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THE EFFECT OF EARLY LIFE STRESS ON BRAIN WHITE MATTER INTEGRITY AND WORKING MEMORY PERFORMANCE

A Master's Thesis

By

SEDA ARSLAN

Department of Psychology

Bilkent University

Ankara

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The Graduate School of Economics and Social Sciences
Of
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SEDA ARSLAN

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I certify that I have read this thesis and have found that it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Arts.

Prof. Dr. Timothea Toulopoulou
Supervisor

I certify that I have read this thesis and have found that it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Arts.

Assist. Prof. Burcu Ayşen Urgen
Examining Committee Member

I certify that I have read this thesis and have found that it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Arts.

Prof. Dr. Hatice Kader Karlı Oguz
Examining Committee Member

Approval of the Graduate School of Economics and Social Sciences

Halime Demirkan
Director of the Graduate School

ABSTRACT

EFFECT OF THE EARLY LIFE STRESS ON THE BRAIN WHITE MATTER INTEGRITY AND WORKING MEMORY PERFORMANCE

Arslan, Seda

M.A. in Psychology

Supervisor: Prof. Dr. Timothea Toulopoulou

August 2019

Former studies revealed that exposure to early life adversity is correlated with alterations in the white matter structure, particularly, in the areas associated with executive functioning and memory. Those alterations include both volume and microstructural white matter integrity reductions in the brain. A vast amount of the studies focused on volume reductions, and it is not clear whether the alterations in the white matter integrity is associated with cognitive functioning. The current study investigated the influence of early life stress on white matter integrity in the anterior cingulate cortex (ACC)and corpus callosum (CC) among the forty-six healthy participants. Participants were split into two groups based on the Childhood Experience of Care and Abuse Questionnaire (CECA.Q). Participants with relatively low early life stress were compared with participants with relatively high early life stress on fractional anisotropy (FA) and mean diffusivity (MD) values in the ACC and CC. Another analysis investigated the working

memory performance of the participants in the n-back task. Findings revealed that low-level early life stress did not significantly differ from high-level of early life stress in terms of FA values. However, there were significantly higher MD values in the high-level early life stress group compared to low-level early life stress group. In terms of cognitive performance, there were no performance differences between the two groups on the n-back task. The findings suggest that the high level of early life stress is associated with subtle white matter integrity changes in the brain but does not affect the performance.

Keywords: Diffusion Tensor Imaging, Early Life Stress, Working Memory Performance.

ÖZET

BEYİN BEYAZ CEVHER MADDE BÜTÜNLÜĞÜ VE ÇALIŞMA BELLEK PERFORMANSI ÜZERİNE ERKEN YAŞAM STRESİNİN ETKİSİ

Arslan, Seda

Yüksek Lisans, Psikoloji

Tez Danışmanı: Prof. Dr. Timothea Toulopoulou

Ağustos 2019

Önceki çalışmalar, erken dönemde yaşam sıkıntısına maruz kalmanın, özellikle yürütücü işlevsellik ve hafıza ile ilgili alanlarda, beyaz cevher dokusundaki değişikliklerle ilişkili olduğunu ortaya koydu. Bu değişiklikler beyindeki hem hacim hem de mikroyapısal beyaz cevher bütünlüğü azalmasını içerir. Bununla birlikte, araştırmaların büyük bir kısmı hacim azalmasına odaklanmıştır ve beyaz cevher bütünlüğündeki değişikliklerin bilişsel işlevsellik ile ilişkili olup olmadığı açık değildir. Çalışma, kırk altı sağlıklı katılımcı arasında, erken yaşam stresinin, ön singulat korteks ve korpus kallosumdaki beyaz cevher bütünlüğü üzerindeki etkisini araştırdı. Katılımcılar Çocukluk Bakım Deneyimi ve Suistimal Anketi (CECA.Q) temelinde iki gruba ayrıldı. Göreceli olarak erken yaşam stresi düşük olan katılımcılarla göreceli olarak erken yaşam stresi yüksek olan katılımcılar anterior singulat korteks (ACC) ve korpus kallosumdaki (CC) fraksiyonel anizotropi (FA) ve ortalama difüzivite (MD) değerleri bakımından

karşılaştırıldı. Başka bir analizde, katılımcıların n-back task üzerinde çalışma belleği performansı araştırıldı. Bulgular, düşük seviyeli erken yaşam stresinin, FA değerleri açısından yüksek erken yaşam stresinden önemli ölçüde farklı olmadığını ortaya koydu. Bununla birlikte, yüksek seviye erken yaşam stres grubunda, düşük seviye erken yaşam stres grubuna göre anlamlı olarak daha yüksek MD değerleri bulundu. Bilişsel performans açısından, n-back taskta iki grup arasında performans farkı görülmedi. Mevcut çalışmanın bulguları, erken yaşam stresinin yüksek seviyesinin, beyindeki beyaz cevher bütünlüğü değişiklikleriyle ilişkili olduğunu, ancak performansı etkilemediğini göstermektedir.

Anahtar Sözcükler: Çalışma Belleği Performansı, Difüzyon Tensör Görüntüleme, Erken Yaşam Stresi.

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CHAPTER 1

INTRODUCTION

1.1 A Brief Overview on Early Life Stress

Early life stress is also known as childhood trauma or maltreatment and stands for stressful events that happen before the age of 18 involving psychological, physical or sexual abuse, neglect, and bullying. Prevalence of early life adversity is high in the population. Accordingly, 10 % of the population experienced emotional abuse, 26 % experienced physical abuse, while 21 % of the population had sexual abuse in their early life period (Dong et al., 2004). Various researches revealed that early life stress often increases the risk to develop adult psychopathology and psychiatric disorders such as major depressive disorder, post-traumatic stress disorder, bipolar disorder (Calabrese, Molteni, Racagni & Riva, 2009; Pruessner et al., 2010; Heim, & Binder, 2012). Furthermore, early life adversity significantly has a deleterious effect on individuals' well-being. Accordingly, individuals exposed to early life stress were significantly associated with an enhanced risk for cardiovascular disease and strokes, especially in women population (Korkeila et al., 2010). Besides, it increases the risk of premature death. Accordingly, the study of Brown et al. (2009) in which included 17.337 participants indicated that participants who had six or more than six stressors in early life died approximately 20 years earlier than individuals without early life stress.

1.2 The Effect of Early Life Stress on Working Memory Performance

The vast amount of literature indicates that early life stress has a debilitating effect on cognitive functioning in adulthood (Irigaray et al., 2013; Lu et al., 2017; Masson, Bussières, East-Richard, R-Mercier, & Cellard, 2015). There is a growing amount of studies which investigates the relationship between early-life stress and working memory. Working memory is part of the cognitive system that enables holding information temporarily to process and manipulate the hold information (Miyake & Priti, 1999). It is closely associated with complex cognitive abilities, such as problem-solving and decision-making (Kyllonen & Christal, 1990). N-back task is one of the main well-validated working memory tasks in which participants are presented with multiple stimuli during the encoding phase, and then a response phase in which participants are required to specify whether the stimuli presented is the same as the stimuli presented in the encoding phase (Owen, McMillan, Laird & Bullmore, 2005). Recent studies demonstrated the deleterious impact of early life stress on working memory performance (Fuge et al., 2014; Majer, Nater, Lin, Capuron & Reeves, 2010; Goodman, Freeman & Chalmers, 2019; Bos, 2009). For instance, in the study of Majer et al. (2010), healthy adults who exposed to childhood adversity had poorer working memory performance. Moreover, in the study of Bos (2009), children with the early history of institutional care had impaired working memory performance compared to their peers with no history of institutional care.

It is worth noting that diffusion tensor imaging (DTI) studies shed light on the neurodevelopment of the white matter during childhood and adolescence. Majority of

the myelination is produced in the first two years, and the critical process proceeds through adolescence and adulthood (Yakovlev & Lecours, 1967). Development of the microstructure of white matter is vulnerable to environmental effect, especially during that period. During the development of the brain, remodeling of the synapse, myelination and programmed cell death are crucial processes that affect both organization of white matter and gray matter (de Graaf-Peters & Hadders-Algra, 2006). Thus, malicious experiences during this period create a possibility to disrupt the neurodevelopmental process and cognitive development (Hart & Rubia, 2012). According to both structural and functional neuroimaging research, prefrontal cortex (PFC), cingulate gyrus, and corpus callosum are essential working memory-related areas, and structural alterations in those areas are widely associated with malfunctioning in working memory performance (Owen, McMillan, Laird & Bullmore, 2005).

1.3 Relationship between Early Life Stress and Anterior Cingulate Cortex, Corpus Callosum

Early life stress considerably influences brain structure, function, and volume (Paul et al., 2008). The hypothalamic-pituitary-adrenal axis (HPA) is considered as one of the significant factors for the brain abnormalities in case of exposure to stress, and early life adversity provokes persistent alterations in the HPA axis (Juruena, 2014; Hunter, Minnis & Wilson, 2011). Briefly, the HPA axis regulates the hormonal response system to stress, and glucocorticoid is known as the primary stress hormone. The paraventricular nucleus (PVN) of hypothalamus secretes

corticotrophin-releasing factor (CRF) and arginine vasopressin (AVP) into vessels bonding hypothalamus and pituitary gland. PVN and CRF affect pituitary gland to generate and release adrenocorticotropic hormone (ACTH). ACTH leads to synthesis and secretion of glucocorticoid from the adrenal glands. In humans, the primary glucocorticoid is cortisol. Inhibitory and excitatory neurotransmitters on PVN regulates the activation of the hypothalamus to organize the glucocorticoid activity. In order to prevent extended activity, negative feedback loops regulate HPA axis to preserve prearranged hormone degrees and homeostasis. For that purpose, cortisol related negative feedback controls the release of CRF, ACTH, and AVP through the anterior pituitary gland, PVN, and hippocampus. One of the cortisol receptors is mineralocorticoid (MR), and in a stressful situation, cortisol density increases and MR binds to glucocorticoids receptors (GR) to activate them. As a result, GR ends the stress response (Stephens & Wand, 2012). Various studies on rats indicated that as well as the hippocampus, medial prefrontal cortex involving anterior cingulate have a significant role in the regulation of the glucocorticoid (Diorio, Viau & Meaney, 1993; Sullivan & Gratton, 2002; Mizoguchi, Ishige, Aburada, Tabira, 2003). For instance, according to the study of Diorio (1993), lesions on the cingulate cortex significantly enhanced the level of ACTH and corticosterone after exposure to 20 minutes of a controlled stressor. Several human studies showed the significance of the medial prefrontal cortex, including cingulate cortex on stress regulation. An experiment with adolescents who gave salivary sample following a social stress test and resting-state fMRI demonstrated a positive correlation between higher cortisol reactivity with functional connectivity in the anterior cingulate cortex (Thomason,

Hamilton & Gotlib, 2011).

