EFFECTS OF RECREATIONAL CANNABIS USE AND SUBCLINICAL PSYCHOSIS RISK ON BRAIN WHITE MATTER INTEGRITY AND STRUCTURAL CONNECTIVITY IN ADOLESCENCE

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Effects of Recreational Cannabis Use and Subclinical Psychosis Risk on Brain White Matter Integrity and Structural Connectivity in Adolescence

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

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ABSTRACT

EFFECTS OF RECREATIONAL CANNABIS USE AND SUBCLINICAL PSYCHOSIS RISK ON BRAIN WHITE MATTER INTEGRITY AND STRUCTURAL CONNECTIVITY IN ADOLESCENCE

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The impact of cannabis use on the psychosis risk in the healthy population has been less examined in the literature. Furthermore, previous diffusion tensor imaging and structural connectivity studies investigating the effects of cannabis use and psychosis risk offer contradictory results. To address these gaps and inconsistencies in the literature, the author examined whether recreational use of cannabis increases the risk of subclinical psychosis. The author further examined the relationship between recreational cannabis use, subclinical psychosis, and white matter microstructure or structural network connectivity. Twenty-five adolescent cannabis users and 25 demographically matched controls participated in the study. The Cannabis Experience Questionnaire (CEQ) was used to assess cannabis consumption. Subclinical psychosis was evaluated with the Community Assessment of Psychic Experience (CAPE-42) questionnaire. While ROI-based Tract Based Spatial Statistics (TBSS) was used to examine white matter integrity in specified region of interests, Structural Connectivity Analysis was performed to examine brain structural topology. White matter integrity was assessed by four diffusion tensor derived measures: fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity, while structural network topology was examined by several graph-theory metrics: global efficiency, local efficiency and clustering coefficient. In order to eliminate possible confounding effects of alcohol and tobacco use, weekly alcohol and daily tobacco consumption were also considered. The findings revealed that cannabis users scored higher on subclinical psychosis compared to non-users. ROI-based TBSS analysis indicated that cannabis use and subclinical psychosis do not affect white matter integrity in corpus collosum and superior longitudinal fasciculus. Similarly, the network connectivity parameters were not affected by the recreational cannabis use and psychosis risk. These

results might indicate that recreational cannabis use increases the psychosis risk in adolescence, but that recreational cannabis use and subclinical psychosis risk together do not affect white matter microstructure and topology.

Keywords: cannabis use, subclinical psychosis risk, diffusion tensor imaging, network connectivity.

ÖZET

ERGENLİK DÖNEMİNDE EĞLENCE AMAÇLI ESRAR KULLANIMININ VE SUBKLİNİK PSİKOZ RİSKİNİN, BEYNİN BEYAZ MADDE BÜTÜNLÜĞÜNE VE YAPISAL BAĞLANTISINA ETKİSİ

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Literatürde sağlıklı populasyonda esrar kullanımının psikoz riskine etkisini araştıran az sayıda çalışma bulunmaktadır. Ayrıca, önceki difüzyon tensor görüntüleme ve yapısal bağlantıyı araştıran çalışmalar metodolojideki çeşitlilikler sebebiyle tartışmalı bulgular ortaya koymaktadır. Bu tez literatürdeki eksiklikleri tamamlayabilmek amacıyla 1) esrar kullanımının klinik düzeyde olmayan psikoza bir etkisinin var olup olmadığını; 2) kronik olmayan esrar kullanımının ve psikoz riskinin birlikte beyin beyaz madde bütünlüğü ve yapısal bağlantısı üzerinde bir etkisinin olup olmadığını araştırmaktadır. Çalışmaya ergenlik ve genç yetişkinlik dönemlerinde olan 25 esrar kullanıcısı ve hayatında hiç esrar deneyimlememiş 25 katılımcı katılmıştır. Bu çalışmada bölgesel Trakt Tabanlı Mekansal İstatistik ve Yapısal Network analizleri yapılmıştır. Beyin beyaz madde bütünlüğünü inceleyebilmek amacıyla fraksiyonel anizotropi (FA), ortalama difüzivite (MD), axiyel (AD) ve radial difüziviteyi kapsayan difüzyon tensor ölçütleri elde edilirken, yapısal bağlantıyı değerlendirebilmek amacıyla yapısal bağlantı parametreleri (genel etkililik, lokal etkililik ve kümeleme katsayısı) incelenmiştir. Esrar kullanımı, Esrar Deneyim Ölçeği ile değerlendirilmiştir. Klinik anlamda olmayan psikozu değerlendirmek amacıyla Toplumda Psişik Yaşantıları Değerlendirme Ölçeği (CAPE-42) kullanılmıştır. Alkol ve tütün kullanımının olası bozucu etkilerini engelleyebilmek amacıyla, haftalık alkol ve gündelik sigara tüketimi göz önünde bulundurulmuştur. Sonuçlar, esrar kullanımı olan grubun kullanmayanlara kıyasla daha fazla subklinik psikoz riskine sahip olduğunu ortaya koymaktadır. Trakt Tabanlı Mekansal İstatistik (TBSS) analizinin sonucuna göre, esrar kullanımının ve klinik anlamda olmayan psikoz riskinin korpus kallozum ve

superior longitudinal fasikulus bölgesindeki beyaz madde bütünlüğüne bir etkisi bulunmamaktadır. Benzer şekilde, yapısal network parametreleri üzerinde esrar kullanımı ve psikoz riskinin bir etkisi gözlemlenmemiştir. Bu sonuçlar ergenlik döneminde kronik anlamda kullanılmayan esrarın subklinik psikoz riskini arttırabildiğini ancak esrar kullanımı ve psikoz riskinin birlikte beyin beyaz madde bütünlüğünü ve topolojisini etkilemediğini ortaya koymaktadır.

Anahtar sözcükler: esrar kullanımı, subklinik psikoz riski, difüzyon tensör görüntüleme, network analizi.

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This lab includes several master's and PhD students who are involved in the recruitment and data collection. During my master's degree I recruited 24 participants and completed environmental assessments of 91 individuals and neurocognitive testing of 88 individuals. In addition to these, I took blood samples from 24 participants. All MRI and statistical analyzes in the thesis were made by myself.

The preprocessing and parcellation stages in connectivity analysis were done through the scripts that Prof. Martijn van den Heuvel prepared in MATLAB.

Dedication

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Chapter 1

Introduction

1.1 A Brief Overview of Cannabis Consumption

Cannabis which takes its name from plant cannabis sativa, is alternatively known as marijuana. It is known that it has been used for centuries, generally for its euphoric effects, and is one of the leading drugs of abuse in recent times [3]. It is the second most frequently used substance in the world after alcohol [4]. Over the past 30 years, with changing socio-political perceptions and legalization of cannabis use for recreational or medical purposes in 22 countries and over 30 states in the USA, there has been a dramatic change in attitude towards cannabis use [5]. It has been reported that over 200 million people use cannabis, and habitual users begin using it during adolescence [6]. According to the 2020 European Drug Report, 27.2% of 90.2 million adults aged 15 to 64 have experienced at least once, and around 15% of the 80 million young adults (15-34) reported using cannabis in the last year. Considering the age, it is noteworthy that the prevalence of cannabis use is higher in the 15-24 age group, with 19% of 10.4 million in the last year. When examined in terms of gender, cannabis use is more common in men than in women, as is the case with other substance use [7].

The National Cannabis Survey carried out in Canada (2019) stated that the use rate in the last three months was 30% for men and 14% for women. These statistics regarding cannabis consumption in Canada mirror evidence from the USA and Europe, where men also report a higher prevalence of cannabis use [4]. Turkish Statistical Institute (2010) demonstrated that 0.93% of the population experienced drugs at least once in a lifetime; 1.26% of this rate is male and 0.61% females [8]. According to the research results conducted with a 1720 university student sample, 6.4% reported having used a substance; 2.8% used one in the last year. Moreover, the prevalence of cannabis use at least once in time was reported as 5.9% [8].

Bachman and colleagues analyzed data from 14 different cohort studies involving high school seniors and university students who were followed from age 18 to 35 to examine the impact of major life transitions (for example; entering university, getting a job, marrying, and having children) on the rates of consumption of cannabis in the last 30 days. Their results showed a gradual diminish in cannabis use rate from the early and mid-20s to early 30s [9]. Another study conducted with a single cohort of high school students that was followed from their adolescence to middle adulthood period revealed that cannabis consumption peaked in the early 20s and reduced consistently through the 20s and into the 30s by depending on the increase of societal responsibilities for life [10]. Consequently, although the use rate of cannabis decreases with age, this rate increases in adolescence in both where the sale and use of cannabis is legal and illegal, and the age of consumption decreases day by day to a lower age range.

1.2 The Neurobiology of Cannabis

The cannabis sativa includes over 400 compounds and a total of 66 cannabinoids [11]. One of the main psychoactive components of cannabis is delta-9-tetrahydrocannabinol (THC). Also, it is known that the rewarding effect of cannabis use, which is directly related to the addictive effect, is caused by this component. These rewarding and positive reinforcing effects of THC are mediated by the G-protein-coupled receptor family known as CB1 and CB2 cannabinoid receptors [12].

The cannabinoid type 1 (CB1) receptor is known as a presynaptic receptor, and it is broadly expressed throughout the brain with a high concentration in some regions like the hippocampus, cerebellum, and striatum, while it is a low concentration in the amygdala, cerebral cortex [13]. Moreover, it has an essential role in neurotransmitter release and concentration across neural systems [14].

The cannabinoid type 2 (CB2) is expressed only in peripheral tissues, mainly in the immune system, and it is also thought to play a role in depression and substance abuse [15]. The cannabinoid CB1 receptor is mainly concentrated in the central nervous system and participates in various brain function modulations such as executive, emotional, and memory processing [16]. Endocannabinoids have an important role in synaptic plasticity by helping and constraining neurotransmission throughout a broad extent of brain regions, and changing its function during essential phases of neural development could lead to enduring alteration in the brain function and structure [17].

Principally, the mechanism of the endocannabinoid signaling operates differently from most of the neurotransmitter systems. It is known that endocannabinoids are released on demand from post-synaptic cells and acting as retrograde signals, and travel backwards across the synapse, where they bind pre-synaptically located CB1 receptors and decrease the amount of neurotransmitter release [18]. Clearly, as the person consumes cannabis, the THC passes from the lungs or digestive tract into the bloodstream, and it is carried to the brain, where it binds

quickly to cannabinoid receptors throughout the brain and body by overwhelming the endocannabinoid system [19]. And it is known that, orally consumed THC is absorbed much more slowly, and it can enter the bloodstream and reveal its psychoactive effect between 1 hour and 3 hours [9].

1.3 The Impacts of Cannabis Use on Brain Development in Adolescence

1.3.1 Adolescence and Brain Maturation

The word adolescence is originated from the Latin *adolescere-* to grow up [20] and is defined as a special period in which various physical, psychological, cognitive, and social changes are experienced, and it acts as a bridge between childhood and adulthood. It can be said that brain development is a highly organized and dynamic process consisting of many steps, which are genetically determined, epigenetically directed and environmentally influenced [21]. Although the World Health Organization (WHO) defines this period of development as corresponding approximately to the period between the ages of 10 and 19 years, it is indicated that 10 and 24 years corresponds more appropriately to adolescent growth and popular understanding of this life phase [20]. Moreover, it is thought that the brain is steadily developing until the age of about 25 [22]. Even though it is not defined in precise boundaries, adolescence chiefly covers the stage between non-reproductive and reproductive stages [23], and this process begins with the release of maturation of sex hormones in the hypothalamic pituitary-adrenal gonadal axis [24].

During this transition period, various dramatic neurodevelopmental alterations in brain growth and connectivity are observed in addition to hormonal and physical developments. It has been reported that neural networks are reconstructed, changes are observed in some brain regions, and there is an increase in white matter and a decrease in the amount of gray matter in general [25] ; [26]. The

adolescent brain's reconstruction process is carried out through similar mechanisms with neural networks that play a role in early brain development [27]. With the transition to this period, the brain's wiring changes and develops in several ways; axons continuously become more insulated by myelin, and myelin alterations are dramatic during adolescence, with the amount of it doubling in some regions in the brain [28]. This insulating effect acts as an accelerator role in the transmission of messages and impulses along the axon. Synchronously, dendrites that receive a transmission from adjacent axons expand branches and increase their connectivity. Simultaneously, the corpus callosum, which acts as a bridge between the two hemispheres, thickens and improves communication effectiveness between these hemispheres. Also, more robust connections are being built between the prefrontal cortex and other brain regions. For instance, connections between the hippocampus and frontal regions are consolidated, facilitating better cognitive processes like integrated memory and advanced decision-making in the adolescent brain [28]. Furthermore, some changes in the hippocampus, the nucleus accumbens, and the amygdala regions are responsible for emotional processing like impulsivity and risk assessment [29].

Undoubtedly, because the brain is restructured with the occurrence of neurobiological processes such as neuron formation, synapse formation, synaptic pruning, cell loss, the growth of axonal extensions, dendritic elongation, and shortening, adolescence is indicated as a neurodevelopmentally critical period [30] ; [31]. The brain does not mature in entire regions simultaneously: important regions like those facilitating movement and somatosensory functions and general information processing mature first in the childhood period, while others such as impulse control, strategic thinking, social behaviors mature later in adolescence behavior with the maturation of prefrontal cortex [32]. Additionally, the major brain transformations in the prefrontal cortex, limbic regions, and dopamine input pathways can be seen along with physiological, cognitive, and hormonal changes in individuals' lives. These neurobiological processes can make the adolescent brain more sensitive to various stressors and constitute part of the neural circuitry modulating the motivational value of drugs and other reinforcing stimuli [33], such as increased risk-taking behaviors, problems with the regulation of behavior and

emotions, and thrill-seeking [34]. During these reorganizational processes, the adolescents' brains become highly sensitive to exogenous effects, such as from psychotropic substances, creating a window of vulnerability to the occurrence of developmental disorders resulting from such exposure [6]. Notably, this is true for substances such as cannabis, which target the endocannabinoid system, which is the cornerstone of adolescents' neural maturation [35]. When using cannabis, the endocannabinoid system, responsible for homeostatic regulation of various physiological processes, may be affected, and desensitization or down-regulation of receptors may occur [36] ; [37]. Moreover, when cannabis is consumed chronically, the endocannabinoid receptor in cortical regions may be hindered [38]. Additionally, adolescence onset chronic cannabis consumption, in contrast to adulthood onset, leads to neuroplastic alterations and could drive long-term structural and functional changes by disrupting cognitive performances [39].

