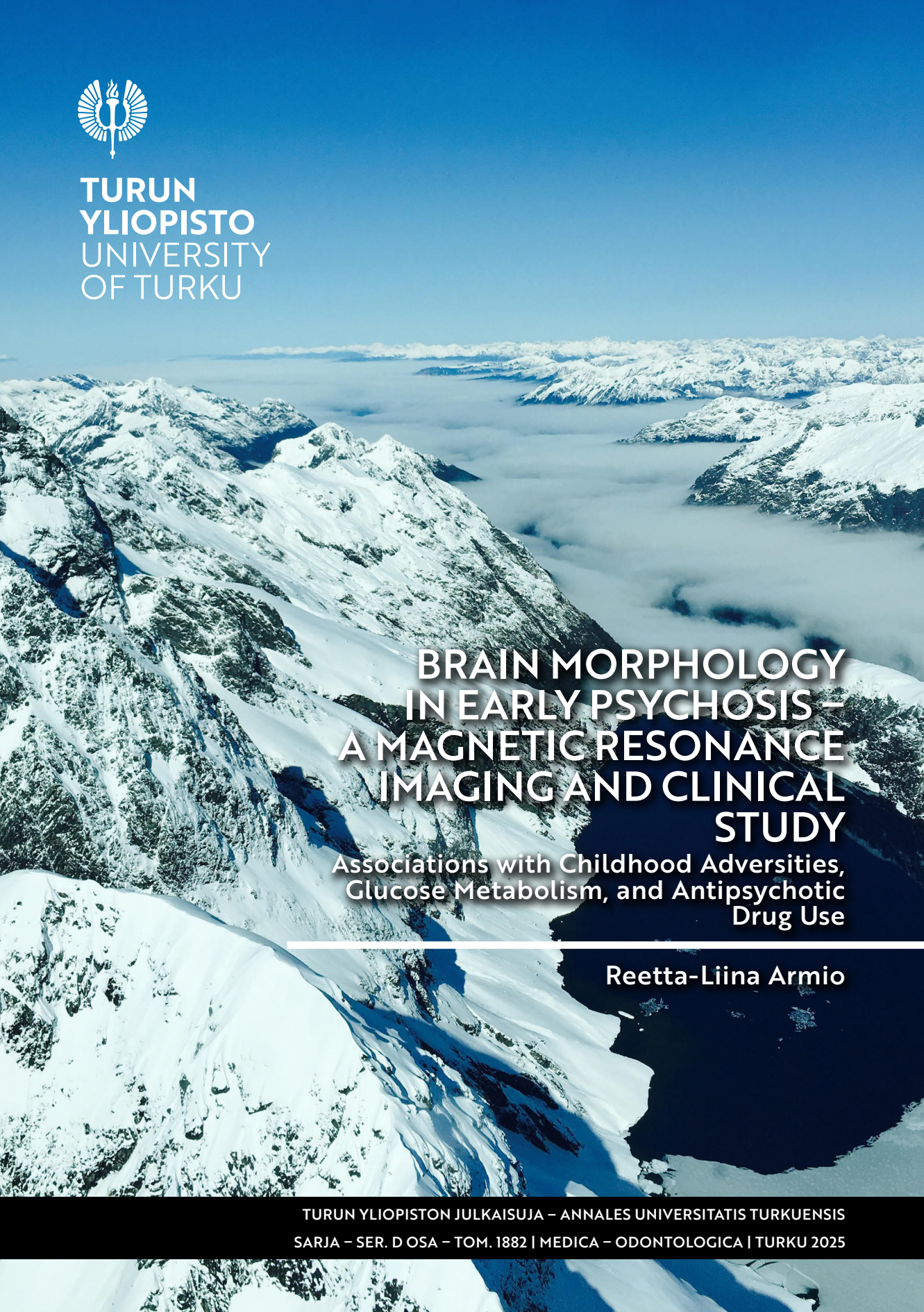

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BRAIN MORPHOLOGY IN EARLY PSYCHOSIS – A MAGNETIC RESONANCE IMAGING AND CLINICAL STUDY

Associations with Childhood Adversities, Glucose Metabolism, and Antipsychotic Drug Use

Reetta-Liina Armio

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The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

Cover Image: Reetta-Liina Armio

ISBN 978-952-02-0158-6 (PRINT)
ISBN 978-952-02-0159-3 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2025

To Ville and our sons, Frans and Volter

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Clinical Medicine
Psychiatry
REETTA-LIINA ARMIO: Brain Morphology in Early Psychosis – A Magnetic Resonance Imaging and Clinical Study: Associations with Childhood Adversities, Glucose Metabolism, and Antipsychotic Drug Use
Doctoral Dissertation, 240 pp.
Doctoral Programme of Clinical Research
May 2025

ABSTRACT

The etiology of psychotic disorders is multifactorial and developmental, influenced significantly by genetic factors and various environmental factors, such as childhood adversity. Psychotic disorders, such as schizophrenia, are associated with structural and functional changes in the brain circuits, especially in the frontal and temporal areas. We examined the amygdala subnuclei and hippocampus subfield structures in patients with early psychosis and control subjects. We tested whether the morphology of these structures is linked to psychiatric symptomatology, environmental factors, and metabolic parameters (I, II). Finally, we examined whether antipsychotic drugs affect cortical morphology with respect to different aspects of functional and structural cortical organization (III).

We found that the volume of the lateral nucleus of the amygdala was smaller both in clinical high-risk patients (CHR) and in first episode of psychosis patients (FEP), with the basal nucleus only smaller in FEP. Adverse childhood experiences were associated with the smaller lateral nucleus in FEP (I). Hippocampal subfield volumes were consistently lower in FEP, especially in non-affective psychoses, with less marked changes in CHR. These morphological changes remained stable during the one-year follow-up. Higher fasting plasma insulin and insulin resistance were associated with smaller hippocampal tail volumes in non-diabetic FEP. The glucometabolic deterioration during the follow-up period, independent of antipsychotic drugs, was associated with clinical outcomes such as the transition to psychosis and poor functioning in CHR (II). Study III suggests multiple neurobiological mechanisms, potentially contributing to antipsychotic-associated cortical thinning.

Specific morphological changes in the amygdala and hippocampus are observed in the early psychosis. Some of these changes likely reflect early neurodevelopmental vulnerabilities, while others may emerge at the onset of the first psychotic episode. These features could serve as biomarkers for identifying individuals at high risk of psychosis. The worsening of glucose metabolism parameters, linked to functional impairment in CHR, suggests that careful management of metabolic health should be included in early intervention programs. Finally, our findings on brain features associating with antipsychotic-related cortical thickness could provide further leads in the understanding of antipsychotic drug action.

KEYWORDS: first episode of psychosis, magnetic resonance imaging, clinical high risk for psychosis, hippocampus, amygdala, cortex, glucose metabolism, childhood adversity, antipsychotic medication

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Psykiatria
REETTA-LIINA ARMIO: Aivojen Morfologia Varhaisessa Psykoosissa – Magneettikuvaus- ja Kliininen Tutkimus: Yhteydet Lapsuuden Vastoinkäymisiin, Glukoosimetaboliaan ja Antipsykoottiseen lääkitykseen
Väitöskirja, 240 s.
Turun kliininen tohtoriohjelma
Toukokuu 2025

TIIVISTELMÄ

Psykoottisten häiriöiden etiologia on monitekijäinen ja kehityksellinen, ja siihen vaikuttavat geneettiset tekijät sekä ympäristötekijät, kuten lapsuuden haitalliset kokemukset. Psykoottisissa häiriössä, kuten skitsofreniassa, on havaittu aivojen rakenteellisia ja toiminnallisia muutoksia erityisesti etu- ja ohimolohkoissa.

Tutkimme amygdalan ja hippokampuksen osa-alueiden volyymeja psykoosiriskipotilailla, ensipsykoosipotilailla ja väestöverrokeilla sekä amygdalan ja hippokampuksen osa-alueiden morfologian yhteyttä psykiatrisiin oireisiin, ympäristötekijöihin tai glukoosimetaboliaan psykoosin varhaisvaiheissa (I ja II). Lopuksi tutkimme, ovatko psykoosilääkkeet yhteydessä aivokuoren paksuuteen ja edelleen aivokuoren rakenteellisiin tai toiminnallisiin ominaisuuksiin (III).

Havaitsimme, että amygdalan lateraalisen nukleuksen tilavuus oli pienempi sekä kliinisen korkean psykoosiriskin potilailla (CHR) että ensipsykoosipotilailla (FEP), mutta basaalinukleus oli pienempi vain FEP:lla. Lapsuuden haitalliset kokemukset liittyivät pienempään lateraalinukleuksen tilavuuteen FEP:lla. (I). Havaitsimme, että hippokampuksen osa-alueiden tilavuudet olivat laajalti pienentyneet FEP:lla, mutta muutokset olivat vähäisempiä CHR:lla (II). Nämä muutokset pysyivät muuttumattomina vuoden seurannan aikana. Korkeampi paastoplasman insuliinipitoisuus ja insuliiniresistenssi liittyivät pienempään hippokampuksen hännän tilavuuteen ei-diabeettisilla FEP:lla. Glukoosiaineenvaihdunnan heikkeneminen oli yhteydessä psykoosiin sairastumiseen ja heikentyneeseen toimintakykyyn CHR:lla (II). III osatutkimuksessa havaitsimme, että psykoosilääkkeisiin liittyvä aivokuoren oheneminen saattaa johtua useista neurobiologisista mekanismeista.

Tiettyjä morfologisia muutoksia amygdalassa ja hippokampuksessa havaitaan jo psykoosin varhaisvaiheissa. Osa näistä saattaa heijastaa varhaista hermoston kehityksellistä haavoittuvuutta, kun taas osa kehittyy vasta ensimmäisen psykoosijakson kynnyksellä. Tällaisia piirteitä voitaisiin käyttää biomarkkereina korkean psykoosiriskin yksilöiden tunnistamisessa. Glukoosiaineenvaihdunnan heikkeneminen on yhteydessä toimintakyvyn heikentymiseen CHR:lla, joten glukoosimetabolian hallinta on tärkeää varhaisen vaiheen interventio-ohjelmien osana. Tuloksemme antipsykoottisen lääkityksen ja aivokuoren paksuuden välisestä yhteydestä ja sen taustamekanismeista voivat tarjota uusia näkökulmia psykoosilääkkeiden vaikutusmekanismien ymmärtämiseen.

AVAINSANAT: ensipsykoosi, magneettikuvantaminen, kliininen psykoosiriski, hippokampus, amygdala, aivokuori, glukoosimetabolia, lapsuuden haitalliset kokemukset, antipsykoottinen lääkitys

Table of Contents

Abbreviations

ACC	Anterior Cingulate Cortex
ACTH	Adrenocorticotropic hormone
AP-related	antipsychotic-related
APS	Attenuated Positive Symptom Prodromal Syndrome
ANCOVA	Analysis of Covariance
BIPS	Brief Intermittent Psychosis Prodromal Syndrome
BLA	BasoLateral Amygdala
BMI	Body Mass Index
BNDF	Brain-Derived Neurotrophic Factor
BNST	Bed Nucleus of the Stria Terminalis
BOLD	Blood-Oxygen-Level-Dependent
BPRS	Brief Psychiatric Rating Scale
BSD	Bipolar Spectrum Disorder
CA	Cornu Ammonis -regions
CB	Cannabinoid Receptor
CAR	Cortisol Awakening Response
CAARMS	Comprehensive Assessment of At-Risk Mental States
CHR-C	Clinical High-Risk for psychosis Converting to psychosis
CHR-NC	Clinical High-Risk for psychosis Not Converting to psychosis
CMRGlu	Cerebral Metabolic Rate for Glucose
CPZ	Chlorpromazine
ECN	Executive Control Network
CBV	Cerebral Blood Volume
CeA	Central Nucleus of Amygdala
CEN	Central Executive Network
CHR	Clinical High Risk for psychosis
CI	Confidence Interval
CMA	Centro-Medial Nucleus
CNS	Central Nervous System
CNV	Copy Number Variations
CRH	Corticotropin
CT	Computed Tomography
CTR	Population Control
dex/CRH	Dexamethasone and Corticotrophin-Releasing Hormone
DG	Dentate Gyrus

DMN	Default Mode Network
DOI	Duration Of Illness
DSM-IV	Diagnostic and Statistical Manual of mental disorders. 4th edition
DUP	Duration of Untreated Psychosis
DTI	Diffusion tensor imaging
ED	Estimated Difference
ES	Effect Size
ENIGMA	Enhancing NeuroImaging Genetics through Meta-Analysis
FDR	False Discovery Rate
FEP	First-Episode Psychosis
FOV	Field of View
fMRI	Functional Magnetic Resonance Imaging
FPN	FrontoParietal Network
GABA	Gamma-AminoButyric Acid
GAF	Global Assessment of Functioning
GCMLDG	The Granule Cell layer and Molecular Layer of the dentate gyrus
GRDS	Genetic Risk and Deterioration Prodromal Syndrome
HATA	The Hippocampal-Amygdaloid Transition Area
HOMA2-IR	Homeostasis Model Assessment – Insulin Resistance, model 2
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
IGF	Insulin-Like Growth-Factor
IGF1R	Insulin-like Growth Factor Receptor, type 1
IQ	Intelligence Quotient
LHA	Lateral Hypothalamic Area
MDD	Major Depressive Disorder
MeA	Medial Nucleus of the Amygdala
MEG	Magnetoencephalography
ML	Molecular Layer of the subiculum and cornu ammonis regions
MRI	Magnetic Resonance Imaging
mPFC	Medial Prefrontal Cortex
NAP	Non-Affective Psychosis
NMDAR	N-Methyl-D-Aspartate Receptor
SCI-PANSS	Structured Clinical Interview for the Positive and Negative Syndrome Scale
SOFAS	Social and Occupational Functioning Assessment Scale
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PTSD	Post-Traumatic Stress Disorder
PVN	Paraventricular nucleus
rCBF	regional Cerebral Blood Flow
SANS	Scale for the Assessment of Negative Symptoms
SCID-I/NP	Structured Clinical Interview for DSM-IV disorders I (non-patient edition)
SCZ	Schizophrenia

SIPS	Structured Interview for Prodromal Symptoms
SN	Salience Network
SNP	single nucleotide polymorphism
SOPS	Scale of Prodromal Symptoms
SPI	Schizophrenia Proneness Instrument
T1DM	Diabetes Mellitus Type 1
T2DM	Diabetes Mellitus Type 2
TADS	Trauma and Distress Scale
TIV	Total Intracranial Volume
TR	Time to Repeat
TE	Time to Echo
UCBJ	Uniporter-coupled Calcium-Binding protein-J
UHR	Ultra-High Risk
VAChT	Vesicular AcetylCholine Transporter
VAMI	Vakavien Mielenterveyshäiriöiden etiologia ja hoito –research program; The Etiology and treatment of severe mental health disorders –research program
VMN	Ventromedial Nucleus
22q11.2DS	22q11.2 deletion syndrome
5-HT	5-hydroxytryptamine
5-HTT	5-hydroxytryptamine transporter

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals I-III:

I Armio R-L, Laurikainen H, Ilonen T, Walta M, Salokangas RKR, Koutsouleris N, Hietala J, Tuominen L. Amygdala subnucleus volumes in psychosis high-risk state and first-episode psychosis. *Schizophrenia Research*, 2020; 215:284-292.

II Armio R-L, Laurikainen H, Ilonen T, Walta M, Sormunen E, Tolvanen A, Salokangas RKR, Koutsouleris N, Tuominen L, Hietala J. Longitudinal study on hippocampal subfields and glucose metabolism in early psychosis. *Schizophrenia*, 2024; 10(1):66.

III Tuominen L*, Armio R-L*, Hansen J, Walta M, Koutsouleris N, Laurikainen H, Salokangas RKR, Misic B, Hietala J. Molecular, physiological and functional features underlying cortical thinning related to antipsychotic medication use. *Translational Psychiatry,* 2025; 15(1):129.
*equal contribution

1 Introduction

> "*The world was a series of strange, unpredictable events, and I was trying to find a pattern, a meaning, a way to make it all fit together*."
>
> (Vonnegut, 1975)

In his memoir *The Eden Express,* Mark Vonnegut describes the onset of his schizophrenia, where reality becomes fractured and chaotic. This description captures the intense confusion, cognitive strain, loss of coherence and search for meaning that defines many psychotic episodes. It illustrates the initial disintegration of reality that often marks the onset of psychosis, where the individual is confronted with a reality that no longer aligns with their previous understanding, beginning a difficult process of trying to make sense of it.

Psychosis and psychotic disorders are thought to result from a complex interaction between the genetic risk, differences in the brain development, and exposure to environmental factors, such as childhood adverse experiences. The main findings on the brain structure and function in schizophrenia, the most common type of psychotic disorder, include smaller volumes of the hippocampus and amygdala, thinner temporal and prefrontal cortices, and disrupted connectivity between these areas and other central brain regions (van Erp et al., 2018). Some of these changes likely represent endophenotypes—genetic traits less influenced by environmental factors—while the phenotype is primarily shaped by the interaction between genetic predispositions and environmental influences. This genetic and environmental interaction defines how an organism's phenotype is formed, manifesting as traits and states. However, in psychotic disorders, these traits and states are likely fundamentally altered and interlinked across various organ systems in humans.

Consequently, psychosis affects multiple dimensions of an organism's phenotype, including metabolism, immune and hormonal systems, brain function and structure, behaviour, and ultimately resilience, relative to healthy controls. The phenotype of a psychotic disorder is a combination of common diagnostic and subclinical symptoms, with individual variation. It is further thought that psychoses might be divided into multiple subtypes beyond the current diagnostic criteria, with different emphasis on brain morphology (Guimond et al., 2021; Koen et al., 2023),

systemic (Pillinger et al., 2023) and genetic alterations (Singh et al., 2022; Xia et al., 2024) that might be further differently shaped by environmental factors (Trotti et al., 2023).

The relationship between stress, metabolism, and psychosis is complex, involving multiple biological, psychological, and social factors. In relation to environmental factors, childhood maltreatment appears to increase the risk for glucose metabolism disturbances (Deschênes et al., 2024; Kudinova et al., 2024; Li et al., 2017; McKay et al., 2021; Souama et al., 2024) and psychosis (Croft et al., 2019; Fusar-Poli et al., 2017; Marangoni et al., 2016; Trotta et al., 2015) and is related to its outcome (Bailey et al., 2018; Thomas et al., 2019). Childhood maltreatment is also related to reduced total amygdala volume and altered stress responses in the first episode of psychosis (Aas et al., 2012). Further, antipsychotic medications, known to alter the cortical grey matter volume (Fusar-Poli et al., 2013b), are initiated at the time of the first psychotic episode to alleviate symptoms, that reflect widespread disturbances in interacting central and systemic functioning. The exact effects and mechanisms of metabolic disturbances, experienced childhood adversities or the effects of antipsychotic medication on specific brain structures in the timeline of psychosis development, are unknown. Therefore, it is important to study these factors in relation to time—before, during, and after the onset of the first psychotic episode.

Psychotic disorders share a psychotic symptom dimension within a continuum of severity and duration. However, it is evident that there are also other converging clinical symptom dimensions, phenomena and mechanisms related to the trajectory leading to the onset of psychosis. Currently, there are no objective biological measures or biomarkers, available to guide diagnostic or treatment decisions. Thus, it is essential to study psychotic disorders as a transdiagnostic group with cross-sectional and longitudinal designs near the onset of the first psychosis. These observations might provide an opportunity to identify clinical characteristics and mechanisms leading to optimized treatments and even early prevention strategies.

2 Review of the Literature

2.1 What is psychosis?

Human reality—defined as an experience of being—involves a conscious and unconscious subjective purpose, relevance, sensations, thoughts, feelings and their mutual interaction in relation to the present and past. The concept of human reality also includes inter-subjectivity with social and cultural dimensions. The philosopher Edmund Husserl (1859-1938) has used the term intersubjectivity as an interchange of thoughts and feelings, both conscious and unconscious, between two persons, as facilitated by empathy.

Psychosis is a state in which the sense of human reality fails. This means the external reality is conflictingly interpreted and distorted internal representations are formed. In other words, the basic structure of the self could depend on the balance between intrinsic and extrinsic self-processing, that is unbalanced in psychotic disorders. The concept of psychosis is a complex with philosophical, empirical, phenomenological, and cultural dimensions. Schizophrenia was first described over a century ago by Emil Kraepelin in his textbook under the name dementia praecox, meaning "early-onset dementia" (Kraepelin, 1893). The concept of schizophrenia was clinically introduced by the Swiss psychiatrist Eugen Bleuler in 1911 (Bleuler, 1911). Bleuler, in fact, considered psychotic symptoms in schizophrenia as a secondary phenomenon and complication of the primary four problem areas: the 4 A's representing affect, associative processing, autism (social cognition), and ambivalence. In this way, he shifted the focus from seeing schizophrenia only as a condition of psychosis to understanding it as a complex disorder involving broader cognitive and emotional dysfunctions.

In this thesis we approach the concept of psychosis from the medical viewpoint, based on the definition of diagnostic manuals and neuroscience but accepting a dimensional view on psychotic disorders. This view defines psychosis as a disorder of thought, perception, interpretation, speech and behavior. The basic collection of symptoms in psychoses are hallucinations, delusions, as well as incoherent and disordered thinking, speech, and behavior.

2.2 Clinical characteristics of psychotic disorders

The first episode psychosis (FEP) is regarded as important for both clinical and research reasons. As a concept, FEP includes diagnostic uncertainty, that may lead to delayed treatment and inconsistent care. Also, the responsiveness to antipsychotic drugs is better in the first episode of psychosis than what is seen in later relapses. Some studies have found that in two years' follow-up of FEP, approximately one-third are diagnosed with an affective psychotic disorder, while around two-thirds fall within the schizophrenia spectrum (Prakash et al., 2021).

Psychotic disorders, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), comprise conditions characterized by specific symptomatology and defined temporal criteria. These include schizophrenia, schizophreniform disorder, schizoaffective disorder, schizotypal disorder, psychotic mania, psychotic depression, delusional disorder, brief psychotic disorder, shared psychotic disorder, organic or substance-induced psychotic disorders, and psychotic disorders not otherwise specified. In psychotic disorders symptoms are divided into eight symptom dimensions: hallucinations, delusions, disorganized speech, abnormal psychomotor behavior, negative symptoms, cognitive deficits, depression and mania. The negative symptoms are anhedonia, asociality, affective flattening, impoverishment of speech and language and loss of motivation. These symptoms typically lead to a decline in daily functioning.

Psychotic disorders are increasingly conceptualized as dimensional constructs, reflecting the growing recognition that psychotic symptoms exist on a spectrum, i.e. in terms of severity and duration. However, diagnostic categories are still used. Further, psychotic disorders are thought to be syndromes with a variety of symptoms, including metabolic and immunological alterations, in addition to the cardinal symptoms of psychotic disorders. Therefore, it is essential to conduct research across diagnostic boundaries and incorporate both psychotic and systemic alterations. It is important to study the shared phenomena of these clinical manifestations during the development of a psychotic disorder to better understand the most prevalent mechanisms behind the onset of a psychotic disorder and the antipsychotic drug action.

2.2.1 Schizophrenia spectrum disorders, non-affective psychotic disorders

Non-affective psychotic disorders (NAP) include schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, shared psychotic disorder and delusional disorder and psychosis not otherwise specified, defined by DSM-IV. The subgroup of non-affective psychotic disorders are schizophrenia spectrum disorders, including schizophrenia, schizophreniform disorder,

schizoaffective disorder, brief psychotic disorder, and delusional disorder, which share common features with schizophrenia, but may vary in severity, duration, and specific symptoms.

Schizophrenia is the most well-known and severe disorder on the spectrum, as it is a serious mental illness widely affecting a person's thinking, feeling and behavior, and further areas of life, including personal, family, social, educational, and occupational functioning. The lifetime prevalence of schizophrenia is 0.3-1.2% worldwide and 1-1.5% in Finland (Charlson et al., 2018; GBD, 2022; Perälä et al., 2007) In Finland there are an estimated 50 000 patients with schizophrenia, and 0.8 - 4.3 for every 10 000 people is the yearly amount of novel schizophrenia cases diagnosed. The prevalence rates of schizophrenia in Finland are high compared to other countries. At the global level, the prevalence of schizophrenia is increasing (Charlson et al., 2018; Solmi et al., 2023b). Both globally and domestically, there are considerable differences in the rates of schizophrenia, which cannot be solely attributed to variations in diagnostic practices or research methods (Perälä et al., 2008; Saha et al., 2006). The familial risk for schizophrenia among siblings is 5 to 10 times higher than in the general population. First-degree relatives of a person with schizophrenia have an eight-fold higher risk of developing the disorder, and this risk increases to 11-fold when two family members have schizophrenia (Le et al., 2020) (Gottesman et al., 2010). The heritability in schizophrenia is high being up to 80% in European and U.S. twin and family studies (Sullivan et al., 2003). Also, the risk is 1.4 times higher in males compared to females. Heritability refers to the proportion of variation in a trait or disorder within a population that can be attributed to genetic factors rather than environmental influences.

People with schizophrenia are two to three times more likely to die early than the general population (Allebeck, 1989; Crump et al., 2013; Keinänen et al., 2018; Laursen et al., 2014; Saha et al., 2007). Thus, the life expectancy is approximately 15-20 years below that of the general population (Hjorthøj et al., 2017; Laursen et al., 2014). This is often due to physical illnesses, such as cardiovascular, metabolic, infectious diseases, and cancer, as well as suicide, homicide and accidents. Accelerated aging might be one factor in a shorter life (Constantinides et al., 2023; Olfson et al., 2015; Wolkowitz, 2018).

The prognosis of schizophrenia is worse compared to other psychotic disorders, such as bipolar disorder, psychotic depression and brief psychotic disorder (Nietola et al., 2018). Slightly over two-thirds of persons suffering from schizophrenia achieved clinical remission and slightly below a third, functional remission during a three-year follow-up in a global multinational study of outcomes in schizophrenia (Haro et al., 2011) Generally, psychotic disorders are a significant financial burden in the developed countries (GBD, 2022).

The diagnostic criteria defined by DSM-IV for schizophrenia are two symptoms from the following symptom categories with a duration of at least one month: delusions, hallucinations or disorganized speech, abnormal psychomotor behavior, or negative symptom dimensions. At least one symptom needs to be delusions, hallucinations, or disorganized speech. Secondly, social or professional functioning is significantly disturbed. Thirdly, these combined symptoms have lasted at least six months and other disorders are excluded. The symptom profile in schizophrenia can vary from person to person, both in pattern and severity. Other typical related other symptom complexes are depression and anxiety, as well as also somatic disturbances, such as cardiovascular, bone, lung and metabolic diseases, including glucose disturbances (Dieset et al., 2016).

2.2.2 Affective psychotic disorders

Affective psychotic disorders are a category of mental health disorders where symptoms of mood disturbances, affective symptoms, are predominant and accompanied by psychotic features such as delusions, hallucinations, or disorganized thinking. These disorders, such as bipolar and major depressive disorder with psychotic features according to DSM-IV, primarily affect a person's mood and emotions, but the psychotic symptoms are significant enough to impact one's reality perception. Affective psychotic disorders are characterized by a significant presence of mood disturbances along with psychosis, whereas in schizophrenia, mood symptoms are less central and often secondary to the main psychotic features.

Affective psychosis is conceptualized as a mood-congruent or mood-incongruent psychotic phenomenon. In mood-congruent psychosis, the psychotic symptoms are consistent with the individual's mood state. For instance, in the depressive phase, the individual may experience delusions of guilt or inadequacy, while in the manic phase, the delusions may involve grandiosity or invincibility. Mood-incongruent psychotic features are less common and involve delusions or hallucinations that do not align with the individual's mood, e.g., delusions of persecution during a manic episode. There is currently limited knowledge regarding affective prodromal symptoms; however, it has been observed that psychotic mania is often preceded by affective symptoms, though in some cases no prior symptoms are present. (Salvatore et al., 2021; Zhao et al., 2021)

2.2.3 Clinical high risk for psychosis

The prodromal phase of a psychotic disorder is the non-specific symptom period before full psychotic symptoms appear, often called the clinical high-risk state. These early symptoms are mild but may gradually worsen over time, leading to more

recognizable psychotic symptoms. During the prodromal period of a psychotic disorder, individuals may exhibit a range of subtle but significant changes in behavior, thoughts, and emotions. Further, increased anxiety, sleep disorders, withdrawal from social activities, and cognitive difficulties may occur. This phase can vary in duration, lasting weeks to years. The prodromal phase is a critical time for intervention, and increased awareness among individuals, families, and healthcare providers can lead to better outcomes by addressing emerging symptoms before they escalate into more severe psychosis.

The widely used clinical assessment tools to identify individuals who are at high risk of developing a psychotic disorder are semi-structured interviews SIPS (Structured Interview for Prodromal Symptoms), Comprehensive Assessment of At-Risk Mental States (CAARMS), and SPI (Schizophrenia Proneness Instrument). (Fusar-Poli et al., 2013a) In this thesis we define clinical high-risk for psychosis (CHR) with a SIPS interview.

The SIPS interview includes a biopsychosocial history and ratings along four major symptom dimensions on the Scale of Prodromal Symptoms (SOPS): positive, negative, disorganized and general/affective symptoms. The SIPS/SOPS diagnoses three types of prodromal syndromes, listed in order of the typical sample prevalence:

1. Attenuated Positive Symptom Prodromal Syndrome (APS): Attenuated positive psychotic symptoms present at least once per week, started or worsened in that past year (unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/distortions, and conceptual disorganization)
2. Brief Intermittent Psychosis Prodromal Syndrome (BIPS): Brief and intermittent fully psychotic symptoms that have started recently.
3. Genetic Risk and Deterioration Prodromal Syndrome (GRDS): Either a family history of a psychotic disorder in any first-degree relative and decline of at least 30% in the past 12 months on the Global Assessment of Functioning (GAF) scale or meets the criteria for schizotypal personality disorder and has had a decline of 30% on the GAF in the past year.

There is evidence that only 20-35% of CHR individuals in the age range of 12 to 35 years will develop the first episode of psychosis within 2 years (Fusar-Poli et al., 2012). During the prodromal phase, patients are at a greater risk of suicide, attempted suicide, and aggression. Prodromal symptoms are often non-specific and sometimes hard to differ from normal adolescence adjustment or other psychiatric conditions. This leads to delayed treatment and poorly coordinated care, which may worsen the course and outcome of an incipient psychotic disorder (McGlashan et al., 2006;

McGorry et al., 2002). Further, building adherence to the treatment and increasing insight is crucial during the risk phase. Better early identification and intervention of the psychosis risk would therefore be important. However, it is important to highlight the retrospective nature of the concept, alongside the heterogeneous outcomes observed in individuals at a clinical risk for psychosis, including asymptomatic presentations, affective disorders, and other manifestations.

2.2.4 Other psychoses

Psychosis can be one symptom dimension in many neuropsychiatric, neurologic, neurodevelopmental, medical conditions or a consequence of substance use. Medical conditions occasionally inducing psychotic symptoms include e.g. different forms of neurodegenerative disorders, temporal epilepsy, brain tumor, central nervous infections, autoimmune encephalitis and endocrinological disorders. Substances inducing psychotic symptoms are particularly cannabis, amphetamines and possibly hallucinogens (Myran et al., 2024). Also, medications such as anticholinergics, corticosteroids and levodopa might induce psychotic symptoms.

2.2.5 Main treatment lines of psychotic disorders

The treatment of a psychotic disorder is based on an individual treatment plan. The considerations in the treatment plan are: symptom severity and spectrum, phase of illness, functional, cognitive and social capacity, somatic health, and the cultural background of the patient. Antipsychotic medication combined with psychosocial treatments form the cornerstones of psychotic disorder treatment (*Schizophrenia. Current Care Guidelines*, 2024) (*Bipolar disorder. Current Care Guidelines*, 2024). Typically, the first episode of psychosis is treated with second-generation antipsychotics, that act on both dopamine and serotonin receptors. Treatment resistant psychosis is managed with clozapine, which is the most efficacious antipsychotic drug (Wagner et al., 2021). Clozapine has a broad range of mechanisms of action and thus, also adverse effects that limit its clinical use (Pillinger et al., 2020). Clozapine is a second-generation antipsychotic but has a more complex impact on multiple receptor systems affecting multiple neurotransmitter systems, including dopamine, serotonin, noradrenaline, glutamate, histamine, and acetylcholine. Other classes of drugs, such as mood stabilizers, antidepressants, and anxiolytics, are also used based on individual needs. Sometimes, in addition to drugs, neuromodulation is used, particularly electroconvulsive treatment.

Other combined treatment modalities for psychotic disorders are psychoeducation, psychotherapies such as cognitive behavioral therapy and cognitive remediation therapy, family interventions, training in socials skills and

daily living, vocational rehabilitation and individually tailored supported employment (Bighelli et al., 2021; Solmi et al., 2023a). Finally, the monitoring and managing of somatic health is an important part of the treatment plan with a clear positive effect on the overall prognosis of patients with a psychotic disorder (Crump et al., 2013; Keinänen et al., 2018).

2.3 Etiological hypotheses of schizophrenia

Schizophrenia is recognized as a disorder with a multifactorial etiology and is the most studied form of non-affective psychotic disorders. The etiological hypotheses of schizophrenia are partly overlapping and cumulative. The primary etiological model is a vulnerability-stress model that explains the phenotype of psychosis as a result of the interaction of both genetic and environmental factors. The broader concept of a vulnerability-stress model includes multiple interacting etiological factors such as genetic anomalies, abnormal neurodevelopment, an imbalance of brain excitation and inhibition, alterations in brain-gut axis communication, abnormalities in multiple neurotransmitter systems and imbalances in their excitation and inhibition. These interacting aberrant intrinsic factors are further influenced by environmental stressors, particularly childhood adversities. These hypotheses are summarized in a later section.

2.3.1 Vulnerability-stress model

The vulnerability-stress model is a theoretical framework that explains the development and progression of schizophrenia or psychosis as the result of the interaction between early biological vulnerabilities and environmental stressors (Zubin & Spring, 1977) (Wahlberg et al., 1997) (Meehl, 1989). The development of a psychotic disorder generally requires a combination of both internal and external factors, thus the interaction between genes and environment (Sullivan et al., 2003). The internal factors, such as inter-related genetics, are described as endophenotypes. The biological vulnerability factors in psychoses may extend from these genetic features to the brain's structural and functional, as well as metabolic, immunological, and hormonal factors. However, without a negative environmental modulation on the psychosis endophenotype, psychosis may not develop, even in those who are genetically and biologically vulnerable, and vice versa.