Furthermore, women with medial prefrontal cortex lesion displayed higher cortisol response during the Trier social stress test (Buchanan et al., 2010). Accordingly, a study with children indicated that girls with higher cortisol reactivity to stress had disrupted white matter integrity in the right anterior cingulate cortex (Sheikh et al., 2014). In another study, smaller left ACC volumes were associated with the dysregulated HPA axis in healthy men participants (MacLullich et al., 2006). Those human and animal studies shed light on the crucial role of the cingulate cortex on the HPA axis.

Myelinated areas like cingulum, which constitutes the core part of cingulate gyrus white matter, and corpus callosum, which is a nerve tract connecting the two hemispheres of the brain, are vulnerable to effects of the early exposure to a high degree of stress hormones since it suppresses glial cells which are essential for myelination (Lauder, 1983). For instance, individuals with early life adversity demonstrated a significant deterioration in the function of the oligodendrocytes in the cingulate cortex, which is an indicator of disrupted myelination in that area. However, depressed individuals with no history of abuse during childhood show no such results. Altogether, these results show the significant influence of early life stress on myelination in the cingulate cortex (Lutz et al., 2017). There are numerous neuroimaging studies in humans to investigate the impact of early life stress on white matter morphometry in ACC and CC. Accordingly, healthy individuals who had a history of early life stress had significantly decreased ACC white matter volume

compared to healthy individuals with no history of early life stress (Cohen et al., 2006; Baker et al., 2013). Similarly, high level of early life stress was associated with decreased ACC white matter volume and with poorer spatial working memory performance (Hanson et al., 2012). Moreover, early childhood adversity rather than psychiatric disease was correlated with decreased CC size in children with post-traumatic stress disorder (Teicher et al., 2004; Teicher et al., 1997).

In opposition to morphometry studies, few studies examined the microstructural integrity of brain white matter in case of exposure to early life stress. Accordingly, young adults who had exposure to verbal abuse in early life had reduced white matter integrity in the cingulum, temporal gyrus, and left body of the fornix (Choi, Jeong, Rohan, Polcari & Teicher, 2009). Similarly, children exposed to early neglect had decreased white matter integrity in cingulum (Hanson et al., 2013). Moreover, adolescents who experienced childhood adversity had lower white matter integrity in CC and cingulum bundle (Huang, Gundapuneedi & Rao, 2012). Children and older adults who had early life stress demonstrated lower white matter integrity in the genu of the corpus callosum (Seckfort et al., 2008; McCarthy-Jones et al., 2018; Lu et al., 2013).

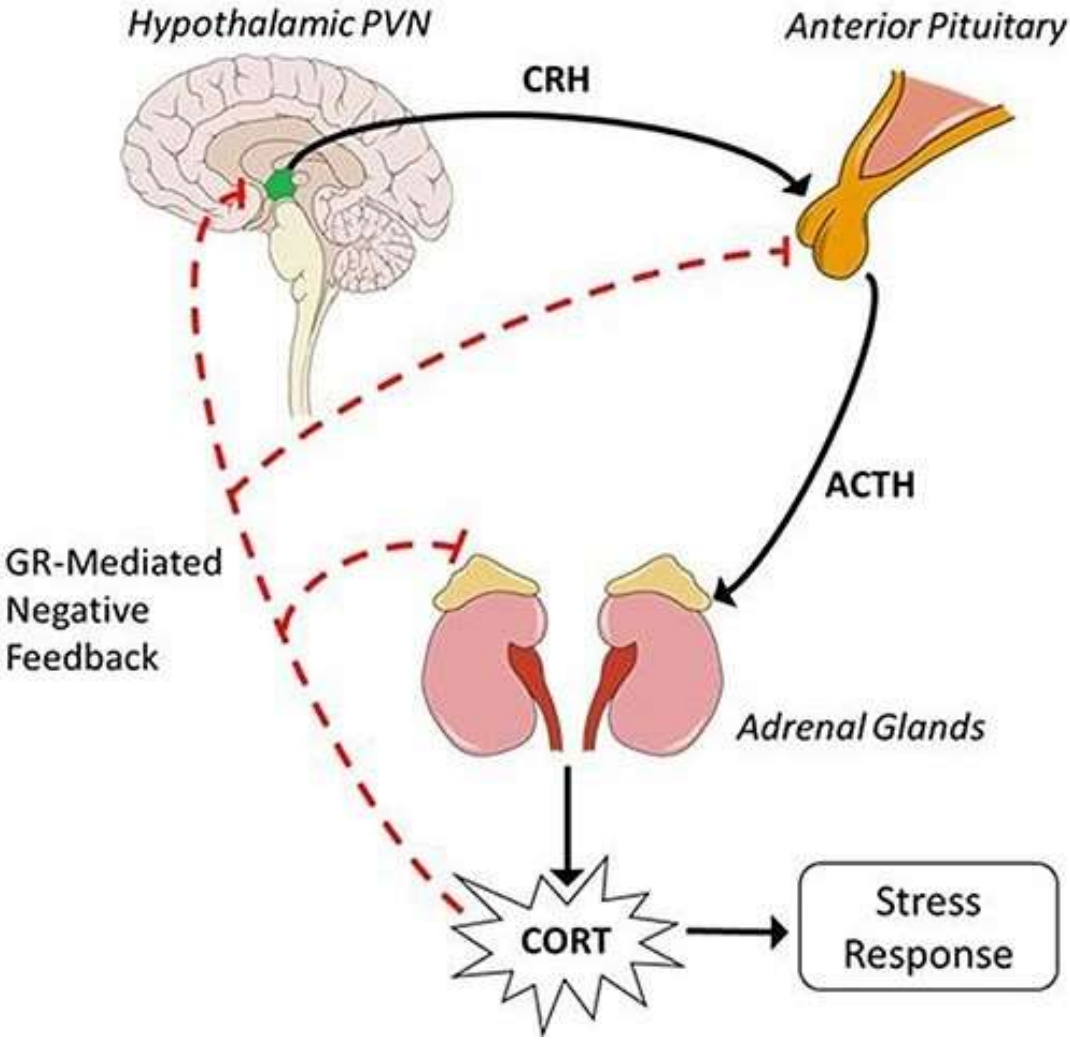


Figure 1.3. Demonstration of hypothalamic-pituitary-axis adapted from the study by Tapp et al. (2019)

1.4 The Relationship between White Matter Integrity and Working Memory Performance

White matter is responsible for connecting individual neurons in different brain areas, and it fills approximately half of the brain, and it plays a vital role in action potentials. Myelinated axons primarily constitute the main structure of white matter (Charlton et al., 2010). Several studies on aging suggested that there is a significant relationship between white matter integrity and working memory performance (Charlton et al., 2010; Zahr, Rohlfing, Pfefferbaum & Sullivan, 2009; Charlton et al., 2008; Kennedy & Raz, 2009). Similarly, children who had decreased white matter integrity had reduced performance on working memory performance (Hanson et al., 2013).

Studies with patients also have a contribution to investigate the relationship between working memory and white matter integrity. Notably, patients who are at the very early stage of multiple sclerosis had altered functional connectivity in working memory-related areas, and the alteration was related to changes of the white matter diffusivity (Au Duong et al., 2005). Similarly, multiple sclerosis patients with impaired cognition had severe reductions in white matter integrity compared to patients with preserved cognition (Hulst et al., 2013). In case of schizophrenia, severe white matter integrity reductions in the cingulum bundle and CC is demonstrated and those white matter reductions were associated with poorer working memory performance and increased reaction time (Kubicki et al., 2003; Wang et al., 2004; Kubicki et al., 2009).

1.5 A Brief Overview on Fractional Anisotropy and Mean Diffusivity

The common white matter microstructure measures are fractional anisotropy (FA) and mean diffusivity (MD) and they are measured by using Diffusion Tensor Imaging (DTI). Briefly, diffusion tensor imaging has diffusion tensors, which involves eigenvectors ($\hat{e}_1$, $\hat{e}_2$, $\hat{e}_3$) and eigenvalues (λ_1, λ_2, λ_3). In terms of FA, diffusion of the water molecules varies from 0 to 1. Value of 1 means the occurrence of the diffusion is along one axis (anisotropic diffusion), and the value of 0 means diffusion occurs along with all directions (isotropic diffusion). Axons limits the travel of the water molecules, hence, create an anisotropic diffusion. In the case of anisotropic diffusion, eigenvalues are significantly different than each other ($\lambda_1 > \lambda_2 > \lambda_3$) while in case of isotropic diffusion, they are nearly equal ($\lambda_1 \sim \lambda_2 \sim \lambda_3$). FA indicates axonal diameter, axonal density, and complexity of the fiber tracts. Mainly, reduced FA can be ascribed to deterioration of the myelin sheaths and membranes of axons (O'Donnell & Westin, 2011).

Another common scalar to investigate white matter integrity is mean diffusivity. It is calculated by averaging the eigenvalues of tensors ($(\lambda_1+\lambda_2+\lambda_3)/3$). It calculates total diffusivity in a specific tissue and depicts the average movement of the water molecules as independent of tissue directivity (Fushimi et al., 2007). Particularly, MD increase can indicate escalated tissue water or cell proliferation.

1.6 The Role of Anterior Cingulate Cortex and Corpus Callosum in Working Memory Function

Neuroimaging techniques, which comprise DTI, provided crucial information related to roles of anterior cingulate cortex and corpus callosum on cognitive processing.

The development of diffusion tensor imaging enabled scientists to examine the white matter integrity more elaborately. According to DTI studies, cingulate gyrus and corpus callosum (CC) are significant working memory-related white matter pathways (Charlton, Barrick, Lawes, Markus & Morris, 2010). Also, white matter integrity in both cingulum and CC significantly associated with working memory performance in the early adult population (Privado et al., 2014). Accordingly, healthy subjects who have lower white matter integrity in anterior cingulate demonstrated lower accuracy in 2-back working memory task (Takahashi et al., 2010). An analysis of white matter tracts with young and old adults indicated white matter integrity in the genu of CC and working memory correlations (Zahr, Rohlfing, Pfefferbaum & Sullivan, 2009). Accordingly, white matter integrity in CC and working memory performance demonstrated a significant association in children population, although the effect of age was removed (Nagy, Westerberg & Klingberg, 2004). Researches with patient groups involving subjects with multiple sclerosis, alcoholism demonstrated working memory impairments and white matter damage in the cingulum and CC (Harris et al., 2008; Dineen et al., 2009). Furthermore, children with traumatic brain injury had lower white matter integrity in CC and decreased

white matter integrity in CC predicted imperfect verbal working memory (Treble et al., 2013). According to fMRI studies, the anterior cingulate cortex is one of the significant activated areas during the working memory tasks in both children and adults (Botvinick, Cohen, Carter, 2004; Kerns et al., 2004; Lenartowicz, McIntosh, 2005; McCarthy et al., 1994; Casey et al., 1995; Nelson et al., 2000; Glabus et al., 2003). Moreover, a study combined both fMRI and DTI analysis indicated white matter integrity in the ACC and CC were correlated with fMRI activation in those areas during the working memory task (Olesen, Nagy, Westerberg & Klingberg, 2003).