1.3.2 Development of White Matter Microstructure and Brain Structural Network

White matter is found in the cerebral cortex under the gray matter in the brain and comprises millions of bundles of nerve fibers that connect neurons in different brain areas into functional circuits [40]. It takes its name from the myelin sheaths that surround it and speeds up the transmission of information. In parallel with various brain changes, alterations in the white matter structure are also observed with the transition to adolescence. The myelin sheaths begin to thicken,and axonal diameters increase, the organization of white matter improves, signal transduction accelerates and consequently, these critical processes ensure optimal cognitive, behavioral and emotional development in adolescence [41].

Studies conducted with different methods reveal various findings in terms of brain white matter development. According to postmortem histological studies, it has been found that there is an increase in the amount of white matter with the transition from childhood to adolescence [41]. In studies conducted with magnetic resonance imaging (MRI), an increase was observed in white matter in

terms of volume and density [42] ; [43]. These changes are commonly attributed to increases in the diameter, myelination of the axons constituting the fiber tracts, increased neuronal size and glia proliferation [44]. A large longitudinal study carried out on children and adolescents demonstrated a linear increase in the white matter volume regardless of the specific region [42]. On the other hand, according to the results of the whole brain morphometry study by Reiss and colleagues (1996), there was an increase in the volume of white matter in the frontal region in childhood. In addition to these, it is known that there is an increase in white matter integrity in some tracts and left fronto-temporal pathways [43].

In recent years, changes in the white matter have been examined primarily with the help of diffusion magnetic imaging (dMRI) techniques, which use magnetic resonance signal to visualize the movement of water molecules within axons and provide indirect measures of white matter microstructure [41]. The characteristics of diffusion indicate variations in white matter structure associated with fiber organization, membrane proliferation, fiber myelination, and DTI processing generates quantitative parameters that have been revealed that are susceptible to maturity and age-dependent changes [45] ; [46]. White matter tissue integrity, such as the degree of myelination and coherence of fiber tracts has an important role in the developing brain in terms of adequate cortical connectivity [14]. The quantification of dMRI is typically obtained in a tensor model, and it is indicated as diffusion tensor imaging (DTI) [47]. With this method, various parameters are acquired: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD), which are thought to provide the necessary information to detect changes in white matter development. Several cross-sectional and longitudinal DTI studies have documented maturation in the white matter microstructure throughout evolution from childhood to adolescence.

Moreover, it has been shown that there are distinct changes in DTI parameters depending on age. While MD and RD decreases, FA increases in many white matter regions with increasing age, but there are inconsistencies regarding the value of AD [48]. Increases in fractional anisotropy and decreases in mean diffusivity refer to healthy white matter development from childhood to early adulthood [22]. When looking at the studies, it can be seen that there is sufficient evidence that

adolescence has an important role in white matter maturity, although not all of these studies specifically focus on the same point of brain white matter integrity. It has been revealed that the relationship between age and white matter integrity is nonlinear [49] ; [50] ; [51]. While there is a sudden increase in the FA value throughout the transition period from childhood to adolescence, this increase decreases gradually from adolescence to adulthood [51]. It is known that increasing FA value in white matter integrity during this period may point out more firmly regulated fiber orientation and stronger myelination in major white matter tracts as maturation increases [52]. The timing and proportions of the DTI related developmental alterations vary region to region in the brain, and these contribute to the particular aspect of behavior and vulnerabilities characteristics of this stage of development [53].

In addition to several microstructural changes, MRI studies have revealed that adolescence alters the mechanism of large-scale structural and functional neural networks, including strengthening long-range connections between distal brain regions [54]. Changing the strength of the connection increases the capacity of information integration and topology, which is progressively capable of facilitating higher-level cognitive functions. These processes result in significant alterations in the connectome architecture [55]. During the early adolescence period, the local and global efficiency of the brain's structural network increases [56]. While many topological properties of the network are preserved, a considerable increase in local efficiency is observed in adolescence [57].

1.3.3 The Effects of Cannabis Use on White Matter Integrity and Structural Network Topology

Adolescence is also known as a period that can include risk-taking behaviors such as alcohol, tobacco and cannabis consumption, and these experiences may affect a person's ability to complete the fundamental life transitions of adolescence [58]. Jacobus and Tapert (2014) stated that neurotoxic impairments that may occur in brain development due to regular cannabis use do not only alter neurochemical

communication and genetic expression of neural development but may also have a neurotoxic effect on the brain tissue, and consequently, changes may occur in the trajectory of the neurodevelopmental process [14]. For example, changes in white and gray matter due to cannabis experience may impact cognitive and daily functionality required for healthy brain development from childhood to adulthood [14].

In the study conducted in 2009, researchers found that adolescents with chronic cannabis use who participated in drug treatment and rehabilitation had decreased FA and increased MD in temporal-parietal fiber tracts [59]. According to a study carried out by Yucel and colleagues (2010), there was reduced FA in both cortical and subcortical areas in heavy cannabis users compared to matched controls [60]. Following these, in a study investigating the effect of cannabis use with concomitant alcohol consumption, it is shown that poorer white matter integrity depends on decreased FA and increased MA in various fiber tracts in adolescence between the ages of 16 and 19 [61]. Considering the changes in white matter integrity in specific regions of interest depending on cannabis use, there are inconsistent findings in the literature, especially in younger users. Several studies showed that cannabis users had lower FA value in the anterior corpus callosum [62] ; [63]; [64], uncinate fasciculus [65], temporal-parietal fiber tracts [59], and throughout temporal and parietal areas [61]. According to 2-year follow-up study on young adulthood cannabis users and control group, cannabis users had decreased longitudinal growth in FA in the central and parietal regions of the right and left superior longitudinal fasciculus, in the left corticospinal tract, and the right anterior thalamic radiation lateral to the genu of the corpus callosum [17]. They found a correlation between a high amount of cannabis consumption and decreased longitudinal growth in FA, and they concluded that regular cannabis uses in adolescence and young adulthood period changes continuing development of white matter microstructure. Another longitudinal study, including alcohol use, revealed that adolescents who do not regularly use cannabis and alcohol have a healthier white matter microstructure and better neurocognitive performance [14]. Contrary to many studies investigating the effect of heavy and

chronic cannabis on white matter integrity, the result of the study investigating its recreational use (not daily basis) showed that there was an association between earlier age of cannabis consumption and lower white matter integrity [66]. Kim et al. (2011) applied graph theory to diffusion tensor imaging and fiber tractography in order to investigate both global and local brain network properties in adult cannabis users and healthy controls. They found that cannabis users had markedly decreased global network efficiency and increased clustering coefficients. Additionally, cannabis users showed changed local network patterns in the cingulate region [2].

1.4 The Relationship Between Cannabis Use and Psychosis Proneness

The first written information on cannabis for health and diseases comes from Chinese medicine between the first and second century B.C. [67]. The negative impacts of cannabis on mental health were first revealed by physician Iban Beiter between the 12th and 13th centuries [68]. After a long time, in 1845, the French psychiatrist Jacque-Joseph Moreau stated that specific effects might be due to cannabis and defined these effects as follows: acute psychotic reactions that are usually lasting for several hours or rarely for a week, reactions may be dose-dependent, and their main characteristics are illusions, delusions, hallucinations, depersonalization, confusion, excitement and agitation [69]. When it comes to the 21st century, the adverse effects of cannabis consumption on the person are classified as follows: firstly,depending on the dose used, various psychological reactions such as anxiety, panic, depression, or psychosis may occur.Secondly, it can affect pre-existing mental disorders, trigger a mental disorder, or act as a risk factor. Thirdly, it may lead to addiction or withdrawal effects [70]. It is known that psychotic experiences consist of, among other symptoms, various types of hallucinations, delusions, disorganization, thought-related disorder, and psychotic fear [71]. Although these symptoms may occur in other psychiatric disorders, they are primarily seen in schizophrenia or other disorders related to psychosis.

Cannabis consumption has been linked with subclinical psychotic experiences and clinical psychotic disorder, even though this relationship's direction has not been revealed [72].

Various hypotheses have been put forward to explain this relationship's direction, one of which is called 'self-medication hypothesis'. According to this, individuals attempt to consume cannabis to alleviate their psychotic symptoms and change their mood [73]. Another hypothesis is known as the 'damage hypothesis' offers a different perspective, claiming that cannabis can increase such symptoms and worsen their course [74]. As the findings of the longitudinal study conducted by Ferdinand and colleagues (2005) reveal, there is a bidirectional relationship between cannabis consumption and psychotic experiences or symptoms of psychosis [75].

Neurobiological studies have explained how cannabis use elicits psychotic experiences: when an excessive amount of THC binds to the cannabinoid receptors on glutamatergic and GABAergic neurons, it disturbs the normal endocannabinoid retrograde signaling from the dopaminergic neurons [76]. This disruption causes an increase in the firing rate of the dopaminergic neurons, which raises the amount of dopamine in the forebrain. This increase in dopamine triggers the basic mechanism of psychosis [77]. In addition, although THC is known to have a temporary impact on the physiological control of the endogenous cannabinoid system on GABA and glutamate release under normal conditions, it has been suggested that this may have adverse effects on the undergoing development of neural circuits, especially prefrontal cortex throughout the adolescence period [72].

As a result of a comprehensive study by Stefanis and colleagues (2004), cannabis use in adolescence was positively correlated with both the negative and positive symptoms of schizophrenia, suggesting that when cannabis is consumed in the adolescence period, it is a risk factor for the development of schizophrenia [78]. According to another study conducted by Miettunen and colleagues (2008), on 15-16 years, adolescents who had tried cannabis were very likely to experience three or more symptoms of psychosis later in life [79].

1.4.1 Relationship Between Psychosis Risk and Brain Structure

Several studies have revealed that the prevalence of psychotic-like experiences is high, although the prevalence rate of psychotic disorders is low in the community (almost 0.5%- 1%) [80]. Linscott and van Os reported that the prevalence of psychotic-like experiences in the community's general population could be approximately between 7% and 13% [81]. In addition, it has been suggested that healthy adolescents who report having psychotic-like experiences also have impaired white matter integrity [80] ; [82].

The central nervous system includes two main components: gray matter and white matter. Gray matter comprises mainly nerve cells bodies, their dendrites, and glia, while white matter is made up of bundles of myelinated axons branched into tracts concentrated mostly in the brain's inner-part; these tracts aid to make easier communication between neural regions producing neural networks [83]. Myelin envelopes the axons to produce insulation and play a critical role in the transmission of electrical signals. Since lipids are the major elements of myelin, it is named white matter because of its white color [84]. It is known that white matter encompasses nearly half of the human brain [85].

Adolescence is a critical period in white matter development, as other structural changes in the brain. Disruption can be observed, especially in the long association tracts due to complex psychiatric disorders like schizophrenia, and it is known that these white matter tracts promote the development of cognitive functions that are impaired even in the early stages of psychosis [86]. There are controversial findings in the literature investigating the relationship between white matter integrity and psychosis. Several studies have reported that white matter-related changes occur in various parts of the brain. Karlsgodt et al. (2009) found that decreased white matter integrity in the superior longitudinal fasciculus [87] ; a significant reduction was reported in the corpus callosum by Katagiri et al. (2015) and Saito et al. (2017); Wang and colleagues (2016) reported reduced white matter integrity in the cingulum [87] ; [88] ; [89].

DeRosse et al. (2017) conducted a study including tract-based spatial statistics and probabilistic tractography methods in healthy children and adolescents aged between 8 and 18 to understand whether abnormalities in white matter microstructure were predictive of later social functioning in those with subsyndromal psychotic experiences. As a result, they observed an association between a lower FA value in the regions close to superior longitudinal fasciculus, corticospinal tract, inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus and psychotic-like experiences. Furthermore, baseline FA in the superior longitudinal fasciculus was predictive of social competence after a 12-month follow-up [90].

On the other hand, some studies have revealed no significant differences. Mittal and colleagues (2013) conducted a study on a total of 68 adolescents (33 ultra-high psychosis risk and 35 healthy control group) found that there were no significant differences in white matter integrity between the two groups [91]. Moreover, von Hohenberg et al. (2014) performed a whole-brain DTI analysis on 28 participants meeting clinical high risk for psychosis and 34 healthy participants and revealed no statistically significant differences [92]. In addition to these studies, Bernard and colleagues (2015) performed a study with 26 individuals with ultra-high risk and 21 healthy individuals. They evaluated their symptoms and diffusion tensor scans at baseline and 12 months later. They observed a significant group-by-time interaction suggesting reduced white matter integrity in the ultra-high-risk group and increased white matter integrity in the control group after 12 months [93].

Finally, there are studies on psychosis, white matter, and cannabis use in combination. Rapp et al. (2012) performed a systematic review in structural imaging and post mortem studies in individuals diagnosed with psychosis with and without cannabis experience. According to structural imaging results, there were substantial differences, particularly in frontal regions, between the group with cannabis experience and those who never experienced it [94]. Furthermore, Haller et al. (2014) conducted a tract-based spatial statistic (TBSS) to examine the impact of cannabis consumption and first-episode psychosis on white matter integrity. Participants were divided into light cannabis users, heavy users, and non-cannabis users as a control group. They observed no difference between

users and non-users in terms of white matter integrity. Following that, compared to heavy users vs. light users, they also found no significant difference between these two groups [95]. Dekker et al. (2010) performed a high resolution structural and diffusion tensor imaging to examine three different schizophrenia-like diagnosed groups: those who started cannabis use before the age of 15 and continued regular use (early-onset), those who started at the age of 17 or later (late-onset) and those who never experienced cannabis use. Their results showed no differences between early and late-onset cannabis users. It was found that fractional anisotropy (FA) was reduced in the never-experienced group compared to the early onset group [96]. As Thomason and Thompson (2011) noted before, lower fractional anisotropy is present prior to the beginning of the disease in young people with a high predisposition to psychosis [52]. Lastly, Michielse et al. (2020) examined white matter microstructure and network connectivity in adults with psychotic-like experiences. They reported no differences between groups in connectivity measures and tensor-derived indices. However, they found a higher positive symptom distress score was associated with higher local efficiency and clustering coefficient in the right middle temporal lobe in the group with psychotic experiences [97].

