THE IMPACT OF STRESS AND CHILDHOOD TRAUMA ON ATTENUATED PSYCHOTIC SYMPTOMS AND WHITE MATTER INTEGRITY

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ABSTRACT

Recent studies have found associations between prolonged stress response and white matter (WM) microstructure in individuals with schizophrenia, as well as correlations between early life trauma and WM integrity in individuals with schizophrenia and non-psychiatric controls; however, psychosocial correlates of WM dysfunction have not yet been adequately explored in individuals experiencing attenuated psychotic symptoms (APS, subthreshold versions of positive psychotic symptoms). This study examines WM microstructure using traditional and free-water corrected diffusion metrics within a community sample of 66 16 to 30-year-olds experiencing a range of APS to examine the contribution of perceived stress and childhood trauma to the relationship between APS and WM abnormalities, as well as examine the moderating influence of sex assigned at birth (herein referred to as sex) to these relationships. We found that overall symptom severity on the Structured Interview for Psychosis-risk Syndromes (SIPS) was associated with higher extracellular free-water (FW) across the whole brain, lower free-water corrected fractional anisotropy values (FA_T), and higher free-water corrected radial diffusivity (RD_T). Further, childhood trauma significantly moderated the relationship between SIPS scores and both FA_T and RD_T, controlling for biological sex at birth, such that in the presence of APS, childhood trauma was associated with higher FA_T and lower RD_T, and in lower APS the opposite pattern was seen, with childhood trauma associated with lower FA_T and lower RD_T. After stratifying for sex, childhood trauma moderated the SIPS – FA_T and RD_T relationships in males similar to findings in the whole sample, though this relationship was not present in females. Perceived stress was not a significant moderator in the total sample, though was a significant moderator of the APS – FA relationship in males only. This study represents an important step

toward identifying mechanisms for WM dysfunction within individuals with psychosis spectrum disorders, as well as identifying important targets for interventions.

This dissertation is dedicated to:

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whose grit has been a constant source of inspiration and motivation;

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a colleague, friend, and life-long cheerleader;

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for supporting and feeding me along the way.

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EXPANDED LITERATURE REVIEW

ABSTRACT

Alterations in white matter microstructure are a core feature of psychosis spectrum disorders and are found in individuals with schizophrenia, those at clinical high-risk (CHR) for psychosis, and individuals with psychotic-like experiences (PLEs). There are many bio-behavioral factors that increase both risk for psychosis and contribute to structural brain alterations, including white matter microstructure. In this review, we examine the nature of postnatal stress, trauma, and inflammation and how these factors individually and additively contribute to white matter dysfunction in the psychosis spectrum and in non-psychiatric populations. The influence of biological sex is discussed as it relates to all above variables (stress, trauma, inflammation, psychosis risk, and white matter microstructure). We conclude that stress, trauma, and inflammation are likely contributors to white matter dysfunction, both in non-psychiatric populations and crucially, along the psychosis spectrum. Further, we note that it is important to consider sex differences in examinations of these variables, and that pre- and perinatal adversity likely prime sensitivity to postnatal stress and trauma. Future work is needed, ideally longitudinal examinations of birth cohorts examining pre-, peri-, and postnatal stressors, trauma, and inflammation and their impact on white matter microstructure in adulthood.

Introduction

White matter alterations have been found across the psychosis spectrum: in those with schizophrenia (Cetin-Karayumak et al., 2019; Grazioplene et al., 2018; Kelly et al., 2018; Kochunov et al., 2019; Pasternak et al., 2015), at clinical high-risk (CHR) for psychosis (Bernard et al., 2017; Carletti et al., 2012; Clemm von Hohenberg et al., 2014; Hoptman et al., 2008; Karlsgodt et al., 2009; Peters et al., 2010; Tang et al., 2019), and in non-psychiatric samples of individuals experiencing psychotic-like experiences (PLEs; subthreshold, attenuated versions of positive psychotic symptoms; Cooper et al., 2018; Drakesmith et al., 2016; Jacobson et al., 2010; O'Hanlon et al., 2015). Although white matter alterations in individuals on the psychosis spectrum hve been well established, the factors contributing to white matter alterations and the mechanisms through which this dysfunction occurs are largely unexplored.

There are several bio-behavioral factors that could putatively affect the relationship between psychosis and changes in brain structure, including psychosocial stress, childhood traumatic life events (TLEs), immune-related processes such as inflammation, and genetic influences. It is possible that these factors partially account for structural differences found in individuals along the psychosis spectrum, given that a number of these factors have been associated with similar white matter dysfunction both in clinical and non-clinical samples. White matter abnormalities (lower fractional anisotropy, or FA in the right anterior corona radiata, right fornix stria terminalis, and right superior longitudinal fasciculus, or SLF) have been found to adversely impact cognitive functioning in individuals at CHR, including worse performance on measures of verbal learning, verbal fluency, working memory, processing speed, problem solving, cognitive flexibility, and sustained attention (Kristensen et al., 2019). Further, FA in the SLF and cingulum has been found to be related to school attainment/performance in non-

psychiatric samples, such that lower FA in these regions was associated with attaining fewer years of education (Noble et al., 2013). As cognition and school attainment are negatively associated with psychotic illness, it is crucial to understand the environmental factors that contribute to this relationship.

White Matter Integrity in Psychosis Spectrum Disorders

It has been well established that white matter dysfunction is present across the psychosis spectrum, and there are several recent and exhaustive review papers focusing on this topic (see: Karlsgodt, 2020). In this review, we will focus primarily on findings related to white matter microstructure, as measured by diffusion-weighted imaging (DWI), rather than white matter macrostructure or volume, which is typically measured using standard structural (T1) magnetic resonance imaging, as white matter microstructure allows for estimation of both intra- (e.g., myelination) and extra-cellular (such as inflammation and atrophy) changes (Karlsgodt, 2020). Summarily, the preponderance of DWI studies reveal reductions in fractional anisotropy (FA) in individuals with schizophrenia, but there is much variability in specific tract-based alterations between studies. FA is the most commonly reported DWI metric and measures the preferential direction of diffusion of water at the voxel level, such that higher FA reflects higher white matter integrity, and is often inferred to reflect myelination (Karlsgodt, 2020; Poletti et al., 2020; Soares et al., 2013).

Large, multi-site examinations of individuals diagnosed with schizophrenia, such as the ENIGMA-Schizophrenia DTI working group, reveal lower average FA across the entire white matter skeleton compared to controls as the largest effect found, with the anterior corona radiata, the entire corpus callosum, and the genu emerging as the specific regions for which the largest

effect sizes are seen (Kelly et al., 2018). Studies of individuals earlier in the course of the disorder, including individuals at CHR (Carletti et al., 2012; Hoptman et al., 2008; Karlsgodt et al., 2009; Muñoz Maniega et al., 2008; Peters et al., 2008, 2010; Tang et al., 2019) and individuals experiencing PLEs (Cooper et al., 2018; DeRosse et al., 2014, 2017; Drakesmith et al., 2016; Jacobson et al., 2010; O'Hanlon et al., 2015) also display white matter alterations; however, results vary and include both FA increases and decreases (see: Karlsgodt, 2020 for review).

These discrepancies confirm the need for larger coordinated studies using advanced DWI techniques prior to psychosis onset, but also demonstrate that white matter dysfunction is present before the onset of frank psychotic symptoms. Meta-analytic studies of individuals with bipolar disorder reveal widespread white matter microstructural abnormalities and found that effect sizes were largest in the corpus callosum and cingulum (Favre et al., 2019). Similar alterations in FA are also found in individuals with bipolar disorder, which have phenotypic overlap with psychotic disorders, including a shared reduction in radial diffusivity in the left external capsule and a reduction in trace (the magnitude of diffusion in a voxel, Soares et al., 2013) in the right extreme capsule in both individuals with schizophrenia and bipolar disorder compared to nonpsychiatric controls (Joo et al., 2021). At least one study reported that family members of individuals diagnosed with schizophrenia have decreased FA relative to non-psychiatric controls, but higher FA than individuals with schizophrenia (Knöchel et al., 2012), and systematic reviews report that the corpus callosum and frontal and temporal white matter are most consistently impacted in unaffected relatives of individuals with schizophrenia (Arat et al., 2015). Taken together, these findings indicate that dysfunction in white matter integrity may in fact be a transdiagnostic endophenotype of psychosis; however, variability in these results is present,

likely due to small sample sizes in early studies and improvements in white matter microstructural measures over time allowing for better determination of kissing/crossing fibers. Given the wealth of findings of white matter dysfunction along the psychosis spectrum, examining factors that have been found to impact both white matter microstructure and psychosis risk is warranted.

For the purposes of this review, we will focus on stress, trauma, and their interaction, and a potential biological mechanism through which stress and trauma impact white matter (inflammation). Stress and trauma have been consistently associated with both psychosis-risk (Mittal & Walker, 2019; Read et al., 2005), and with white matter microstructure in non-psychiatric populations (Choi et al., 2009, 2012; Poletti et al., 2020). There appears to be evidence of sex differences in the development of white matter microstructure (Chou et al., 2011; Simmonds et al., 2014; Lebel, Treit, & Beaulieu, 2019) and stress responsivity (Bangasser et al., 2018; Brydges et al., 2020; Pruessner et al., 2008), albeit investigations in white matter microstructure in individuals with psychotic disorders are more mixed (Schwehm et al., 2016; Bora et al., 2011). As such, we will discuss the role of biological sex at birth in these processes. Whereas many variables may impact white matter, either by increasing perceived stress and/or inflammation or through their own unique processes, examining stress and trauma is an important first step in determining biopsychosocial influences on white matter microstructure.

White Matter Development in Non-Psychiatric Populations

In examining disturbances in white matter, we must first discuss its normative development. The brain undergoes rapid changes in white matter microstructure, observed by large increases in FA and decreases in mean diffusivity (MD), over the first few years of life

which slow around age five, which is confirmed in autopsy studies to reflect increases in axon diameter and myelination (Lebel, Treit, & Beaulieu, 2019). Following this initial reorganization, white matter integrity continues to increase with age at a more gradual pace, eventually reaching maturity in adolescence; however, maturation of specific white matter tracts varies across brain region/tract and continues into adulthood. Several regions reach maturity in late childhood including colossal tracts, interhemispheric connections, and the inferior longitudinal fasciculus, whereas the majority of association tracts (e.g., superior longitudinal fasciculus, inferior fronto-occipital fasciculi) show changes into adolescence (Lebel et al., 2008). Fronto-temporal white matter and connections, such as the cingulum, uncinate, superior longitudinal fasciculus, and superior fronto-occipital fasciculus, show the slowest rate of growth and continue to mature into early adulthood (Lebel et al., 2008; Lebel, Treit, & Beaulieu, 2019). These later-developing tracts are primarily associated with cognitive and executive functioning and the integration of cognitive-emotional processes (Simmonds et al., 2014). As psychotic symptomatology often emerges in late adolescence/young adulthood, this lends credence to the role of white matter in the neurodevelopmental hypothesis of schizophrenia, in which genetic and environmental risk factors lead to vulnerabilities in neural systems that are then "activated" by normative pruning processes and white matter maturation later in development (Karlsgodt et al., 2011).

Sex Differences in White Matter Development

Various sex differences in WM microstructure have been documented and may be explained in part by pubertal development and sex hormones (Herting et al., 2012; Lebel, Triet, & Beaulieu, 2019); however, evidence is mixed. Many studies report that males generally exhibit greater FA and reduced MD compared to females in the majority of white matter regions, although some studies find regional differences, with higher FA in the frontal white matter for

males and higher FA in occipital regions for females (see: Lebel, Treit, & Beaulieu for review). Longitudinal examinations of white matter development also have found significant sex differences in growth trajectories. Researchers have found that in males, white matter integrity increases steadily from childhood into adulthood, whereas females show white matter growth primarily in adolescence (Simmonds et al., 2014), indicative of an age x sex interaction in white matter development (Geeraert, Lebel, & Lebel, 2019). This highlights the importance of accounting for age and sex in examinations of white matter integrity in adolescents and young adults.

Sex differences also have been investigated using methods that focus on whole brain structural connectivity rather than on individual white matter tracts and associated regions. Ingalhalikar and colleagues (2014) examined the structural connectome in a large sample of individuals ages 8 to 22 and found greater within-hemispheric connectivity in males and between-hemispheric connectivity in females that was apparent in the youngest cohort and increased in older cohorts. The opposite relationship was found in relation to cerebellar connectivity, where males demonstrated higher cross-hemispheric connectivity.

Further, sex differences in the timing of white matter development should be considered relative to sex differences in incidence, onset, and symptom profile in psychosis. Although prevalence rates are relatively equal among males and females, males have an earlier average age of onset (Aleman et al., 2003) and women experience a second peak of risk at mid-life, around the time of ovarian senescence (Nemeroff, 2007). Males and females also deviate in symptom presentation, such that males have greater deficits in social functioning and higher risk for suicidality and hospitalization and females experience more affective symptoms (Remington & Seeman, 2015). Males who go on to develop schizophrenia appear to have more complications in

the premorbid period, including obstetric difficulties, developmental disabilities, and substance use (Remington & Seeman, 2015).

The foundations for sex differences in risk and presentation for psychotic disorders begin *in-utero,* as prenatal adversity (e.g., stress, infection) may disrupt normal organizational sexual dimorphic processes, resulting in "hypomasculinization" of the brain (Bale et al., 2010). Disruptions in normative sexual dimorphisms of the brain may have resulting impacts on stress response and neuroinflammatory processes. In fact, there is evidence that, at baseline, the developing male brain is at a higher inflammatory state, and brain masculinization can be reversed by the presence of anti-inflammatory agents, perhaps contributing to increased risk for neuropsychiatric disorders (McCarthy, 2016; Amateau & McCarthy, 2004).

Over the course of premorbid development, pubertal hormones also may have activational effects. Mismatch between gonadal hormone profiles in childhood and adolescence and organizational programming in utero may result in neuropsychiatric risk (Bale & Epperson, 2015). As white matter development for a number of tracts occurs over a longer period of time in males (Pohl et al., 2016; Seunarine et al., 2016), this perhaps allows for greater impact of environmental factors, as well as immune/endocrine factors, on white matter integrity and the observed earlier onset of psychosis spectrum disorders in males. This coincides with evidence that earlier maturation, myelination, and higher levels of estrogen in female offspring protects them from early stressors, such as obstetric complications (Seeman & Lang, 1990). Nonetheless, evidence of the deleterious effects of prenatal adversity tends to emerge in female offspring around adolescence in the form of internalizing symptoms, perhaps also accounting for differences in symptomatic profiles across the sexes in psychotic disorders (Sandman et al., 2013). As such, the impact of sex differences on stress response, inflammation, and

neurodevelopment in individuals with psychosis must be understood with a developmental lens, beginning in the prenatal period, and with attention to the waxing and waning of gonadal hormones throughout the lifespan.

Individual Factors that Confer Psychosis Risk and White Matter Abnormalities

Psychosocial Stress

One of the longest-standing models of the etiology of schizophrenia is the vulnerability-stress model (Nuechterlein & Dawson, 1984), and psychosocial stress has been found to precipitate spontaneous relapse of both organic (Bebbington et al., 1993) and drug-induced psychoses (Yui et al., 2000). Individuals along the psychosis spectrum are more reactive in the face of stressors (van Winkel et al., 2008), including individuals experiencing PLEs (Myin-Germeys & van Os, 2007), indicating that stress sensitivity is a likely endophenotype of psychotic disorders as well. This increased sensitivity to stress is not due to greater incidences of stress, as individuals diagnosed with schizophrenia do not experience significantly more stressful life events than peers (Walker et al., 2008). Additionally, an attenuated cortisol response to laboratory-based stressors has been associated with higher levels of daily life stress in individuals at CHR (Pruessner et al., 2013), implying a desensitization of the HPA axis even prior to the onset of frank psychosis. Lower levels of cortisol during recovery from a stressor are also seen in non-psychiatric samples of individuals who experienced high levels of chronic stress, compared to individuals with low levels of chronic stress (Kudielka & Kirschbaumb, 2005).

A study of patients with schizophrenia linked prolonged cortisol response (a measure of the body's activation in response to stress) in reaction to a laboratory-induced stressor to

impaired white matter integrity (Nugent et al., 2015). Prolonged cortisol response (40 minutes after a lab-based stressor) was inversely associated with overall FA in patients and trended with (did not survive corrected significance threshold) inverse relationship with FA in the corpus callosum body, fornix, corona radiata, sagittal striatum, cingulum, and SLF (Nugent et al., 2015). However, it has yet to be determined if this sensitivity to stressors is associated with white matter abnormalities prior to the onset of frank psychotic symptoms, and whether there are any sex differences that might be present in the stress – white matter relationship in individuals on the psychosis spectrum. This is especially important given that psychotropic medication including antipsychotics and antidepressants impact the HPA axis and are associated with reductions in basal cortisol levels (Subramaniam et al., 2019), one way in which medications might confound previous DWI findings. These findings are especially important given that antipsychotic treatment also has been associated with reductions in FA in individuals in the first episode of psychosis (Szeszko et al., 2014). Examinations prior to the onset of frank psychosis and controlling for the use of antipsychotics or other psychotropic medications will be crucial for understanding the process by which HPA axis dysfunction impacts white matter integrity.

The timing of stress exposure appears to have crucial and differential effects on both white matter integrity and psychosis risk in non-psychiatric populations. Longitudinal examinations of birth cohorts found stress exposure at different developmental time points is associated with alterations of white matter microstructure in the corpus callosum of young Caucasian adult males (Jensen et al., 2018). Specifically, prenatal maternal stress was associated with lower myelin water fraction (MWF) and lower FA in portions of the corpus callosum, controlling for other obstetric complications. Stress in early childhood (ages 0-4) was not associated with any microstructural changes, and stress during adolescence (ages 12-16) was

associated with lower MTR in the genu (Jensen et al., 2018). It is important to highlight that only male subjects were included in this study and results may differ for female participants; however, these findings suggest that timing of stress exposure potentially has distinct effects on the brain. Prenatal maternal stress also has been found to be associated with greater microstructural organization (higher FA and lower perpendicular diffusivity) in the right UF of offspring scanned at age 6-9 (Sarkar et al., 2014). However, animal models reveal that risk for psychosis may in fact be highest in individuals who experience both prenatal stress/immune activation **and** stress later in development such as during adolescence, termed the two-hit model of schizophrenia (Feigenson et al., 2014; Monte et al., 2017).

Sex differences in stress reactivity, and the ensuing effect on white matter, should also be considered. Adult females tend to have elevated reactivity to stress compared to adult males, using Experience Sampling Methods (Myin-Germeys & van Os, 2007) and questionnaire-based methods (Gibson et al., 2014). In response to both real world and laboratory-based stress tasks, male participants display higher levels of adrenocorticotropic hormone (ACTH) and cortisol than female participants, but also recover faster (Kudielka & Kirschbaumb, 2005). Similar sex differences in response to stress have been observed in rodents, providing converging evidence for sex differences within psychiatric disorders (see: Bangasser et al., 2018; Bangasser & Valentino, 2014; Brydges et al., 2020).

In non-psychiatric samples of adults, sex-specific effects of stress on white matter integrity are seen. Poletti and colleagues (2020) examined the impact of early life and recent low and mild stress on white matter integrity (FA) in males and females. Females exposed to low levels of early life stress displayed lower FA than males; alternatively, recent mild stress was associated with higher FA in females (Poletti et al., 2020). When considered additively, early

stress and recent stress in females were associated with lower FA overall (Poletti et al., 2020). These findings may highlight the importance of considerations of stress timing relative to pubertal onset and circulating gonadal hormones (Herting et al., 2012). This is especially relevant as there is evidence of interactions of the HPA and hypothalamic-pituitary-gonadal axis (HPG), such that estrogen stimulates levels of cortisol as well (Oyola & Handa, 2017). Additionally, rodent studies during which a stressor is administered during the juvenile stage, inducing a large corticosterone response, also have found sex differences (Breton et al., 2021). They found that corticosterone response to the stressor were positively correlated with myelin levels shortly after the stressor in the prefrontal cortex of female mice and in the amygdala and hippocampi of male mice, lending credence to hypothesized early maturation of limbic circuits, or alterations of developmental trajectories of white matter within the brain following a stressor. Further, oligodendrocyte density was reduced in the prefrontal cortex and hippocampus for females, but not males. In the long term, the rodent juvenile stress model was associated with long-term reduction in myelin-based proteins in the prefrontal cortex, amygdala, and hippocampus in female mice, but not in males (Breton et al., 2021), coinciding with evidence of a critical window during which stressors may impact the brain, and that this period may differ for males and females. This study also suggests that corticosterone increases associated with stress reduces oligodendrocyte density, impacting white matter integrity. Taken together, it is clear that stress impacts both psychosis-risk and white matter microstructure, and this effect varies due to both biological sex at birth and timing of stress exposure.