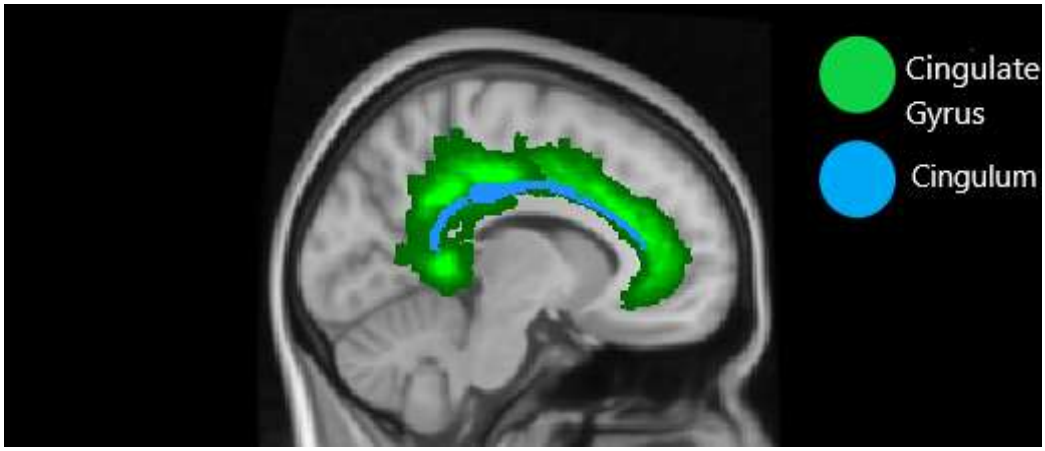
Lesion studies provide insights on the contribution of the ACC to working memory. Lesions, which involves orbitofrontal tissue together with the cingulate cortex, damaged spatial working memory performance in monkeys (Bachevalier & Mishkin, 1986).

The diagnosis of the participants exposed to early life stress is based on assessment tools, which include assessments on abuse, neglect, and household dysfunction. Childhood Abuse and Care Questionnaire (CECA-Q) is one of the extensively used tools for measuring the early life adversity within participants. It was produced and tested in UK women population with a history of abuse, depression, and neglect. Its reliability and validity are proven by several studies (Li et al., 2014; Bifulco, Bernazzani, Moran & Jacobs, 2005).

Prevailing literature suggests that white matter integrity in ACC and CC is significantly affected by early life stress and white matter integrity in those areas are

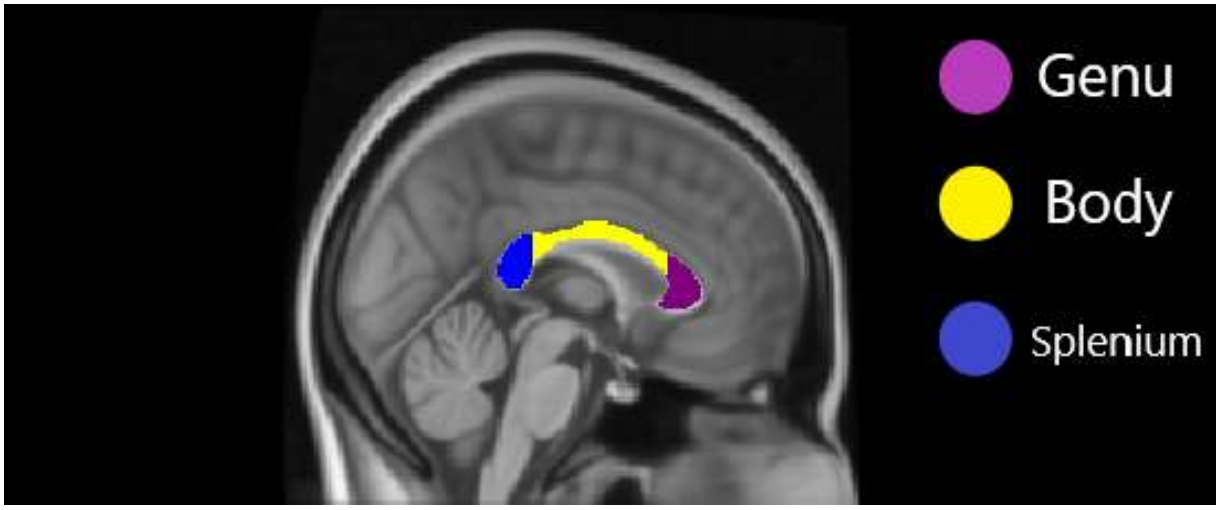
important for working memory function. There is a gap in the literature in terms of observing the interactive relationship between the effect of early life stress on the white matter integrity in ACC, CC, and working memory performance. Besides, the researches which investigated the effect of early life stress on white matter integrity mostly focused on observing the changes in the diffusivity of the water molecules in the brain (FA). Thus, this study investigates the underlying neuronal effects of early life stress on ACC and CC in a broader way by also analyzing the average movements of the water molecules in the region of interest in order to investigate more elaborately the microstructure of the tissue, and examines their relationship on the working memory performance at the exploratory level.

Based on the literature, the primary hypothesis of the current study is that early life stress is associated with decreased FA values and increased MD values in cingulate cortex and corpus callosum and since the altered white matter integrity in ACC and CC is associated with altered working memory performance as indicated above, secondary hypothesis is that early life stress is associated with a poorer working memory performance as a result of altered white matter integrity in the cingulate cortex and corpus callosum.



Note. Cingulate cortex was generated via Harvard-Oxford Cortical Structural Atlas in FSL. Cingulum was generated via JHU (John Hopkins University) white matter tractography atlas in FSL.

Figure 1.6.1. Regions of Cingulate Gyrus and Cingulum on MNI152 Standard Image



Note. Generated via JHU (John Hopkins University) white matter tractography atlas in FSL

Figure 1.6.2. Regions of Corpus Callosum on MNI152 Standard Image

CHAPTER 2

METHOD

2.1 Participants

The current study involved 46 Turkish participants. The age of the participants was between 17 and 24 (*M*= 20.15, *SD*= 2.29). 22 of the participants were male, and 24 of them were female. Participants were recruited via posters and advertisements across schools, universities, and cafes in Ankara. The prerequisite for participating in the study was a normal visual perception to be able to perceive the working memory task accurately on the screen. Before joining the study, participants had to sign a written informed consent. Legal guardians were required to sign the informed consent for the participants whose ages were under 18. Participants who completed the experiment received 50 liras. Participants with neurological or psychiatric disorders were excluded from the study.

2.2 Assessment of Early Life Stress

Childhood Care and Abuse Questionnaire (CECA.Q) assess the level of stress exposure before the age of 17. It is a comprehensive and reliable assessment of early life adversity. The instrument screens both early life adversity (ages of 0-12) and adversity during the later stages of childhood (ages of 12-16). The questionnaire consists of 3 sections which examine family arrangement (e.g., parental loss and parental separation), physical neglect, and abuse (e.g., physical abuse and sexual

abuse).

In terms of scoring, each item includes a two-point Likert scale either for yes/no questions or for three multiple-choice questions. (0 point for no, 1 point for yes, 2 point for refused to answer). ‘’Yes’’ indicates the presence of related stress factor while no indicates the opposite. For instance, ‘‘Ever had any unwanted sexual experiences’’ is a sexual abuse-related question whose answer options are yes or no.

After summing the total points of each participant, the total score of the participants whose score fell within and below the mean (*M*= 5.46) was classified as low early life stress exposure (n= 24) while scores above mean were classified as high early life stress exposure (n= 22).

In addition to CECA.Q assessment, psychological, physical abuse and bullying assessments were used to assess the severity and type of the early life adversity. In the psychological abuse assessment, participants are asked whether they had experienced humiliation, rejection before the age of 17, and if they had, they were required to provide information on the severity of the abuse (e.g. ‘0= None, 1= Some, 2=Moderate, 3= Marked’’). In the physical abuse assessment, participants are required to answer whether they experienced an attack or hitting before the age of 17 and again, the severity of the adversity is scored as alike to psychological abuse assessment. In the bullying assessment, participants are asked whether people who were similar age said hurtful things or hurtful names, ignored or hit them before the age of 17, and the same severity scores were used. Adversities were scored in a dichotomous manner in which adverse experience was either present or absent in the

individual, and the maximum score was three, which indicates participants were exposed to all three of early life adversities.

2.3 Acquisition of Diffusion-Weighted Images

Diffusion-weighted images of the entire brain were acquired by using an echo-planar imaging sequence lasting 7 minutes 22 seconds to acquire slices in sagittal (R>> L), coronal (A>>P) and transversal (F>>H) planes [repetition time (TR), 10740 ms; echo time (TE), 102 ms; slice thickness, 2 mm; b-values, 1000 s/mm^2; diffusion gradient directions, 33; field of view (FoV), 256 mm; acquisition matrix, 256 x 256; voxel size 2x2x2 mm].

2.4 Cognitive Paradigm

In the current study, working memory performance was assessed via a well-validated arithmetic n-back task. In the working memory paradigm, participants were applied numerical size tasks or more complex tasks, which involves numerical computations as well as numerical size judgments (Tan et al., 2012). Participants were given a brief presentment of the task, which informs the participants about the significant points that are required to pay attention before performing the working memory paradigm in the MRI scanner. The response phase was presented for 3 seconds, and participants were required to decide by pressing the either right or left button.

The events included a judgment task where participants were presented two-digit number during the encoding phase, and they were required to hold that information

and in the response phase, they were expected to choose the larger or smaller number based on the instruction which says choose larger or smaller remembered number , and computational judgement in which participants were required to make a numerical subtraction of 2 or 3 from the remembered number on the left or right side in the encoding phase and then, choose larger or smaller number in the response phase based on the instruction screen. Encoding phase was shown on the screen for 0.5 seconds, and a fixation point appeared for 4 seconds after it. The numbers of the correct and incorrect answers were equally spread either on the left or the right side. The total numbers of the events included ten trials.