1.4.2 Relationship Between Corpus Callosum, Superior Longitudinal Fasciculus and Psychosis Risk

Studies investigating the effect of cannabis use on white matter integrity have shown that cannabis users have reduced FA in several tracts that are also sites of reduced FA in psychosis, including the superior longitudinal fasciculus, corpus callosum, and others [98].

The corpus callosum (CC) is the brain's major commissural pathway located between the right and the left cerebral hemispheres. It is the largest fiber bundle and the most concentrated white matter in the brain [99]. The corpus callosum is C-shaped and segmented into various subparts from front to back: rostrum, genu, trunk (body), and splenium. Earlier studies focusing on the psychosis spectrum

revealed a significant reduction in fractional anisotropy in the callosal splenium [100] and the corpus callosum's splenium [101]. Consistently, Ardekanie et al. (2003) reported a decreased FA parameter in the same region [102]. Bora et al. (2011) conducted a meta-analysis regarding DTI studies in schizophrenia, and they reported a significant reduction in FA value in the genu of the corpus callosum and a reduction in other regions [103]. Moreover, Carletti et al. (2012) conducted a longitudinal study to investigate whether there was a change in the white matter microstructure before the onset of psychosis. For this aim, they examined three groups: ultra-high risk (UHR) for psychosis, patients with first-episode psychosis, and healthy controls. As a result, they found that white matter DTI features were significantly distinct between these groups. Importantly, they reported that relative to controls, first-episode patients had extensive reductions in several regions, including the corpus callosum in FA value, while the UHR group had a more moderate reduction [104]. According to Von Hohenberg and colleagues' study on clinical high risk (CHR) and healthy control groups, the CHR group had white matter alterations in superior longitudinal fasciculus, corona radiata, and corpus callosum compared to the healthy group [92]. Additionally, Katagiri et al. (2015) performed a longitudinal study on participants with an at-risk mental state (ARMS), and they found a significant FA reduction between the ARMS group and their control group in a genu and body of the corpus callosum [105]. On the other hand, Peters and colleagues (2008) conducted a tractography study, and they did not find any white matter microstructure differences in terms of corpus callosum between ultra-high risk and healthy control groups [106].

The superior longitudinal fasciculus (SLF) is a broad white matter tract that chiefly connects parietal and frontal lobes and provides a partial network to the temporal lobe [107]. There is an increase in the fractional anisotropy and decrease in diffusivity during childhood and adolescence throughout all the major fiber tracts, and most of these alterations are complete towards the end of adolescence, while superior longitudinal fasciculus and several fiber tracts continue their development into early adulthood [108]. Psychotic spectrum disorders are generally known as disorders of dysconnectivity, and several studies showed a decrease

in FA value in long-range association tracts, including superior longitudinal fasciculus in adolescents with psychosis [109]. Looking at the literature, it is seen that the SLF is a region of interest frequently involved in psychosis and schizophrenia studies. Karlsgodt et al.(2009) showed abnormalities through the SLF in individuals at risk of psychosis [87]. Similarly, von Hohenberg and colleagues (2014) reported that white matter microstructure is abnormal throughout several regions, most notably in the SLF in clinical high-risk individuals [92]. Following these, Schwehm et al. (2016) researched psychosis patients and healthy volunteers and they concluded that there was a lower FA through SLF in patients with psychosis [110]. Furthermore, DeRosse et al. (2014) examined the relationship between the accumulation of risk factors such as low IQ, low parental socioeconomic status, history of childhood trauma, cannabis experience during adolescence, high levels of subclinical psychotic-like experiences and neural development in healthy adults. As a result of their study, they revealed a significant association between cumulative risk for psychosis and lower FA value in the left superior longitudinal fasciculus [90].

1.5 A Brief Overview on Diffusion Tensor Indices

Diffusion Tensor Imaging (DTI) is an advanced MRI technique and provides detailed in vivo information regarding white matter at the microstructural level. This method is mainly based on the diffusion of water molecules. If mentioned in general terms, diffusion tensors are represented with eigenvectors (ê1, ê2, ê3) and eigenvalues ($\lambda 1$, $\lambda 2$, $\lambda 3$) which identify the directions and apparent diffusivity through the axis of main diffusion. The most frequently preferred white matter microstructure measures are fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD).
Fractional anisotropy (FA) represents the degree of anisotropy of water molecules

ranging from 0 (isotropic) to 1(anisotropic), and it does not provide any information about the orientation.The formula of fractional anisotropy is:

$$FA = \sqrt{\frac{\left(\lambda 1 - \lambda 2\right)^2 + \left(\lambda 2 - \lambda 3\right)^2 + \left(\lambda 1 - \lambda 3\right)^2}{2\left(\lambda 1^2 + \lambda 2^2 + \lambda 3^2\right)}}$$

This parameter allows inferences about axonal diameter, fiber density, and myelin structure [111]. Briefly, water molecules diffuse without restriction in any direction, but this movement may be affected by the existence of macromolecules such as cell membranes and myelin sheath. Terminologically, while the movement of these molecules in a random way is defined as isotropic diffusion, the fact that this movement occurs along an axis, is defined as anisotropy. Briefly, water molecules diffuse without restriction in any direction, but this movement may be affected by the existence of macromolecules such as cell membranes and myelin sheath. Terminologically, while the movement of these molecules in a random way is defined as isotropic diffusion, the fact that this movement occurs along an axis, is defined as anisotropy. Clearly, diffusion is thought of as isotropic when the eigenvalues are almost equal ($\lambda 1 \approx \lambda 2 \approx \lambda 3$). On the other hand, when eigenvalues are significantly different in terms of magnitude, diffusion tensor is anisotropic.On the other hand, when eigenvalues are significantly different in terms of magnitude, diffusion tensor is anisotropic ($\lambda 1 \backsim \lambda 2 \backsim \lambda 3$) [112].

It is known that higher FA values represent that diffusion is much greater in one direction, whereas lower FA values represent that diffusion is approximately equal in all directions [45]. At many points, a higher FA value indicates fibers that are more abundant, thicker, more myelinated, and more organized in terms of orientation [52]. Generally, the decrease in fractional anisotropy value indicates deterioration in myelin sheath and axonal membranes [113]. When FA values of all brain voxels are shown on an anatomical map, higher FA values appear whiter, while lower FA values appear darker. Moreover, FA is used as an essential measure of white matter integrity in many studies [45].

Another commonly preferred parameter is mean diffusivity (MD), representing the rotationally invariant magnitudes of water diffusion in the brain tissue. It can be a useful measure to index the maturation of white matter [45]. The

collection of three eigenvalues ($\lambda 1 + \lambda 2 + \lambda 3$) constitutes the traces, and mean diffusion is obtained by dividing this sum by three $(\lambda 1 + \lambda 2 + \lambda 3)/3$. Generally, the MD value is expected to be higher in damaged tissue because of increased free diffusion (perpendicular to the axons in a white matter fiber tract); whereas the FA value is expected to decrease because of the loss of coherence in the principal diffusion direction (parallel to the axons in a white matter fiber tract)[114]. It is mainly used to detect pathological changes in the white matter integrity [115]. Furthermore, axial diffusivity (AD) and radial diffusivity are frequently examined parameters. Axial diffusivity ($\lambda \| = \lambda 1 > \lambda 2, \lambda 3$) indicates the magnitude of diffusion parallel to a tract. Radial diffusivity $\lambda \perp = (\lambda 2 + \lambda 3)/2$, refers to the apparent diffusion coefficient in the direction perpendicular to the tract [116]. In some circumstances, lower FA and greater MD value display damaged fiber integrity contingent upon the alterations' cellular basis [52]. Similarly, lower AD might indicate axonal injury or less coherent orientation of axons [117], while lower RD might represent demyelination or glia cell impairment [118].

1.6 A General Overview of the Components of Structural Network Topology

The human brain is a very complex system, and it can be modeled as a network. Regions within the brain can be represented as nodes (vertices), and the connectivity between them are the edges (links). Therefore, the brain is quite suitable to be examined by graph theory, which is a branch of mathematics. The connections of a graph can be adequately represented with the help of a connectivity matrix, where the ith row presents the outgoing connections from node i and the jth column presents incoming connections to node j.

There are several network measures that can be classified into two main categories: global and local measures in order to investigate connectivity. While global measures indicate the global characteristics of the graph, local measures indicate the characteristics of the nodes within the graph. One characteristic that

is frequently investigated is global efficiency (*E global*), which is an index of the efficiency of distant information exchange in a network and can be defined as the inverse of the average characteristic path length between all nodes in a network. Global efficiency is formulated as $E\ global = \frac{1}{N(N-1)} \sum_{i,j \in Gi} \frac{1}{Li,j}$ where N is the group of all nodes and Li,j is the average distance between nodes i and j in the network. It ranges between 0 and 1, the value of 1 represents maximum global efficiency [119].

In contrast to global efficiency, local efficiency (*E local*) is an index of the capacity to exchange information within the neighbors of a given node and is defined as the inverse of the shortest path length of each node [2]. It is calculated as $E\ local = \frac{1}{NGi(NGi-1)} \sum_{i,j \in Gi} \frac{1}{Li,j}$ where NGi, symbolizes the number of nodes in the neighbor Gi and it varies between 0 and 1, as in global efficiency.As value gets closer to 1, the network's local efficiency increases [119].

Another commonly studied measure is the clustering coefficient, which gives information regarding the prevalence of clustered connectivity around an individual node [120]. The mean of clustering coefficient (C) for all nodes in a given network is formulated as $C = \frac{1}{N} \sum_{i \in} NCi$ where Ci indicates the likelihood of interconnection between each node.

1.7 Hypotheses and Goals

Numerous studies indicate that cannabis use causes the onset of psychotic symptoms. Similarly, prevailing literature has examined the effects of cannabis use and subclinical psychosis risk on brain white matter integrity. However, there are only few studies investigating the effects of cannabis use and psychosis risk on brain structural connectivity. Additionally, while the vast majority of cannabis studies focus on the impact of heavy use, studies investigating psychosis risk generally focus on the effects of clinically diagnosed psychosis on brain development and provide inconsistent results. Looking at the literature, it is seen that only one study investigated the white matter coherence in sporadic cannabis use in adults. This study revealed no differences between cannabis users and controls in white matter microstructure. However, when considering the age of onset of cannabis use, they found that an earlier age of cannabis use was related with lower FA and greater RD in a large cluster of the right hemisphere, including superior longitudinal fasciculus, inferior longitudinal fasciculus, forceps major and forceps minor [66].

Only two studies have focused on cannabis use so far in terms of brain structural connectivity. Kim et al. (2011) performed the first graph theory-based study in adult cannabis to users, and this study showed decreased brain network efficiency and increased clustering in cannabis users compared to the control group [2]. Another study investigated the effect of regular cannabis use on axonal fibre connectivity, and revealed that axonal connectivity in the right fimbria of the hippocampus (fornix), splenium of the corpus callosum, and commissural fibres were impaired in cannabis users [121].

To the best of my knowledge, there is no study in the literature examining the interaction of recreational cannabis use and psychosis risk on brain development by combining white matter integrity, and structural topology analyses. In order to contribute to the gap in the literature, two specific aims have been proposed. The study's first aim is to understand whether recreational cannabis use increases the sub-clinical psychosis risk in the adolescence period. The second aim is to

investigate whether cannabis use and psychosis risk have an impact on brain white matter integrity and structural topology by using ROI based Tract-based Spatial Statistics and Network Connectivity Analysis.

In line with these aims, we propose the following hypotheses: Adolescent cannabis users have a higher subclinical psychosis risk compared to non-users. The second hypothesis is that cannabis use and sub-clinical psychosis risk would exhibit altered white matter microstructure in corpus callosum and superior longitudinal fasciculus and brain network efficiency.

Chapter 2

Method

2.1 Participants

Twin participants between the ages of 14-23 were recruited through posters and social media as part of a larger project on brain development and risk for psychosis (PI Toulopoulou). Only one member of each twin pair was included in this thesis. After quality control of both MRI and behavioral data, recreational cannabis users ($n = 25$) and healthy non-using volunteers ($n = 25$) were included in the final analysis. The age distribution of the participants ranges between 17 and 23 ($M = 20.18$, $SD = 1.94$). 32 of the participants were male (%64), while 18 were female (%36). The study's exclusion criteria were neurological and psychiatric disorders, a diagnosis related to substance abuse, and an IQ <80. At the beginning of the study, all participants were informed about the study and gave informed consent. Parents of minor participants were asked to accompany their children on the day of the study, and they signed the informed consent.

2.2 Assessment of Cannabis Experience

The Cannabis Experience Questionnaire (CEQ) was used to assess the cannabis use of the participants. This questionnaire has 56 items and was developed to evaluate subjective experiences of cannabis use both during and after intoxication [122]. Each participant evaluated their usage frequency according to the five-point Likert Scale ('everyday' = 1, 'more than once a week' = 2, 'a few times each month' = 3, 'a few times each year' = 4, 'only once or twice' = 5). Detailed information regarding the history of cannabis use, current use, age of onset, the type of cannabis use (e.g., hash, herbal cannabis,skunk, super skunk, and others), and other recreational substance use (e.g., tobacco) was also collected.

2.3 Assessment of Alcohol and Tobacco Consumption

Participants' alcohol and tobacco consumption and the amount of consumption were determined through the Alcohol and Tobacco Questionnaire. This is a self-reported scale and consists of two separate parts. The first part is about tobacco use, and it includes two questions, while the second part evaluates alcohol use and consists of three questions. The tobacco part asks whether there has been any tobacco use in the last 12 months ('yes'= 1, 'no' = 0). Then, it asks how many cigarettes or tobacco-related products have been used daily in the last 12 months. Daily cigarette consumption covers certain range values in order to be able to classify ('never smoked' = 0, 'smoked less than cigarettes per day' = 1, 'smoked 10 or more cigarettes' = 2). In the alcohol-related part, the first question asks whether alcohol consumption or not ('yes' = 1, 'no' = 0). Secondly, it is asked whether at least 12 and more alcoholic beverages have been drunk in the last 12 months ('yes' = 1, 'no' = 0). Lastly, it asked how many glasses of alcoholic beverages have been consumed on average per day for a week.