The biological vulnerability influences how individuals respond to environmental factors, shaping their reactions to stressors. Thus, biological vulnerability may also manifest as increased sensitivity to stress, that underscores the cyclical and cumulative nature of the vulnerability-stress model. The pathway to chronic schizophrenia presumably evolves in a periodic manner in the presence of

challenging environmental factors. The simplified illustration of the vulnerability-stress model modified from (Hietala & Tuulio-Henriksson, 2021) adjusted for the resilience and temporal development of schizophrenia is presented in **Figure 1**.

To conclude, the vulnerability-stress model of schizophrenia suggests that biological vulnerability does not itself induce schizophrenia. The onset of schizophrenia is contingent upon an individual's developmental genetic and epigenetic vulnerability, which, when coupled with sufficiently intense or prolonged stress at specific timepoints, can precipitate the development of the disorder. However, the individual variation and further subtypes of psychoses in the disease process should also be considered in the light of the complex factor combinations of the vulnerability-stress model.

2.3.2 Genetic factors

There is strong evidence of genetic risk factors for schizophrenia with multiple similar genetic changes, such as single nucleotide polymorphism (SNP) and copy number variations (CNV), particularly deletions (Grozeva et al., 2010; Lee et al., 2013; Sklar, 2008; Stefansson et al., 2009; Szatkiewicz et al., 2014; Tam et al., 2009). Further, epigenetic changes in genetic regulation mechanisms, such as methylation and histone modifications, are also observed. (Magwai et al., 2021) Both common and rare genetic variants, such as SNP and CNV, respectively, are two types of genetic variations that differently increase the risk of schizophrenia. Common variants are frequent in the population and individually have a small impact on the risk, while rare variants are much less common but can have a stronger effect on the risk. Despite their different impact on the risk for schizophrenia, a recent study showed that both common variants and rare gene variants seem to affect the same core biological mechanisms such as neurodevelopment and synaptic plasticity that likely contribute to schizophrenia (Singh et al., 2022).

There is evidence of a generalized neurodevelopmental role for many of these genetic and epigenetic changes associated with the risk of schizophrenia (Jaffe et al., 2018; Trubetskoy et al., 2022). The growing evidence suggests that several mild genetic abnormalities cumulatively affect the risk of disease, i.e. altering the normative neurodevelopment at different time points (B. Wang et al., 2023) (van der Meer et al., 2024) At earliest neurodevelopmental stages, epigenetic regulation might increase or decrease the effects of risk genes by altering the expression of specific genes. This disturbed regulation of genetic activation might be due to perinatal environmental factors such as maternal infection, severe maternal depression, stress, malnutrition or toxins during pregnancy, perinatal brain damage, childbirth complications and paternal age at conception. (Brown & Derkits, 2010;

Davies et al., 2020; Khandaker et al., 2013; Khashan et al., 2008; Malaspina et al., 2001)

2.3.3 Environmental factors

2.3.3.1 Childhood adversity

Childhood adverse events are associated with a higher risk and prevalence of mental illness, especially psychosis, psychotic symptoms, and schizophrenia (Carvalho Silva et al., 2024; Hughes et al., 2017; Kaufman & Torbey, 2019; Matheson et al., 2013; Salokangas et al., 2020; Schreier et al., 2009; Trotta et al., 2015; van Dam et al., 2012; Varese et al., 2012). For example, a previous meta-analysis determined that reducing childhood adversities would decrease the incidence of schizophrenia spectrum disorders by 37.84%. (Dragioti et al., 2022).

There are indications, that children with a genetic risk for schizophrenia are more sensitive to these stressors, which further relate to clinical trajectories (Loewy et al., 2019), and to accumulative biological vulnerabilities (Berthelot et al., 2022). Also, psychosis patients with traumatic experiences might respond differently to antipsychotics (Misiak & Frydecka, 2016; Thomas et al., 2019). Some meta-analyses indicate that individuals at high risk for psychosis also experience higher levels of traumatic events (Kraan et al., 2015; Peh et al., 2019). This further highlights the significance of early life adversities, and their cumulative effect, but also, partly heterogenous, adversity-related clinical trajectories, such as transition to psychosis, symptom severity and comorbid psychiatric symptoms (Brew et al., 2018; Loewy et al., 2019; Peh et al., 2019; Russo et al., 2014; Sahin et al., 2013). Thus, the psychosocial stress, emotional atmosphere, stressful events and circumstances of childhood can apply to both the etiology and prognosis of schizophrenia.

Childhood adversity encompasses a range of experiences, including physical, emotional, or sexual abuse, as well as physical and emotional neglect. The emotional atmosphere of a family can be disturbed by socioeconomical difficulties and social isolation, such as parental unemployment, poverty, single parenthood, immigration and belonging to an ethnic minority, that are related to the increased risk for schizophrenia (Kirkbride et al., 2017). Other childhood stressors, such as parental death, separation from a parent, have also been reported as risk factors for schizophrenia and bipolar disorder. (Misra et al., 2019; Paksarian et al., 2015) The most frequently reported traumas associated with psychotic symptoms are sexual, physical and emotional abuse (Carr et al., 2013; Fisher et al., 2010; Read et al., 2005; Salokangas, 2022). However, different adversity types are highly correlated (Zorowitz & Tuominen, 2022) and many previous studies support the view of a dose-

dependent relationship between the amount of childhood adversity and symptoms of psychotic disorders (Read et al., 2005; Schenkel et al., 2005; Trauelsen et al., 2015).

Childhood maltreatment itself appears also to increase the risk of somatic diseases, including HPA-axis (hypothalamic-pituitary-adrenal axis) dysregulation (Bremne & Vermetten, 2001; Van Voorhees & Scarpa, 2004) and glucose metabolism disturbances (Deschênes et al., 2024; Fuller-Rowell et al., 2019; Thomas et al., 2008), also in psychoses (Tosato et al., 2020). These effects may be more pronounced in individuals with vulnerability for psychiatric disorders in general (Murphy et al., 2022) Although related mechanisms in the development of psychotic disorders are not well understood, the roles of a dysregulated glucose metabolism and stress system, as well as a higher number of childhood maltreatment have been suggested. This interaction is supported by the prior research suggesting that childhood adversity and adult stress are salient predictors of glucose metabolism (Fuller-Rowell et al., 2019; Lee et al., 2018). Thus, early adversity plays a crucial role in influencing individual differences in vulnerability to both physical and mental disorders later in life (Kessler et al., 2010).

2.3.3.2 Other environmental factors

There is evidence of cannabis use during development that increases the risk for schizophrenia and psychotic symptoms (Andréasson et al., 1987; Gage et al., 2016) (French et al., 2015; Hides et al., 2009; Large et al., 2011), and is causally related schizophrenia (Vaucher et al., 2018). Also, stimulant use has been observed to have a significant influence on FEP incidence with an earlier onset (Gallagher et al., 2022; Moran et al., 2015; Rodríguez-Toscano et al., 2023). The prevalence of schizophrenia appears to be higher in urban areas than rural areas, and the difference is not explained by social determinants of health (Vassos et al., 2012) (Suokas et al., 2024). The urbanization-related factors, such as air pollution and green space reduction, have been explored to relate to the risk of psychosis and schizophrenia. (Vassos et al., 2012) (Grover et al., 2024)

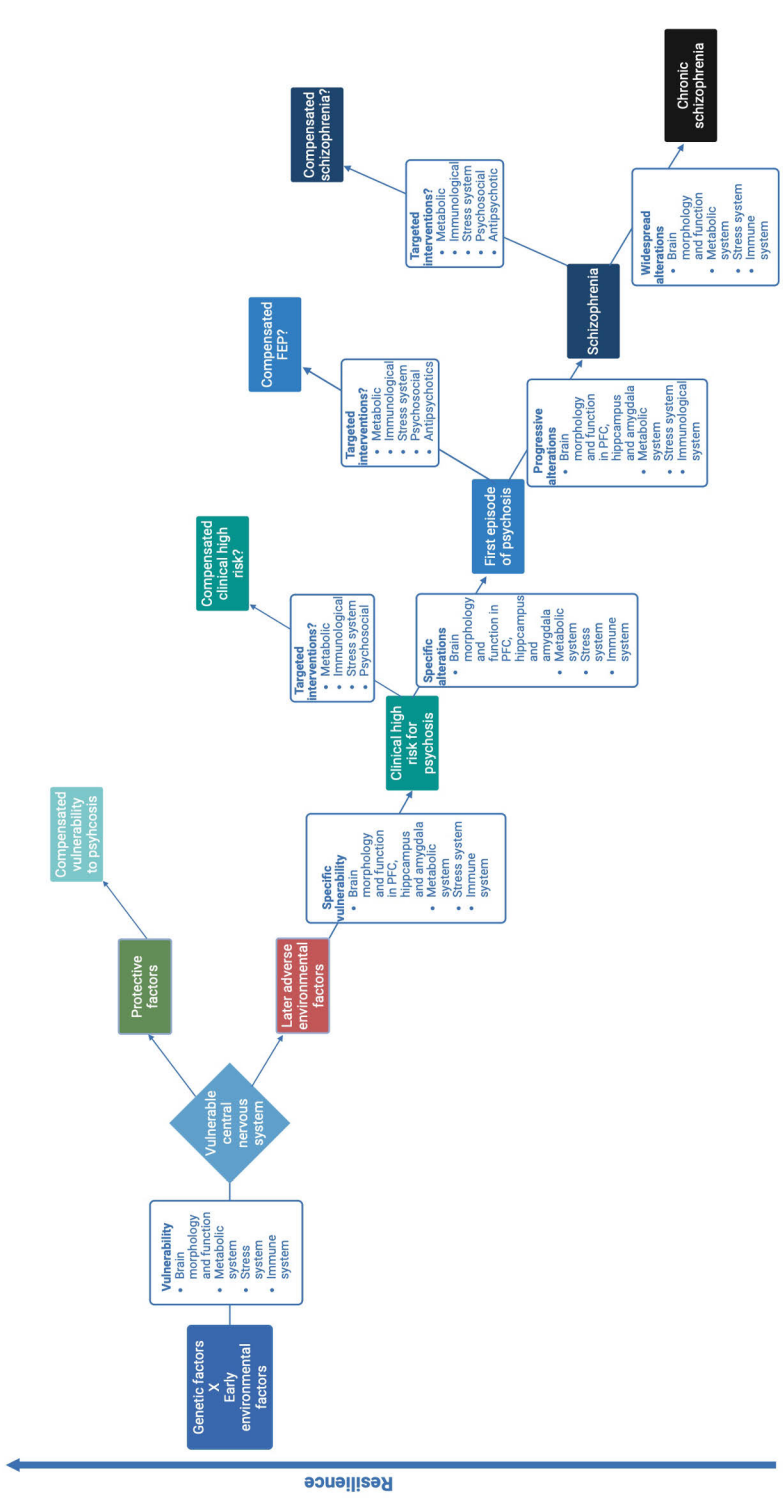


Figure 1. The simplified illustration of the modified vulnerability-stress model of psychosis adjusted for the resilience and temporal development from early psychosis to chronic schizophrenia. The flow chart is extrapolated and modified from the illustration of Hietala & Tuulio-Henriksson (2021). Created by the author with BioRender.com.

2.4 Functional brain changes in patients with psychotic disorders and psychosis risk

2.4.1 Altered brain equilibrium and rhythm

Alterations in neurotransmitter systems, neurochemicals and brain metabolic imbalances can increase susceptibility to psychosis (Stahl, 2018). Additionally, stress-related changes may predispose individuals to these alterations and further exacerbate psychotic symptoms (Cullen et al., 2024). In addition to alterations in neurotransmitter systems and dysfunctional neuronal networks, abnormalities in the brain rhythm, such as in the synchronized oscillatory and energy consumption-related activity of neurons, may have a central role in the pathophysiology of schizophrenia (Lisman, 2012; Spellman & Gordon, 2015; Uhlhaas & Singer, 2010). Thus, traits and states, in the context of neurochemical, metabolic and electrical balances, might be represented differently (Keshavan et al., 2008).

The dysfunction of neurotransmitter systems in psychoses is thought to arise from an imbalance between excitatory and inhibitory processes within distinct neurotransmitter systems. This imbalance worsens by unusual interactions not only between different neurotransmitter systems, but also due to metabolic disturbances, disrupted rhythms and the timing of brain activity. Hypothetically, the neurodevelopmental abnormalities with genetic and environmental influences may lead to disturbances in the neurotransmission between glutamate and Gamma-AminoButyric Acid (GABA) neurons, that further project to dopamine and serotonin systems near the manifestation of a psychotic disorder. Thus, the pre-existing structural and functional brain abnormalities interact with these further defected neurotransmitter systems and related electrical and metabolic changes.

At the neurotransmitter and synaptic level in schizophrenia, there is evidence of dysfunction in dopaminergic, glutamatergic, serotonergic, GABAergic and endocannabinoid (Borgan et al., 2019) signaling. A model, where glutamate dysregulation, starting from the anterior hippocampus, particularly in Cornu Ammonis 1 (CA1), impacts and causes dopamine and GABA dysfunction in schizophrenia, is the most prevalent explanatory mechanism (Howes & Kapur, 2009; Schobel et al., 2013).

2.4.1.1 Excitation-inhibition imbalance and neural asynchrony

Neurotransmitter systems, their excitation-inhibition balance and structural defects interact with the brain networks, influencing the connectivity and functionality of the networks in schizophrenia. Disruptions in the excitation-inhibition balance can

relate to abnormal brainwave patterns (Başar & Güntekin, 2008; Bruining et al., 2020).

Brain oscillations represent important correlates of human information processing and cognition (Begleiter & Porjesz, 2006). In schizophrenia, there are well-documented abnormalities in brainwave patterns, particularly in the theta, alpha, beta, and gamma frequency ranges (Spellman & Gordon, 2015; Uhlhaas & Singer, 2010). These abnormalities are thought to reflect the underlying disruptions in neural communication, connectivity, and the excitation-inhibition balance that are central to the cognitive, perceptual, and emotional disturbances seen in the psychotic disorders. In schizophrenia, studies have demonstrated disrupted synchronization of brain waves—neural oscillations—in the prefrontal cortex, hippocampus, and thalamus, regions critically involved in cognition, emotion, and perception. These altered brain waves reflect the broader dysconnectivity between brain networks that contributes to the disorder.

Neural dysconnectivity can also be measured using functional MRI (fMRI), which detects blood-oxygen-level-dependent (BOLD) signals. These signals reflect changes in oxygen consumption and the ratio of oxygenated to deoxygenated blood in each brain region, providing an indication of neural activity and function. Resting-state fMRI (rs-fMRI) is a specific type of fMRI that measures brain activity while the participant is not engaged in any specific task, often referred to as the 'resting' state. This allows researchers to study functional connectivity, which refers to the temporal correlations in brain activity between different brain regions, without the influence of external tasks. The default mode network is often identified using rs-fMRI. The evidence suggests there are disruptions between and within-connections especially in the default mode network, salience network, central executive network, limbic network, and frontoparietal network in schizophrenia (Orliac et al., 2013; Supekar et al., 2019) (Cole et al., 2011; Keyvanfard et al., 2023; Limongi et al., 2020; Repovs et al., 2011; Ruiz-Torras et al., 2023). Further, the ability to shift between the networks might be altered in schizophrenia (Woodward et al., 2016). Frontoparietal network dysfunction has been observed already in an at-risk state (Unschuld et al., 2014), and higher fMRI-activation in the right frontal gyrus during cognitive tasks has been noted even in first-degree relatives of schizophrenia patients compared to healthy controls (Saarinen et al., 2020).

While positron emission tomography (PET) is not directly used to measure functional connectivity (i.e., synchronized neural activity over time), but it contributes to our understanding regarding the functions of the brain network functioning by offering insights into metabolic processes, receptor activity, and neurotransmitter dynamics. Parameters that can be measured with PET are i.e. metabolic activity, receptor binding, transporter levels, and blood flow. The main findings from PET studies in schizophrenia indicate alterations in dopaminergic

activity, notably hyperdopaminergia in the striatum (Fusar-Poli & Meyer-Lindenberg, 2013; Hietala et al., 1995), alongside broader subcortical hyperdopaminergic activity, but also hypodopaminergia (Slifstein et al., 2015) and hypometabolism (Townsend et al., 2023) in the prefrontal cortex.

Additionally, reductions in frontal cortical metabolism, serotonin system dysfunction and impaired glucose metabolism—particularly in the prefrontal cortex and temporal lobes—have been documented (Brugger et al., 2020; Howes & Kapur, 2009; Kim et al., 2021; Tauscher et al., 2002; Townsend et al., 2023). Increased metabolic activity and perfusion (Allen et al., 2018; Allen et al., 2016) in the hippocampus, particularly in the anterior region, may disrupt normal neural functioning and balance already in the early stages of psychosis.

These imbalances may arise from neurodevelopmental structural defects or traits, progressively worsening particularly around the onset of the first psychotic episode. This suggests that both functional and structural abnormalities interact and contribute to the pathophysiology of schizophrenia and become more pronounced during the transition to psychosis. Neural dysconnectivity thus represents both a trait, long-standing vulnerability, and a state, acute psychotic manifestation, in the development of psychosis. Thus, in schizophrenia, these characteristics indicate an altered equilibrium within the brain, encompassing the excitation-inhibition imbalance, neural asynchrony, brain metabolic changes, and modifications in neural activity patterns. In a wider context, these may also be associated more extensively with metabolic imbalances and dysregulations in multiple organ systems in psychotic disorders. All this happens in interaction with environmental factors.

2.4.1.2 Dopamine

The dopamine hypothesis of schizophrenia, hyperdopaminergia particularly in the stratum, is the most known etiological theory with robust in vivo findings (Hietala et al., 1995). However, it has been shown that lesions of dopamine neurons in the prefrontal cortex result in increased levels of dopamine and its metabolites and D2–receptor density in the striatum, while the application of dopamine agonists to prefrontal areas reduced dopamine metabolite levels in the striatum. (Pycock et al., 1980) (Howes & Kapur, 2009; Scatton et al., 1982) These findings suggest cortical modulation of striatal dopaminergic function and provides a mechanism to propose that schizophrenia is characterized by frontal hypodopaminergia resulting in striatal hyperdopaminergia. However, evidence suggests that both genetic and environmental factors contribute to disrupted glutamate and dopamine systems in schizophrenia. Genetic factors primarily seem to affect glutamate function, while few genetic variants directly impact dopamine (McCutcheon et al., 2020). This indicates that abnormal dopamine signaling may largely result from other influences.

Heterogeneity in dopaminergic function have also been suggested to relate at least on treatment resistance in schizophrenia (McCutcheon et al., 2020).

2.4.1.3 Hippocampus, glutamate, GABA and NMDA-receptors

In the glutamate theory of psychosis (Olney & Farber, 1995), it is thought that the subtype of glutamate receptor, NMDA receptor (NMDAr), is neurodevelopmentally hypofunctional in the prefrontal cortex. Glutamate is the main excitatory neurotransmitter. These NMDArs are localized in GABAergic interneurons. In addition to prefrontal cortex (Gao et al., 2022; Kaar et al., 2019), there is also evidence of the role of dysfunctional hippocampus in glutamate signaling (Tamminga et al., 2012). Hippocampal hyperactivity driven by GABAergic interneuron deficits and NMDAr hypofunction is associated with the hyperglutaminergic and further hyperdopaminergic state often observed in schizophrenia (Grace, 2016, 2017; Heckers & Konradi, 2015; Kiemes et al., 2022; Lodge & Grace, 2008; Santos-Silva et al., 2024). However, only increased thalamic glutamate or glutamine concentrations, but no hippocampal or striatal, basal ganglia or prefrontal glutamate alterations, have been observed in genetic high-risk individuals (McCutcheon et al., 2021a).

The dysfunctional mesocortical dopamine projections are thought to be the consequence of NMDA receptor hypofunction, dysfunction (Yang & Tsai, 2017) that develops during the period from pregnancy to adulthood. These receptor level dysfunctions in the development of schizophrenia are most likely related to changes in synaptic plasticity, input and output connectivity, neuronal inhibition and excitation, and further changes in homeostatic, functional and structural plasticity, especially in the developing frontal and temporal lobes and brain regions and circuitries connected to these (Gao et al., 2022). Thus, the dysregulation of dopamine likely represents the final common pathway to psychosis (Howes & Kapur, 2009).

The deviant interaction of excitatory glutamate pyramidal neurons and inhibitory GABA interneurons may be due to neurodevelopmental defects particularly in GABA interneurons. These GABA interneurons lose their function and do not inhibit the glutamate neurons inducing glutamate hyperactivity, which ultimately drives the final dopaminergic pathway. The hyperactive hippocampus due to excessive glutamate release, overstimulates the ventral tegmental area, leading to an increased release of dopamine in regions such as the striatum. In the hippocampus, especially its CA1 and subiculum subfields are suggested to have neurodevelopmental defects that relate to its NMDA and $GABA_A$ receptor dysfunction, functional and structural loss of GABAergic interneurons, leading to the loss of GABA inhibition, and further hyperactive glutamatergic pyramidal neurons and a hyperactive hippocampus in the models of schizophrenia (Kiemes et al., 2022; Lieberman et al., 2018).

2.4.1.4 Serotonin

The serotonin network may both modulate itself and regulate directly and indirectly, other neurotransmitter systems and thus affect widely a variety of behaviours and phenotypes in psychiatric disorders. (Berger et al., 2009) Serotonin (5-hydroxytryptamine, 5-HT) also regulates the endocrine system and energy metabolism by modulating the hypothalamic–pituitary–adrenal axis (Berger et al., 2009; Gershon & Tack, 2007). 5HT-circuits arise from the brainstem nuclei, such as the median and dorsal raphe nuclei that project to a wide range of cortical and subcortical brain areas, such as prefrontal cortex, locus coeruleus and ventral tegmental area, hypothalamus and basal forebrain. Thus, serotonin interacts in a neuronal network of all major neurotransmitter systems. For example, 5-HT in the CNS has a complex regulatory influence on the neurotransmission involving glutamate and GABA (Ciranna, 2006). This complex regulation is mediated by various 5-HT receptor subtypes, leading to diverse effects. The serotonin theory of psychosis suggests that hyperactivity and/or imbalance of serotonin, particularly via the 5-HT_{2A} receptor, presumably in interaction with dopamine can result in psychosis (Jiménez-Trejo et al., 2024; Madsen et al., 2019; Quednow et al., 2020).

2.5 Morphological brain changes in patients with psychotic disorders and psychosis risk

2.5.1 Brain morphology in clinical high-risk for psychosis

Previous studies have shown morphological changes in individuals at a clinical high risk for psychosis. In CHR, cortical thinning has been found in the prefrontal, anterior cingulate, inferior parietal, and parahippocampal cortices, and superior temporal gyrus compared with healthy control subjects (Jung et al., 2011). Further, there is evidence of cortical thinning in the banks of the superior temporal sulcus, transverse temporal gyrus, pars triangularis (Del Re et al., 2021), as well as the parahippocampal, orbitofrontal, cerebellar, paracentral, fusiform, and superior temporal cortices in CHR individuals converting to psychosis, with less prominent or no changes in subcortical volumes or areas. (Haas et al., 2024; Jalbrzikowski et al., 2021; Pantelis et al., 2003; Velakoulis et al., 2006). However, these studies did not study the hippocampus or amygdala on a subfield– or subnuclei–level, respectively.

A recent machine learning study discovered that the surface area of specific brain regions, including the right superior frontal, right superior temporal, and bilateral insular cortices, strongly contribute in distinguishing CHR individuals converting to psychosis, from healthy controls (Zhu et al., 2024). Further, abnormal age

associations (ages 12-16) have been observed, especially in the left paracentral and fusiform cortices, in those converting to psychosis. Thus, specific frontal and temporal cortical alterations may have a neurodevelopmental origin that may relate to later abnormal synaptic pruning defects and/or compensatory myelination during adolescence (Jalbrzikowski et al., 2021). However, the evidence of accelerated reduction in cortical thickness among CHR individuals who developed psychosis have been found to apply only to those who were 18 years of age or older (Chung et al., 2018). However, another systematic review further suggested that CHR subjects show an accelerated decline in gray matter primarily in temporal, frontal, cingulate and parietal cortices, particularly those who convert to psychosis, but may normalize by early adulthood in remitters (Merritt et al., 2021). Thus, the cortical neuroanatomical measures estimating the onset of psychosis are suggested to differ depending on the age of onset and phase of prodromal symptoms.

In ultra high-risk patients, some evidence of aberrations in also white matter, especially in the superior longitudinal fasciculus, the inferior longitudinal fasciculus, and the inferior fronto-occipital fasciculus, have been found, suggesting the presence of specific white matter alterations before the onset of first psychosis (Waszczuk et al., 2021). Also, the study found that the normative increase in the regions of the cingulum, thalamic radiation, cerebellum, retrolenticular part of the internal capsule, and hippocampal–thalamic tracts was absent in CHR individuals. In those who transitioned, white matter volume and fractional anisotropy reduced over time in the inferior and superior fronto-occipital fasciculus, corpus callosum, anterior limb of the internal capsule, superior corona radiata, and calcarine cortex (Merritt et al., 2021).

Increased parietal and occipital lobe gyrification have been recently suggested to predict conversion to psychosis in clinical high-risk patients (Basavaraju et al., 2023). Since the gyrification index is considered a proxy marker of early cortical neurodevelopmental abnormalities (Kalantar-Hormozi et al., 2023; White et al., 2010), these findings collectively support the view that developmental maturation is aberrant in psychotic disorders. Specific grey and white matter abnormalities appear to be present already during the risk stage, particularly in the frontal and temporal cortices. However, the mechanisms underlying age-related changes in cortical and white matter structure in CHR individuals, or even in schizophrenia, remain poorly understood, as does the extent to which these trajectories diverge from typical neurodevelopment (Chiapponi et al., 2013).

2.5.2 Brain morphology in first episode of psychosis

Studies on the first episode of psychosis have revealed various abnormalities in the brain structure that are associated with the onset of psychosis. These alterations are

typically observed in regions critical for cognition, emotion regulation, and sensory processing, and often involve reductions in gray matter volume, cortical thickness, and abnormalities in white matter connectivity. Alterations in hippocampal volume have been observed in the early stage of the first episode of psychosis (Brunner et al., 2022). Also, particularly FEP patients with early persistent negative symptoms following the first episode of psychosis have been found to have significantly reduced left amygdalar and right hippocampal volumes (Makowski et al., 2017). However, the hippocampal reductions appear to be less prominent, emphasizing the anterior region (Chopra et al., 2023), in the first episode of psychosis, compared to chronic schizophrenia (Velakoulis et al., 1999; Wood et al., 2001).

The grey matter volume reductions are located mainly in bilateral fronto–temporal, insular and occipital areas, independent of antipsychotic medication. More widespread changes relate to the more severe of symptoms and a longer duration of illness (Vieira et al., 2021). However, recent machine learning techniques have been recognizing the subtypes of schizophrenia patients with greater reductions in subcortical and cortical structures and poorer outcomes and cognitive performance (Chand et al., 2020; Chand et al., 2022; Q. Zhao et al., 2022). Also, morphological subtypes have been found in the youth with psychosis spectrum symptoms (Chand et al., 2022), and at the first episode of psychosis (Dwyer et al., 2023) using machine learning. These findings suggest that a subtype of psychosis characterized by greater cortical volumetric reductions—associated with poorer clinical outcomes and a higher genetic liability for schizophrenia—may already be morphologically distinguishable at the early stage of illness. This indicates that specific brain morphological patterns, likely reflecting premorbid neurodevelopmental trajectories, are present in FEP and may contribute to differential outcomes (Chand et al., 2020). However, the age of onset may contribute to these subtype differences, with the early onset of psychosis pertaining to a more severe psychotic disorder trajectory due to the prior disturbances during critical early neurodevelopmental stages (Pan et al., 2020; Remschmidt & Theisen, 2012; Zhan et al., 2023).

2.5.3 Brain morphology in schizophrenia and affective psychoses

In particularly, hereditary subcortical and limbic volume and shape in families with schizophrenia have been suggested (Roalf et al., 2015). Also, meta-analysis (S. Sun et al., 2023) has suggested robust cortical thickness reduction in the inferior frontal gyrus, insula, and superior temporal gyrus, among patients with schizophrenia, particularly in those with chronic schizophrenia. Large-scale studies have revealed that patients with schizophrenia have a smaller hippocampus, amygdala, thalamus, accumbens, intracranial volumes, as well as a larger pallidum and lateral ventricle

volumes, compared to healthy controls (Haijma et al., 2013; Ho et al., 2019; van Erp et al., 2018; G. Zhao et al., 2022). The most pronounced reductions in cortical thickness have been found in in the frontal and temporal areas, which have been suggested to progress across the course of the illness (van Haren et al., 2011). Thus, specific morphological changes may be potential endophenotypic markers in schizophrenia. Earlier studies suggest that specific structural brain changes in schizophrenia might be due to the neurodevelopmental defects that relate to genetic and epigenetic changes and further gene expression (Li & Chen, 2022; Whelan et al., 2016). Defects are most likely to originate from the temporal regions, which have already been observed in clinical high-risk patients later converting to psychosis (Haas et al., 2024).

There is evidence of shared etiology and genetics in bipolar disorder and schizophrenia (Cheon et al., 2022; Lee et al., 2013). This might mean they share common ancestry, genetic similarity, or involvement in the same biological processes regarding the brain structure (Chang et al., 2018). Diffusion tensor imaging (DTI) studies have shown the reduced structural integrity of white matter pathways particularly in callosal and commissural fibers (Samartzis et al., 2014; Vitolo et al., 2017), and in the fronto-temporal-limbic pathways, including the uncinate fasciculus tract, that connects the amygdala with the frontal cortices, in both schizophrenia (Vitolo et al., 2017) and bipolar disorder (Ho et al., 2019). Further, a recent multimodal meta-analysis compared white matter changes between bipolar disorder and schizophrenia and found a shared decrease in the bilateral corpus callosum and corona radiata in both white matter volume and fractional anisotropy, the latter reflecting the reduced integrity and function of white matter tracts, in both bipolar disorder and schizophrenia (G. Zhao et al., 2022). However, volumetric differences in the amygdala between patients with schizophrenia and those with bipolar disorder have been observed (Ohi et al., 2022).

On the other hand, recent machine learning studies on schizophrenia have suggested distinct subtypes based on differential morphological changes even within the group of individuals diagnosed with schizophrenia. Subtype 1 showed widespread grey matter volume reductions, which were the most prominent in the thalamus, nucleus accumbens, medial temporal, insular, medial prefrontal and frontal cortices, negatively correlating with illness duration, and worse premorbid functioning and cognitive performance. Instead, subtype 2 had normal and stable anatomy, except for a larger basal ganglia and internal capsule. (Chand et al., 2020; Chand et al., 2022) These morphological subtypes have been observable even in the youth with psychotic symptoms (Chand et al., 2022), and at the first-episode of psychosis (Dwyer et al., 2023) with elevated schizophrenia polygenic risk scores (Chand et al., 2022). The observations regarding these morphological subtypes within the clinically high-risk population require further research.

Although the findings on major depressive disorder with psychotic features are more limited, they suggest morphological changes, particularly in the prefrontal cortex (L. Zhang et al., 2021). However, a recent systematic review observed overlapping affected areas are in the temporal, frontal, and limbic lobes of hospitalized serious mental disorders, such as schizophrenia, bipolar disorder and major depressive disorder (MDD) (Brenner et al., 2022). Patients diagnosed with schizophrenia or MDD were reported to have gray matter reductions in the frontal, temporal, insular, and limbic lobes, whereas affective psychoses patients, including both bipolar disorder and MDD with psychotic features, had only temporal and limbic lobe alterations reported.

2.6 Hippocampus subfields and amygdala subnuclei in psychotic disorders – functional neuroanatomy

2.6.1 Hippocampus and functional neuroanatomy

There is evidence that the hippocampal subfields and amygdala subnuclei have distinct functions and connectivity patterns (Tamminga et al., 2010). The hippocampus can be divided in multiple ways based on different anatomical and functional characteristics. In humans, the hippocampus is divided into anterior and posterior regions, while in rodents it is divided into partly anatomically corresponding ventral and dorsal regions, respectively. In relation to posterior–anterior division of hippocampus, posterior hippocampus might be more the prominent for cognitive function and the anterior hippocampus for mood and affect (Ayhan et al., 2021).

The hippocampus consists of distinct subfields, including the Cornu Ammonis (CA) regions (CA1, CA2, CA3, CA4), presubiculum, subiculum, fissure, dentate gyrus (DG), and fimbria. The preceding methodological MRI (Magnetic Resonance Imagin) advances in automated hippocampal segmentation methods permit accurate (Kahhale et al., 2023) *in vivo* measurements of hippocampal subfield volumes. (Iglesias et al., 2015; Winterburn et al., 2013) These techniques have been used to show that hippocampal subregions are differently affected in schizophrenia (Haukvik et al., 2015; Ho et al., 2017b; Mathew et al., 2014; McHugo et al., 2024; Vargas et al., 2018) and that varying effects might already be present in the prodromal stage of the illness (Ho et al., 2017a; Vargas et al., 2018).

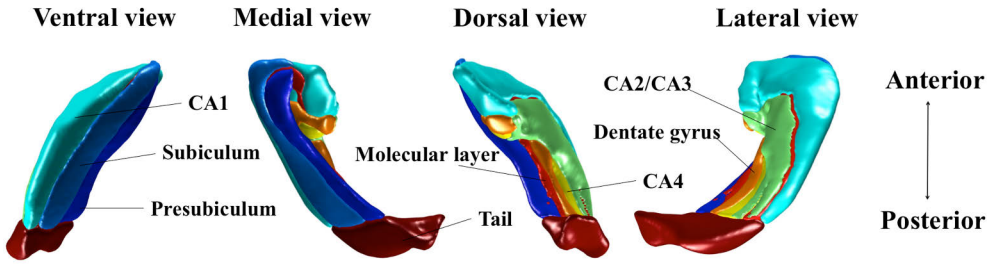


Figure 2. A surface rendering of hippocampal subfields from the lateral view that is based on a segmentation of the MNI152 template and is used for illustration only. Modified and reprinted from Original Publication II (Armio et al., 2024).

The hippocampus is known for its function in memory formation and retrieval. The trisynaptic loop (entorhinal cortex-DG, DG-CA3, C3-CA1) is crucial in the formation and stabilization of long-term episodic and spatial memories (Stepan et al., 2015) It has been proposed that the trisynaptic circuit is responsible for the generation of hippocampal theta waves. Oscillations, including theta waves, result from the rhythmic patterns of synchronized electrical activity among the networks of neurons. These waves are responsible for the synchronization of different brain regions.