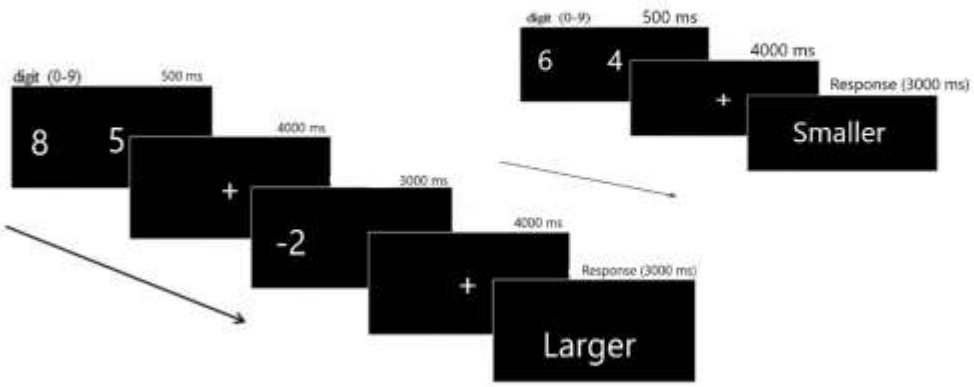


Figure 2.4. Demonstration of Working Memory Paradigm

2.5 Behavioral Data

Working memory performance was measured by using the percentage of the correct responses and analysis of the behavioral data was run in IBM SPSS Statistics version 22. Accordingly, an independent samples t-test was applied in order to check whether two stress groups (low vs. high) significantly differ from each other in terms of age and gender. Independent samples t-test was applied to check whether total CECA.Q scores of participants in both groups significantly differed. Also, a correlational analysis was run in order to investigate whether the total scores of each participant in CECA.Q assessment were significantly correlated with the score of the psychological, physical abuse and bullying scores to observe the consistency of the early life adversity reports of the participants between two assessments. Additionally, we used a frequency analysis in order to investigate the overall severity levels of early life stress. Moreover, early life adversity between 0-12 and 12-16 ages were compared via paired samples t-test in order to find whether early life stress differed for the same participants within those different age intervals. In order to investigate whether working memory performance significantly differs between the two stress groups (high vs. low), an independent samples t-test is applied. The dependent variable was working memory performance while the independent variable was the level of exposure to early life stress.

A correlation analysis was conducted to determine whether the total score of early life stress was covaried with working memory performance on the n-back task. The threshold of significance was set at 0.05.

2.6 MRI Scanner

3 Tesla Siemens Magnetom scanner was used at the Bilkent University National Magnetic Resonance Research Center (UMRAM), Ankara, Turkey to produce diffusion-weighted images and to enable the whole brain coverage; radio-frequency pulses were utilized via a 32-channel head coil. In order to protect subjects from the noise of the scanner, flexile earplugs were used and prevent the head motion of the participants, and head stabilizer cushions were applied both sides of the head. 31.5'' telemedicine LCD 59 Hz refresh rate and 1920x1080 pixel resolution monitor was utilized to present the stimuli to the participants who were lying in the scanner. To be able to bring the monitor into the visual field of the participants, a mirror was put onto the head coil. Generation of the stimulus and accuracy of the responses were provided via Neurobehavioral Systems program. Moreover, participants' responses were recorded and transferred to an excel file during the working memory task via the fiber-optic response box.

2.7 Analysis of Diffusion-Weighted Images

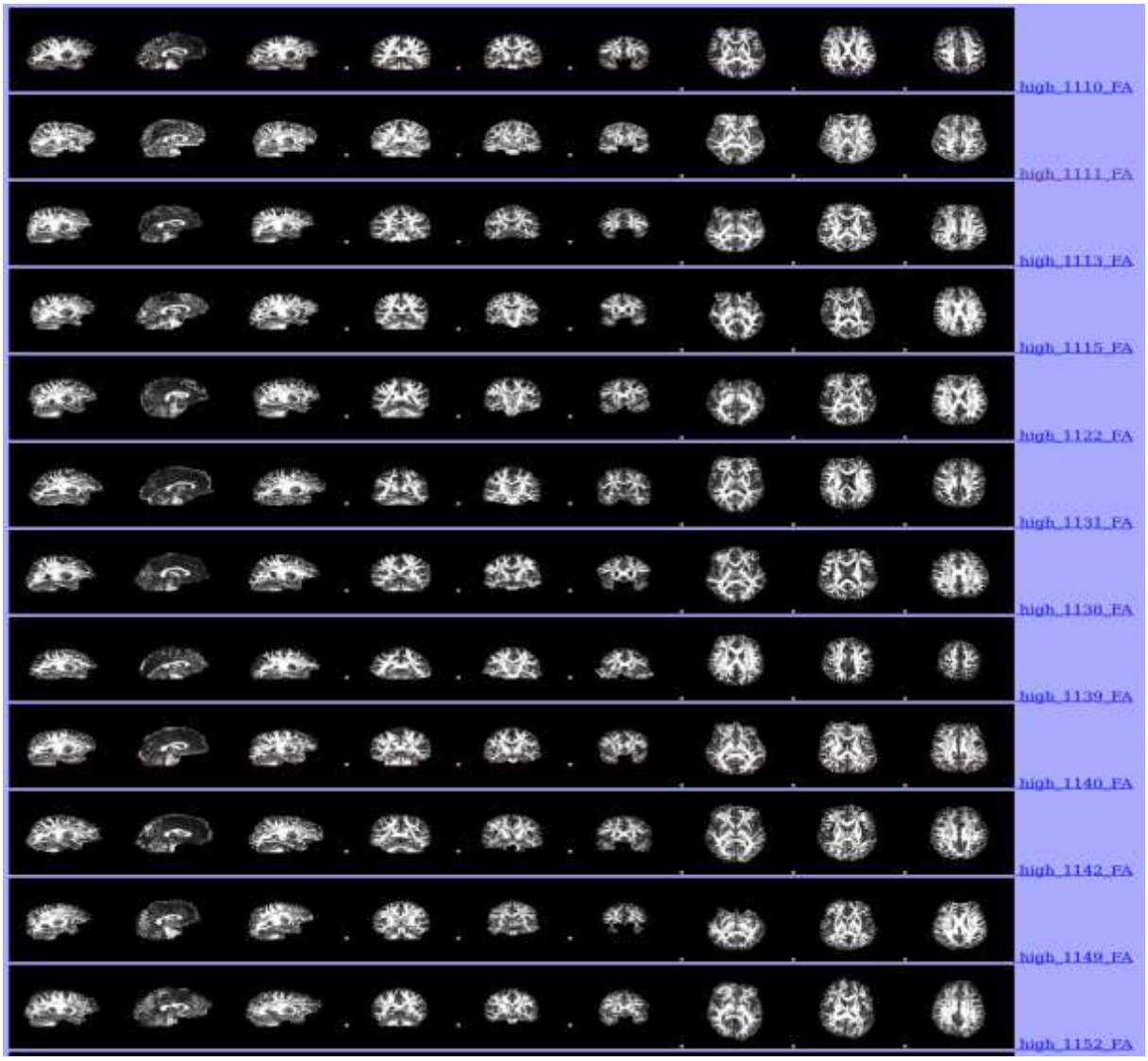
2.7.1 Preprocessing

The raw diffusion-weighted images with 33 volumes, which includes 128x128x64 voxels with 2x2x2mm resolution were stored by Snygo MR B17 software system in the computer of magnetic resonance scanner. DICOM2NII software program was used to convert to raw Dicom image files (.ima extension) into nifti (.nii extension) files to be able to continue the data analysis. Then, all data were analyzed via

FMRIB's Diffusion Toolbox in FSL 5.0 (Functional MRI of the Brain Software Library), which uses the Linux operating system. For the preprocessing step, all the diffusion-weighted images were aligned with each other to correct the head motion of the subjects and eddy current distortions by using Eddy tool. Then, a brain mask was created and non-brain tissue, such as the skull, was removed based on the binary brain mask created by BET tool in FSL. After the preprocessing steps, diffusion tensors were calculated by using b values, and finally, maps of diffusion anisotropy (FA) and mean diffusivity (MD) were generated.

Each step was individually repeated for every 46 participants in the study. In order to make group comparison, tract-based spatial statistics (TBSS) was performed. In the first step of TBSS, all the processed FA images were placed into a new subdirectory called as FA and generated a file called as *slicedir* which involved each input images respectively (see Figure 2.7.1.1 and Figure 2.7.2.1). In the second step of TBSS, individual FA images were aligned into a common 1x1x1 mm standard space (FMRIB58_FA). In the third step of TBSS, the whole aligned data were transformed into common space MNI152 (Montreal Neuroimaging Institute). The mean of affine-transformed data was averaged in order to generate mean FA, and then, skeletonized mean FA was derived from the mean FA. In the fourth step, the individual FA image values were projected onto each voxel of the skeleton for the fine alignment. The threshold value of 0.2 for the FA levels was chosen in order to prevent low mean FA regions and variability of the inter-subject (see Figure 2.7.3). Group comparison for MD analysis, MD images of each participant were gathered in the TBSS directory,

and original non-linear registration was implemented to MD data. After unifying the warped MD data of entire participants with 4D file, the revealed images were projected onto original skeletonised mean FA. As a result, we had MD images of each participant as skeletonised (see Figure 2.7.4).



Note. It enables the comparison of each participants' brain images to see whether there is a problem with the alignment and shape of the brain images and allows checking the place of each participant within the group

Figure 2.7.1.1. Automatically produced pre-processed brain images of first 12 participants in the high-level of ELS groups.