2.4 Assessment of Psychosis Proneness

The Community Assessment of Psychic Experience (CAPE) modified version was used to assess participants' psychotic-like experiences related to cannabis use. The CAPE- 42 is a reliable, comprehensive, and valid self-reported questionnaire which that has been developed to evaluate the lifetime prevalence of psychotic-like experiences in the general population [123]. The instrument includes 42 items covering three subdimensions: positive, negative, and depressive. It consists of 20 items related to positive symptoms, 14 items to negative symptoms, and 8 items on depressive symptoms. These three dimensions have adequate discriminant validity [123]. In respect of scoring, each of the items in the questionnaire was calculated using a two 4- Likert scales: the first one specifies the frequency of symptoms ('never' = 1, 'sometimes' = 2, 'often' = 3 and 'nearly always' = 4, and the second one specify the level of distress of symptoms caused by experience ('not distressed' = 1, 'a bit distressed' = 2, 'quite distressed' = 3 and 'very distressed' = 4. The overall scores in both dimensions range from 42 to 168 [124].

2.5 Acquisition of Diffusion Weighted Images (DWI)

Diffusion MRI images were acquired using a 3T Siemens Magnetom Trio scanner equipped with a 32-channel head coil at the Bilkent University National Magnetic Resonance Research Center (UMRAM) - Aysel Sabuncu Brain Research Center, Ankara, Turkey. Diffusion-weighted images (DWI) of the whole brain were collected using an echo-planar imaging (EPI) sequence to obtain slices in coronal (A>>P), sagittal (R>> L), and transversal (F>>H) planes with the following parameters: (TR = 10740 ms, TE = 102 ms, matrix = 256 x 256 on a 256 mm FOV (field of view), slice thickness = 2 mm, b value = 1000 s/ mm^2, for a total acquisition time of 7 min 22 s. In order to segmentation and registration, high-resolution T1-weighted MRI was acquired with the following parameters (TR = 2600 ms, TE = 3.02 ms, matrix = 256 x 256 with 176 slices, slice thickness = 1

mm, and the duration of imaging sequence was 7 min 18 sec.

2.6 Analysis of Diffusion Weighted Images

2.6.1 DWI Preprocessing

Firstly, the diffusion-weighted data with 33 volumes, 128 x 128 x 64 voxels, and 2 x 2 x 2 mm resolution on the computer of MRI scanner were converted from dicom extension file to nifti extension file via DICOM2NII software in Macintosh. All processing of the diffusion weighted-images was completed with FMRIB Software Library (version 6.0 ; http://www.fmrib.ox.ac.uk/fsl). Diffusion-weighted images were improved in terms of head motion and eddy current to eliminate distortions and non-linear artifacts by performing affine alignment of each diffusion weighted image to the reference volume of the data without gradient (b = 0) by way of Eddy Tool. After that, a binary mask was created from b = 0 image via the Brain Extraction Tool (BET) in FSL. After completing these preprocessing steps, diffusion tensors were fit using b val (b factor) and b vec (diffusion direction matrix). In order to create maps containing fractional anisotropy (FA) and mean diffusivity (MD) values of the entire brain, eigenvalues and eigenvectors were calculated for each voxel.

2.6.2 Tract Based Spatial Statistics

After the preprocessing steps were applied to each participant individually, tract-based spatial statistics (TBSS) was performed to make a group comparison. Since DTI studies that work with a prespecified ROI restrict the areas of investigation, they may miss the significant findings in other regions. Additionally, identifying ROIs can be time-consuming and generally rely on observer accuracy [125]. Due to these limitations, comparing multiple brain regions between larger groups

becomes difficult. On the other hand, TBSS provides several advantages to researchers. One of its most important benefits is that it allows investigating the entire white matter tracts of participants without the need for predetermined ROI. Secondly, this approach is fully automated and observer-independent for evaluating fractional anisotropy in the whole white matter tracts on a voxel-wise basis between groups [126].

In the first stage of the TBSS, the FA images of each participant were obtained, these values of all participants were collected in a separate folder. All processed FA images were moved into a new subdirectory called slicesdir. Then, all FA images were aligned into 1 x 1x 1 mm standard space defined as FMRIB58FA. Afterwards, the entire aligned images were converted into a standard template called MNI152, and was generated by Montreal Neuroimaging Institute. Once this was completed, the mean value of affine-transformed images was averaged to constitute mean FA value, and skeletonized FA value was acquired from that mean FA. In the last step of TBSS analysis, the process of projection of FA value onto the skeleton was applied to obtain neat alignment, and the frequently used threshold value (0.2) was preferred (see Figure 2.1).

MD images of each participant were collected in a new folder in the TBSS directory in order to obtain MD values for group comparison, and then, non-linear registration was applied to MD data. Last of all, MD data of each participant were combined with the 4D file, and the resulting image was reflected on the original skeletonized mean FA to acquire skeletonized MD images of each participant. L1 images of each participant were gathered in a new folder called AD in TBSS analysis directory to obtain AD. The original nonlinear registration was applied to data by merging all subjects' warped images into 4D file. Then, obtained data was projected onto the original mean FA skeleton. Lastly, to compute RD, L3 image was added on L1 and then divided by L2 image via *fslmaths* command. This step was applied to the data of all participants. Following this, all adjusted RD images of participants were collected in a new folder in the main TBSS directory. Same as previous stages to obtain other indices, the original linear registration was performed by merging all subjects' warped RD images into a 4D file. As a result, 4D projected data was acquired.

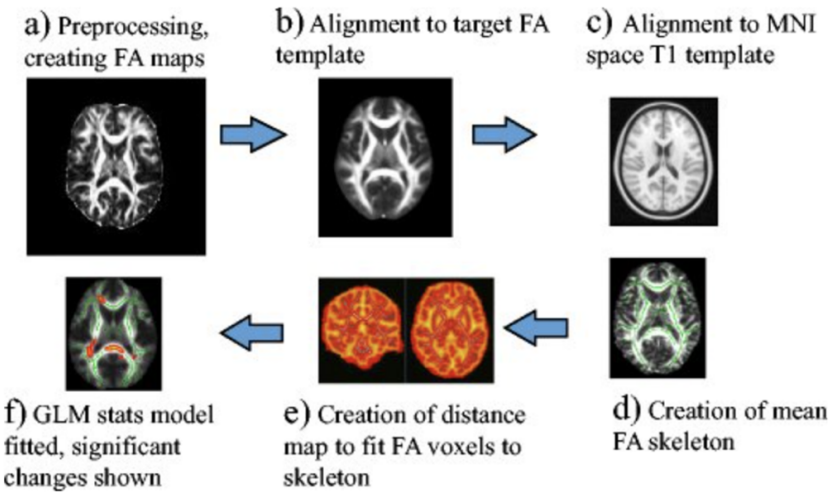

Figure 2.1: Flowchart describes the general steps of TBSS analysis [1].

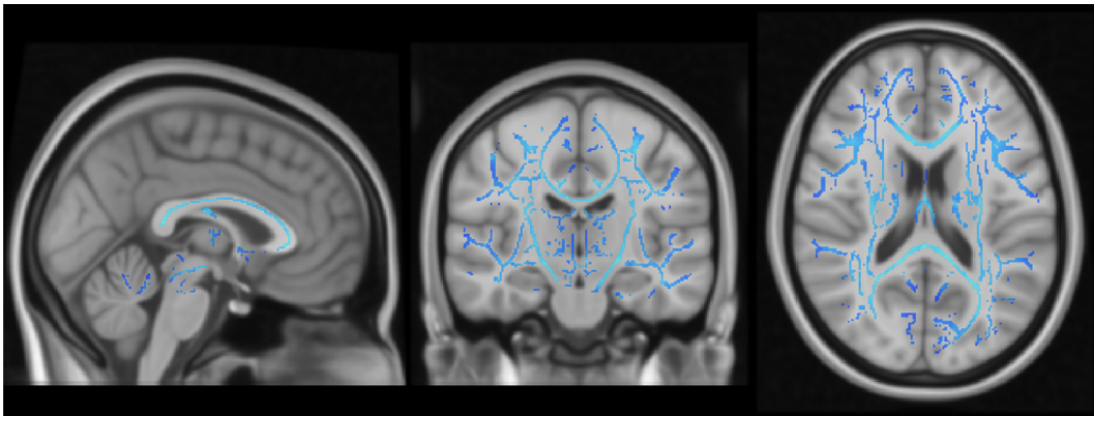

Figure 2.2: Skeletonized mean FA of the participants on standard MNI152 structural template.

2.6.3 Structural Connectivity and Network Construction

After preprocessing was completed, the cortex was parcellated into separate brain regions as 57 unique cortical regions per hemisphere by 114 region-subdivision of the Desikan-Killany Atlas of FreeSurfer (http:// surfer.nmr.mgh.harvard.edu) [127]. In order to reconstruct the fibers, deterministic streamline tractography based on the Fiber Assignment by Continuous Tracking (FACT) algorithm was applied [128]. The structural brain network was then generated with the reconstructed white matter tracts and the individual parcellation map [129]. To construct the network, the following steps were applied: Firstly, parcellated brain regions were set to represent nodes in the analysis. Two nodes i and j in the network were identified as being connected when a bunch of fibers was found from the whole group of reconstructed streamlines which interconnected them.

On the other hand, i and j were defined as unconnected when no streamlines were found between them [130]. Information about the connection between i and j was created in the connection matrix. Each cell in this matrix represented the interconnected streamlines between these nodes. As a result, the individual brain network of each participant was represented with 114 x 114 weighted adjacency matrix (see Figure 2.3). In addition to analyzing weighted network based on the number of streamlines [130], inter-regional connection weights using scalar index (fractional anisotropy) obtained from the eigenvalues of the diffusion tensor, and FA-weighted adjacency matrix, which represents the mean FA connections between distinct brain regions was generated (see Figure 2.4) [54].

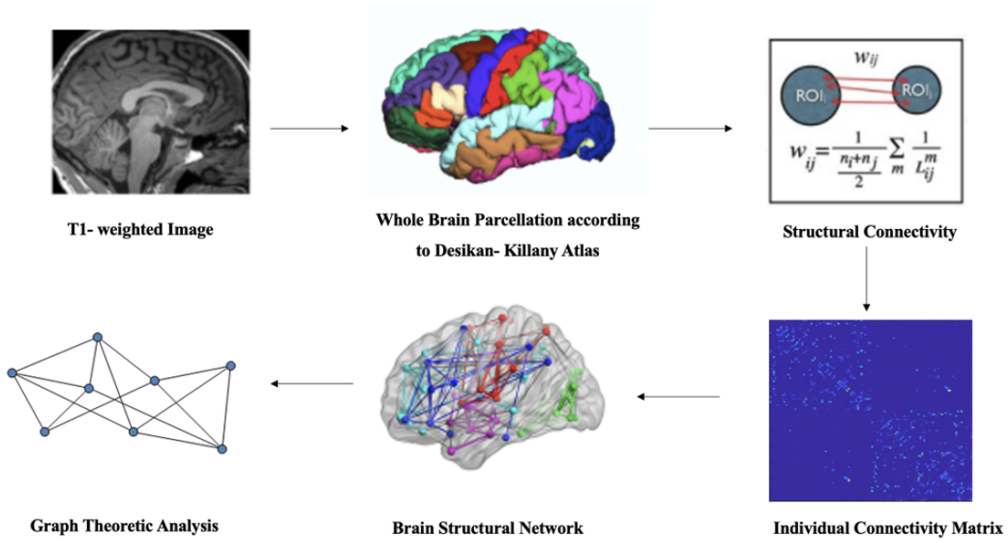

Figure 2.3: Flowchart of describing the acquisition of the graph theoretical measurements. This flowchart was modified from the flowchart in the paper by Kim et al.[2]

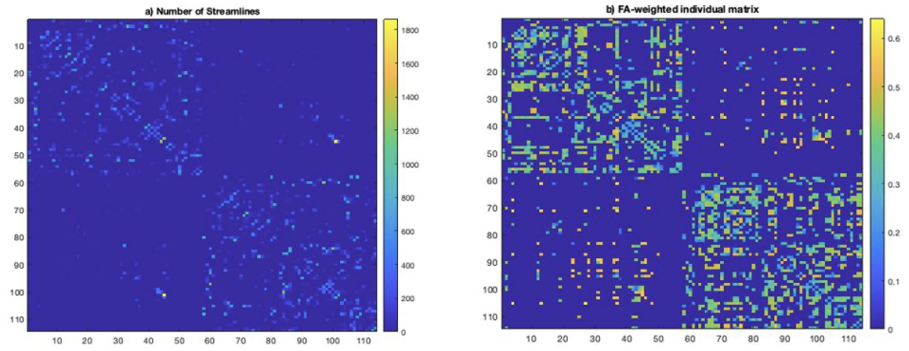

Figure 2.4: Individual connectivity matrices were obtained after network construction processes.The left matrix (a) represents the individual's number of streamlines, while the right (b) matrix represents the FA-weighted connectivity matrix.

2.7 Statistical Analysis

2.7.1 Tract-Based Spatial Statistics

General Linear Model (GLM) tool in FSL was used to conduct higher-level analysis for the skeletonized diffusion-weighted data. It generated appropriate design matrices and voxel-wise contrasts for the whole skeleton to statistically evaluate group differences in mean FA, MD, AD and RD. A Univariate GLM analysis was performed to understand the differences between cannabis users and control group. In the design matrix created in GLM, the cannabis group is placed in the first column, and the control group is placed in the second column. To eliminate the possible effects of daily tobacco and weekly alcohol consumption on white matter microstructure, they were added as covariates to the matrix. The mean of daily tobacco uses and weekly alcohol use was subtracted from each individual's daily tobacco and alcohol consumption. After that, 5000 permutations were carried out by *randomize* command to evaluate whether the groups were statistically different.Contrasts were processed with the help of Threshold-free cluster enhancement (TFCE). The clusters were thresholded according to the level of $p < 0.05$, and family-wise error correction (FWE) was performed to correct false-positives. These steps were applied separately for each DTI indices. The significant clusters were examined in two directions : cannabis group $>$ control group and control group $>$ cannabis group as $p < 0.05$.

2.7.2 TBSS-ROI Analysis

For the region of interest analysis, the tensor-derived parameters (FA, MD, AD, and RD) of cannabis users and non-users in the corpus callosum and superior longitudinal fasciculus were extracted. To generate the anatomic location of a region of interest, *fslmaths* command was used according to the specific intensity of the regions in the JHU White Matter Atlas. After that, fslmeants command was applied to extract the values within each region of interest (see Figures 2.5 and

2.6). In order to investigate the impact of tobacco and alcohol use on the relationship between cannabis use, psychosis risk, and DWI parameters, daily tobacco and weekly alcohol use were added as covariates. Multivariate Linear Regression analysis was performed. While performing this analysis, cannabis use and subclinical psychosis risk were included in the analysis as independent variables, DTI parameters as dependent variables and cannabis and alcohol consumption as covariates. Other important demographic variables such as gender, intelligence and education level were not included analysis as covariates since there was no significant difference between cannabis users and non-users. To evaluate statistical significance, a probability level of $p < 0.05$ was defined.