In schizophrenia, the hippocampus may be a primary region affected by deviant brain development (Lipska et al., 1993) due to its high levels of neuroplasticity, as it exhibits high levels of plasticity compared to other brain regions (Knight et al., 2022). Moreover, the hippocampus is the most pronounced brain region in relation to psychosis risk, with observed increases in blood perfusion. (Allen et al., 2018; 2016) Particularly the anterior hippocampus has been observed to be a putative epicenter of early brain pathology during psychosis from which dysfunction may spread to affect connected areas. (Chopra et al., 2023; McHugo et al., 2024) More specifically, studies have observed diverse biological changes in the CA1 subfield of the hippocampus in FEP and chronic schizophrenia, as well as in the CHR population (**Table 1**) (Schobel et al., 2013; 2009).

2.6.1.1 CA1 subfield in the development of schizophrenia

A loss of parvalbumin interneurons in the prefrontal cortex (PFC) and ventral hippocampus is associated with diminished oscillatory activity in an animal model of schizophrenia (Lodge et al., 2009), potentially contributing to hippocampal hyperactivity and a subsequent hyperdopaminergic state. Studies on schizophrenia patients have shown alterations particularly in theta and gamma rhythms (Newson & Thiagarajan, 2018; Tanaka-Koshiyama et al., 2020; Uhlhaas & Singer, 2010)

(Hirano et al., 2015), which are crucial for cognitive functioning, attention, and memory. Interneurons, particularly GABAergic interneurons, known to be reduced in number and/or dysfunctional in the hippocampus of schizophrenia patients, are critical in generating and regulating neural oscillations across the brain (Lodge et al., 2009).

An earlier study in mice observed that in the CA1 layer, a specific type of mid-frequency gamma occurs at the peaks of theta waves; meanwhile, in the dentate gyrus, fast and slow gamma oscillations happen at the troughs of theta waves (Lasztóczi & Klausberger, 2017). Thus, hippocampal gamma oscillations in these subfields control the neuron activity differently. Another recent study found that neurons in the medial septum fire together with hippocampal theta waves and influence changes in CA1's beta and gamma oscillations, via enthorinal cortical and CA3 inputs, in rodents (Király et al., 2023). Disrupted gamma and theta oscillations in these regions lead to impaired synchronization and abnormal information flow, particularly between the hippocampus and prefrontal cortex.

Already in the CHR, hippocampal hypermetabolism has been observed to originate in the CA1 region and subsequently extend to the subiculum following the onset of psychosis, accompanied by structural and functional defects in these hippocampal subfields (Schobel et al., 2013). Also, baseline cerebral blood volume (CBV) abnormalities within the CA1 subfield have been shown to differentially predict the clinical progression from a prodromal state to full psychosis, particularly schizophrenia (Schobel et al., 2009). Recent studies support the idea that the mechanism behind dopaminergic dysfunction is the neurodevelopmental disruption of the hippocampus, especially due to the N-Methyl-D-Aspartate Receptor (NMDAR) hypofunction in GABAergic interneurons in CA1 (Kiemes et al., 2022; Schobel et al., 2013; Schobel et al., 2009; Zhang & Reynolds, 2002). NMDA receptor hypofunction can lead to hyperdopaminergia through disrupted GABAergic inhibition, creating a neurochemical imbalance and further hypermetabolic state. These mechanisms are central in the development of psychotic symptoms.

The microstructural basis behind the variable and partly distinct defects is suggested to pertain to the subfield-specific increases in the excitatory circuitry, decreases in inhibitory neurotransmission, and damaged mitochondria in hippocampal subfields, particularly in CA1 and CA3, that lead to hippocampal hypermetabolism in schizophrenia (Farmer et al., 2023). Studies on schizophrenia suggest decreased numbers of inhibitory synapses and decreased functional integrity of parvalbumin interneurons in CA3 and increased numbers of excitatory synapses, greater synaptic strength and decreased functional integrity in CA1 (Farmer et al., 2023). Changes in the homeostatic function and fewer mitochondria have also been shown in the molecular layer of the dentate gyrus in schizophrenia (Farmer et al., 2023; Schoonover et al., 2021).

These results highlight the role of the CA1 subfield in disruptions of theta and gamma rhythms, as well as in metabolic and neurochemical changes. They also point to broader desynchronization, particularly between the hippocampus, prefrontal cortex (Soltani Zangbar et al., 2020) and amygdala, as observed in schizophrenia.

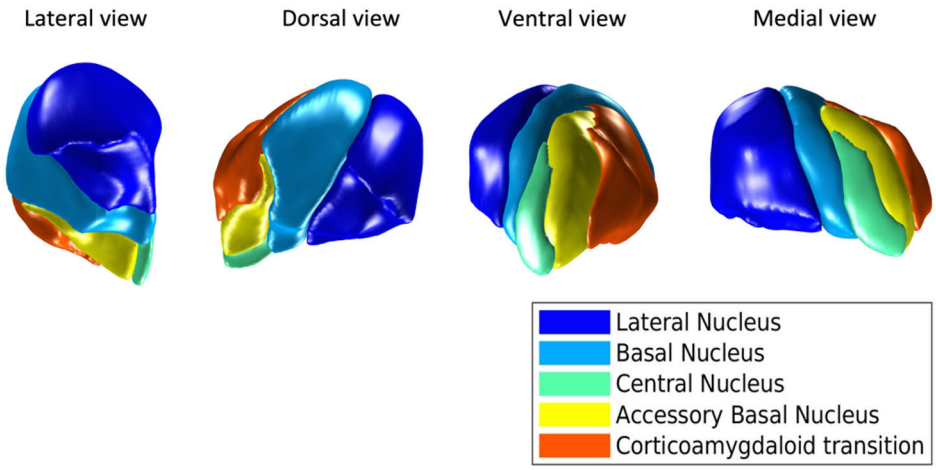


Figure 3. A surface rendering of amygdala subnuclei, which is based on a segmentation of the MNI152 template and is used for illustration only. Modified and reprinted from Original Publication I (Armio et al., 2020).

2.6.2 Amygdala and functional neuroanatomy

The amygdala is a structurally and functionally diverse and complex region composed of multiple subnuclei: the lateral nucleus, basal nucleus, accessory basal nucleus, cortico–amygdaloid transition area, central nucleus, medial nucleus, cortical nucleus, paralaminar nucleus, and anterior amygdaloid area, based on post-mortem studies (Saygin et al., 2017). It plays major roles in emotional processing, social cognition, fear and threat detection, valence attribution, emotional memories, and others stress- related functions. (Beyeler et al., 2016; Hall et al., 2008; Pignatelli & Beyeler, 2019) (Adolphs, 2010; Anticevic et al., 2012; LeDoux, 2007; Roozendaal et al., 2009).

The differentiation of amygdala subnuclei refers to the distinct structural and functional divisions within the amygdala. These subnuclei, such as the basolateral, central, and medial nuclei, each have specialized roles in processing emotions, memory, and responses to stress, and are connected to different regions of the brain to regulate various emotional and behavioral functions.

The lateral nucleus of the amygdala is thought to be interconnected with the hippocampus, sensory thalamus, medial prefrontal cortex, anterior cingulate cortex,

and superior temporal gyrus, serving as a hub for receiving sensory input from these areas (Whalen & Phelps, 2009). The lateral nucleus is the primary entry point for sensory information into the amygdala (LeDoux, 2007), where the information is integrated prior to transmission to the basal nucleus and other subsequent subnuclei. Thus, it acts as a major input center of the amygdala, processing sensory cues, particularly those linked to fear and threat-related stimuli (Bigot et al., 2024; Duvarci & Pare, 2014; Janak & Tye, 2015).

The basal nucleus is involved in integrating information from the lateral nucleus and further processing emotional and cognitive responses, as it is essential for modulating social behavior and decision-making. The basal nucleus also participates in fear conditioning thought it is more involved in the regulation and expression of emotional responses (Beyeler et al., 2016). The basal nucleus has strong connections with both the prefrontal cortex and the central nucleus. The accessory basal nucleus also plays a role in emotional processing and memory formation, working alongside the lateral and basal nuclei. It is connected to other amygdalar regions and cortical areas involved in higher-order emotional processing.

In relation to psychoses, patients with 22q11.2 deletion syndrome (22q11.2DS), a known genetic model for psychosis susceptibility, showed a distinct pattern of brain connectivity characterized by reduced communication between the basolateral amygdala (BLA) and the frontal regions of the brain, while there was increased connectivity between the BLA and the hippocampus (Delavari et al., 2023). As suggested by this recent study, early BLA-dysfunction and centro-medial nucleus (CMA)–frontal dysconnectivity might be a markers of impaired tolerance to daily stress in 22q11.2DS, a population with a heightened risk of mental health disorders, such as schizophrenia. Additionally, a developmental drop in CMA–frontal connectivity has been observed to be the most severe in patients at a higher risk for positive psychotic symptoms (Delavari et al., 2023), as well as in patients with attenuated psychotic symptoms and first episodes of schizophrenia (Kim et al., 2020).

The functional disturbances in the amygdala subnuclei may at least partly correlate with the altered structure. (Suárez et al., 2020) (Bullmore & Sporns, 2009) Thus, the morphological and functional defects of the basal, lateral, central and medial nuclei of the amygdala may be of neurodevelopmental origins pertaining to stress sensitivity and stress-related functions in schizophrenia, but possibly with a different temporal emphasis.

Table 1. Key findings of MRI studies on amygdala subnuclei volumes in the development of psychotic disorder (clinical high-risk subjects, first episode of psychosis, schizophrenia and bipolar disorder).

Study	Sample Size	Key amygdala subnuclei findings
(Damme et al., 2020)	37 low-risk for bipolar-spectrum disorders, 47 high-risk for bipolar-spectrum disorders, 30 bipolar-spectrum disorder groups (BSD)	**BSD vs Low-risk:** Larger right lateral subnuclei in the BSD group. **BSD vs High-risk:** Larger left medial and left central subnuclei in the BSD group. **All groups:** No significant differences in the left basal or lateral subnuclei between the groups A greater number of lifetime hypo/mania episodes was associated with a larger right central subnuclei and smaller right basal subnuclei.
(Tesli et al., 2020)	24 violent schizophrenia (SCZ-V), 51 non-violent schizophrenia (SCZ-NV), 90 CTR	**SCZ-V vs CTR:** Smaller basal nucleus, accessory basal nucleus, the cortico-amygdaloid transition area, and paralaminar nucleus volumes in SCZ-V. **SCZ-NV vs CTR:** Smaller basal and paralaminar nucleus volumes in SCZ-NV. **SCZ-NV vs SCZ-V:** No significant differences in amygdala nuclei volumes between SCZ-V and SCZ-NV.
(Barth et al., 2021)	452 schizophrenia patients (SCZ), 316 bipolar disorder patients (BD), 753 healthy controls (CTR)	Reductions in the amygdala subnuclei were the most widespread in schizophrenia. The lateral, cortical, paralaminar, and central nuclei reduced only in schizophrenia. Volume differences in the basolateral complex were the most prominent in schizophrenia. Bilateral total amygdala and all nuclei volumes, except the medial and central nuclei were smaller in both SCZ and BD compared to CTR.
(Bell et al., 2022)	29 Violent schizophrenia (PSY-V), 67 Non-violent schizophrenia (PSY-NV) 89 CTR	**PSY-V vs CTR:** A smaller basal nucleus, anterior amygdaloid area, and cortical amygdalar transition area in PSY-V. **PSY-NV vs CTR:** A smaller cortical amygdalar transition area in PSY-NV.
(Hu et al., 2023)	40 SCZ with violent behavior (VS), 26 SCZ non-violent (NVS), 28 CTR	**SCZ vs CTR:** A smaller volume of the left basal nucleus in SCZ. **VS vs NVS:** A smaller volume of the left amygdala central nucleus in VS.

2.6.3 Hippocampus and amygdala morphology in clinical high-risk for psychosis

There is evidence of morphological alterations in both the hippocampal subfields and amygdala subnuclei in the development of psychotic disorders. The main findings of structural MRI studies in the clinical high-risk for psychosis, first-episode psychosis, schizophrenia and bipolar disorder are listed for amygdala subnucleus and hippocampal subfield volumetry in the **Table 1** and **2**, respectively.

There is no evidence of the hippocampal or amygdala total volume contributing to transition to psychosis in CHR individuals (Hinney et al., 2020; Velakoulis et al., 2006; Walter et al., 2016). However, based on the available studies on hippocampal subfields, it appears that especially CA1 and the anterior hippocampus (Chopra et al., 2023) could be biomarkers of CHR transitioning to psychosis (Ho et al., 2017a; Ho et al., 2017b; Provenzano et al., 2020; Sasabayashi et al., 2021), and especially to schizophrenia (McHugo et al., 2020).

Earlier studies on the amygdala subnuclei in clinical high-risk patients have not been conducted. However, limited evidence of decreased amygdala total volume in CHR (Chan et al., 2011), as well as altered dorsomedial amygdala shape in familial high-risk youth, has been observed (Guimond et al., 2022).

2.6.4 Hippocampus and amygdala morphology in first episode of psychosis

In FEP, reduced hippocampal subfield volumes of particularly the CA1, CA4, and granule cell layer, but also reductions in the subiculum, and presubiculum, have been found, independent of antipsychotic medication (Baglivo et al., 2018; Briend et al., 2020; McHugo et al., 2024; Park et al., 2021). Smaller CA1, molecular layer, subiculum, presubiculum, and hippocampal tail volumes have been found to be associated with longer duration of untreated psychosis in FEP (Briend et al., 2020), however correlations between the duration of illness and subfield volumes are not congruent (Baglivo et al., 2018; P. Cao et al., 2023; Nakahara et al., 2018). Similar studies on the amygdala subnuclei in FEP patients have not been conducted.

2.6.5 Hippocampus and amygdala morphology in schizophrenia and bipolar disorder

Earlier studies show specific volume reductions in the hippocampus and amygdala in psychotic disorders. In effect, there is evidence of shared genetic architecture between schizophrenia and subcortical brain volumes, including the amygdala and hippocampus (Cheng et al., 2022). However, a recent study on the hippocampal subfield suggests that at least partly early neurodevelopmental genetic processes are

also behind specific subfield alterations, by observing unique subfield-specific molecular profiles in schizophrenia postmortem samples, implicating astrocytes in the dentate gyrus, immune mechanisms in CA3, and synaptic scaling in CA1 (Perez et al., 2021). The results suggest subfield-specific increases at least in the excitatory circuitry, decreases in inhibitory neurotransmission and fewer or damaged mitochondria.

Left hippocampal volume reduction, associated with stressful life events, global functioning, and executive functioning, have been suggested to be a common feature across schizophrenia spectrum disorders, bipolar disorder, and MDD (Brosch et al., 2022). On the other hand, post-mortem studies on hippocampal morphology in patients with schizophrenia generally support the notion that hippocampal subregions, and anterior and posterior parts of the hippocampus, are differently affected by the illness (Benes et al., 1991; Falkai et al., 2016). Overall, genetic factors seem to play a larger role in the relationship between the anterior hippocampus and schizophrenia, while environmental factors and disease progression may have a stronger impact on the widespread hippocampal volume loss observed in the later stages (Choi et al., 2022). A greater impact of genetic factors on the volumes of anterior CA volumes, applying also to the CA1 and molecular layer of CA fields, have been observed (van der Meer et al., 2020). There is also evidence that the hippocampal tail volume is linked to genes associated with schizophrenia (Choi et al., 2022).

Some meta-analyses (Haukvik et al., 2022; 2018) found widespread subfield reductions in both schizophrenia and bipolar disorder; CA1 being the most affected in schizophrenia (Ho et al., 2017b; K. Wang et al., 2023), and bipolar disorder type 1 having more widespread reductions (Haukvik et al., 2022). Especially the CA1 subfield of hippocampus is suggested to be hyperactive (Nakahara et al., 2018), hyperdopaminergic (Krieckhaus et al., 1992), deformed in shape (Zierhut et al., 2013), and smaller in volume in schizophrenia (Haukvik et al., 2018; McHugo et al., 2020; McHugo et al., 2024). However, the volume appears to be stable during the early years of psychosis, in individuals who progress to schizophrenia (McHugo et al., 2020).

Volumetric studies suggest a smaller total amygdala volume in subjects with schizophrenia than bipolar disorder (Ho et al., 2019; Mahon et al., 2012). More specifically, a study, using a high-field 7T atlas, found that the left basolateral and centromedial subnuclei complex show the largest proportion of atrophy in schizophrenia as compared to psychotic bipolar disorder (Mahon et al., 2015). Shape alterations, especially in the basolateral complex (lateral, basal, and accessory basal nuclei), are more prominent and widespread in schizophrenia compared to bipolar disorder (Mahon et al., 2015), both of which share volume reductions of the basal nucleus, accessory basal nucleus, and cortico-amygdaloid transition area (Barth et al., 2021).

To conclude, these findings highlight that the early neurodevelopmental morphological alterations in the hippocampus and amygdala, particularly in the CA1 subfield and basolateral nuclei, likely precede those of later neurodevelopmental defects of the cortical areas and centromedial subnuclei, and further those of more widespread changes in the first episode of psychosis and finally, schizophrenia. However, it is challenging to determine what is the exact timelines of these alterations are during the developmental phases in the etiology of schizophrenia **(Figure 12**).

Table 2. Key findings of MRI studies on hippocampal subfield volumetry in the development of psychotic disorders (clinical high-risk subjects, first-episode of psychosis, schizophrenia and bipolar disorder).

Study	Sample Size	Key hippocampal subfield findings
(Mathew et al., 2014)	49 schizophrenia (SCZ), 50 controls (CTR)	**SCZ VS CTR:** CA2/3 and dentate gyrus subfields were the most affected in schizophrenia.
(Ho et al., 2017a)	147 ultra-high risk (UHR), 54 controls	**UHR VS CTR:** Progressive Decline in Hippocampal CA1 Volume in UHR with poor outcomes.
(Ho et al., 2017b)	Data set 1: 155 schizophrenia patients (DOI 7y), 79 CTR Data set 2: 46 schizophrenia patients (DOI 18y), 46 CTR	Early atrophy of CA1 in schizophrenia, with extension to other hippocampal subfields in the progression of the psychotic disorder.
(Baglivo et al., 2018)	58 FEP, 76 CTR	**FEP vs CTR:** Left CA1, CA3, CA4, GCL, and ML volumes were lower in FEP. No correlation was found between the hippocampal subfield volumes and duration of illness (DOI).
(Haukvik et al., 2018)	Systematic review and meta-analysis: 9 studies	Volume reductions in all subfields in SCZ and BD compared to CTRs. CA1 as the most affected region.
(Nakahara et al., 2018)	Systematic review	Smaller CA1 volumes and CA1 hyperactivation in schizophrenia. Smaller CA1 and CA4/DG volumes in first-episode schizophrenia. More widespread reductions in subfield volumes with a longer DOI.
(Vargas et al., 2018)	61 ultra-high risk (UHR), 91 schizophrenia (SCZ), 70 controls (CTR)	**UHR vs CTR:** Bilaterally smaller CA1, CA2/3, and C4/DG volumes in UHR. **UHR vs SCZ:**

		Bilaterally smaller CA2/3, 4/DG, presubiculum, and subiculum volumes in SCZ.
(Wannan et al., 2019)	52 chronic schizophrenia-spectrum disorder, 28 youth ROP 52 older controls, 28 younger controls	No differences in ROP compared to younger CTRs. More widespread changes in chronic patients compared to older CTRs.
(Briend et al., 2020)	54 antipsychotic-naïve first episode psycosis (FEP), 41 controls (CTR)	**FEP vs CTR:** Reduced CA1, CA4, GCL, subiculum, and presubiculum volumes. Smaller CA1, molecular layer, subiculum, presubiculum, and hippocampal tail volumes were significantly associated with a longer DUP.
(Ohi et al., 2021)	138 schizophrenia patients (SCZ), 47 unaffected first-degree relatives (FR), 162 controls (CTR)	**SCZ vs CTR:** Larger right hippocampal fissure volumes and smaller bilateral CA1, right presubiculum, bilateral parasubiculum, bilateral molecular layer, right fimbria and bilateral HATA in SCZ (uncorrected). **SCZ vs FR:** Smaller bilateral CA1, left presubiculum, bilateral ML, right GCMLDG, right fimbria and right HATA volumes in SCZ (Bonferroni corrected). **FR vs HC:** No significant differences.
(Park et al., 2021)	41 First episode psychosis (FEP), 27 controls (CTR)	**FEP VS CTR:** Reduced hippocampal volumes in FEP, while CA4-dentate gyrus showed the greatest reductions with 7 Tesla MRI.
(Sasabaya shi et al., 2021)	51 ARMS, 77 schizophrenia, 87 controls	Smaller CA1, left tail, right ML in both SCZ and ARMS Smaller tail in chronic SCZ.
(Y. Sun et al., 2023)	A systematic review	**SCZ vs CTR:** Reduced volumes in the bilateral CA 1, GCMLDG, subiculum, parasubiculum, ML, hippocampal tail and HATA; in the left CA4 and presubiculum; and in the right fimbria.
(K. Wang et al., 2023)	49 adolescent schizophrenia patients (SCZ), 67 non-psyhcotic major depressive disorder patients (MDD), 34 controls (CTR)	**SCZ vs HC:** Smaller CA1, ML, subiculum, parasubiculum. DG compared to CT, most robust reductions in CA1 and ML. **SCZ vs MDD:** Greater trend of reductions in all subfields in SCZ, particularly in CA regions.
(McHugo et al., 2024)	90 individuals in the early stage (< 2y) of a non-affective psychosis and 70 CTR.	Smaller anterior CA1 and DG volumes in the early stage of non-affective psychosis.

2.7 Childhood adversities affect hippocampus and amygdala

Childhood maltreatment, such as sexual abuse, emotional or physical abuse, or neglect, has a significant and lasting effect on the trajectory of brain development in children (Teicher & Samson, 2013; Teicher et al., 2016). The brain structural vulnerability might relate to disturbances in normative increased neuronal plasticity, myelination, changes in synaptic integration and stability, but also synaptic pruning, that occur in adolescence (Paolicelli et al., 2011). On the other hand, early and chronic stress disrupts cellular homeostasis through mitochondrial dysfunction and increased oxidative stress, which can lead to structural defects and a higher risk of developing various diseases (Goh & Agius, 2010). Thus, particularly early life stress may disrupt normative structural and functional development of the brain.

Recent population-representative birth cohort study showed that adversity-related structural differences are evident across the entire brain, specifically in gray matter across cortical and subcortical structures (Gehred et al., 2021). However, it suggested that only the amygdala, hippocampus, and cerebellum show reductions when examining both retrospectively and prospectively reported adverse experiences. This might imply that the amygdala, hippocampus, and cerebellum are particularly vulnerable, showing consistent and robust reductions. A meta-analysis of published whole-brain voxel-based morphometry studies also demonstrated that the most consistent gray matter abnormalities in individuals exposed to childhood maltreatment are in prefrontal-limbic-temporal regions. (Lim et al., 2014) Further, the diminished structural integrity of the brain circuitries between fronto-limbic connections, involving the hippocampus, amygdala and prefrontal cortex, appears to be specifically compromised by adversities also in healthy controls (Quidé et al., 2024) (Lim et al., 2014).

Based on animal models, particularly the hippocampus, amygdala, corpus callosum, anterior commissure, cerebral cortex, cerebellum and hypothalamus have been shown to be affected by prenatal stress both macroscopically and microscopically (Charil et al., 2010). However, one meta-analysis on general population controls found only a modest association between childhood adversities and lower hippocampal total volumes, but no association with the amygdala volumes (Calem et al., 2017), while another suggested that hippocampal volume deficits from childhood maltreatment may not be apparent until adulthood (Woon & Hedges, 2008). Thus, childhood adversity is suggested to have a relatively minor influence on stress-related brain structures in individuals without significant mental health issues (Calem et al., 2017; Janiri et al., 2017; Teicher & Samson, 2013).

2.7.1 Morphology and function of amygdala and hippocampus in relation to childhood adversities

Earlier studies suggest a greater sensitivity to adversity and stress in those who develop psychiatric disorders (Aas et al., 2012; Calem et al., 2017; Lawson et al., 2017; Salokangas et al., 2021). Adverse experiences are damaging to the developing brain, particularly in children prone to schizophrenia, that are even more sensitive to the environmental stressors (Haidl et al., 2020; Loewy et al., 2019). Also, the temporal occurrence and number of stressful experiences is a critical factor in neurodevelopmental processes, particularly in the hippocampus and amygdala (Herzog et al., 2020) (Riem et al., 2015).

In first-episode psychosis, while the evidence supporting a relationship between increased childhood trauma and reduced total amygdala volumes is relatively robust, the association between childhood trauma and hippocampal volumes is less consistent and more variable (Aas et al., 2012). The hippocampus is the only known brain region where physiological neurogenesis continues into adulthood across mammalian species and in humans. This heightened plasticity, while beneficial for learning and adaptation, may also render the hippocampus more vulnerable to disturbances caused by environmental factors. Consequently, its significant neuroplasticity and neurogenesis ability could lead to increased susceptibility to negative influences, such as stress, trauma, or metabolic pressure (Lieberman et al., 2018) (Knight et al., 2022). In fact, already in subjects at an ultra-high risk for psychosis childhood trauma scores have been found to be positively correlated with rCBF values in the bilateral hippocampus and negatively associated with rCBF in the left prefrontal cortex, regions central in psychosis etiology (Allen et al., 2018).

Studies have demonstrated that hippocampal function is disrupted in psychotic states following early life stress (Borges et al., 2013) (Murphy et al., 2022), potentially due to the abnormal input from the basolateral amygdala (Kim & Diamond, 2002). The lateral nucleus of the amygdala shares strong connections with the CA1 subfield of the hippocampus, and both the CA1 and CA3 subfields appear to play central roles in modulating stress responses and influencing systemic glucose regulation, including HPA-activity (Lowry, 2002). Thus, beyond adversity-related structural effects, the hippocampus may be a primary region affected by deviant brain development relating to its dysfunction (Lipska et al., 1993) (Knight et al., 2022). This may be due to its high levels of neuroplasticity compared to other brain regions (Knight et al., 2022).

The amygdala is recognized for its significant involvement in emotion and motivation, playing an essential part in processing both fearful and rewarding environmental stimuli. Within the amygdala, information is transmitted from the lateral nucleus to the basal nucleus, which subsequently relays this information to the hippocampus, nucleus accumbens, prefrontal cortex, and other amygdala subnuclei

(Roozendaal et al., 2009). The lateral nucleus is involved in reward processing (Hiroi & White, 1991; Hsiang et al., 2014), fear conditioning, fear extinction processes (Duvarci & Pare, 2014; Pape & Pare, 2010), and valence attribution (Janak & Tye, 2015). These all relate to stress reactions, since stress amplifies fear conditioning by enhancing the negative valence attribution and solidifying fear memories, while it simultaneously impairs fear extinction, making it harder to suppress conditioned fear responses. Stress hormones like cortisol and norepinephrine increase activity in the amygdala, intensifying the fear learning process.

In schizophrenia patients, higher levels of sexual abuse and physical neglect during childhood have been found to associate with decreased connectivity between the amygdala and the posterior cingulate/precuneus region (Cancel et al., 2017). Further, especially BLA and its connections to PFC have been suggested to be vulnerable to stress. During adolescence, stress-related heightened activity in the basolateral amygdala may speed up the development of BLA-PFC plasticity (Uliana et al., 2021). This increased BLA activity could interfere with the two-way communication between the BLA and the medial prefrontal cortex (mPFC) following stress in adulthood, particularly in the models of schizophrenia. (Delavari et al., 2023; Uliana et al., 2021) Animal models of schizophrenia have stated that impaired fear extinction is further related to abnormalities in connectivity between the basolateral nucleus and medial prefrontal cortex (Uliana et al., 2018). Also, human research has shown that fear extinction is impaired in patients with schizophrenia and this impairment is related to abnormal medial prefrontal cortex activation (2012; Holt et al., 2009). The functional connectivity between the amygdala and prefrontal cortex have been noted to reduce only in early and chronic schizophrenia. (Anticevic et al., 2014). However, more specifically reduced communication between BLA and the frontal regions of the brain, and increased connectivity between the BLA and the hippocampus have been observed in patients with 22q11.2 deletion syndrome, a known genetic model for schizophrenia susceptibility (Delavari et al., 2023). Thus, the effects of excess stress and childhood adverse experiences may have subnucleus-specific effects on the amygdala subnuclei.

These results support the idea that the influence of childhood trauma on the risk of psychosis may be mediated through brain circuit dysfunction including both the amygdala and hippocampus.

2.7.2 Hippocampus and amygdala as central hubs in brain networks related to childhood adversities

Both genetic and environmental influences can lead to dysregulated connectivity within and between key brain networks, such as the default mode network (DMN),

salience network (SN), central executive network (CEN), and frontoparietal network (FPN), which may underlie symptoms such as hallucinations, delusions, and cognitive impairments in psychoses (Menon et al., 2023) (Manoliu et al., 2014).

The DMN comprises a number of brain regions, 'nodes', that exhibit correlated low-frequency activity at rest and are thought to play a role in processing information related to the self in regions including the hippocampus and prefrontal cortex (Menon, 2023). The SN comprises a group of brain nodes that are involved in detecting and responding to salient stimuli in the environment, which can include emotionally significant events or important changes in the surroundings. The key brain regions in the SN are the anterior insula, anterior cingulate cortex, but also prefrontal cortex and amygdala (Kowalski et al., 2021). The SN is involved in processing emotional information and linking it to motivational states, which can influence behavior.

The overall dysfunctions in brain networks of the DMN, SN, FPN and central executive network (CEN) have been associated with several disorders including schizophrenia, depression, anxiety, dementia and autism (Hardi et al., 2024; Menon, 2011; Menon et al., 2023). Also, in children who experienced multiple adversities, or only elevated maternal depression, had worse mental health and differences in DMN, SN and FPN functioning during adolescence (Bluhm et al., 2009; Hardi et al., 2024). Recent study (Mu et al., 2024) has suggested that the risk of schizophrenia is causally related to increases in the connectivity of the default mode and central executive network and to decreases in the connectivity of the broader attention network. In schizophrenia, dysregulation in the SN has been associated with the misinterpretation of external stimuli as significant or threatening, and thus to psychotic symptoms (Kowalski et al., 2021). Further, the SN plays a role in switching between the DMN and the CEN, and both the switching (Nekovarova et al., 2014) and SN functioning (Palaniyappan et al., 2012) are suggested to be disturbed in schizophrenia. Thus, in individuals with schizophrenia, abnormalities in these brain networks can manifest in various ways, influencing symptoms and functional outcomes, and are thought to relate to childhood adversities (Dauvermann et al., 2021).

To conclude, the hippocampus, prefrontal cortex, amygdala and insula are suggested to be important central hubs of the brain's functional and structural networks in relation to schizophrenia pathogenesis, but also in relation to early childhood adversities.

2.8 The effects of antipsychotic medication on brain morphology and function

Antipsychotic medications are the primary pharmacological treatment for managing psychotic symptoms in conditions like schizophrenia and other

psychotic disorders (Kaar et al., 2020). These medications effectively reduce positive psychotic symptoms, such as hallucinations and delusions (McCutcheon et al., 2021b). Over time, the continued use of these medications has been shown to lower the risk of relapses, rehospitalizations, and aggressive or suicidal behaviors, while also contributing to a reduction in the overall mortality in people with schizophrenia.

Studies on healthy rodents and nonhuman primates have shown that the chronic administration of antipsychotics reduce gray matter, particularly in the frontal and parietal regions (Dorph-Petersen et al., 2005; Guma et al., 2018; Vernon et al., 2011). The study on healthy rodents by Vernon et al. (2011) suggests that antipsychotic drugs exert a selective effect on the cortex, particularly the frontal cortex, while subcortical regions remain unaffected. Since previous studies on humans are mainly association studies, they identify correlations but do not establish direct causality. Also, caution should be applied when extrapolating results from animal studies to humans. However, a recent randomized controlled trial supports a causal relationship between antipsychotic use and a decrease in cortical thickness, at least in patients with psychotic depression (Voineskos et al., 2020).

2.8.1 Antipsychotic drugs and physiological features of brain function

In humans a number of longitudinal studies including studies in previously drug-naïve schizophrenia patients have demonstrated an association between cumulative exposure to antipsychotics and decreased gray matter volume, particularly in cortical gray matter (Fusar-Poli et al., 2013b; Ho et al., 2011), and more specifically in the temporal and frontal cortical thickness (S. Sun et al., 2023; van Erp et al., 2018; van Haren et al., 2011). The mechanisms behind these reductions are largely unknown.

Antipsychotics may influence neuroplasticity. (Konradi & Heckers, 2001) Neuroplasticity enables learning and memory, adaptation to new experiences, and recovery from brain injuries by reshaping the existing neural circuits, adjusting its structure, function, and connections in response to experiences, learning, or injury. This adaptability occurs throughout life, though it is generally more pronounced in childhood. Neuroplasticity changes may occur via synaptic pruning, changes in the levels of brain-derived neurotrophic factor (BDNF) (Hong et al., 2003; Huang, 2013), or through glutamate or striatal dopamine regulation involved in plasticity.

Neurotrophins play key roles in growth and differentiation during development as well as in plasticity and the survival of adult hippocampal and cortical structures. In schizophrenia, the effects of abnormal BDNF function are likely related to abnormal cortical development, that is more vulnerable to antipsychotic effects,

but further, BNDF function might also be linked to antipsychotic-related cortical thinning due to medication-specific effects (Fernandes et al., 2015). Indeed, there is evidence typical antipsychotics decrease BDNF levels, while second-generation antipsychotics maintain or increase serum BDNF levels (Favalli et al., 2012; González-Pinto et al., 2010). Thus, the reduced cortical thinning related antipsychotic drug use may relate to these factors and their combination, but the effect might be partly heterogenous based on the used antipsychotics (C. Wang et al., 2023). Particularly the chronic and cumulative use of antipsychotics may disrupt normal synaptic pruning processes, especially in vulnerable populations and at vulnerable neurodevelopmental stages, potentially leading to cortical thinning.