Traumatic Life Events/Childhood Trauma

Another environmental factor robustly associated with risk for psychosis is traumatic life events (TLEs). Numerous studies have found positive correlations between TLEs and psychotic

symptoms in individuals with schizophrenia (Borges et al., 2013; Ciufolini et al., 2014; Pruessner et al., 2013), those at risk for developing the disorder (Loewy et al., 2019; Mayo et al., 2017; Thompson et al., 2009), and in nonclinical populations experiencing PLEs (Ered et al., 2017; Ered & Ellman, 2019; Gibson et al., 2014). Individuals at clinical high-risk for psychosis are more likely to have experienced several different types of childhood trauma, including physical abuse, psychological abuse, sexual abuse, and emotional neglect (Addington et al., 2013). The TLE – psychosis relationship also has been found to have a dose-dependent effect in longitudinal examinations of psychosis risk, with each additional incidence of TLEs predicting later, more severe psychotic symptoms (Borges et al., 2013), though our previous work has found that this effect plateaus after four TLEs (Gibson et al., 2014).

TLEs, particularly those occurring in childhood, have been associated with white matter abnormalities in several populations, including in individuals diagnosed with post-traumatic stress disorder (PTSD; Daniels et al., 2013), in individuals with schizophrenia (Asmal et al., 2019; Cancel et al., 2019; Poletti et al., 2015), and in non-clinical samples (Choi et al., 2009, 2012; DeRosse et al., 2020; Gur et al., 2019). Traumatic events occurring in childhood are particularly relevant both for psychosis-risk and brain structure, as childhood and adolescence are critical periods for brain development during which rapid increases in white mattery integrity are seen. TLEs during this time are associated with long-term changes in stress reactivity and brain structure and function (Kaufman et al., 2000) and occur in the context of several neuropsychiatric disorders (Daniels et al., 2013; Frodl et al., 2012), as well as in non-clinical samples (Choi et al., 2009, 2012; DeRosse et al., 2020; Gur et al., 2019; Lu et al., 2013). As such, this review will focus on individuals exposed to traumatic events in childhood, rather than those with a diagnosis of PTSD.

Early studies using structural magnetic resonance imaging (sMRI) to examine white matter have found that, whereas trauma in adults has been associated with reduced grey matter volume in the hippocampus, children who have experienced trauma show reduced area of white matter in the medial and posterior portions of the corpus callosum compared to children who have not experienced abuse (Teicher et al., 2004), which also has been found in pre-pubertal primates (Sánchez et al., 1998). Conversely, a study of individuals with psychosis found no significant relationship between white matter volume and childhood trauma both globally and with individual trauma subtypes (Sheffield et al., 2013); however, the authors examined white matter macrostructure using sMRI methods (volume-based morphometry, or VBM, rather than DWI-based indicators of white matter microstructure, such as FA), which does not capture extracellular changes such as inflammation that may be occurring in this sample. In a study of children who have experienced intrafamilial abuse and were diagnosed with PTSD, sMRI findings of reduced white matter area in the medial and posterior corpus callosum were confirmed using DWI methods, with children with PTSD showing significantly lower FA in the corpus callosum (Jackowski et al., 2008). Although early DWI studies and sMRI studies should be interpreted with caution due to vast improvements in imaging parameters in the interim allowing for better signal-to-noise ratio, improvements in resolutions, and better determinations for kissing/crossing fibers, these findings are supported by large, transdiagnostic studies of white matter microstructure in children, in which TLEs were associated with higher FA values in the UF, anterior thalamic radiation, cingulum bundle, IFOF, and SLF (Gur et al., 2019).

Individual aspects of childhood maltreatment have been examined to determine their specific effects on white matter abnormalities using large, population-based samples of healthy adults. Individuals who experienced parental verbal abuse in childhood showed reduced FA in

the left arcuate fasciculus, left cingulum bundle, and the left body of the fornix (Choi et al., 2009). In addition, results indicate that children who witness domestic violence display lower FA in the left ILF in adulthood, and this relationship was strongest in participants with longer duration of exposure to verbal domestic violence and only brief exposure to physical violence (Choi et al., 2012). Similar patterns of white matter disruption have been found in adolescents who were exposed to trauma in childhood, showing lower FA in the bilateral SLF, right cingulum bundle, left IFOF, and the splenium of the corpus callosum (Huang et al., 2012). However, examinations of the accumbofrontal tract (which connects the orbitofrontal cortex and nucleus accumbens) in a non-psychiatric sample found that the severity of childhood trauma, rather than the trauma type, was associated with accumbofrontal FA reductions (DeRosse et al., 2020). It is evident that, even in non-psychiatric populations, childhood trauma is associated with white matter microstructure.

In individuals with schizophrenia, adverse experiences in childhood have been negatively associated with FA (Cancel et al., 2019; Poletti et al., 2015). Specifically, increased severity of childhood adverse experiences have been associated with decreased FA in corpus callosum, left cingulum, left corona radiata, bilateral SLF, left ILF, and left anterior thalamic radiation (Poletti et al., 2015). Recent systematic reviews also have identified the ILF, SFL, IFOF, and forceps major as areas of white matter alterations in individuals with psychosis who have experienced trauma in childhood (Cancel et al., 2019). These tracts all have been previously found to show alterations in white matter integrity in individuals with schizophrenia, implying that these adverse experiences early in life may contribute to the white matter dysfunction observed across the psychosis spectrum. (Poletti et al., 2015).

Inflammation/Immune System Dysregulation & Infection

Recently, inflammation and immune system dysregulation have gained popularity as mechanisms through which psychiatric disorders develop (Bauer & Teixeira, 2019). Psychotic disorders have similarly been suggested to arise through a combination of genetic susceptibility and exposure to early life events that prime an individual towards future hypersensitivity to stressful experiences (Cannon et al., 2003; Phillips et al., 2006). Heightened stress responsivity (e.g., excessive glucocorticoid release) may contribute to altered myelination and or excessive or aberrant pruning which takes place in late adolescence thereby contributing to the onset of psychotic symptomatology (Karlsgodt et al., 2008; Meknatkhah et al., 2019). Much of the evidence connecting inflammation and later psychotic symptoms and structural brain abnormalities has focused on prenatal infection and inflammation (see: Ellman et al., 2010; Ellman et al., 2019; Lipner et al., 2019); however, there also is some support for inflammation contributing to psychosis during the prodrome and early course of psychotic symptoms (Boerrigter et al., 2017; Cullen et al., 2020; Feigenson et al., 2014; Fineberg & Ellman, 2013; Khoury & Nasrallah, 2018; Perkins et al., 2015). Postmortem studies of the brains of individuals with schizophrenia reveal alterations in neuroinflammatory markers, primarily indicating elevation in microglial activity; however, systematic review shows that evidence is inconsistent between studies (see Trépanier et al., 2016 for review). Postmortem studies are considered to be the "gold standard"; however, it should be noted that in this particular population, there are interpretive problems due to high incidence of individuals who died by suicide and/or chronic medication usage within samples, although there are confirmatory findings from positron emission tomography (PET) and imaging peripheral inflammatory blood biomarkers. PET studies reveal elevations in microglial activity in the brains of individuals in the chronic phase of

schizophrenia (Bloomfield et al., 2015; Doorduin et al., 2009), as well as in those at high risk for developing the disorder compared to non-psychiatric controls, which was further associated with symptom severity (Bloomfield et al., 2015). Chronically elevated serum levels of several inflammatory cytokines have been found in individuals in the first-episode and chronic phases of schizophrenia (Di Nicola et al., 2013; Miller et al., 2011). Meta-analyses reveal that cytokines have been shown to be both acutely and chronically elevated or show both a state **and** trait relationship of inflammation and psychosis (Miller et al., 2011). Inflammation may be one mechanism through which environmental risk factors impact white matter integrity in individuals on the psychosis spectrum (Nugent et al., 2015; Poletti et al., 2015). Markers of systemic inflammation including high-sensitivity C-reactive protein (CRP) have been found to be inversely associated with whole brain FA in healthy adults, and CRP significantly mediated the relationship between behavioral risk-factors for chronic physical illness such as smoking and waist circumference (adiposity) and white matter integrity (Gianaros et al., 2013).

With the advent of newer diffusion imaging methods such as free-water imaging, there is emerging evidence that this method may be related to the neural effects of inflammation. Free-water imaging has been proposed as a possible technique to provide some leverage in assessing neuroinflammation and is better able to quantify extracellular free-water such as CSF that may contaminate traditional DWI metrics (see: Karlsgodt, 2019 for review). An increase in extracellular free-water is thought to be associated with higher levels of neuroinflammation (Karlsgodt, 2019), as neuroinflammation impacts the interstitial extraneuronal space in which immunoreactive cells such as migroglia mediate inflammatory processes and increase isotropic extracellular water content (Pasternak et al. 2012). Increases in extracellular free-water have been identified in the chronic phase of schizophrenia (Pasternak et al., 2015) and during a first

episode of psychosis, which was stable over the course of 12 months (Guo et al., 2020), but decreased at 24 months (Bergé et al., 2020). Increased extracellular free-water also was significantly correlated with increased positive symptoms in chronic schizophrenia patients (Gurholt et al., 2020). Although extracellular free-water alterations have not been found in individuals at CHR (Tang et al., 2019), a recent study found that CHR individuals who later transitioned to psychosis demonstrated elevated free-water at baseline that correlated with positive symptoms (Nägele et al., 2021). This, alongside a lack of evidence for free-water alterations in unaffected siblings of individuals with schizophrenia, suggest that the accumulation of extracellular free-water may be associated with the transition to psychosis and full-threshold symptomatology (Chang et al., 2021). Although the aforementioned results indicate that neural inflammation may be involved in the pathophysiology of the transition to frank psychosis, it is important to note that in the acute phase of neural inflammation, edema can cause accumulations of water in the extracellular space and thus elevated extracellular free-water (Lyall et al., 2018). It is possible that individuals at CHR may not be in the acute phase of inflammation, and thus do not present with increases in free-water. Additional prospective, longitudinal examinations of free-water in the CHR period and before (e.g., individuals experiencing PLEs) and utilizing advanced DWI acquisition methods are needed to help clarify the psychosis onset – neuroinflammation relationship.

The Intersection of Stress, Trauma, and Inflammation

It is notable that a history of trauma in childhood interacts with stress sensitivity in adulthood in individuals with psychosis to predict psychotic intensity (Lardinois et al., 2011; Ruby et al., 2014). Additionally, in non-clinical samples of individuals experiencing PLEs, stress sensitivity has been found to significantly mediate the relationship between TLEs and PLEs in

females (Gibson et al., 2014). Inflammatory biomarkers also have been shown to be associated with childhood trauma in individuals in the first-episode (Mondelli et al., 2011) and chronic phases of schizophrenia (Dennison et al., 2012). In other psychiatric populations with phenotypic overlap with psychosis, such as individuals with depression, free-water corrected indices (e.g., FA_t), but not traditional DWI indices (FA), showed significant differences between depressed individuals and non-psychiatric controls (Bergamino et al., 2016). Further, a significant negative association with perceived stress was found between free-water corrected metrics, but not traditional DWI metrics (Bergamino et al., 2016). These findings indicate that using free-water corrected DWI methods rather than traditional DWI could be crucial for uncovering both differences from non-psychiatric controls and stress-related brain pathology in individuals along the psychosis spectrum.

It is possible that, for individuals on the psychosis spectrum, childhood trauma primes the brain through dysfunction in the HPA axis for increased stress sensitivity and greater reactivity to life events. Thus, it may in fact be the interaction of TLEs in childhood, increased sensitivity to daily life stressors, and a resulting pro-inflammatory state that leads to white matter dysfunction in these individuals. Although this has yet to be explored with respect to stressors in the premorbid period, primate models of maternal immune activation provide evidence of this proposed model. Maternal immune activation has been utilized to model the impact of prenatal adversity on specific outcomes in preclinical models of neuropsychiatric disorders (Brown & Meyer, 2018). Elevations in proinflammatory cytokines in the prenatal period are associated with increased risk for both schizophrenia (Fineberg & Ellman, 2013) and higher stress sensitivity (Osborne et al., 2018) in offspring. One study examining rhesus monkeys exposed to a viral agent inducing higher levels of cytokines showed significantly higher extracellular free-water in

both grey and white matter at 2 years than control animals (Carter et al., 2020). Future studies may seek to clarify if stress, trauma, and resulting increases in inflammation in the premorbid period induce the same changes to WM.

Conclusions

This review presents evidence of psychosocial (stress and trauma) and biological (inflammation/immune dysfunction) influences on white matter integrity along the psychosis spectrum, including in individuals experiencing subsyndromal symptoms. Wide-spread white matter microstructural alterations are present and related to early traumatic life events, stress sensitivity, and increased inflammation, both in individuals on the psychosis spectrum and in the general population. Childhood trauma predicts later stress sensitivity in individuals experiencing psychosis, which are further associated with a pro-inflammatory state. Further, there are significant sex differences between males and females in all aforementioned processes. Taken together, this indicates a possible mechanism for the development of white matter dysconnectivity, as well as a potential pathway to psychosis spectrum symptoms (see Figure 1).

Notably, this review focuses on the impact of *postnatal* stress, trauma, and inflammation on white matter microstructure in individuals with psychosis. The psychosis literature repeatedly has demonstrated the deleterious impact of stress and inflammation on risk for psychosis as early as the prenatal period (Lipner et al., 2019; Fineberg & Ellman, 2013), identifying neurodevelopmental changes, such as in the HPA axis, as a meaningful mechanism underlying this increased risk (Coussons-Read, 2013). As such, prenatal adversities like maternal stress, infection, and obstetric complications, also associated with increases in inflammation, may prime the brain for increased sensitivity to postnatal trauma in an additive manner (Estes &

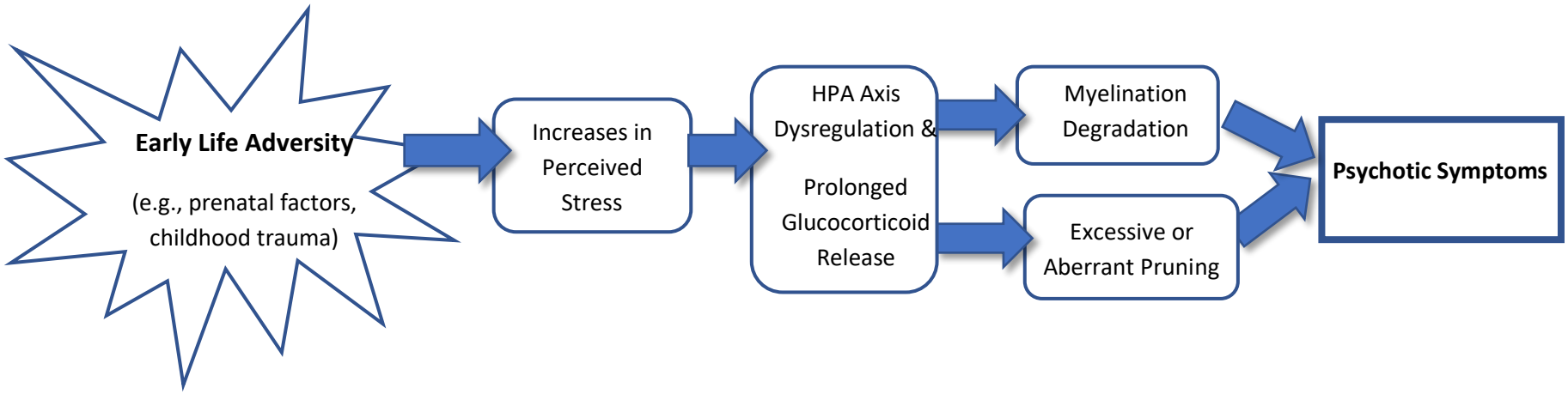
McCalister, 2016; Giovanoli et al., 2013). Preliminary findings also suggest that there may be premorbid alterations in white matter microstructure related to prenatal depression (Borchers et al., 2021) and stress (Sarkar et al., 2014); however, these studies suffer from small sample sizes and additional research is needed. One study specifically examined the relationship between maternal levels of interleukin-6 and FA in the uncinate fasciculus bilaterally, identifying that higher levels of prenatal IL-6 were associated with lower FA at birth and throughout the first year of life (Rasmussen et al., 2019). Given that sex differences in the course of psychotic disorders also begin as early as the prenatal period, future examinations of this trajectory from stress, trauma, and inflammation to alterations in WM microstructure in psychosis may serve to extend this examination earlier into the developmental lifespan.

Examinations of other variables that may influence inflammation, stress sensitivity, and white matter integrity are also necessary. Namely, socioeconomic status (Brito & Noble, 2014; DeRosse et al., 2014; Gur et al., 2019), urbanicity (Frissen et al., 2014; Lammeyer et al., 2019), racial discrimination (Flores et al., 2008; Oh et al., 2014; Ong et al., 2009), immigrant status (Flores et al., 2008; Morgan et al., 2010) , air pollution (Calderón-Garcidueñas et al., 2016), lead exposure (Brubaker et al., 2009), cannabis use (DeRosse et al., 2014; Epstein & Kumra, 2015; Scott et al., 2019), and other factors that may contribute to psychosis risk, stress sensitivity, inflammation, and/or white matter integrity should be considered. It is of crucial importance to note that many of these factors disproportionately impact racial and ethnic minorities, particular Black people, due to systemic racism (Anglin et al., 2020). As such, future work would be remiss not to explore how racial/ethnic identity may moderate these relationships.

Psychosis spectrum disorders have been associated with significant disability, including cognitive deficits that are further predictive of lower school/occupational functioning (Cowman

et al., 2021). As white matter abnormalities are similarly associated with cognitive and school performance in non-psychiatric populations (Kristensen et al., 2019; Deutsch et al., 2005; Noble et al., 2013), identifying modifiable environmental factors that impact both psychosis risk and white matter dysfunction is crucial to early identification and prevention efforts. To best understand how psychosis risk, white matter dysfunction, and mediating/moderating variables of this relationship interact, large scale population-based studies examining these factors prospectively and prior to the diagnosis of frank psychotic disorders are warranted.

Figure 1. Proposed mechanism from early life adversity to white matter dysfunction and psychosis spectrum symptoms



CHAPTER TWO

ABSTRACT

Recent studies have found associations between prolonged stress response and white matter (WM) microstructure in individuals with schizophrenia, as well as correlations between early life trauma and WM integrity in individuals with schizophrenia and non-psychiatric controls; however, psychosocial correlates of WM dysfunction have not yet been adequately explored in individuals experiencing attenuated psychotic symptoms (APS, subthreshold versions of positive psychotic symptoms). This study examines WM microstructure using traditional and free-water corrected diffusion metrics within a community sample of 66 16 to 30-year-olds experiencing a range of APS to examine the contribution of perceived stress and childhood trauma to the relationship between APS and WM abnormalities, as well as examine the moderating influence of sex assigned at birth (herein referred to as sex) to these relationships. We found that overall symptom severity on the Structured Interview for Psychosis-risk Syndromes (SIPS) was associated with higher extracellular free-water (FW) across the whole brain, lower free-water corrected fractional anisotropy values (FA_T), and higher free-water corrected radial diffusivity (RD_T). Further, childhood trauma significantly moderated the relationship between SIPS scores and both FA_T and RD_T, controlling for biological sex at birth, such that in the presence of APS, childhood trauma was associated with higher FA_T and lower RD_T, and in lower APS the opposite pattern was seen, with childhood trauma associated with lower FA_T and lower RD_T. After stratifying for sex, childhood trauma moderated the SIPS – FA_T and RD_T relationships in males similar to findings in the whole sample, though this relationship was not present in females. Perceived stress was not a significant moderator in the total sample, though was a significant moderator of the APS – FA relationship in males only. This study

represents an important step toward identifying mechanisms for WM dysfunction within individuals with psychosis spectrum disorders, as well as identifying important targets for interventions.

Introduction

Psychosis spectrum disorders, such as schizophrenia, are associated with high burden of disease, including significant deficits in neurocognition and social and occupational functioning (Breitborde, Moe, Ered, Ellman, & Bell, 2017). The combined indirect and direct costs of schizophrenia represent a tremendous public health burden, costing an estimated $155.7 billion per year in the United States (Cloutier et al., 2016), despite individuals with schizophrenia comprising only 1% of the population (McGrath, Saha, Chant, & Welham, 2008). Additionally, the length of time between first onset of psychotic symptoms and entry into treatment (duration of untreated psychosis, or DUP), is particularly relevant, as longer DUP has been associated with a more severe course of illness, worse treatment response, and poorer functional outcome (Breitborde et al., 2017). Therefore, early intervention/identification programs increasingly have been established to help identify those at risk for psychosis with the hope of preventing conversion to psychosis and decreasing DUP.