2.7.3 Statistical Analysis of Structural Network Topology

After generating connectivity matrices, graph theory metrics (global, local efficiency, and clustering coefficient) were calculated with the help of Brain Connectivity Toolbox [120] in MATLAB. For each participant, these metrics were extracted for nodes of streamlines and fractional anisotropy. In order to obtain the mean clustering coefficient and local efficiency, the averages of 114 regions were calculated. Following these, the effects of cannabis use and psychosis risk were investigated on structural topology using the Multivariate Linear Regression model, covarying for tobacco and alcohol consumption after testing assumptions of normality and homogeneity of variances. Gender, intelligence and education level were not included analysis as covariates since there was no significant difference between cannabis users and non-users.

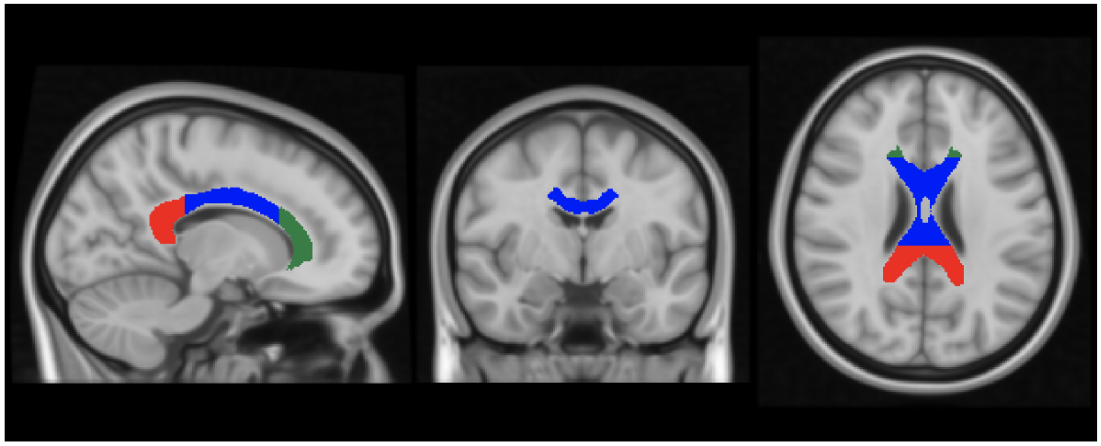

Figure 2.5: Subregions of the Corpus Callosum on MNI152 Standard Image.
Note: Corpus Callosum was generated via John Hopkins University (JHU) white matter tractography atlas in FSL.The sub-region highlighted in red represents the splenium, the sub-region highlighted in blue indicates the body, and the sub-region highlighted in green represents the genu of the corpus callosum.

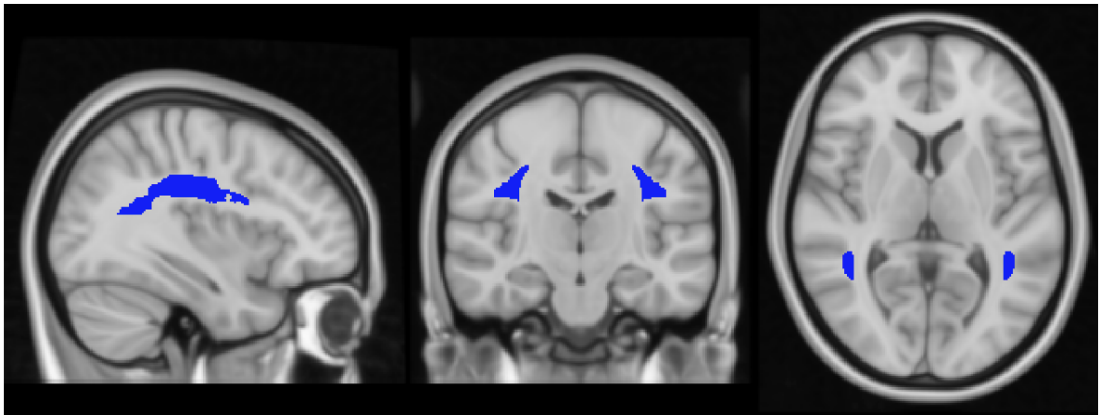

Figure 2.6: Regions of Right and Left Superior Longitudinal Fasciculus on MNI152 Standard Image.
Note: Right and left superior longitudinal fasciculus was generated with John Hopkins University (JHU) white matter tractography atlas in FSL.

Chapter 3

Results

3.1 Analysis of Demographics

The statistical analysis was performed using SPSS software, version 25.0 (SPSS, Chicago, IL, USA). The descriptive statistics included chi-square tests for categorical variables, and t-tests for continuous variables. The means, standard deviations, and p-values are presented in Table 3.1.1). Firstly, the Shapiro Wilk test was used to check whether the distribution of variables was normal or not. Demographics that met the normality criterion were compared between groups with the independent sample t-test, and the demographics that did not show normal distribution were compared with the non-parametric Mann Whitney U test.

Independent sample t-test showed that there were no age differences between cannabis users ($M = 20.40$, $SD = 1.94$) and non-users ($M = 19.76$, $SD = 1.90$) ($t\,(48) = 1.18$, $p = .24$). No significant differences in intelligence were found between cannabis group ($M = 107.42$, $SD = 16.84$) and non-users ($M = 100.24$, $SD = 12.02$) ($t\,(48) = 1.72$, $p = .09$). A chi-square test of independence demonstrated that there were no significant sex differences between groups (χ^2 $(1,\ N = 50) = .08,\ p = .76$). Additionally, education level did not differ significantly between cannabis users and non-users (χ^2 $(2,\ N = 50) = 1.17,\ p = .56$). Independent

sample t test showed that, there were significant weekly alcohol consumption between the cannabis users and control group (t (48) = 2.14, p = .04), suggesting that cannabis users consume more alcohol than non-users. Moreover, cannabis group reported that they consumed more tobacco per day compared to control group (t (48) = 2.27, p = .03).

Mann-Whitney U test showed that there were significant differences between groups in terms of CAPE-42 questionnaire including positive (U = 162.00, z = -2.76, p = .001), negative (U = 151.00, z = -2.99, p = .006) and depressive (U = 176.00, z = -1.73, p = .01) dimensions. In particular, it suggested that cannabis users have higher scores on the positive, negative and depressive dimensions compared to non-users. On the other hand, no significant difference was observed in the distress scores of positive (U = 228.00, z = -1.67, p = .09), negative (U = 244.50, z = -1.33, p = .18) and depressive (U = 225.00, z = -1.72, p = .08) dimensions between the groups.

3.2 Tract- Based Spatial Statistics Results

To understand the white matter differences between groups, a Univariate GLM analysis was carried out. The amount of alcohol consumed in a week and daily tobacco use were added to the analysis as covariates since there was a significant difference in tobacco and alcohol consumption between cannabis users and non-users.Whole brain TBSS analyses did not show significant differences in FA, MD, AD, and RD between cannabis users and non-cannabis users (TFCE corrected, FWE $p < 0.05$). Furthermore, in order to investigate whether the interaction of cannabis use and psychosis risks affect the tensor derived parameters in the corpus callosum and superior longitudinal fasciculus, indices were extracted according to JHU White Matter Atlas. FA, MD, AD and RD values were compared with Multivariate Linear Regression analysis by adding alcohol and tobacco consumption as predictors. Before performing multivariate analysis, the necessary pre-criteria such as normality and collinearity were tested. The outliers in the parameters have been removed.

As a result of analysis, the recreational cannabis use did not affect the tensor derived parameters in corpus callosum and superior longitudinal fasciculus F (8, 33) = 2.07, $p = 0.07$ Wilks' $\Lambda = .67$. Similarly, the psychosis risk did not have a significant impact on the tensor derived parameters in that region of interest F (8, 33) = 2.25, $p = 0.05$ Wilks' $\Lambda = .65$. Furthermore, there were no statistically significant effect of tobacco use F (8, 33) = 1.74, $p = 0.13$ Wilks'$\Lambda = .70$) and alcohol use F (8, 33) = .55, $p = 0.81$ Wilks' $\Lambda = .88$) on the tensor derived parameters in corpus callosum and superior longitudinal fasciculus.

3.3 Results of Parameters Based on Graph Theory

Global efficiency, mean local efficiency and mean clustering coefficient parameters for both nodes of streamlines and fractional anisotropy were obtained to understand whether cannabis use and psychosis risk have an effect on brain connectivity parameters. Multivariate Linear Regression analysis was performed by adding tobacco use per day and alcohol consumption in a week. The prerequisites such as linearity of variables, no multicollinearity and normality of residuals necessary to perform the analysis were tested. The outliers in the parameters have been removed.The outliers in the parameters have been removed.

As a result of the analysis, the recreational cannabis use does not affect the network parameters in the brain F (6, 38) = 1.71 p = 0.14 Wilks' Λ = .79. Accordingly, the subclinical psychosis risk does not impact the network parameters in the brain F (6, 38) = 1.32, p = 0.14 Wilks' Λ = .79. Additionally, there was no statistically significant effect of tobacco use (F (6, 38) = 1.25, p = 0.80 Wilks' Λ =.93) and alcohol use (F (6, 38) = 1.25, p = 0.76 Wilks' Λ =.92) on the brain connectivity parameters.

Table 3.1: Demographic characteristics of participants

	Non-Users	**Cannabis Users**	**Statistic**	**P-value**
Age	19.76 (1.90)	20.40 (1.94)	*t (48) = 1.18*	0.24
Gender (n, %)			*X2 (1, N=50)= 0.8*	.76
Male	15 (46.9 %)	17 (53.1 %)		
Female	10 (55.6 %)	8 (44.4 %)		
IQ	100.24 (12.02)	107.42 (16.84)	*t (48) = 1.72*	0.09
Education Level (n, %)			*X2 (2, N=50) = 1.17*	.56
Secondary School	4 (12.0 %)	3 (16.0 %)		
High School	20 (80.0 %)	19 (76.0 %)		
University Graduate	3 (6.0 %)	1 (2.0 %)		
Cannabis Use				
Age of onset (years)		17.36 (2.56)		
Duration of regular use (years)		3.12 (2.08)		
Frequency of use (n, %)				
Everyday		0 (0.0 %)		
More than once a week		8 (32 %)		
A few times each month		8 (32 %)		
A few times each year		9 (36 %)		
Only once or twice		0 (0.0 %)		
Other substance experience(n,%)				
Never tried		17 (68 %)		
Experienced		8 (32%)		
Alcohol use (week)	1.48 (2.17)	2.75 (2.02)	*t (48) = 2.14*	0.04 *
Tobacco use (day)	5.81 (6.74)	10.58 (8.17)	*t (48) = 2.27*	0.03 *
CAPE-42 questionnaire				
Total CAPE	63.20 (8.85)	79.36 (17.44)		< 0.01 **
Positive Dimension	27.76 (4.57)	32.20 (5.03)		< 0.01 **
Negative Dimension	22.80 (4.14)	30.16 (8.48)		< 0.01 **
Depressive Dimension	11.48 (2.20)	15.04 (5.07)		< 0.01 **
The positive dimension distress	3.00 (1.63)	4.00 (2.34)		0.09
The negative dimension distress	3.32 (2.51)	4.28 (2.82)		0.18
The depressive dimension distress	3.08 (1.68)	4.40 (2.72)		0.08

Chapter 4

Discussion and Conclusion

This thesis aimed to investigate whether recreational cannabis use in adolescence increases the risk for subclinical psychosis and the effects of cannabis use and psychosis risk on brain white matter integrity and structural topology. In order to assess the microstructural and topological structure in the brain, two different analysis methods were used: ROI-based Tract-Based Spatial Statistics (TBSS), which examines white matter microstructure in the specific regions Structural Connectivity analysis which examines structural topology in brain. The confounding effects of alcohol and tobacco consumption were controlled in all analyzes.

Our main findings were as follows: (1) adolescent cannabis users are at greater risk of subclinical psychosis than non-users; (2) cannabis use and psychosis risk had no effect on the tensor-derived parameters in the corpus callosum and superior longitudinal fasciculus, as well as on the parameters related to the structural topology of the brain.

The current thesis found that recreational cannabis use in adolescence may increase the subclinical psychosis risk. This result is similar to earlier investigations. The study by Kuepper et al. (2011) focused on whether cannabis in adolescence elevates the risk for psychotic symptoms in the general population aged 14 to

24 years. They showed that regular cannabis consumption increased adolescents' risk for developing psychotic disorders by leading them to experience persistent subclinical psychotic symptoms that are normally transitory and quite common [131]. Beardslee and colleagues (2016) revealed that regular cannabis use during adolescence might increase subclinical and clinical psychosis risk [132]. Similarly, Bechtold et al. (2016) found that the level of subsequent subclinical symptoms of adolescents who engaged in regular cannabis use rose by 21 % each year and the effect of cumulative regular cannabis use on consecutive subclinical psychotic symptoms continued even after a year of stopping cannabis consumption. Lastly, as a result of both observational and experimental research, cannabis use has an important role in the initiation and persistence of psychotic disorders [133].

On the other hand, some authors were more skeptical about findings of cannabis-induced psychotic-like experiences. The first criticism is that people who use cannabis may be psychologically more vulnerable than non-users. However, Newbury and colleagues conducted a longitudinal study that controlled for psychotic symptoms at age 11, and they still revealed a significant relationship between cannabis use and later psychotic symptoms [134]. The second criticism is that people may use cannabis to alleviate their symptoms, but there is limited evidence in the literature [135]. One study found that once minor psychotic symptoms first appear, people prefer to use less cannabis [136]. In addition to these, there are criticisms that other substances accompanying the use of cannabis might affect psychosis risk. However, several studies did not find sufficient effects to refute the impact of cannabis use after looking for the effect of tobacco consumption [135].