The effects of antipsychotic-related (AP-related) cortical thinning are suggested to depend on efficient mitochondrial function, adequate regional blood supply, functioning neurovascular coupling, and the ability to respond to oxygen demands (Turkheimer et al., 2020). Thus, there are suggestions that antipsychotics might push the cortex into an unsustainable metabolic envelope and increased state of oxidative stress, which would in turn lead to adaptive changes in the cortical morphology during treatment (Turkheimer et al., 2020). For example, regional cerebral blood flow (rCBF) measures obtained by PET showed that both drug naïve first-episode psychosis patients and healthy volunteers using a single dose of antipsychotics, had increased perfusion after their treatment with antipsychotics (Goozée et al., 2014). The changes in rCBF were observed particularly in the frontal and basal ganglia regions, but different antipsychotic generations had differential effects on rCBF. On the other hand, medicated patients have been observed to have frontal hypometabolism relative to controls, while metabolism in drug-free patients did not differ significantly from controls (Townsend et al., 2023). Further, another study found that administration of sertindole, a second-generation antipsychotic, was associated with higher metabolic rates in the dorsolateral prefrontal cortex, approaching normative levels, and lower metabolic rates in the orbitofrontal cortex compared to haloperidol, a first-generation antipsychotic (Buchsbaum et al., 2009). However, the relationship between these changes and treatment responses remains unclear.

To conclude, second-generation antipsychotics have heterogenous neurotrophic, metabolic and antioxidant effects, but collectively there is evidence that antipsychotic medication is associated with a thinner cortex, particularly in the prefrontal, occipital and temporal cortex.

2.8.2 Antipsychotic drugs and neurotransmitter systems

Antipsychotic drugs primarily exert their effects by interacting with various neurotransmitter receptors in the brain, particularly dopamine and serotonin receptors (Charron et al., 2015; de Bartolomeis et al., 2023; Schmidt et al., 1995). Additionally, many antipsychotics, especially second-generation ones, block H1–histamine receptors, leading to sedative effects, but also to increased appetite and weight gain. Some antipsychotics block muscarinic M1–receptors, which are involved in cognitive function and parasympathetic nervous system activity. The blockade of alpha-1–adrenergic receptors through antipsychotics results in sedation and orthostatic hypotension. Many second-generation antipsychotics, such as risperidone and olanzapine, are antagonists of 5-HT_{2A}, which is thought to contribute to their efficacy in treating both positive and negative symptoms of schizophrenia (Alvarez-Herrera et al., 2024) , while some second-generation antipsychotics can act as agonists of 5-HT_{1A} receptors. Also, second-generation antipsychotics predominantly act as antagonists or partial agonist at D_2–receptors, some may exhibit partial agonist activity, contributing to their varied therapeutic effects and side effect profiles. (Sykes et al., 2017) In many cases, second-generation antipsychotics have a higher affinity for these serotonin receptors compared to D_2–receptors. (Schmidt et al., 1995) In contrast, typical antipsychotics block dopamine D2–receptors. (Chokhawala & Stevens, 2025)

Earlier rodent studies have linked particularly typical antipsychotic-related cortical thinning to dopamine D2 receptors. (Guma et al., 2018). However, especially the interactions between dopamine and serotonin receptors are known to alleviate the positive symptoms of psychosis, such as hallucinations, delusions, and disorganized thinking, as well as negative symptoms, such as social withdrawal and flat affect. (McCutcheon et al., 2021b)

To conclude, while antipsychotics are effective in managing the psychotic symptoms of schizophrenia via several neurotransmitter systems. However, their impact on brain morphology is complex. Since previous studies on humans are mainly association studies, they identify correlations but do not establish direct causality. In schizophrenia, specific cortical inflammatory imbalances, metabolic alterations, oxidative stress, impaired neuroplasticity, and morphological changes are proposed as mechanisms underlying neurodevelopmental abnormalities and subsequent psychotic processes. These alterations, particularly in the prefrontal and temporal cortices, are considered potential therapeutic targets for antipsychotic treatments (Tendilla-Beltrán et al., 2021). However, it remains unclear whether the mechanisms of antipsychotic action are central to their therapeutic effects, clinical outcomes, side effects of antipsychotic medication, or a combination of these factors. Further, it is

unknown whether these regions are more susceptible due to some underlying molecular, vascular, physiological or functional features.

2.9 Psychotic disorders as systemic diseases

2.9.1 Metabolic system alterations

Some recent meta-analyses have shown that metabolic syndrome has a higher prevalence in schizophrenia patients (Hagi et al., 2021; Pillinger et al., 2019) (Mitchell et al., 2013b); worsening metabolic problems during the course of the illness also have been found (Mitchell et al., 2013a; Vancampfort et al., 2015). Similar findings regarding the higher prevalence of metabolic syndrome in bipolar disorder have been observed (Vancampfort et al., 2013). However, there is evidence of greater variability in the metabolic parameters of FEP relative to controls, suggesting possible different biotypes related to, i.e., clinical outcomes (Pillinger et al., 2023).

Some studies have also shown there is evidence of a slightly higher prevalence of metabolic syndrome already in unmedicated patients at risk for psychosis, including a higher blood pressure, increased waist circumference, and increased fasting blood glucose (Cordes et al., 2017). Also, the lipidome and proteome, of subjects who reported psychotic experiences at 18 years of age, have shown to be altered already at 12 years of age, indicating that metabolic dysregulation may contribute to an early vulnerability to psychotic experiences (Madrid-Gambin et al., 2019). There are also observations that the unaffected siblings of individuals with schizophrenia are already at a high risk for metabolic syndrome (Enez Darcin et al., 2015), and have signs of abnormal glucose metabolism and insulin signaling (Chouinard et al., 2019). Also, shared at-risk variants for both diabetes and schizophrenia have been observed (Hansen et al., 2011; Liu et al., 2013). Further, a potential shared role of inflammation in insulin resistance and schizophrenia has been found, with causal evidence (Perry et al., 2021a). Thus, inflammation might be a common factor linking insulin resistance and schizophrenia, offering potential new targets for treatment or prevention.

2.9.1.1 Introduction to the development systemic glucose metabolism disturbances in psychotic disorder

"*Diabetes is a disease which often shows itself in families in which insanity prevails*", wrote Henry Maudsley already in 1879 (Maudsley, 1879). Indeed, there are observations of glucose metabolism disturbances from the pre-neuroleptic era suggesting that schizophrenia itself might predispose individuals to abnormal

glucose metabolism (Kohen, 2004). Also, impaired systemic glucose homeostasis and insulin resistance have been observed already in the first episode of psychosis, both in patients using antipsychotic medication (Pillinger et al., 2020) and in drug-naïve patients (Enez Darcin et al., 2015; Greenhalgh et al., 2017; Petrikis et al., 2015). Especially the dysregulation of systemic glucose metabolism appears to be pronounced in psychotic disorders already in the early phase of the illness.

There is inconsistent evidence of marked insulin changes during childhood and adolescence in individuals with a later diagnosis of schizophrenia-spectrum disorder by the age of 40 (Perry et al., 2021b; Sormunen et al., 2022). On the other hand, higher fasting insulin level trajectory from mid-childhood has been associated with a psychosis at-risk mental state and psychotic disorder, but not depression, in the population, with the onset occurring by the age of 24 (Perry et al., 2021b). Since puberty is a time of considerable normative metabolic and hormonal changes, particularly with a marked decrease in insulin sensitivity that recovers at puberty completion (Kelsey & Zeitler, 2016), it is possible, that this recovery is either not completed, or not implemented correctly in psychotic disorders. This might partly explain abnormalities in insulin resistance observed at the prodromal phase and further the psychotic disorders. In the study by Sormunen et al (2022) the insulin was not measured clearly above the pubertal age, and the prodromal periods could not be defined, and additionally, Perry et al (Perry et al., 2021b) studied early-onset psychoses where the CHR stage overlaps with the last data point measurements. Based on these findings, it remains unclear whether insulin resistance in psychotic disorders is more closely associated with incomplete recovery from pubertal insulin resistance, neurodevelopmental disruptions in metabolic trajectories, or whether is primarily linked to the initiation of the high-risk state, or all of these. Also, the disrupted insulin sensitivity observed from mid-childhood associating with adult psychosis, might also be a marker of a specific biotype of the psychotic disorder with early glucometabolic alterations (Perry et al., 2021b).

2.9.1.2 Central systemic glucose metabolism regulation

The systemic metabolism and brain metabolism are intricately related, as they both depend on the body's overall metabolic processes. The brain glucose delivery seems to be dependent on plasma glucose and cerebral blood flow. However, brain regions with heterogeneous cell composition and cell-type-specific profiles of glucose metabolism suggest that metabolic networks within the brain are complex (Claassen et al., 2021; S. Zhang et al., 2021).

Glucose homeostasis is achieved through a complex interaction between glucose detection systems and various processes that respond to changes in metabolism. The brain receives metabolic signals from organs like the liver, pancreas, fat tissue, gut,

and muscles. Specialized neuronal networks in the brain coordinate adaptive changes in response to altered metabolic conditions (Roh et al., 2016). In healthy individuals, the body closely controls food intake and energy use through homeostatic processes to maintain a stable energy balance. Substantial evidence indicates that the brain, particularly the hypothalamus, is primarily responsible for the regulation of energy homeostasis. (Pan et al., 2023) (Herrera Moro Chao et al., 2022) (Morton et al., 2014) (Huang et al., 2022) (Yoon & Diano, 2021) (Benzo, 1983) Further, the growing evidence suggests that especially the hypothalamus and brainstem play a role in directly controlling blood glucose levels. Energy balance is also strongly influenced by various hormone systems, such as the hypothalamic-pituitary-thyroid–axis (Cheng et al., 2023), the hypothalamic-pituitary-gonadal–axis, and the hypothalamic-pituitary-adrenal–axis (Bose et al., 2009) (Janssen, 2022). A key common link among these systems is their regulation via the hypothalamus (Dumbell, 2022).

A direct measure of insulin resistance has been observed to be associated with reduced hippocampal total volume in non-psychotic adults, suggesting the role of the hippocampus in central glucose regulation, and/or bidirectional effects in healthy individuals (Frangou et al., 2022). Evidence on the role of insulin signaling within the amygdala and hippocampus, in systemic glucose homeostasis, has been suggested (Soto et al., 2019). On the other hand, hyperglycemia has been shown to alter the synaptic function and cause neuronal loss in the CA1 and CA3 subfields of the hippocampus, as observed in some studies on diabetic rats. (Kamal et al., 1999) (Sima et al., 2004), although these studies did not investigate the hippocampal tail. This bidirectional relationship might create a self-perpetuating cycle. Thus, the possible developmental defects in these subfields, possibly starting from CA1, might be related to the development of dysregulation of both direct central glucose metabolism regulation pathways but also indirectly via HPA–axis regulation, in patients who develop psychosis.

To conclude, the hypothalamus is one of the core structures in the central regulation of systemic glucose metabolism, either solely, or via the HPA-axis, or both. Moreover, the roles of the hippocampus and amygdala in glucose homeostasis have been suggested. The simplified illustration of plausible central regulation patterns of peripheral glucose homeostasis via the HPA-axis, hippocampus-amygdala-PFC-complex, liver, pancreas and gut-brain-axis, is presented in **Figure 4.**

2.9.1.3 Insulin signaling in psychoses

Dysfunctional insulin signaling at the molecular level is frequently implicated in the pathogenesis of systemic insulin resistance. The hippocampus, amygdala,

hypothalamus, midbrain dopamine neurons (Figlewicz, 2016), striatum, cerebral cortex, and cerebellum are widely distributed with insulin receptors in rodents (Agarwal et al., 2020; Hopkins & Williams, 1997; Kleinridders et al., 2014). It has been suggested that central nervous system concentrations of insulin are proportional to circulating plasma insulin levels (Schwartz et al., 1990; Strubbe et al., 1988), and systemic insulin resistance has been observed to significantly affect brain glucose metabolism (Chen et al., 2022). Human studies suggest that insulin enhances glucose metabolism in the brain, especially in regions like the ventral striatum, prefrontal cortex, amygdala, hippocampus, and cerebellum (Anthony et al., 2006; Bingham et al., 2002). Thus, insulin resistance suggests a reverse effect and reduction in brain glucose metabolism in these regions.

Insulin-like growth factor 1 (IGF-1) is involved in metabolic processes and can modulate insulin sensitivity and glucose metabolism, thought it plays broader roles in the growth, development, and the functioning of various organs, including the brain. The 'IGF-1 deficiency hypothesis' of the schizophrenia pathogenesis suggests that reduced levels or impaired function in IGF-1 may play a critical role in the development of schizophrenia, however, the timeline and mechanisms are inconclusive (Gunnell & Holly, 2004). Insulin receptor/IGF1R -deletion in both the hippocampus and amygdala have shown to lead to impaired glucose tolerance in mice (Soto et al., 2019). In the hippocampus, this appears to be due to a combination of systemic insulin resistance and a decreased insulin secretion (Soto et al., 2019). However, while insulin signaling is suggested to regulate both central and peripheral glucose metabolism (Agrawal et al., 2021; Kullmann et al., 2020), the interplay between central and peripheral glucose metabolism is complex even in the normative physiological context. Therefore, further studies are needed to explore this relationship in psychotic disorders.

Regarding psychotic disorders, the abnormalities in insulin signaling may be intrinsic, meaning it could exist independently of external factors such as medication or lifestyle, potentially arising from the underlying neurobiological alterations characteristic of psychotic disorders (Agarwal et al., 2020). A recent study (Lee et al., 2024) suggests, that hypothalamic and hippocampal insulin resistance may already overlap with psychotic disorders during the first episode via pathways of inflammation, endoplasmic reticulum stress (Cai et al., 2020), which is related to cell apoptosis, and neuroplasticity. Further, it has been found that CNS (central nervous system) insulin can regulate striatal dopamine levels by increasing dopamine reuptake acutely but downregulating it chronically (Nash, 2017). On the other hand, the short-term antagonism of dopamine D_2-receptors via antipsychotics increases insulin secretion (Lopez Vicchi et al., 2016; Nash, 2017). Also, both CNS insulin and striatal dopamine can regulate peripheral glucose homeostasis (Agarwal et al., 2020; Heni et al., 2014; Ter Horst et al., 2018).

These results would suggest that prolonged insulin activity and increased insulin sensitivity would lead to lower dopamine levels in the striatum, and further psychotic symptom remission. Therefore, bidirectional insulin action may play a crucial role in understanding the onset of first psychosis, the pathophysiology of schizophrenia, and the development of new therapeutic approaches (Agarwal et al., 2021).

2.9.2 Stress system

The stress system involves a combination of functions from multiple systems, including the nervous system, endocrine system, immune system and the enteric nervous system. These systems work together to handle acute and chronic stress, maintaining the body's balance. The HPA-axis is the core component of the neuroendocrine system, which is crucial for responding to stress. HPA-axis is essential for controlling the body's stress response by regulating several physiological processes, including metabolism, immune function (Palma-Gudiel et al., 2021), and emotional responses. Alterations in the HPA–axis, relating to both glucose metabolism and stress regulation, have been observed in psychotic disorders (Belvederi Murri et al., 2016; Berger et al., 2016; Girshkin et al., 2014; Myers et al., 2021; Pillinger et al., 2017; Pillinger et al., 2019; Roh et al., 2016).

Psychological stress is common in many physical illnesses and is increasingly seen as a risk factor for disease onset and progression (Hackett & Steptoe, 2017). There is also evidence childhood adversity may relate to latent stress vulnerability in adulthood (Clemens et al., 2020; Simon & Admon, 2023). A dysfunctional HPA-axis may further contribute to these associations (Burghy et al., 2012; Li et al., 2015), particularly in psychoses, in relation to heightened stress sensitivity and higher levels of childhood adversities. Chronic stress can further lead to the overactivation of the HPA–axis (Knezevic et al., 2023).

Earlier studies suggest the severity of the early maltreatment may be related to the basal cortisol pattern (van der Vegt et al., 2009). Activation of the autonomic nervous system and HPA–axis during stress leads to increased plasma glucose availability through hormonal changes. Also, chronic stress can result in insulin resistance and impaired glucose regulation. (McEwen, 2017; Yaribeygi et al., 2022) Understanding this relationship is essential for addressing stress-related phenomena, particularly in the context of psychotic disorder, as it pertains to both abnormal glucose metabolism and a dysregulated HPA-axis (Soeters & Soeters, 2012).

Alterations in the HPA-axis function in psychotic disorders are likely related to disturbances in stress responses and stress sensitivity, as well as disturbances in the regulation of glucose metabolism. These alterations may partly develop during neurodevelopmental stages leading to both glucose metabolism and stress system regulation vulnerability (**Figure 1 and Figure 12**).

2.9.2.1 Altered HPA-axis and stress responses in psychotic disorders

While regulating stress, HPA–axis activates a hormonal cascade of corticotropin (CRH)–adrenocorticotropic hormone (ACTH)–cortisol, enabling the body to respond to stress by mobilizing the body, energy and other resources, known as the fight or flight state. Cortisol prepares the body to deal with stress by increasing blood glucose levels, suppressing non-essential functions, such as digestion and reproduction, to focus on the stressor, but also modulating immune function to prevent inflammation. When the stress subsides, the system self-regulates to restore balance through a negative feedback loop.

Emerging evidence indicates that the hormonal and autonomic pathways relating to the hypothalamus may be disrupted in both schizophrenia and bipolar disorder (Ruggeri et al., 2024). Regional-specific alterations in hypothalamic subunit volumes have been observed, particularly the smaller paraventricular, supraoptic, medial, and lateral mammillary nuclei in schizophrenia compared to controls, with no such changes observed in bipolar disorder (Ruggeri et al., 2024). These results have relevance to HPA-axis dysregulation, circadian rhythm disruption, and cognition impairment particularly in schizophrenia. In contrary, an earlier study observed larger anterior hypothalamus volumes, including the paraventricular nucleus (PVN) and mamillary body nuclei, in schizophrenia patients and nonpsychotic relatives, respectively (Goldstein et al., 2007).

HPA-axis function is measured through various tests, including the combined dexamethasone and corticotrophin-releasing hormone (dex/CRH) test, the dexamethasone suppression test, and basal cortisol level measurement. The first two tests represent the dynamic function of the HPA-axis, while the latter assesses its static state. The HPA-axis hyperactivity and a blunted HPA-axis response to stress is suggested to be present already at the onset of psychosis (Borges et al., 2013). Earlier meta-analyses have found increased morning cortisol levels in individuals with both schizophrenia and bipolar disorder, but also in those transitioning to psychosis (Girshkin et al., 2014; Walker et al., 2013). In schizophrenia, there is evidence of an attenuated cortisol awakening response (CAR) reflecting dysfunctional HPA-axis (Belvederi Murri et al., 2016). Also, in high-risk children with a family history of illness, a blunted CAR has been observed relative to healthy controls (Cullen et al., 2014). However, another meta-analysis found an attenuated CAR in FEP, but not in psychosis risk states (Misiak et al., 2021). One study found that people with bipolar disorder, both remitted and non-remitted patients, had a significantly greater cortisol response to the dex/CRH-test compared to healthy individuals, suggesting that their HPA–axis is dysregulated (Watson et al., 2004).

These findings suggest that certain abnormalities in the HPA–axis associated with psychosis occur before the onset of the illness reflecting neurodevelopmental

origins, possibly reflecting the trait-like characteristics of heightened stress sensitivity, that is in line with the stress-vulnerability model.

2.9.2.2 Hippocampus, amygdala and prefrontal cortex regulate HPA-axis function

There is a well-established relationship between the prefrontal cortex (PFC), amygdala, hippocampus, and the hypothalamic-pituitary-adrenal axis, of which detailed connections studied mainly in animal studies (Herman et al., 2005; Kamali et al., 2023; Kim et al., 2024). In relation to the HPA-axis function, particularly the prefrontal cortex and hippocampus (Bang et al., 2022), via the bed nucleus of the stria terminalis (BNST) in the rostral amygdala, are the key regions that inhibit the HPA-axis, while the amygdala is generally associated with the activation of the HPA-axis.

The PFC (Rempel-Clower & Barbas, 1998; Sullivan & Gratton, 2002), anterior cingulate cortex (ACC), and insular cortex modulate the HPA-axis through indirect pathways that typically involve the amygdala, hippocampus, and BNST. The BNST acts as a relay station for integrating emotional and stress-related information from the hippocampus and amygdala to the hypothalamus (Lee & Davis, 1997). These structures then relay the information to the PVN of the hypothalamus, which is the primary output center for HPA-axis activation. The PFC is particularly crucial in maintaining homeostasis by preventing excessive or maladaptive reactions to stressors (**Figure 4**).

2.9.2.3 Hippocampal subfield defects of in HPA–axis dysregulation

The hippocampus provides negative feedback to the HPA–axis by inhibiting its activity, particularly after the stressor has passed, helping to return the body to a normal state (Bang et al., 2022). High levels of cortisol over long periods, chronic stress, can damage the hippocampus (Kim & Diamond, 2002), reducing its ability to control the HPA-axis, which can lead to prolonged stress responses. There is inconsistent evidence of the association between reduced hippocampal volume and an attenuated cortisol awakening response as well as the diurnal cortisol level, that might be markers of increased stress vulnerability in first-episode psychosis patients (Gunduz-Bruce et al., 2007; Mondelli et al., 2010; Pruessner et al., 2015), highlighting the role of the hippocampus in the HPA-axis function.

The ventral hippocampus sends many indirect projections through the BNST to the PVN, but a few direct projections to the PVN (Cole et al., 2022). More specifically, hippocampal inputs to the hypothalamus arise mainly from the subiculum and CA1 regions of ventral hippocampus.(Cenquizca & Swanson, 2006;

Kishi et al., 2000). These connections further inhibit the HPA-axis function. Previous studies on rodents have shown that lesions in the ventral hippocampus, including the ventral subiculum and CA1, lead to increased neuroendocrine responses to psychological stress and raise the expression of corticotropin-releasing factor mRNA in the PVN of the hypothalamus, highlighting the role of subiculum and CA1 in stress regulation (Cenquizca & Swanson, 2006; Kishi et al., 2000). However, the detailed connections of hippocampal CA1 are complex (Cenquizca & Swanson, 2007).

On the other hand, hyperglycemia induces changes in the synaptic function and neuronal loss particularly in the CA1 and CA3 subfields, in the studies on diabetic rats (Biessels et al., 1996; Hao et al., 2019; Kamal et al., 1999; Sima et al., 2004), while stress has also been implicated in morphological changes and reductions in dendritic spine density within the subiculum, CA1, CA3, and dentate gyrus (Belujon & Grace, 2011; Conrad, 2006; Steullet et al., 2010). The effects on the hippocampal tail were not investigated in these studies. These alterations in morphology might further deteriorate the ability of the hippocampus to regulate the HPA-axis.

These findings highlight the bidirectional effects between the hippocampal morphology, function and HPA-axis activity.

2.9.2.4 Amygdala subnuclei defects in HPA-axis dysregulation

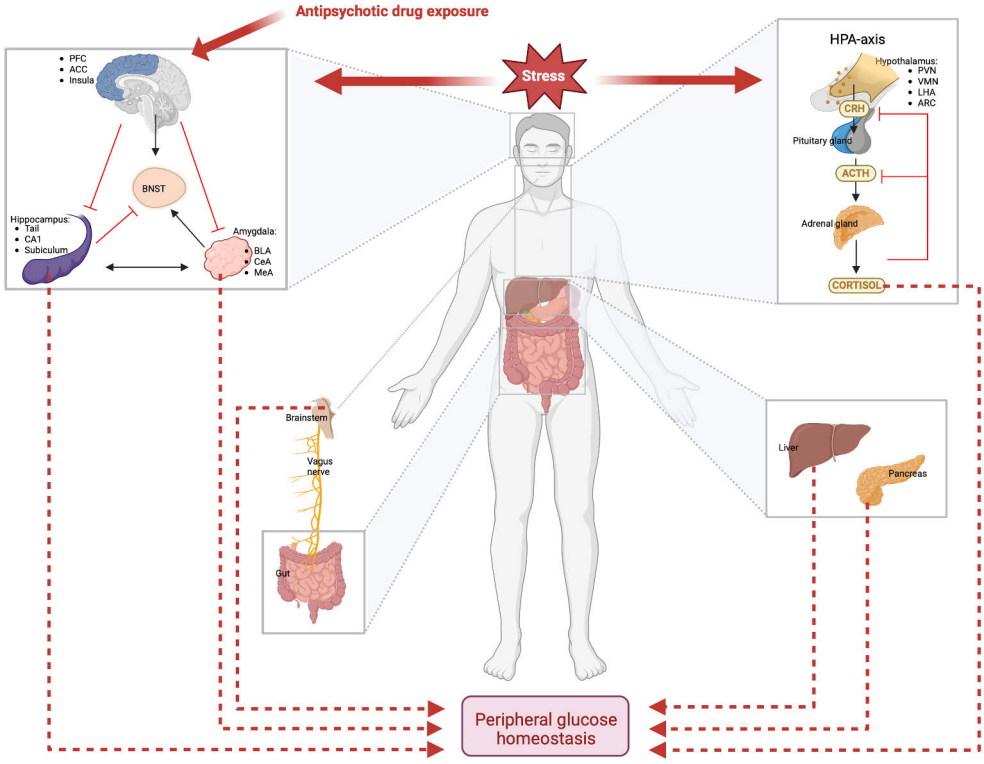
The amygdala is involved in processing emotional responses, especially fear and stress (see Chapter 2.7). It activates the HPA-axis when the brain perceives a threat, triggering the release of stress hormones by HPA-axis response (Herman et al., 2005). The activity of amygdala is balanced by inputs from both the hippocampus and the PFC, as noted above.

The BLA receives strong innervation from the thalamus, hippocampus, and medial prefrontal cortex (Stamatakis et al., 2014), and further targets the downstream structures such as the BNST in rostral amygdala. All these regions are important for processing and coordinating sensory and emotional information related to stress and fear. (Maita et al., 2021; Stamatakis et al., 2014) The BLA, both independently, and in interaction with the PFC, help modulate the HPA-axis function (Reppucci & Petrovich, 2016).

The BLA is involved in higher-order emotional processing and helps modulate how the amygdala integrates stress-related information and influences HPA activity. The BLA influences stress responses particularly by sending signals to other regions such as the central nucleus of the amygdala (CeA), BNST, and PFC (Whalen & Phelps, 2009). The CeA is also an activator of the HPA–axis, primarily through indirect pathways via BNST to the PVN (Maita et al., 2021). The CeA is a primary output region for fear and stress-related signals. The medial nucleus of the amygdala

(MeA) plays a key role in innate emotional behaviors by relaying olfactory information to hypothalamic nuclei involved in reproduction and defense (Keshavarzi et al., 2014). Though less studied, it also has connections to the BNST and hypothalamus. The MeA may contribute to autonomic and hormonal responses to stress. However, the CeA–BNST–PVN pathway is one of the main routes through which the amygdala influences HPA-axis activation in response to fear, anxiety, and stress.

To conclude, particularly the prefrontal cortex, hippocampus, and BNST are the key regions that inhibit the HPA-axis, while the amygdala is generally associated with the activation of the HPA-axis. Further, specific regions such as the basolateral amygdala, central nucleus of amygdala, and CA1 and subicular subfields of the hippocampus—in interaction with the PFC—modulate the HPA–axis function. Indirect inhibitory control is achieved via these connections, primarily through PFC regulation. These findings highlight that several brain regions linked to schizophrenia, particularly those involved in emotion and cognition, contribute to the complex regulation of the HPA-axis and further stress reactivity and related hormonal and metabolic changes (**Figure 4 and Figure 12**).



◄ **Figure 4.** Simplified illustrations of the interacting regulatory organs involved in glucose homeostasis under the influence of environmental stressors and antipsychotic drug exposure at the onset of first-episode psychosis. The plausible bidirectional regulatory loops are illustrated only from the perspective of upstream central systemic glucose regulation. Interactions between the systems have not been illustrated. In psychotic disorders both the disorder and external factors, such as childhood adversities and later antipsychotic exposure, may affect the brain regions regulating glucose homeostasis. Especially paraventricular nucleus (PVN), ventromedial nucleus (VMN) and lateral hypothalamic area (LHA) in hypothalamus might be important in processing the brain-liver (O'Hare & Zsombok, 2016) conncetion, but based on recent rodent study, also brain-pancreas (Faber et al., 2020; Papazoglou et al., 2022) connection, that further regulate insulin secretion and affect peripheral glucose homeostasis. Another way for the brain to maintain glucose homeostasis is by the modulation of pancreatic islet function via the dorsomedial (Huang et al., 2022) and dorsolateral hypothalamus and, i.e., the dorsal vagal complex of the brainstem. Plasma insulin levels are altered rapidly by various perturbations that disrupt normal activity of these brain–liver and brain-pancreas connections (Jo & Chua, 2013; Mirzadeh et al., 2022). Particularly the prefrontal cortex (PFC), hippocampus, and bed nucleus of the stria terminalis (BNST) are the key regions that inhibit the HPA-axis, while the amygdala is generally associated with the activation of HPA-axis, that further affect glucose homeostasis. Specific regions such as the basolateral amygdala (BLA), central nucleus of amygdala (CeA), medial nucleus of the amygdala (MeA), and CA1 and subicular subfields of the hippocampus—in interaction with the PFC—are suggested to modulate the HPA-axis function. Indirect inhibitory control is achieved via these connections, primarily through PFC regulation. The PFC exerts its influence primarily through indirect projections to the paraventricular nucleus (PVN) of the hypothalamus via intermediaries such as the bed nucleus of the stria terminalis (BNST), hippocampus, and amygdala. Also, the gut–brainstem connections, via the vagus nerve, are suggested to be important mediators in the regulation of blood glucose levels (Borgmann & Fenselau, 2024). The hypothalamus is one of the core structures in the central regulation of systemic glucose metabolism, either solely, or via the HPA-axis, or both, and the roles of hippocampus and amygdala in glucose homeostasis have been suggested. Key cortical areas that contribute to HPA-axis regulation include the PFC, insular cortex, and anterior cingulate cortex (ACC). CRH = corticotropin, ACTH = adrenocorticotropic hormone. Created by the author with BioRender.com.

2.9.3 Immune system

Several lines of research support immune system dysregulation in psychotic disorders. There is evidence that infections and traumas of the central nervous system during childhood and adolescence, are related to the risk of schizophrenia (Cheslack-Postava & Brown, 2022; Sutterland et al., 2015; Xiao et al., 2009; Zhang et al., 2018). Also, the prevalence of autoimmune diseases in schizophrenia is higher (Y. Cao et al., 2023). In addition, there is also genetic support for immune dysregulation in schizophrenia, i.e., shared genetic loci between blood cell counts and schizophrenia (Astle et al., 2016; Corvin, 2014; Steen et al., 2023). While the role of the immune system in schizophrenia has been increasingly explored, it has not yet been conclusively proven (Birnbaum & Weinberger, 2020).

Based on previous meta-analyses, alterations in C-reactive protein levels, lymphocytes and further pro-inflammatory and anti-inflammatory cytokine levels have been observed in schizophrenia (Fernandes et al., 2016; Miller et al., 2011;

Miller et al., 2013; Zhou et al., 2021). There are also similarities in the pattern of cytokine alterations in schizophrenia, bipolar disorder and MDD during the acute and chronic phases of illness (Goldsmith et al., 2016; Wang & Miller, 2018), which may be related to shared vulnerability factors of the immune system between these mental disorders. Inflammatory cytokines have also been shown to be altered already in individuals at clinical high-risk for schizophrenia (Goldsmith et al., 2019; Karanikas et al., 2017; Ouyang et al., 2022; Zeni-Graiff et al., 2016), and in FEP (Laurikainen et al., 2020). These results suggest the different state- and trait-like alterations of immune system function before and near the onset of the psychotic episode.

2.9.4 Brain-gut–axis

The gut-brain axis is a bidirectional functional system composed of the gut microbiota, the immune system, the enteroendocrine system, the enteric nervous system, and the central nervous system (Carabotti et al., 2015). The microbiota and the brain interact through multiple pathways, through the tryptophan metabolism, immune system, the vagus nerve, and the enteric nervous system (Ahmed et al., 2022; Loh et al., 2024; Morais et al., 2021). The gut microbiota regulate the production, transportation, and functioning of neurotransmitters, such as glutamate, GABA, serotonin, and dopamine, in healthy population (Strandwitz, 2018) but this regulation may altered in psychiatric and neurodegenerative diseases (Chen et al., 2021; Strandwitz et al., 2019). Microbial influence particularly on tryptophan metabolism (Gao et al., 2020), and particularly the serotonergic and GABAergic systems are suggested to be important factors in gut-brain–axis dysfunction already at the first episode of schizophrenia (Wang et al., 2024). Also, dysbiosis has been demonstrated in patients with drug-naïve first-episode schizophrenia (Schwarz et al., 2018; Yuan et al., 2022). It is suggested the microbiota is important for the normal development and maintenance of brain function (Obata & Pachnis, 2016; Sharon et al., 2016). On the other hand, the developing serotonergic system may exhibit heightened susceptibility to variations in microbial colonization patterns prior to the establishment of a stable, adult-like gut microbiota (Clarke et al., 2014; O'Mahony et al., 2015).

Also, gut microbial balance and the intestinal barrier integrity have been found to relate to worse systemic insulin resistance in mice (Gueddouri et al., 2022). Moreover, the gut microbiota has been associated with the development of obesity, metabolic syndrome, and the onset of type 2 diabetes, primarily through mechanisms involving reduced glucose tolerance and increased insulin resistance (Iatcu et al., 2021). Further, stress has a profound influence on the microbiota and gut-brain axis

across various stages of life (Cryan et al., 2019), and there is evidence of a crosstalk between the HPA-axis and the gut-brain axis (Misiak et al., 2020).

To conclude, altered gut microbiota and a dysfunctional gut-brain axis are associated with HPA-axis dysregulation, insulin resistance, and alterations in neurotransmitter production and function—particularly serotonin—all of which are interlinked factors observed in psychotic disorders.

3 Objectives of the study

This thesis aims to narrow the knowledge gaps concerning specific brain morphological changes in early psychosis in relation to environmental and systemic stressors, such as the deterioration of glucose metabolism and childhood adversity, but also in relation to antipsychotic drug use.

The objectives were as follows:

1. To investigate amygdala subnuclei volumes and their association with clinical parameters, such as childhood adverse experiences, symptoms, antipsychotic drug exposure, and duration of illness, in first-episode psychosis, clinical high-risk patients and population controls.

2. To examine hippocampal subfield volumes and their associations with fasting plasma glucose metabolism measures and antipsychotic exposure in first-episode psychosis, clinical high-risk patients, and population controls. A longitudinal research design was utilized in analyses concerning hippocampal morphometry and outcome measures, such as functioning, remission, and transition.

