f: female, y: years, ns: not significant, M1: primary motor cortex, SMA: supplementary motor area, THA: thalamus, GP: globus pallidus, STR: striatum, L: Left, R: Right, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

		ANOVA $F(1,10)$					
		CMMD		Controls		factor 1: factor 2: factor 3:	
		Group	Task	Hemisphere	Interaction		
N	2	-	-	-	-	-	
Sex (m/f)	2/0	-	-	-	-	-	
Age (y)	29.5	30.9	5.04	-	-	0.377(10)	
M1	-	10.761**	0.018	0.019	factor 2 $\times$ factor 3	L M1:-2.686*	R M1:-4.014**
SMA	-	0.822	0.077	6.884*	factor 2 $\times$ factor 3	ns	
					20.235***		
					5.666*		
THA	-	8.686*	0.049	0.064	factor 1 $\times$ factor 3		
					9.225*		
GP	-	4.893	0.487	0.586	factor 2 $\times$ factor 3	L THA:-2.935*	R THA:-2.495*
					10.028*		
STR	-	7.069*	0.769	0.868	ns	ns	
					ns	R STR:-3.337**	

R: Right, L: Left.

Table 4.3: Diffusion indices for healthy controls and the CMMD patient in crossed and uncrossed corticospinal tracts (CSTs). 95% confidence intervals for the control group is computed by a non-parametric bootstrap procedure (see Methods). Conventional null-hypothesis significance (p value) is computed using one-sample t-test (*p<0.05, **p<0.01, all FDR-corrected. +: patient value outside of 95% CI).

		Control Group		
		95% CI	Patient	p values
Crossed CST	FA	0.3664, 0.4216	0.3318+	0.0093*
	MD	0.0011, 0.0014	0.0016+	0.0036**
	RD	0.0009, 0.0012	0.0015+	0.0039**
	AD	0.0015, 0.0017	0.0019+	0.0075*
Uncrossed CST	FA	0.3583, 0.4102	0.3384+	0.0277
	MD	0.0011, 0.0013	0.0014+	0.0062**
	RD	0.0009, 0.0011	0.0012+	0.0068*
	AD	0.0015, 0.0016	0.0017+	0.0295

FA:fractional anisotropy, MD:mean diffusivity, RD:radial diffusivity, AD:axial diffusivity

axonal and myelin disruption accompanied with reduced microstructural integrity in the patient (Table 4.3.2). Note that in a recent study Gallea et al. (2013) found higher FA and lower RD in uncrossed fibers in CMMD patients and attributed this to architectural alterations [204]. We do not know the reason of the discrepancy between the two studies. It could indicate heterogeneity of the disorder or it could be due to differences in the methods.

Cortico-cerebellar connections Cortico-cerebellar information loop is composed of dentate-rubro-thalamo-cortical (DRTC) and cortico-ponto-cerebellar (CPC) including FPC, TPC, PPC, OPC pathways [209]. Table 4.4 shows diffusion indices for DRTC and subdivisions of CPC. Results show that the FA is reduced in all subdivisions of CPC passing through the right hemisphere in the

patient. MD was reduced in left TPC and bilateral PPC tracts, RD was increased in right TPC and right PPC tracts, and reduced in the left TPC tract in the patient. In brief summary, we found reduced FA and generally elevated RD and/or MD in the components of CPC in the right hemisphere of the CMMD patient suggesting demyelination and reduced white matter integrity in these pathways. Interestingly, we found higher FA and reduced RD values in the left DRTC in the patient. None of the other comparisons in DRTC met the statistical criteria (Table 4.4).

4.3.3 Functional Connectivity

We next investigated functional connectivity between cortex, cerebellum, thalamus and basal ganglia using the resting state fMRI data. We used coherence of fMRI responses between different structures as a measure of connectivity. Because coherence (unlike correlation) is not affected by differences between hemodynamic response functions and reflects the similarity of underlying neuronal activity more reliably [81]. We then compared the connectivity between structures in controls to that of the patient (Supplementary Table F.1, Figure 4.3).

Connections involving the cerebellum, thalamus and the red nucleus

Our analyses revealed reduced functional connectivity in most of the thalamo-cerebellar connections in the CMMD patient. We found significant group differences in contralateral and ipsilateral connectivities between dentate nucleus and thalamus, dentate and red nuclei, red nucleus and thalamus, thalamus and M1. Contralateral connectivities between right/left dentate nucleus and left/right thalamus, right/left thalamus and left/right red nucleus were significantly lower in the patient. The only increased contralateral connectivity was observed between left dentate and right red nuclei. The patient had significantly lower functional connectivity between the following structures: right M1 and right thalamus, right/left dentate nucleus and right/left thalamus, right red nucleus and right thalamus, left dentate and left red nuclei. The only ipsilateral connectivity where the patient had a higher score was between right dentate and right red

Table 4.4: White matter diffusion indices in cortico-cerebellar pathways. 95% confidence intervals for the control group are computed by using a non-parametric bootstrap procedure. Conventional null hypothesis testing is used to obtain the p values. DRTC:Dentato-rubro-thalamo-cortical, FPC:Fronto-ponto-cerebellar, TPC:Temporo-ponto-cerebellar, PPC:Parieto-ponto-cerebellar, OPC:Occipito-ponto-cerebellar, R:Right, L:Left. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, all FDR corrected. +:patient value outside of 95% CI.)

		Control Group	Patient	p values
		95% CI		
L DRTC	FA	0.3542, 0.3905	0.4044+	0.0273*
	MD	0.00085, 0.00092	0.00084+	0.0344*
	RD	0.00068, 0.00075	0.00066+	0.0448
	AD	0.0012, 0.0013	0.0012	0.0397
R DRTC	FA	0.3603, 0.3885	0.3623	0.198
	MD	0.00085, 0.00091	0.00091	0.121
	RD	0.00067, 0.00074	0.00075+	0.095
	AD	0.00120, 0.00124	0.00124	0.151
L FPC	FA	0.3997, 0.4168	0.4086	0.8395
	MD	0.00086, 0.00091	0.00089	0.5453
	RD	0.00067, 0.00072	0.00071	0.5057
	AD	0.00123, 0.00128	0.00126	0.5931
R FPC	FA	0.3859, 0.4136	0.3814+	0.0184*
	MD	0.00085, 0.00091	0.0009	0.3422
	RD	0.00066, 0.00073	0.00073	0.1922
	AD	0.0012, 0.0013	0.0012	0.689
L TPC	FA	0.3583, 0.3967	0.3916	0.3236
	MD	0.00088, 0.00092	0.00086+	0.01909*
	RD	0.00070, 0.00074	0.00069+	0.0299*
	AD	0.0012, 0.0013	0.0012	0.07193

Table 4.4 (*continued on next page*)

		Control Group	Patient	<i>p</i> values
		95% CI		
R TPC	FA	0.3654, 0.3773	0.3447+	<0.001***
	MD	0.00087, 0.00091	0.00091	0.15195
	RD	0.00069, 0.00073	0.00076+	0.01016*
	AD	0.0012, 0.0013	0.0012	0.05381
L PPC	FA	0.3595, 0.3844	0.3628	0.1277
	MD	0.00087, 0.00091	0.00093+	0.01997*
	RD	0.00069, 0.00074	0.00076+	0.01495*
	AD	0.001199, 0.001245	0.001248+	0.1056
R PPC	FA	0.3618, 0.3854	0.3537+	0.01406*
	MD	0.000873, 0.00092	0.00095+	0.0033**
	RD	0.00070, 0.00075	0.00079+	0.00281**
	AD	0.0012, 0.0013	0.0013	0.09035
L OPC	FA	0.38, 0.41	0.39	0.579
	MD	0.828, 0.854	0.855+	0.1583
	RD	0.647, 0.678	0.683+	0.0827
	AD	1.166, 1.219	1.199	0.8258
R OPC	FA	0.3757, 0.3967	0.3643+	0.00625**
	MD	0.00082, 0.00086	0.00083	0.2962
	RD	0.00064, 0.00069	0.00067	0.6308
	AD	0.001167, 0.001211	0.001142+	0.00369**

nuclei. Thus, in the patient the right red nucleus was abnormally more strongly connected to both left and right dentate nuclei.

Connections involving the basal ganglia The patient had significantly lower functional connectivity in most of the contralateral connections involving the basal ganglia. Patient's connectivity values between right/left M1 and left/right putamen, left globus pallidus and right caudate, right globus pallidus and left putamen were statistically significantly lower than those of the control

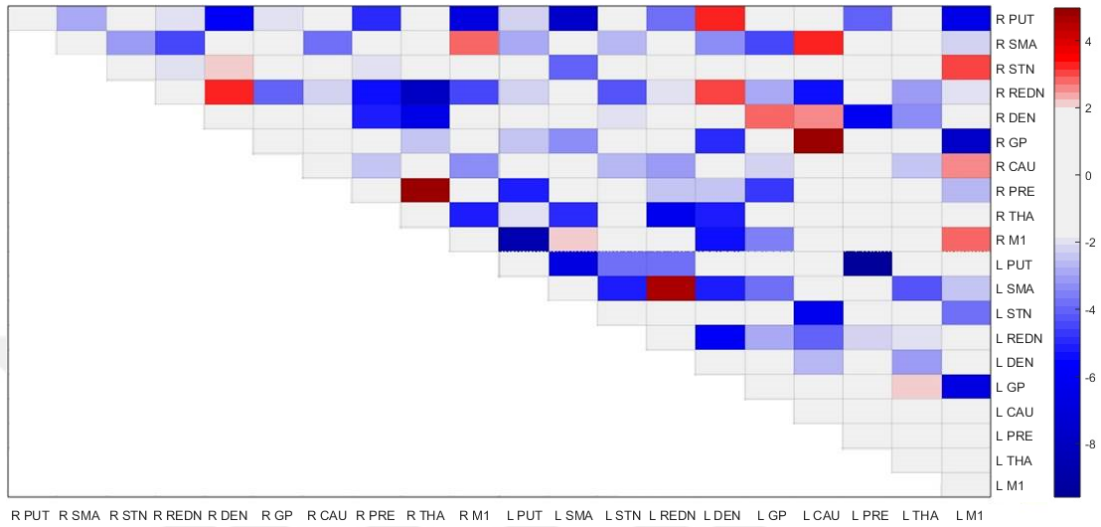


Figure 4.3: Difference in functional connectivity between the patient and the control group. Colors represent t-statistics. Blue: control group's values lower than the patient's, red: control group's values higher than patient's

group. Ipsilaterally, the patient had significantly lower values in the right hemisphere between M1 and caudate, M1 and putamen, globus pallidus and thalamus. On the other hand the patient had significantly higher functional connectivity between left M1 and right caudate, left caudate and right globus pallidus, left globus pallidus and left thalamus. There was no statistical difference between the groups for connections between globus pallidus and subthalamic nucleus.