The second finding in the study is that the ROI-based TBSS analysis with adjusted covariates showed that cannabis use and psychosis risk do not affect white matter integrity in corpus callosum and superior longitudinal fasciculus. Despite many studies in the literature suggesting the opposite, there are some studies in line with our findings. The result of the earlier study investigating the use of cannabis on brain development during adolescence revealed that it had no effect on white matter, and they explained that frequent cannabis use might not have neurotoxic impact [137]. Another study revealed that cannabis use has no effect

on white matter integrity in adolescents and adults, while frequent alcohol use does [138]. Lastly, Cousijn et al (2021) did not find a difference between near-daily cannabis users and controls regarding whole-brain white matter integrity. There are not many studies in the literature investigating the effect of subclinical psychosis risk on brain white matter integrity in a healthy population [139]. The majority of studies generally focused on individuals in the high-risk group or diagnosed with first-episode psychosis, and they revealed that white matter integrity is impaired due to the risk of psychosis.

The third finding in the study is that Structural Network Connectivity with adjusted covariates showed that cannabis use and psychosis risk do not affect the global brain network connectivity parameters, including global efficiency, mean local efficiency, and mean clustering coefficient for streamlining fractional anisotropy nodes. Although Kim et al. (2012) found significant alterations, especially in these parameters, their sample size was markedly smaller than ours, and they also included an adult population. However, a recent study investigating the effects of cannabis use disorder on brain structure and function in African Americans revealed that cannabis users show no disruption in terms of structural connectivity, whereas they show functional dysconnectivity [140]. Even though functional changes have been widely found across cognitive domains of adolescent and adult cannabis users, structural changes related to cannabis use have not provided consistent results [141]. A whole brain structural connectome study, which investigates the impact of cannabis use on brain global-local graph theory metrics, revealed reduced local efficiency and global efficiency in individuals with psychotic like experiences [142]. Similarly, another study suggested that individuals with psychotic like experiences have altered network organization in several metrics compared to healthy control [143]. However, these studies mainly focused on the adult and clinical-level populations. This current thesis first sought to understand the relationship between recreational cannabis use and subclinical psychosis risk in a healthy sample. Since adolescence is a critical period for brain development, it also investigated whether cannabis use and the risk of psychosis together have an effect on brain development with two different analysis methods. This study contributes to the literature since no study examines the

effects of recreational (e.g., not daily base) cannabis use and subclinical psychosis with two different methods. Even though TBSS is a frequently used method in both cannabis and psychosis studies, the number of studies with structural network analysis is relatively few. Therefore, combining these two analysis methods aimed to provide the reader with more detailed information.

On the contrary, this study has several methodological shortcomings. Firstly, the relatively small sample size was used because of strict inclusion and exclusion criteria. Secondly, this is a cross-sectional study, and longitudinal studies are needed to understand the cumulative effect of cannabis consumption on brain development. Furthermore, only two regions were examined in this thesis, future studies shoud focus on more regions in TBSS analysis. Similarly, examining other topology-related metrics in structural network analysis in further studies may provide more reliable and qualified results..Objective measures such as blood and urine analysis could be included in the study to evaluate the recent use of cannabis. The difficulty of reliably measuring the history of cannabis use is a common problem in cannabis studies and potentially contributes to mixed results [139]. While the confounding effects of alcohol and tobacco could be controlled in this study, other drug use effects were not included. Because the drug usage was minimal and reported to be experienced once or twice by the participants, the effects of other drug use should be considered in future studies. Finally, future studies may focus on how brain development (brain structural connectivity and white matter integrity) mediates the relationship between cannabis use and subclinical psychosis risk. In particular, including chronic cannabis use in the study and examining chronic, recreational, and control groups may provide important insights.

In conclusion, recreational cannabis use during adolescence increases the subclinical psychosis risk. However, when the effects of psychosis risk and cannabis use are examined in terms of brain development, it is not observed in white matter microstructure and structural topology. These results suggest that recreational cannabis use during adolescence has an impact on psychosis risk, but their interaction did not affect brain development.

Bibliography

[1] E. Herbert, P. Engel-Hills, C. Hattingh, J.-P. Fouche, M. Kidd, C. Lochner, M. J. Kotze, and S. J. van Rensburg, "Fractional anisotropy of white matter, disability and blood iron parameters in multiple sclerosis," *Metabolic brain disease*, vol. 33, no. 2, pp. 545–557, 2018.

[2] D.-J. Kim, P. D. Skosnik, H. Cheng, B. J. Pruce, M. S. Brumbaugh, J. M. Vollmer, W. P. Hetrick, B. F. O'Donnell, O. Sporns, A. Puce, *et al.*, "Structural network topology revealed by white matter tractography in cannabis users: a graph theoretical analysis," *Brain connectivity*, vol. 1, no. 6, pp. 473–483, 2011.

[3] M. E. Abood and B. R. Martin, "Neurobiology of marijuana abuse," *Trends in Pharmacological Sciences*, vol. 13, pp. 201–206, 1992.

[4] L. Greaves and N. Hemsing, "Sex and gender interactions on the use and impact of recreational cannabis," *International journal of environmental research and public health*, vol. 17, no. 2, p. 509, 2020.

[5] J.-M. N. Ferland and Y. L. Hurd, "Deconstructing the neurobiology of cannabis use disorder," *Nature Neuroscience*, vol. 23, no. 5, pp. 600–610, 2020.

[6] G. Blest-Hopley, M. Colizzi, V. Giampietro, and S. Bhattacharyya, "Is the adolescent brain at greater vulnerability to the effects of cannabis? a narrative review of the evidence," *Frontiers in psychiatry*, vol. 11, p. 859, 2020.

[7] "European drug report 2020."

[8] I. Ö. Ilhan, F. Yıldırım, H. Demirbaş, and Y. B. Doğan, "Prevalence and sociodemographic correlates of substance use in a university-student sample in turkey," *International journal of public health*, vol. 54, no. 1, pp. 40–44, 2009.

[9] L. Degenhardt, W. Hall, and M. Lynskey, "Alcohol, cannabis and tobacco use among australians: a comparison of their associations with other drug use and use disorders, affective and anxiety disorders, and psychosis," *Addiction*, vol. 96, no. 11, pp. 1603–1614, 2001.

[10] K. Chen and D. B. Kandel, "The natural history of drug use from adolescence to the mid-thirties in a general population sample.," *American journal of public health*, vol. 85, no. 1, pp. 41–47, 1995.

[11] A. M. Elkashef, R. A. Rawson, A. L. Anderson, S.-H. Li, T. Holmes, E. V. Smith, N. Chiang, R. Kahn, F. Vocci, W. Ling, *et al.*, "Bupropion for the treatment of methamphetamine dependence," *Neuropsychopharmacology*, vol. 33, no. 5, pp. 1162–1170, 2008.

[12] Z. D. Cooper and M. Haney, "Actions of delta-9-tetrahydrocannabinol in cannabis: relation to use, abuse, dependence," *International Review of Psychiatry*, vol. 21, no. 2, pp. 104–112, 2009.

[13] M. Glass and C. C. Felder, "Concurrent stimulation of cannabinoid cb1 and dopamine d2 receptors augments camp accumulation in striatal neurons: evidence for a gs linkage to the cb1 receptor," *Journal of Neuroscience*, vol. 17, no. 14, pp. 5327–5333, 1997.

[14] J. Jacobus and S. F Tapert, "Effects of cannabis on the adolescent brain," *Current pharmaceutical design*, vol. 20, no. 13, pp. 2186–2193, 2014.

[15] E. S. Onaivi, H. Ishiguro, S. Gu, and Q.-R. Liu, "Cns effects of cb2 cannabinoid receptors: beyond neuro-immuno-cannabinoid activity," *Journal of psychopharmacology*, vol. 26, no. 1, pp. 92–103, 2012.

[16] J. Wu, "Cannabis, cannabinoid receptors, and endocannabinoid system: Yesterday, today, and tomorrow," 2019.

[17] J. Becker, M. P. Schaub, G. Gmel, and S. Haug, "Cannabis use and other predictors of the onset of daily cigarette use in young men: what matters most? results from a longitudinal study," *BMC Public Health*, vol. 15, no. 1, pp. 1–10, 2015.

[18] E. Zamberletti, T. Rubino, and D. Parolaro, "The endocannabinoid system and schizophrenia: integration of evidence," *Current pharmaceutical design*, vol. 18, no. 32, pp. 4980–4990, 2012.

[19] "Cannabis (marijuanna) drug facts," 2019.

[20] S. M. Sawyer, P. S. Azzopardi, D. Wickremarathne, and G. C. Patton, "The age of adolescence," *The Lancet Child & Adolescent Health*, vol. 2, no. 3, pp. 223–228, 2018.

[21] G. Z. Tau and B. S. Peterson, "Normal development of brain circuits," *Neuropsychopharmacology*, vol. 35, no. 1, pp. 147–168, 2010.

[22] C. Lebel and C. Beaulieu, "Longitudinal development of human brain wiring continues from childhood into adulthood," *Journal of Neuroscience*, vol. 31, no. 30, pp. 10937–10947, 2011.

[23] M. G. Bossong and R. J. Niesink, "Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia," *Progress in neurobiology*, vol. 92, no. 3, pp. 370–385, 2010.

[24] A. P. Abreu and U. B. Kaiser, "Pubertal development and regulation," *The lancet Diabetes & endocrinology*, vol. 4, no. 3, pp. 254–264, 2016.

[25] F. M. Benes, "Why does psychosis develop during adolescence and early adulthood?," *Current Opinion in Psychiatry*, vol. 16, no. 3, pp. 317–319, 2003.

[26] H. P. Blumberg, J. Kaufman, A. Martin, R. Whiteman, J. H. Zhang, J. C. Gore, D. S. Charney, J. H. Krystal, and B. S. Peterson, "Amygdala and hippocampal volumes in adolescents and adults with bipolar disorder," *Archives of general psychiatry*, vol. 60, no. 12, pp. 1201–1208, 2003.

[27] M. Arain, M. Haque, L. Johal, P. Mathur, W. Nel, A. Rais, R. Sandhu, and S. Sharma, "Maturation of the adolescent brain," *Neuropsychiatric disease and treatment*, vol. 9, p. 449, 2013.

[28] A. Griffin, "Adolescent neurological development and implications for health and well-being," in *Healthcare*, vol. 5, p. 62, Multidisciplinary Digital Publishing Institute, 2017.

[29] B. J. Casey, S. Getz, and A. Galvan, "The adolescent brain," *Developmental review*, vol. 28, no. 1, pp. 62–77, 2008.

[30] S. L. Rankin, G. D. Partlow, R. D. McCurdy, E. D. Giles, and K. R. Fisher, "Postnatal neurogenesis in the vasopressin and oxytocin-containing nucleus of the pig hypothalamus," *Brain research*, vol. 971, no. 2, pp. 189–196, 2003.

[31] F. M. Benes, J. B. Taylor, and M. C. Cunningham, "Convergence and plasticity of monoaminergic systems in the medial prefrontal cortex during the postnatal period: implications for the development of psychopathology," *Cerebral Cortex*, vol. 10, no. 10, pp. 1014–1027, 2000.

[32] A. Colver and S. Longwell, "New understanding of adolescent brain development: relevance to transitional healthcare for young people with long term conditions," *Archives of disease in childhood*, vol. 98, no. 11, pp. 902–907, 2013.

[33] L. P. Spear, "The adolescent brain and age-related behavioral manifestations," *Neuroscience & biobehavioral reviews*, vol. 24, no. 4, pp. 417–463, 2000.

[34] D. M. Walker, M. R. Bell, C. Flores, J. M. Gulley, J. Willing, and M. J. Paul, "Adolescence and reward: making sense of neural and behavioral changes amid the chaos," *Journal of Neuroscience*, vol. 37, no. 45, pp. 10855–10866, 2017.

[35] M. Ellgren, A. Artmann, O. Tkalych, A. Gupta, H. Hansen, S. Hansen, L. Devi, and Y. Hurd, "Dynamic changes of the endogenous cannabinoid

and opioid mesocorticolimbic systems during adolescence: Thc effects," *European Neuropsychopharmacology*, vol. 18, no. 11, pp. 826–834, 2008.

[36] M. Martin, C. Ledent, M. Parmentier, R. Maldonado, and O. Valverde, "Involvement of cb1 cannabinoid receptors in emotional behaviour," *Psychopharmacology*, vol. 159, no. 4, pp. 379–387, 2002.

[37] L. J. Sim-Selley and B. R. Martin, "Effect of chronic administration ofr-(+)-[2, 3-dihydro-5-methyl-3-[(morpholinyl) methyl] pyrrolo [1, 2, 3-de]-1, 4-benzoxazinyl]-(1-naphthalenyl) methanone mesylate (win55, 212-2) or δ9-tetrahydrocannabinol on cannabinoid receptor adaptation in mice," *Journal of Pharmacology and Experimental Therapeutics*, vol. 303, no. 1, pp. 36–44, 2002.

[38] J. Hirvonen, R. Goodwin, C.-T. Li, G. Terry, S. Zoghbi, C. Morse, V. Pike, N. Volkow, M. Huestis, and R. Innis, "Reversible and regionally selective downregulation of brain cannabinoid cb1 receptors in chronic daily cannabis smokers," *Molecular psychiatry*, vol. 17, no. 6, pp. 642–649, 2012.

[39] K. M. Lisdahl, E. R. Gilbart, N. E. Wright, and S. Shollenbarger, "Dare to delay? the impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function," *Frontiers in psychiatry*, vol. 4, p. 53, 2013.

[40] R. D. Fields, "Change in the brain's white matter," *Science*, vol. 330, no. 6005, pp. 768–769, 2010.

[41] N. Barnea-Goraly, V. Menon, M. Eckert, L. Tamm, R. Bammer, A. Karchemskiy, C. C. Dant, and A. L. Reiss, "White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study," *Cerebral cortex*, vol. 15, no. 12, pp. 1848–1854, 2005.

[42] J. N. Giedd, J. Blumenthal, N. O. Jeffries, F. X. Castellanos, H. Liu, A. Zijdenbos, T. Paus, A. C. Evans, and J. L. Rapoport, "Brain development during childhood and adolescence: a longitudinal mri study," *Nature neuroscience*, vol. 2, no. 10, pp. 861–863, 1999.

[43] T. Paus, A. Zijdenbos, K. Worsley, D. L. Collins, J. Blumenthal, J. N. Giedd, J. L. Rapoport, and A. C. Evans, "Structural maturation of neural pathways in children and adolescents: in vivo study," *Science*, vol. 283, no. 5409, pp. 1908–1911, 1999.