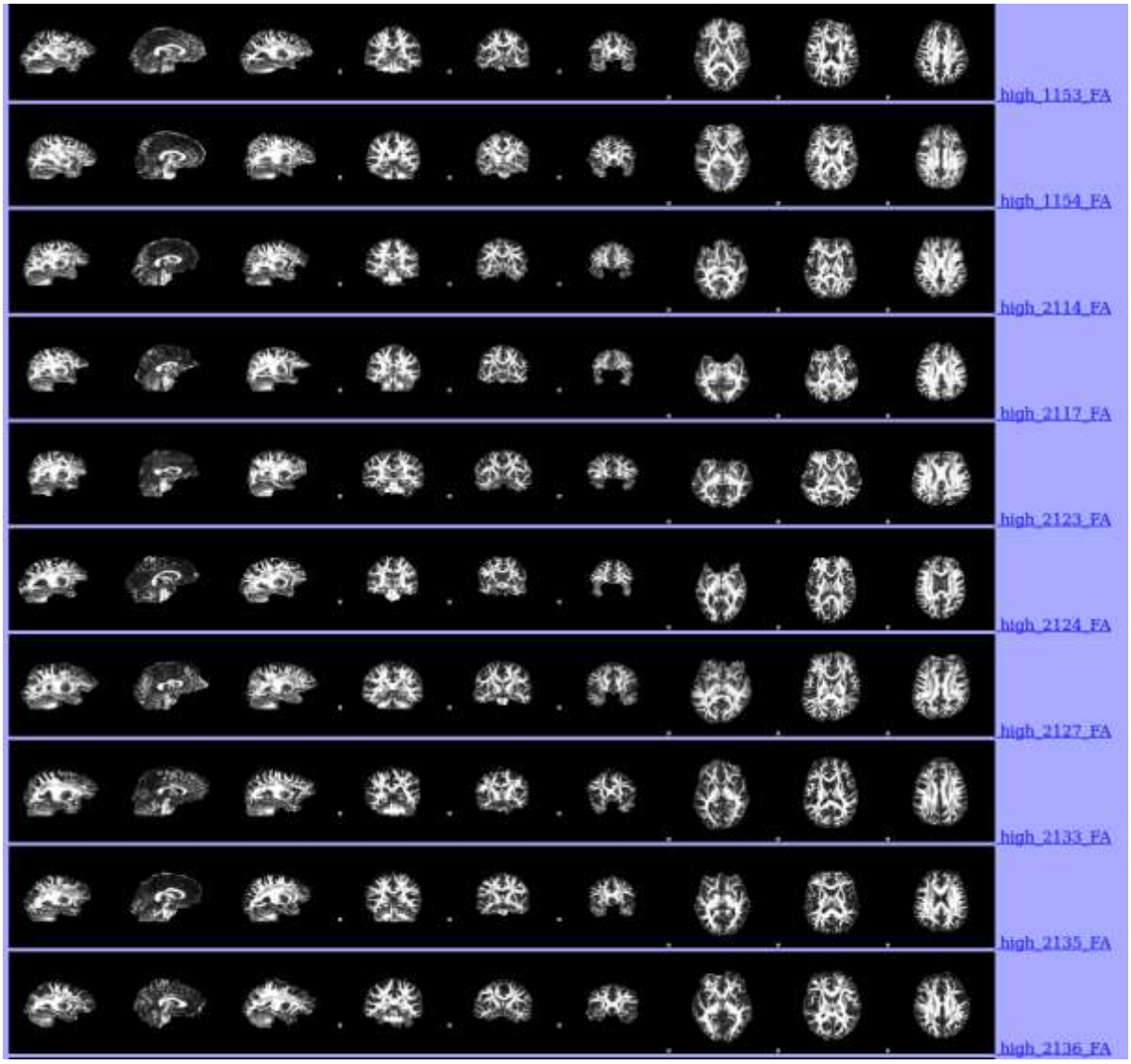


Figure 2.7.1.2. Automatically produced pre-processed brain images of last 10 participants in the high-level of ELS group

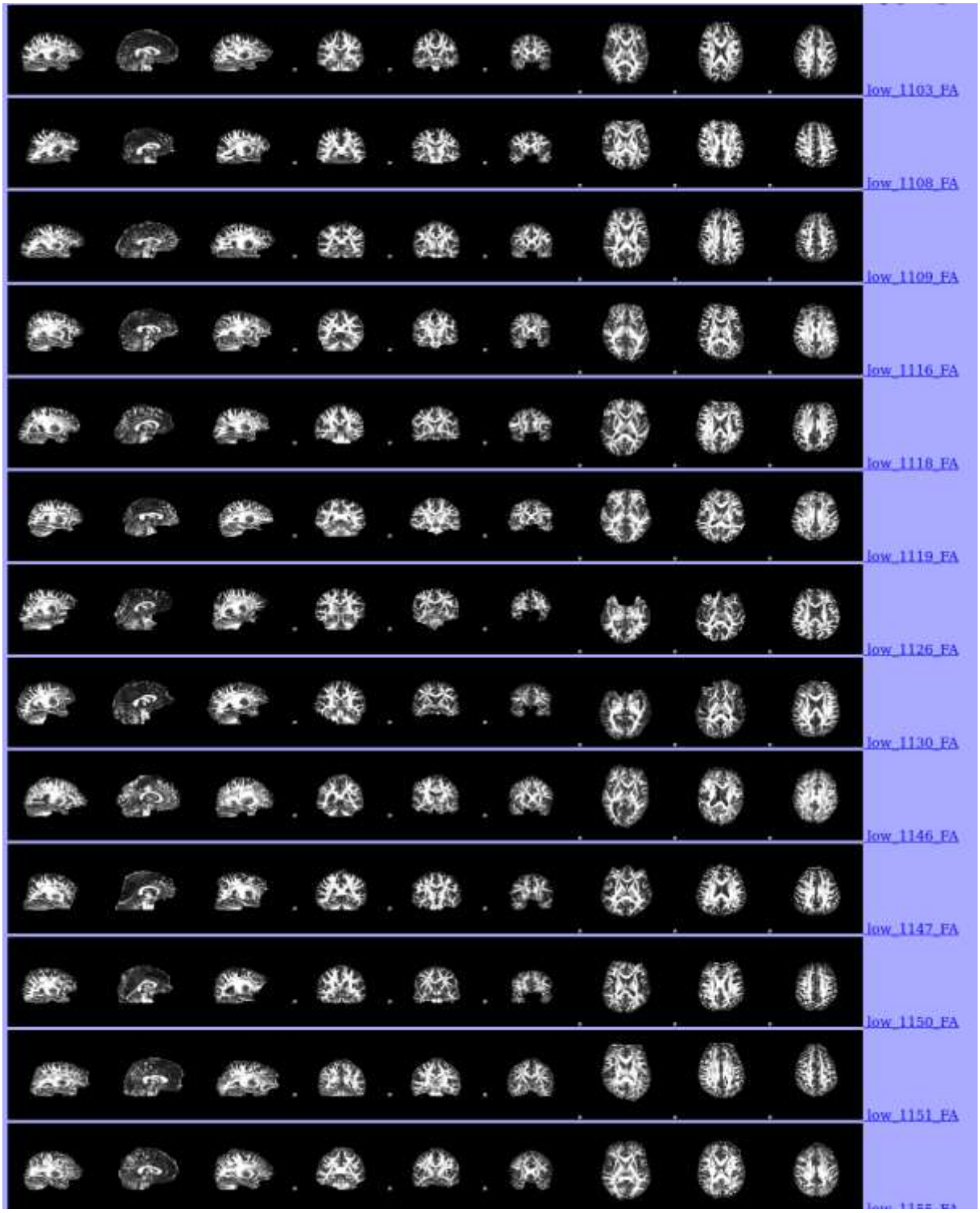


Figure 2.7.2.1. Automatically produced pre-processed brain images of first 13 participants in low-level ELS group

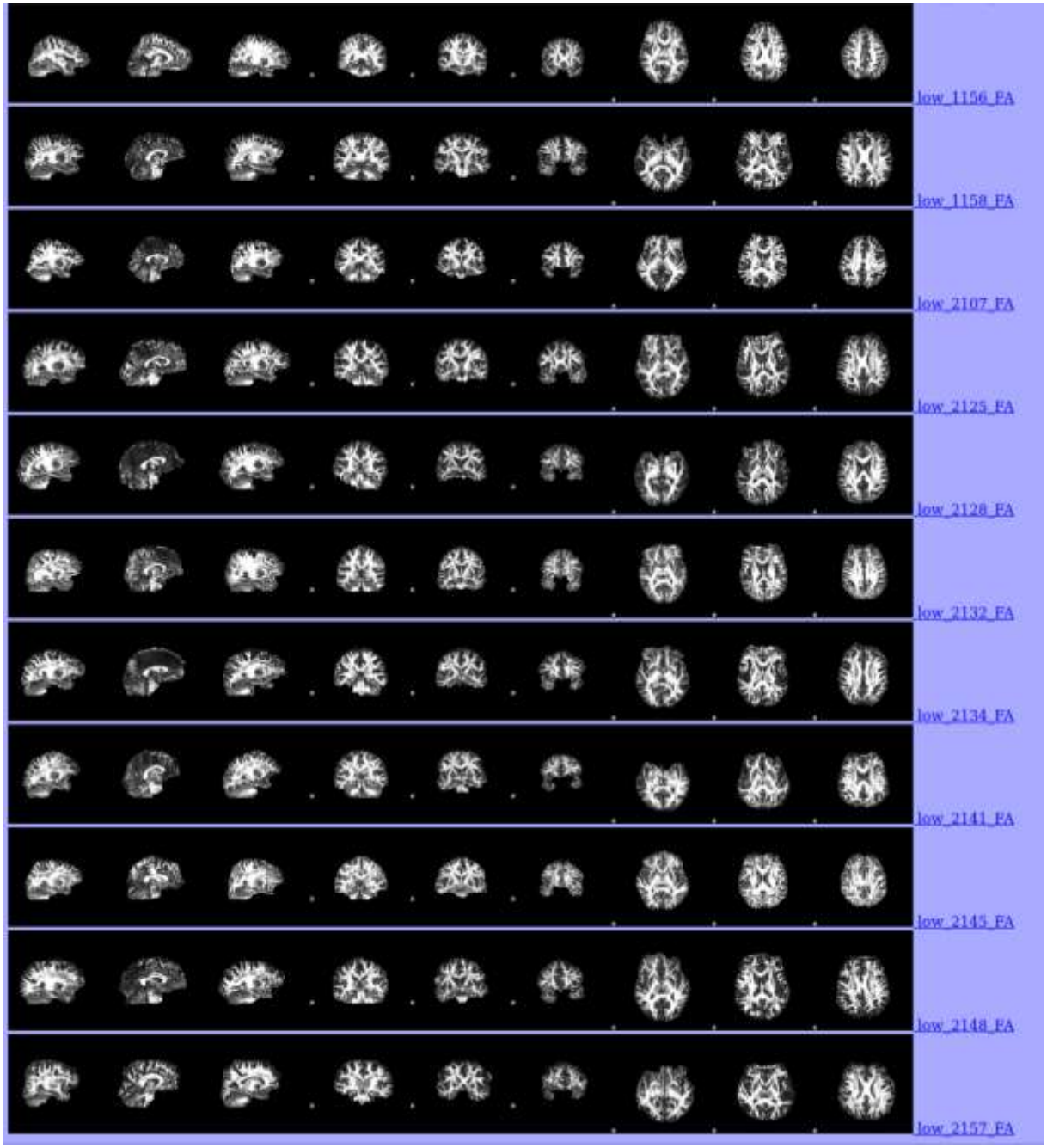
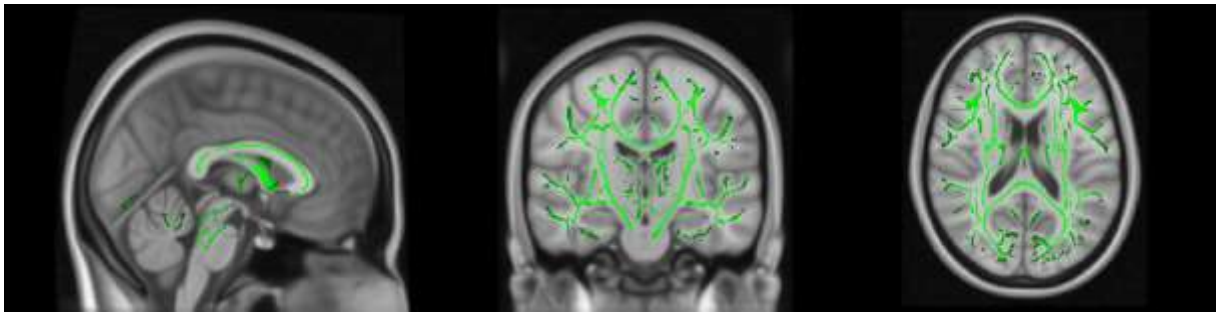
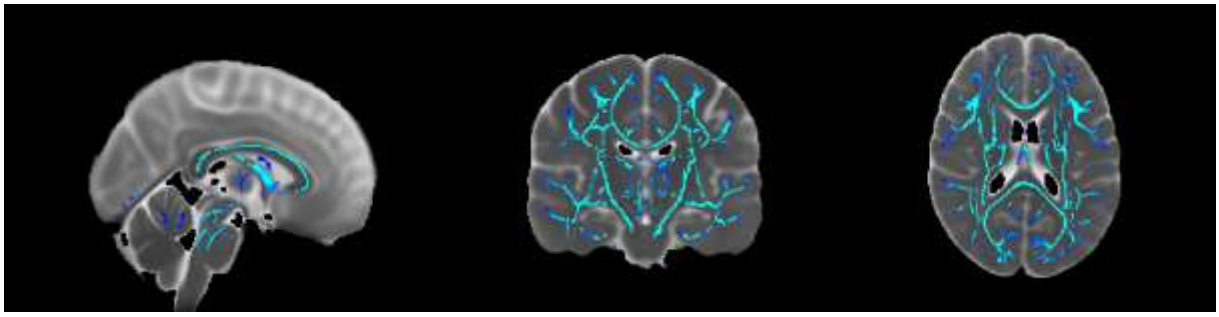