One method of identifying risk factors and pathways to illness is through the use of community samples experiencing attenuated psychotic symptoms (APS; subthreshold versions of positive psychotic symptoms). Those experiencing APS share demographic and experiential risk factors with more severe forms of psychotic illness and are at increased risk for developing psychosis spectrum disorders (DeRosse & Karlsgodt, 2015). As such, the use of community samples including individuals experiencing APS allows researchers to examine psychotic processes in larger, more ecologically valid samples while minimizing the influence of many illness-related factors that could affect brain structures, such as antipsychotic medication use (Minami et al., 2003).

Long considered a disorder of cortical connectivity (Rapoport, Giedd, & Gogtay, 2012), many studies have identified white matter (WM) dysfunction along the psychosis spectrum, including in individuals with schizophrenia (Karlsgodt, 2016) and in those at clinical high-risk for psychosis (von Hohenberg et al., 2013), noting decreased fractional anisotropy (FA; a summary measure of the direction of diffusivity) primarily in long-range association tracts including the superior longitudinal fasciculus, cingulum bundle, uncinate fasciculus, inferior longitudinal fasciculus, inferior frontal occipital fasciculus, and arcuate fasciculus (Karlsgodt, 2016). There also is some early evidence for WM abnormalities in those experiencing APS (Cooper, Alm, Olson, & Ellman, 2018; Jacobson et al., 2010; O'Hanlon et al., 2015). More specifically, reduced FA in individuals with APS has been seen globally across the whole brain (Karlsgodt, 2016), as well as in the inferior frontal occipital fasciculus (Jacobson et al., 2010), the cingulum (Jacobson et al., 2010), the superior longitudinal fasciculus (Jacobson et al., 2010; O'Hanlon et al., 2015), and the inferior longitudinal fasciculus (Cooper et al., 2018; Jacobson et al., 2010). Additionally, there has been evidence of increased FA or increased asymmetry between hemispheres in the uncinate fasciculus (O'Hanlon et al., 2015). Summarily, white matter abnormalities are found along the psychosis spectrum, including in subclinical samples of individuals with APS, with the majority of studies finding decreased FA in long-range association tracts. Characterizing intermediary factors of white matter changes is essential for prevention efforts, as this identifies modifiable risk factors such as perceived stress that can be targeted using psychotherapeutic interventions and allows for clinicians to identify individuals who are at greater risk for development of white matter alterations and psychosis, e.g, those who have experienced childhood trauma.

Diffusion weighted imaging (DWI) provides a proxy measure of white matter microstructure and examines the directional flow of water molecules in tissue (Soares et al., 2013). Diffusion of water is isotropic in areas such as cerebrospinal fluid and grey matter where there is no directional constraint of water molecules and diffusion is equal in all directions, and anisotropic in regions with directional constraints such as white matter (Beaulieu, 2002). While commonly used DWI metrics such as FA (a summary metric of diffusion directionality that includes myelination, neural fiber coherence, axon diameter, and organization of white matter tracts) and radial diffusivity (RD; diffusion perpendicular to the axon) are thought to reflect myelination status (Karlsgodt 2020), they also relate to other factors associated with axonal integrity, tract spacing, and organization of axons and fibers, reflected by the presence anisotropic diffusion prior to myelination (Wozniak & Lim, 2006). While DWI provides important indices of white matter microstructure, is non-invasive, and costs substantially less to obtain compared to other measures such as positron emission tomography (PET) imaging, the precise meaning and utility of alterations in DWI variables is somewhat vague and requires further probing to define the nature of these changes.

Recently, DWI studies have begun utilizing free-water correction, which allows for better estimation of WM integrity. Free-water in the brain is found as cerebrospinal fluid (CSF), in which water molecules have unrestricted diffusion, do not demonstrate flow, and are isotropic, whereas water molecules in WM flow, have restricted movement, and are anisotropic (Pasternak, Sochen, Gur, Intrator, & Assaf, 2009). Free-water correction better accounts for partial volume effects than standard DWI models such as diffusion tensor imaging, as free-water correction parses out CSF contamination at the voxel level and eliminates the effect, whereas standard DWI simply averages across the voxel, artificially driving down FA (Pasternak et al, 2009). The free-

water elimination model provides standard DWI metrics such as FA and radial diffusivity (RD, which reflects diffusion across the radius of the axon), a measure of extracellular free-water (FW) and free-water corrected FA and RD (termed FA_T and RD_T, where T stands for tissue).

Free-water correction is crucial for this project, as regions that are likely to be affected by stress/childhood trauma cross close to the ventricles, including limbic tracts such as the fornix and cingulum (Concha, Gross, & Beaulieu, 2005; Papadakis et al., 2002). Further, free-water corrected measures have been found to demonstrate significant relationships with increased stress in individuals with major depressive disorder, even when standard DWI measures were not significant (Bergamino et al., 2016), likely due to CSF contamination artificially driving down standing DWI metrics. Further, extracellular free-water has been found to be related to markers of inflammation, including positive associations between extracellular free-water and pro-inflammatory cytokines in individuals with schizophrenia (Di Biase et al., 2021). This coincides with evidence of neuroinflammatory markers in schizophrenia from post-mortem studies (Trépanier et al., 2016).

Individuals along the psychosis spectrum have been found to have elevated extracellular free-water compared to non-psychiatric controls, including individuals diagnosed with schizophrenia spectrum disorders (Figueiredo et al., 2022) and individuals in the early course of schizophrenia (Lesh et al., 2021). Further, free-water corrected measurements of white matter integrity (traditional DWI measures, adjusted for the effect of elevated free-water, as the free-water correction algorithm provides: 1) a measure of extracellular free-water, 2) traditional DWI metrics, 3) and free-water corrected DWI metrics) have been found to be altered along the psychosis spectrum, including in individuals with chronic schizophrenia (Oestereich et al., 2017), individuals in the first episode of schizophrenia (del Re et al., 2019; Pasternak et al.,

2012; Lyall et al., 2018; Hegde et al., 2020), and those at clinical high-risk (CHR) for psychosis (Tang et al., 2019; Nägele et al., 2021). Further, evidence from meta-analyses shows that increases in extracellular free-water in individuals with schizophrenia spectrum disorders compared to non-psychiatric controls are moderated by sex, such that smaller effects are found in samples with more females (Figueiredo et al., 2022). This coincides with evidence of sexual dimorphism in the development of white matter tracts, such that these processes occur over a longer period of time in males (Pohl et al., 2016; Seunarine et al., 2016), and may allow for a longer time period in which environmental and/or neuroinflammatory processes impact the brains of males.

Investigations of WM in individuals with APS have utilized imaging methods with poor signal to noise ratio, have not applied free-water correction and/or examined extracellular free-water. Further, the effects of known contributors to psychosis risk (e.g., psychosocial stress and trauma) have not yet been examined within the context of WM integrity in individuals with APS. Determining how these environmental risk factors impact WM integrity is a crucial first step in understanding the contributors to brain disturbances found in psychosis samples, which could ultimately allow us to understand the etiologies of these serious disorders.

Individual Factors that Confer Psychosis Risk and Affect White Matter Integrity

Psychosocial Stress

One long-standing model of the etiology of schizophrenia is the vulnerability-stress model (Nuechterlein & Dawson, 1984), which states that biological vulnerability factors interact with environmental stressors to produce psychotic states. Substantial support for this model includes findings that psychosocial stress has been found to precipitate spontaneous relapse of

both organic (Bebbington et al., 1993) and drug-induced psychoses (Yui, Goto, Ikemoto, & Ishiguro, 2000). In addition, individuals along the psychosis spectrum, including those experiencing APS (Van Winkel, Stefanis, & Myin-Germeys, 2008), have been found to be more reactive to daily-life stressors, endorsing life events as significantly more stressful than non-psychiatric counterparts (Myin-Germeys & van Os, 2007). This increased sensitivity to stress is not due to increased incidences of stress, as individuals diagnosed with schizophrenia do not appear to experience significantly more stressful life events than peers in cross-sectional studies (Walker et al., 2008). It is notable that individuals along the psychosis spectrum, including those experiencing APS, do experience more traumatic life events, which further predicts increased sensitivity to stress (Corcoran et al., 2003; Myin-Germeys & van Os, 2007; Walker et al., 2008). This evidence suggests the use of subjective measures of stress, rather than objective measures, is crucial in studying psychosis risk. Particularly as individuals at risk for psychosis endorse increased suspiciousness, the use of subjective stress measures better accounts for reactivity in response to situations that may not be perceived as threatening to non-psychiatric controls but could be highly stressful to individuals experiencing APS, such as a negative interaction with a stranger (Walker et al., 2008).

Recently, prolonged cortisol response (a measure of the body's activation in response to stress) in reaction to a laboratory-induced stressor has been linked to impaired whole brain WM integrity within patients with schizophrenia (Nugent et al., 2015). Prolonged cortisol reactivity has also been shown to differentially impact white matter microstructure in individuals with schizophrenia compared to controls, such that it was negatively correlated with white matter in individuals with schizophrenia and positively correlated with white matter in non-psychiatric controls (Goldwaser et al., 2021). Extending the finding that prolonged cortisol response to a

stressor is associated with WM integrity in schizophrenia patients to more chronic, naturalistic forms of stress using measurements that address reactivity to multiple, ongoing forms of stressors, may allow for a better understanding of the interaction between psychosocial stress and white matter integrity. Additionally, examining these processes across the psychosis spectrum will help to determine the pathways through which WM dysfunction relates to the development of psychosis spectrum disorders.

When examining psychosocial stress, it is imperative to consider sex differences in reactivity. Studies have consistently found that females report elevated stress reactivity compared to male counterparts (Myin-Germeys & van Os, 2007; Gibson et al., 2014), and although males generally show higher levels of stress hormones in response to laboratory and real-world stressors, they recover faster than female participants (Kudielka & Kirschbaumb, 2005). These findings highlight the importance of exploring sex differences in studies of stress reactivity. It is possible that prolonged stress response in females compared to males may lead to greater impact on white matter microstructure in females in the presence of higher perceived stress.

Traumatic Life Events and Childhood Trauma

Another factor consistently associated with risk for psychosis is childhood traumatic life events (TLEs). Numerous studies have found positive correlations between TLEs and psychotic symptoms in schizophrenia patients (Heins et al., 2011; Lardinois, Lataster, Mengelers, Van Os, & Myin-Germeys, 2011), and in community samples experiencing APS (Heins et al., 2011). This relationship has been found to be dose-dependent in longitudinal examinations of psychosis risk, with each additional incidence of TLEs predicting later, more severe psychotic symptoms (Read, Os, Morrison, & Ross, 2005), though our previous work has found a curvilinear

relationship between APS and TLEs, with increased APS leveling off at four TLEs (Gibson et al., 2014). Additionally, recent evidence from our lab indicates that the relationship between TLEs and APS may be specific to APS themselves, and not due to other commonly comorbid psychological symptoms (Gibson, Cooper, Reeves, Anglin, & Ellman, 2017).

Traumatic life events, particularly those occurring in childhood, also have been associated with WM abnormalities, in individuals diagnosed with post-traumatic stress disorder (PTSD; see Daniels, Lamke, Gaebler, Walter, & Scheel, 2013 for review), in non-psychiatric human samples (Choi, Jeong, Rohan, Polcari, & Teicher, 2009; DeRosse et al., 2014; Huang, Gundapuneedi, & Rao, 2012; Paul et al., 2008), and in animals (Howell et al., 2013), implicating both overall reductions in WM integrity and decreases in WM integrity in the cingulum (Daniels et al., 2013) and superior longitudinal fasciculus (Daniels et al., 2013; DeRosse et al., 2014). This relationship similarly may function through the activation of the HPA axis, as individuals with early life TLEs have been found to show elevated daily cortisol (Gunnar, Morison, Chisholm, & Schuder, 2001) and increased salivary cortisol response to laboratory stressors, particularly in women (Heim et al., 2000). However, individuals diagnosed with PTSD display lower levels of salivary cortisol than non-psychiatric controls not exposed to TLEs, with these results largely being driven by females (Meewisse, Reitsma, De Vries, Gersons, & Olff, 2007). The pathway from TLEs to APS and WM abnormalities may, in fact, function through sensitivity to stress, as our work has previously found that perceived stress mediates the relationship between TLEs and APS in women (Gibson et al., 2014). Again, it is notable that sex differences are found in reaction to TLEs in addition to stress reactivity.

Examining childhood trauma is of particular importance, as individuals with schizophrenia who have experienced different subtypes of childhood abuse had distinct

differences in white matter microstructure compared to patients without childhood trauma exposure (Asmal et al., 2019). Further, childhood trauma is associated with a proinflammatory state in adulthood in individuals with schizophrenia (Dennison et al., 2012) and at CHR (Kelsven, 2021). Nevertheless, no study has examined the relationship between childhood trauma and white matter in individuals across the range of APS, which the proposed study will help clarify. As this is the first study to examine the impact of these environmental stressors in the context of APS and white matter integrity, we will examine white matter metrics averaged across the whole brain as a first step in delineating the impact of stressors on the APS – white matter relationship.

Aims & Hypotheses

Aim 1. To examine the moderating influence of psychosocial stress on the attenuated psychotic symptoms – white matter integrity relationship. We will extend previous findings within schizophrenia patients implicating stress reactivity in response to an acute stressor in impaired WM integrity by examining the influence of more chronic forms of psychosocial stress, such as perceived stress, which has been previously linked to APS within our sample.

Hypothesis 1. We hypothesized that stress would significantly moderate the relationship between APS and WM integrity, averaged across the whole brain, such that higher levels of perceived stress will strengthen the relationship between APS and WM integrity, with lower white matter integrity at higher levels of perceived stress.

Aim 2. To examine childhood trauma as a moderator of the relationship between attenuated psychotic symptoms and white matter integrity. Childhood trauma has been linked to WM abnormalities in non-psychiatric controls, as well as in those with trauma-related disorders. As childhood trauma has been robustly associated with psychosis risk and severity of

symptoms, childhood trauma may account for a portion of the variance associated with the APS – WM integrity relationship.

Hypothesis 2. We hypothesized that childhood trauma would significantly moderate the relationship between attenuated psychotic symptoms and white matter integrity, averaged across the whole brain. As such, we hypothesize that higher incidences of childhood trauma will strengthen the APS – WM relationship, worsening white matter integrity at higher levels of childhood trauma.

Exploratory Aim. To examine how stress/trauma moderate the relationship between APS and white matter integrity differentially by sex. Given previous findings of the differential impact of trauma and stress by sex, we anticipate sex differences will be present in our moderation models.

Exploratory Hypothesis 1. We hypothesized that both perceived stress and childhood trauma would significantly moderate the relationship between APS and white matter integrity across the whole brain differentially by sex, such that moderating relationships of perceived stress and childhood trauma would be present in females but not males.

Method

Participants and Procedures

Participants included 73 16 – 30-year-olds recruited from the Greater Philadelphia Area, which is racially, ethnically, and socioeconomically diverse. Of the overall sample, 219 individuals were invited to complete a clinical interview during this project's period, with 144 individuals who met for Questionnaire High Risk (QHR; see Measures for description) and 75 individuals at Questionnaire Low Risk (QLR; see Measures). All participants were invited to participate in a multimodal neuroimaging session if MRI eligible (see Exclusion Criteria). This

sample was selected as adolescence/young adulthood is a critical age period of risk for psychosis spectrum psychopathology, and our diverse sample drawn from the community will better generalize to the population at large. By March 2020, 1162 surveys and 219 clinical interviews had been collected. Scanning began in August 2018 and 73 scans were completed by March 2020.

Inclusion Criteria

Adolescents and young adults were eligible for inclusion if they (a) were aged 16 - 30 years old at time of enrollment (corresponding with the typical age of onset for psychosis spectrum disorders), (b) had normal or corrected vision, and (c) completed clinical interview and self-report questionnaires from previous study visits.

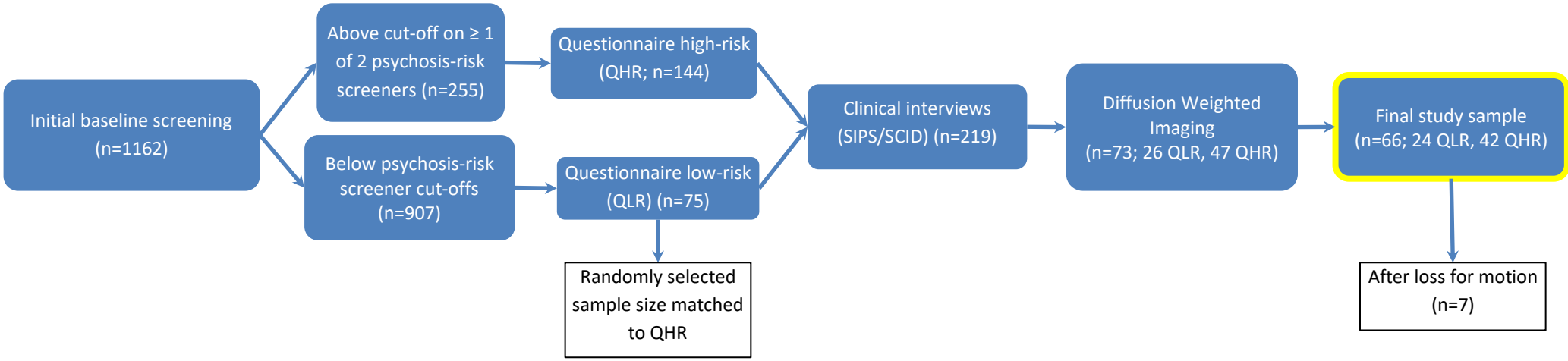
Exclusion Criteria

Participants were excluded if they failed to meet the above inclusion criteria. Participants were not excluded based on sex, ethnicity/race, or other demographic variables; however, at 4-month intervals the sex distribution of the overall sample was examined, and if there were differences in sex distributions, we only recruited the underrepresented sex for a period to maintain equal sex distributions among study participants. Participants were excluded based on (a) an inability to provide informed consent, (b) pregnancy or postpartum (< 6 weeks after delivery or miscarriage), and (c) any metal in the body.

Recruitment and Informed Consent

Participants for the current study were drawn from Dr. Ellman's R01 grant (see Figure 1 for recruitment at each study stage). The 5-year overall study sample (n=4000) was recruited using flyers in the Greater Philadelphia area and advertisements online (e.g., Facebook, Google, and Craigslist) targeting individuals who meet the necessary age requirements. For participants

Figure 1. Study sample



under 18, parents were targeted in recruitment efforts and asked if their child would be interested in participating in the study. If interested, participants received a link to an online survey to complete the initial informed consent/assent and a questionnaire battery. For participants under 18, a parent received a link to complete the initial informed consent and were then provided with a link for his/her child to complete an initial informed assent form and a questionnaire battery. Participants received a $10 gift card upon completion of the survey. Participants selected to complete the clinical interview portion (219 during the current study period) received a phone call or email requesting their participation in the clinical interview portion. Participants at this time point received $100 for the interview visit ($80 for the interview and $20 for travel).

Participants for the neuroimaging study (n=73) were recruited from the interview sample in Dr. Ellman's R01, either in person, by email, or by phone, upon completion of the interview portion of the study. Participants who consented to participate were paid $50 for the neuroimaging visit. In total, 73 neuroimaging subjects completed scans (n= 47 QHR, 26 QLR). After excluding for motion by visual inspection of scans by two trained raters and consensus decision made by the author, 66 subjects had usable data (n= 42 QHR, 24 QLR).

Measures

Self-Report Measures

Prodromal Questionnaire (PQ; Loewy, Bearden, Johnson, Raine, & Cannon, 2005): Attenuated psychotic symptoms (APS) were measured using the 45-item positive scale of the full-length, 92-item PQ. Individuals were asked whether, in the last month, they have experienced symptoms while not under the influence of drugs, alcohol, or medications. Endorsing 8 or more distressing APS on the PQ has been validated against the Structured Interview for Psychosis-risk Syndromes (SIPS) for predicting psychosis risk syndromes with

90% sensitivity and 49% specificity (Loewy et al., 2005; Loewy, Johnson, & Cannon, 2007). Thus, we used 8 distressing APS as the threshold for this measure.

Prime Screen (Miller, 2004): The Prime screen is a questionnaire that was designed to be similar in structure and content to SIPS positive symptom items. The original author-recommended screening threshold (≥2 endorsements of "somewhat" or "definitely agree", which was used in the proposed study) yielded sensitivity of 0.90 and specificity of 1.00 with regard to SIPS CHR for psychosis diagnoses [n=36 U.S. adolescents and young adults referred for CHR evaluation (Miller, 2004)], as well as 80% sensitivity, 48% specificity, and positive predictive value (PPV) of 0.52 in a sample of U.S. adolescents/young adults receiving mental health services (Kline, Wilson, Ereshefsky, Denenny, et al., 2012).