Cortico-cortical connectivity There were significant group differences for contralateral and ipsilateral connectivities between M1 and SMA, M1 and premotor cortex but not between SMA and premotor cortex. The patient had significantly lower values between left M1 and right premotor cortex, left M1 and right SMA, left M1 and left SMA. Interestingly the patient had significantly higher functional connectivity between left M1 and right M1, right M1 and left SMA, right M1 and right SMA.

4.4 Discussion

In this study using magnetic resonance imaging, we investigated functional and anatomical connections of the CMM patients with RAD51 mutation and found abnormal ipsilateral CST fiber accompanied by abnormal anatomical and functional connections among the cerebellum, basal ganglia and cortex. Our study is critical to reveal the function of RAD51 gene in CMMD through affecting the control mechanism of the basal ganglia and cerebellum on the motor movement. Comparison of CMMD patients and controls highlights that execution of unilateral motor movements highly depends on the healthy interhemispheric communications not only at the cortical level but also at subcortical and cerebellar levels.

Direct and healthy connection between corticospinal system and the motor pool is critical for the everyday demanding digital dexterity [221]. In humans, a small number of CST axons, approximately 10% of the total, do not decussate at the medullary pyramid and descent ipsilaterally whereas approximately 90% of the corticospinal fibers cross to the contralateral side at the decussation pyramid and control the muscles on the contralateral limbs [222, 223]. A possible functional importance of this architecture could be the functional recovery after a possible uni-hemispheric neuronal loss [224]. This hypothesis was suggested in a case study, results of a patient with congenital hemiparesis and CMMD indicated an abnormal ipsilateral projection of corticospinal fibers branching to affected hand enables them to execute a lateralized movement [225]. CMMD could be revealed as a result of imbalance between crossed and uncrossed CST. Abnormal ipsilateral corticospinal protrusions in CMMD were previously reported in the literature [222, 197, 215, 226, 204]. The connection between abnormal ipsilateral CST and CMMD behavior was previously established in patients with Klippel-Feil Syndrome [227], and X-linked Kallman Syndrome [194, 193, 228]. The literature shows that although the genetic background is different, mirror movements might have a common defect pattern. In the light of these, two major aspects of the extend of reorganization of the motor system in CMMD cases, alterations were found in functional and WM integrity among cerebellum, subcortical structures

and cortical motor areas; and the microstructural reorganization in abnormal corticospinal projections.

In addition to the abnormal ipsilateral corticospinal projections lack of inter-hemispheric inhibition were discussed as another mechanism that leads to the CMMD since unilateral movement also needs a suppressing activity of the ipsilateral cortical motor area. The possible explanation based on the findings that when a subject prepares to execute a specific task movement, temporary inhibition in the ipsilateral M1 area arose [164]. Thus, facilitation of TMS-induced MEP responses in the contralateral M1 and inhibition in homologous M1 basically linked to existence of interhemispheric inhibition in healthy individuals during a unimanual movement [165]. The phenomenon has been tested on CMMD cases with a variety of genetic background. More importantly Gallea and his colleagues(2013) showed the relation between RAD51 haploinsufficiency and decreased interhemispheric inhibition between primary motor hand areas in CMMD patients. Although our functional data from the resting state did not manifest difference between healthy controls and the patient, task-based fMRI analysis revealed group difference between the groups. Bilateral cortex activation could possibly show that not only interhemispheric inhibition but also lack of basal ganglia and cerebellum control mechanism on the motor cortex might feed the CMMD.

An increasing evidence suggests that the asymmetry in interhemispheric inhibition could be effective on hand preference by inhibiting undesired movement more deeply in dominant hemisphere [229, 165]. Moreover, symmetrical inter-hemispheric inhibitory activity during the preparation of the movement changes in an asymmetrical trend when dominant hand is active [229]. The balance between inhibitory mechanisms seems to be critical for the unilateral movement. The difference in resting state and the task-based fMRI results on M1 area might reflect the involvement of interhemispheric inhibition mechanisms during the execution of the movement. Also more intact integrity in the dominant hemisphere-left- than healthy controls could be the results of reorganization based on the interhemispheric inhibition mechanism.

Furthermore, the supplementary motor area is critical element in the motor system by regulating the activity of M1 area. A lesion study evidence from a man who had an infarction in his right SMA resulted in mirror movements in writing and specific bimanual tasks [230]. Moreover, similarly lack of bimanual coordination was observed in unilateral SMA ablated animal studies [231]. Hence SMA activity has been associated with the nonmirroring transformation of the motor movement in unilateral primary motor activation [165]. Due to the involvement of SMA activity in unimanual motor coordination, understanding the regulatory activity of SMA on primary motor area in CMMD is critical. Interestingly enough, increased connectivity between SMA and left hemisphere was found bilaterally in the patient with CMMD (Figure 4.1). However, the connectivity in the left hemisphere did not reach the FDR corrected significance level. Abnormal connectivity of right SMA with right primary motor area and thalamus may lead increased connectivity between M1 and caudate. Lack of regulatory effect of either basal ganglia or SMA might be a contributing mechanism to CMMD.

Basal ganglia could be a key player in sequential movements in timing and selecting the specific muscles for the execution of the movement [232]. It also is shown that SMA receives strong indirect projections from the basal ganglia via the thalamus [233]. Abnormal connectivity of bilateral SMA along with the increased globus pallidus/putamen and thalamic activity during the task execution in the patients may lead to CMMD through blocking nonmirroring transformation of unilateral movement in SMA. Increased SMA and thalamus activity were even significant during the resting state. In this sense, we provide the first evidence that disrupted involvement of the basal ganglia might lead to CMMD.

Another gating and timing mechanism in the motor loop is cerebellum. Cerebellum is connected to other brain regions via three main peduncles, receiving input through afferent CPC and SC tracts and sending output via efferent DRTC pathway [209]. Since it is highly associated with the integration of sensory and motor functions for fine movements feed-back and feed-forward connections of the cerebellum is worth investigating. Reduced diffusivity in CPC tract especially in the right hemisphere indicated the disrupted microstructural integrity in non-dominant hemisphere in the patient. Nevertheless increased WM integrity

accompanied by reduced functional connectivity in the left DRTC pathway which is the afferent connection showed that anatomical reorganization might not necessarily reflect the functional communications.

White matter maturation is highly correlated with the increased FA and decreased MD scores during the first 2 or 3 years of life [70]. The period during which these dramatic changes occur is critical for the maturation of the neural pathways and thereupon the development of the functional connectivity among brain areas. Reduction in radial diffusivity is closely related with the myelination of corpus callosum fibers myelination process. The studies showed that disruption of the myelin sheet is seen as an increase in radial diffusivity without affecting axial diffusivity [74]. Additionally destruction of the neurofibrils such as neurofilaments, glial cells and microtubules or axonal injury is found to be related with increment in axial diffusivity. Using FA, MD, RD and AD indicators, possible demyelination and axonal injury were identified in corticosubcortical nuclei connections. Right frontocerebellar, temporocerebellar, parietocerebellar and occipitocerebellar WM connections showed reduced diffusivity in the CMMD patient. These areas including the inferior parietal lobule, inferior frontal gyrus, supplementary motor area, and cerebellum mainly related to the encoding and retrieving the rhythm information [234]. Rhythm information is important to organize the perceived sensory input especially information about bodily movements. Undesired sensory input from the mirroring hand might also affect the information processing of bodily movements in CMM.

Underlying mechanisms of CMMD with RAD51 gene mutation were investigated. Our findings suggest that CMMD with RAD51 mutation is highly correlated with the reduced microstructural integrity in CST projections and disrupted connectivity among cerebellum, basal ganglia and the cortex. We provide the first evidence of disrupted involvement of basal ganglia and cerebellum on the motor system.

4.5 Conclusion

We have found widespread abnormalities in the function and structure of brains of CMMD patients with RAD51 gene mutation. Our findings suggest that mirror movements are highly correlated with reduced microstructural integrity in CST projections and disrupted connectivity in pathways involving the cerebellum, thalamus, basal ganglia and the cortex, as well as abnormal neuronal activity during the performance of unimanual finger movements. These findings highlight the critical roles of different components and connections in the motor system to accomplish coordinated unimanual movements in healthy individuals. However, given the remarkable plasticity of the central nervous system, some of the findings could be linked to compensatory mechanisms that developed to suppress the movement of the unintended hand and reduce the mirror movements.

Chapter 5

General Discussion and Conclusion

5.1 Genetic Influences on Neurodevelopment

Structure and function of the human central nervous system is largely determined by both genetic and environmental influences. The fundamental importance in neuroscience studies is to determine to what degree they are effective on nervous system and eventually on behavior. Large-scale multimodal studies that have both genetic and neuroimaging components provided critical information on identification of the effects of specific gene expression on activation patterns in brain [235, 236]. Since these kinds of studies are limited with the number of the effected individuals, genetic and environmental effects on the activity of the brain is less affected from the other confounding factors. Statistical comparisons on those limited number of individuals require more conservative intervals. Thus, -including all of the present work- persisted genetic and brain structure/function or genetic and behavior relationships after statistical adjustments point out critical information regarding an effect of a specific genetic pattern.

Brain development during the prenatal period through childhood progresses

rapidly and maturation of human brain progress more slowly during the adolescence and young adulthood until it follows a descending trajectory with aging [237]. During the first phase of postnatal period individual experiences affect the organization of brain [238]. Nevertheless, 10,000 genes -approximately 33% of the whole human genome are only expressed during the neurodevelopment [239, 240]. Turning on and off the expression of the genes occur more rapidly during the fetal development compared to childhood and early adolescence and it is stabilized during adulthood. Genetic expression pattern also changes after age 50 as it is in prenatal period and early period with distinct redirection of alteration in speed of genetic expression [241]. Specific genes that are highly expressed during prenatal period neurodevelopment decreased in expression in older adults' brains, on the other hand specific genes that have low expression rate during the prenatal period show higher expression rate in aging brain [241]. Interaction between expressed genes and developing human brain provides valuable information to enlighten the genetic control on human brain structure, function and possibly behavior. In the present study, how specific three genetic mutations affect human brain structure and function are discussed based on their expression time interval during neurodevelopment. Expressions of LAMC3, HTRA2, RAD51 genes mainly correspond to neuronal migration, apoptosis and myelination processes respectively. Product proteins of these mutations affect the structure or function of different brain areas possibly due to the maturation differences among brain areas during neural development.

Genetic influences on brain studies consist of heritable brain structure studies and genetic mutation studies. Both of these studies provide essential and complementary information on human brain. Twin studies are important to identify particularly heritable structures in human brain. More specifically, effects on monozygotic twin pairs who are genetically identical individuals and dizygotic twin pairs who share half of their genetic backgrounds are critical to separate genetic factors from environmental factors. Specifically, gray matter volume in middle frontal, sensorimotor and temporal cortices are influenced by genetic factors [242, 243] whereas superior fronto-occipital connections and corpus callosum are influenced by genetic factors [115]. In parallel with this, in the present study

affected motor areas as well as fronto-occipital and callosal tracts are revealed under different genetic mechanisms.