3. To explore the effects of lifetime antipsychotic exposure on the cortical thickness, and investigate related molecular, physiological and functional mechanisms in the Turku discovery sample of first-episode psychosis and individuals at clinical high-risk for psychosis. These analyses were replicated using independent data from a large Enhancing NeuroImaging Genetics through Meta-Analysis -consortium (ENIGMA) meta-analysis on schizophrenia patients.

4 Materials and Methods

4.1 Study subjects

All study protocols were approved by the Ethics Committee of the Hospital District of Southwest Finland and the studies were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their participation in the study. The subjects for Studies I-III were recruited through the VAMI-project (Vakavien Mielenterveyshäiriöiden etiologia ja hoito – research program; The Etiology and Treatment of Severe Mental Health Disorders – research program).

FEP and CHR individuals were recruited from psychiatric services of the Turku City Psychiatric services (fused with the Hospital District of Southwest Finland in 2017). The general population control group was recruited from the same geographic area using a random sample of the national population register. DSM-IV Axis I diagnoses were confirmed using the Structured Clinical Interview for DSM-IV disorders (SCID-I/NP). The follow-up time transition to psychosis in CHR was defined with SCID-I/NP, conducted at the follow-up timepoint. The included diagnoses of the FEP are listed in **Table 3**. Approximately 50% of the patients had a baseline diagnosis within the schizophrenia spectrum in Studies I-III. In this study we excluded organic and substance-induced psychoses. The clinical high-risk status of all subjects in Studies I-III were assessed using the structured interview for prodromal syndromes (Miller et al., 1999).

Participants who did not meet the criteria for a psychotic disorder were further evaluated for one of three psychosis-risk syndromes: 1) brief intermittent psychotic symptoms psychosis-risk syndrome, 2) attenuated psychotic symptom psychosis-risk syndrome, or 3) genetic risk and deterioration psychosis-risk syndrome, based on the SIPS criteria in the 3.0/5.0 version of the Structured Interview for Prodromal Syndromes (SIPS/SOPS). The presence of any one of these syndromes classified individuals as being in the clinical high-risk group.

Table 3. Diagnoses of the study group of the first episode of psychosis, and the subgroups of affective, non-affective psychoses, and schizophrenia spectrum disorders (in italics) according to DSM-IV. Sample sizes are drawn from Study II.

Diagnoses of non-affective psychoses	**Number of diagnoses**
Schizophrenia	8
Schizophreniform disorder	18
Schizoaffective disorder	4
Brief psychotic disorder	5
Delusional disorder	4
Psychosis not otherwise specified	17
Diagnoses of affective psychoses	
Bipolar disorder with psychotic features	13
Major depressive disorder with psychotic features	9

4.1.1 Study I

The intent-to-study groups consisted of age- and sex -matched 86 first-episode psychosis patients (FEP), 56 clinical high-risk patients (CHR), and 87 population controls (CTR) between 18 and 50 years of age. Population controls were excluded if they had a history of a psychotic disorder or a current psychotic disorder, or a first-degree relative with a psychotic disorder. Seven controls had a diagnosis of a non-psychotic axis-I DSM-IV disorder. The exclusion criteria were: 1) intelligence quotient (IQ) under 70, 2) somatic or neurological illness possibly affecting the brain structure or function, 3) previous head injury with loss of consciousness for over five minutes, 4) alcohol or illicit drug dependence during the preceding six months, 5) coincidental MRI findings in a clinical neuroradiological assessment, 6) visible motion artifact in T1-scan, and 7) failed segmentation. One patient was excluded due to the lateral nucleus outlier volume based on standard residuals and Cook's distance. After the exclusions, the final sample comprised 75 first-episode psychosis patients, 45 clinical high-risk patients, and 76 population controls.

4.1.2 Study II

The intent-to-study groups consisted of age- and sex -matched 88 FEP, 56 CHR, and 96 population controls between 18 and 50 years of age. The exclusion criteria were same for Studies I-III. One control participant was excluded due to a CA3 volume being a statistical outlier, and one patient was excluded due to the whole hippocampus volume being a statistical outlier, based on standard residuals and

Cook's distance. Additionally, individuals who did not attend laboratory assessments, those diagnosed with diabetes mellitus, and those whose laboratory samples were affected by hemolysis were excluded from the glucose metabolism-related analyses. The final baseline sample comprised 78 first-episode psychosis patients, 48 clinical high-risk for patients for psychosis patients and 83 randomly selected general population controls of similar age and sex. At the follow-up, the number of retained participants in each group were 34 FEPs, 23 CHRs, and 53 CTRs.

4.1.3 Study III

4.1.3.1 Early psychosis – Turku discovery sample

The intent-to-study group consisted of age- and sex-matched 87 FEP and 56 CHR between 18-50 years of age. The exclusion criteria were same for all three studies. Further, one CHR patient was excluded for having incomplete records of past antipsychotic use. In total 131 individuals were included in the final discovery sample.

4.1.3.2 Schizophrenia – ENIGMA replication sample

The results from the discovery sample were analyzed for replication using data from a large meta-analysis (N≥2168) conducted by the ENIGMA Consortium on cortical thickness in schizophrenia (van Erp et al., 2018*)*. The independent ENIGMA sample consists of more chronic schizophrenia (population DOI = 10.5). The mean age of the ENIGMA sample was 32.3 years.

4.2 General methodology

4.2.1 Magnetic resonance imaging protocols

Tissues in the human body contain free hydrogen nuclei, protons. In different tissues, such as fluid, fat, and muscle, these protons exist in varying magnetic environments. In magnetic resonance imaging, these differing properties of tissues are highlighted using distinct pulse series, known as sequences. Magnetic resonance imaging (MRI) is intended to enhance tissue contrast in the images, providing significantly better soft tissue resolution compared to techniques like computed tomography (CT) or X-rays.

MRI is based on the behavior of proton spins in a strong magnetic field. In a strong external magnetic field, proton spins align either with or against the direction

of the external field. Out of the millions of spins, a slightly larger number aligns parallel with the external primary magnetic field, resulting in a net magnetization vector of the spins, known as longitudinal magnetization, which is oriented in the same direction as the primary magnetic field. The protons also rotate, or "precess," at a frequency known as the Larmor frequency, given by the formula $f = \gamma \times B_0$, where B_0 is the magnetic field strength and γ is the gyromagnetic ratio. This frequency depends on the strength of the magnetic field, and in a 3-tesla magnetic field, it is approximately 127.74 MHz. The tesla is the unit of measurement for magnetic field strength, also referred to as magnetic flux density. The T1-weighted image formation is presented in **Figure 5**.

T1-weighting is the most used imaging technique when assessing structural contrast in anatomical images. Images are termed T1-weighted when the contrast is primarily derived from tissue-specific T1-relaxation times. In addition to relaxation times, the relative proton density also influences the contrast. In T1-weighted images, the fluid appears black, gray matter is represented in dark gray, and white matter appears light gray. The weighting of the imaging sequence can be adjusted to T1 by modifying the TR and TE times (TR, time to repeat; TE, time to echo). T1-weighted images can be obtained using either gradient echo-based or spin echo-based sequences for image formation. In this study, a gradient echo-based T1-weighted sequence was utilized. In a T1-weighted gradient echo-based sequence, refocusing is achieved using gradients. Refocusing refers to the restoration of spin phase coherence, which enables the generation of the echo signal used for image formation (Chavhan, 2022).

In our studies (I-III), a 3D T1 sequence was used to visualize brain structures. All subjects were scanned with a Philips Ingenuity TF 3-T PET MR scanner using T1-weighted (Ultrafast Gradient Echo 3D, TR-time 8.1 ms, TE-time 3.7 ms, flip angle 7°, Field of View (FOV) 256 × 256 × 176 mm3 and voxel size 1 ×1 × 1 mm3) sequence. The T1-weighted images were inspected for motion during the scan session and sequences were repeated when excessive motion was present. Quality control, to detect motion artifacts and tissue misclassifications, was done by visual inspection for all T1-weighted images and according to datasets to all segmented cortex, hippocampus, and amygdala in the coronal, axial and sagittal planes by R.-L.A. Reconstructed cortical surfaces were manually corrected and reprocessed as needed by R.-L.A. All MRI scans were examined by a neuroradiologist for coincidental findings.

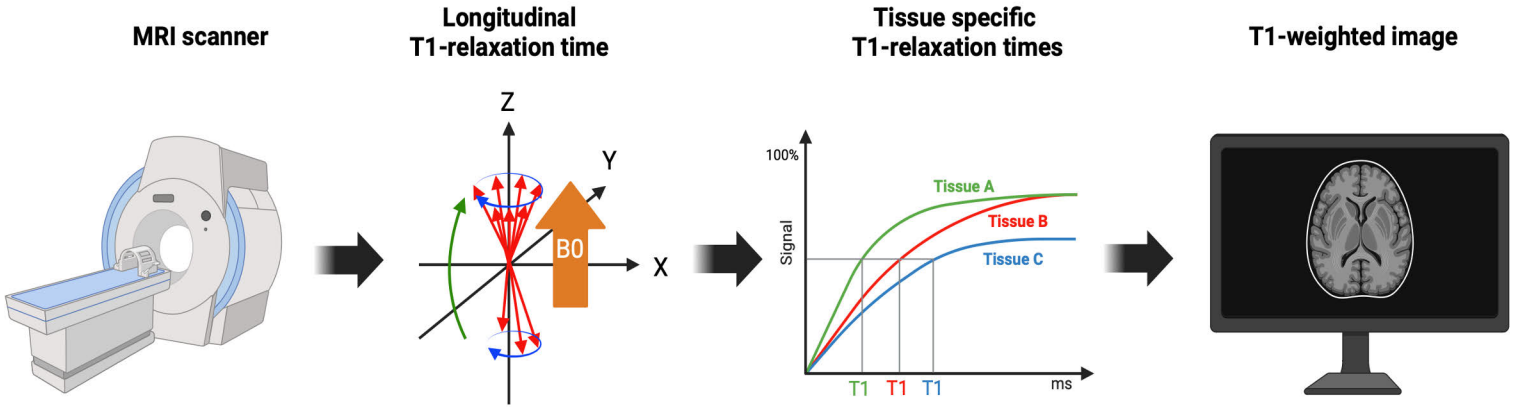


Figure 5. In magnetic imaging, a radiofrequency (RF) pulse is applied at the Larmor frequency to the tissues. The Larmor frequency RF pulse excites, thus rotates, an excess portion of the spins (red arrows) from the direction of the main magnetic field (orange arrow) (parallel direction) to the opposite direction (antiparallel direction), and the spins are moving to a higher energy state. When the excess of spins that were initially aligned in the parallel direction is rotated 180 degrees by the RF pulse, the net magnetization becomes zero, effectively transitioning to a horizontal orientation. At this point, the RF pulse is referred to as an RF90 pulse phase. Following the RF90 pulse, the antiparallel spins begin to realign back to a lower-energy parallel state (green arrow), ultimately returning to their original configuration, where the net magnetization of the spins is again aligned with the external magnetic field. The time taken for the recovery of this longitudinal magnetization is known as the T1 relaxation time, which partially depends on the characteristics of the tissue. Differences in the T1 relaxation times among various tissues are utilized to enhance the contrast in magnetic images, T1-weighted images. Blue arrow demonstrates the Larmor frequency of the precessing spins. B0 is the constant main magnetic field. T1 weighting is the most used imaging technique when assessing structural contrast in anatomical images. Images are termed T1-weighted when the contrast is primarily derived from tissue-specific T1 relaxation times. In addition to relaxation times, the relative proton density also influences the contrast. In T1-weighted images, fluid appears black, gray matter is represented in dark gray, and white matter appears light gray. The weighting of the imaging sequence can be adjusted to T1 by modifying the TR and TE times (TR, time to repeat; TE, time to echo). T1-weighted images can be obtained using either gradient echo-based or spin echo-based sequences for image formation. In this study, a gradient echo-based T1-weighted sequence was utilized. In a T1-weighted gradient echo-based sequence, refocusing is achieved using gradients. Refocusing refers to the restoration of spin phase coherence, which enables the generation of the echo signal used for image formation. Created by author with BioRender.com.

4.2.2 Segmentation procedures with FreeSurfer

4.2.2.1 Segmentation of amygdala (Study I)

The amygdala subnuclei were segmented using a previously developed and validated algorithm (Saygin et al., 2017) available in the FreeSurfer development version (freesurfer-Darwin-OSX-ElCapitan-dev-20180207-e9879ec181) (https://surfer.nmr.mgh.harvard.edu/fswiki/HippocampalSubfieldsAndNucleiOfAmygdala). This algorithm employs Bayesian modeling to segment and estimate the volumes of nine amygdala subnuclei. The underlying amygdala atlas was created by manually segmenting and hand-labeling post-mortem amygdala samples with high-resolution 7T MRI. The algorithm was validated by demonstrating its ability to distinguish healthy controls from patients with Alzheimer's disease and autism (Saygin et al., 2017). To further assess the reliability of this method, we scanned 5 healthy participants twice during the same day. The scans were separated by approximately 5 h. Each scan was segmented with the algorithm and test-retest metrics were calculated. The segmentation algorithm showed excellent test-retest reliability, with the variability ranging from 1.1 to 5.5% and intraclass correlation values from 0.83 to 0.99.

All nine subnuclei were included in the primary analyses: the lateral nucleus, basal nucleus, accessory basal nucleus, corticoamygdaloid transition area, central nucleus, medial nucleus, cortical nucleus, paralaminar nucleus, and anterior amygdaloid area. It's important to note that this segmentation distinguishes between the lateral, basal, and accessory basal nuclei, which are commonly grouped together as the basolateral nucleus (LeDoux, 2007).

To further evaluate the method's reliability, we conducted two scans on five healthy participants within the same day, with a roughly 5-hour interval between scans. Each scan was processed using the segmentation algorithm, and test-retest metrics were calculated. The algorithm demonstrated strong reliability, with variability ranging between 1.1% and 5.5%, and intraclass correlation values ranging from 0.83 to 0.99.

4.2.2.2 Segmentation of hippocampus (Study II)

From the preprocessed T1 images, the 12 hippocampal subfield volumes were segmented using the longitudinal FreeSurfer pipeline in version 7.1.1 (Iglesias et al., 2015; Samann et al., 2022) (https://surfer.nmr.mgh.harvard.edu/fswiki/HippocampalSubfieldsAndNucleiOfAmygdala). The underlying hippocampus atlas was created by manually segmenting and hand-labeling post-mortem hippocampus samples with high-resolution 7T MRI delineate its subfields. The small head and body subdivisions were merged to

represent each entire subfield, reducing the number of comparisons. Eight subfields were selected for the statistical analysis: the subiculum, cornu ammonis 1 (CA1), presubiculum, molecular layer of the subiculum and cornu ammonis regions (ML), the granule cell layer and molecular layer of the dentate gyrus (GCMLDG), cornu ammonis 2 and 3 (CA2 and CA3), cornu ammonis 4 (CA4), and the hippocampal tail. The hippocampal-amygdaloid transition area (HATA), hippocampal fissure, and parasubiculum were excluded due to the lower reliability in segmenting these regions, given their small volumes relative to the voxel size.

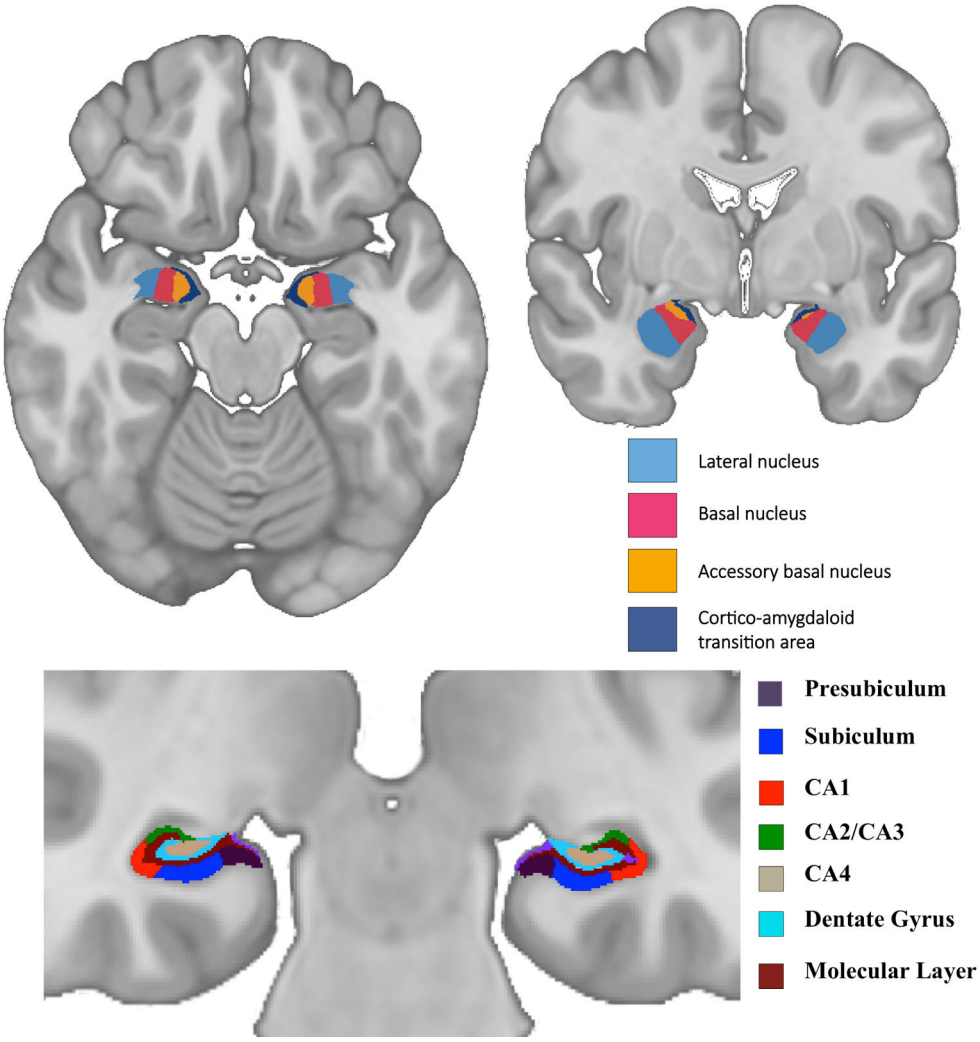


Figure 6. Above Segmentation of the amygdala (upper: axial and coronal orientations) and hippocampus (lower: coronal orientation) shown on a MNI152 template. Only part of the subnuclei is visible.

4.2.2.3 Measuring cortical thickness (Study III)

All participants underwent an MRI scan with a Philips Ingenuity TF 3-Tesla PET/MR scanner. T1-weighted (Ultrafast Gradient Echo 3D, TR = 8.1 ms, TE-time = 3.7 ms, flip angle 7°, FOV = 256x256x176 mm3 and voxel size 1x1x1 mm3) images were collected from all subjects. The T1 images were preprocessed using the longitudinal pipeline in Freesurfer v7.1.1. (Fischl, 2012) We measured the cortical thickness with a group analysis of FreeSurfer (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/GroupAnalysis).

The regional effects of lifetime antipsychotic exposure on the cortical thickness were assessed using vertex-wise analyses, performed with the glm-fit function in Freesurfer 7.1.1. The cortex is often represented as a mesh of vertices. Each vertex corresponds to a point on the cortical surface. A vertex-wise analysis allows to analyze various metrics, such as thickness, curvature, or surface area, at each vertex individually rather than aggregating data across larger regions, such as entire lobes.

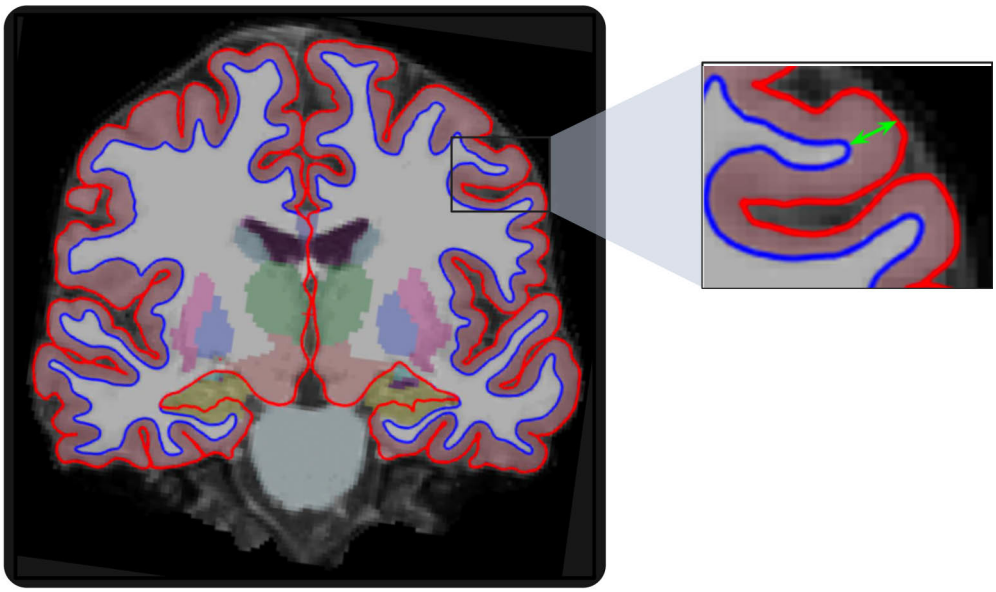


Figure 7. Demonstration of a cortical thickness measure (green arrow) acquired from a segmented T1-weighted MRI sequence. Created by the author with BioRender.com.

4.2.3 NeuroMaps (Study III)

NeuroMaps is a computational toolbox designed to integrate and analyze data from various sources of human brain mapping (Hansen et al., 2022; Markello et al., 2022). It provides standardized tools to compare and analyze normative brain maps derived

from different modalities, such as structural, functional, and molecular imaging, including neuroreceptor atlases. It facilitates the understanding of how different aspects of brain organization, e.g., molecular, functional, and structural, are related to each other. In Study III our own Turku discovery sample and further replication sample of ENIGMA neuroimaging data were loaded into NeuroMaps. Specifically, in this case, the maps of antipsychotic related cortical thinning were compared against the existing normative maps or templates based on the different modalities and brain organizations in the standard template space (**Figure 8**).

The vertex-wise map of the effects of lifetime antipsychotic exposure on cortical thickness from the Turku sample was first parcellated using the Desikan-Killiany cortical atlas. The ENIMGA replication data was parcellated similarly. Selected feature annotations provided by the NeuroMaps were also parcellated using the same atlas. Group level statistical maps, parcel-wise partial correlation values and the code for the validation and replication of all NeuroMaps analyses and figures are available online: https://github.com/ltuominen/AP_brainorganization.

4.2.4 NeuroSynth (Study III)

NeuroSynth (https://neurosynth.org) is a database used for a large-scale, automated meta-analysis of functional magnetic resonance imaging (fMRI) data (Poldrack et al., 2011; Yarkoni et al., 2011). It defines the normative cognitive function networks from the fMRI results of multiple articles and analyzes them to find patterns of brain activity related to various cognitive functions or psychological states based on the text-mining of scientific articles. With NeuroMaps we investigated our data samples of antipsychotic related cortical thinning in relation to the existing normative cognitive fMRI maps in the standard template space (**Figure 8**).

4.3 Clinical variables

In Studies I-III, symptoms were assessed using either the Positive and Negative Symptom Scale (SCI-PANSS) or the Brief Psychiatric Rating Scale (BPRS) (24-items, version 4.0) (Kay et al., 1987; Overall, 1974). The PANSS scores were converted to correspond to the BPRS 18-item scores and the BPRS 24-item scores reduced to correspond to the BPRS 18-item scores (Leucht et al., 2013). Thus, in the studies I-III, the total symptom score refers to the sum of those 18 items, positive symptoms score to the sum of the 8 positive symptom items and negative symptoms score to the sum of the 5 negative symptom items. All items were rated on a scale of 1 to 7.

In Studies I-III, all daily doses of antipsychotics before each scanning date were recorded using available medical records. These doses were then converted to

chlorpromazine (CPZ) equivalent daily dosages (Leucht et al., 2016) and summed to calculate the total cumulative lifetime exposure to antipsychotics at each study time point. Medications administered on an as-needed basis were excluded.

4.3.1 Childhood adversity, Study I

In Study I, the primary clinical variable examined was childhood adverse experiences. Childhood adversity was be measured with the Trauma and Distress Scale (TADS), which divides experiences in five categories; emotional abuse, physical abuse, physical neglect, emotional neglect, sexual abuse, and total trauma score (Salokangas et al., 2016). In our study, the TADS is based on retrospective evaluation, meaning that participants reflect on and report their childhood experiences when completing the assessment.

4.3.2 Parameters of glucose metabolism, Study II

In Study II, the primary clinical variables examined were fasting plasma glucose, fasting plasma insulin and insulin resistance at the baseline and at one-year follow-up time point. The homeostatic Model Assessment, HOMA2-IR (https://www.dtu.ox.ac.uk/homacalculator/), was used as a proxy for insulin resistance instead of HOMA1-IR. (Song et al., 2016; Wallace et al., 2004). HOMA2-IR is considered to be a more accurate measure of insulin resistance and beta-cell function, as it represents both the hepatic glucose output and peripheral glucose uptake. Blood samples. including fasting plasma glucose and fasting plasma insulin, were acquired from the subjects. The fasting glucose values included in the analysis were at non-diabetic level ranges (below 7.0 mmol/l; ranging from 4.0 mmol/l to 6.5 mmol/l).

All antipsychotic daily doses preceding each scanning date were documented using available medical records. The daily doses were then converted to CPZ-equivalent daily dosages (Leucht et al., 2016) after which they were summed up to obtain the total cumulative lifetime antipsychotic exposures at each study time point. The information on the use of antidepressive and mood stabilizing medications were also collected.

4.3.3 Outcome trajectories, Study II

For the analysis of clinical outcome trajectories, we divided patients into two groups based on their follow-up assessments, considering the levels of functioning, remission status, and transition to psychosis. The CHR group was split into two subgroups: those who transitioned to psychosis (CHR converting, CHR-C, n = 11)

and those who did not (CHR non-converting, CHR-NC, n = 37), resulting in a 23% transition rate within the CHR group over the one-year follow-up period. However, only seven of the eleven CHR-C individuals were available for analysis due to dropouts. Functioning was assessed using the GAF scale, which was categorized into two groups: poor functioning (GAF < 65) and good functioning (GAF ≥ 65) based on follow-up evaluations. The remission status, thus remission or non-remission, was determined using scores from the BPRS, along with three additional items from the Scale for the Assessment of Negative Symptoms (SANS) or the Positive and Negative Symptom Scale (SCI-PANSS) measured at the follow-up time point (Andreasen et al., 2005).

4.3.4 Study III

4.3.4.1 Early psychosis – Turku discovery sample

Effect of antipsychotic effect on cortical thickness

The main clinical variable used in Study III is lifetime antipsychotic exposure that was collected and calculated from electronic medical records of the psychiatric services of the Hospital District of Southwest Finland by M.W. and R.-L.A. Medications administered on an as-needed basis were excluded. Four FEPs (4.9 %) and 22 CHRs (44.9 %) were antipsychotic-naive, and the rest of the sample were exposed to antipsychotics. The average daily dose at the time of scanning in those who were taking antipsychotics was 321.84 (± 233.09) mg chlorpromazine in the FEP group and 167.06 (±129.33) mg chlorpromazine in the CHR group. The most frequently prescribed antipsychotics were risperidone, quetiapine, olanzapine, and aripiprazole. None of the patients were on clozapine. In the discovery sample, 12% of the participants had used first-generation antipsychotics during their lifetime exposure.

In addition to the prescribed antipsychotic medications, we recorded the duration of inpatient stays and the number of admissions for each participant in a mental health hospital. Symptom scores, measures of function, length of hospitalizations, and number of admissions were utilized as indicators of illness severity. The GAF scale and the Social and Occupational Functioning Assessment Scale (SOFAS) were utilized to evaluate functioning (Endicott et al., 1976; Morosini et al., 2000).

The association between underlying cortical structural or functional features and antipsychotic-related cortical thinning

Associations between regional antipsychotic effects on cortical thickness and regional variations in underlying brain features were examined using the NeuroMaps toolbox (Markello et al., 2022). For the discovery analyses, we selected a total of 33 unique normative structural and functional features of cortical organization provided as a part of the NeuroMaps toolbox. These included neuroreceptor maps for dopamine, serotonin, acetylcholine, glutamate, GABA, cannabinoid, histamine, and opioid systems, measures of blood flow, metabolism, average cortical thickness, myelination, and synaptic density. Further, we measured associations between antipsychotic related cortical thinning and the resting state functional MRI connectivity measure of unimodal–transmodal functional gradient, which explores how brain activity transitions from simple sensory tasks (basic sensory areas, unimodal) to complex cognitive tasks (higher-order processing areas, transmodal) across different brain regions. Finally, we collected magnetoencephalography (MEG) -derived neural oscillatory power distributions for six canonical frequency bands (alpha, beta, delta, low gamma, high gamma and theta) from published studies (Hansen et al., 2022). Six receptors and transporters were measured using more than one PET-tracer. These duplicate neuroreceptor maps were included in a supplementary analysis for completeness. PET-measures of cortical dopamine transporters were omitted, as the sensitivity of these tracers in the cortex remains uncertain.

4.3.4.2 Schizophrenia – ENIGMA replication sample

Effect of antipsychotic effect on cortical thickness

In the replication analyses with the ENIGMA sample, the current daily dose of antipsychotics was utilized instead of the lifetime antipsychotic exposure measured in the discovery sample. In the subset of patients from the ENIGMA sample for whom the antipsychotic medication dose at the time of scanning was available, 2,236 (66%) were on second-generation (atypical) antipsychotics, 447 (13%) were on first-generation (typical) antipsychotics, and 265 (8%) were on a combination of both second- and first-generation antipsychotics. The current antipsychotic dose was converted to chlorpromazine equivalents based on Woods' calculations (www.scottwilliamwoods.com/files/Equivtext.doc).

NeuroMaps: The association between underlying cortical structural or functional features and antipsychotic related cortical thinning

For the replication analyses using the ENIGMA sample, we selected only the features that were statistically significantly ($p_{spin} < 0.05$) associated with the effects of lifetime antipsychotic exposure in the discovery sample in NeuroMaps analyses. These replicated analyses were serotonin $5HT_{2A}$, and $5HT_4$ receptors, nicotinic $\alpha4\beta2$* receptors, cannabinoid receptor 1, μ-opioid receptors, fMRI functional gradient, neurophysiological measures of delta, low and high gamma, theta power, and intrinsic time scale, synaptic vesicles and cerebral metabolic rate for glucose.

NeuroSynth: Post-hoc analyses on the associations between underlying cognitive features and antipsychotic-related cortical thinning

We used the Neurosynth database to conduct voxel-wise meta-analyses for 123 cognitive terms from the Cognitive Atlas (Poldrack et al., 2011; Yarkoni et al., 2011). These terms include umbrella terms (e.g., “attention,” “emotion”), specific cognitive processes (e.g., “visual attention,” “episodic memory”), behaviors (e.g., “eating,” “sleep”), and emotional states (e.g., “fear,” “anxiety”). The terms were then grouped into 11 categories (“Action,” “Learning and Memory,” “Emotion,” “Attention,” “Reasoning and Decision Making,” “Executive/Cognitive control,” “Social Function,” “Perception,” “Motivation,” “Language,” and “other”) (http://www.cognitiveatlas.org/concepts/categories/all) (Poldrack et al., 2011).

4.4 Statistical methods

4.4.1 Study I

Differences in amygdala subnuclei between FEP, CHR and CTR and associations with childhood adverse experiences

The subnuclei volumes were averaged across both hemispheres in further analyses to avoid unnecessary multiple comparisons, since there were no significant differences in subnuclei volumes between the left and right hemispheres, nor any group by hemisphere by subnuclei interactions.

First, we tested overall group differences in the total amygdala volume using ANCOVA, controlling for age, sex, and total intracranial volume. After which, a linear mixed-effects model was used to examine whether there was a group by subnucleus interaction.

Then we tested whether the TADS total score was linearly associated with subnuclei volumes. The models were fit separately for each group and limited to the subnuclei that were smaller in either FEP or CHR. In all statistical analyses, p-values < 0.05 were considered statistically significant. Multiple comparisons were corrected using the false discovery rate (FDR) correction at p-value < 0.05. All analyses were carried out with R version 3.5.2 (Eggshell Igloo)(R Core Team, 2017). A detailed description of the statistical methods used in Study I can be found in the appendices.

4.4.2 Study II

Analyses of hippocampal volumetry and glucose parameters

Cross-sectional analyses

The differences in hippocampal subfield volumes across FEP, CHR, and CTR groups were analyzed using a linear mixed-effects model. Subfields were treated as a repeated measure within subjects, with volume as the dependent variable. Group status, subfield, their interaction, and the covariates (age, sex, body mass index (BMI), and total intracranial volume (TIV)) were the independent variables. Post-hoc pairwise comparisons of subfield volumes between groups were performed using estimated marginal means, with the false discovery rate correction applied.

The relationships between glucose metabolism parameters and hippocampal volumes (both subfield and total) were tested separately for the FEP, CHR, and control groups. This analysis was done for all metabolic indexes and volumes, as well as at both time points, using a linear model.

Longitudinal analyses

We used a linear mixed-effects model to analyze baseline and one-year follow-up data, aiming to detect longitudinal changes in hippocampal subfield volumes, total hippocampal volumes, and glucose parameter values over time across the FEP, CHR, and CTR groups. Post-hoc comparisons of volume or glucose parameter changes within each group between the baseline and one-year follow-up were conducted using estimated marginal means.

As above, a mixed-effects linear model was used to assess whether reductions in subfield volumes at baseline, baseline glucose parameter levels, or longitudinal changes in volumes and glucose parameters during the follow-up were linked to clinical outcomes, such as the transition to psychosis, level of functioning, or remission status at the follow-up.

The effect of lifetime antipsychotic exposure at each MRI scan time point was controlled by using it as a covariate for each test of this study separately. All analyses

were carried out with R version 4.2.1 (2022-06-23) “Funny-Looking Kid” (R Core Team, 2022). A detailed description of the statistical methods used in Study I can be found in the appendices.