Participants met for Questionnaire High Risk (QHR) status based on meeting the threshold for **any one** of the above two screening questionnaires (Prodromal Questionnaire and Prime-Screen). Participants met for Questionnaire Low Risk (QLR) based on not meeting cutoffs for **both** of the questionnaires. Participants were **not** excluded based on diagnosis of a DSM-5 psychotic disorder or SIPS psychosis-risk syndrome; therefore, the whole spectrum of APS is represented in this sample.

Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983): The PSS was used to determine level of perceived psychosocial stress among participants. This scale measures perceived global stress over the month prior to assessment, with a focus on the predictability and controllability of these events. The PSS has high concurrent and predictive validity with psychiatric outcomes and is highly correlated with physiological measurements of stress (Hewitt, Flett, & Mosher, 1992; Palmier-Claus, Dunn, & Lewis, 2012), as well as experience sampling methods of perceived stress (Tso, Grove, & Taylor, 2012). The PSS sum score was used.

Childhood Trauma Questionnaire Short-Form (CTQ) (Bernstein & Fink, 1998):

Childhood trauma was measured using the CTQ. This inventory, validated for ages 12 and older, assesses five types of maltreatment (emotional, physical, and sexual abuse, and emotional and physical neglect). The CTQ shows good sensitivity and specificity, internal consistency, and convergent validity in both clinical and community samples (Bernstein et al., 1994). An abbreviated version of the CTQ excluding potentially reportable items (4, 9, 11, 12, 15, 17, 20, 21, 23, 24, 25, and 27) was administered at Time 1, and the full version was administered to a subset (n=51) of subjects at visit 2. Our abbreviated version was significantly correlated with the full version ($r = .877$, $p < .001$). The CTQ sum score at Time 1 was used.

Potential Covariates/Confounders

Additional factors were considered as possible covariates or confounders. If factors were correlated with the study IV (APS) and DV (WM integrity), we covaried to control for these variables.

Demographic Characteristics: Previous studies have found that age and sex have been correlated with PLEs in our prior samples (Ered et al., 2018). Additionally, age, sex (Inano et al., 2011), and higher body mass index (BMI; Verstynen et al., 2012) also have been shown to be highly correlated with WM integrity in community samples. Participants self-reported height and weight at time of questionnaires, and individuals scoring below the 10^{th} (19.76) and above the 90^{th} (31.00) percentile for BMI were checked against self-report at time of scan to ensure accuracy. Age and biological sex at birth were self-reported by participants.

Anxiety Symptoms: Trait generalized anxiety symptoms were measured using the State-Trait Anxiety Index- Trait Form- Anxiety Subscale (STAI; Spielberger, 1983). This version excludes items related to depression. The STAI has good construct (Bieling, Antony, & Swinson,

1998), discriminant, and convergent validity (Bieling et al., 1998; Spielberger, 1983), and test-retest reliability (Rule & Traver, 1983). Anxiety symptoms have been found to be highly comorbid with PLEs in our previous studies (Ered, Cooper, & Ellman, 2018). Further, anxiety symptoms, even at the subclinical level, have been found to be positively correlated with FA in the fornix and uncinate fasciculus (Modi et al., 2013).

Depressive Symptoms: Depression symptoms were assessed with the 14-item version of the Center for Epidemiologic Studies-Depression Scale (CES-D) (Radloff, 1977; Carleton et al., 2013), which assesses presence and severity of depressive symptoms over the past week. This scale has been found to be reliable and valid across samples (Radloff, 1977; Roberts, 1980; Roberts, Vernon, & Rhoades, 1989). CES-D depressive symptoms have been previously associated with PLEs within our sample (Ered et al., 2018) and have been found to relate to WM integrity in several of our regions of interest across phase of the disorder. Individuals with major depressive disorder have been found to have decreased FA in the superior longitudinal fasciculus and anterior thalamic radiation (Lai & Wu, 2014), and adolescents with sub-clinical levels of depression show lower total WM volume (Medina, Nagel, Park, McQueeny, & Tapert, 2007). Individuals with familial risk for depression show decreased FA in the cingulum, splenium, superior longitudinal fasciculi, uncinate fasciculus, and inferior frontal occipital fasciculus (Huang, Fan, Williamson, & Rao, 2011).

Clinical Interviews

Structured Interview for Psychosis-risk Syndromes (SIPS) version 5.6 (Miller, 2004; Miller et al., 2003; Woods et al., 2014): The SIPS is the most commonly used interview for assessing psychosis-risk syndromes within the United States (Cannon et al., 2008). The SIPS has established predictive validity of conversion to psychosis, specificity, and interrater reliability

(Miller et al., 2003; Miller et al., 2002). We used the SIPS to determine clinical high-risk (CHR) for psychosis, based on the presence of one psychosis-risk syndrome, including DSM-5 attenuated psychosis syndrome. Further, we examined the relationship of SIPS-rated attenuated psychotic symptoms (APS), utilizing P-item severity summed across P1 to P5 (SIPS Severity).

Structured Clinical Interview for DSM-5 (SCID; First, Spitzer, Gibbon, & Williams, 1995): Presence of any Axis-I DSM-5 mental diagnoses was assessed using the SCID. The SCID is considered the "gold standard" clinical diagnostic tool and demonstrates moderate-to-strong reliability (Steiner, Tebes, Sledge, & Walker, 1995). This measure was not included in analyses but to determine presence of DSM-5 schizophrenia spectrum disorder (SSD). Participants who meet criteria for a DSM-5 SSD at study entry were included; however, none of the individuals within the present sample met criteria for any SSD.

Training and Reliability

All clinicians conducting clinical interviewing were advanced level graduate students or research assistants with bachelor's degrees and at least 2-3 years of experience working with clinical populations. All study clinicians were SIPS certified by Dr. Barbara Walsh of Yale University's PRIME clinic or another certified SIPS trainer. Interviewers were blind to QHR or QLR condition. Each interviewer wrote a narrative following the interview, which was reviewed by an advanced interviewer to ensure reliability. More complex cases were further reviewed by a consensus group of advanced interviewers, and if no consensus was made the decision was then made by the overall study's PIs.

Neuroimaging

Image Collection: Diffusion weighted imaging (DWI) was collected in an 11-minute scan using a Seimans 3T scanner located at the Temple University Brain Research and Imaging

Center (TUBRIC) in the basement of Weiss Hall. Imaging parameters were TR=2400 ms and TE=2.28 ms. 98 directions of diffusion vectors were applied with diffusion-weighting of up to b = 3500 s/mm with an MB acceleration factor of 3. Neuroimaging staff were blind to subject QHR or QLR condition.

Image Analysis: Diffusion weighted images were preprocessed using tools in the FMRIB Software Library (FSL v 6.0.5) and a standardized pipeline from Dr. Olson's laboratory. Motion and eddy current-induced distortions were corrected (Andersson et al. 2003; Andersson and Sotiropoulos 2016), non-brain tissue was removed and a binary brain mask created with FSL's Brain Extraction Tool from each subject's non-diffusion (b0) weighted image volume, and the dtifit program was used to fit a diffusion tensor to each voxel and compute eigenvectors, eigenvalues, MD, and FA (Pierpaoli et al., 1996), in native anatomical space. Dipy software (Garyfallidis, Brett, Amirbekian, Rokem, Van Der Walt, Descoteaux, & Nimmo-Smith, 2014) was used to run an algorithm from collaborator Dr. Ofer Pasternak's laboratory, which provides an isolated measure of extracellular free-water (FW), standard tensor-modeled measures including fractional anisotropy (FA) and radial diffusivity (RD), as well as free-water corrected measures of FA and RD (FA_T and RD_T), using tract-based spatial statistics (TBSS, see Smith et al., 2006 for review) across the whole brain as an initial step in determining the moderating relationship of psychosocial stressors and childhood trauma on the APS – WM relationship.

Analytic Strategy

Power Analysis

Although power can be difficult to estimate for DWI studies, as power varies across brain region, previous studies from coauthor, Dr. Olson (Nugiel, Alm, & Olson, 2016), have shown that, in fact, inclusion of 60 participants lends sufficient power for whole brain analyses. Even

after participant loss that is typical in imaging studies (due to subject movement, etc.), we obtained 66 usable scans, which is highly powered using more conservative estimates.

Data Analysis

Only participants with complete data on the primary study variables were invited back for neuroimaging and thus used in this study. The neuroimaging subsample did not differ from the total sample demographically; however, the neuroimaging sample did have significantly higher scores on the PQ and PROD, as we oversampled from QHR group based on these two measures. Further, individuals in the neuroimaging sample also had significantly higher scores on the CTQ and PSS than the total sample, likely due to this oversampling as well. The residuals of regressions between independent variable (SIPS Severity) and dependent variables (WM integrity, measured by FW, FA, FA_T, RD, and RD_T) were first examined visually/statistically for normality and homoscedasticity. Bivariate Pearson's correlations for all study variables were conducted, as well as for potential covariates. First, potential study IVs [APS measures: Total PQ positive items (PQ), total PQ distressing items (PQ-D), total Prime Screen score (Prime), and sum of SIPS P items (SIPS)] and study DVs (white matter integrity: FA, RD, FW, FA_T, RD_T) were examined.

Regarding covariates, age and gender are correlated with APS in our prior samples (Ered et al., 2018) and age, sex (Inano, Takao, Hayashi, Abe, & Ohtomo, 2011), and higher body mass index (BMI; Kullmann, Schweizer, Veit, Fritsche, & Preissl, 2015; Stanek et al., 2011; Verstynen et al., 2012) also have been shown to be highly correlated with WM integrity in community samples. Thus, we also examined these variables as potential covariates. Further, anxiety and depression have been previously associated with APS in our samples (Ered et al., 2018), and have been found to be related to WM integrity (Modi et al., 2013; Lai & Wu, 2014;

Schollenbarger et al., 2015). Thus, we examined these variables as potential covariates as well. If any potential covariates were related to our study IVs (APS: PQ, PQ-D Prime Screen, and SIPS Total P Item Severity) and DVs (WM integrity: FW, FA, FA_T, RD, RD_T), we included them as covariates. Additionally, as sex has been found to be related to WM integrity (Inano et al., 2011) and stress sensitivity has been found to mediate the relationship between TLEs and APS in our previous studies (Gibson et al., 2014), we examined whether our findings differ by sex (see Exploratory Aim 1).

Moderation analyses were conducted in R (R Core Team, 2020) version 4.2.1 and RStudio (RStudio Team, 2020). First, the APS – WM integrity relationship, moderated by PSS was examined (Aim 1). Next, we tested CTQ as a moderator of APS – WM integrity (Aim 2). We then separated the sample by sex and examined the aforementioned models in males and females separately (Exploratory Aim). Finally, sensitivity analyses excluding individuals on antipsychotic medications and hormonal therapy due to gender nonconformity or Turner syndrome were conducted to determine the impact of these medications on our models, ensuring that results were still significant after removing these individuals.

Results

First, regression residuals were examined visually and statistically for normality and homoscedasticity. Bivariate relationships were examined between study IVs and DVs (see Table 1), as well as study moderators. Traditional DWI metrics (FA and RD) were not associated with measures of APS (SIPS Severity, PQ, PQ-D, or Prime). Regarding moderators, the PSS was significantly correlated with self-report measures of APS (PQ, PQ-D, Prime) at the $p<.001$ level, and trended with our interview-based measure of APS (SIPS, $p=.058$). CTQ was significantly correlated with both interview-based measures and self-report measures of APS (SIPS, PQ, and

Table 1. Pearson correlations between variables of interest (n=66)

	FW	FA	FA_T	RD	RD_T	SIPS	PQ	PQ-D	Prime	PSS	CTQ
FW	-										
FA	-.506**	-									
FA_T	-.657**	.557**	-								
RD	.609**	-.893**	-.406**	-							
RD_T	.569**	-.663**	-.903**	.608**	-						
SIPS	.257*	-.037	-.287*	.066	.305*	-					
PQ	.031	-.044	-.110	.044	.141	.648**	-				
PQ-D	.028	-.054	.045	.143	.022	.413**	.666**	-			
Prime	.032	-.013	-.058	.047	.100	.482**	.605**	.521**	-		
PSS	-.146	.094	-.020	-.161	-.019	.235^	.349**	.535**	.319**	-	
CTQ	.115	-.126	-.119	.187	.191	.323**	.410**	.358**	.301*	.224^	-

FW= Whole Brain Extracellular Free-water, FA= Whole Brain Fractional Anisotropy, FA_T= Whole Brain Free-water Corrected Fractional Anisotropy, RD= Whole Brain Radial Diffusivity, RD_T= Whole Brain Free-water Corrected Radial Diffusivity, SIPS= Structured Interview for Psychosis-Risk Syndromes Total P Severity Score, PQ= Prodromal Questionnaire Positive Scale Total Score, PQ-D= Prodromal Questionnaire Positive Scale Distressing Total Score, Prime= Prime Screen Total Score, PSS= Perceived Stress Scale Total Score, CTQ= Childhood Trauma Questionnaire Total Score, ^= <.10*= <.05, **=<.001

PQ-D $p<.001$, Prime $p=.014$). Extracellular free-water and free-water corrected DWI metrics (FA_T and RD_T) all were significantly correlated with SIPS Severity, but not self-report measures of APS (PQ, PQ-D or Prime). Bivariate relationships for potentially related demographic factors (age, sex, BMI, race, ethnicity) and clinical variables (STAI, CES-D) were examined. Sex was significantly correlated with one study DV (mean FW), so we controlled for sex assigned at birth in order to take a conservative approach. Due to small variances (.000 - .002), all five DVs (FW, FA, FA_T, RD, RD_T) were scaled by multiplying by 1000 in these variables to ensure interpretability of effects. Demographics and clinical characteristics of the total sample, as well as male and females separately, are presented in Table 2.

Moderation Analyses

Moderation was examined, utilizing our significant IV (APS measured using SIPS Severity), moderators (Perceived Stress Scale, Childhood Trauma Questionnaire), and five DVs (FW, FA, FA_T, RD, RD_T), resulting in ten total models. Main effects were found of SIPS Severity predicting FW, FA_T, and RD_T, but not traditional DWI metrics (FA and RD). There were no significant main effects of perceived stress or childhood trauma on any white matter integrity variables.

Perceived stress was not found to significantly moderate the relationship between SIPS Severity and white matter integrity (FW, FA, FA_T, RD, RD_T). Childhood trauma exposure did not moderate the relationship between SIPS Severity and FW, FA, or RD, but **did** significantly moderate the relationship between SIPS Severity and both FA_T and RD_T (see Tables 3 – 12), such that for individuals at low levels of APS, higher levels of childhood trauma predicted worse white matter integrity (lower FA_T and higher RD_T) and at higher levels of APS, higher levels of

Table 2. Demographic and clinical characteristics of the sample

	Full Imaging Sample (n=73)	Final Sample (n=66)	Males Only (n=25)	Females Only (n=41)	Difference (X^2 or t, p)
Age M (SD) [range]	20.38 (2.24) [18-30]	20.35 (2.27) [18-30]	20.40 (2.00) [18-24]	20.32 (2.44) [18-30]	.143, .887
Biological sex at birth Female (n)%	43 (59%)	41 (62%)	-	-	-
Race					5.95, .114
Asian n (%)	18 (25%)	16 (24%)	3 (12%)	13 (32%)	
Black n (%)	9 (12%)	8 (12%)	4 (16%)	4 (10%)	
White n (%)	43 (59%)	39 (59%)	18 (72%)	21 (51%)	
Multiracial n (%)	3 (4%)	3 (5%)	0 (0%)	3 (7%)	
Ethnicity Hispanic n (%)	4 (6%)	3 (5%)	2 (8%)	1 (2%)	1.195, .274
SIPS CHR Status CHR n (%)	23 (32%)	20 (30%)	7 (28%)	13 (32%)	.101, .751
Questionnaire High Risk n (%)	47 (64%)	42 (64%)	14 (56%)	28 (68%)	1.014, .314
SIPS Severity M (SD) [range]		5.67 (4.16) [0-17]	6.32 (5.01) [0-17]	5.27 (3.56) [0-12]	.996, .323
PQ Positive M (SD) [range]	16.21 (10.08) [0-37]	16.08 (10.12) [0-37]	17.52 (10.34) [1-37]	15.20 (10.01) [0-37]	.904, .369
PQ Positive Distressing M (SD) [range]	8.14 (7.16) [0-35]	8.05 (7.28) [0-35]	7.36 (8.20) [0-35]	8.46 (6.73) [0-32]	-.595, .554
Prime Screen M (SD) [range]	1.01 (1.83) [0-10]	1.00 (1.87) [0-10]	1.24 (2.09) [0-9]	0.85 (1.74) [0-10]	.811, .420
CTQ Total (Time 1) M (SD) [range]	25.85 (10.29) [14-59]	25.38 (9.51) [14-49]	22.08 (6.65) [14-34]	27.39 (10.46) [14-49]	-2.52, .014*
CTQ Total (Time 2) M (SD) [range]	41.29 (13.52) [26-88]	40.07 (11.31) [26-70]	35.00 (7.24) [26-49]	43.58 (12.37) [26-70]	-2.89, .006**
PSS sum M (SD) [range]	29.70 (6.39) [16-42]	29.63 (6.37) [16-42]	27.92 (6.87) [16-40]	30.68 (5.88) [18-42]	-1.74, .09

SIPS= Structured Interview for Psychosis-risk Syndromes, CHR= Clinical High Risk, PQ= Prodromal Questionnaire, CTQ= Childhood Trauma Questionnaire, PSS= Perceived Stress Scale, *= p<.05, **=p<.01

childhood trauma predicted better white matter integrity (higher FA_T and lower RD_T), though this does not survive Bonferroni correction for multiple comparisons.

After stratifying by sex and examining males and females separately, for males, main effects of APS were seen for FA_T and RD_T only, and there were no significant main effects of childhood trauma or perceived stress on WM integrity. In females, a main effect of childhood trauma was seen for RD_T, with no main effects of APS or perceived stress found. In males, childhood trauma significantly moderated the APS – WM integrity relationship for FA, FA_T, and RD_T, similar to the whole sample ($p < .05$, RD_T), but these interactions were not present in female participants, though it should be noted that these findings are exploratory due to low power (see Table 3 - 12). For male participants only, perceived stress also moderated the APS – FA relationship ($p < .05$) in a similar pattern to childhood trauma, such that for males at low levels of APS, higher levels of perceived stress predicted worse white matter integrity (lower FA_T and higher RD_T) and at higher levels of APS, higher levels of childhood trauma predicted better white matter integrity (higher FA_T and lower RD_T).

Sensitivity Analyses

Two sensitivity analyses were conducted to explore the effect of antipsychotic medications and hormone therapy on our results. For both sensitivity analyses, all subjects excluded were assigned female at birth; as such, the total sample and female only analyses were examined. In both sensitivity analyses, moderation results were consistent with results reported above which included these subjects.