5.2 Genetic Influences on White Matter Integrity

Genetic influences on white matter development is investigated mainly on clinical perspective. Heritability on white matter integrity was also examined across the lifespan. Studies investigating heritability in white matter integration assesses development of white matter structure based on white matter indices in neonates [244, 245] and adolescents [246, 247]. Genetic influences on FA in whole white matter structure is higher in newborns (approximately FA:60% and RD:53%) [244, 245] compared to children (approximately FA: 54%) [247, 246] and adults (FA:52% and RD:37%) [248]. On the other hand, heritability of AD is mild in newborns (approximately 57%) [245] compared to children (approximately 33-46%) [249]. However, heritability studies could not find any significant results in adults [250]. Higher genetic influences on white matter microstructural integrity in newborns indicate early organization of white matter connections.

Genetic influences on white matter structure also higher in structures that mature earlier [251]. However, development of the interhemispheric microstructural connections is exceptional. Although genu matures later than splenium heritability of FA is higher in genu area than in splenium in any age [249, 248]. During the maturation process diffusion indices reflect alterations in fiber organization, myelin sheath or presence/absence of glial cells [252]. Some indices are also sensitive to the changes in other indices. For example, FA values could be influenced by alterations in RD values [252]. Thus, information from all diffusion indices is required to understand the whole maturation process. Thus, all white matter indices are reported in the present study to discuss significant alterations comprehensively.

5.3 Genetic Influences on Functional Connectivity

Genetic influences on white matter integrity could possibly affect the functional connectivity or vice versa. Functional connectivity is assessed by the temporally dependent neuronal activation patterns of anatomically different brain regions. Functional connectivity analyses on twins showed that global efficiency is highly heritable (approximately 60%) [253]. Although genetic studies are conducted on small populations to be able to limit confounding variables other than genetic background results of these studies indicate that heritability of global functional connectivity increases in parallel with maturation of the brain [237]. Although our studies were also limited in sample sizes, by using super conservative statistical methods, our results pointed abnormal functional connectivity among brain areas possibly indicating effects of a specific gene mutation.

5.4 Genetic Influences on Brain Morphometry

Functional connectivity is highly related to alterations in brain morphometry such as cortical volume as well as microstructural integrity. Morphometry assessments provide quantitative measures of brain size, genetic influences on morphometric measures are assessed via longitudinal studies. Genetic influences on total gray matter are lower in newborns (56%) compared to children who are in 5 to 18 age range (77%-80%) [254, 255, 256] and adults (82%) [257]. On the other hand, genetic influences in white matter volumetric measures in newborns are similar in the same age range children (approximately 85%) [256, 254] and in adults (87%) [257]. One of our studies revealed that a specific gene mutation could be effective on brain morphometry and these differences are powerful enough to remain as significant even after false-discovery rate corrections.

5.5 Overall Conclusion

Expressions of the specific genes that are effective during the neurodevelopment regulate organization of the human brain in many ways. Critical involvements of these genes are fundamental to precise functioning of systems. Their involvement of these processes in neurodevelopmental processes could be divided into two main categories: genetic/heritable influences and environmental influences on nervous system development. Genetic/heritable influences on neural system is consist of processes that are determined by genetics and these processes are effective on differentiation, migration and axonal guidance processes of the neural development. Environmental influences include modification of synapses and synapse elimination processes based on neural activity and/or sensory experiences. Three genes that were investigated in the present study are thought to be effective on different processes based on their expression time intervals. Their involvement in any or combination of the neurodevelopmental processes creates significantly different both structural and functional connectivity patterns compared to healthy controls. Future studies including more affected individuals from the same families are needed to assess the effect of hetero- or homozygosity in these neurodevelopmental disorders and also it would be helpful to increase the statistical power in these samples.

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Appendix A

White Matter Connections in Bilateral Occipital Pachygyria Case

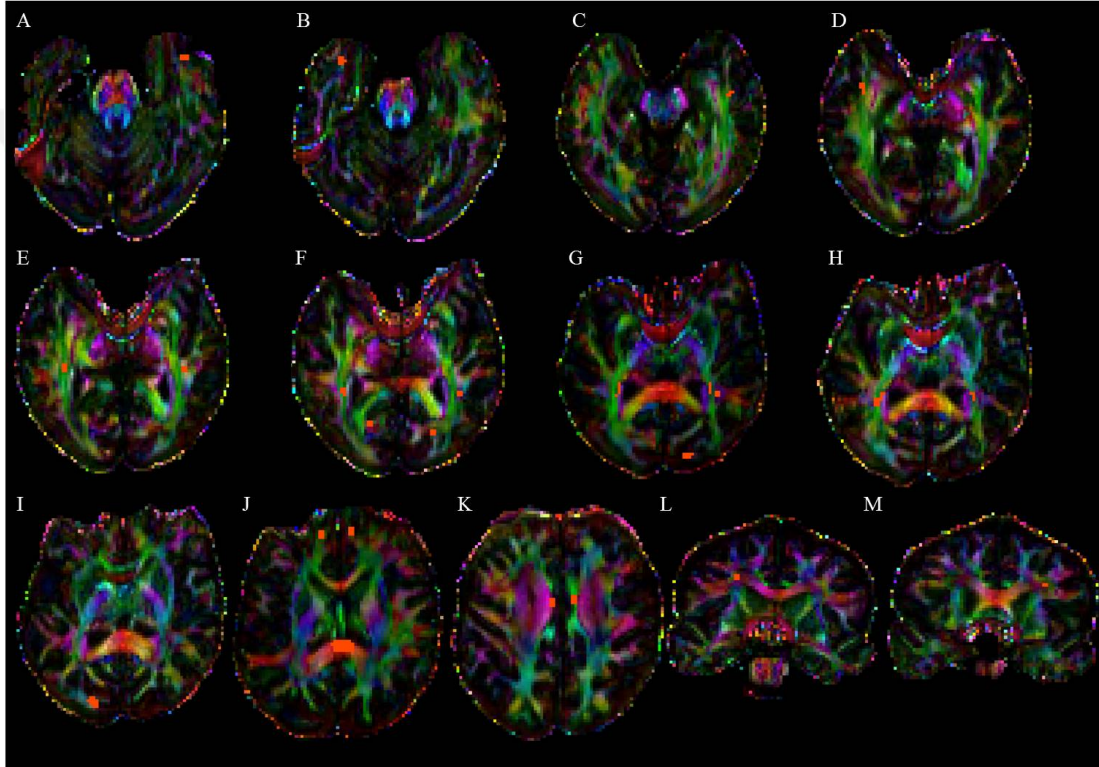


Figure A.1: ROI locations that were used in probabilistic tractography A. Left anterior part of ILF, B. Right anterior part of ILF, C. Left superior lateral part of ILF, D. Right superior lateral part of ILF, E. Left and right temporal part of ILF, F. Left and right occipital part of IFOF, left and right posterior part of ILF, G. Left optic radiation part of IFOF, left and right tapetum, left calcarine, H. right optic radiation part of IFOF, left and right tapetum, I. Right calcarine, J. Splenium, left and right frontal part of IFOF, K. Left and right cingulate, L. Right SLF, M. Left SLF. IFOF: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus.

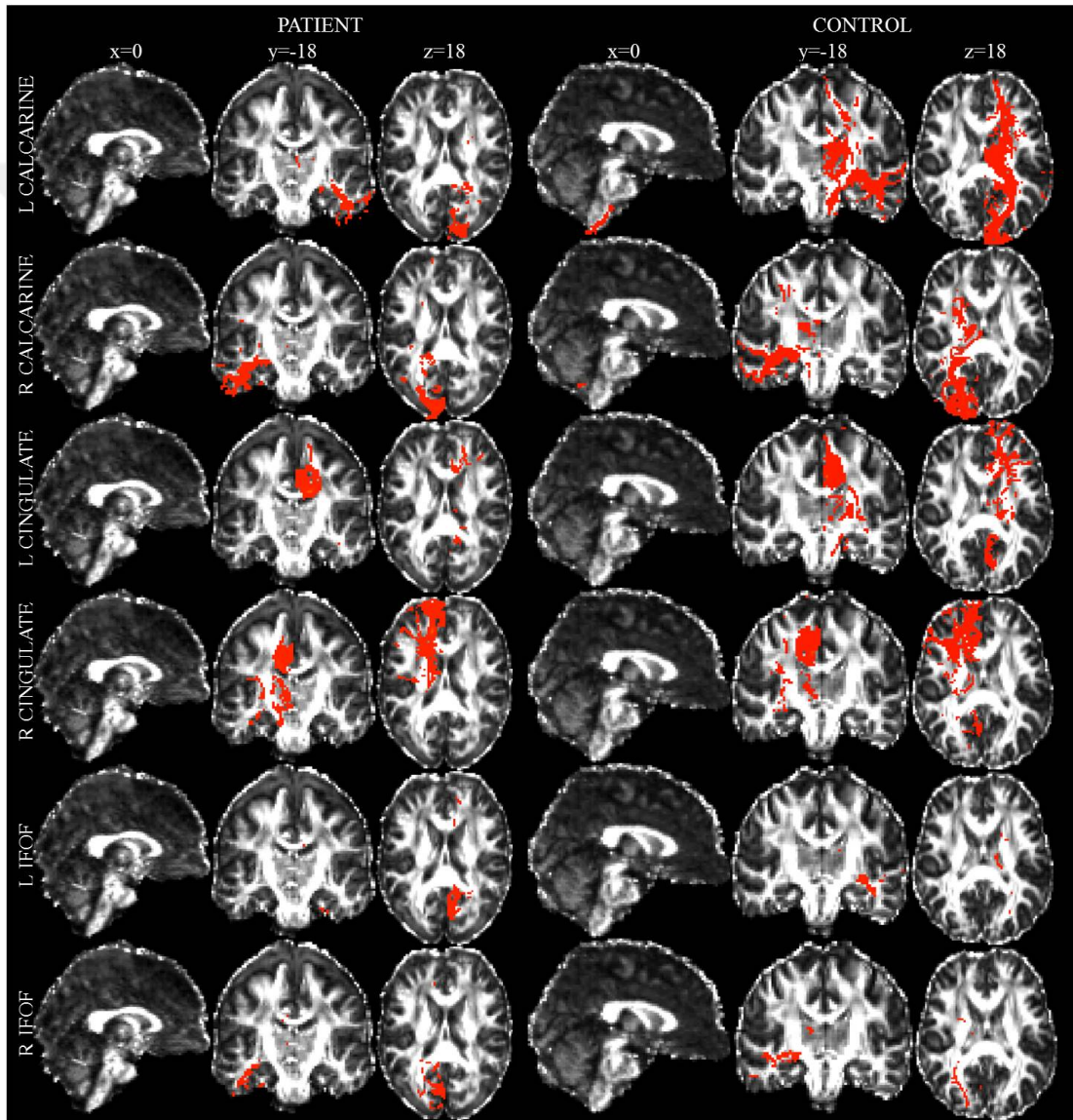


Figure A.2: 2D probabilistic tractography of bilateral calcarine, cingulate, IFOF in the occipital pachygyria patient and a representative control.