4.4.3 Study III

4.4.3.1 Early psychosis – Turku Discovery sample

Effect of antipsychotic drugs on cortical thickness

We started by estimating how lifetime antipsychotic use affects the overall thickness of the brain’s cortex. The average cortical thickness across the whole cortical mantle was used as the outcome measure and lifetime antipsychotic exposure, age, sex, and group as explanatory variables in a linear regression model. Because illness severity might explain both increased antipsychotic use and reduced cortical thickness, we performed a series of sensitivity analyses. The regional effects of lifetime antipsychotic exposure on cortical thickness were assessed using vertex-wise analyses, performed with the glm-fit function in Freesurfer 7.1.1. In this analysis, vertex-wise cortical thickness was predicted using lifetime antipsychotic exposure with age, sex, and group as covariates.

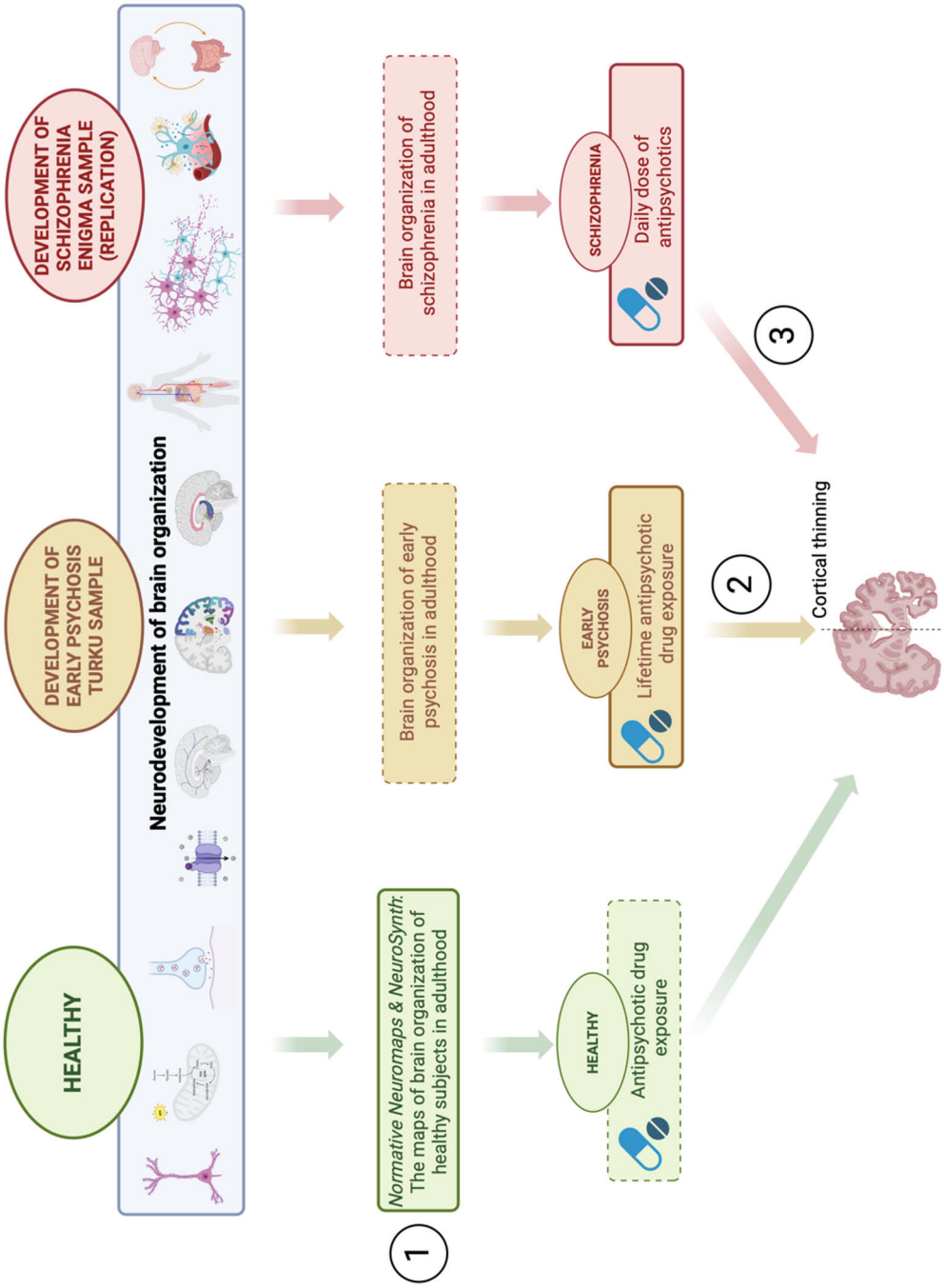
NeuroMap and NeuroSynth

The association between the cortical structure or function and antipsychotic-related cortical thinning was studied with NeuroMaps and post-hoc analyses on the associations between underlying cognitive features and antipsychotic-related cortical thinning were investigated with NeuroSynth.

4.4.3.2 Schizophrenia – ENIGMA replication sample

To replicate the findings from the discovery sample, we used data from an ENIGMA consortium study to study correlations between the current chlorpromazine-equivalent dose and cortical thickness. As above, the association between the cortical structure, function, or cognitive features and antipsychotic-related cortical thinning were studied with NeuroMaps and NeuroSynth. A detailed description of the statistical methods used in Study I can be found in the appendices.

Figure 8. ► Visualization of the methods in the Study III. The associations between normative maps of the brain molecular, physiological and functional features (1) and antipsychotic drug use –related cortical thinning in early psychosis Turku discovery sample (2), and replication of the discovery findings between normative maps (1) and antipsychotic drug use –related cortical thinning in the Enigma schizophrenia sample (3) were studied. The boxes outlined with dashed borders were not examined in this study. The early psychosis discovery sample consists of both first episode of psychosis and clinical high-risk patients. The antipsychotic drug use was measured as lifetime exposure in the Turku discovery sample and as a daily dose in the schizophrenia sample. Created by the author with BioRender.com.


HEALTHY
DEVELOPMENT OF EARLY PSYCHOSIS TURKU SAMPLE
DEVELOPMENT OF SCHIZOPHRENIA ENIGMA SAMPLE (REPLICATION)
Neurodevelopment of brain organization
Normative Neuromaps & NeuroSynth: The maps of brain organization of healthy subjects in adulthood
1
Brain organization of early psychosis in adulthood
Brain organization of schizophrenia in adulthood
HEALTHY
Antipsychotic drug exposure
EARLY PSYCHOSIS
Lifetime antipsychotic drug exposure
SCHIZOPHRENIA
Daily dose of antipsychotics
2
3
Cortical thinning

5 Results

5.1 Study I: Amygdala subnuclei morphology in early psychosis and link to Childhood adversity

We found that there were subnucleus volume specific effects of groups (group by subnucleus interaction $F_{16,1544} = 2.203$, $p = 0.0040$) while controlling for age, sex, and the total intracranial volume. The post-hoc pairwise comparison analysis revealed that the volume of the lateral nucleus was smaller in both the FEP (FDR $p < 0.001$, estimated difference between the groups in mm^3 (ED) = 24.84, pooled standard error of the difference (SE_{pooled}) = 7.41, unadjusted pooled standard deviation of the difference (SD_{pooled}) = 79.04) and CHR (FDR $p < 0.001$, ED = 25.52, SE_{pooled} = 8.57, SD_{pooled} = 76.47) compared to the control group. Also, the basal nucleus was smaller in the FEP (FDR $p < 0.001$, ED = 21.03, SE_{pooled} = 7.41, SD_{pooled} = 53.39), but not in the CHR (FDR $p = 0.5750$, ED = 8.36, SE_{pooled} = 8.57, SD_{pooled} = 54.25), when compared to the control group (**Table 4**).

Table 4. Reductions in amygdala subnuclei volumes in pairwise comparisons between first-episode psychosis (FEP), clinical high-risk psychosis (CHR) and population controls (CTR).

Amygdala subnuclei	A) Volume reduction compared to CTR		B) Volume reduction compared to CHR
	FEP	CHR	FEP
Lateral nucleus	↓	↓	n.s.
Basal nucleus	↓	n.s.	n.s.
Accessory basal nucleus	n.s.	n.s.	n.s.
Central nucleus	n.s.	n.s.	n.s.
Cortico-amygdaloid transition area	n.s.	n.s.	n.s.
Medial nucleus	n.s.	n.s.	n.s.
Cortical nucleus	n.s.	n.s.	n.s.
Anterior amygdaloid area	n.s.	n.s.	n.s.
Paralaminar nucleus	n.s.	n.s.	n.s.

* An arrow indicates a statistically significant reduction in subfield volumes relative to population controls (A) or CHR (B). n.s.= non-significant.

In the FEP group, we found that there was a significant inverse association between the TADS total score and lateral nucleus (beta = –1.45, t_{62} = – 2.852, FDR corrected p = 0.0354) while controlling for age, sex, and intracranial volume.

5.2 Study II: Hippocampus subfield morphology in early psychosis and link to glucose metabolism

5.2.1 Volumes of hippocampal subfields

The hippocampal subfield volumes did not differ significantly between FEPs, CHRs and CTRs (subfield by group interaction $F_{14,1442}$ = 1.33, p = 0.183) at the baseline. However, the pairwise repeated measures analysis showed that in the FEP group, the volumes of the subiculum (FDR p = 0.044, ED =18.88, confidence interval (CI) = [4.22–33.5], SE_{pooled} = 10.52, SD_{pooled} = 47.68), presubiculum (FDR p = 0.020, ED = 10.98, CI [6.90–36.2], SE_{pooled} = 10.52, SD_{pooled} = 34.08), molecular layer (FDR p < 0.001, ED = 29.98, CI [15.32–44.6], SE_{pooled} = 10.52, SD_{pooled} = 57.41), CA1 (FDR p < 0.001, ED = 31.44, CI [16.78–46.1], SE_{pooled} =10.52, SD_{pooled} = 83.72), GCMLDG (FDR p = 0.044, ED = 18.28, CI [3.62–32.9], SE_{pooled} = 10.52, SD_{pooled} = 27.56), and tail (FDR p < 0.001, ED = 34.44, CI [19.78–49.1], SE_{pooled} =10.52, SD_{pooled} = 71.16) were significantly reduced compared to CTRs, whereas no statistically significant differences were observed in the combined CA2 and CA3 subfield (FDR p = 0.148, ED = 13.64, CI [-1.02–28.3], SE_{pooled} = 10.52, SD_{pooled} = 30.57), or CA4 (FDR p = 0.058, ED = 17.20, CI [2.54–31.9], SE_{pooled} = 10.52, SD_{pooled} = 23.71), after FDR corrections (8 subfields and 3 contrasts per subfield; total 24 tests per FDR correction). FEPs also had just significantly smaller CA1 volumes (FDR p = 0.044, ED = 21.24, CI [4.31–38.2], SE_{pooled} = 12.15, SD_{pooled} = 81.40) compared to CHRs, but no differences in other subfields were observed between FEP and CHR. Also, the hippocampal tail (FDR p = 0.010, ED = 27.28, CI [10.40–44.2], SE_{pooled} = 12.10, SD_{pooled} = 72.84) was significantly smaller in CHR compared to CTR (**Table 5**).

Based on these, and taken in to account the conversion to psychosis during the 1-year follow-up time, in the CA1 and tail; only CHR-NC had a smaller tail volume (FDR p < 0.001, ED = 35.22, CI [16.83–53.6], SE_{pooled} = 13.19, SD_{pooled} = 69.84) compared to CTR, but there was no significant difference between CHR-C and CHR-NC (FDR p = 0.142, ED = 34.650, CI [2.92–66.4], SE_{pooled} = 22.76, SD_{pooled} = 77.06) in the tail volume. The CA1 volumes did not differ significantly between CHR-C and CHR-NC (FDR p = 0.657, ED = -13.63, CI [-45.36–18.1], SE_{pooled} = 22.76, SD_{pooled} = 82.64). The CA1 was not statistically significantly reduced in CHR-C (FDR p = 0.513, ED = 20.71, CI [-9.01–50.4], SE_{pooled} =21.31, SD_{pooled} = 87.55) or CHR-NC (FDR p = 0.662, ED = 7.08, CI [-11.31–25.5], SE_{pooled} =13.19, SD_{pooled} =

83.61) compared to CTR. However, a trend level reduction in FEP versus CHR-NC (FDR p = 0.079, ED = 24.36, CI [5.91–42.8], SE_{pooled} =13.23, SD_{pooled} = 80.01), but not in FEP vs CHR-C (FDR p = 0.672, ED = 10.74, CI [-18.99–40.5], SE_{pooled} =21.32, SD_{pooled} = 83.30), was observed in CA1 at the baseline. All pairwise comparisons of the baseline subfield volumes of subgroups based on follow-up outcomes are presented in the original publication. Hippocampal subfield volumes remained stable during the one-year follow-up time in FEP and CHR.

5.2.2 Glucose metabolism

There was a subfield specific effect of fasting insulin and insulin resistance in FEP at the follow-up time point (subfield by insulin $F_{3.4,72} = 3.73$, p = 0.011; subfield by insulin resistance $F_{3.4,71} = 3.45$, p = 0.017). We found a statistically significant association between smaller hippocampal tail volume and the deterioration of fasting plasma insulin or insulin resistance index (insulin: t = -3.42, beta = -7.41, 95% CI [-11.9, -2.9], p = 0.003 FDR p = 0.024; insulin resistance: t = -17.85, beta = -58.90, 95% CI [-96.0, -21.8], p = 0.003, FDR p = 0.024) in non-diabetic FEP, at the follow-up time point. Adjusting for lifetime exposure to antipsychotic medication, or the use of antidepressants did not change these results. There were no significant associations between subfield volumes or the total hippocampal volume and glucose parameters in any group at the baseline, or in CHR and CTR at the follow-up time point.

There was a statistically significant increase in insulin ($t_{74} = 3.334$, p = 0.0013, estimate = 4.49, 95% CI [1.8, 7.2], Effect size (ES) (Cohen's d) = 1.12, ES 95% CI [0.4, 1.8],) and insulin resistance ($t_{74} = 3.232$, p = 0.0018, estimate = 0.549, 95% CI [0.2, 0.9], ES (Cohen's d) = 1.08, ES 95% CI [0.4,1.8]) levels in CHR, but not in FEP or CTR during the follow-up period. While observing the subgroups of CHR further, we observed that during the follow-up period, insulin ($t_{73} = 3.705$, p = 0.0004, estimate = 9.97, 95% CI [4.6, 15.3], ES (Cohen's d) = 2.5, ES 95% CI [1.1, 3.9],) and insulin resistance ($t_{73} = 3.539$, p = 0.0007, estimate = 1.205, 95% CI [0.5, 1.9], ES (Cohen's d) = 2.4, ES 95% CI [1.0, 3.8],) levels significantly increased in the CHR-C, but not in CHR-NC (**Figure 9**). In addition to CHR transition, this increase in plasma insulin levels and insulin resistance was further related to poorer GAF and worse symptoms at the follow-up in the CHR group. These results were not affected by adjusting the model for lifetime antipsychotic exposure.

Table 5. Reductions in hippocampal subfield volumes in pairwise comparisons between first-episode psychosis (FEP), clinical high-risk psychosis (CHR), and population controls (CTR).

Hippocampus subfields at baseline	**A) Volume reduction compared to CTR**		**B) Volume reduction compared to CHR**
	FEP	**CHR**	**FEP**
Tail	↓	↓	n.s.
Presubiculum	↓	n.s.	n.s.
Subiculum	↓	n.s.	n.s.
CA1	↓	n.s.	↓
Molecular layer	↓	n.s.	n.s.
GCMLDG	↓	n.s.	n.s.
CA2 and CA3	n.s.	n.s.	n.s.
CA4	n.s.	n.s.	n.s.

*An arrow indicates a statistically significant reduction in subfield volumes relative to population controls (A) or CHR (B). n.s.= non-significant. CA = cornu ammonis, GCMLDG = The Granule Cell layer and Molecular Layer of the dentate gyrus.

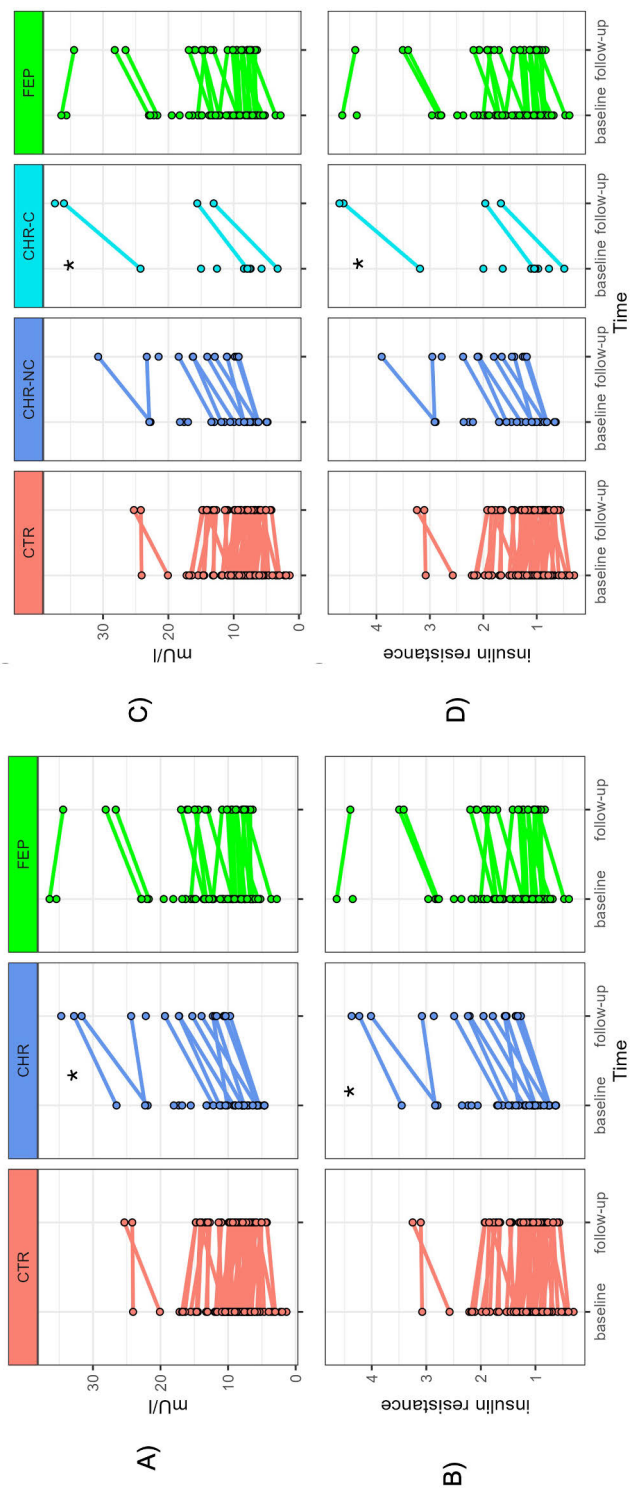


Figure 9. The change in fasting plasma insulin (panel A and C) and in insulin resistance levels (panel B and D) in CHR, FEP and CTR (panel A and B), or in CHR, CHR-NC, CHR-C and CTR (panel C and D) during the one-year follow-up in. Statistically significant changes marked with an asterisk. CHR = Clinical High-Risk patients, FEP = First Episode of Psychosis patient, CHR-C = CHR converting to psychosis, CHR-NC = CHR not converting to psychosis during 1-year follow-up, CTR = population control. Modified from Original Publication II (Armio et al., 2024).

5.3 Study III: Association between antipsychotic drug exposure and cortical thinning in early psychosis

We found that, higher lifetime antipsychotic exposure was associated with thinner mean cerebral cortex when covarying for age, sex and group (clinical high risk or first-episode psychosis) (regression coefficient = -0.00000113, 95%CI = -0.000001666– -5.892429e-07, df = 126, t-value = -4.159, p-value = 0.000059). Cortical thinning was the most prominent in the prefrontal, parietal and cingulate cortices (**Figure 10**). Biological features, associated with antipsychotic-related cortical thinning, were studied in the discovery sample and replicated in the ENIMGA sample. We found that antipsychotic-associated cortical thinning was related with several molecular, physiological, functional and, post-hoc studied, cognitive features of the brain. The most prominent common biological mechanisms both in the early psychosis discovery and replication data of schizophrenia patients relating to antipsychotic drug –induced cortical thinning were: 1) the serotonin system, 2) functional networks, and 3) neural oscillatory power distributions typical for regions involved in higher cognitive functions, such as motivation, but also executive and cognitive control.

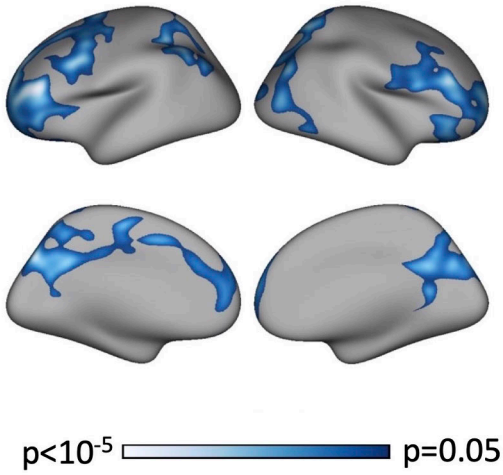


Figure 10. Cortical areas of the most prominent cortical thinning related to lifetime antipsychotic exposure in the discovery Turku sample were the prefrontal cortex, parietal cortex and posterior cingulate cortex (in blue), N = 131. The model includes age, sex, and diagnostic group as nuisance variables. The color bar indicates p-value and results are permutation corrected for multiple comparisons at $p < 0.05$. Two upper images show a lateral view, while two lower images show a medial view. Modified and reprinted from Original Publication III (Tuominen, 2024).

Table 6. Shows below, the similar patterns of cortical thinning associated with antipsychotic medication observed in both the Turku Early Psychosis cohort and the ENIGMA Schizophrenia sample. The downward arrow indicates a negative association, while the upward arrow indicates a positive association between the studied normative feature and antipsychotic-related cortical thinning (more antipsychotic-related cortical thinning and more the studied feature). CBV = cerebral blood volume, HTT = hydroxytryptamine transporter, HT = hydroxytryptamine.

Normative features of cortical thinning - related brain organization	Class	Direction of correlation
5-HTT	serotonin	↓
5-HT2A	serotonin	↑
5-HT4	serotonin	↑
α4β2*	acetylcholine	↑
μ-opioid	opioid	↑
Cannabinoid 1	cannabinoid	↑
Functional gradient	functional	↑
Alpha power	functional	↓
Low Gamma power	functional	↑
Theta power	functional	↑
T1/T2 (myelination maps)	structural	↓
Synaptic vesicles	structural	↑
CBV	metabolic	↓

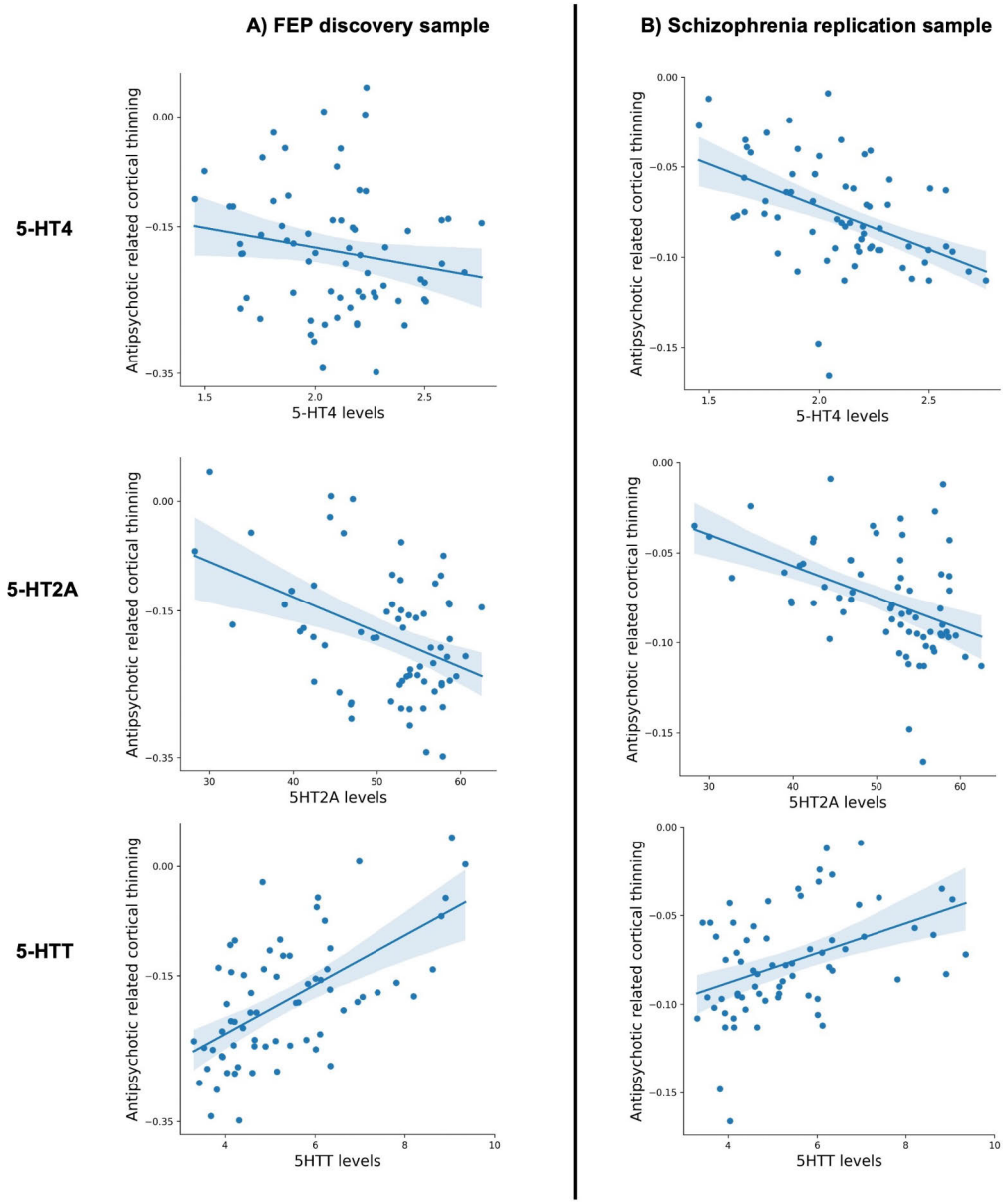


Figure 11. The image shows a normative serotonin receptor and transporter levels associating differently with antipsychotic medication related cortical thinning in the FEP sample (A). The discovery findings are further replicated in the schizophrenia sample (B). 5-HT =5-hydroxytryptamine, 5-HTT = 5-hydroxytryptamine transporter.

6 Discussion

6.1 Main findings

In Study I, we observed that the lateral nucleus of the amygdala was smaller in both CHR and FEP patients, whereas the basal nucleus was significantly reduced only in FEP. Adverse childhood experiences were linked to smaller lateral nucleus volumes in FEP.

In Study II, hippocampal subfield volumes were consistently reduced in FEP, particularly in non-affective psychoses, but the reductions were less pronounced in the CHR group. These structural changes remained stable over a one-year follow-up. Additionally, higher fasting plasma insulin and insulin resistance were associated with smaller hippocampal tail volumes in non-diabetic FEP patients at the follow-up. Clinically, insulin resistance worsened in CHR during the follow-up, correlating with poorer clinical outcomes, such as the transition to psychosis and reduced functioning.

In Study III we found that, higher lifetime antipsychotic exposure was associated with a thinner cerebral cortex. Lifetime exposure to antipsychotic medications remained significantly linked to reduced mean cortical thickness when accounting for illness severity. In the discovery sample of early psychosis, antipsychotic-related cortical thinning was the most pronounced in the prefrontal, parietal, and cingulate cortices, with no regions showing increased thickness. Specifically, exposure to approximately 90 g of chlorpromazine equivalent antipsychotic medication was associated with a 0.1 mm decrease in cortical thickness. This corresponds to using 100 mg of CPZ daily over 900 days, which is associated with a 0.1 mm thinning of the cortex. We compared antipsychotic related cortical thinning in the discovery and replication sample of ENIGMA to assess comparability and observed that the antipsychotic-related cortical thinning was similar in the two samples. Finally, Study III identified multiple novel neurobiological mechanisms that may underlie antipsychotic-associated cortical thinning, offering new insights into the effects of antipsychotic drugs. These were the serotonin system, functional networks and neural oscillatory power distributions, identified as typical for regions involved in higher cognitive functions.

6.2 Amygdala subnuclei are reduced in early psychosis

In relation to the previous literature, our findings of Study I showing reductions in the lateral and basal nuclei in FEP, and the reduction in the lateral nucleus in CHR, are novel, as no prior studies have addressed this topic, by now, specifically in early psychosis. Recent studies have confirmed widespread reductions in amygdala subnuclei also in schizophrenia (Barth et al., 2021; Tesli et al., 2020), but the results on bipolar spectrum disorder are more conflicting (Barth et al., 2021; Damme et al., 2020) (**Table 1**). In schizophrenia, the basolateral amygdala reductions are suggested to be the most prominent. The main limitations of comparing of the studies on amygdala subnuclei are partly different segmentation and/or the segmentation procedure of these structures, since only a few studies separate the BLA into its subnuclei–lateral, basal, and accessory basal nuclei; the difference in the phase of the illness, and the unknown duration of untreated psychosis, which might relate to progressive volume loss (Goff et al., 2018).

The most replicable findings together with our study are volume reductions particularly in the basolateral amygdala in FEP and schizophrenia (**Table 1**). In Study I, the most robust reductions also in CHR were observed in both the lateral and basal nuclei. However, the statistical power of the smaller sample might have limited the results to the lateral nucleus only. The effects in the basal and lateral nucleus were not explained by antipsychotic drug exposure and are likely to have a neurodevelopmental origin. Our findings in CHR further suggest that particularly a smaller lateral nucleus may be a biomarker for the psychosis risk. A spread of amygdala subnuclei reductions from the lateral to basal nucleus after the onset of psychotic disorder could be interpreted as progressive morphology change and could be associated with the clinical progression of schizophrenia and multiple environmental or GxE effects. Yet, longitudinal high-resolution MRI imaging studies on early psychosis are needed to further characterize the time course of morphological changes in the amygdala subnuclei.

Given the amygdala's role in processing emotions and stress (Anticevic et al., 2012; LeDoux, 2007; Roozendaal et al., 2009), salience attribution, valence attribution (Beyeler et al., 2016; Hall et al., 2008; Pignatelli & Beyeler, 2019), fear learning and social cognition (Adolphs, 2010), amygdala volume reductions may be associated with disruptions in these functions, which are often impaired in psychotic disorders. More specifically, the BLA and particularly lateral nucleus are important in valence attribution (Beyeler et al., 2016; Bigot et al., 2024; Janak & Tye, 2015), fear conditioning and fear extinction processes (Duvarci & Pare, 2014; Pape & Pare, 2010). Thus, our finding on a reduced lateral nucleus in both CHR and FEP might relate to the broader impairments in emotion processing, stress reactivity, and

salience detection often seen in psychotic disorders, providing a possible neuroanatomical basis for these functional disruptions.

To conclude, the structural reductions in the lateral nucleus observed in CHR and FEP in Study I may contribute to the hallmark symptoms of psychotic disorders, including emotional dysregulation, heightened stress sensitivity, and impaired salience attribution. This is particularly relevant, as the lateral nucleus is considered the main sensory input region to the amygdala (LeDoux, 2007), relaying information to the basal nucleus and further to the hippocampus, nucleus accumbens, and prefrontal cortex (Roozendaal et al., 2009), acting as a central node in these critical neural circuits.

6.2.1 Lateral nucleus of amygdala and childhood adversities

Particularly in first-episode psychosis, the evidence supports a relationship between increased childhood trauma and reduced total amygdala volumes (Aas et al., 2012), similar studies on the subnuclei-level have not been conducted before. In Study I, we found that higher levels of childhood adversity experiences were associated with a lower volume of the lateral nucleus in the first episode of psychosis. Thus, our study adds that especially lateral nucleus appears to be the most affected subnuclei in relation to childhood adversities in FEP. Since we did not study associations between lateral nucleus volumes and childhood adversity in CHR-C, due to the cross-sectional study design, it is not possible to determine whether such an association exists or emerges only in those who transition to their first psychotic episode.

The amygdala is central in relation to the effects of childhood adversity on the brain structure and function. Particularly in schizophrenia patients, higher levels of sexual abuse and physical neglect during childhood have been found to be associated with decreased connectivity between the amygdala and the posterior cingulate/precuneus region (Cancel et al., 2017). To add, specific regions such as the basolateral amygdala, central nucleus of the amygdala, and the CA1 and subicular subfields of the hippocampus—in interaction with the PFC—modulate the HPA–axis function and in stress reactions. HPA-axis dysfunction has been connected to childhood adversities (Bremne & Vermetten, 2001; Van Voorhees & Scarpa, 2004). Further, the amygdala is an essential node in the salience network and default mode network (Xu et al., 2024), which have been suggested to be dysfunctional in schizophrenia (Nekovarova et al., 2014; Palaniyappan et al., 2012), and related to childhood adversities (Dauvermann et al., 2021; Hardi et al., 2024).

The evidence from animal models suggests the crucial role of the BLA in stress sensitivity (Gyawali & James, 2022; Pesarico et al., 2022). More specifically, based on animal models, there is also some evidence that the lateral nucleus may be

particularly vulnerable to stress during the development, already due to prenatal stress (Charil et al., 2010) (Kraszpulski et al., 2006). The observed reduction in the lateral nucleus in Study I might relate to the reduced numbers of neurons and glial cells (Charil et al., 2010; Kraszpulski et al., 2006), disruptions in the GABAergic interneurons (Zhang & Rosenkranz, 2016), dendritic abnormalities (Wang et al., 2012) of the lateral nucleus, or reduction in intercalated cell (ITC) clusters (Aksoy-Aksel et al., 2024; Millhouse, 1986), that further relate to alterations in the amygdala function (Kraszpulski et al., 2006). This is important particularly in relation to heightened stress sensitivity (Delavari et al., 2023), disturbed emotion regulation, valence attribution or fear extinction (Aksoy-Aksel et al., 2024), and further psychosis. These findings suggest that the lateral nucleus may be particularly vulnerable to the harmful effects of early life stress.

6.3 Hippocampal subfields are reduced in early psychosis

Study II showed that the hippocampus has specific volume reductions in the early phase of psychosis. In FEP, particularly non-affective psychosis patients had more widespread reductions in hippocampal subfields, such as the hippocampal tail, presubiculum, subiculum, CA1, molecular layer (of the CA fields and subiculum), and GCMLDG. Earlier studies suggest a generalized hippocampal subfield volume reduction in early psychosis, especially in schizophrenia, with a possibly more pronounced effect on the CA1 area (see **Table 1**). Our results on FEP are in line with these.