Table 3. Hierarchical linear regression models of attenuated psychotic symptoms and perceived stress predicting extracellular free-water (FW) (B= unstandardized beta, * p<.05)

Total Sample (n=66)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	**.95***	**.09, 1.81**	**.07**	**-.04, .18**	**.145* [.00,.28]**
	PSS	-.39	-.95, .18	.03	-.04, .10	
Step 2	APS x PSS	.00	-.13, 0.13	.00	-.00, .00	.145* [.00, .26]
Males Only (n=25)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	1.06	-.07, 2.18	.15	-.11, .40	.148 [.00, .37]
	PSS	-.08	-.90, .74	.00	-.03, .03	
Step 2	APS x PSS	.07	-.10, .23	.03	-.09, .13	.175 [.00, .37]
Females Only (n=41)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	.87	-.50, 2.23	.04	-.08, .14	.074 [.00,.23]
	PSS	-.63	-1.45, .20	.06	-.08, .20	
Step 2	APS x PSS	-.14	-.39, .11	.03	-.07, .13	.105 [.00, .25]

Table 4. Hierarchical linear regression models of attenuated psychotic symptoms and perceived stress predicting fractional anisotropy (FA) (B= unstandardized beta, * p<.05)

Total Sample (n=66)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	-.12	-1.18, .93	.00	-.01, .01	.040 [.00,.13]
	PSS	.17	-.53, .87	.00	-.02, .03	
Step 2	APS x PSS	.09	-.07, .25	.02	-.04, .08	.059 [.00, .15]
Males Only (n=25)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	.38	-1.05, 1.82	.03	-.07, .12	.017 [.00, .15]
	PSS	-.19	-1.24, .85	.01	-.06, .07	
Step 2	APS x PSS	**.21***	**.02, .40**	**.20**	**-.08, .48**	.217 [.00, .41]
Females Only (n=41)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	-.83	-2.46, .80	.03	-.07, .12	.044 [.00, .18]
	PSS	.55	-.43, 1.54	.03	-.07, .14	
Step 2	APS x PSS	-.03	-.33, .28	.00	-.02, .02	.045 [.00, .16]

Table 5. Hierarchical linear regression models of attenuated psychotic symptoms and perceived stress predicting free-water corrected fractional anisotropy (FA_T) (B= unstandardized beta, * p<.05)

Total Sample (n=66)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	**-2.67**	**-5.11, -.23**	**.07**	**-.05, .19**	.100 [.00,.22]
	PSS	.11	-1.51, 1.73	.00	-.01, .01	
Step 2	APS x PSS	.13	-.24, .49	.01	-.03, .04	.106 [.00, .22]
Males Only (n=25)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	-3.48	-7.44, .48	.13	-.11, .37	.159 [.00, .38]
	PSS	-.75	-3.64, 2.14	.01	-.06, .09	
Step 2	APS x PSS	.14	-.44, .73	.01	-.06, .08	.169 [.00, .36]
Females Only (n=41)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	-1.78	-5.10, 1.54	.03	-.07, .13	.034 [.00, .16]
	PSS	.73	-1.28, 2.73	.01	-.06, .08	
Step 2	APS x PSS	.08	-.54, .70	.00	-.02, .03	.036 [.00, .14]

Table 6. Hierarchical linear regression models of attenuated psychotic symptoms and perceived stress predicting radial diffusivity (RD) (B= unstandardized beta, * p<.05)

Total Sample (n=66)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	.00	-.00, .00	.01	-.03, .05	.052 [.00,.15]
	PSS	-.00	-.00, .00	.02	-.05, .09	
Step 2	APS x PSS	-.00	-.00, .00	.02	-.05, .09	.074 [.00, .17]
Males Only (n=25)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	.00	-.00, .00	.00	-.01, .01	.025 [.00, .17]
	PSS	-.00	-.00, .00	.02	-.09, .14	
Step 2	APS x PSS	-.00	-.00, .00	.09	-.12, .30	.114 [.00, .29]
Females Only (n=41)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	.00	-.00, .00	.02	-.07, .11	.036 [.00, .17]
	PSS	-.00	-.00, .00	.03	-.07, .12	
Step 2	APS x PSS	-.00	-.00, .00	.01	-.06, .08	.049 [.00, .17]

Table 7. Hierarchical linear regression models of attenuated psychotic symptoms and perceived stress predicting free-water corrected radial diffusivity (RD_T) (B= unstandardized beta, * p<.05)

Total Sample (n=66)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	**.00***	**.00, .00**	**.10**	**-.04, .23**	.102 [.00,.22]
	PSS	-.00	-.00, .00	.01	-.03, .05	
Step 2	APS x PSS	-.00	-.00, .00	.02	-.04, .09	.125 [.00, .24]
Males Only (n=25)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	**.00**	**.00, .00**	**.18**	**-.09, .45**	.179 [.00, .40]
	PSS	-.00	-.00, .00	.01	-.05, .06	
Step 2	APS x PSS	-.00	-.00, .00	.02	-.08, .12	.198 [.00, .39]
Females Only (n=41)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	.00	-.00, .00	.03	-.07, .14	.033 [.00, .16]
	PSS	-.00	-.00, .00	.01	-.04, .06	
Step 2	APS x PSS	-.00	-.00, .00	.01	-.06, .08	.047 [.00, .16]

Table 8. Hierarchical linear regression models of attenuated psychotic symptoms and childhood trauma predicting extracellular free-water (FW) (B= unstandardized beta, * p<.05)

Total Sample (n=66)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	.63	-.27, 1.52	.03	-.05, .10	**.133* [.00,.26]**
	CTQ	.20	-.20, .60	.01	-.04, .07	
Step 2	APS x CTQ	-.04	-.14, .05	.01	-.04, .06	**.146* [.00, .27]**
Males Only (n=25)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	1.10	-.07, 2.28	.15	-.11, .40	.151 [.00, .37]
	CTQ	-.15	-1.04, .73	.01	-.05, .06	
Step 2	APS x CTQ	-.03	-.19, .13	.01	-.05, .07	.158 [.00, .35]
Females Only (n=41)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	.08	-1.34, 1.51	.00	-.01, .01	.064 [.00,.22]
	CTQ	.34	-.15, .82	.05	-.08, .18	
Step 2	APS x CTQ	-.03	-.16, .11	.00	-.03, .04	.069 [.00, .20]

Table 9. Hierarchical linear regression models of attenuated psychotic symptoms and childhood trauma predicting fractional anisotropy (FA) (B= unstandardized beta, * p<.05)

Total Sample (n=66)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	.26	-.81, 1.34	.00	-.02, .03	.075 [.00,.19]
	CTQ	-.39	-.87, .10	.04	-.05, .13	
Step 2	APS x CTQ	.07	-.04, .19	.02	-.05, .10	.099 [.00, .21]
Males Only (n=25)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	.52	-.97, 2.01	.02	-.09, .14	.035 [.00, .20]
	CTQ	-.41	-1.53, .72	.02	-.09, .14	
Step 2	APS x CTQ	**.23***	**.05, .40**	**.24**	**-.05, .53**	.276 [.00, .47]
Females Only (n=41)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	-.08	-1.77, 1.62	.00	-.01, .01	.049 [.00, .19]
	CTQ	-.35	-.92, .23	.04	-.08, .15	
Step 2	APS x CTQ	.00	-.16, .16	.00	-.00, .00	.049 [.00, .16]

Table 10. Hierarchical linear regression models of attenuated psychotic symptoms and childhood trauma predicting free-water corrected fractional anisotropy (FA_T) (B= unstandardized beta, * p<.05, **p<.01)

Total Sample (n=66)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	-2.33	-4.85, .19	.05	-.05, .15	.105 [.00,.23]
	CTQ	-.35	-1.49, .79	.01	-.03, .04	
Step 2	APS x CTQ	**.27***	**.00, .53**	**.06**	**-.05, .16**	**.161* [.00, .28]**
Males Only (n=25)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	**APS**	**-4.20**	**-8.32, -.09**	**.17**	**-.10, .44**	.170 [.00, .39]
	CTQ	1.14	-1.95, 4.24	.02	-.08, .13	
Step 2	APS x CTQ	**.70****	**.24, .1.17**	**.26**	**-.01, .54**	**.169** [.05, .60]**
Females Only (n=41)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	-.22	-3.58, 3.15	.00	-.01, .01	.082 [.00, .25]
	CTQ	-.91	-2.05, .28	.06	-.08, .20	
Step 2	APS x CTQ	-.10	-.41, .22	.01	-.05, .07	.092 [.00, .23]

Table 11. Hierarchical linear regression models of attenuated psychotic symptoms and childhood trauma predicting radial diffusivity (RD) (B= unstandardized beta, * p<.05)

Total Sample (n=66)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	-.00	-.00, .00	.00	-.02, .02	.089 [.00,.21]
	CTQ	**.00***	**-.02, .00**	**.06**	**-.05, .17**	
Step 2	APS x CTQ	-.00	-.00, .00	.02	-.04, .08	.109 [.00, .22]
Males Only (n=25)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	-.00	-.00, .00	.01	-.06, .08	.039 [.00, .21]
	CTQ	.00	-.00, .00	.04	-.11, .19	
Step 2	APS x CTQ	-.00	-.00, .00	.08	-.12, .29	.122 [.00, .30]
Females Only (n=41)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	-.00	-.00, .00	.00	-.01, .01	.073 [.00, .23]
	CTQ	.00	-.00, .00	.06	-.08, .21	
Step 2	APS x CTQ	-.00	-.00, .00	.01	-.04, .06	.080 [.00, .22]

Table 12. Hierarchical linear regression models of attenuated psychotic symptoms and childhood trauma predicting free-water corrected radial diffusivity (RD_T) (B= unstandardized beta, * p<.05, ** p<.01)

Total Sample (n=66)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	.00	-.00, .00	.06	-.05, .16	.107 [.00,.23]
	CTQ	.00	-.00, .00	.01	-.04, .06	
Step 2	APS x CTQ	**-.00***	**-.00, -.00**	**.09**	**-.03, .21**	**.196** [.02, .32]**
Males Only (n=25)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	**.00***	**.00, .00**	**.21**	**-.08, .49**	.208 [.00, .43]
	CTQ	-.00	-.00, .00	.04	-.09, .16	
Step 2	APS x CTQ	**-.00****	**-.00, -.00**	**.28**	**.01, .55**	**.485** [.10, .64]**
Females Only (n=41)						
	Predictor	**B**	**95% CI (B)**	**sr^2**	**95% CI (sr^2)**	**r^2 Fit [95% CI]**
Step 1	APS	.00	-.00, .00	.00	-.00, .00	.139 [.00, .32]
	CTQ	**.00***	**.00, .00**	**.11**	**-.07, .29**	
Step 2	APS x CTQ	.00	-.00, .00	.00	-.01, .01	.139 [.00, .30]

Discussion

We found evidence that experiences of childhood trauma in interaction with APS are associated with white matter microstructural abnormalities. Main effects with APS were specific to free-water corrected metrics rather than standard DWI metrics, indicating that these abnormalities are in fact capturing tissue differences in white matter, rather than elevations in extracellular free-water. As standard measures do not account for CSF contamination and simply average across the voxel, traditional DWI metrics are artificially driven down and are less sensitive to white matter tissue differences than free-water corrected measures. Given that extracellular FW was significantly positively correlated with SIPS Severity score, this implicates a potential role of neuroinflammation in the pathophysiology of psychosis. Further, this confirms that it is crucial for samples of individuals with disorders that result in increases in extracellular free-water (e.g., schizophrenia spectrum disorders, Alzheimer's Disease) to utilize free-water corrected DWI metrics to accurately capture white matter tissue differences.

Self-report measures of APS (Prodromal Questionnaire, Prime Screen) were not significantly correlated with white matter microstructure, but our interview-based measure (SIPS) was significantly correlated with FW, FA_T, and RD_T. It is possible that this is due to our self-report measures of APS assessing only presence vs. absence of symptoms, which relies heavily on the participant's insight into their own symptoms, while the SIPS also captures symptom severity. Further, in interview-based measures, trained raters can ensure that the symptom endorsed is truly an APS, rather than a symptom with phenotypic overlap or misinterpretation of the question (e.g., paranoia vs. social anxiety). Given these factors, the specificity of correlations between white matter microstructure and SIPS severity score indicates that these differences are associated specifically with interview-assessed measures of attenuated

positive symptoms and may be more closely associated with severity of these symptoms, rather than simply their presence.

Notably, at high levels of APS, childhood trauma did not worsen the impact of symptoms on white matter integrity as hypothesized, but rather acted as a protective factor. One possible mechanism by which childhood trauma could impact white matter development is through the activation of the hypothalamic-pituitary-adrenal (HPA) axis. In individuals with psychosis spectrum disorders, HPA axis activity has been found to be abnormal. Individuals at clinical high risk (CHR) for psychosis and diagnosed with schizophrenia show blunted cortisol reactivity (Ciufolini, Dazzan, Kempton, Pariante, & Mondelli, 2014; Pruessner et al., 2013) and prolonged cortisol reactivity (Nugent et al., 2015) to laboratory stress tasks, as well as elevated diurnal cortisol levels, and blunted cortisol awakening response (Borges, Gayer-Anderson, & Mondelli, 2013). Abnormal HPA axis response to stress may increase exposure to cortisol for females especially, which, in turn, may 1) suppress the proliferation of oligodendrocytes and delay myelination of major WM tracts, 2) allow myelin and lipid membranes to become more vulnerable to oxidative damage, and 3) lead to increases in proinflammatory cytokines, which may indirectly influence WM development (Nugent et al., 2015). Proinflammatory cytokines also have been implicated as mediators of the socioeconomic status-WM integrity relationship in non-psychiatric samples (Gianaros, Marsland, Sheu, Erickson, & Verstynen, 2013). As such, studying how stress influences WM integrity in those experiencing APS has biological plausibility and empirical support from non-psychosis and psychosis samples and examining the biological underpinnings of these relationships is a necessary future step.

Although exploratory due to insufficient power, we found some evidence for sex-specific indirect effects, with the interaction between APS and childhood trauma predicting white matter

alterations in male participants only. There are several factors that may leave males less vulnerable to the impact of environment factors such as childhood trauma on white matter microstructure. Namely, typically developing females show earlier maturation and myelination of white matter tracts, whereas white matter development in males occurs over a longer period, which allows more time for male brains to adjust for factors such as a proinflammatory state resulting from early life adversity (Pohl et al., 2016; Seunarine et al., 2016), though there is evidence that higher levels of estrogen protects females from early stressors (Seeman & Lang, 1990). Further, the robust evidence of earlier age of onset of psychosis in males (Castle, Sham, & Murray. 1998) may speak to an impact of APS on white matter earlier in development, during a critical period in brain development. Our findings indicate that, in the presence of APS, childhood trauma may protect males from white matter dysfunction in this sample; however, these results should be interpreted with caution due to low power for sex difference analyses.

Our community-based sample allows for examination of factors that influence psychosis-risk processes prior to the onset of more severe symptomatology, avoids the impact of illness-related factors such as medication on brain regions, and further allows for greater generalizability to the general population. Further, we included both questionnaire and interview-based measurements of PLEs; however, our measures of perceived stress and childhood trauma are both self-report, and retrospective in the case of the latter. Retrospective measures of childhood trauma have been found to underestimate trauma exposure when compared to prospective measures, with meta-analyses finding that 52% of individuals who reported childhood trauma prospectively did not report this retrospectively (Baldwin et al., 2019). Additionally, information relating to timing and sequence of traumatic events is not captured by the CTQ, and timing is crucial to determining the impact of childhood trauma on white matter integrity and attenuated

psychotic symptoms, given evidence that timing of stress exposure has differential effects on white matter (Jensen et al., 2018). Future studies should examine the relationship between childhood trauma and white matter integrity prospectively, in large longitudinal studies to confirm our findings. Additionally, larger samples may choose to explore subtypes of childhood trauma to identify if a specific subtype most impacts white matter integrity.

Although our measure of perceived stress also relied on self-report data, the PSS has been well-validated against experience sampling methods (Palmier-Claus, Dunn, & Lewis, 2012), physiological measures of stress sensitivity or inflammation, such as heart rate variability, cortisol levels and inflammatory cytokines, may better capture HPA Axis dysfunction and provide evidence of a mechanism through which white matter microstructural alterations occur in individuals with PLEs who have experienced childhood trauma. Childhood trauma has been associated with increases in C-reactive protein and proinflammatory cytokines in the general population (Boelho et al., 2013), as well as in schizophrenia spectrum disorders (Dennison et al., 2012) and other disorders such as depression (Grosse, et al., 2016). It is possible that childhood trauma impacts white matter integrity indirectly through higher levels of proinflammatory cytokines, which previously have been found to be related to increased free-water in individuals with schizophrenia (Di Biase et al., 2021). Another limitation of this study is that the cross-sectional nature of these data do not allow us to determine the temporal relationship of the associations probed in the current study, even though childhood trauma clearly preceded the other study variables. This study is a first step in confirming psychosocial stress and childhood trauma as modifiers of the relationship between APS and WM alterations.

Although we have examined the interaction effects of childhood trauma and perceived stress in this study, there are other environmental and psychosocial factors that also may interact

with PLEs to impact white matter alterations. Namely, variables such as socioeconomic status (Brito & Noble, 2014; DeRosse et al., 2014; Gur et al., 2019), neighborhood disadvantage (Bell et al., 2021), urbanicity (Frissen et al., 2014; Lammeyer et al., 2019), racial discrimination (Flores et al., 2008; Oh et al., 2014; Ong et al., 2009; Fani et al., 2022), immigrant status (Flores et al., 2008; Morgan et al., 2010), air pollution (Calderón-Garcidueñas et al., 2016), lead exposure (Brubaker et al., 2009), and cannabis use (DeRosse et al., 2014; Epstein & Kumra, 2015; Scott et al., 2019) have been found to be associated with psychosis-risk and/or white matter integrity. Many of these factors disproportionately impact people of color due to systemic racism; thus, future work must explore how racial/ethnic identity may further moderate the impact of these factors on the PLE – WM relationship (Anglin et al., 2021). Further, there is evidence that other early insults, particularly those occurring during the pre- and perinatal periods, may additively produce white matter alterations in the presence of later stressors, such as childhood trauma. Rodent models of maternal immune activation (MIA) with and without prepubertal stress revealed oligodendrocyte and myelin abnormalities in the MIA condition and stress only conditions, as well as accelerated loss of neurons in the prefrontal cortex of the MIA + stress condition compared to MIA alone (Namvarpour et al., 2022). These findings indicate that whereas both inflammation from MIA and early life stress both lead to white matter alterations, the combination of the two is most detrimental, which is of particular relevance to neurodevelopmental disorders such as schizophrenia. Finally, although this study identified whole brain microstructural differences related to PLEs and childhood trauma, future work is needed to identify which specific white matter tracts are affected.

This study identified experiences of childhood trauma as a potential protective mechanism of white matter abnormalities along the psychosis continuum, with some preliminary

evidence of sex differences in this relationship. Determining moderators of the relationship between PLEs and white matter abnormalities marks a step toward identifying targets for intervention (e.g., trauma-focused cognitive behavioral therapy), which may help to prevent early maltreatment from developing into white matter dysfunction and more severe forms of psychotic illness by modulating HPA axis reactivity (Kuhlman, Geiss, Vargas, & Lopez-Duran, 2018) and decreasing the generalizability of negative cognitions resulting from childhood trauma, particularly for younger children (Ready et al., 2015).

BIBLIOGRAPHY

Addington, J., Stowkowy, J., Cadenhead, K. S., Cornblatt, B. A., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., & Cannon, T. D. (2013). Early traumatic experiences in those at clinical high risk for psychosis. *Early Intervention in Psychiatry*, *7*(3), 300–305.

Aleman, A., Kahn, R. S., & Selten, J.-P. (2003). Sex Differences in the Risk of Schizophrenia: Evidence From Meta-analysis. *Archives of General Psychiatry*, *60*(6), 565–571.

Amateau, S. K., & McCarthy, M. M. (2004). Induction of PGE2 by estradiol mediates developmental masculinization of sex behavior. *Nature neuroscience*, *7*(6), 643–650.

Andersson, J. L., Skare, S., & Ashburner, J. (2003). How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *Neuroimage*, *20*(2), 870-888.

Andersson, J. L., & Sotiropoulos, S. N. (2016). An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *Neuroimage*, *125*, 1063-1078.

Anglin, D. M., Ereshefsky, S., Klaunig, M. J., Bridgwater, M. A., Niendam, T. A., Ellman, L. M., DeVylder, J., Thayer, G., Bolden, K., Musket, C. W., Gratten, R. E., Lincoln, S. H., Schiffman, J., Lipner, E., Bachman, P., Corcoran, C. M., Mota, N. B., van der Ven, E. (2021). From womb to neighborhood: a racial analysis of social determinants of psychosis in the United States. American Journal of Psychiatry, 178(7), 599-610.

Anglin, D. M., Galea, S., & Bachman, P. (2020). Going Upstream to Advance Psychosis Prevention and Improve Public Health. *JAMA Psychiatry*, *77*(7), 665–666.

Arat, H. E., Chouinard, V.-A., Cohen, B. M., Lewandowski, K. E., & Öngür, D. (2015). Diffusion tensor imaging in first degree relatives of schizophrenia and bipolar disorder patients. *Schizophrenia Research*, *161*(2), 329–339.

Asato, M. R., Terwilliger, R., Woo, J., & Luna, B. (2010). White matter development in adolescence: a DTI study. *Cerebral cortex*, *20*(9), 2122-2131.

Asmal, L., Kilian, S., Du Plessis, S., Scheffler, F., Chiliza, B., Fouche, J. P., Seedat S., Dazzan, P., Emsley, R. (2019). Childhood trauma associated white matter abnormalities in first-episode schizophrenia. *Schizophrenia Bulletin*, *45*(2), 369-376.

Baldwin, J. R., Reuben, A., Newbury, J. B., & Danese, A. (2019). Agreement between prospective and retrospective measures of childhood maltreatment: a systematic review and meta-analysis. JAMA psychiatry, 76(6), 584-593.

Bale, T. L., Baram, T. Z., Brown, A. S., Goldstein, J. M., Insel, T. R., McCarthy, M. M., Nemeroff, C. B., Reyes, T. M., Simerly, R. B., Susser, E. S., & Nestler, E. J. (2010). Early life programming and neurodevelopmental disorders. *Biological psychiatry, 68*(4), 314–319.