Figure 2.7.2.2. Automatically produced pre-processed brain images of last 11 participants in low-level ELS group



Note. The image depicted on standard MNI152 structural template

Figure 2.7.3. Skeletonized mean FA of the participants



Note. The image depicted on FSL_HCP1065_MD standard image

Figure 2.7.4. Skeletonised Mean Diffusivity image

2.7.2 Statistical Analysis

The skeletonised diffusion-weighted data underwent a higher-level analysis by using GLM Setup tool in FSL. It enabled to generate voxel-wise contrasts for the entire skeleton to carry out the group comparison. For the group comparison, two samples unpaired t-test was applied. The first column included the relatively high-

early life stress group, while the second column included a relatively low-early life stress group in the statistical matrix design. Moreover, a univariate GLM analysis was used to investigate whether age affects the group differences. Mean age was subtracted from each participant's age and added in the third column as a covariate in order to interpret the differences between the groups. The voxel-wise comparison was finished by using *Randomise* command in order to investigate where the significantly reduced FA and MD values were between two groups by using 5000 permutations. Family-wise error correction was carried out in the randomise command, which enabled correction for false positives. The significant clusters ($p<0.05$) were displayed by *tbss_fill* command, which shows the significant results thicker as an overlay on the white matter skeleton. Anatomic location of the region of interest was produced by using MNI Atlas, JHU ICBM-DTI-81 White Matter Labels and Harvard-Oxford Cortical Structural Atlases in FSL Atlas tool.

CHAPTER 3

RESULTS

3.1 Analysis of Behavioral Data

No significant age difference was found between relatively lower level of ELS group (*M*= 19.88, *SD*= 2.32) and relatively higher level of ELS group (*M*= 20.45, *SD*= 2.28) as a result of independent sample t-test analysis (t(44) = -0.851, *p* = 0.399). No significant gender differences between two groups (relatively lower ELS vs. relatively higher ELS) were found as a result of independent sample t-test analysis (t(44) = 0.86, *p* = 0.394). Independent samples t-test also indicated that the total CECA-Q assessment scores of participants in low-level early life stress group (*M* = 2.42, *SD* = 1.58) were significantly lower than the total CECA-Q assessment scores of the participants in the high-level early life stress group (*M* = 8.77, *SD* = 2.11; t(44)= -11,59 *p* = 0.00). Moreover, Pearson correlation analysis revealed a strong positive correlation between total score in CECA.Q assessment (*M*= 5.46, *SD*= 3.69) and total score in psychological, physical abuse and bullying assessment (*M*= 1.09, *SD*= 0.93; r(44)= 0.54, *p*< 0.01). According to frequency analysis, 13% of the participants had marked level psychological abuse, 2% of the participants had marked level physical abuse and 13% of the participants experienced marked level bullying (see Table 3.1.1). Moreover, early life adversity between 0 to 12 years old (*M*= 2.50, *SD*= 1.94) and early life adversity between 12 to 16 years old (*M*= 2.32,

SD=1.68) were compared via paired samples t-test. We found a significant positive correlation between two age intervals (r(44) = 0.76, $p < 0.001$), and no significant mean difference between two groups (t(43) = 0.95, $p = 0.34$; see Figure 3.1.1).

We found no significant difference in working memory performance between higher level early life stress group (*M*= 90.87, *SD*= 3.35) and lower level early life stress group (*M*= 92.13, *SD*= 1.72) as a result of independent samples t-test (t(44)= 1.62, *p*= 0.11). Moreover, Pearson correlation analysis showed no correlation between working memory performance (*M*=91.52, *SD*=2.67) and total score of each participant in CECA.Q assessment (*M* = 5.28, *SD* = 3.89; r(44) = -0.13, *p* = 0.36).

Table 3.1.1. The number and the percentage of the severity of the early life adversity types in the subject population

Severity	**Type of the Adversity [n (percentage)]**		
	Psychological Abuse	Physical Abuse	Bullying
None	32 (69.6%)	33 (71.7%)	23 (50%)
Some	2 (4.3%)	4 (8.7%)	9 (19.6%)
Moderate	5 (10.9%)	8 (17.4%)	8 (17.4%)
Marked	7 (15.2%)	1 (2.2%)	6 (13%)

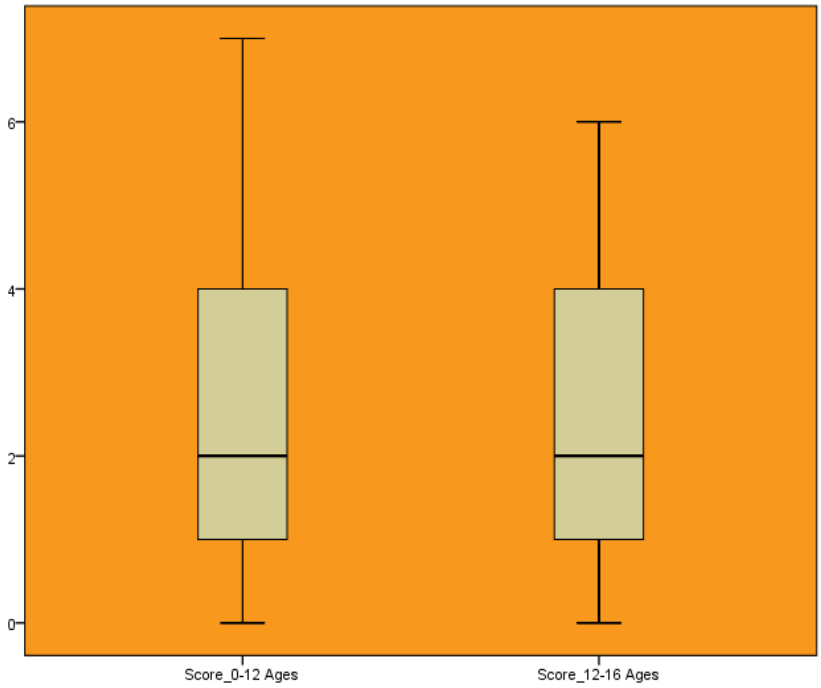


Figure 3.1.1. The comparative boxplot illustrates the CECA.Q scores between two age intervals

Table 3.1.2. Descriptive statistics and results of working memory accuracy

	Low-ELS			High-ELS				
	N	*M*	*SD*	*N*	*M*	*SD*	*F*	*p*
Age	24	19.88	2.32	22	20.45	2.28	0.72	0.39
Gender (Females)	14			10				
Working Memory Performance	24	92.13	1.72	22	90.87	3.35	2.63	0.11

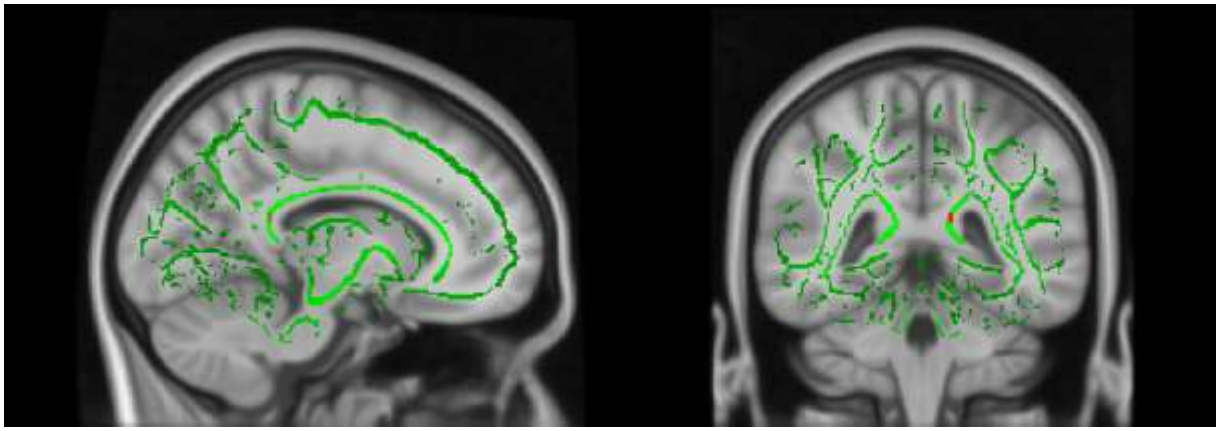
3.2 Tract-based Spatial Statistics Results

In order to investigate the white matter integrity differences in anterior cingulate cortex and corpus callosum between two groups (low level of ELS vs. high level of ELS), an unpaired two-sample t-test was applied in GLM analysis. We found no significant differences between high level of ELS (M= 0.385, SD= 0.14) compared to low level of ELS group in terms of FA values (M= 0.387, SD= 0.28; (t(44)= 0.32, p= 0.74); see Figure 3.2.1 and Table 3.2.1 for coordinates). As a result of Univariate GLM Analysis, age did not affect the group difference in terms of FA values in the region of interests. In other words, we found no significant difference between two groups whilst adjusting age as covariate (F(1,44)= 0.048, p= 0.82, see Figure 3.2.3 and Table 3.2.3 for coordinates).