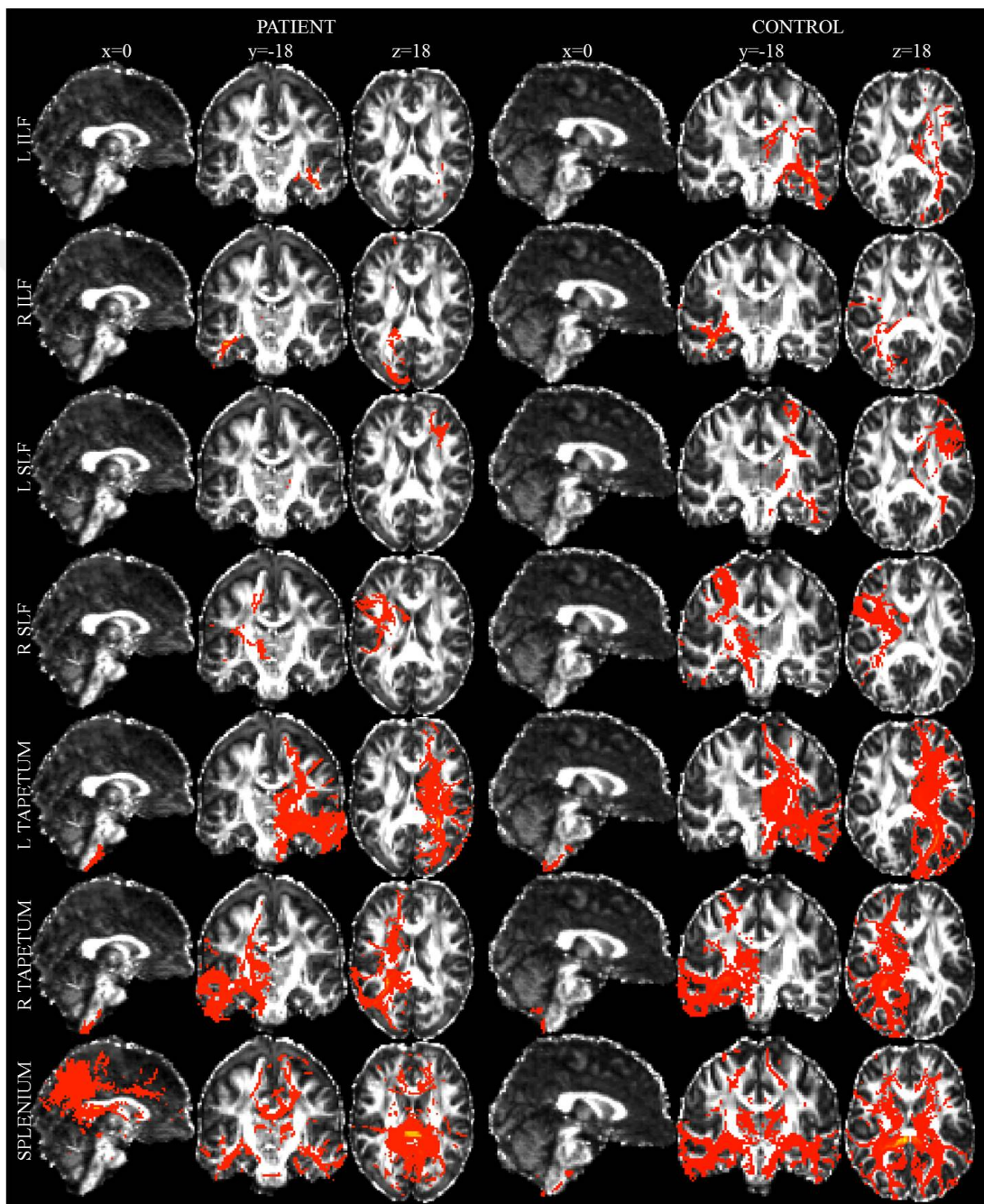


Figure A.3: 2D probabilistic tractography of bilateral ILF, SLF, tapetum and splenium in the occipital pachygyria patient and a representative control.

Appendix B

Functional Connectivity in Bilateral Occipital Pachygyria Case

Table B.1: MNI coordinates of the center of the spherical ROIs that were used in resting state fMRI comparisons. IFOF: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, CALC: calcarine sulcus, SLF: Superior longitudinal fasciculus, CIN: cingulate cortex, TAP: tepetum

Tracts	Region	MNI Coordinates (x y z) Left/Right
IFOF	Lateral Orbitofrontal	-36.6 46.4 -14 / 39 46.4 -14
	Rostral Middle Frontal	-38.4 35.6 22 / 40.8 35.6 22
	Superior Frontal	-6 39.2 47.2 / 8.4 39.2 47.2
	Pericalcarine	-6 -83.2 2.2 / 8.4 -83.2 2.2
	Lateral Occipital	-18.6 -94 5.8 / 21 -94 5.8
	Lingual	-6 -83.2 -6.8 / 8.4 -83.2 -6.8
ILF	Parahippocampal	-16.8 -34.6 -15.8 / 19.2 -34.6 -15.8
	Entorhinal	7-24 -2.2 -37.4 / 26.4 -2.2 -37.4
	Fusiform	-36.6 -32.8 -24.8 / 35.4 -32.8 -24.8
	Middle Temporal	-58.2 -25.6 -12.2 / 60.6 -25.6 -12.2
	Superior Temporal	-54.6 -9.4 -8.6 / 57 -9.4 -8.6
	Cuneus	-6 -86.8 22 / 8.4 -86.8 22
	Lingual	-6 -83.2 -6.8 / 8.4 -83.2 -6.8
	Lateral Occipital	-18.6 -94 5.8 / 21 -94 5.8
	Pericalcarine	-6 -83.2 2.2 / 8.4 -83.2 2.2
CALC	Cuneus	-6 -86.8 22 / 8.4 -86.8 22
	Lingual	-6 -83.2 -6.8 / 8.4 -83.2 -6.8
	Lateral Occipital	-18.6 -94 5.8 / 21 -94 5.8
	Pericalcarine	-6 -83.2 2.2 / 8.4 -83.2 2.2
	Precuneus	-6 -54.4 52.6 / 8.4 -54.4 52.6
SLF	Precenral	-31.2 -22 67 / 33.6 -22 67
	Postcentral	-13.2 -43.6 65.2 / 15.6 -43.6 65.2

	Caudal Middle Frontal	-38.4 14 34.6 / 40.8 14 34.6
	Cuneus	-6 -86.8 22 / 8.4 -86.8 22
	Pericalcarine	-6 -83.2 2.2 / 8.4 -83.2 2.2
CIN	Isthmus Cingulate	-6 -50.8 23.8 / 8.4 -50.8 23.8
	Rostral Anterior Cingulate	-6 37.4 4 / 8.4 37.4 4
	Caudal Anterior Cingulate	-6 15.8 34.6 / 8.4 15.8 34.6
TAP	Cuneus	-6 -86.8 22 / 8.4 -86.8 22
	Lateral Occipital	-18.6 -94 5.8 / 21 -94 5.8

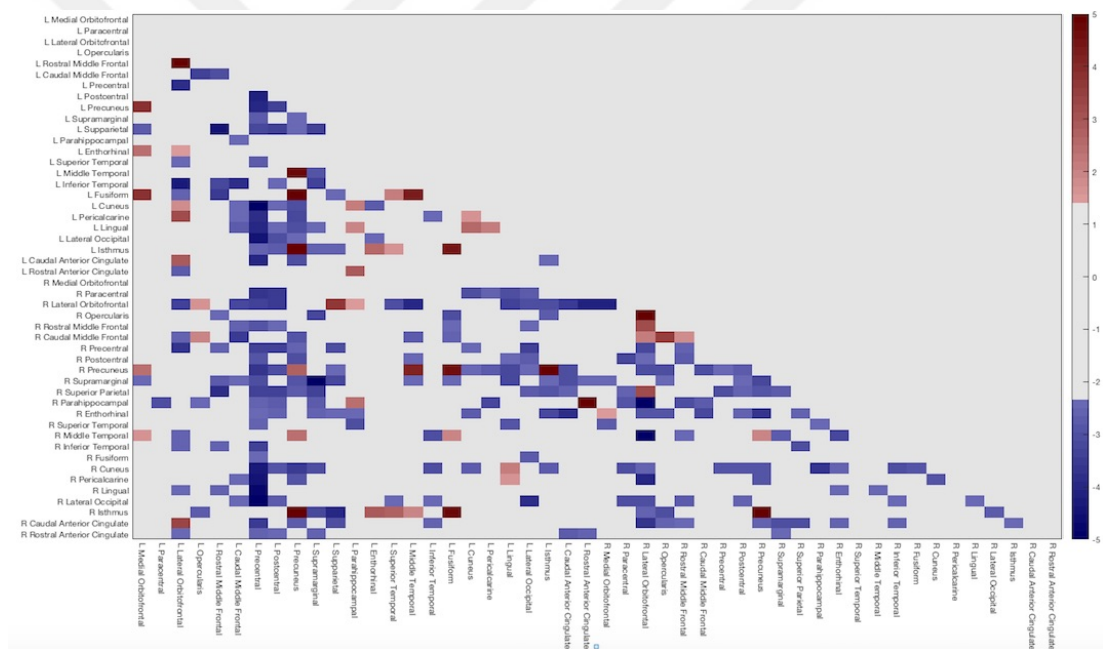


Figure B.1: 2D probabilistic tractography of bilateral ILF, SLF, tapetum and splenium in the occipital pachygyria patient and a representative control.