Bale, T. L., & Epperson, C. N. (2015). Sex differences and stress across the lifespan. *Nature neuroscience, 18*(10), 1413-1420.

Bangasser, D. A., Eck, S. R., Telenson, A. M., & Salvatore, M. (2018). Sex differences in stress regulation of arousal and cognition. *Physiology & Behavior*, *187*, 42–50.

Bangasser, D. A., & Valentino, R. J. (2014). Sex differences in stress-related psychiatric disorders: Neurobiological perspectives. *Frontiers in Neuroendocrinology, 35*(3), 303–319.

Bauer, M. E., & Teixeira, A. L. (2019). Inflammation in psychiatric disorders: what comes first?. *Annals of the New York Academy of Sciences*.

Bava, S., Boucquey, V., Goldenberg, D., Thayer, R. E., Ward, M., Jacobus, J., & Tapert, S. F. (2011). Sex differences in adolescent white matter architecture. *Brain research*, *1375*, 41-48.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system–a technical review. *NMR in Biomedicine: An International Journal Devoted to the Development and Application of Magnetic Resonance In Vivo, 15*(7-8), 435-455.

Bebbington, P., Wilkins, S., Jones, P., Foerster, A., Murray, R., Toone, B., Lewis, S. (1993). Life events and psychosis: Initial results from the Camberwell Collaborative Psychosis Study. *The British Journal of Psychiatry, 162*(1), 72-79.

Bell, K. L., Purcell, J. B., Harnett, N. G., Goodman, A. M., Mrug, S., Schuster, M. A., Elliott, M. N., Tortolero Emery, S., Knight, D. C. (2021). White matter microstructure in the young adult brain varies with neighborhood disadvantage in adolescence. *Neuroscience, 466*, 162-172.

Bergamino, M., Pasternak, O., Farmer, M., Shenton, M. E., & Paul Hamilton, J. (2016). Applying a free-water correction to diffusion imaging data uncovers stress-related neural pathology in depression. *NeuroImage: Clinical*, *10*, 336–342.

Bergé, D., Mané, A., Lesh, T. A., Bioque, M., Barcones, F., Gonzalez-Pinto, A. M., Parellada, M., Vieta, E., Castro-Fornieles, J., Rodriguez-Jimenez, R., García-Portilla, M. P., Usall, J., Carter, C. S., Cabrera, B., Bernardo, M., Janssen, J., Mezquida, G., Amoretti, S., Pina-Camacho, L., … Pomarol-Clotet, E. (n.d.). Elevated Extracellular Free-Water in a Multicentric First-Episode Psychosis Sample, Decrease During the First 2 Years of Illness. *Schizophrenia Bulletin*.

Bernard, J. A., Orr, J. M., & Mittal, V. A. (2017). Cerebello-thalamo-cortical networks predict positive symptom progression in individuals at ultra-high risk for psychosis. *NeuroImage: Clinical*, *14*, 622–628.

Bernstein, D. P. & Fink, L. (1998). *Childhood trauma questionnaire: A retrospective self-report: Manual*: Psychological Corporation.

Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E., Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *The American journal of psychiatry*, *151*(8), 1132.

Bieling, P. J., Antony, M. M., Swinson, R. P. (1998). The State--Trait Anxiety Inventory, Trait version: structure and content re-examined. *Behaviour research and therapy*, *36*(7), 777-788.

Bloomfield, P. S., Selvaraj, S., Veronese, M., Rizzo, G., Bertoldo, A., Owen, D. R., Bloomfield, M. A. P., Bonoldi, I., Kalk, N., Turkheimer, F., McGuire, P., de Paola, V., & Howes, O. D. (2015). Microglial Activity in People at Ultra High Risk of Psychosis and in Schizophrenia: An [11C]PBR28 PET Brain Imaging Study. *American Journal of Psychiatry*, *173*(1), 44–52.

Boerrigter, D., Weickert, T. W., Lenroot, R., O'Donnell, M., Galletly, C., Liu, D., Burgess, M., Cadiz, R., Jacomb, I., Catts, V. S., Fillman, S. G., & Weickert, C. S. (2017). Using blood cytokine measures to define high inflammatory biotype of schizophrenia and schizoaffective disorder. *Journal of Neuroinflammation*, *14*(1), 188.

Bora, E., Fornito, A., Radua, J., Walterfang, M., Seal, M., Wood, S. J., Yücel, M., Velakoulis, D., & Pantelis, C. (2011). Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophrenia research, 127(1-3), 46–57.

Borchers, L. R., Dennis, E. L., King, L. S., Humphreys, K. L., & Gotlib, I. H. (2021). Prenatal and postnatal depressive symptoms, infant white matter, and toddler behavioral problems. *Journal of affective disorders*, *282*, 465–471.

Borges, S., Gayer-Anderson, C., Mondelli, V. (2013). A systematic review of the activity of the hypothalamic–pituitary–adrenal axis in first episode psychosis. *Psychoneuroendocrinology*, *38*(5), 603-611.

Breitborde, N. J., Moe, A. M., Ered, A., Ellman, L. M., Bell, E. K. (2017). Optimizing psychosocial interventions in first-episode psychosis: current perspectives and future directions. *Psychology research and behavior management*, *10*, 119.

Brito, N. H., & Noble, K. G. (2014). Socioeconomic status and structural brain development. Frontiers in Neuroscience, 8.

Brown, A. S., & Meyer, U. (2018). Maternal immune activation and neuropsychiatric illness: a

translational research perspective. *American Journal of Psychiatry*, *175*(11), 1073-1083.

Brubaker, C. J., Schmithorst, V. J., Haynes, E. N., Dietrich, K. N., Egelhoff, J. C., Lindquist, D. M., Lanphear, B. P., Cecil, K. M. (2009). Altered myelination and axonal integrity in adults with childhood lead exposure: A diffusion tensor imaging study. *NeuroToxicology*, *30*(6), 867–875.

Brydges, N. M., Best, C., & Thomas, K. L. (2020). Female HPA axis displays heightened sensitivity to pre-pubertal stress. *Stress*, *23*(2), 190–200.

Calderón-Garcidueñas, L., Reynoso-Robles, R., Vargas- Martínez, J., Gómez-Maqueo-Chew, A., Pérez-Guillé, B., Mukherjee, P. S., Torres-Jardón, R., Perry, G., & Gónzalez-Maciel, A. (2016). Prefrontal white matter pathology in air pollution exposed Mexico City young urbanites and their potential impact on neurovascular unit dysfunction and the development of Alzheimer's disease. *Environmental Research*, *146*, 404–417.

Cancel, A., Dallel, S., Zine, A., El-Hage, W., & Fakra, E. (2019). Understanding the link between childhood trauma and schizophrenia: A systematic review of neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *107*, 492–504.

Cannon, T. D., Cadenhead, K., Cornblatt, B., Woods, S. W., Addington, J., Walker, E., Seidman, L.J., Perkins, D., Tsuang, M., McGlashan, T., Heinssen, R. (2008). Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Archives of general psychiatry, 65*(1), 28-37.

Cannon, T. D., van Erp, T. G., Bearden, C. E., Loewy, R., Thompson, P., Toga, A. W., ... & Tsuang, M. T. (2003). Early and late neurodevelopmental influences in the prodrome to schizophrenia: contributions of genes, environment, and their interactions. *Schizophrenia bulletin*, *29*(4), 653-669.

Carleton, R. N., Thibodeau, M. A., Teale, M. J., Welch, P. G., Abrams, M. P., Robinson, T., Asmundson, G. J. (2013). The center for epidemiologic studies depression scale: a review with a theoretical and empirical examination of item content and factor structure. *PloS one*, *8*(3), e58067.

Carletti, F., Woolley, J. B., Bhattacharyya, S., Perez-Iglesias, R., Fusar Poli, P., Valmaggia, L., Broome, M. R., Bramon, E., Johns, L., Giampietro, V., Williams, S. C. R., Barker, G. J., & McGuire, P. K. (2012). Alterations in White Matter Evident Before the Onset of Psychosis. *Schizophrenia Bulletin*, *38*(6), 1170–1179.

Carter, C., Lesh, T., Iosef, A.-M., Tanase, C., Vaslova, R., Styner, M., Maddock, R., & Bauman, M. (2020). T33. Neuroimmune mechanisms of psychiatric disorders: Longitudinal evaluation of diffusion measures of extracellular free water in a non-human primate model of maternal immune activation. *Schizophrenia Bulletin*, *46*(Supplement_1), S244–S244.

Castle, D., Sham, P., & Murray, R. (1998). Differences in distribution of ages of onset in males and females with schizophrenia. *Schizophrenia research*, 33(3), 179-183.

Cetin-Karayumak, S., Di Biase, M. A., Chunga, N., Reid, B., Somes, N., Lyall, A. E., Kelly, S., Solgun, B., Pasternak, O., Vangel, M., Pearlson, G., Tamminga, C., Sweeney, J. A., Clementz, B., Schretlen, D., Viher, P. V., Stegmayer, K., Walther, S., Lee, J., … Kubicki, M. (2019). White matter abnormalities across the lifespan of schizophrenia: A harmonized multi-site diffusion MRI study. *Molecular Psychiatry*, 1–12.

Chang, X., Mandl, R. C. W., Pasternak, O., Brouwer, R. M., Cahn, W., & Collin, G. (2021). Diffusion MRI derived free-water imaging measures in patients with schizophrenia and their non-psychotic siblings. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *109*, 110238.

Choi, J., Jeong, B., Polcari, A., Rohan, M. L., & Teicher, M. H. (2012). Reduced fractional anisotropy in the visual limbic pathway of young adults witnessing domestic violence in childhood. *NeuroImage*, *59*(2), 1071–1079.

Choi, J., Jeong, B., Rohan, M. L., Polcari, A. M., Teicher, M. H. (2009). Preliminary evidence for white matter tract abnormalities in young adults exposed to parental verbal abuse. *Biological psychiatry, 65*(3), 227-234.

Chou, K.-H., Cheng, Y., Chen, I.-Y., Lin, C.-P., & Chu, W.-C. (2011). Sex-linked white matter microstructure of the social and analytic brain. *NeuroImage*, *54*(1), 725–733.

Ciufolini, S., Dazzan, P., Kempton, M. J., Pariante, C., Mondelli, V. (2014). HPA axis response to social stress is attenuated in schizophrenia but normal in depression: evidence from a meta-analysis of existing studies. *Neuroscience & Biobehavioral Reviews, 47*, 359-368.

Clemm von Hohenberg, C., Pasternak, O., Kubicki, M., Ballinger, T., Vu, M.-A., Swisher, T., Green, K., Giwerc, M., Dahlben, B., Goldstein, J. M., Woo, T. W., Petryshen, T. L., Mesholam-Gately, R. I., Woodberry, K. A., Thermenos, H. W., Mulert, C., McCarley, R. W., Seidman, L. J., Sheton, M. E. (2013). White matter microstructure in individuals at clinical high risk of psychosis: a whole-brain diffusion tensor imaging study. *Schizophrenia bulletin, 40*(4), 895-903.

Cloutier, M., Aigbogun, M. S., Guerin, A., Nitulescu, R., Ramanakumar, A. V., Kamat, S. A., DeLucia, M., Duffy, R., Legacy, S. N., Henderson, C., Francois, C., Wu, E. (2016). The economic burden of schizophrenia in the United States in 2013. *The Journal of clinical psychiatry, 77*(6), 764-771.

Coelho, R., Viola, T. W., Walss-Bass, C., Brietzke, E., & Grassi-Oliveira, R. (2014). Childhood maltreatment and inflammatory markers: a systematic review. *Acta Psychiatrica Scandinavica*, *129*(3), 180-192.

Cohen, S., Kamarck, T., Mermelstein, R. (1983). A global measure of perceived stress. *Journal of health and social behavior*, 385-396.

Concha, L., Gross, D. W., Beaulieu, C. (2005). Diffusion tensor tractography of the limbic system. *American Journal of Neuroradiology, 26*(9), 2267-2274.

Cooper, S., Alm, K. H., Olson, I. R., Ellman, L. M. (2018). White matter alterations in individuals experiencing attenuated positive psychotic symptoms. *Early intervention in psychiatry, 12*(3), 372-379.

Coussons-Read, M. E. (2013). Effects of prenatal stress on pregnancy and human development: mechanisms and pathways. *Obstetric medicine*, *6*(2), 52–57.

Cowman, M., Holleran, L., Lonergan, E., O'Connor, K., Birchwood, M., & Donohoe, G. (2021). Cognitive predictors of social and occupational functioning in early psychosis: A systematic review and meta-analysis of cross-sectional and longitudinal data. *Schizophrenia bulletin*, *47*(5), 1243-1253.

Cullen, A. E., Addington, J., Bearden, C. E., Stone, W. S., Seidman, L. J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Tsuang, M. T., Woods, S. W., & Walker, E. F. (2020). Stressor-Cortisol Concordance Among Individuals at Clinical High-Risk for Psychosis: Novel Findings from the NAPLS Cohort. *Psychoneuroendocrinology*, *115*, 104649.

Daniels, J. K., Lamke, J. P., Gaebler, M., Walter, H., Scheel, M. (2013). White matter integrity and its relationship to PTSD and childhood trauma—A systematic review and meta-analysis. *Depression and anxiety, 30*(3), 207-216.

Dennison, U., McKernan, D., Cryan, J., Dinan, T. (2012). Schizophrenia patients with a history of childhood trauma have a pro-inflammatory phenotype. *Psychological medicine, 42*(9), 1865-1871.

DeRosse, P., Ikuta, T., Peters, B. D., Karlsgodt, K. H., Szeszko, P. R., Malhotra, A. K. (2014). 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, 224*(3), 296-302.

DeRosse, P., Ikuta, T., Karlsgodt, K. H., Peters, B. D., Gopin, C. B., Szeszko, P. R., & Malhotra, A. K. (2017). White Matter Abnormalities Associated With Subsyndromal Psychotic-Like Symptoms Predict Later Social Competence in Children and Adolescents. *Schizophrenia Bulletin*, *43*(1), 152–159.

DeRosse, P., Ikuta, T., Karlsgodt, K. H., Szeszko, P. R., & Malhotra, A. K. (2020). History of childhood maltreatment is associated with reduced fractional anisotropy of the accumbofrontal 'reward' tract in healthy adults. *Brain Imaging and Behavior*, *14*(2), 353–361.

DeRosse, P. & Karlsgodt, K. H. (2015). Examining the psychosis continuum. *Current behavioral neuroscience reports, 2*(2), 80-89.

Di Biase, M. A., Zalesky, A., Cetin-Karayumak, S., Rathi, Y., Lv, J., Boerrigter, D., North, H., Tooney, P., Pantelis, C., Pasternak, O., Weickert, C. S., Cropley, V. L. (2021). Large-scale evidence for an association between peripheral inflammation and white matter free water in schizophrenia and healthy individuals. *Schizophrenia bulletin*, *47*(2), 542-551.

Di Nicola, M., Cattaneo, A., Hepgul, N., Di Forti, M., Aitchison, K. J., Janiri, L., Murray, R. M., Dazzan, P., Pariante, C. M., & Mondelli, V. (2013). Serum and gene expression profile of cytokines in first-episode psychosis. *Brain, Behavior, and Immunity*, *31*, 90–95.

Doorduin, J., Vries, E. F. J. de, Willemsen, A. T. M., Groot, J. C. de, Dierckx, R. A., & Klein, H. C. (2009). Neuroinflammation in Schizophrenia-Related Psychosis: A PET Study. *Journal of Nuclear Medicine*, *50*(11), 1801–1807.

Drakesmith, M., Dutt, A., Fonville, L., Zammit, S., Reichenberg, A., Evans, C. J., Lewis, G., Jones, D. K., & David, A. S. (2016). Mediation of Developmental Risk Factors for Psychosis by White Matter Microstructure in Young Adults With Psychotic Experiences. *JAMA Psychiatry*, *73*(4), 396–406.

Ellman, Lauren M., Deicken, R. F., Vinogradov, S., Kremen, W. S., Poole, J. H., Kern, D. M., Tsai, W. Y., Schaefer, C. A., & Brown, A. S. (2010). Structural brain alterations in schizophrenia following fetal exposure to the inflammatory cytokine interleukin-8. *Schizophrenia Research*, *121*(1), 46–54.

Ellman, L.M., Murphy, S. K., Maxwell, S. D., Calvo, E. M., Cooper, T., Schaefer, C. A., Bresnahan, M. A., Susser, E. S., & Brown, A. S. (2019). Maternal cortisol during pregnancy and offspring schizophrenia: Influence of fetal sex and timing of exposure. *Schizophrenia Research*, *213*, 15–22. Scopus.

Epstein, K. A. & Kumra, S. (2015). White matter fractional anisotropy over two time points in early onset schizophrenia and adolescent cannabis use disorder: A naturalistic diffusion tensor imaging study. *Psychiatry Research: Neuroimaging*, *232*(1), 34–41.

Ered, A., Cooper, S., Ellman, L. M. (2018). Sleep quality, psychological symptoms, and psychotic-like experiences. *Journal of psychiatric research, 98*, 95-98.

Ered, A., & Ellman, L. M. (2019). Specificity of Childhood Trauma Type and Attenuated Positive Symptoms in a Non-Clinical Sample. *Journal of Clinical Medicine*, *8*(10), 1537.

Ered, A., Gibson, L. E., Maxwell, S. D., Cooper, S., Ellman, L.M. (2017). Coping as a mediator of stress and psychotic-like experiences. *European Psychiatry, 43*, 9-13.

Estes, M. L., & McAllister, A. K. (2016). Maternal immune activation: Implications for neuropsychiatric disorders. *Science*, *353*(6301), 772–777.

Favre, P., Pauling, M., Stout, J., Hozer, F., Sarrazin, S., Abé, C., Alda, M., Alloza, C., Alonso-Lana, S., Andreassen, O. A., Baune, B. T., Benedetti, F., Busatto, G. F., Canales-Rodríguez, E. J., Caseras, X., Chaim-Avancini, T. M., Ching, C. R. K., Dannlowski, U., Deppe, M., … Houenou, J. (2019). Widespread white matter microstructural abnormalities in bipolar disorder: Evidence from mega- and meta-analyses across 3033 individuals. *Neuropsychopharmacology*, *44*(13), 2285–2293.

Fani, N., Harnett, N. G., Bradley, B., Mekawi, Y., Powers, A., Stevens, J. S., Ressler, K. J., Carter, S. E. (2022). Racial Discrimination and White Matter Microstructure in Trauma-Exposed Black Women. *Biological psychiatry*, *91*(3), 254-261.

Feigenson, K. A., Kusnecov, A. W., & Silverstein, S. M. (2014). Inflammation and the two-hit hypothesis of schizophrenia. *Neuroscience & Biobehavioral Reviews*, *38*, 72–93.

Figueiredo, I. C., Borgan, F., Pasternak, O., Turkheimer, F. E., Howes, O. D. (2022). White-matter free-water diffusion MRI in schizophrenia: a systematic review and meta-analysis. *Neuropsychopharmacology*, 1-8.

Fineberg, A. M., & Ellman, L. M. (2013). Inflammatory Cytokines and Neurological and Neurocognitive Alterations in the Course of Schizophrenia. *Biological Psychiatry*, *73*(10), 951–966.

First, M. B., Williams, J. B., Karg, R. S., Spitzer, R. L. (2016). User's guide for the SCID-5-CV Structured Clinical Interview for DSM-5 disorders: Clinical version. American Psychiatric Publishing, Inc.

Flores, E., Tschann, J. M., Dimas, J. M., Bachen, E. A., Pasch, L. A., de Groat, C. L. (2008). Perceived Discrimination, Perceived Stress, and Mental and Physical Health Among Mexican-Origin Adults. *Hispanic Journal of Behavioral Sciences*, *30*(4), 401–424

Frissen, A., Lieverse, R., Drukker, M., Delespaul, P., Lataster, T., Myin-Germeys, I., van Os, J. (2014). Evidence that childhood urban environment is associated with blunted stress reactivity across groups of patients with psychosis, relatives of patients and controls. *Social Psychiatry and Psychiatric Epidemiology*, *49*(10), 1579–1587.

Frodl, T., Carballedo, A., Fagan, A. J., Lisiecka, D., Ferguson, Y., & Meaney, J. F. (2012). Effects of early-life adversity on white matter diffusivity changes in patients at risk for major depression. *Journal of Psychiatry & Neuroscience : JPN*, *37*(1), 37–45.

Garyfallidis, E., Brett, M., Amirbekian, B., Rokem, A., Van Der Walt, S., Descoteaux, M., Nimmo-Smith, I. (2014). Dipy, a library for the analysis of diffusion MRI data. *Frontiers in neuroinformatics*, *8*, 8.