Correlation analysis indicated a non-significant correlation between FA values of each participant (M= 0.38, SD = 0.022) and working memory performance (M = 91.52, SD = 2.67; r(44) = 0.13, p = 0.38).

High-level ELS group significantly differed from the low-level ELS group in terms of MD values as a result of unpaired two-sample t-test. MD values in high level ELS group (MD=0.00069, SD=0.00008) was significantly higher than low level ELS group (M= 0.00064, SD= 0.00005, p< 0.031; see Figure 3.2.2, see Table 3.2.2).

Moreover, correlation analysis showed no significant correlation between MD values of each participants (M= 0.00067, SD= 0.00007) and working memory performance (M= 91.52, SD= 2.67; r(44)=0.72, p=0.64).

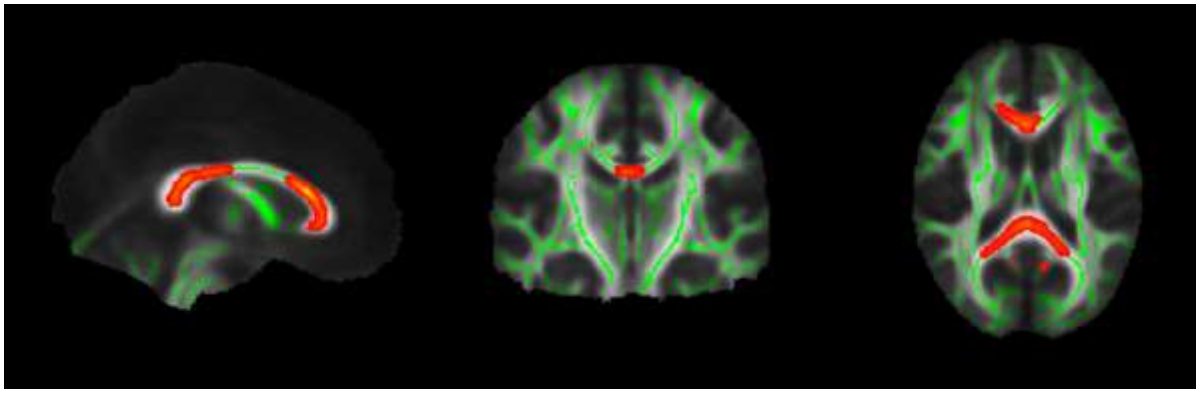


Note. Green indicates the mean FA skeleton. FA reduction clusters depicted on standard MNI152 structural template. Red-orange demonstrates clusters of voxels (FWE corrected for multiple comparisons) with reduced values in high-ELS compared to low-ELS. Abbreviations: FA= fractional anisotropy; ELS= Early life stress; FWE= Family-wise errors

Figure 3.2.1. Insignificant FA value differences in the splenium of corpus callosum between high-level of ELS and low-level of ELS groups

Table 3.2.1. The location of insignificant lower FA values

Lower FA Values	x	y	z
Splenium of Corpus Callosum	-10	-42	-17

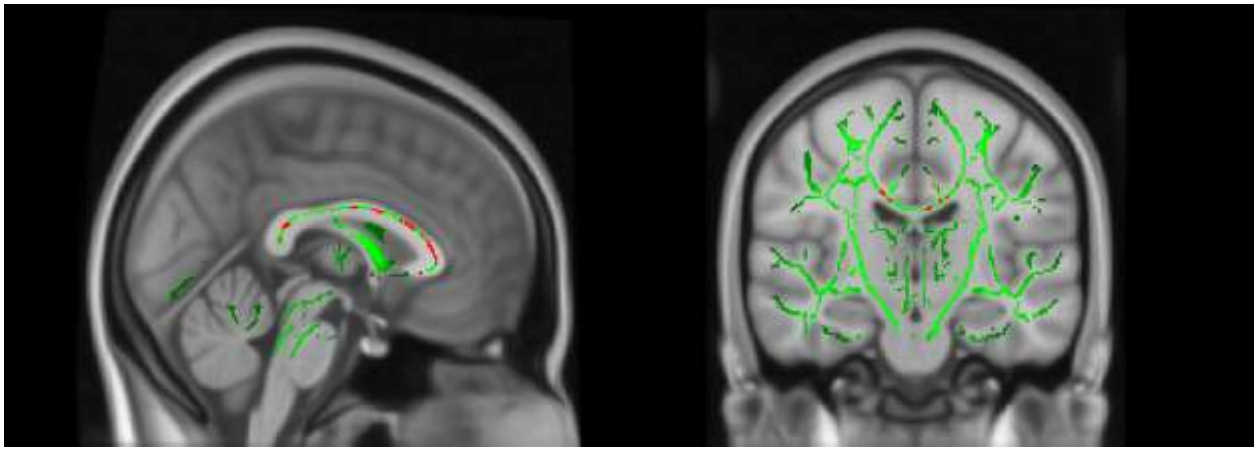


Note. Green demonstrates mean FA skeleton superimposed on mean FA image. Red-orange indicates significant clusters of voxels (FWE corrected for multiple comparisons at $p < .05$) with higher values in high-ELS compared to the low-ELS group.

Figure 3.2.2. Group difference depicting increment of MD values in the region of interest

Table 3.2.2. Coordinates of the significant MD values

MD Clusters	Anatomical Definition of Location of the Cluster	x	y	z
7	Right Cingulum (Cingulate Gyrus)	11	-31	34
8	Right Superior Corona Radiata	17	14	30
9	Right Cingulum (Cingulate Gyrus)	9	12	30
10	Body of Corpus Callosum	18	12	32
11	Genu of Corpus Callosum	1	17	0
12	Left Posterior Corona Radiata	-17	-37	38
16	Body of Corpus Callosum	1	11	23
18	Left Cingulum (Cingulate Gyrus)	-10	-48	25
19	Body of Corpus Callosum	18	-18	36
20	Body of Corpus Callosum	17	19	26
21	Splenium of Corpus Callosum	-14	-50	20
30	Genu of Corpus Callosum	2	21	17
31	Body of Corpus Callosum	1	-19	25



Note. Green indicates the mean FA skeleton. FA reduction clusters depicted on standard MNI152 structural template. Red-orange demonstrates clusters of voxels (FWE corrected for multiple comparisons)

Figure 3.2.3. Insignificant FA value differences between groups while age is covaried

Table 3.2.3. The coordinates of the insignificant lower FA values while age is covaried

Lower FA Values	x	y	z
Cingulum (Cingulate Gyrus) L	-6	-5	36

CHAPTER 4

DISCUSSION AND CONCLUSION

The current thesis primarily aims to assess whether participants with a higher level of early life stress had altered white matter integrity in the anterior cingulate cortex and corpus callosum. A secondary aim was to assess whether decreased white matter integrity in anterior cingulate cortex and corpus callosum was associated with differences in the working memory performance between two groups. Although there are studies which demonstrated the decreased white matter in the related areas, those studies mostly focused on the macrostructural alterations in the white matter, and there are few studies which focused on microstructural white matter alterations in the region of interest and its effect on the cognitive performance. As a result, the current study indicated that exposure to the high level of early life stress before the age of 17, did not significantly affect the FA values but revealed significantly increased MD values in the cingulum, the corpus callosum, and superior corona radiata. The level of the ELS was not associated with working memory performance.

In terms of mean diffusivity alterations, high level of ELS group significantly had higher MD values compared to low-level ELS group in the corpus callosum, anterior corona radiata, and cingulum. Previous DTI studies related to the development of the white matter integrity during childhood and adolescence indicated that MD continues to decrease in a normal developing brain at this period (Tamnes, Roalf, Goddings &

Lebel, 2018). Alterations in MD might indicate a variance inside of intra and extracellular space and decrease in neuropil (Selemon & Goldman-Rakic, 1999) or altered boundaries which limit the movement of the water molecules such as cell membranes (Bosch et al., 2012). Thus, increased MD values in the current study might reflect an abnormal white matter integrity development as a consequence of exposure to stressful events in early life. The results of the current study were consistent with the study by Teicher et al. (2010). According to their research, subjects exposed to verbal abuse in school years had higher MD values in the corpus callosum and the corona radiata. Moreover, the level of verbal abuse exposure was correlated with elevated MD values in those areas (Teicher, Samson, Sheu, Polcari & McGreenery, 2010).

The result might be explained via the exacerbation of the inflammation in the brain. Precisely, stress causes glucocorticoid release through activating the HPA axis. Glucocorticoids can influence the neuro-inflammation by increasing the circulation of the pro-inflammatory molecules (Marsland, Walsh, Lockwood & John-Henderson, 2017), and stress seems to increase the inflammatory state by increasing the secretion of the pro-inflammatory molecule and then, inflammation engenders water increases in the tissue, hence, causes increased mean diffusivity. A recent study indicated that children who had early life stress showed continued elevated inflammatory levels in adulthood (Danese, Pariante, Caspi, Taylor & Poulton, 2007). Consequently, findings of the present study might suggest that the stress level in the high-ELS group was sufficient to affect neuro-inflammation by altering the release of the glucocorticoids

as a response to stress. Unlike MD values, a weak association between FA values and circulation degrees of inflammatory cytokine interleukin-6 was revealed in the study by Molesworth et al. (2014).

In terms of the fractional anisotropy alterations in the white matter integrity, the data may suggest that axonal or myelination outcomes of early life stress may not be apparent in healthy participants until a threshold of the severeness is attained. In the study by Kim et al. (2005), patients with post-traumatic stress disorders (PTSD) had lower FA values in the anterior cingulate cortex, and the decrease level of the white matter integrity was related to the severity level of the PTSD symptoms. Furthermore, research by Sara et al. (2018) revealed that major depressive disorder patients who experienced early life stress had reduced FA values in the cingulum and corpus callosum compared to healthy patients exposed to early life stress. As indicated above, while the participants in this study experienced ELS, none of them were currently having any psychological problem at the clinical level as a result of ELS, this may also indicate that participants might be moderately resilient to stress.

Besides, different stressors have different structural and functional consequences. Especially, emotional abuse and sexual abuse are early life stress events that are considered to have more harmful impacts on the brain development. In the study of Hanson et al. (2013), children who experienced early life adversity had lower FA values in anterior cingulate cortex and disruptions performance in the working memory, however, the population in the study included children who grew up in the institutionalized settings, hence, they had insufficient one to one interaction with the

care-provider, inadequate amount of toy, inadequate linguistic stimulant, and nutrition. Additionally, children exposed to early deprivation had reduced FA values and increased MD values in cingulum. Also, the time of the exposure to early deprivation shown a reverse association with FA values, but independent from MD values (Kumar et al., 2014). Each of these severe experiences may significantly influence the brain structure, especially in the developmental period. Thus, the severity of the adverse experiences in early life might play a key role in fractional anisotropy alteration, which, as discussed before, is an index of myelination. In the present study, overall ELS severity was low, specifically, 15.2% of the participants experienced marked level psychological abuse, and 13% of the participants had marked level bullying while 2.2% of the participants had marked level physical abuse experience. Thus, because of the small sample size, the effect of the severity of the early life adversity could not be analyzed; thus, it requires further analysis.