Since in CHR, the hippocampal tail volume was statistically significantly reduced, particularly in those not converting to psychosis, it is possible that some CHR-NC transition to psychosis only after the one-year follow-up period. Also, due to the heterogeneity of CHR, this could suggest that the volume reduction in the tail of the CHR is not specific to psychosis, or it may be influenced by the effect of antidepressants (Nogovitsyn et al., 2020; Qi et al., 2021) or untreated duration of comorbid depression (MacQueen et al., 2008; Maller et al., 2018; Nogovitsyn et al., 2020) or other non-psychotic disorders. However, we did not find associations between hippocampus subfield volumes and antidepressant use in any group. The severity of possible comorbid depression was not assessed in our study.

It has also been suggested that CA1 morphology change could be related to the transition to psychosis. (Ho et al., 2017a; McHugo et al., 2020; Provenzano et al., 2020) More broadly, the role of the CA1 subfield has been highlighted multimodally in the progression and etiology of schizophrenia and related psychoses (see Chapter 2.6.1.1.). In our study, the CA1 volume was not significantly smaller in CHR-C compared to CTR, even though the volume reduction was greater in CHR-C

compared to CTR than between CHR-NC and CTR. Furthermore, the volume of CA1 showed a trend-level difference between FEP and CHR-NC, but no similar difference was observed between FEP and CHR-C. This suggests that the CA1 volume in CHR-C could be more similar to that of FEP than to CHR-NC. In our sample of CHR-C, the majority convert to non-affective psychosis. The heterogeneity of our results might relate to the fact some CHR might convert to non-affective psychoses while others convert to affective psychoses, which affects hippocampal morphology differently (see **Table 2**). This is further supported by our results on NAP having more widespread reductions in hippocampal subfields compared to affective psychosis. Thus, our results on the alterations in CA1 morphology as the transition risk in CHR, particularly to schizophrenia, are mainly in line with earlier studies.

Only a few MRI studies on hippocampal subfields have used a longitudinal design. In line with our one-year follow-up results, McHugo et al (McHugo et al., 2020) found that the subfield volume remains stable during the two-year follow-up period after the onset of the first psychosis, as well as in CHR and further CHR-C and CHR-NC. The findings of our study and the earlier study suggest that the hippocampal subfield volumes remain predominantly stable in early psychosis. These results support the view that morphological changes in the hippocampus may be manifested earlier in the course of psychosis. While there may be early neurodevelopmental alterations, particularly in the CA1 subfield, the exact timeline for later widespread changes remains unclear. However, a progressive decline in the CA1 volume in individuals at ultra-high risk for psychosis who do not remit has been observed in an earlier longitudinal study (Ho et al., 2017a). We did not find longitudinal changes in subfield volumes in relation to the follow-up remission status or poor or good functioning measured with GAF in CHR, CHR-C or CHR-NC in Study II. This might be due to the sample characteristics, particularly the phase of the psychotic disorder, the rate of transition, the age of the onset of psychotic or prodromal symptoms (Chung et al., 2018) and the shorter follow-up time of the Study II.

In the future, it might be useful to examine the correlation between subfield volumes and the duration of untreated psychosis, as it might explain the progressive hippocampal volume loss and its potential episodic pattern near the onset of the first psychosis (Briend et al., 2020). This could clarify whether delayed treatment contributes to the progressive nature of hippocampal alterations in first episode of psychosis but also in CHR. Finally, CHR is heterogeneous group, as it includes patients with diverse symptom profiles and varying levels of risk for transitioning to different types of psychosis, i.e., affective or non-affective. Some may develop other mental health disorders, while others may experience psychosis much later. Bigger sample sizes are needed to study these subgroups separately. Only about one-third

of CHR subjects typically develop psychosis, which can make it challenging to draw definitive conclusions, especially in small sample studies with negative results. Negative results in such samples might reflect the variability and heterogeneity within the FEP and CHR groups, as well as limitations in statistical power due to their smaller subgroup sizes. This applies to both Studies I and II. Further cohort studies targeting children and adolescents who later develop psychosis, as well as longitudinal studies near the onset of the first psychosis, are needed to investigate both amygdala and hippocampal substructures. These studies are essential for better understanding of the timeline of both hippocampus subfield and amygdala subnuclei abnormalities and their roles in the emergence of psychotic disorders. However, the purpose of this thesis was to study common morphological phenomena in early psychosis; from this perspective, the hippocampal tail and CA1 subfield may play a crucial role.

6.3.1 Hippocampal subfields and childhood adversities

It has been suggested that there are clinically and neurobiologically distinct subtypes also in individuals with childhood adversity experiences as well, particularly relating to the hippocampus and amygdala (Teicher & Samson, 2013). However, the results are inconclusive (Hanson et al., 2015; Paquola et al., 2016; Samplin et al., 2013; Woon & Hedges, 2008), and may be partly explained by suggested sex differences in adversity effects on hippocampus and amygdala functional connectivity (Herringa et al., 2013) but also morphology (Samplin et al., 2013), or different vulnerability periods between the hippocampus and amygdala during the neurodevelopment (Cullen et al., 2024). Other related factors, that might explain the inconsistent findings, are the normative nonlinear development of both the amygdala and hippocampus (Wierenga et al., 2014), and the timing and severity (Croft et al., 2019; Herzog et al., 2020; Ogle et al., 2013; Riem et al., 2015) of adversities during stress sensitive developmental periods.

There is no evidence supporting an association between childhood adversities and the hippocampal volume in FEP (Aas et al., 2012). Similarly, we did not find any associations between TADS scores and the hippocampal subfield or total volumes in either the FEP or CHR groups in Study II (unpublished data), which is consistent with these findings. This might be due to the more prominent effects of childhood adverse events on the amygdala, instead of the hippocampus; this idea is supported also by meta-analysis on general population (Calem et al., 2017). Additionally, hippocampal dysfunction, rather than altered subfield morphology, may primarily be linked to childhood adversities in early psychosis (Aas et al., 2012). However, altered connections between the BLA and particularly CA1 are strong (Pikkarainen et al., 1999), and have been observed to link to adversities and stress

adaptation (W. H. Zhang et al., 2021), thus, at least the indirect effects on hippocampal subfields are presumably also involved.

To mention possible sources of biases, TADS is a retrospective questionnaire, which limits its strength and power, as retrospective data collection may be subject to the recall bias, inaccuracies in participants' memories, and the influence of time-related factors that can affect the validity and reliability of the reported information. This might lead to lower rates of reported maltreatment (Goodman et al., 2003), and possibly a smaller observed effect. Further, a psychotic disorder might however influence how participants respond to TADS, as cognitive and perceptual alterations associated with the disorder could bias their answers. However, the trauma ratings have demonstrated strong internal consistency, as well as reliability and validity. (Fisher et al., 2011; Salokangas et al., 2016) Finally, post-traumatic stress disorder (PTSD), a potential comorbidity that could particularly impact the amygdala, hippocampus, and prefrontal cortex, was not accounted for in our analyses (Alexandra Kredlow et al., 2022; Haris et al., 2023). Future studies incorporating the PTSD assessment would be valuable to disentangle the overlapping effects of these conditions on brain morphology.

In conclusion, these findings based on earlier findings and our results suggest that the impact of childhood trauma on the risk of psychosis may be mediated by brain circuit dysfunction, involving particularly the changes in the amygdala morphology, with an emphasis on the role of the lateral nucleus. Our results propose that early adversities might already affect the lateral nucleus during early neurodevelopment in the progression of psychotic disorders. Due to essential connections between the basal nucleus, lateral nucleus and hippocampal subfields, particularly the subiculum and CA1, the effects presumably also involve the hippocampus and its function (see Chapter 2.8), but not its subfield morphology near the onset of first psychosis (**Figure 4** and **Figure 12**).

6.4 Synthesis: Hippocampus and amygdala subnuclei as part of neural circuitry predisposing to psychotic disorders

In schizophrenia, one or more of the vital developmental normative processes may be disrupted due to neurodevelopmental gene-environment interactions. Both early and later neurodevelopmental structural vulnerability factors are likely related to the progression of psychotic disorders. In the light of the earlier literature (see **Table 1** and **2**) and the results of our Studies I through III, it is possible that the hippocampus, amygdala, frontal and temporal cortices are some of the most vulnerable structures of the brain in the context of the evolvement and neurodevelopment of psychotic disorder. Thus, their alterations as the central nodes of brain networks can result in

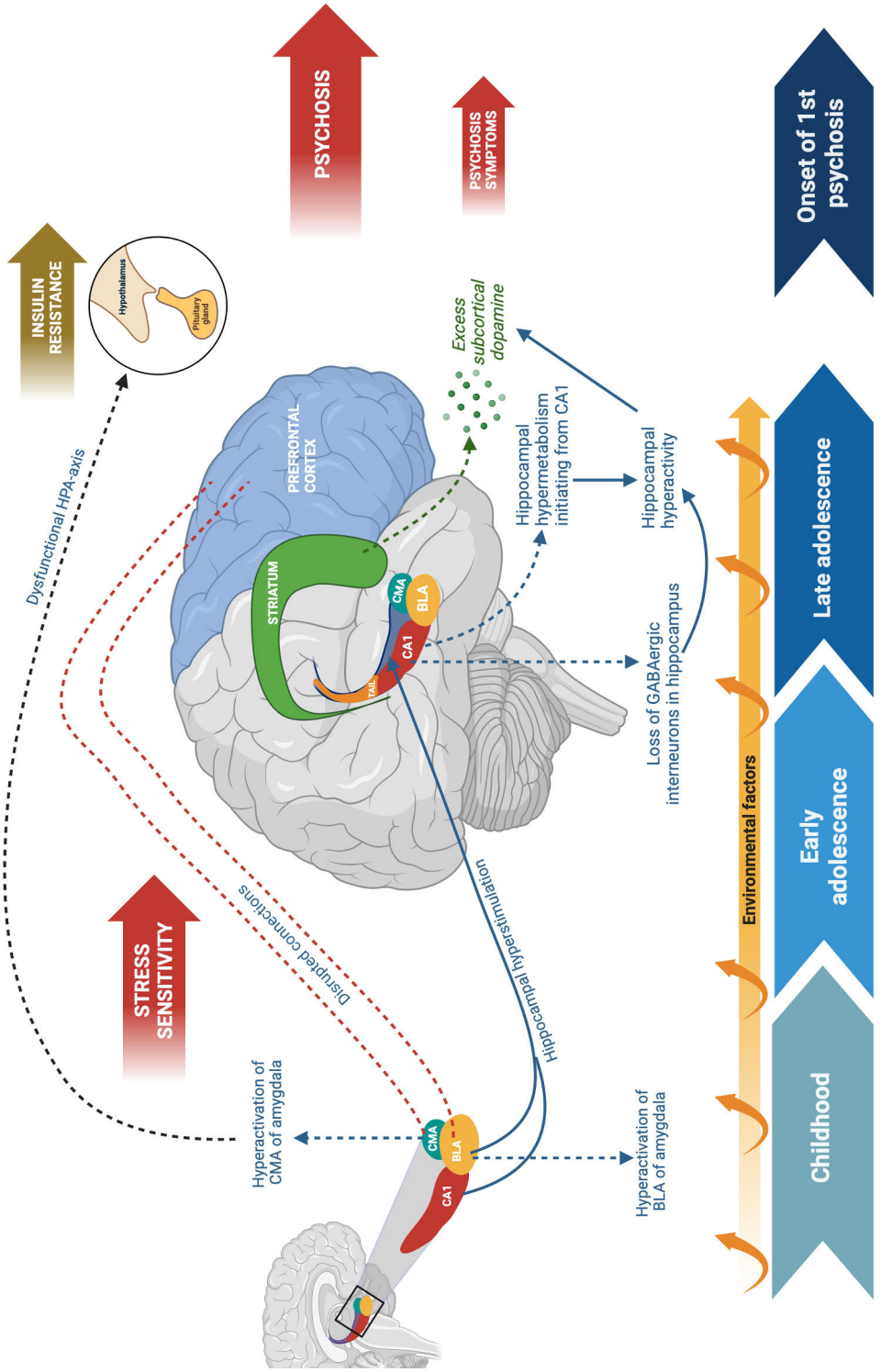
the disintegration of these networks by seriously disrupting the flow of information, integration and synchrony (Sporns, 2013). Structural changes in these regions have been frequently observed in individuals with psychotic disorders, often emerging in from early neurodevelopmental stages to young adulthood, which are critical periods for brain maturation. (Chiapponi et al., 2013) This is in line with a previous study that found the dysfunction of the amygdalar subnuclei, particularly early alterations in the BLA, drives stress and later psychosis symptoms (Delavari et al., 2023).

Early structural BLA and CA1, and later prefrontal cortex defects during neurodevelopment might represent trait-like features of the brain's structural vulnerabilities, which further predispose individuals to state-like features, such as psychotic symptoms and the deterioration of glucose metabolism. These developmental structural abnormalities evolve in interaction with, i.e., immune, stress and metabolic systems, but also with environmental factors. Our findings on the reduced lateral nucleus volume associating with a higher exposure of childhood adverse experiences in FEP, as well as earlier studies on the amygdala and hippocampal volume and function relating to childhood adversities underlines this link. Further, our finding of the reduced lateral nucleus volume being altered in high-risk patients, highlights the trait-like feature of lateral nucleus abnormality already in an at-risk state. The structural vulnerability, i.e., trait features, further affects the connectivity, functionality, and synchronization of closely interconnected brain regions, such as connections from the BLA, to the hippocampal subiculum, CA1, entorhinal cortex, PFC, and hypothalamus (Delavari et al., 2023; Petrovich et al., 2001). Moreover, the effects of a reduced volume in the hippocampus and amygdala likely relate to wider dysfunctionality between these regions. The significance of these findings in relation to the etiology of psychosis may be linked to the fact that basal and lateral nucleus has crucial partly bidirectional connections to other brain regions such as the CA1 subfield of the hippocampus, BNST and further PVN of the hypothalamus, as well as the prefrontal cortex (**Figure 12**). All of these are essential regions in the development of psychosis, particularly in relation to altered metabolism, disrupted neurotransmitter function, and aberrant functional networks observed in psychotic disorders, particularly in schizophrenia (**Figure 4).**

Overall, in the development of a psychotic disorder, there is a complex interaction among various biological factors — including structural brain changes, neurotransmitter dysfunction, excitation-inhibition imbalance, and alterations in the gut-brain axis, immune, metabolic, and stress systems. Thus, the high risk for a psychosis state may already result from the involvement of these multiple dysfunctional organ systems, defected biological factors in interaction with environmental factors, that jointly form the combination of vulnerability traits and further states in the acute phase of psychosis. It is presumable, that the predisposing trait-like characteristics are particularly related to the structure and function of the

BLA, CA1, and PFC, with a different temporal emphasis, that further lead to the onset of the first psychosis. **(Figure 4** and **Figure 12).**

Figure 12. ►Simplified illustration of the most prominent neurodevelopmental defects in the hippocampus and amygdala in the development of the first psychotic episode. The effects of environmental factors (orange arrows) may vary depending on their cumulative nature, timing and quality (protective versus unprotective), relating to the age of onset of the first psychotic episode. Modified from (Delavari et al., 2023). Created by the author with BioRender.com.


INSULIN RESISTANCE
Hypothalamus
Pituitary gland
PSYCHOSIS
PSYCHOSIS SYMPTOMS
Onset of 1st psychosis
Dysfunctional HPA-axis
PREFRONTAL CORTEX
STRIATUM
CMA
BLA
CA1
TAIL
Excess subcortical dopamine
Hippocampal hypermetabolism initiating from CA1
Hippocampal hyperactivity
Loss of GABAergic interneurons in hippocampus
Hippocampal hyperstimulation
Disrupted connections
STRESS SENSITIVITY
Hyperactivation of CMA of amygdala
Hyperactivation of BLA of amygdala
Environmental factors
Childhood
Early adolescence
Late adolescence

6.5 Insulin resistance is linked to hippocampal morphology in early psychosis

In Study II, we also found that elevated fasting plasma insulin levels and insulin resistance were linked to smaller hippocampal tail volumes only in non-diabetic first-episode of psychosis patients at the follow-up time point. Further, the worsening in insulin resistance was observed during the follow-up in CHR, and it was associated with poorer outcomes, including the transition to psychosis and decreased functional ability. These results were not explained by lifetime antipsychotic exposure. Our findings suggest that metabolic dysfunction may contribute to hippocampal structural changes already in early psychosis, particularly after the onset of the illness. This is supported, since we did not identify any explanatory differences in the characteristics of the FEP or CHR samples when comparing the baseline to the follow-up. This suggests that patients appear to be missing at random, and the data does not seem to be particularly selective regarding the association between tail volume reduction and insulin resistance, which was observed in FEP only at the follow-up time point. Thus, it is possible that the different stage of the illness is the major explanation for the tail atrophy and its relation to glucose metabolism deterioration.

As a proxy for insulin resistance, we used HOMA2-IR (Song et al., 2016; Wallace et al., 2004), which is considered to be a more accurate measure of insulin resistance and beta-cell function as it represents both hepatic glucose output and peripheral glucose uptake. Hence, it is possible to speculate that our results on higher systemic insulin resistance and lower hippocampal subfield and amygdala subnuclei volumes in FEP and CHR-C may particularly reflect abnormalities in the central glucose metabolism regulatory pathway, which controls hepatic glucose production. The association between a lower tail volume and higher insulin resistance in FEP appears to be particularly essential in this process. Specifically, the hepatic pathway involves the hippocampal and amygdalar connections to the PVN and the LHA of the hypothalamus, mainly via the BNST (**Figure 4**). The PVN is one of the key nuclei of the hypothalamus that further regulate hepatic glucose metabolism (Pan et al., 2023). Further, cannabinoid type 1 (CB1) -receptors, altered in FEP (Borgan et al., 2019) (Dickens et al., 2020), are highly expressed in the hippocampus, and there is evidence that activating CB1 receptors in the central nervous system alone can disrupt the body's ability to maintain stable blood glucose levels, through hepatic glucose production (O'Hare et al., 2011). Also, insulin receptor/IGF1R deletion in both the hippocampus and amygdala have shown to lead to impaired glucose tolerance (Soto et al., 2019). Thus, changes in both insulin receptors and/or CB1 receptors might be one mechanism behind the observed associations between the hippocampal tail volume and deterioration of systemic insulin resistance in FEP.

In CHR or CHR-C, the hippocampal tail volume was not associated with insulin resistance, unlike in FEP during the follow-up. The tail volume was smaller in FEP, particularly in NAP, but also in CHR, particularly in CHR-NC. However, the difference in the hippocampal tail volume between CHR-C and CHR-NC or NAP and affective psychosis was not significant after multiple corrections. This may suggest that the processes influencing the tail volume differ between CHR-C, CHR-NC, and further between affective and NAP groups. This discrepancy may also reflect differences in the stage of illness, with metabolic dysregulation and its impact on hippocampal morphology potentially becoming more pronounced as the psychosis progresses from the CHR to the FEP stage and further NAP and schizophrenia. However, the relatively small sample sizes of CHR-C, CHR-NC, NAP and affective psychosis limit the power of results and need further studies.

To add, our findings of the correlations between a smaller hippocampal tail volume and worse insulin resistance in Study II might partly reflect the effect of related sources of biases or other factors that have been found in connection to psychotic disorders. These sources of biases might be a dysfunctional blood brain barrier (Butler et al., 2010; Davidson & Stevenson, 2024; SCHARRER, 1940; Schobel et al., 2009; Spallazzi et al., 2019), mitochondrial function (Roberts, 2017; Whitehurst & Howes, 2022) (Holper et al., 2019; Kung & Roberts, 1999; McDermott & de Silva, 2005; Najjar et al., 2017; Zaki et al., 2022), and defected insulin and glucose transporters (McDermott & de Silva, 2005), as well as, alterations in cytokine (Rochfort & Cummins, 2015) or dopamine levels (Heni et al., 2014; Ter Horst et al., 2018) (Agarwal et al., 2020), and/or imbalances in brain oscillations (Walker et al., 2021) —all of which have been observed in psychotic disorders. All these mechanisms might be involved in the observed heightening of insulin resistance near the onset of the first psychosis.

Bidirectionally, impaired glucose metabolism may affect the hippocampal structure, while the dysfunctional hippocampus may, in turn, further contribute to disrupted glucose regulation. These effects may be primarily due to the effects of hyperglycemia on mitochondrial function, which can lead to an increase in reactive oxygen species and disrupt axonal transport, that contribute to the development of i.e. structural changes particularly in the hippocampus (Morella et al., 2022). The results of our Study II support this, since we found a negative association between the tail volume and insulin or insulin resistance significant only at the follow-up. This association was not observed in CHR. This delayed association may suggest that sustained metabolic dysfunction over time is required to induce observable structural changes. In psychoses this might be more prominent due to the pre-existing alterations in hippocampus morphology and function. Also, the heterogeneity of the groups may have influenced the results.

To conclude, these results suggest that subfield-specific findings related to glucose metabolism may provide additional temporospatial insights in relation to neurodevelopmental subfield alterations in early psychosis. While some subfield abnormalities are detectable already in CHR, other subfields show volume reductions that are associated with higher insulin and insulin resistance only at the follow-up of FEP. These findings may reflect distinct trait- and state-related changes during the different stages of psychosis progression. However, the mechanisms driving the specificity of these associations remain unclear. The hippocampus is the only known brain region where physiological neurogenesis continues into adulthood across mammalian species and in humans. Thus, its significant neuroplasticity and neurogenesis ability could lead to increased susceptibility to negative influences, such as stress, trauma, or metabolic pressure (Lieberman et al., 2018). Also, the hippocampus is highly metabolically active and sensitive to changes in energy metabolism. There is also evidence of differential metabolism between anterior and posterior hippocampus, with specific network connectivity (Maleki Balajoo et al., 2023). This recent study also suggest that 'metabolic subregions', which account for anterior–posterior differentiation, offer a more sensitive model than anatomical segments to study hippocampal subregional local metabolism. Further research is needed to explore these potential mechanisms of bidimensional hippocampal differentiation and clarify the nature of these associations in psychotic disorders.

6.5.1 Synthesis: The hippocampus is associated with impaired glucose tolerance inherent in schizophrenia?

Both in psychotic disorders and diabetes, there have been observed associations between higher insulin resistance and lower volume in the hippocampus (Milne et al., 2018), in multiple subfields, including the tail (Monereo-Sanchez et al., 2023; W. Zhang et al., 2021). In fact, already in non-psychotic healthy adults the hippocampal total volume has been observed to be associated with a direct measure of insulin resistance, suggesting the role of the hippocampus in central glucose regulation (Frangou et al., 2022). One study on diabetes mellitus type 1 (T1DM) and type 2 (T2DM) demonstrated distinct cerebral grey matter effects, T1DM was associated with thalamic and cortical atrophy while T2DM was related particularly to global cerebral atrophy and hippocampal atrophy (Moulton et al., 2015). Also, fewer white matter connections between the hippocampus and frontal lobe have been observed in T2DM (Liu et al., 2020; van Bussel et al., 2016). This might highlight the similarities and overlaps in both schizophrenia and diabetes. However, the glucose disturbances seem to progress in parallel to the psychosis onset, which directs to the idea that the mechanisms other than only comorbid are shared.

In Study II, we report, for the first time, an association between a reduced hippocampal tail volume and elevated insulin resistance in FEP patients, even in non-diabetic states. Further, we found that insulin and insulin resistance worsened in CHR during the follow-up period. The worsening of glucose metabolism was statistically significant only in CHR-C, but not in CHR-NC. Also, the hippocampal tail volume associating with insulin and insulin resistance was observed only in FEP. Since widespread reductions in subfields, including the hippocampal tail have been recently reported in T2DM (Monereo-Sanchez et al., 2023), but not in prediabetes, it is possible that a more progressive decline in the tail volume associating with dysfunctional glucose metabolism already in the prediabetic state in FEP, may correlate to the mechanisms in psychosis etiology rather than diabetes, or their more complex combination. Observations of altered glucose metabolism in chronic schizophrenia as a part of the psychotic disorder originated in the late 19th century (Kohen, 2004; Maudsley, 1879). Based on the earlier findings in progressive tail volume loss in chronic schizophrenia (Sasabayashi et al., 2021), the glucose homeostasis disturbances and tail volume reductions, may be related to a more chronic non-affective psychosis, or more specifically to chronic schizophrenia. In line with this, the associations between a smaller tail volume and increased insulin resistance in FEP, were observed only at the follow-up in Study II. Specifically, this highlights that the insulin resistance-related volume loss, which begins in the hippocampal tail, manifests after the onset of the first psychosis, and may correspond with a worsening clinical course or more severe progression of schizophrenia over time.

In conclusion, the glucose disturbances accompanying psychotic disorder suggest that the link between the two could be mechanistically interrelated, with partly shared brain abnormalities, rather than purely coincidental or a comorbid psychotic disorder and diabetes. This highlights the potential for shared neurobiological mechanisms and co-occurrence, such as insulin signaling, inflammation and reduced hippocampal volume, but also the role of the hippocampus and amygdala in glucose regulation (Gralle et al., 2021; Soto et al., 2019), that contribute to both diabetes and schizophrenia. However, in psychotic disorders, impaired glucose metabolism might be connected to a broader and more intricate disruption of bioenergetic coupling processes, already present in the high-risk state and in non-diabetic states (Bryll et al., 2020; Morella et al., 2022; Sullivan et al., 2018; Whitehurst & Howes, 2022). Even though it is not possible to draw direct causal conclusions between brain morphology and clinical variables regarding their causes, effects, or their temporal order, these findings emphasize that understanding psychotic disorders requires integrating these different modalities at different time points in the progression of psychotic disorder to capture its multifaceted character.

6.6 Insulin resistance is linked to transition to psychosis and worse clinical outcomes in high-risk individuals

In Study II, we found that insulin resistance in the CHR group deteriorated over the follow-up period, aligning with worse outcomes, including the transition to psychosis and impaired functioning, measured with GAF. It is possible to assume that this effect stems from individual health behaviors, such as exercise (Sormunen et al., 2017) and diet, which may be influenced by symptom severity. However, a recent longitudinal study observed worsening fasting glucose levels in individuals with recent-onset psychosis, even as lifestyle habits improved (Shin et al., 2020), clinical symptoms diminished, and antipsychotic medication use decreased (Alonso et al., 2022). These findings together with our results support the view that declining glucose metabolism may be more closely linked to the progression of psychotic illness itself rather than to unhealthy behaviors or the metabolic effects of antipsychotic medication, which is also in line with the historical perspective (Andreassen, 2017; Kohen, 2004; Maudsley, 1879). Our findings are further supported by recent studies indicating a partial shared genetic basis for schizophrenia, cardiometabolic, and inflammation-related traits (Perry et al., 2022).

We did not find an association between clinical outcome and glucose metabolism deterioration in FEP, but only in CHR. In general, FEP patients already had higher insulin resistance levels at the baseline, while the worsening was most prominent in CHR-C. Thus, the worsening of insulin resistance in the CHR, particularly in those who transit to psychosis, might be the initial marker of the state change related to the impending onset of psychosis itself. These findings could be discussed further in the context of how disruptions in the glucose metabolism regulatory networks and structures may contribute to systemic metabolic dysfunctions observed near the onset of the first episode of psychosis. The findings of Study II suggest that specifically hippocampal subfield abnormalities and worsening glucose metabolism in early psychosis are interconnected, and deteriorating insulin resistance may play a role in the progression of psychotic disorders and their outcome already in the clinical high-risk state.

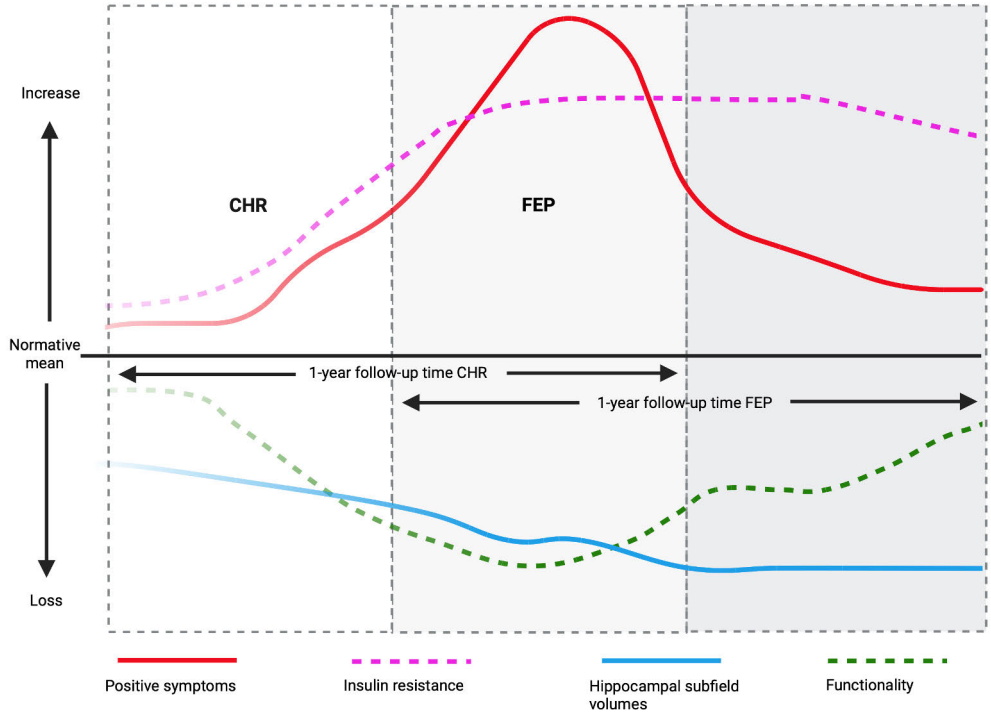


Figure 13. Illustration of a theoretical model depicting overlaps between the progression of glucose metabolism disturbances, hippocampal subfield volume changes in first-episode psychosis (FEP), and the deterioration in clinical outcomes in clinical high-risk subjects (CHR), as derived from our research findings from our longitudinal Study II. Functionality is assessed using the Global Assessment of Functioning (GAF) scale. Created by the author with BioRender.com.

6.7 Antipsychotic drug use associates with cortical thinning in early psychosis and schizophrenia

It is likely that the molecular mechanisms of antipsychotic drug action, the illness itself, and environmental factors all contribute to cortical thinning seen in psychotic disorders. These factors are also interconnected and cumulative. The effects of both psychotic and non-psychotic illness processes might be present (Patel et al., 2021). Therefore, the observed cortical thickness in both previous studies and our Study III reflects a combination of processes occurring throughout a longer period of life.

In schizophrenia and psychotic disorders, the effects of antipsychotic medication on cortical thickness (Fusar-Poli et al., 2013b; Ho et al., 2011; Konttajärvi et al., 2024; S. Sun et al., 2023; van Erp et al., 2016; van Haren et al., 2011) have been consistently found in particular in frontotemporal regions (Chung et al., 2018) that may also be relevant regions as far as the illness pathology is concerned. A recent randomized controlled trial supports this causal relationship, at least in psychotic

depression (Voineskos et al., 2020). These results are mainly in line with ours from Study III that shows the most prominent cortical thinning in the prefrontal, cingulate, and parietal cortices. However, conflicting evidence exists, with some studies finding no effect of antipsychotics on grey matter volume in previously antipsychotic-naïve first-episode psychosis patients (Chopra et al., 2021), while an earlier study suggests the excessive thinning of the cortex appears to relate to the outcome and antipsychotic medication type, at least in schizophrenia (van Haren et al., 2011). These discrepancies might relate to the features of the sample population, particularly to the phase of the psychotic disorder. Compared to our results on antipsychotic-related cortical thinning, the same cortical regions have been observed to be thinner already in CHR (Jung et al., 2011).

Environmental factors, such as childhood adversities (beta range of significant cortical regions [-0.32;-0.48]) (Gold et al., 2016) and allostatic load (partial correlation r = -0.64) (Chiappelli et al., 2017), the combination of these, particularly in schizophrenia, may relate to the observed cortical thinning. Also, lifestyle habits and metabolic conditions, such as insulin resistance (Shin et al., 2020) and obesity (Gómez-Apo et al., 2021), have been observed to be associated with a thinner cortex. The effect of insulin resistance on cortical thickness should be tested in future analyses with our data samples as well. However, adiposity-related insulin resistance has been found to be associated with lower cortical thickness only in middle-aged women older than 50 years (beta = -0.28) (Shin et al., 2020), which is above the total age range of the discovery sample and above the mean age of the replication sample. Still, the effects could be different and manifesting at an earlier stage in psychotic disorders compared to healthy controls.

Other lifestyle factors, including substance abuse, such as tobacco (r = -0.09) (Rabinowitz et al., 2022) (Li et al., 2022), alcohol (r = -0.10) (Rabinowitz et al., 2022), and cannabis use (r = -0.54 to -0.67) (Wittemann et al., 2021), but also physical activity (beta = 0.001) (Angelo et al., 2022), have been proposed as potential confounding variables in studies on cortical morphological changes (Zipursky et al., 2013). The shared genetic etiology between cortical brain morphology and substance use behaviors suggests that genetic variants associated with substance use behaviors may be causally related to brain structure differences (Rabinowitz et al., 2022). In the early psychosis discovery sample, substance use at a dependency level was an exclusion criterion, thus controlling for this factor to some degree. The effects of the BMI on cortical thickness are inconclusive (Chen et al., 2023). However, in our sensitivity analyses of the discovery sample the inclusion of the BMI in the model did not affect the significancy of the thinning effect of AP-medication on the cortex.

Based on earlier studies, the overlapping thinner cortical regions from CHR-C to chronic schizophrenia are in the prefrontal and temporal cortices. Our observed antipsychotic-related cortical thinning in both early psychosis and schizophrenia

samples overlap with these regions. These findings might suggest that both illness- and antipsychotic-related mechanisms associating with a thinner cortex might be linked and/or complementary and located in the same cortical regions. However, as our sensitivity analyses, controlling for factors indicative of illness severity—such as symptom scores, functional measures, total days hospitalized, and frequency of hospital admissions—did not alter the results, it is plausible that the observed effects of antipsychotics on cortical thickness are more pronounced than the effects attributable to illness severity in our samples. This point of view is also important due to the heterogenous group of particularly CHR, that may also have other non-psychotic manifesting symptoms (Rutigliano et al., 2016) (Simon et al., 2011). Thus, illness severity in FEP and CHR might be represented differently, though it was not prominently related to an AP-related thinner cortex in either group in our sensitivity analyses.