[44] A. Giorgio, L. Santelli, V. Tomassini, R. Bosnell, S. Smith, N. De Stefano, and H. Johansen-Berg, "Age-related changes in grey and white matter structure throughout adulthood," *Neuroimage*, vol. 51, no. 3, pp. 943–951, 2010.

[45] H. M. Feldman, J. D. Yeatman, E. S. Lee, L. H. Barde, and S. Gaman-Bean, "Diffusion tensor imaging: a review for pediatric researchers and clinicians," *Journal of developmental and behavioral pediatrics: JDBP*, vol. 31, no. 4, p. 346, 2010.

[46] C. K. Tamnes, M. M. Herting, A.-L. Goddings, R. Meuwese, S.-J. Blakemore, R. E. Dahl, B. Güroğlu, A. Raznahan, E. R. Sowell, E. A. Crone, *et al.*, "Development of the cerebral cortex across adolescence: a multisample study of inter-related longitudinal changes in cortical volume, surface area, and thickness," *Journal of Neuroscience*, vol. 37, no. 12, pp. 3402–3412, 2017.

[47] C. K. Tamnes and K. Mills, "Imaging structural brain development in childhood and adolescence," 2020.

[48] C. K. Tamnes, D. R. Roalf, A.-L. Goddings, and C. Lebel, "Diffusion mri of white matter microstructure development in childhood and adolescence: Methods, challenges and progress," *Developmental cognitive neuroscience*, vol. 33, pp. 161–175, 2018.

[49] P. Mukherjee, J. H. Miller, J. S. Shimony, T. E. Conturo, B. C. Lee, C. R. Almli, and R. C. McKinstry, "Normal brain maturation during childhood: developmental trends characterized with diffusion-tensor mr imaging," *Radiology*, vol. 221, no. 2, pp. 349–358, 2001.

[50] L. Hermoye, C. Saint-Martin, G. Cosnard, S.-K. Lee, J. Kim, M.-C. Nassogne, R. Menten, P. Clapuyt, P. K. Donohue, K. Hua, *et al.*, "Pediatric diffusion tensor imaging: normal database and observation of the white matter maturation in early childhood," *Neuroimage*, vol. 29, no. 2, pp. 493–504, 2006.

[51] C. Lebel, C. Rasmussen, K. Wyper, L. Walker, G. Andrew, J. Yager, and C. Beaulieu, "Brain diffusion abnormalities in children with fetal alcohol spectrum disorder," *Alcoholism: Clinical and Experimental Research*, vol. 32, no. 10, pp. 1732–1740, 2008.

[52] M. E. Thomason and P. M. Thompson, "Diffusion imaging, white matter, and psychopathology," *Annual review of clinical psychology*, vol. 7, pp. 63–85, 2011.

[53] M. R. Asato, R. Terwilliger, J. Woo, and B. Luna, "White matter development in adolescence: a dti study," *Cerebral cortex*, vol. 20, no. 9, pp. 2122–2131, 2010.

[54] S. T. Baker, D. I. Lubman, M. Yücel, N. B. Allen, S. Whittle, B. D. Fulcher, A. Zalesky, and A. Fornito, "Developmental changes in brain network hub connectivity in late adolescence," *Journal of Neuroscience*, vol. 35, no. 24, pp. 9078–9087, 2015.

[55] G. Collin and M. P. Van Den Heuvel, "The ontogeny of the human connectome: development and dynamic changes of brain connectivity across the life span," *The Neuroscientist*, vol. 19, no. 6, pp. 616–628, 2013.

[56] M. M. Koenis, R. M. Brouwer, M. P. van den Heuvel, R. C. Mandl, I. L. van Soelen, R. S. Kahn, D. I. Boomsma, and H. E. Hulshoff Pol, "Development of the brain's structural network efficiency in early adolescence: a longitudinal dti twin study," *Human Brain Mapping*, vol. 36, no. 12, pp. 4938–4953, 2015.

[57] Z. Chen, M. Liu, D. W. Gross, and C. Beaulieu, "Graph theoretical analysis of developmental patterns of the white matter network," *Frontiers in human neuroscience*, vol. 7, p. 716, 2013.

[58] W. Hall, J. Leung, and M. Lynskey, "The effects of cannabis use on the development of adolescents and young adults," *Annual Review of Developmental Psychology*, vol. 2, pp. 461–483, 2020.

[59] M. Ashtari, K. Cervellione, J. Cottone, B. A. Ardekani, and S. Kumra, "Diffusion abnormalities in adolescents and young adults with a history of heavy cannabis use," *Journal of psychiatric research*, vol. 43, no. 3, pp. 189–204, 2009.

[60] M. Yücel, E. Bora, D. I. Lubman, N. Solowij, W. J. Brewer, S. M. Cotton, P. Conus, M. J. Takagi, A. Fornito, S. J. Wood, *et al.*, "The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample," *Schizophrenia bulletin*, vol. 38, no. 2, pp. 316–330, 2012.

[61] S. Bava, L. R. Frank, T. McQueeny, B. C. Schweinsburg, A. D. Schweinsburg, and S. F. Tapert, "Altered white matter microstructure in adolescent substance users," *Psychiatry Research: Neuroimaging*, vol. 173, no. 3, pp. 228–237, 2009.

[62] D. Arnone, T. R. Barrick, S. Chengappa, C. E. Mackay, C. A. Clark, and M. Abou-Saleh, "Corpus callosum damage in heavy marijuana use: preliminary evidence from diffusion tensor tractography and tract-based spatial statistics," *Neuroimage*, vol. 41, no. 3, pp. 1067–1074, 2008.

[63] S. A. Gruber, M. K. Dahlgren, K. A. Sagar, A. Gönenç, and S. E. Lukas, "Worth the wait: effects of age of onset of marijuana use on white matter and impulsivity," *Psychopharmacology*, vol. 231, no. 8, pp. 1455–1465, 2014.

[64] K. A. Epstein and S. Kumra, "Altered cortical maturation in adolescent cannabis users with and without schizophrenia," *Schizophrenia Research*, vol. 162, no. 1-3, pp. 143–152, 2015.

[65] S. G. Shollenbarger, J. Price, J. Wieser, and K. Lisdahl, "Poorer frontolimbic white matter integrity is associated with chronic cannabis use, faah genotype, and increased depressive and apathy symptoms in adolescents and young adults," *NeuroImage: Clinical*, vol. 8, pp. 117–125, 2015.

[66] J. M. Orr, C. J. Paschall, and M. T. Banich, "Recreational marijuana use impacts white matter integrity and subcortical (but not cortical) morphometry," *NeuroImage: Clinical*, vol. 12, pp. 47–56, 2016.

[67] E. J. Brand and Z. Zhao, "Cannabis in chinese medicine: are some traditional indications referenced in ancient literature related to cannabinoids?," *Frontiers in pharmacology*, p. 108, 2017.

[68] J. M. Bostwick, "Blurred boundaries: the therapeutics and politics of medical marijuana," in *Mayo Clinic Proceedings*, vol. 87, pp. 172–186, Elsevier, 2012.

[69] M. Colizzi and S. Bhattacharyya, "Does cannabis composition matter? differential effects of delta-9-tetrahydrocannabinol and cannabidiol on human cognition," *Current Addiction Reports*, vol. 4, no. 2, pp. 62–74, 2017.

[70] A. Johns, "Psychiatric effects of cannabis," *The British Journal of Psychiatry*, vol. 178, no. 2, pp. 116–122, 2001.

[71] A. Hasan, R. von Keller, C. M. Friemel, W. Hall, M. Schneider, D. Koethe, F. M. Leweke, W. Strube, and E. Hoch, "Cannabis use and psychosis: a review of reviews," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 270, no. 4, pp. 403–412, 2020.

[72] M. Griffith-Lendering, J. Wigman, A. Prince van Leeuwen, S. Huijbregts, A. C. Huizink, J. Ormel, F. C. Verhulst, J. van Os, H. Swaab, and W. A. Vollebergh, "Cannabis use and vulnerability for psychosis in early adolescence–a trails study," *Addiction*, vol. 108, no. 4, pp. 733–740, 2013.

[73] E. J. Khantzian, "The self-medication hypothesis of substance use disorders: A reconsideration and recent applications," *Harvard review of psychiatry*, vol. 4, no. 5, pp. 231–244, 1997.

[74] T. H. Moore, S. Zammit, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M. Burke, and G. Lewis, "Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review," *The Lancet*, vol. 370, no. 9584, pp. 319–328, 2007.

[75] R. F. Ferdinand, F. Sondeijker, J. Van Der Ende, J.-P. Selten, A. Huizink, and F. C. Verhulst, "Cannabis use predicts future psychotic symptoms, and vice versa," *Addiction*, vol. 100, no. 5, pp. 612–618, 2005.

[76] M. A. Bloomfield, A. H. Ashok, N. D. Volkow, and O. D. Howes, "The effects of δ9-tetrahydrocannabinol on the dopamine system," *Nature*, vol. 539, no. 7629, pp. 369–377, 2016.

[77] F. H. Farah, "Schizophrenia: An overview," *Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm*, vol. 12, no. 02, 2018.

[78] D. T. Malone, M. N. Hill, and T. Rubino, "Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models," *British journal of pharmacology*, vol. 160, no. 3, pp. 511–522, 2010.

[79] J. Miettunen, S. Törmänen, G. K. Murray, P. B. Jones, P. Mäki, H. Ebeling, I. Moilanen, A. Taanila, M. Heinimaa, M. Joukamaa, *et al.*, "Association of cannabis use with prodromal symptoms of psychosis in adolescence," *The British journal of psychiatry*, vol. 192, no. 6, pp. 470–471, 2008.

[80] E. O'Hanlon, A. Leemans, I. Kelleher, M. C. Clarke, S. Roddy, H. Coughlan, M. Harley, F. Amico, M. J. Hoscheit, L. Tiedt, *et al.*, "White matter differences among adolescents reporting psychotic experiences: a population-based diffusion magnetic resonance imaging study," *JAMA psychiatry*, vol. 72, no. 7, pp. 668–677, 2015.

[81] R. Linscott and J. Van Os, "An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders," *Psychological medicine*, vol. 43, no. 6, pp. 1133–1149, 2013.

[82] J. Schoorl, M. C. Barbu, X. Shen, M. R. Harris, M. J. Adams, H. C. Whalley, and S. M. Lawrie, "Grey and white matter associations of psychotic-like experiences in a general population sample (uk biobank)," *Translational psychiatry*, vol. 11, no. 1, pp. 1–11, 2021.

[83] T. Paus, "Growth of white matter in the adolescent brain: myelin or axon?," *Brain and cognition*, vol. 72, no. 1, pp. 26–35, 2010.

[84] S. G. Waxman, J. D. Kocsis, P. K. Stys, *et al.*, *The axon: structure, function, and pathophysiology*. Oxford University Press, USA, 1995.

[85] A. Miller, R. Alston, and J. Corsellis, "Variation with age in the volumes of grey and white matter in the cerebral hemispheres of man: measurements with an image analyser," *Neuropathology and applied neurobiology*, vol. 6, no. 2, pp. 119–132, 1980.

[86] B. D. Peters and K. H. Karlsgodt, "White matter development in the early stages of psychosis," *Schizophrenia research*, vol. 161, no. 1, pp. 61–69, 2015.

[87] K. H. Karlsgodt, T. A. Niendam, C. E. Bearden, and T. D. Cannon, "White matter integrity and prediction of social and role functioning in subjects at ultra-high risk for psychosis," *Biological psychiatry*, vol. 66, no. 6, pp. 562–569, 2009.

[88] C. Wang, F. Ji, Z. Hong, J. Poh, R. Krishnan, J. Lee, G. Rekhi, R. Keefe, R. Adcock, S. Wood, *et al.*, "Disrupted salience network functional connectivity and white-matter microstructure in persons at risk for psychosis: findings from the lyriks study," *Psychological medicine*, vol. 46, no. 13, pp. 2771–2783, 2016.

[89] J. Saito, M. Hori, T. Nemoto, N. Katagiri, K. Shimoji, S. Ito, N. Tsujino, T. Yamaguchi, N. Shiraga, S. Aoki, *et al.*, "Longitudinal study examining abnormal white matter integrity using a tract-specific analysis in individuals with a high risk for psychosis," *Psychiatry and Clinical Neurosciences*, vol. 71, no. 8, pp. 530–541, 2017.

[90] P. DeRosse, T. Ikuta, B. D. Peters, K. H. Karlsgodt, P. R. Szeszko, and A. K. Malhotra, "Adding insult to injury: childhood and adolescent risk factors for psychosis predict lower fractional anisotropy in the superior longitudinal fasciculus in healthy adults," *Psychiatry Research: Neuroimaging*, vol. 224, no. 3, pp. 296–302, 2014.

[91] V. A. Mittal, D. J. Dean, J. A. Bernard, J. M. Orr, A. Pelletier-Baldelli, E. E. Carol, T. Gupta, J. Turner, D. R. Leopold, B. L. Robustelli, *et al.*, "Neurological soft signs predict abnormal cerebellar-thalamic tract development and negative symptoms in adolescents at high risk for psychosis: a longitudinal perspective," *Schizophrenia bulletin*, vol. 40, no. 6, pp. 1204–1215, 2014.

[92] C. Clemm von Hohenberg, O. Pasternak, M. Kubicki, T. Ballinger, M.-A. Vu, T. Swisher, K. Green, M. Giwerc, B. Dahlben, J. M. Goldstein, *et al.*, "White matter microstructure in individuals at clinical high risk of psychosis: a whole-brain diffusion tensor imaging study," *Schizophrenia bulletin*, vol. 40, no. 4, pp. 895–903, 2014.

[93] J. A. Bernard, J. M. Orr, and V. A. Mittal, "Abnormal hippocampal–thalamic white matter tract development and positive symptom course in individuals at ultra-high risk for psychosis," *NPJ schizophrenia*, vol. 1, no. 1, pp. 1–6, 2015.

[94] C. Rapp, H. Bugra, A. Riecher-Rossler, C. Tamagni, and S. Borgwardt, "Effects of cannabis use on human brain structure in psychosis: a systematic review combining in vivo structural neuroimaging and post mortem studies," *Current pharmaceutical design*, vol. 18, no. 32, pp. 5070–5080, 2012.