Another essential factor for changes in fractional anisotropy values might be social support. It is considered as the central preservative agent against the neurobiological and mental influence of early life adversity. In the study of Leicht-Deobald et al. (2018), participants with ELS who have high social support from work environment showed lower stress reactivity to psychosocial stress test. Moreover, there are studies which indicated that social support was significantly correlated with decreased cortisol levels in saliva as the reaction to acute stress (Ditzen et al., 2008; Heinrichs, Baumgartner, Kirschbaum & Ehlert, 2003; Eisenberger, Taylor, Hilmert & Lieberman, 2007). Furthermore, research by Rosal et al. (2004) suggested that social

support in daily life can have a favorable influence on the HPA axis. Accordingly, 81.39% of our participants had social support either from adults or peers. Thus, it could have protected the participants from having altered white matter integrity as assessed by FA values.

In terms of working memory performance, the results of the present study are consistent with the study by Seckfort et al. (2008) which examined working memory performance in a population with early life stress whose ages varied between 8 and 73 years old. Their results showed no difference in the memory performance when compared to the control group with no childhood adversity, although they found decreased white matter integrity in the corpus callosum. Thus, early life stress might create subtle alterations on the brain structure but not on the function.

In the current thesis, grouping method was double-checked by using psychological, physical abuse, and bullying assessment. Total scores in CECA.Q assessment were correlated strongly (0.54) with scores in psychological, physical abuse, and bullying assessments. It means that when the rating of the participants increased in CECA.Q assessment, their score increased in another assessment accordingly. Thus, it shows the reliability of the grouping method in the current experiment.

The CECA.Q assessment enabled us to investigate the early life stress experiences of the participants between age 0-12 and 12-16 in order to investigate whether early life stress differed for the same participants within those different age intervals and results indicated that life experiences in age interval of 0-12 are approximately similar with age interval of 12-16.

The first limitation of the current study was small sample size. We found insignificant lower FA values in the splenium of the corpus callosum area of the high-level ELS group. That area might not reach a significant level because of the small sample size, which may cause the reflection of the type-II error. Thus, the small sample size should be considered as an essential factor while interpreting the results. Another limitation was that early life experiences in this study were based on the retrospective reports. Hence, it is vulnerable to subjectivity bias in the comprehension of early life experiences. Objective measurements like medical reports and saliva analysis would be involved in the future study.

As a conclusion, the high level of early life stress was associated with higher mean diffusivity in the left and right cingulum and corpus callosum. However, high-level early life stress had no significant influence on fractional anisotropy values in those areas and did not cause the distortions in the working memory performance. Psychiatric disorders and cognitive abnormalities presumably occur because of the convergence of the genetic vulnerability and early-life adversity in the critical development period (Andersen & Teicher, 2008).

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APPENDIX A

Figures

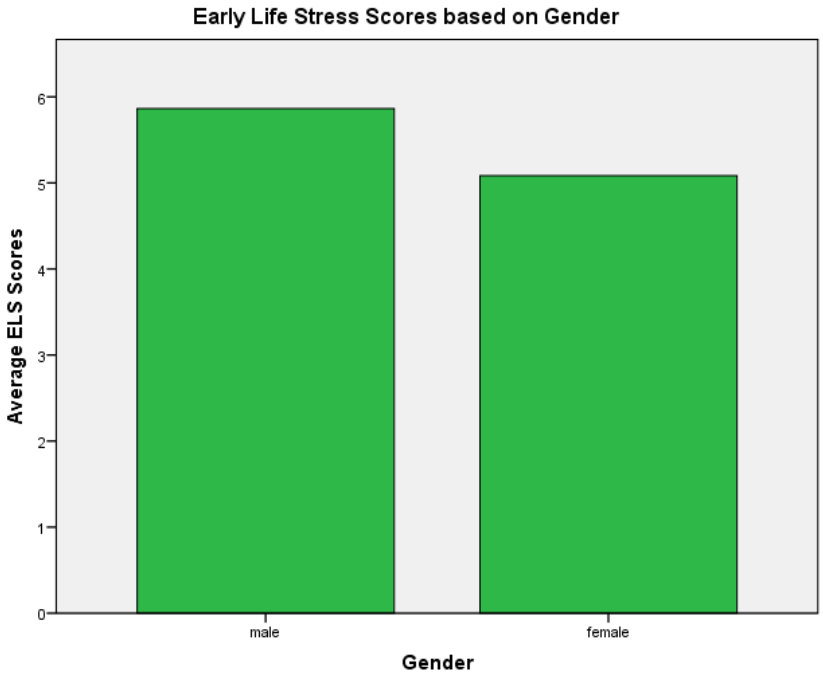

Figure A.1. Bar plots of average CECA.Q scores based on gender

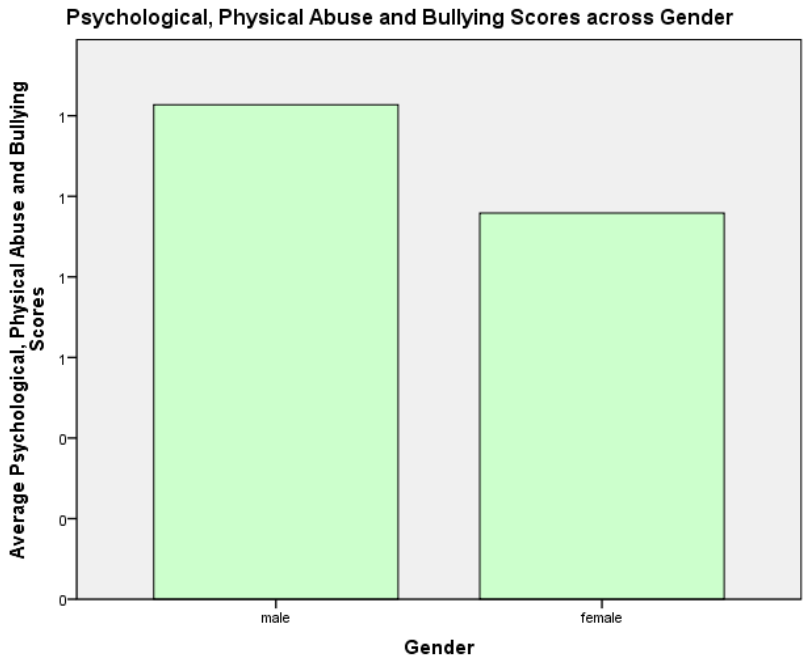

Figure A.2. Bar plots of average psychological, physical abuse and bullying assessment scores based on gender

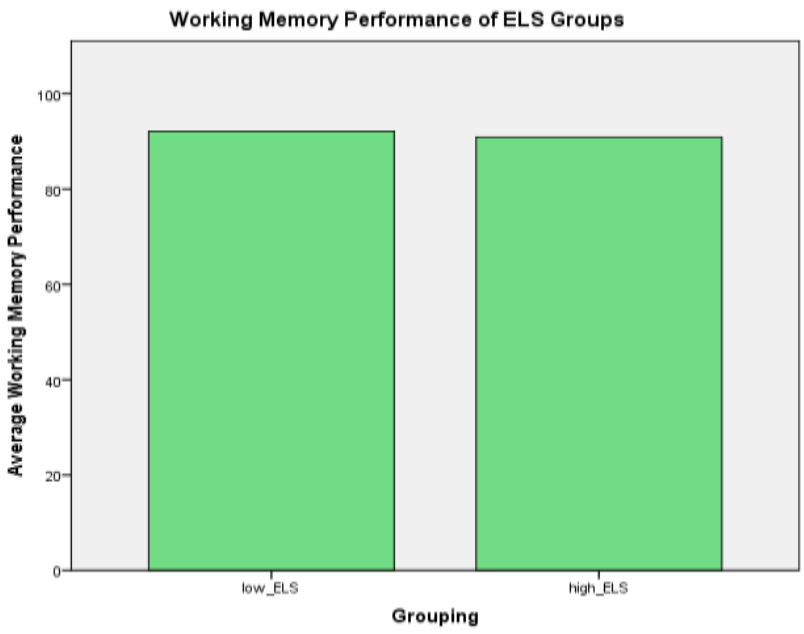

Figure A.3. Bar plots of average n-back task performance scores between low-level early life stress and high-level early life stress groups

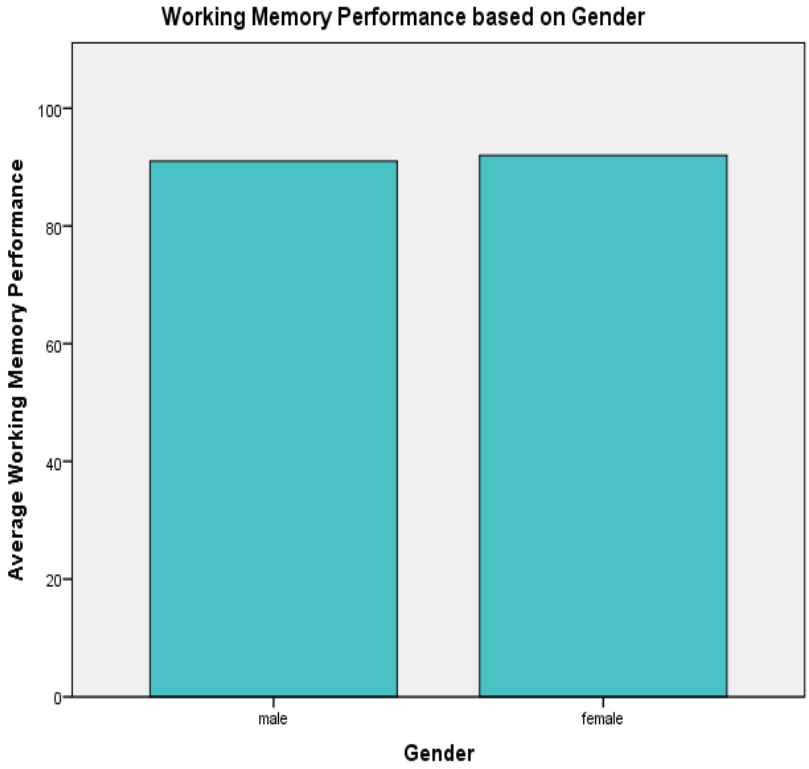

Figure A.4. Bar plots of average n-back task performance scores based on gender