Geeraert, B. L., Lebel, R. M., & Lebel, C. (2019). A multiparametric analysis of white matter maturation during late childhood and adolescence. *Human brain mapping*, *40*(15), 4345-4356.

Gianaros, P. J., Marsland, A. L., Sheu, L. K., Erickson, K. I., & Verstynen, T. D. (2013). Inflammatory pathways link socioeconomic inequalities to white matter architecture. *Cerebral Cortex (New York, N.Y.: 1991)*, *23*(9), 2058–2071.

Gibson, L. E., Anglin, D. M., Klugman, J. T., Reeves, L. E., Fineberg, A. M., Maxwell, S. D., Kerns, C.M., Ellman, L.M. (2014). Stress sensitivity mediates the relationship between traumatic life events and attenuated positive psychotic symptoms differentially by gender in a college population sample. *Journal of psychiatric research, 53*, 111-118.

Gibson, L.E., Cooper, S., Reeves, L.E., Anglin, D.M., Ellman, L.M. (2017). The association between traumatic life events and psychological symptoms from a conservative, transdiagnostic perspective. *Psychiatry Research, 252*, 70-74.

Giovanoli, S., Engler, H., Engler, A., Richetto, J., Voget, M., Willi, R., Winter, C., Riva, M. A., Mortensen, P. B., Feldon, J., Schedlowski, M., & Meyer, U. (2013). Stress in puberty unmasks latent neuropathological consequences of prenatal immune activation in mice. *Science*, *339*(6123), 1095–1099.

Grazioplene, R. G., Bearden, C. E., Subotnik, K. L., Ventura, J., Haut, K., Nuechterlein, K. H., & Cannon, T. D. (2018). Connectivity-enhanced diffusion analysis reveals white matter density disruptions in first episode and chronic schizophrenia. *NeuroImage: Clinical*, *18*, 608–616.

Goldwaser, E. L., Chiappelli, J., Kvarta, M. D., Du, X., Millman, Z. B., Adhikari, B. M., O'Neill, H., Sewell, J., Lightner, S., Vodapalli, S., Ma, Y., Bruce, H. Chen, S., Tan, Y., Kochunov, P., Hong, L. E. (2021). White matter in prolonged glucocorticoid response to psychological stress in schizophrenia. *Neuropsychopharmacology*, *46*(13), 2312-2319.

Granö, N., Karjalainen, M., Itkonen, A., Anto, J., Edlund, V., Heinimaa, M., Roine, M. (2011). Differential results between self-report and interview-based ratings of risk symptoms of psychosis. *Early intervention in psychiatry, 5*(4), 309-314.

Grosse, L., Ambrée, O., Jörgens, S., Jawahar, M. C., Singhal, G., Stacey, D., Arolt, V., Baune, B. T. (2016). Cytokine levels in major depression are related to childhood trauma but not to recent stressors. Psychoneuroendocrinology, 73, 24-31.

Gunnar, M.R., Morison, S.J., Chisholm, K., Schuder, M. (2001). Salivary cortisol levels in children adopted from Romanian orphanages. *Development and psychopathology, 13*(3), 611-628.

Guo, J. Y., Lesh, T. A., Niendam, T. A., Ragland, J. D., Tully, L. M., & Carter, C. S. (2020). Brain free water alterations in first-episode psychosis: A longitudinal analysis of diagnosis, course of illness, and medication effects. *Psychological Medicine*, 1–10.

Gur, R. E., Moore, T. M., Rosen, A. F. G., Barzilay, R., Roalf, D. R., Calkins, M. E., Ruparel, K., Scott, J. C., Almasy, L., Satterthwaite, T. D., Shinohara, R. T., Gur, R. C. (2019). Burden of Environmental Adversity Associated With Psychopathology, Maturation, and Brain Behavior Parameters in Youths. *JAMA Psychiatry*, *76*(9), 966–975.

Gurholt, T. P., Haukvik, U. K., Lonning, V., Jönsson, E. G., Pasternak, O., & Agartz, I. (2020). Microstructural White Matter and Links With Subcortical Structures in Chronic Schizophrenia: A Free-Water Imaging Approach. *Frontiers in Psychiatry*, *11*.

Hegde, R. R., Kelly, S., Lutz, O., Guimond, S., Karayumak, S. C., Mike, L., Mesholam-Gately, R. I., Pasternak, O., Kubicki, M., Eack, S. M., Keshavan, M. S. (2020). Association of white matter microstructure and extracellular free-water with cognitive performance in the early course of schizophrenia. *Psychiatry Research: Neuroimaging*, *305*, 111159.

Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M., Bonsall, R., Miller, A.H., Nemeroff, C.B. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *Jama*, *284*(5), 592-597.

Heins, M., Simons, C., Lataster, T., Pfeifer, S., Versmissen, D., Lardinois, M., Marcelis, M., Delespaukl, P., Krabbendam. L., van Os, J., Myin-Germeys, I. (2011). Childhood trauma and psychosis: a case-control and case-sibling comparison across different levels of genetic liability, psychopathology, and type of trauma. *American Journal of Psychiatry, 168*(12), 1286-1294.

Hermoye, L., Saint-Martin, C., Cosnard, G., Lee, S. K., Kim, J., Nassogne, M. C., ... & Mori, S. (2006). Pediatric diffusion tensor imaging: normal database and observation of the white matter maturation in early childhood. *Neuroimage*, *29*(2), 493-504.

Herting, M. M., Maxwell, E. C., Irvine, C., & Nagel, B. J. (2012). The impact of sex, puberty, and hormones on white matter microstructure in adolescents. *Cerebral cortex*, *22*(9), 1979-1992.

Hewitt, P. L., Flett, G. L., Mosher, S. W. (1992). The Perceived Stress Scale: Factor structure and relation to depression symptoms in a psychiatric sample. *Journal of Psychopathology and Behavioral Assessment, 14*(3), 247-257.

Hoptman, M. J., Nierenberg, J., Bertisch, H. C., Catalano, D., Ardekani, B. A., Branch, C. A., & DeLisi, L. E. (2008). A DTI study of white matter microstructure in individuals at high genetic risk for schizophrenia. *Schizophrenia Research*, *106*(2), 115–124.

Howell, B. R., McCormack, K. M., Grand, A. P., Sawyer, N. T., Zhang, X., Maestripieri, D., Hu, X., Sanchez, M. M. (2013). Brain white matter microstructure alterations in adolescent rhesus monkeys exposed to early life stress: associations with high cortisol during infancy. *Biology of mood & anxiety disorders*, *3*(1), 21.

Huang, H., Fan, X., Williamson, D. E., Rao, U. (2011). White matter changes in healthy adolescents at familial risk for unipolar depression: a diffusion tensor imaging study. *Neuropsychopharmacology*, *36*(3), 684.

Huang, H., Gundapuneedi, T., Rao, U. (2012). White matter disruptions in adolescents exposed to childhood maltreatment and vulnerability to psychopathology. *Neuropsychopharmacology*, *37*(12), 2693.

Inano, S., Takao, H., Hayashi, N., Abe, O., Ohtomo, K. (2011). Effects of age and gender on white matter integrity. *American Journal of Neuroradiology*.

Ingalhalikar, M., Smith, A., Parker, D., Satterthwaite, T. D., Elliott, M. A., Ruparel, K., ... & Verma, R. (2014). Sex differences in the structural connectome of the human brain. *Proceedings of the National Academy of Sciences*, *111*(2), 823-828.

Jackowski, A. P., Douglas-Palumberi, H., Jackowski, M., Win, L., Schultz, R. T., Staib, L. W., Krystal, J. H., & Kaufman, J. (2008). Corpus callosum in maltreated children with posttraumatic stress disorder: A diffusion tensor imaging study. *Psychiatry Research: Neuroimaging*, *162*(3), 256–261.

Jacobson, S., Kelleher, I., Harley, M., Murtagh, A., Clarke, M., Blanchard, M., Connoly, C., O'Hanlon, E., Garavan, H., Cannon, M. (2010). Structural and functional brain correlates of subclinical psychotic symptoms in 11–13 year old schoolchildren. *Neuroimage, 49*(2), 1875-1885.

Jensen, S. K. G., Pangelinan, M., Björnholm, L., Klasnja, A., Leemans, A., Drakesmith, M., Evans, C. J., Barker, E. D., & Paus, T. (2018). Associations between prenatal, childhood, and adolescent stress and variations in white-matter properties in young men. *NeuroImage*, *182*, 389–397.

Joo, S. W., Kim, H., Jo, Y. T., Ahn, S., Choi, Y. J., Park, S., ... & Lee, J. (2021). White matter impairments in patients with schizophrenia: A multisite diffusion MRI study. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 110381.

Kanaan, R. A., Allin, M., Picchioni, M., Barker, G. J., Daly, E., Shergill, S. S., ... & McGuire, P. K. (2012). Gender differences in white matter microstructure. *PloS one*, *7*(6), e38272.

Karlsgodt, K. H. (2016). Diffusion imaging of white matter in schizophrenia: progress and future directions. *Biological psychiatry: cognitive neuroscience and neuroimaging*, *1*(3), 209-217.

Karlsgodt, K. H. (2019). Using Advanced Diffusion Metrics to Probe White Matter Microstructure in Individuals at Clinical High Risk for Psychosis. *American Journal of Psychiatry*, *176*(10), 777–779.

Karlsgodt, K. H. (2020). White Matter Microstructure across the Psychosis Spectrum. *Trends in Neurosciences*.

Karlsgodt, K. H., Ellman, L. M., Sun, D., Mittal, V. A., & Cannon, T. D. (2011). The neurodevelopmental hypothesis of schizophrenia. In *Schizophrenia The Final Frontier—A Festschrift for Robin M. Murray* (pp. 3–18). Psychology Press.

Karlsgodt, K. H., Niendam, T. A., Bearden, C. E., & Cannon, T. D. (2009). White Matter Integrity and Prediction of Social and Role Functioning in Subjects at Ultra-High Risk for Psychosis. *Biological Psychiatry*, *66*(6), 562–569.

Karlsgodt, K. H., Sun, D., Jimenez, A. M., Lutkenhoff, E. S., Willhite, R., Van Erp, T. G., & Cannon, T. D. (2008). Developmental disruptions in neural connectivity in the pathophysiology of schizophrenia. *Development and psychopathology*, *20*(4), 1297-1327.

Kaufman, J., Plotsky, P. M., Nemeroff, C. B., & Charney, D. S. (2000). Effects of early adverse experiences on brain structure and function: Clinical implications. *Biological Psychiatry, 48*(8), 778–790.

Kelly, S., Jahanshad, N., Zalesky, A., Kochunov, P., Agartz, I., Alloza, C., Andreassen, O. A., Arango, C., Banaj, N., Bouix, S., Bousman, C. A., Brouwer, R. M., Bruggemann, J., Bustillo, J., Cahn, W., Calhoun, V., Cannon, D., Carr, V., Catts, S., … Donohoe, G. (2018). Widespread white matter microstructural differences in schizophrenia across 4322 individuals: Results from the ENIGMA Schizophrenia DTI Working Group. *Molecular Psychiatry, 23*(5), 1261–1269.

Kelsven, S. (2021). *Does the Experience of Childhood Trauma Lead to a Pro-Inflammatory Phenotype in Youth at Clinical High Risk for Psychosis?*. University of California, San Diego.

Khoury, R., & Nasrallah, H. A. (2018). Inflammatory biomarkers in individuals at clinical high risk for psychosis (CHR-P): State or trait? *Schizophrenia Research*, *199*, 31–38.

Kline, E., Wilson, C., Ereshefsky, S., Denenny, D., Thompson, E., Pitts, S. C., Bussell, K., Reeves, G., Schiffman, J. (2012). Psychosis risk screening in youth: a validation study of three self-report measures of attenuated psychosis symptoms. *Schizophrenia research, 141*(1), 72-77.

Kline, E., Wilson, C., Ereshefsky, S., Tsuji, T., Schiffman, J., Pitts, S., Reeves, G. (2012). Convergent and discriminant validity of attenuated psychosis screening tools. *Schizophrenia research, 134*(1), 49-53.

Knöchel, C., O'Dwyer, L., Alves, G., Reinke, B., Magerkurth, J., Rotarska-Jagiela, A., Prvulovic, D., Hampel, H., Linden, D. E. J., & Oertel-Knöchel, V. (2012). Association between white matter fiber integrity and subclinical psychotic symptoms in schizophrenia patients and unaffected relatives. *Schizophrenia Research, 140*(1), 129–135.

Kochunov, P., Huang, J., Chen, S., Li, Y., Tan, S., Fan, F., Feng, W., Wang, Y., Rowland, L. M., Savransky, A., Du, X., Chiappelli, J., Chen, S., Jahanshad, N., Thompson, P. M., Ryan, M. C., Adhikari, B., Sampath, H., Cui, Y., … Hong, L. E. (2019). White Matter in Schizophrenia Treatment Resistance. *American Journal of Psychiatry*, *176*(10), 829–838.

Kristensen, T. D., Mandl, R. C. W., Raghava, J. M., Jessen, K., Jepsen, J. R. M., Fagerlund, B., Glenthøj, L. B., Wenneberg, C., Krakauer, K., Pantelis, C., Nordentoft, M., Glenthøj, B. Y., & Ebdrup, B. H. (2019). Widespread higher fractional anisotropy associates to better cognitive functions in individuals at ultra-high risk for psychosis. *Human Brain Mapping*, *40*(18), 5185–5201.

Kudielka, B. M., & Kirschbaumb, C. (2005). Sex differences in HPA axis responses to stress: A review. *Biological Psychiatry*, *69*(1), 113–132.

Kuhlman, K. R., Geiss, E. G., Vargas, I., Lopez-Duran, N. (2018). HPA-axis activation as a key moderator of childhood trauma exposure and adolescent mental health. Journal of abnormal child psychology, 46(1), 149-157.

Kullmann, S., Schweizer, F., Veit, R., Fritsche, A., Preissl, H. (2015). Compromised white matter integrity in obesity. *Obesity reviews*, *16*(4), 273-281.

Lai, C. H. & Wu, Y. T. (2014). Alterations in white matter micro-integrity of the superior longitudinal fasciculus and anterior thalamic radiation of young adult patients with depression. *Psychological medicine*, *44*(13), 2825-2832.

Lammeyer, S., Dietsche, B., Dannlowski, U., Kircher, T., Krug, A. (2019). Evidence of brain network aberration in healthy subjects with urban upbringing – A multimodal DTI and VBM study. *Schizophrenia Research*, *208*, 133–137.

Lardinois, M., Lataster, T., Mengelers, R., Van Os, J., Myin-Germeys, I. (2011). Childhood trauma and increased stress sensitivity in psychosis. *Acta Psychiatrica Scandinavica*, *123*(1), 28-35.

Larsen, T. K., Friis, S., Haahr, U., Joa, I., Johannessen, J. O., Melle, I., Opjordsmoen, S., Simonsen, S., Vaglum, P. (2001). Early detection and intervention in first-episode schizophrenia: a critical review. *Acta Psychiatrica Scandinavica, 103*(5), 323-334.

Lebel, C., Treit, S., & Beaulieu, C. (2019). A review of diffusion MRI of typical white matter development from early childhood to young adulthood. *NMR in Biomedicine*, *32*(4), e3778.

Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *Neuroimage*, *40*(3), 1044-1055.

Lesh, T. A., Maddock, R. J., Howell, A., Wang, H., Tanase, C., Ragland, D. J., Niendam, T. A., Carter, C. S. (2021). Extracellular free water and glutathione in first-episode psychosis—a multimodal investigation of an inflammatory model for psychosis. *Molecular psychiatry*, *26*(3), 761-771.

Lipner, E., Murphy, S. K., & Ellman, L. M. (2019). Prenatal Maternal Stress and the Cascade of Risk to Schizophrenia Spectrum Disorders in Offspring. *Current Psychiatry Reports*, *21*(10), 99.

Loewy, R. L., Corey, S., Amirfathi, F., Dabit, S., Fulford, D., Pearson, R., Hua, J. P. Y., Schlosser, D., Stuart, B. K., Mathalon, D. H., & Vinogradov, S. (2019). Childhood trauma and clinical high risk for psychosis. *Schizophrenia Research*, *205*, 10–14.

Loewy, R. L., Bearden, C. E., Johnson, J. K., Raine, A., Cannon, T. D. (2005). The prodromal questionnaire (PQ): preliminary validation of a self-report screening measure for prodromal and psychotic syndromes. *Schizophrenia research, 79*(1), 117-125.

Loewy, R. L., Johnson, J. K., Cannon, T. D. (2007). Self-report of attenuated psychotic experiences in a college population. *Schizophrenia research, 93*(1), 144-151.

Lu, S., Wei, Z., Gao, W., Wu, W., Liao, M., Zhang, Y., Li, W., Li, Z., & Li, L. (2013). White matter integrity alterations in young healthy adults reporting childhood trauma: A diffusion tensor imaging study. *Australian & New Zealand Journal of Psychiatry*, *47*(12), 1183–1190.

Lyall, A. E., Pasternak, O., Robinson, D. G., Newell, D., Trampush, J. W., Gallego, J. A., Fava, M., Malhotra, A. K., Karlsgodt, K. H., Kubicki, M., Szeszko, P. R. (2018). Greater extracellular free-water in first-episode psychosis predicts better neurocognitive functioning. *Molecular psychiatry*, 23(3), 701.

Mayo, D., Corey, S., Kelly, L. H., Yohannes, S., Youngquist, A. L., Stuart, B. K., Niendam, T. A., & Loewy, R. L. (2017). The Role of Trauma and Stressful Life Events among Individuals at Clinical High Risk for Psychosis: A Review. *Frontiers in Psychiatry*, *8*.

McCarthy M. M. (2016). Sex differences in the developing brain as a source of inherent risk. *Dialogues in clinical neuroscience*, *18*(4), 361–372.

McGrath, J., Saha, S., Chant, D., Welham, J. (2008). Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic reviews*, *30*(1), 67-76.

Medina, K. L., Nagel, B. J., Park, A., McQueeny, T., Tapert, S. F. (2007). Depressive symptoms in adolescents: associations with white matter volume and marijuana use. *Journal of Child Psychology and Psychiatry*, *48*(6), 592-600.

Meewisse, M.-L., Reitsma, J. B., De Vries, G.-J., Gersons, B. P., Olff, M. (2007). Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. *The British Journal of Psychiatry, 191*(5), 387-392.

Meknatkhah, S., Sharif Dashti, P., Mousavi, M. S., Zeynali, A., Ahmadian, S., Karima, S., ... & Riazi, G. H. (2019). Psychological stress effects on myelin degradation in the cuprizone-induced model of demyelination. *Neuropathology*, *39*(1), 14-21.

Miller, B. J., Buckley, P., Seabolt, W., Mellor, A., & Kirkpatrick, B. (2011). Meta-Analysis of Cytokine Alterations in Schizophrenia: Clinical Status and Antipsychotic Effects. *Biological Psychiatry*, *70*(7), 663–671.

Miller, T. (2004). The SIPS-Screen: a brief self-report screen to detect the schizophrenia prodrome. *Schizophr Res*, 78.

Miller, T. J., McGlashan, T. H., Rosen, J. L., Cadenhead, K., Ventura, J., McFarlane, W., Perkins, D. O., Pearlson, G. D., Woods, S. W. (2003). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophrenia bulletin*, *29*(4), 703-715.

Miller, T. J., McGlashan, T. H., Rosen, J. L., Somjee, L., Markovich, P. J., Stein, K., Woods, S. W. (2002). Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. *American Journal of Psychiatry*, *159*(5), 863-865.

Minami, T., Nobuhara, K., Okugawa, G., Takase, K., Yoshida, T., Sawada, S., Ha-Kawa, S., Ikeda, K., Kinoshita, T. (2003). Diffusion tensor magnetic resonance imaging of disruption of regional white matter in schizophrenia. *Neuropsychobiology, 47*(3), 141-145.

Mittal, V. A., & Walker, E. F. (2019). Advances in the neurobiology of stress and psychosis. *Schizophrenia Research*, *213*, 1–5.

Modi, S., Trivedi, R., Singh, K., Kumar, P., Rathore, R. K., Tripathi, R. P., Khushu, S. (2013). Individual differences in trait anxiety are associated with white matter tract integrity in fornix and uncinate fasciculus: preliminary evidence from a DTI based tractography study. *Behavioural brain research*, *238*, 188-192.

Mondelli, V., Cattaneo, A., Murri, M. B., Di Forti, M., Handley, R., Hepgul, N., Miorelli, A., Navari, S., Papadopoulos, A. S., Aitchison, K. J., Morgan, C., Murray, R. M., Dazzan, P., & Pariante, C. M. (2011). Stress and inflammation reduce BDNF expression in first-episode psychosis: A pathway to smaller hippocampal volume. *The Journal of Clinical Psychiatry*, *72*(12), 1677–1684.