Table B.2: Resting state fMRI connectivity comparison between the ROIs along Inferior Fronto-Occipital Fasciculus (IFOF) by using standard null hypothesis testing (one-sample t-test) and nonparametric bootstrap procedure. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, all FDR corrected)

IFOF	Lateral Orbitofrontal	Postcentral	Supramarginal	Precuneus
Rostral Middle Frontal	L:-7.477***,0.477 [0.1031-0.2732]	L:1.673,0.074 [0.0806-0.4256]	L:1.233,0.181 [0.1282-0.4816]	L:1.385,0.105 [0.0990-0.4583]
	R:-3.278*,0.394 [0.1197-0.3426]	R:2.798* [0.1009-0.4161]	R:1.640,0.131 [0.1261-0.4002]	R:1.898,0.081 [0.0953-0.4553]
Medial Orbitofrontal	L:1.215,0.328 [0.1423-0.4469]	L:1.924,0.080 [0.0915-0.3641]	L:2.320,0.068 [0.0912-0.3187]	L:-3.886**,0.051 [0.1003-0.4112]
	R:4.077*,0.037 [0.0835-0.1742]	R:0.791,0.130 [0.0694-0.3450]	R:2.375,0.044 [0.0963-0.3206]	R:1.240,0.14 [0.0959-0.4157]
Caudal Middle Frontal	L:2.290,0.084 [0.1033-0.3279]	L:1.197,0.124 [0.0903-0.3775]	L:1.253,0.118 [0.865-0.3809]	L:0.614,0.185 [0.0975-0.4187]
	R:-2.174,0.31 [0.1442-0.3217]	R:3.156*, 0.03 [0.128-0.4624]	R:1.258,0.131 [0.1040-0.3776]	R:3.125*,0.035 [0.1209-0.41]
Supramarginal	L:-0.905,0.18 [0.0589-0.2395]	L:-0.083,0.302 [0.1530-0.4808]	L:0.000 [0.1550-0.4760]	L:2.373,0.109 [0.1474-0.4446]
	R:1.389 [0.0697-0.1759]	R:2.440,0.112 [0.1550-0.4760]	R:0.000	R:3.155*,0.066 [0.1450-0.4179]
Pericalcarine	L:-3.241*, 0.22 [0.0756-0.1991]	L:2.089,0.117 [0.1458-0.4338]	L:1.853,0.093 [0.1039-0.39]	L:3.269*, 0.078 [0.1816-0.5041]
	R:4.025**,0.055 [0.0971-0.1873]	R:0.547,0.2 [0.1379-0.4101]	R:0.272,0.189 [0.093-0.3751]	R:2.914*,0.077 [0.1626-0.4723]
Cuneus	L:-1.827,0.175 [0.0647-0.1865]	L:2.492*, 0.111 [0.1581-0.4551]	L:2.069,0.093 [0.1114-0.3817]	L:3.101*, 0.073 [0.1702-0.4998]
	R:2.525*,0.074 [0.0854-0.1656]	R:2.967*,0.049 [0.1282-0.3828]	R:1.733,0.116 [0.1161-0.3532]	R:2.886*,0.047 [0.1309-0.4314]
Lateral Occipital	L:2.194,0.074 [0.0818-0.1904]	L:3.078*,0.089 [0.1788-0.4302]	L:1.265,0.111 [0.0918-0.3259]	L:2.485,0.103 [0.1530-0.4512]
	R:3.028*,0.048 [0.0752-0.1882]	R:2.543*,0.111 [0.1637-0.4193]	R:1.789,0.077 [0.1016-0.3545]	R:2.002,0.111 [0.129-0.4456]

Table B.3: Resting state fMRI connectivity comparison between the ROIs along Superior Longitudinal Fasciculus (SLF) by using standard null hypothesis testing (one-sample t-test) and nonparametric bootstrap procedure. (*p<0.05, **p<0.01, ***p<0.001, all FDR corrected)

SLF	Caudal Middle Frontal	Precentral	Postcentral	Paracentral	Opercularis
Rostral Middle Frontal	L:2.222,0.068 [0.0913-0.3570] R:1.989,0.091 [0.108-0.3789]	L:0.000 R:1.719,0.208 [0.19-0.4752]	L:4.065**,0.144 [0.2672-0.5351] R:3.244*,0.056 [0.1531-0.4665]	L:0.201,0.18 [0.0589-0.2395] R:0.000 [0.0851-0.436]	L:1.574,0.143 [0.1236-0.4166] R:2.138,0.043
Paracentral	L:0.748,0.133 [0.0707-0.3875] R:2.171,0.046 [0.0755-0.3624]	L:2.256,0.14 [0.1545-0.433] R:1.719,0.208 [0.19-0.4752]	L:3.371,0.009 [0.1583-0.4952] R:3.244*,0.056 [0.1531-0.4665]	L:0.000 R:0.000	L:1.792,0.07 [0.086-0.3936] R:2.138,0.043 [0.0851-0.436]
Superior Parietal	L:1.930,0.113 [0.1135-0.4733] R:3.629,0.051 [0.1690-0.4779]	L:2.222,0.071 [0.1613-0.4573] R:3.019*,0.072 [0.1439-0.4295]	L:1.197,0.124 [0.0903-0.3775] R:2.643*,0.051 [0.1135-0.4517]	L:1.666,0.039 [0.061-0.3748] R:2.552,0.040 [0.1002-0.3885]	L:0.612,0.254 [0.1916-0.4983] R:-0.159,0.36 [0.2308-0.5129]
Supramarginal G.	L:1.253,0.118 [0.865-0.3809] R:1.258,0.131 [0.1040-0.3776]	L:2.690*,0.05 [0.1229-0.457] R:1.225,0.177 [0.1418-0.4314]	L:-0.083,0.302 [0.1530-0.4808] R:2.440,0.112 [0.1550-0.4760]	L:0.889,0.129 [0.0725-0.3982] R:1.264,0.125 [0.0977-0.3839]	L:2.207,0.083 [0.115-0.4669] R:2.461*,0.097 [0.1477-0.4628]
Precuneus	L:0.614,0.185 [0.0975-0.4187] R:3.125*,0.035 [0.1209-0.41]	L:3.948**,0.066 [0.1907-0.4483] R:2.450*,0.119 [0.1538-0.4157]	L:3.371*,0.051 [0.1690-0.4779] R:2.750*,0.063 [0.1275-0.4556]	L:0.201,0.185 [0.0845-0.3953] R:0.455,0.192 [0.0929-0.4197]	L:1.733,0.073 [0.0844-0.4123] R:3.091,0.03 [0.128-0.4624]
Pericalcarine	L:2.476*,0.0144 [0.0778-0.4208] R:0.916,0.187 [0.1551-0.428]	L:3.897**,0.062 [0.1838-0.4567] R:0.164,0.26 [0.1687-0.4156]	L:2.089,0.117 [0.1458-0.4338] R:0.547,0.2 [0.1379-0.4101]	L:1.067,0.145 [0.119-0.4324] R:2.294,0.08 [0.1372-0.466]	L:1.568,0.074 [0.0829-0.4072] R:0.550,0.154 [0.0848-0.4203]
Lingual G.	L:2.791*,0.048 [0.1156-0.4028] R:1.009,0.177	L:3.941**,0.075 [0.1826-0.4388] R:0.721,0.241	L:2.354,0.123 [0.1455-0.4013] R:1.536,0.156	L:1.255,0.124 [0.1053-0.3507] R:1.851,0.136	L:1.806,0.076 [0.0877-0.3704] R:1.245,0.133

	[0.1326-0.4252]	[0.1594-0.4392]	[0.1375-0.4085]	[0.1417-0.4106]	[0.1191-0.3985]
Cuneus	L:2.376,0.029	L:4.995**,0.063	L:2.492*,0.111	L:1.699,0.119	L:1.748,0.082
	[0.0825-0.3838]	[0.2150-0.4444]	[0.1581-0.4551]	[0.1328-0.4311]	[0.0914-0.3917]
	R:1.475,0.141	R:2.932*,0.131	R:2.967*,0.049	R:3.074,0.0.048	R:0.669,0.138
	[0.1354-0.3763]	[0.1781-0.3928]	[0.1282-0.3828]	[0.1447-0.4212]	[0.0779-0.3686]



Table B.4: Resting state fMRI connectivity comparison between the ROIs along Inferior Longitudinal Fasciculus (ILF) by using standard null hypothesis testing (one-sample t-test) and nonparametric bootstrap procedure. (*p<0.05, **p<0.01, ***p<0.001, all FDR corrected)

ILF	Entorhinal	Fusiform	Parahippocampal G.	Supramarginal G.	Pericalcarine
Superior Temporal	L:-1.020,0.239	L:-2.151,0.238	L:1.149,0.106	L:0.694,0.148	L:1.761,0.09
	[0.0889-0.3475]	[0.0624-0.2574]	[0.0876-0.2679]	[0.0728-0.3842]	[0.119-0.4505]
	R:2.021,0.053	R:1.423,0.082	R:2.449	R:3.383*,0.051	R:2.15,0.049
	[0.0723-0.2402]	[0.0766-0.3826]	[0.1109-0.2352]	[0.1690-0.4779]	[0.0988-0.4301]
Middle Temporal	L:-0.027,0.135	L:-4.274**,0.357	L:1.324,0.08	L:2.864,0.056	L:1.575,0.054
	[0.0596-0.2769]	[0.0813-0.2774]	[0.0642-0.2911]	[0.1152-0.3404]	[0.0676-0.3558]
	R:3.246*,0.035	R:1.314,0.075	R:0.471,0.117	R:2.741,0.025	R:2.009,0.035
	[0.0766-0.2072]	[0.0634-0.3658]	[0.083-0.2206]	[0.098-0.3458]	[0.0867-0.406]
Inferior Temporal	L:1.393,0.056	L:1.101,0.118	L:1.053,0.074	L:3.420**,0.053	L:2.467*,0.076
	[0.0592-0.2268]	[0.0834-0.3406]	[0.0544-0.2406]	[0.1114-0.2704]	[0.1035-0.2976]
	R:2.026,0.062	R:0.56,0.201	R:-0.434,0.149	R:0.910,0.154	R:0.346,0.261
	[0.0616-0.2236]	[0.1234-0.4075]	[0.0632-0.2431]	[0.0936-0.3994]	[0.1426-0.4864]
Precuneus	L:-1.173,0.243	L:-5.348***,0.415	L:2.129,0.098	L:2.373,0.109	L:3.269*,0.078
	[0.0815-0.3211]	[0.0867-0.2824]	[0.1067-0.2961]	[0.1474-0.4446]	[0.1816-0.5041]
	R:3.681**,0.033	R:0.964,0.15	R:1.894,0.134	R:3.155*,0.066	R:2.914*,0.077
	[0.1049-0.2829]	[0.1139-0.3685]	[0.1151-0.3407]	[0.1450-0.4179]	[0.1626-0.4723]
Cuneus	L:2.725*,0.044	L:1.296,0.085	L:-2.118,0.218	L:2.069,0.093	L:-1.637,0.602
	[0.1064-0.3293]	[0.0728-0.2745]	[0.0885-0.2394]	[0.1114-0.3817]	[0.397-0.6467]
	R:2.527*,0.84	R:2.910*,0.078	R:3.619**,0.095	R:1.733,0.116	R:2.824*,0.360
	[0.1135-0.2740]	[0.1436-0.4048]	[0.1364-0.2453]	[0.1161-0.3532]	[0.4198-0.6588]
Lingual G.	L:1.459,0.094	L:0.662,0.139	L:-1.899,0.231	L:2.447,0.058	L:-2.139,0.659
	[0.0892-0.2948]	[0.075-0.3101]	[0.0719-0.2576]	[0.0972-0.3481]	[0.4562-0.6603]
	R:2.458*,0.093	R:1.637,0.128	R:-0.447,0.249	R:1.182,0.182	R:1.391,0.411
	[0.1069-0.2626]	[0.1189-0.4258]	[0.1332-0.3306]	[0.1522-0.3837]	[0.3454-0.6767]
Lateral Occipital	L:2.473*,0.052	L:1.159,0.092	L:0.863,0.104	L:1.265,0.111	L:2.228,0.279
	[0.0941-0.3010]	[0.0704-0.2776]	[0.069-0.2426]	[0.0918-0.3259]	[0.2955-0.5912]
	R:1.302,0.121	R:2.081,0.05	R:0.198,0.178	R:1.789,0.077	R:0.071,0.471
	[0.0989-0.2667]	[0.089-0.3503]	[0.1306-0.248]	[0.1016-0.3545]	[0.3209-0.6409]