[95] S. Haller, L. Curtis, M. Badan, S. Bessero, M. Albom, F. Chantraine, A. Alimenti, K.-O. Lovblad, P. Giannakopoulos, and M. Merlo, "Combined grey matter vbm and white matter tbss analysis in young first episode psychosis patients with and without cannabis consumption," *Brain Topography*, vol. 26, no. 4, pp. 641–647, 2013.

[96] N. Dekker, A. Smeerdijk, R. Wiers, J. Duits, G. Van Gelder, K. Houben, G. Schippers, D. Linszen, and L. De Haan, "Implicit and explicit affective associations towards cannabis use in patients with recent-onset schizophrenia and healthy controls," *Psychological Medicine*, vol. 40, no. 8, pp. 1325–1336, 2010.

[97] S. Michielse, I. Lange, J. Bakker, L. Goossens, S. Verhagen, M. Wichers, R. Lieverse, K. Schruers, T. van Amelsvoort, J. van Os, *et al.*, "White matter microstructure and network-connectivity in emerging adults with subclinical psychotic experiences," *Brain imaging and behavior*, vol. 14, no. 5, pp. 1876–1888, 2020.

[98] R. M. Murray, A. Englund, A. Abi-Dargham, D. A. Lewis, M. Di Forti, C. Davies, M. Sherif, P. McGuire, and D. C. D'Souza, "Cannabis-associated psychosis: Neural substrate and clinical impact," *Neuropharmacology*, vol. 124, pp. 89–104, 2017.

[99] A. Fitsiori, D. Nguyen, A. Karentzos, J. Delavelle, and M. Vargas, "The corpus callosum: white matter or terra incognita," *The British journal of radiology*, vol. 84, no. 997, pp. 5–18, 2011.

[100] J. Foong, M. Maier, C. Clark, G. Barker, D. Miller, and M. Ron, "Neuropathological abnormalities of the corpus callosum in schizophrenia: a diffusion tensor imaging study," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 68, no. 2, pp. 242–244, 2000.

[101] I. Agartz, J. L. Andersson, and S. Skare, "Abnormal brain white matter in schizophrenia: a diffusion tensor imaging study," *Neuroreport*, vol. 12, no. 10, pp. 2251–2254, 2001.

[102] B. A. Ardekani, J. Nierenberg, M. J. Hoptman, D. C. Javitt, and K. O. Lim, "Mri study of white matter diffusion anisotropy in schizophrenia," *Neuroreport*, vol. 14, no. 16, pp. 2025–2029, 2003.

[103] E. Bora, A. Fornito, J. Radua, M. Walterfang, M. Seal, S. J. Wood, M. Yücel, D. Velakoulis, and C. Pantelis, "Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis," *Schizophrenia research*, vol. 127, no. 1-3, pp. 46–57, 2011.

[104] F. Carletti, J. B. Woolley, S. Bhattacharyya, R. Perez-Iglesias, P. Fusar Poli, L. Valmaggia, M. R. Broome, E. Bramon, L. Johns, V. Giampietro, *et al.*, "Alterations in white matter evident before the onset of psychosis," *Schizophrenia bulletin*, vol. 38, no. 6, pp. 1170–1179, 2012.

[105] N. Katagiri, C. Pantelis, T. Nemoto, A. Zalesky, M. Hori, K. Shimoji, J. Saito, S. Ito, D. B. Dwyer, I. Fukunaga, *et al.*, "A longitudinal study investigating sub-threshold symptoms and white matter changes in individuals with an 'at risk mental state'(arms)," *Schizophrenia Research*, vol. 162, no. 1-3, pp. 7–13, 2015.

[106] B. Peters, N. Schmitz, P. Dingemans, T. Van Amelsvoort, D. Linszen, L. De Haan, C. Majoie, and G. den Heeten, "Preliminary evidence for reduced frontal white matter integrity in subjects at ultra-high-risk for psychosis.," *Schizophrenia research*, vol. 111, no. 1-3, pp. 192–193, 2009.

[107] R. Nakajima, M. Kinoshita, H. Shinohara, and M. Nakada, "The superior longitudinal fascicle: reconsidering the fronto-parietal neural network based on anatomy and function," *Brain imaging and behavior*, vol. 14, no. 6, pp. 2817–2830, 2020.

[108] N. Vijayakumar, N. B. Allen, G. Youssef, M. Dennison, M. Yücel, J. G. Simmons, and S. Whittle, "Brain development during adolescence: A mixed-longitudinal investigation of cortical thickness, surface area, and volume," *Human brain mapping*, vol. 37, no. 6, pp. 2027–2038, 2016.

[109] P. K. Patel, L. D. Leathem, D. L. Currin, and K. H. Karlsgodt, "Adolescent neurodevelopment and vulnerability to psychosis," *Biological Psychiatry*, vol. 89, no. 2, pp. 184–193, 2021.

[110] A. Schwehm, D. G. Robinson, J. A. Gallego, K. H. Karlsgodt, T. Ikuta, B. D. Peters, A. K. Malhotra, and P. R. Szeszko, "Age and sex effects on white matter tracts in psychosis from adolescence through middle adulthood," *Neuropsychopharmacology*, vol. 41, no. 10, pp. 2473–2480, 2016.

[111] E. González-Reimers, C. Martín-González, L. Romero-Acevedo, G. Quintero-Platt, E. Gonzalez-Arnay, and F. Santolaria-Fernández,

"Effects of alcohol on the corpus callosum," in *Neuroscience of Alcohol*, pp. 143–152, Elsevier, 2019.

[112] A. L. Alexander, J. E. Lee, M. Lazar, and A. S. Field, "Diffusion tensor imaging of the brain," *Neurotherapeutics*, vol. 4, no. 3, pp. 316–329, 2007.

[113] L. J. O'Donnell and C.-F. Westin, "An introduction to diffusion tensor image analysis," *Neurosurgery Clinics*, vol. 22, no. 2, pp. 185–196, 2011.

[114] J. M. Soares, P. Marques, V. Alves, and N. Sousa, "A hitchhiker's guide to diffusion tensor imaging," *Frontiers in neuroscience*, vol. 7, p. 31, 2013.

[115] A. Fellgiebel, P. Wille, M. J. Müller, G. Winterer, A. Scheurich, G. Vucurevic, L. G. Schmidt, and P. Stoeter, "Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study," *Dementia and geriatric cognitive disorders*, vol. 18, no. 1, pp. 101–108, 2004.

[116] P. J. Winklewski, A. Sabisz, P. Naumczyk, K. Jodzio, E. Szurowska, and A. Szarmach, "Understanding the physiopathology behind axial and radial diffusivity changes—what do we know?," *Frontiers in neurology*, vol. 9, p. 92, 2018.

[117] N. Solowij, A. Zalesky, V. Lorenzetti, and M. Yücel, "Chronic cannabis use and axonal fiber connectivity," in *Handbook of Cannabis and Related Pathologies*, pp. 391–400, Elsevier, 2017.

[118] P. J. Basser, J. Mattiello, and D. LeBihan, "Mr diffusion tensor spectroscopy and imaging," *Biophysical journal*, vol. 66, no. 1, pp. 259–267, 1994.

[119] M. L. Stanley, S. L. Simpson, D. Dagenbach, R. G. Lyday, J. H. Burdette, and P. J. Laurienti, "Changes in brain network efficiency and working memory performance in aging," *PLoS One*, vol. 10, no. 4, p. e0123950, 2015.

[120] M. Rubinov and O. Sporns, "Complex network measures of brain connectivity: uses and interpretations," *Neuroimage*, vol. 52, no. 3, pp. 1059–1069, 2010.

[121] A. Zalesky, N. Solowij, M. Yücel, D. I. Lubman, M. Takagi, I. H. Harding, V. Lorenzetti, R. Wang, K. Searle, C. Pantelis, *et al.*, "Effect of long-term cannabis use on axonal fibre connectivity," *Brain*, vol. 135, no. 7, pp. 2245–2255, 2012.

[122] M. L. Birnbaum, S. D. Cleary, C. Ramsay Wan, L. Pauselli, and M. T. Compton, "Factor structure of the cannabis experiences questionnaire in a first-episode psychosis sample," *Early intervention in psychiatry*, vol. 13, no. 3, pp. 495–501, 2019.

[123] N. Mossaheb, J. Becker, M. R. Schaefer, C. M. Klier, M. Schloegelhofer, K. Papageorgiou, and G. P. Amminger, "The community assessment of psychic experience (cape) questionnaire as a screening-instrument in the detection of individuals at ultra-high risk for psychosis," *Schizophrenia research*, vol. 141, no. 2-3, pp. 210–214, 2012.

[124] T. C. Boonstra, *Early detection of psychosis; why should we care?* Rob van Giel Onderzoekscentrum, 2011.

[125] E. J. Porter, S. J. Counsell, A. D. Edwards, J. Allsop, and D. Azzopardi, "Tract-based spatial statistics of magnetic resonance images to assess disease and treatment effects in perinatal asphyxial encephalopathy," *Pediatric research*, vol. 68, no. 3, pp. 205–209, 2010.

[126] R. L. O'Gorman, H. U. Bucher, U. Held, B. M. Koller, P. S. Hüppi, C. F. Hagmann, and S. E. N. T. Group, "Tract-based spatial statistics to assess the neuroprotective effect of early erythropoietin on white matter development in preterm infants," *Brain*, vol. 138, no. 2, pp. 388–397, 2015.

[127] L. H. Scholtens, M. A. de Reus, and M. P. van den Heuvel, "Linking contemporary high resolution magnetic resonance imaging to the von economo legacy: A study on the comparison of mri cortical thickness and histological measurements of cortical structure," tech. rep., Wiley Online Library, 2015.

[128] S. Mori and P. C. Van Zijl, "Fiber tracking: principles and strategies–a technical review," *NMR in Biomedicine: An International Journal Devoted*

to the Development and Application of Magnetic Resonance In Vivo, vol. 15, no. 7-8, pp. 468–480, 2002.

[129] G. Collin, M. P. van den Heuvel, L. Abramovic, A. Vreeker, M. A. de Reus, N. E. van Haren, M. P. Boks, R. A. Ophoff, and R. S. Kahn, "Brain network analysis reveals affected connectome structure in bipolar i disorder," *Human brain mapping*, vol. 37, no. 1, pp. 122–134, 2016.

[130] M. P. Van Den Heuvel, O. Sporns, G. Collin, T. Scheewe, R. C. Mandl, W. Cahn, J. Goñi, H. E. H. Pol, and R. S. Kahn, "Abnormal rich club organization and functional brain dynamics in schizophrenia," *JAMA psychiatry*, vol. 70, no. 8, pp. 783–792, 2013.

[131] R. Kuepper, J. van Os, R. Lieb, H.-U. Wittchen, M. Höfler, and C. Henquet, "Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study," *Bmj*, vol. 342, 2011.

[132] J. Bechtold, A. Hipwell, D. A. Lewis, R. Loeber, and D. Pardini, "Concurrent and sustained cumulative effects of adolescent marijuana use on subclinical psychotic symptoms," *American Journal of Psychiatry*, vol. 173, no. 8, pp. 781–789, 2016.

[133] L. Sideli, H. Quigley, C. La Cascia, and R. M. Murray, "Cannabis use and the risk for psychosis and affective disorders," *Journal of dual diagnosis*, vol. 16, no. 1, pp. 22–42, 2020.

[134] J. Newbury, L. Arseneault, A. Caspi, T. E. Moffitt, C. L. Odgers, and H. L. Fisher, "Why are children in urban neighborhoods at increased risk for psychotic symptoms? findings from a uk longitudinal cohort study," *Schizophrenia Bulletin*, vol. 42, no. 6, pp. 1372–1383, 2016.

[135] R. M. Murray, H. Quigley, D. Quattrone, A. Englund, and M. Di Forti, "Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis," *World Psychiatry*, vol. 15, no. 3, pp. 195–204, 2016.

[136] D. M. Fergusson, J. M. Boden, and L. J. Horwood, "Psychosocial sequelae of cannabis use and implications for policy: findings from the christchurch health and development study," *Social psychiatry and psychiatric epidemiology*, vol. 50, no. 9, pp. 1317–1326, 2015.

[137] L. E. DeLisi, H. C. Bertisch, K. U. Szulc, M. Majcher, K. Brown, A. Bappal, and B. A. Ardekani, "A preliminary dti study showing no brain structural change associated with adolescent cannabis use," *Harm reduction journal*, vol. 3, no. 1, pp. 1–6, 2006.

[138] R. E. Thayer, S. YorkWilliams, H. C. Karoly, A. Sabbineni, S. F. Ewing, A. D. Bryan, and K. E. Hutchison, "Structural neuroimaging correlates of alcohol and cannabis use in adolescents and adults," *Addiction*, vol. 112, no. 12, pp. 2144–2154, 2017.

[139] J. Cousijn, Y. J. Toenders, L. S. van Velzen, and A. M. Kaag, "The relation between cannabis use, dependence severity and white matter microstructure: A diffusion tensor imaging study," *Addiction biology*, vol. 27, no. 1, p. e13081, 2022.

[140] M. M. Koenis, J. Durnez, A. L. Rodrigue, S. R. Mathias, A. F. Alexander-Bloch, J. A. Barrett, G. E. Doucet, S. Frangou, E. E. Knowles, J. Mollon, *et al.*, "Associations of cannabis use disorder with cognition, brain structure, and brain function in african americans," *Human brain mapping*, vol. 42, no. 6, pp. 1727–1741, 2021.

[141] F. M. Filbey, S. Aslan, V. D. Calhoun, J. S. Spence, E. Damaraju, A. Caprihan, and J. Segall, "Long-term effects of marijuana use on the brain," *Proceedings of the National Academy of Sciences*, vol. 111, no. 47, pp. 16913–16918, 2014.

[142] M. Drakesmith, A. Dutt, L. Fonville, S. Zammit, A. Reichenberg, C. J. Evans, G. Lewis, D. K. Jones, and A. S. David, "Mediation of developmental risk factors for psychosis by white matter microstructure in young adults with psychotic experiences," *JAMA psychiatry*, vol. 73, no. 4, pp. 396–406, 2016.

[143] E. van Dellen, M. M. Bohlken, L. Draaisma, P. K. Tewarie, R. van Lutterveld, R. Mandl, C. J. Stam, and I. E. Sommer, "Structural brain network disturbances in the psychosis spectrum," *Schizophrenia bulletin*, vol. 42, no. 3, pp. 782–789, 2016.