Monte, A. S., Mello, B. S. F., Borella, V. C. M., da Silva Araujo, T., da Silva, F. E. R., Sousa, F. C. F. de, de Oliveira, A. C. P., Gama, C. S., Seeman, M. V., Vasconcelos, S. M. M., Lucena, D. F. D., & Macêdo, D. (2017). Two-hit model of schizophrenia induced by neonatal immune activation and peripubertal stress in rats: Study of sex differences and brain oxidative alterations. *Behavioural Brain Research*, *331*, 30–37.

Morgan, C., Charalambides, M., Hutchinson, G., Murray, R. M. (2010). Migration, Ethnicity, and Psychosis: Toward a Sociodevelopmental Model. *Schizophrenia Bulletin*, *36*(4), 655–664.

Muñoz Maniega, S., Lymer, G. K. S., Bastin, M. E., Marjoram, D., Job, D. E., Moorhead, T. W. J., Owens, D. G., Johnstone, E. C., McIntosh, A. M., & Lawrie, S. M. (2008). A diffusion tensor MRI study of white matter integrity in subjects at high genetic risk of schizophrenia. *Schizophrenia Research*, *106*(2), 132–139.

Myin-Germeys, I. & van Os, J. (2007). Stress-reactivity in psychosis: evidence for an affective pathway to psychosis. *Clinical psychology review, 27*(4), 409-424.

Nägele, F. L., Pasternak, O., Bitzan, L. V., Mußmann, M., Rauh, J., Kubicki, M., ... & Mulert, C. (2021). Cellular and extracellular white matter alterations indicate conversion to psychosis among individuals at clinical high-risk for psychosis. *The World Journal of Biological Psychiatry*, *22*(3), 214-227.

Namvarpour, Z., Ranaei, E., Amini, A., Roudafshani, Z., Fahanik-Babaei, J. (2022). Effects of prenatal exposure to inflammation coupled with prepubertal stress on prefrontal white matter structure and related molecules in adult mouse offspring. Metabolic Brain Disease, 1-14.

Nemeroff C. B. (2007). Stress, menopause and vulnerability for psychiatric illness. *Expert review of neurotherapeutics, 7*(11 Suppl), S11–S13.

Noble, K. G., Korgaonkar, M. S., Grieve, S. M., & Brickman, A. M. (2013). Higher education is an age-independent predictor of white matter integrity and cognitive control in late adolescence. *Developmental Science*, *16*(5), 653–664.

Nuechterlein, K. H. & Dawson, M. E. (1984). A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophrenia bulletin, 10*(2), 300.

Nugent, K. L., Chiappelli, J., Sampath, H., Rowland, L. M., Thangavelu, K., Davis, B., Du, X., Muellerklein, F., Daughters, S., Kochunov, P., Hong, L. E. (2015). Prolonged Cortisol Reactivity to Stress and White Matter in Schizophrenia. *Psychosomatic medicine, 77*(7), 733.

Nugiel, T., Alm, K. H., Olson, I. R. (2016). Individual differences in white matter microstructure predict semantic control. *Cognitive, Affective, & Behavioral Neuroscience, 16*(6), 1003-1016.

Oestreich, L. K., Lyall, A. E., Pasternak, O., Kikinis, Z., Newell, D. T., Savadjiev, P., Bouix, S., Shenton, M. E., Kubicki, M., Australian Schizophrenia Research Bank, Whitford, T. J., McCarthy-Jones, S. (2017). Characterizing white matter changes in chronic

schizophrenia: A free-water imaging multi-site study. *Schizophrenia research*, 189, 153-161.

O'Farrell, T. J., Fals-Stewart, W., Murphy, M. (2003). Concurrent validity of a brief self-report drug use frequency measure. *Addictive behaviors, 28*(2), 327-337.

Oh, H., Yang, L. H., Anglin, D. M., DeVylder, J. E. (2014). Perceived discrimination and psychotic experiences across multiple ethnic groups in the United States. *Schizophrenia Research, 157*(1–3), 259–265.

O'Hanlon, E., Leemans, A., Kelleher, I., Clarke, M. C., Roddy, S., Coughlan, H., Harley, M., Amico, F., Hoscheit, M. J., Tiedt, L., Tablish, J., McGettigan, A., Frodl, T., Cannon, M. (2015). White matter differences among adolescents reporting psychotic experiences: a population-based diffusion magnetic resonance imaging study. *JAMA psychiatry, 72*(7), 668-677.

Ong, A. D., Fuller-Rowell, T., Burrow, A. L. (2009). Racial discrimination and the stress process. *Journal of Personality and Social Psychology*, *96*(6), 1259–1271.

Osborne, S., Biaggi, A., Chua, T. E., Du Preez, A., Hazelgrove, K., Nikkheslat, N., Previti, G., Zunszain, P. A., Conroy, S., & Pariante, C. M. (2018). Antenatal depression programs cortisol stress reactivity in offspring through increased maternal inflammation and cortisol in pregnancy: The Psychiatry Research and Motherhood – Depression (PRAM-D) Study. *Psychoneuroendocrinology*, *98*, 211–221.

Oyola, M. G., & Handa, R. J. (2017). Hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes: sex differences in regulation of stress responsivity. *Stress*, 20(5), 476–494.

Palmier-Claus, J., Dunn, G., Lewis, S. (2012). Emotional and symptomatic reactivity to stress in individuals at ultra-high risk of developing psychosis. *Psychological medicine, 42*(5), 1003.

Papadakis, N. G., Martin, K. M., Mustafa, M. H., Wilkinson, I. D., Griffiths, P. D., Huang, C. L. H., Woodruff, P. W. (2002). Study of the effect of CSF suppression on white matter diffusion anisotropy mapping of healthy human brain. *Magnetic Resonance in Medicine, 48*(2), 394-398.

Pasternak, O., Sochen, N., Gur, Y., Intrator, N., Assaf, Y. (2009). Free water elimination and mapping from diffusion MRI. *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, 62(3), 717-730.

Pasternak, O., Westin, C. F., Bouix, S., Seidman, L. J., Goldstein, J. M., Woo, T. U. W., Petryshen, T. L., Mesholam-Gately, R. I., McCarley, R. W., Kikinis, R., Shenton, M. E., Kubicki, M. (2012). Excessive extracellular volume reveals a neurodegenerative pattern in schizophrenia onset. *Journal of Neuroscience*, 32(48), 17365-17372.

Pasternak, O., Westin, C.-F., Dahlben, B., Bouix, S., & Kubicki, M. (2015). The extent of diffusion MRI markers of neuroinflammation and white matter deterioration in chronic schizophrenia. *Schizophrenia Research*, *161*(1), 113–118.

Perkins, D. O., Jeffries, C. D., Addington, J., Bearden, C. E., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Mathalon, D. H., McGlashan, T. H., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., & Heinssen, R. (2015). Towards a Psychosis Risk Blood Diagnostic for Persons Experiencing High-Risk Symptoms: Preliminary Results From the NAPLS Project. *Schizophrenia Bulletin*, *41*(2), 419–428.

Peters, B. D., Dingemans, P. M., Dekker, N., Blaas, J., Akkerman, E., van Amelsvoort, T. A., Majoie, C. B., den Heeten, G. J., Linszen, D. H., & de Haan, L. (2010). White matter connectivity and psychosis in ultra-high-risk subjects: A diffusion tensor fiber tracking study. *Psychiatry Research: Neuroimaging*, *181*(1), 44–50.

Peters, B. D., Haan, L. de, Dekker, N., Blaas, J., Becker, H. E., Dingemans, P. M., Akkerman, E. M., Majoie, C. B., Amelsvoort, T. van, Heeten, G. J. den, & Linszen, D. H. (2008). White Matter Fibertracking in First-Episode Schizophrenia, Schizoaffective Patients and Subjects at Ultra-High Risk of Psychosis. *Neuropsychobiology*, *58*(1), 19–28.

Phillips, L. J., McGorry, P. D., Garner, B., Thompson, K. N., Pantelis, C., Wood, S. J., & Berger, G. (2006). Stress, the hippocampus and the hypothalamic-pituitary-adrenal axis: implications for the development of psychotic disorders. *Australian & New Zealand Journal of Psychiatry*, *40*(9), 725-741.

Pierpaoli, C., Jezzard, P., Basser, P. J., Barnett, A., & Di Chiro, G. (1996). Diffusion tensor MR imaging of the human brain. *Radiology*, *201*(3), 637-648.

Pohl, K. M., Sullivan, E. V., Rohlfing, T., Chu, W., Kwon, D., Nichols, B. N., Zhang, Y., Brown, S. A., Tapert, S. F., Cummins, K., Thompson, W. K., Brumback, T., Colrain, I. M., Baker, F. C., Prouty, D., De Bellis, M. D., Voyvodic, J. T., Clark, D. B., Schirda, C., Nagel, B. J., Pfefferbaum, A. (2016). Harmonizing DTI measurements across scanners to examine the development of white matter microstructure in 803 adolescents of the NCANDA study. *Neuroimage*, *130*, 194-213.

Poletti, S., Mazza, E., Bollettini, I., Locatelli, C., Cavallaro, R., Smeraldi, E., & Benedetti, F. (2015). Adverse childhood experiences influence white matter microstructure in patients with schizophrenia. *Psychiatry Research*, *234*(1), 35–43.

Poletti, S., Melloni, E., Mazza, E., Vai, B., & Benedetti, F. (2020). Gender-specific differences in white matter microstructure in healthy adults exposed to mild stress. *Stress*, *23*(1), 116–124.

Pruessner, M., Béchard-Evans, L., Boekestyn, L., Iyer, S. N., Pruessner, J. C., Malla, A. K. (2013). Attenuated cortisol response to acute psychosocial stress in individuals at ultra-high risk for psychosis. *Schizophrenia research*, *146*(1-3), 79-86.

Pruessner, M., Boekestyn, L., Béchard-Evans, L., Abadi, S., Vracotas, N., Joober, R., Pruessner, J. C., & Malla, A. K. (2008). Sex differences in the cortisol response to awakening in recent onset psychosis. *Psychoneuroendocrinology*, *33*(8), 1151–1154.

Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied psychological measurement, 1*(3), 385-401.

Rapoport, J., Giedd, J., Gogtay, N. (2012). Neurodevelopmental model of schizophrenia: update 2012. *Molecular psychiatry*, *17*(12), 1228.

Rasmussen, J. M., Graham, A. M., Entringer, S., Gilmore, J. H., Styner, M., Fair, D. A., Wadhwa, P. D., & Buss, C. (2019). Maternal Interleukin-6 concentration during pregnancy is associated with variation in frontolimbic white matter and cognitive development in early life. *NeuroImage*, *185*, 825–835

R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/

del Re, E. C., Bouix, S., Fitzsimmons, J., Blokland, G. A., Mesholam-Gately, R., Wojcik, J., Kikinis, Z., Kubicki, M., Petryshen, T., Pasternak, O., Shenton, M. E. (2019). Diffusion abnormalities in the corpus callosum in first episode schizophrenia: Associated with enlarged lateral ventricles and symptomatology. *Psychiatry research.*

Read, J., Os, J. v., Morrison, A., Ross, C. A. (2005). Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica, 112*(5), 330-350.

Ready, C. B., Hayes, A. M., Yasinski, C. W., Webb, C., Gallop, R., Deblinger, E., Laurenceau, J. P. (2015). Overgeneralized beliefs, accommodation, and treatment outcome in youth receiving trauma-focused cognitive behavioral therapy for childhood trauma. Behavior therapy, 46(5), 671-688.

Reeves, L. E., Anglin, D. M., Heimberg, R. G., Gibson, L. E., Fineberg, A. M., Maxwell, S. D., Kerns, C. M., Ellman, L. M. (2014). Anxiety mediates the association between cannabis use and attenuated positive psychotic symptoms. *Psychiatry Research, 218*(1), 180-186.

Remington, G., & Seeman, M. V. (2015). Schizophrenia and the influence of male gender. *Clinical Pharmacology & Therapeutics*, *98*(6), 578–581.

Roberts, R. E. (1980). Reliability of the CES-D scale in different ethnic contexts. *Psychiatry Research, 2*(2), 125-134.

Roberts, R. E., Vernon, S. W., Rhoades, H. M. (1989). Effects of language and ethnic status on reliability and validity of the Center for Epidemiologic Studies-Depression Scale with psychiatric patients. *The Journal of nervous and mental disease, 177*(10), 581-592.

RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/.

Ruby, E., Polito, S., McMahon, K., Gorovitz, M., Corcoran, C., & Malaspina, D. (2014). Pathways Associating Childhood Trauma to the Neurobiology of Schizophrenia. *Frontiers in Psychological and Behavioral Science*, *3*(1), 1–17.

Rule, W. R. & Traver, M. D. (1983). Test-retest reliabilities of State-Trait Anxiety Inventory in a stressful social analogue situation. *Journal of Personality Assessment, 47*(3), 276-277.

Sánchez, M. M., Hearn, E. F., Do, D., Rilling, J. K., & Herndon, J. G. (1998). Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys. *Brain Research*, *812*(1), 38–49.

Sandman, C. A., Glynn, L. M., & Davis, E. P. (2013). Is there a viability-vulnerability tradeoff? Sex differences in fetal programming. *Journal of psychosomatic research*, *75*(4), 327–335.

Sarkar, S., Craig, M. C., Dell'Acqua, F., O'Connor, T. G., Catani, M., Deeley, Q., Glover, V., & Murphy, D. G. M. (2014). Prenatal stress and limbic-prefrontal white matter microstructure in children aged 6–9 years: A preliminary diffusion tensor imaging study. *The World Journal of Biological Psychiatry*, *15*(4), 346–352.

Schmithorst, V. J., Holland, S. K., & Dardzinski, B. J. (2008). Developmental differences in white matter architecture between boys and girls. *Human brain mapping*, *29*(6), 696-710.

Schwehm, A., Robinson, D. G., Gallego, J. A., Karlsgodt, K. H., Ikuta, T., Peters, B. D., Malhotra, A. K., & Szeszko, P. R. (2016). Age and Sex Effects on White Matter Tracts in Psychosis from Adolescence through Middle Adulthood. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *41*(10), 2473–2480.

Scott, J. C., Rosen, A. F. G., Moore, T. M., Roalf, D. R., Satterthwaite, T. D., Calkins, M. E., Ruparel, K., Gur, R. E., & Gur, R. C. (2019). Cannabis use in youth is associated with limited alterations in brain structure. *Neuropsychopharmacology*, *44*(8), 1362–1369.

Seeman, M. V., & Lang, M. (1990). The Role of Estrogens in Schizophrenia Gender Differences. *Schizophrenia Bulletin*, *16*(2), 185–194.

Seunarine, K. K., Clayden, J. D., Jentschke, S., Munoz, M., Cooper, J. M., Chadwick, M. J., Banks, T., Vargha-Khadem- F., Clark, C. A. (2016). Sexual dimorphism in white matter developmental trajectories using tract-based spatial statistics. *Brain connectivity*, *6*(1), 37-47.

Sheffield, J. M., Williams, L. E., Woodward, N. D., & Heckers, S. (2013). Reduced gray matter volume in psychotic disorder patients with a history of childhood sexual abuse. *Schizophrenia Research*, *143*(1), 185–191.

Shollenbarger, S. G., Price, J., Wieser, J., Lisdahl, K. (2015). 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, 8,* 117-125.

Simmonds, D. J., Hallquist, M. N., Asato, M., & Luna, B. (2014). Developmental stages and sex differences of white matter and behavioral development through adolescence: A longitudinal diffusion tensor imaging (DTI) study. *NeuroImage*, *92*, 356–368.

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., Ciccarelli, O., Cader, M. Z., Matthews, P. M., Behrens, T. E. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*, *31*(4), 1487-1505.

Soares, J., Marques, P., Alves, V., & Sousa, N. (2013). A hitchhiker's guide to diffusion tensor imaging. *Frontiers in Neuroscience, 7*.

Sobell, L. C. & Sobell, M. B. (1996). Timeline followback user's guide: A calendar method for assessing alcohol and drug use. *Toronto, Ontario, Canada: Addiction Research Foundation*.

Spielberger, C. D. (1983). Manual for the State-Trait Anxiety Inventory STAI (form Y)(" self-evaluation questionnaire").

Stanek, K. M., Grieve, S. M., Brickman, A. M., Korgaonkar, M. S., Paul, R. H., Cohen, R. A., Gunstad, J. J. (2011). Obesity is associated with reduced white matter integrity in otherwise healthy adults. *Obesity*, *19*(3), 500-504.

Steiner, J. L., Tebes, J. K., Sledge, W. H., Walker, M. L. (1995). A comparison of the Structured Clinical Interview for DSM-III—R and clinical diagnoses. *Journal of Nervous and Mental Disease*.

Subramaniam, A., LoPilato, A., & Walker, E. F. (2019). Psychotropic medication effects on cortisol: Implications for research and mechanisms of drug action. *Schizophrenia Research, 213,* 6–14.

Szeszko, P. R., Robinson, D. G., Ikuta, T., Peters, B. D., Gallego, J. A., Kane, J., & Malhotra, A. K. (2014). White Matter Changes Associated with Antipsychotic Treatment in First-Episode Psychosis. *Neuropsychopharmacology*, *39*(6), 1324–1331.

Szeszko, P. R., Vogel, J., Ashtari, M., Malhotra, A. K., Bates, J., Kane, J. M., Bilder, R. M., Frevert, T., & Lim, K. (2003). Sex differences in frontal lobe white matter microstructure: A DTI study. *NeuroReport*, *14*(18), 2469–2473.

Tang, Y., Pasternak, O., Kubicki, M., Rathi, Y., Zhang, T., Wang, J., Li. H., Woodberry, K. A., Xu, L., Qian, Z., Zhu, A., Whitfield-Gabrieli, S., Keshavan, M. S., Niznikiewicz, M., Stone, W. S., McCarley, R. W., Shenton, M. E., Wang, J., Seidman, L. J. (2019). Altered Cellular White Matter But Not Extracellular Free Water on Diffusion MRI in Individuals at Clinical High Risk for Psychosis. *American Journal of Psychiatry*, appi-ajp.

Teicher, M. H., Dumont, N. L., Ito, Y., Vaituzis, C., Giedd, J. N., & Andersen, S. L. (2004). Childhood neglect is associated with reduced corpus callosum area. *Biological Psychiatry*, *56*(2), 80–85.

Thompson, J. L., Kelly, M., Kimhy, D., Harkavy-Friedman, J. M., Khan, S., Messinger, J. W., Schobel, S., Goetz, R., Malaspina, D., & Corcoran, C. (2009). Childhood trauma and prodromal symptoms among individuals at clinical high risk for psychosis. *Schizophrenia Research*, *108*(1), 176–181.

Trépanier, M. O., Hopperton, K. E., Mizrahi, R., Mechawar, N., & Bazinet, R. P. (2016). Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. *Molecular psychiatry*, *21*(8), 1009-1026.

Tso, I. F., Grove, T. B., Taylor, S. F. (2012). Self-assessment of psychological stress in schizophrenia: preliminary evidence of reliability and validity. *Psychiatry Research, 195*(1), 39-44.

Van Winkel, R., Stefanis, N. C., Myin-Germeys, I. (2008). Psychosocial stress and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. *Schizophrenia bulletin, 34*(6), 1095-1105.

Verstynen, T. D., Weinstein, A. M., Schneider, W. W., Jakicic, J. M., Rofey, D. L., Erickson, K. I. (2012). Increased body mass index is associated with a global and distributed decrease in white matter microstructural integrity. *Psychosomatic medicine, 74*(7), 682.

Walker, E., Mittal, V., Tessner, K. (2008). Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. *Annu. Rev. Clin. Psychol., 4*, 189-216.

Woods, S. W., Walsh, B. C., Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Heinssen, R., Perkins, D. O., Seidman, L. J., Tarbox, S. I., Tsuang, M. T., Walker, E. F., McGlashan, T. H. (2014). Current status specifiers for patients at clinical high risk for psychosis. *Schizophrenia research, 158*(1-3), 69-75.

Wozniak, J. R., & Lim, K. O. (2006). Advances in white matter imaging: a review of in vivo magnetic resonance methodologies and their applicability to the study of development and aging. *Neuroscience & Biobehavioral Reviews*, *30*(6), 762-774.

Yui, K., Goto, K., Ikemoto, S., Ishiguro, T. (2000). Stress induced spontaneous recurrence of methamphetamine psychosis: the relation between stressful experiences and sensitivity to stress. *Drug and alcohol dependence, 58*(1-2), 67-75