Table B.5: Resting state fMRI connectivity comparison between the ROIs along calcarine tract by using standard null hypothesis testing (one-sample t-test) and nonparametric bootstrap procedure. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, all FDR corrected)

CALCARINE	Precuneus	Pericalcarine
Pericalcarine	L:3.269*,0.078 [0.1816-0.5041]	L:0.000
	R:2.914*,0.077 [0.1626-0.4723]	R:0.000
Cuneus	L:3.101*,0.073 [0.1702-0.4998]	L:-1.637,0.602 [0.397-0.6467]
	R:2.886*,0.047 [0.1309-0.4314]	R:2.824*,0.360 [0.4198-0.6588]
Lingual G	L:3.035,0.118 [0.18-0.4493]	L:-2.139,0.659 [0.4562-0.6603]
	R:1.977,0.156 [0.1549-0.4556]	R:1.391,0.411 [0.3454-0.6767]

Table B.6: Resting state fMRI connectivity comparison between the ROIs along cingulate tract by using standard null hypothesis testing (one-sample t-test) and nonparametric bootstrap procedure. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, all FDR corrected)

CINGULATE	Caudate Anterior Cingulate
Isthmus	L:2.385,0.042 [0.0882-0.3418] R:2.467*,0.055 [0.0881-0.3085]
Enthornal Gyrus	L:1.550,0.112 [0.1115-0.3359] R:2.582*,0.048 [0.0752-0.2463]
Rostral Anterior Cingulate	L:1.781,,0.107 [0.1002-0.3789] R:2.328,0.037 [0.0886-0.4291]

Appendix C

Demographic Information of Essential Tremor

Table C.1: For tremor +, low amplitude or barely perceivable tremor; ++, moderate amplitude tremor (1-2 cm); +++, large amplitude, severe tremor (>2 cm) (1). For Archimedes spiral test, bradykinesia, rigidity, postural instability and hypomimia: +, mild; ++, moderate; +++, severe. L, left hand; R, right hand

		Tremor												Archimedes													
Individual		Resting		Postural		Kinetic		Intentional		Head		Chin		Voice		Spiral Test			Bradykinesia		Rigidity		Postural Instability	Hypomimia	Dominant Head		
		R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L						
		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
ET-59	14-282	++	+++	+	++	+	++	++	+++	-	-	+	++	+++	-	-	-	-	-	-	-	-	-	+	R		
ET-59	14-285	-	-	+	+	-	+	-	+	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	R		
ET-5	13-018	++	++	++	++	+	+	++	++	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	R		
ET-5	13-015	++	+	+	+	+	+	+	+	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	L		
ET-1	13-001	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	R		
ET-1	10-032	-	-	+	+	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	-	R		
ET-1	15-462	++	-	++	+	-	-	-	-	-	-	-	++	++	+	+	+	+	+	-	-	-	-	-	R		
ET-1	10-026	-	-	++	+++	++	+++	+	+	-	-	-	++	+++	++	++	++	++	++	++	++	++	+	++			
ET-1	15-463	-	-	++	+	-	-	-	-	-	-	-	++	+++	-	-	-	-	-	-	-	-	-	-	R		

Table C.2: Diffusion indices for early-onset essential tremor (EOET) and late-onset essential tremor (LOET) patients versus age-matched healthy controls (HC) in bilateral dentate-rubro-thalamo-cortical tracts (DRTC's). Conventional null-hypothesis significance ($p^* < 0.05$) is computed using independent-sample t-test. FA: Fractional anisotropy, MD: mean diffusivity, RD: radial diffusivity, AD: axial diffusivity, L: Left, R: Right

		EOET vs Young HC		LOET vs Old HC	
		t test score(df)	p values	t test score(df)	p values
L DRTC	FA	-0.812(16)	0.429	-2.758(14)	0.015*
	MD	-0.436(16)	0.669	0.961(14)	0.353
	RD	-0.2(16)	0.844	0.861(14)	0.404
	AD	-0.794(16)	0.439	0.465(14)	0.649
R DRTC	FA	0.351(16)	0.73	1.119(14)	0.282
	MD	0.114(16)	0.91	-0.992(14)	0.338
	RD	-0.212(16)	0.835	-1.096(14)	0.291
	AD	0.112(16)	0.912	-0.627(14)	0.541

Appendix D

Corticospinal fibers reconstruction in CMMD patient

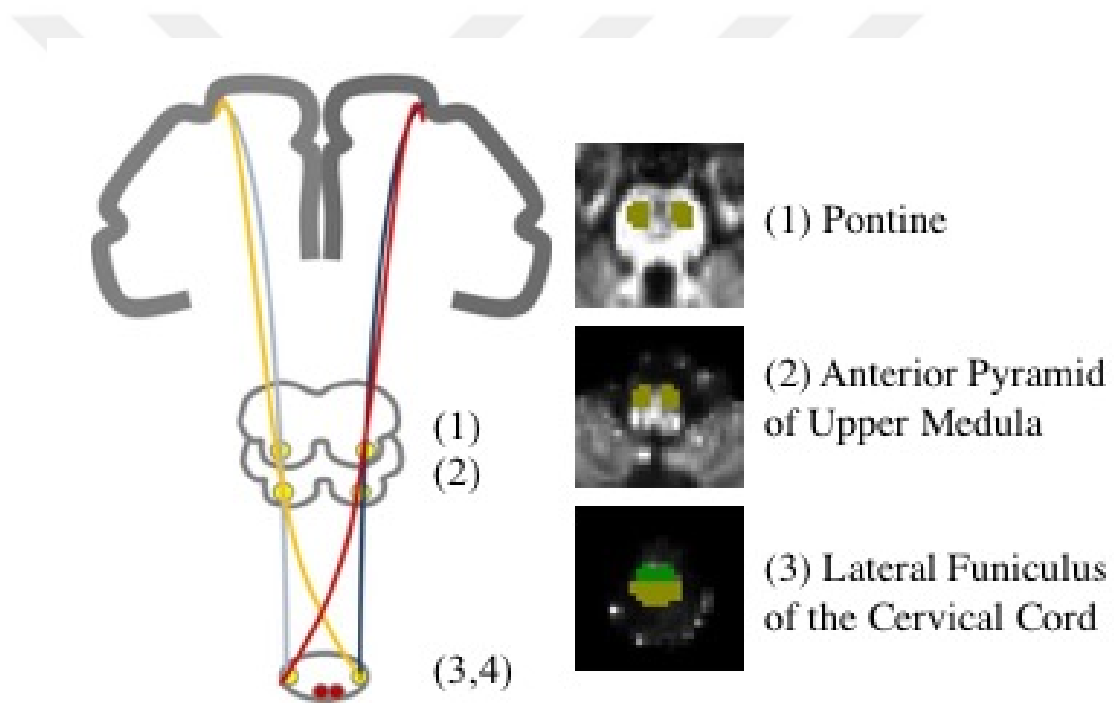


Figure D.1: Region of interests from (1) pontine, (2) anterior pyramid of upper medulla, (3) lateral funiculus of the cervical cord levels of medulla that were used in reconstruction of corticospinal fibers. Yellow and red lines represent crossed fibers, light blue and dark blue lines show uncrossed fibers in corticospinal tract

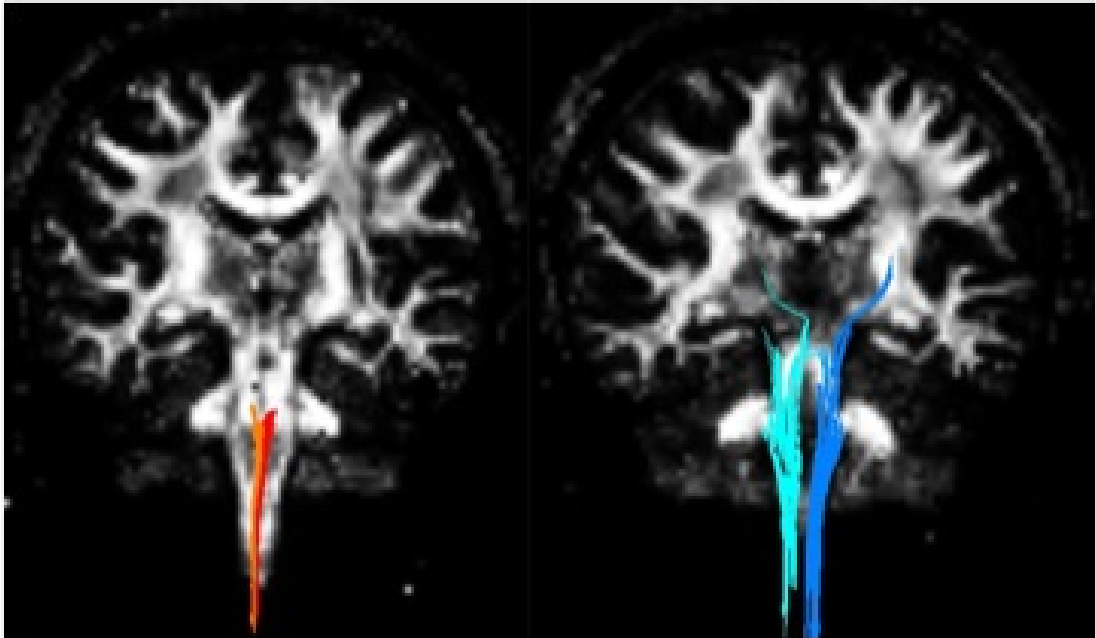


Figure D.2: Representative reconstruction of corticospinal fibers in a CMMD patient. Yellow and Red show crossed fibers, Light and Dark Blue show uncrossed fibers

Appendix E

2D Reconstruction of Dentate Rubro Thalamic and Cortico Ponto Cerebellar Pathways

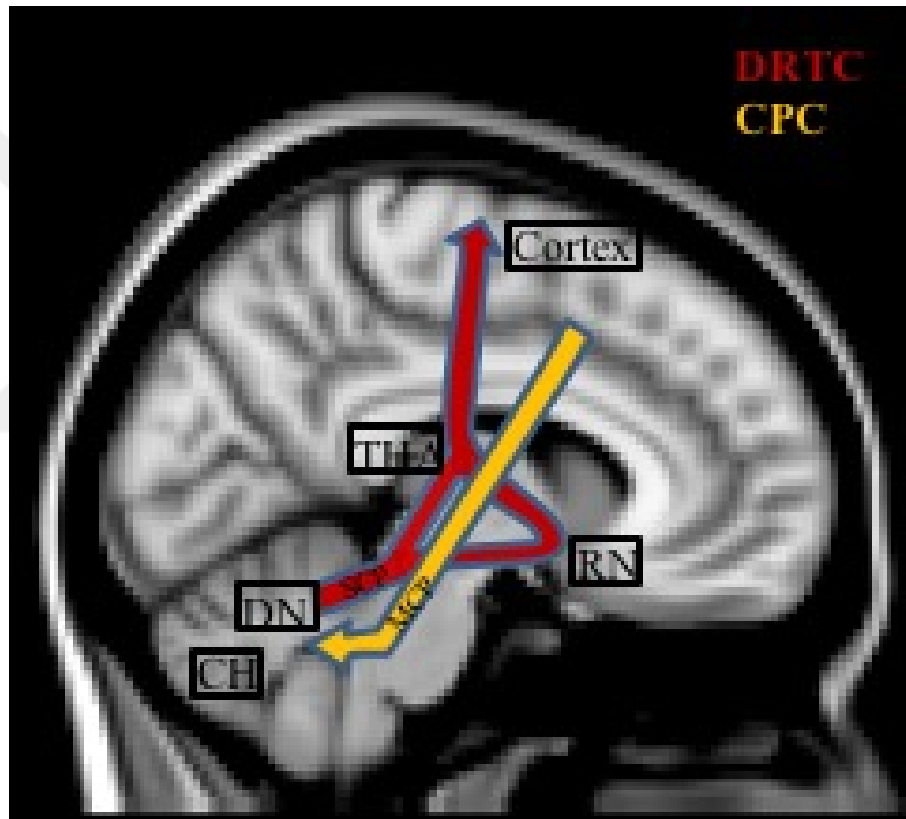


Figure E.1: Schematic representation of afferent (red line) and efferent (yellow line) cerebellocerebral loop pathways. DRTC: Dentate-Rubro-Thalamo-Cortical pathway, CPC: Cortico-Ponto-Cerebellar Pathway, THA: Thalamus, DN: Dentate Nucleus, RN: Red Nucleus, CH: Cerebellar Hemisphere, SCP: Superior Cerebellar Peduncle, MCP: Middle Cerebellar Peduncle

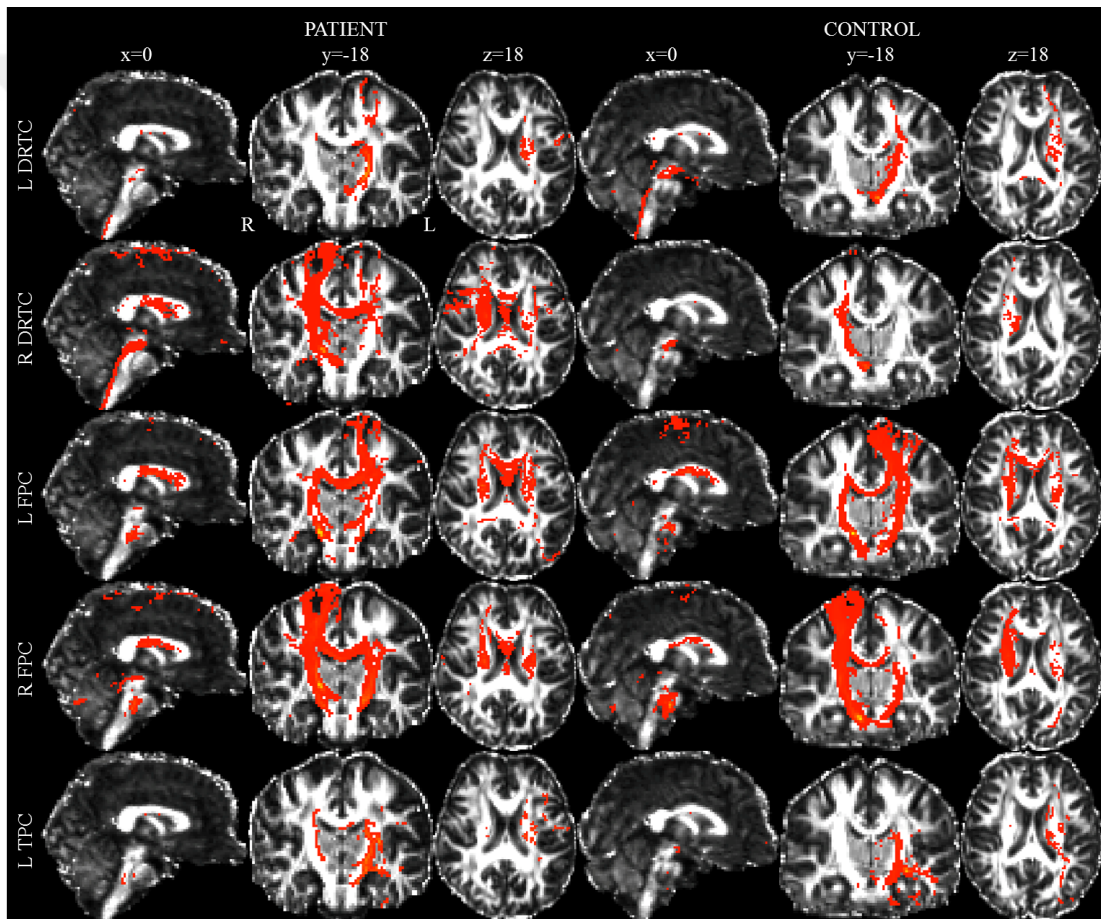


Figure E.2: 2D probabilistic tractography of bilateral DRTC and SCP in the CMMD patient and a representative control.

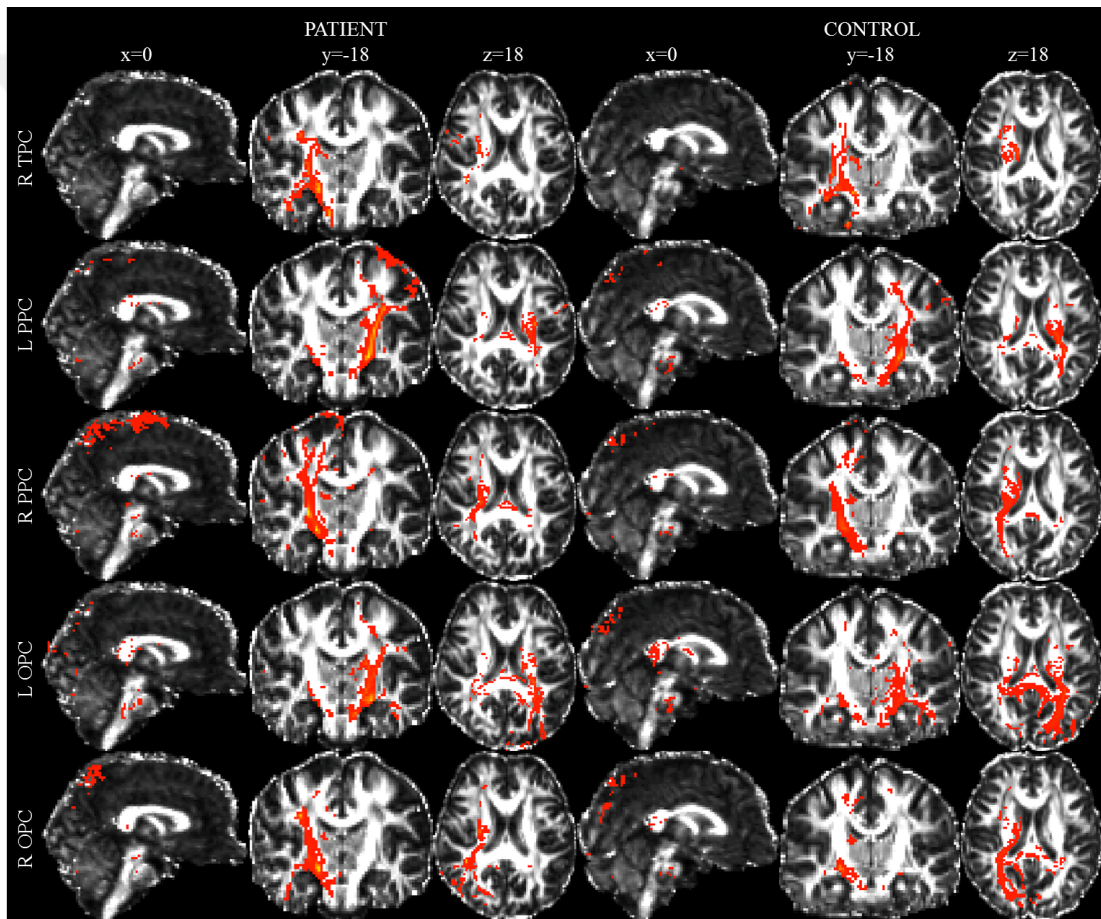


Figure E.3: 2D probabilistic tractography of bilateral DRTC and SCP in the CMMD patient and a representative control.

Appendix F

Functional Connectivity among motor areas in CMMD

Table F.1: Resting state fMRI connectivity between the ROIs located in dentate nucleus (cerebellum), red nucleus, primary MC (hand area), SMA, thalamus, caudate nucleus and globus pallidus. Statistically significant connections are shown. 95 % confidence intervals for the healthy control group are computed using a non-parametric bootstrap procedure. Statistical significance (p values) are computed using standard null hypothesis testing (one-sample t-test). Results of non-parametric bootstrap for Pearson's correlation coefficient r scores in resting-state fMRI data (* p<0.05, ** p<0.01, *** p<0.001, all FDR corrected)

ROI-I	ROI-II	95% CI	Patient	p values
R M1	L M1	0.5593, 0.7428	0.8144	0.0276*
	L THA	0.4114, 0.5720	0.3934	0.11
	L PRE	0.4554, 0.6600	0.6736	0.1154
	L Caudate	0.3708, 0.4868	0.4201	0.9114
	L GP	0.4336, 0.5298	0.3692	0.0084*
	L Dentate	0.4039, 0.5602	0.2125	0.0011**
	L Red Nucleus	0.3567, 0.5489	0.4504	0.9889
	L Subthalamic Nuclues	0.5094, 0.7088	0.4995	0.135
	L SMA	0.4475, 0.58	0.6012	0.0731
	R THA	0.4467, 0.5929	0.2621	0.001164**
	R PRE	0.4830, 0.6425	0.5263	0.5169
	R Caudate	0.3561, 0.5210	0.2614	0.01278*
	R GP	0.3422, 0.5292	0.4696	0.588
	R Dentate	0.3440, 0.4716	0.3321	0.1111
	R Red Nucleus	0.4273, 0.5955	0.2752	0.0031**
	R Subthalamic Nuclues	0.3807, 0.5214	0.3985	0.3055
	R SMA	0.4953, 0.6957	0.7813	0.0231*
L M1	L THA	0.4234, 0.5929	0.4129	0.1303
	L PRE	0.4386, 0.6266	0.6252	0.1548
	L Caudate	0.3155, 0.4836	0.3648	0.6009
	L GP	0.3898, 0.5299	0.1555	<0.001***
	L Dentate	0.3360, 0.4978	0.3586	0.2850
	L Red Nucleus	0.3387, 0.5244	0.3393	0.1747
	L Subthalamic Nuclues	0.4293, 0.5958	0.3085	0.0077**
	L SMA	0.5293, 0.7167	0.4804	0.0431
	R THA	0.4211, 0.6329	0.4335	0.2088

	R PRE	0.3270, 0.4863	0.2609	0.0295*
	R Caudate	0.3719, 0.4537	0.4834	0.0323
	R GP	0.3915, 0.4657	0.2473	<0.001***
	R Dentate	0.3889, 0.5739	0.4688	0.7589
	R Red Nucleus	0.3651, 0.5442	0.3439	0.1044
	R Subthalamic Nuclues	0.5192, 0.7139	0.8149	0.018*
	R SMA	0.4686, 0.6071	0.436	0.0629
R PRE	L THA	0.6052, 0.7758	0.7856	0.1484
	L PRE	0.3716, 0.5661	0.4479	0.7340
	L Caudate	0.4041, 0.5419	0.4078	0.1732
	L GP	0.4359, 0.5503	0.325	0.0025**
	L Dentate	0.3833, 0.5889	0.3211	0.048
	L Red Nucleus	0.4057, 0.5676	0.358	0.0449
	L Subthalamic Nuclues	0.5113, 0.7315	0.5392	0.2609
	L SMA	0.4078, 0.5480	0.4209	0.2661
	R THA	0.4231, 0.527	0.6396	0.0016**
	R Caudate	0.3567, 0.5183	0.3017	0.0387
	R GP	0.3492, 0.5362	0.3497	0.153
	R Dentate	0.4342, 0.5637	0.2738	0.0013**
	R Red Nucleus	0.4362, 0.5634	0.2784	0.0012**
	R Subthalamic Nuclues	0.4444, 0.5812	0.4263	0.0907
	R SMA	0.487, 0.6917	0.5959	0.9266
L PRE	L THA	0.4313, 0.5449	0.4402	0.2065
	L Caudate	0.3655, 0.554	0.4492	0.9585
	L GP	0.3133, 0.5092	0.3257	0.2051
	L Dentate	0.3823, 0.5564	0.3759	0.1512
	L Red Nucleus	0.4190, 0.5581	0.3863	0.0573
	L Subthalamic Nuclues	0.5429, 0.6715	0.5624	0.3354
	L SMA	0.4617, 0.5314	0.4714	0.2986
	R THA	0.3133, 0.4804	0.3376	0.3416
	R Caudate	0.4115, 0.5519	0.4935	0.8691
	R GP	0.3974, 0.4865	0.406	0.261
	R Dentate	0.3907, 0.4852	0.2551	<0.001
	R Red Nucleus	0.3904, 0.5434	0.3899	0.1829
	R Subthalamic Nuclues	0.4475, 0.7107	0.6631	0.3735
	R SMA	0.5236, 0.6270	0.5304	0.2209
	L THA	0.3749, 0.5354	0.4049	0.416

	L Caudate	0.3763, 0.5131	0.5881	0.0159*
	L GP	0.3363, 0.5199	0.1557	0.0028**
	L Dentate	0.4427, 0.5529	0.3781	0.0131*
	L Red Nucleus	0.3666, 0.5027	0.3674	0.1774
	L Subthalamic Nuclues	0.5042, 0.6976	0.4391	0.0369
	L SMA	0.4462, 0.6122	0.4945	0.5292
	R THA	0.4437, 0.6126	0.4945	0.5292
	R Caudate	0.3471, 0.5074	0.2326	0.0077**
	R GP	0.4589, 0.5388	0.5042	0.9165
	R Dentate	0.3414, 0.5262	0.4451	0.7865
	R Red Nucleus	0.3399, 0.4597	0.2265	0.0029**
	R Subthalamic Nuclues	0.3901, 0.5506	0.3066	0.0159*
L SMA	L THA	0.4480, 0.5861	0.3273	0.003897**
	L Caudate	0.3449, 0.4849	0.3744	0.4253
	L GP	0.355, 0.4906	0.2575	0.0066**
	L Dentate	0.3292, 0.4519	0.1856	0.0012**
	L Red Nucleus	0.3786, 0.4875	0.5949	0.0024**
	L Subthalamic Nuclues	0.44, 0.5729	0.2916	0.0014**
	R THA	0.4783, 0.6316	0.3159	0.0019**
	R Caudate	0.353, 0.5213	0.4235	0.8441
	R GP	0.4288, 0.5308	0.3692	0.0129*
	R Dentate	0.4532, 0.5903	0.4714	0.3078
	R Red Nucleus	0.3907, 0.4892	0.4172	0.5183
	R Subthalamic Nuclues	0.4957, 0.6066	0.4085	0.0049**
R THA	L THA	0.5366, 0.7536	0.7892	0.0884
	L Caudate	0.3404, 0.5038	0.4586	0.4864
	L GP	0.399, 0.5701	0.4844	0.9937
	L Dentate	0.3313, 0.4653	0.1772	0.0013**
	L Red Nucleus	0.4085, 0.5282	0.2216	<0.001
	L Subthalamic Nuclues	0.4491, 0.6405	0.5331	0.8631
	R Caudate	0.3677, 0.5287	0.44	0.8907
	R GP	0.4073, 0.4970	0.3855	0.0523
	R Dentate	0.3917, 0.5206	0.1753	<0.001***
	R Red Nucleus	0.3588, 0.4785	0.1057	<0.001***
	R Subthalamic Nuclues	0.4185, 0.5809	0.4042	0.1122
	L Caudate	0.4050, 0.5973	0.4137	0.2123
	L GP	0.4441, 0.6448	0.6781	0.0804

	L Dentate	0.3388, 0.4692	0.2765	0.01947*
	L Red Nucleus	0.3611, 0.5273	0.3366	0.0841
	L Subthalamic Nuclues	0.4227, 0.6308	0.5894	0.3634
	R Caudate	0.4305, 0.6212	0.371	0.041
	R GP	0.4049, 0.4948	0.4992	0.1375
	R Dentate	0.3644, 0.5187	0.2738	0.0127*
	R Red Nucleus	0.3617, 0.5805	0.2466	0.0163*
	R Subthalamic Nuclues	0.4481, 0.5975	0.516	0.8939
R Caudate	L Caudate	0.5528, 0.7198	0.5693	0.2465
	L GP	0.3760, 0.5411	0.3358	0.0632
	L Dentate	0.3345, 0.4941	0.3243	0.11
	L Red Nucleus	0.3850, 0.5367	0.3084	0.0177*
	L Subthalamic Nuclues	0.4148, 0.6124	0.3419	0.0305*
	R GP	0.3972, 0.5322	0.5034	0.39
	R Dentate	0.2787, 0.3834	0.3262	0.964
	R Red Nucleus	0.3832, 0.5082	0.3501	0.0561
	R Subthalamic Nuclues	0.3813, 0.6039	0.5723	0.3119
L Caudate	L GP	0.3723, 0.5521	0.3825	0.2036
	L Dentate	0.3414, 0.4993	0.2775	0.033
	L Red Nucleus	0.3294, 0.4579	0.2244	0.005**
	L Subthalamic Nuclues	0.3864, 0.5544	0.1313	<0.001***
	R GP	0.3757, 0.4722	0.5702	0.0021**
	R Dentate	0.2650, 0.3527	0.3818	0.0365
	R Red Nucleus	0.3938, 0.5170	0.2406	0.0011**
	R Subthalamic Nuclues	0.3259, 0.5097	0.3876	0.6702
R GP	L GP	0.4475, 0.5772	0.4363	0.1142
	L Dentate	0.3459, 0.4348	0.249	0.0018**
	L Red Nucleus	0.4260, 0.5331	0.4612	0.6254
	L Subthalamic Nuclues	0.4573, 0.5714	0.4682	0.2817
	R Dentate	0.3168, 0.4402	0.3224	0.1985
	R Red Nucleus	0.3702, 0.4623	0.2961	0.0055**
	R Subthalamic Nuclues	0.3847, 0.5261	0.4301	0.5728
L GP	L Dentate	0.3422, 0.4381	0.3918	0.8948
	L Red Nucleus	0.3850, 0.5250	0.3323	0.0267*
	L Subthalamic Nuclueus	0.4609, 0.6043	0.5096	0.6378
	R Dentate	0.3568, 0.4675	0.5143	0.0261*
	R Red Nucleus	0.3747, 0.5587	0.2956	0.0276*

	R Subthalamic Nuclues	0.3996, 0.5959	0.6163	0.1031
R Dentate	L Dentate	0.3621, 0.4859	0.4341	0.8738
	L Red Nucleus	0.2991, 0.4451	0.4645	0.0961
	L Subthalamic Nuclueus	0.3662, 0.5171	0.3425	0.0894
	R Red Nucleus	0.3311, 0.4501	0.5117	0.015466*
	R Subthalamic Nuclueus	0.3707, 0.5138	0.5381	0.0797
L Dentate	L Red Nucleus	0.3554, 0.4717	0.1973	<0.001***
	L Subthalamic Nuclueus	0.3908, 0.5030	0.42	0.4792
	R Red Nucleus	0.3195, 0.4383	0.5018	0.0162*
	R Subthalamic Nuclueus	0.3247, 0.4795	0.4329	0.556
R Red Nucleus	L Red Nucleus	0.3466, 0.5206	0.322	0.0934
	L Subthalamic Nuclueus	0.4089, 0.505	0.3218	0.0039**
	R Subthalamic Nuclueus	0.3568, 0.5262	0.3265	0.0798
L Red Nucleus	L Subthalamic Nuclueus	0.3542, 0.5343	0.3877	0.3785
	R Subthal Nuclueus	0.3537, 0.5063	0.3799	0.3532
R Subthal. Nuc.	L Subthal. Nuc.	0.482, 0.6404	0.5925	0.6004