Finally, the correlations between antipsychotic use and cortical thickness were somewhat weaker in the ENIGMA cohort, and several factors may account for this. First, the ENIGMA dataset utilized daily dose as the measure of antipsychotic exposure, whereas the Turku sample assessed lifetime exposure. Second, the patients in the ENIGMA dataset tend to be older, have a longer duration of illness, and have been using antipsychotic medication for a longer period. Moreover, the variability introduced by data being collected across multiple sites and scanners in the ENIGMA study could contribute additional 'noise,' resulting in a weaker correlation. These factors likely explain the diminished associations between antipsychotic use and cortical thickness observed in the ENIGMA cohort.

6.7.1 Neurodevelopmental deficits modulate antipsychotic-related cortical thickness?

Particularly the younger age of onset and progressive antipsychotic exposure-related structural brain changes in schizophrenia have been found to be associated with one another (Konttajärvi et al., 2024). This finding might be explained by critical or vulnerable neurodevelopmental windows—periods when the brain is still developing and thus more sensitive to external influences, such as antipsychotics. These results suggest that the neurodevelopmental phase during the onset of the psychosis and/or during the antipsychotic exposure is crucial. The earlier timing of medication exposure might relate to altered developmental trajectories resulting in more excessive antipsychotic exposure-related cortical thinning.

Our findings support this view, since we observed a relationship between diminished T1/T2-relationship and antipsychotic related cortical thinning. Variations in the T1/T2-ratio can be related to brain maturation processes during neurodevelopment. A higher T1/T2-ratio could potentially indicate a reduction in

myelin among other contributing factors (Glasser & Van Essen, 2011). This suggests that areas with a thinner protective myelin sheet may be more sensitive to the effects of antipsychotic drugs leading to cortical thinning. This might be true particularly in schizophrenia, where there is evidence of impaired developmental myelination (Bergstrom & Fu, 2024; Do et al., 2015; Karlsgodt et al., 2008; Stedehouder & Kushner, 2017). Also, normatively, the hippocampus and frontal lobes, key regions in schizophrenia etiology, undergo the majority of their myelination during adolescence and do not finish until early adulthood (Arnold & Rioux, 2001). These factors together suggest the effect of antipsychotics on cortical thinning could be more pronounced in psychotic patients with ongoing disturbed myelination processes or/and pre-existing disturbances in myelination developed during atypical neurodevelopment. A lower degree of myelination may render the cortex more vulnerable to the effects of antipsychotic medication, but alterations in myelination might also serve as a potential target for antipsychotic medications (Ersland et al., 2017; Tishler et al., 2018). This is supported by the earlier postmortem studies of intracortical myelin deficits in the pathophysiology of schizophrenia, and further notions that targeting these deficits may represent a mechanism of action for antipsychotic medications (Tishler et al., 2018).

Since we used normative measures of brain organization from NeuroMaps, it is possible that the finding is slightly distorted due to the absence of pre-existing neurodevelopmental vulnerability factors of multiple systems present in psychotic disorders. This might be interpreted that our results present optimally at least the heterogenic effect of antipsychotic medication on cortical thickness, while brain organization is represented by normative maps. Also, we do not know how antipsychotics would affect the healthy brain during different neurodevelopmental stages. This cannot be directly concluded from nonhuman primate or rodent studies (Dorph-Petersen et al., 2005; Guma et al., 2018; Vernon et al., 2011), particularly in relation to our results of AP-related cortical thinning localizing to higher-order cortical regions.

To conclude, the antipsychotic related cortical thinning might be due to the interaction of the antipsychotics with pre-existing neurodevelopmental alterations, but also due to direct mechanisms on cortical organization—most likely this is related to the interaction between the two preceding factors. Since antipsychotics are effective in treating positive symptoms of psychosis, the cortical thinning could be part of its favorable effect. This need to be studied further.

6.8 Antipsychotic-related cortical thinning associates with multiple-levels of normative brain organization

Study III uncovered several novel neurobiological mechanisms, related to molecular, physiological and functional features, potentially responsible for antipsychotic-related cortical thinning, providing new perspectives on the impact of antipsychotic medications. Similar studies on antipsychotic-related cortical thinning and its association with multiple levels of brain organization in early psychosis or schizophrenia have not been conducted earlier.

In the discovery sample of Turku early psychosis that combines both FEP and CHR patients, we identified 18 features associated with antipsychotic-related cortical thinning. The features positively correlating with cortical thinning were serotonin $5HT_{2A}$ and $5HT_4$ receptors, nicotinic α4β2* receptors, cannabinoid receptor 1, μ-opioid receptors, fMRI functional gradients, neurophysiological measures such as delta, theta, and low and high gamma power, intrinsic time scale, synaptic vesicles, and cerebral metabolic rate for glucose. In other words, regions with higher levels of these features (e.g., elevated serotonin $5HT_{2A}$ receptor density) exhibited more pronounced antipsychotic-related cortical thinning. Conversely, negatively correlated features included the serotonin transporter, vesicular acetylcholine transporter, alpha power, T1/T2 ratio, and cerebral blood volume levels.

The findings of Study III on the schizophrenia sample from the ENIGMA dataset revealed that from those 18 that were significant in the early psychosis discovery sample, 13 were replicated. The replicated measures were 5-HTT (serotonin transporter), 5-HT_{2A}, 5-HT_4, nicotinic a4b2* receptors, m-opioid receptors, cannabinoid 1 receptors, fMRI functional gradient, alpha, theta, low gamma, and power, T1/T2 ratio, synaptic density and cerebral blood volume. These results suggest that antipsychotic-related changes in the cortical thickness involve multiple biological mechanisms that overlap in both early psychosis and schizophrenia, at least when examined through normative map comparisons.

6.8.1 The role of serotonin system in antipsychotic-related cortical thickness

Our results suggest that antipsychotic-related cortical thinning is related to multiple neurotransmitter systems, particularly the serotonin system. This is in line with earlier results that suggest serotonin to increases neurite extension, dendritic stabilization and generation of new synapses, whereas the depletion of serotonin has been found to lead to the loss of synapses (Mazer et al., 1997). Further, particularly second-generation antipsychotics exhibit varying levels of affinity for serotonin

receptors (Amato, 2015), suggesting that the serotonin system may play a role in mediating part of the cortical remodeling associated with antipsychotic medications. In our study sample, the majority of the patients use second-generation antipsychotics, which might explain the association between the serotonin system and cortical thickness.

Serotonin receptors are widely distributed throughout the brain, and each subtype has a distinct pattern of expression and function (Kumar & Mann, 2014). However, the serotonin receptors most commonly found in the prefrontal cortex, such as 5-HT_{1A}, 5-HT_{2A}, 5-HT_{3A}, and 5-HT_4, are distributed among specific groups of pyramidal neurons and inhibitory interneurons (Puig & Gulledge, 2011). Serotonin receptors, particularly in PFC, are essential for regulating cortical activity and influencing neural oscillations (Puig & Gulledge, 2011). More specifically, serotonin influences the speed and strength of slow brain waves in the PFC by activating 5-HT_{2A}-receptors, generally leading to increased neural activity. (Puig et al., 2010) Thus, given that disturbances in neural oscillations are observed in psychotic disorders, the serotonergic effects of antipsychotic drugs, and further cortical thickness alterations, may also influence oscillatory powers. However, our correlation matrix from Study III suggests, that the associations with AP-related cortical thickness between brain oscillations (theta, low gamma and alpha) and the serotonin system (5-HT_{2A} and 5-HTT) appear not to be clearly correlated, but possibly interacting via the mu-opioid and cannabinoid system.

Further, particularly second-generation antipsychotics block 5-HT_{2A} receptors in the prefrontal cortex. This serotonin system's modulation of dopamine via 5-HT_{2A} receptor blockade may also be linked to cortical thinning associated with antipsychotic use and symptom remission. On the other hand, the effects of serotonin have been linked to reduction in antipsychotic-related side effects (Miller et al., 1990; Praharaj et al., 2015). Thus, the serotonin system might be integral to both the efficacy and side effect profile of antipsychotic medications (Kapur & Remington, 1996).

There are inconsistent results in post-mortem studies and PET-studies of schizophrenia regarding the decreases in 5-HT_2 receptors in the prefrontal cortex in schizophrenic patients (Lewis et al., 1999). More recent studies show that antipsychotic treatment decreases 5-HT_{2A} receptor density in the prelimbic cortex and nucleus accumbens and increase 5-HT_{2A} receptor density in the striatum. It is suggested that the activation of either 5-HT_2 receptors or of 5-HT_{2A} receptors selectively is required for the full expression of antipsychotic-induced dopamine receptor hypersensitivity (Charron et al., 2015). Thus, the observed alterations in 5-HT_2 receptors might represent compensatory changes resulting from the psychotic disorder itself or the mechanisms of antipsychotic drugs, presumably both. However,

it is conclusive that the role of serotonin is essential in psychotic disorders and psychotic symptoms, and it is related to antipsychotic effects on cortical thickness.

In Study III, we found higher levels of cortical serotonin $5HT_{2A}$ and $5HT_4$ – receptors relating to greater cortical thinning. Instead, we found a negative association between the serotonin transporter and antipsychotic-related cortical thinning. Since serotonin transporters and receptors have different roles and functions in serotonin signaling, our results suggest that the mechanisms differ also in relation to antipsychotic effects and cortical thinning (Amato, 2015) (**Figure 11**). This is interesting, since serotonin reuptake inhibitors, which block 5-HTT and increase serotonin in the synaptic cleft, have been shown to promote neuroplasticity and increase cortical thickness and better outcome, at least in MDD (Bartlett et al., 2018). On the one hand, higher 5-HTT levels may represent a more regulated serotonin system, ensuring stable neural signaling and potentially preserving cortical structure, which can act as a protective factor against the cortical thinning typically induced by antipsychotic treatment. On the other hand, blocking 5-HT_{2A} receptors can indirectly affect 5-HTT by altering the serotonin signaling dynamics. Further, psilocybin, a serotonergic psychedelic that produces a schizophrenia-like symptoms, also affects the brain via serotonin-2A receptor activation (Shao et al., 2021). It suggests that psilocybin leads to neural adaptations and structural remodeling in the brain, particularly in the frontal cortex. This indicates that psilocybin can induce synaptic rewiring and influence cortical structure, possibly through serotonergic pathways. Thus, it is presumable that there are more specific and distinct mechanisms behind serotonin-related effects on cortical thickness and psychotic symptoms; part of those presumably represent the treatment response and part of those, the side effects of antipsychotic medication.

Our results suggests that while serotonin signaling plays a crucial role in modulating the cortical structure, elevated receptor densities, especially in the context of antipsychotic treatment, may be linked to neuroplastic changes that promote cortical thinning. Thus, the relationship between serotonin, its receptors, transporters, and cortical thickness is multifaceted, with both serotonergic signaling and receptor dynamics possibly influencing the brain structure in different ways. However, the exact cellular and molecular mechanisms by which the effects on the serotonin system would lead to altered cortical thickness remain unknown.

6.8.2 Other neurotransmitter systems in antipsychotic-related cortical thickness

Elevated levels of nicotinic α4β2*-receptors were linked to cortical thinning. Although antipsychotics do not directly inhibit this receptor, they may function as negative allosteric modulators of α4β2*-receptors, reducing the receptor's activity

(Grinevich et al., 2009). Further, acetylcholine is involved in cortical maturation and plasticity, suggesting that some effects of antipsychotics may also be mediated through this neurotransmitter system (Bruel-Jungerman et al., 2011).

Notably, all currently used antipsychotics act on dopamine D2-receptors. Interestingly, in this study, dopamine D2 or D1 -receptor levels did not show any association with antipsychotic-related cortical thinning. Since the earlier rodent studies linking antipsychotic-related cortical thinning to dopamine D2-receptors have observed mainly typical antipsychotic-related (haloperidol) cortical thinning (Guma et al., 2018), and since our samples in both the discovery and replication sample examined mainly second-generation antipsychotic drug use, this might be explained by the type of the antipsychotics. In the Turku sample, 12%, had used first-generation antipsychotics, compared to 13% in the ENIGMA study.

Also, we observed a positive association between antipsychotic-related cortical thickness and CB1-receptors or μ-opioid-receptors. As antipsychotics do not directly target these receptors, their role in this context remains to be clarified. However, since there is also evidence that since activating CB1-receptors in the central nervous system alone can disrupt the body's ability to maintain stable blood glucose levels (O'Hare et al., 2011), these effects on cortical thickness might be related to metabolic effects. While μ-opioid receptors are not primary targets in the treatment of schizophrenia, their role in cortical functioning and their potential interaction with other neurobiological systems, such as dopamine and serotonin, makes them a relevant area of study for understanding the complex neurobiology of schizophrenia.

Indeed, in the correlation matrix we show positive correlations between the AP-related thinner cortex and 5-HT_{2A}-, 5-HT_4-, α4β2*-, CB1-, or μ-receptor, as well as synaptic vesicle associations. In the ENIGMA analyses the synaptic vesicles were measured with uniporter-coupled calcium-binding protein-J (UCBJ), which reflects synaptic density rather than targeting any single neurotransmitter system. These correlations across multiple neurotransmitter systems with AP-related cortical thinning suggest that the effects may be interconnected temporospatially and/or mediated by shared biological mechanisms. Since antipsychotics do not directly affect synaptic density (Halff et al., 2021; Onwordi et al., 2020), and given the complex interactions of serotonin and other neurotransmitter systems —both within and across receptor classes—as well as normative brain feature data, direct interpretations remain challenging. However, these results suggest that multiple neurotransmitter systems, particularly the serotonin system, are likely involved in the complex mechanisms of the action of antipsychotics on cortical thickness.

6.8.3 The role of brain physiological features in antipsychotic-related cortical thickness

In Study III, we observed associations between antipsychotic-cortical thickness and multiple physiological features of the cortex. Our replicated findings on physiological features in both the discovery and ENIGMA samples were that the AP-related thinner cortex was associated with lower alpha power, higher low gamma power, higher theta power, but also lower CBV. Further, in the discovery sample of early psychosis only, we found that the AP-related thinner cortex was associated with higher delta power, higher high gamma power, and an intrinsic timescale, but also a higher cerebral metabolic rate for glucose. These findings were nonsignificant in the schizophrenia sample. The differences between the findings of our early psychosis sample and replication sample of schizophrenia patients are discussed in a later section.

There is evidence of abnormal CBV decreases in the dorsolateral prefrontal cortex in schizophrenia, that is independent of antipsychotic drug use (Schobel et al., 2009). Further, frontal cortical hypoperfusion has been observed in patients with schizophrenia. (Percie du Sert et al., 2023) In our study, we observed that normatively lower cortical CBV might be related to higher antipsychotic-related thinning both in early psychosis and schizophrenia, but the findings were not significant in relation to CBF. These results suggest that particularly the prefrontal cortex might be more vulnerable to antipsychotic effects due to illness-related lower CBV, and this phenomenon might be present both in the early and later stages of psychotic disorders. The observed frontal cortical hypoperfusion in patients with schizophrenia (Percie du Sert et al., 2023) might explain the prefrontal cortex susceptibility to structural changes, which may be partly related to neurodevelopmental defects in the frontal cortical blood supply and vascular system.

Further, in the discovery sample, we found a higher cerebral metabolic rate for glucose (CMRGlu) associating with greater antipsychotic related cortical thinning, but a lower CBV associating with greater antipsychotic-related cortical thinning. This imbalance between heightened metabolic demand and insufficient vascular support may lead to increased structural fragility. In the replication sample of schizophrenia only a negative association between AP-related cortical thinning and CBV was statistically significant. Normatively cerebral blood flow is adjusted to the cerebral metabolic rate due to flow-metabolism coupling (Papasilekas et al., 2021). In the discovery sample, we did not examine the correlations between AP-related cortical thickness linked to CBV and AP-related cortical thickness linked to CMRGlu, thus, it is unknown whether these mechanisms relating to antipsychotic-related cortical thickness are compensatory and/or related. However, it could be hypothesized that the increase in CBV might be related to reduced antipsychotic-related cortical thinning, and this could be compensatory particularly in regions with

a higher cerebral metabolic rate. On the other hand, these associations between physiological features and AP-related cortical thinning may be a pre-existing physiological characteristic that renders certain cortical regions more susceptible to the effects of antipsychotics. However, trait-like neurodevelopmental physiological characteristics and state-like compensatory functions are presumably related. In this context, as our study focused on normative cortical organization, these findings may serve as hypotheses for future research in cohorts with psychotic disorders.

6.9 Antipsychotic-related cortical thinning localizes to regions with higher-order cognitive functions

Direct relationships between cortical thickness and total cognition, evaluated with cognitive domains, such as episodic memory, reasoning ability, perceptual speed, and vocabulary, have not been observed (Habeck et al., 2020). However, the study revealed a more complex, distributed pattern of regional cortical thickness related to education, indicating more complex interactions or distributed patterns between cortical thickness and cognitive functions. However, in Study III, we observed that antipsychotic-related cortical thinning may be more pronounced in regions involved in higher cognitive functions. These replicated higher-order cognitive parameters were particularly gamma power, theta power, and functional gradient.

Gamma oscillations are the most energy-intensive brain waves due to the rapid and synchronized firing of neurons across networks, especially during complex cognitive tasks (Mably & Colgin, 2018; van Vugt et al., 2010). They are linked to higher-order cognitive functions and require more energy than alpha waves, which are more prevalent in calm, awake states and basic cognitive processes (Galow et al., 2014; Klimesch, 2012). Low gamma oscillations are crucial for cognitive functions such as attention, sensory processing, and memory. Alpha oscillations are linked to attentional control, relaxation, and sensory filtering (Klimesch, 2012), while theta waves are more clearly associated with higher-order processes, such as memory encoding (Herweg et al., 2020), learning, and cognitive flexibility (Yeung et al., 2016).

We found that the power of gamma and theta oscillations show a positive correlation with antipsychotic-related cortical thinning, but alpha oscillation correlated negatively with the thinning. This is interesting, since the oscillation patterns, particularly theta and gamma oscillation, are known to be altered especially in the hippocampus and prefrontal cortex in schizophrenia (Rürup et al., 2020; Soltani Zangbar et al., 2020). Further, alterations in these oscillations have been implicated in schizophrenia, particularly in the context of deficits in higher-order cognition (Rürup et al., 2020). Our findings are in line with these results.

The idea of AP-related cortical thinning localizing to higher-cognitive cortical regions is further supported by our replicated results showing that antipsychotic-related cortical thinning is more pronounced in regions with higher levels of synaptic vesicles, that are generally indicative of increased synaptic activity, enhanced plasticity, and potentially greater neural processing capability. Also, in the discovery sample, the AP-related thinner cortex was associated with a higher level of CMRGlu, indicating that the regions susceptible to antipsychotic effects require more energy, which is typical particularly for cortical regions involved in higher cognitive functions.

Based on our correlation matrix, the links of the AP-related thinner cortex and higher gamma or higher theta power further correlated positively, suggesting similar temporospatial manifestations and/or mutual physiological processes between theta and gamma oscillations in relation to AP-related cortical thinning. Both gamma and theta power were positively associated with AP-related cortical thinning, whereas alpha power showed a negative association with AP-related cortical thinning. The observed differences in associations between AP-related cortical thinning between theta, gamma and alpha oscillation, might be partly explained in their need for energy and cerebral blood volume, and the stage of myelination. Indeed, in the replication sample, we found that increased AP-related cortical thinning was associated with reduced CBV, but also with reduced alpha power and reduced myelination. All these negative associations between replicated physiological features and antipsychotic-related cortical thinning were positively correlated with each other. It could mean that AP-related cortical thinning linking to reduced CBV, alpha power and myelination might occur simultaneously and/or in the same cortical regions, and/or as part of a linked physiological process. In other words, AP-related cortical thinning is not typical for regions with high alpha power, high CBV or myelination. These factors, particularly heightened vascular function and increased myelination, might be protective factors.

Finally, a higher functional gradient was associated with greater AP-related cortical thinning. The functional gradient is a resting state functional MRI connectivity measure that explores how brain activity transitions from simple sensory tasks (basic sensory areas, unimodal) to complex cognitive tasks (higher-order processing areas, transmodal) across different brain regions. This further suggests AP-related cortical thinning is related to higher cognitive functions.

These results suggest that antipsychotic-related cortical thinning localizes regions and/or relates to features associated with higher-order cognitive functions. Consequently, as a follow-up analysis, we tested whether AP-related cortical thinning would correlate positively with the fMRI activation of higher cognitive functions and negatively with activations during somatosensory tasks. We found that brain regions associated with motivation and executive/cognitive control exhibit

consistent positive correlations with antipsychotic-related cortical thinning, while regions primarily involved in perceptual processing appear to be more resistant to the effects of antipsychotics. These findings are in line with our primary findings on AP-related cortical thinning localizing to regions of higher-order cognitive functions.

6.10 Comparison of antipsychotic-related cortical thinning and normative brain organization in early psychosis and schizophrenia

In Study III, we observed associations between antipsychotic-cortical thickness and multiple physiological features of the cortex. Our replicated findings on physiological features in both discovery and ENIGMA samples were that the AP-related thinner cortex was associated with lower alpha power, higher low gamma power, higher theta power but also a lower CBV and higher functional gradient. The majority of the findings of the discovery sample were replicated.

In the discovery sample of early psychosis only, we found lower levels of vesicular acetylcholine transporter (VAChT), higher delta and high gamma power, as well as higher intrinsic timescale and higher CMRGlu to be associate with greater AP-related cortical thinning. This is particularly interesting, since the recently approved antipsychotic drug xanomeline modulates muscarinic receptors, a type of acetylcholine receptor, specifically through M_1- and M_4 -subtype agonism, presenting a promising alternative with a reduced risk of side effects. (Paul et al., 2022) (Kaul et al., 2024b) (Kaul et al., 2024a) Both muscarinic receptors and acetylcholine transporters are involved in acetylcholine signaling.

The differences in the replicated findings between early psychosis and schizophrenia may be related to variations in illness progression, particularly with respect to metabolic, physiological, and higher cognitive processes. On one hand, some of these unreplicated findings might be more specific to the CHR population and/or diagnostically more heterogenous FEP group. On the other hand, the replicated findings could reflect features more characteristic of a chronic population, more stable trait-like features of the schizophrenia. In addition to sample characteristics, the statistical power of a moderately sized discovery sample—such as manageable random variation and a moderate risk of type I errors—may contribute to these differences, though the findings are less prone to being false or exaggerated compared to smaller samples.

Further, the key differences at least partly explaining these discrepancies between the discovery and replication samples of ENIGMA might be the different illness stage, differences in the sample demographics, and/or the methods used to measure antipsychotic drug exposure. In the replication sample, schizophrenia

patients were older and there were slightly more males. In the discovery sample of early psychosis, the lifetime antipsychotic exposure was measured, whereas in the ENIGMA, the current daily dose of antipsychotics was assessed. In the Turku sample 12% had used first-generation antipsychotics, compared to 13% of the daily dose in the ENIGMA study. Also, the discovery sample is a single site study with a homogenous catchment area using a single scanner, while the schizophrenia sample is scanned at multiple locations with various scanners and protocols. Furthermore, since the discovery sample includes both FEP and CHR patients, while the ENIGMA replication sample consists only of individuals with schizophrenia, the replicated findings likely primarily validate the morphological alterations associated with psychotic disorders considering that only approximately 1/3 of individuals in the CHR group develop psychosis within two years. Also, brain organization in early psychosis and chronic schizophrenia might differ (Holmes et al., 2023). However, since the majority of the results in the discovery sample were replicated, these multiple mechanisms might be shared in both early and later stages of psychotic disorders, particularly in schizophrenia.

Finally, here we examine how the normative features of brain organization relate to antipsychotic-related cortical thickness in either the early psychosis or schizophrenia sample; thus, the brain organization maps in psychotic disorders are not observable in our results. (**Figure 8.**) Therefore, our findings on the observed features of brain organizations provide only research hypotheses for further investigation of the antipsychotic-related cortical thinning in more specific study designs.

6.11 Strengths and limitations of Studies I-III

Strengths

1. Our studies included comprehensive characterizations of two representative baseline samples (Study I and III) and a longitudinal one-year follow-up period between the baseline and follow-up samples (Study II). Further, we replicated our early psychosis sample findings with a large schizophrenia replication sample (Study III).
2. We utilized advanced, ex-vivo based, methods to segment the hippocampal subfield and amygdala subnuclei volumes, as well as to measure the cortical thickness. Additionally, we used a more precise measure of antipsychotic medication usage, assessing lifetime cumulative antipsychotic exposure. (Studies I-III).
3. In Study III, we used innovative approaches integrating NeuroMaps, NeuroSynth and cortical thickness measures, to incorporate diverse

normative physiological and cognitive features to study antipsychotic-related cortical thinning in early psychosis.
4. In Studies I-III, the entirety of the Turku discovery sample data was scanned with the same scanner and the quality control of the segmentations and MRI data was made by the same individual (R.-L.A.).

Limitations

1. The CHR group is highly heterogeneous and does not optimally represent the true risk of psychosis. It is heterogeneous both in terms of diagnostic psychiatric outcomes and the stage of the illness. Not all individuals in the CHR group will develop psychosis during the follow-up period; some may develop other mental health disorders, while others may experience psychosis much later. Therefore, the CHR group also reflects the risk for other mental health disorders. Efforts to address this heterogeneity have been made by further dividing the group into CHR-C and CHR-NC. Due to the cross-sectional study design, this was not possible in the Study I.
2. The study samples, particularly in subsamples, such as CHR-C, CHR-NC, NAP, and affective psychosis, are relatively small, thus the replication with larger sample sizes is needed.
3. The connections between systemic and CNS phenomena are difficult to investigate, since, i.e., systemic metabolism and brain morphology involve multiple mediating factors. Based on the associations alone, no definitive conclusions can be drawn regarding causality. More experimental studies, such as randomized controlled trials and longitudinal designs, are needed to establish causality i.e. between metabolic alterations, antipsychotic medication, and cortical thickness.

7 Conclusions, future directions and clinical implications

7.1 Main conclusions

1. Study I showed that the volume of the lateral nucleus of the amygdala is affected in both CHR and FEP. In FEP, a volumetric reduction of the basal nucleus is also present. Further, among FEP patients, greater childhood adverse experiences are associated with a smaller lateral nucleus of the amygdala supporting a role of environmental stressors in altered subnuclei morphology during the development of psychosis.
2. The longitudinal Study II indicates that increased fasting plasma insulin and insulin resistance are linked to reduced hippocampal tail volumes in non-diabetic patients after the onset of the first episode of psychosis. Further, insulin levels and insulin resistance appear to worsen during the one-year follow-up in CHR individuals, particularly among those who transition to the first psychosis. In the CHR, the worsening of glucometabolic parameters is further associated with clinical outcomes, particularly with impaired functioning. These alterations appear to be independent of lifetime antipsychotic exposure.
3. The longitudinal Study II shows that hippocampal subfield volumes are consistently lower in FEP, especially in non-affective psychoses. The reductions in CHR are less marked. These volume defects remain stable during the one-year follow-up period. The most pronounced volume reductions in the FEP group are localized to the hippocampal tail, CA1 subfield and molecular layer of CA fields, independent of lifetime antipsychotic exposure.
4. Study III shows that antipsychotic exposure is associated with a thinner mean cerebral cortex, and more specifically antipsychotic-related cortical thinning is the most prominent in the prefrontal, parietal and cingulate cortices in the early psychosis. Lifetime antipsychotic exposure remained statistically

significantly associated with the mean cortical thickness while covarying for indicators of illness severity.

5. Study III suggests, using independent early psychosis discovery and replication sample of schizophrenia patients, that antipsychotic-related cortical thinning has regional heterogeneity, and it is associated with multiple biological mechanisms. These mechanisms include the serotonin system, as well as functional networks and neural oscillatory power distributions typical for regions involved in higher cognitive functions.

The results from Studies I-III support the notion that, in addition to specific morphological changes in the amygdala, hippocampus, and cortex, systemic changes also occur, particularly around the onset of the first psychotic episode. These morphological changes may follow specific temporal and spatial patterns, and are associated with systemic and environmental factors, as well as various biological mechanisms related to antipsychotic treatment.

7.2 Future directions and clinical implications

Further research is needed to elucidate whether the improved management of glucose homeostasis with medical treatment during the early stages of the first psychotic episode is associated with a long-term prognosis, functional outcomes and further brain morphology and functioning during the follow-up. This could also be important for the development of new therapeutic approaches. There is some recent evidence suggesting that improving glucose metabolism in schizophrenia may enhance cognitive functioning and also strengthen functional connectivity, especially in the prefrontal cortex (Shao et al., 2023).

In Study III, we identified several novel neurobiological mechanisms that may underlie antipsychotic-associated cortical thinning. Specifically, the role of serotonin receptors in modulating the cortical thickness could be tested directly in animal models, potentially offering new insights into treatment targets. Further, it could be investigated how antipsychotic medication -related cortical thinning and its normative (and non-normative) underlying mechanisms differ between individuals who show a good response to the medication after one year of follow-up and those who show a poor response in psychotic disorders. Also, in Study III both discovery and replication samples pooled different antipsychotics together despite their significant pharmacological differences. In the Turku sample, the largest subgroup of people who were exposed only to a single antipsychotic consisted of 24 participants on risperidone, prohibiting further subgroup analyses in this sample. In the future, to elucidate the role of different biological substrates in mediating the effects of antipsychotics on cortical thickness, it would be important to have large

enough samples that allow separation of the effects of different antipsychotics on cortical thickness.

Future studies should also consider examining the direct measures of stress response and HPA-axis function, including dynamic tests such as the dex/CRH and dexamethasone suppression tests, and static assessments like basal cortisol levels, near the onset of the first psychotic episode. These measures should be explored in relation to metabolic changes, functional outcomes, disease severity, and childhood adversities, but also in relation to the amygdala subnuclei, hippocampal subfield and cortical morphology, and the interactions between these clinical and morphological measures. For example, using our study samples I and II, based on childhood adverse experiences, it would be interesting to further study the associations between glucose metabolism parameters, subnuclei or subfield volumes, and their outcome trajectories. These studies would clarify and help to understand the associations found in studies I-III. Studying these factors early in the course of psychotic illness would be essential for developing a better understanding of the disorder and identifying early biomarkers that may be related to clinical outcomes and treatment mechanisms.

Acknowledgements

The studies forming this thesis were conducted as part of The Etiology and Treatment of Severe Mental Health Disorders (VAMI) research program. The MRI scans for this project were performed at the Turku PET Center between 2012 and 2018. I would like to convey my sincere respect to the participants of this study. This thesis would not have been possible without volunteers like you, and the progress in clinical medicine would not be as it is today. Although the journey has been long and at times complex, I have been fortunate to have the most supportive people by my side throughout.

Most importantly, I wish to express my gratitude to my thesis supervisors, Professor Jarmo Hietala and Assistant Professor Lauri Tuominen, for their professional and patient guidance throughout this project. Their steady support, thoughtful supervision, and open attitude encouraged me to seek advice whenever needed and fostered my academic development. I have always found Jarmo to be easily approachable with my questions, creating a safe and supportive environment for learning. Also, his expertise in psychosis research and encouraging presence have greatly contributed to my persistence and progress throughout this project. Lauri has been a fundamental source of support, in methodological matters and overall supervision, but also as a friend. Without his presence and guidance, this journey would have been not only more difficult, but also far less inspiring.

I am also grateful for the expertise the previous head of the Department of psychiatry Emeritus Professor Raimo Salokangas and Professor Jaana Suvisaari, the members of my supervisory committee, shared regarding psychosis research, and their useful advise during this process. Raimo has shared numerous insights grounded in his broad experience in psychiatric research and deepened by his historical perspective. Professor Ole A. Andreassen and Professor Stephen Lawrie are acknowledged for their thoughtful review of this thesis and for providing insightful feedback and constructive criticism. Heidi Morris is warmly thanked for rapid grammatical review of this thesis.

I owe my sincere gratitude to all my co-authors for their collaboration, and to Adjunct Professor Harri Merisaari, statistician Arvi Tolvanen, Rami Mikkola and Marko Tättäläinen who consistently assisted with and answered my questions related

to softwares, data processing, coding, or statistical analyses. Thank you Tiina From for clinical data managing. I also want to thank Professor Lauri Nummenmaa and PhD Tomi Karjalainen for their help and for allowing the use of your server, 'Yngwie,' during the initial stages of image processing and analyses.

I am also deeply grateful to the VAMI group and personnel for the supportive and welcoming atmosphere throughout these years during the regular VAMI meetings; especially to Raimo Salokangas, Jarmo Hietala, Lauri Tuominen, Tuula Ilonen, Tiina From, Päivi Jalo, Maija Walta, Arvi Tolvanen, Iiro Pirhonen, Alexander Denissoff, Anna Avellan, Janina Paju, Akseli Mäkelä, Willehard Haaki and Heli Laukka.

My sincere thanks go to all of the personnel at the Turku PET Center, especially Professor Juhani Knuuti, the director of the Turku PET Center, but also to all of the radiographers, laboratory techicians, particularly Minna Aatsinki and Anne-Mari Jokinen, and hospital physicist PhD Virva Saunavaara. I want to also thank radiologists PhD Mikko Nyman and Professor Jussi Hirvonen, who interpreted the MRI scans of the subjects. This work was partly carried out after long working hours in clinical settings, and partly during research leave. Thus, I would like to thank the head of the Department of Psychiatry Professor Jarmo Hietala and MD PhD Jyrki Heikkilä for a possibility to combine research with clinical work during my specialization training.

I am grateful to all my fellow researchers at the Turku PET Center and Department of Psychiatry. You have inspired and supported me during the project, particularly MD PhD Elina Sormunen, MD PhD Heikki Laurikainen, MD PhD Sandra Manninen, MD Maija Walta, MD Tuomo Noppari and, MD Lasse Lukkarinen. Without my dear friend Elina Sormunen, the final stages of this process would have been far more mentally challenging. Thank you for the shared moments at the library and the weekend ‘breakfasts at Börs’, where we worked side by side on finalizing our dissertations. I am also grateful to my dear friend Maija Walta, whose kindness and support have been invaluable throughout the later years of our shared scientific journey. I would also want to thank senior researcher, Professor Juho Joutsa, Associate Professor Noora Scheinin, Assistant Professor Henry Karlsson, and Professor Lauri Nummenmaa, for their inspiration and friendship. Special thanks go to ‘PET Girls and Boys’ led by Professor Lauri Nummenmaa; particularly Elina Sormunen, Sandra Manninen, Maija Walta, Lauri Tuominen, Henry Karlsson, Jussi Hirvonen, Juho Joutsa, Jetro Tuulari, Jouni Tuisku, Tiina Saanijoki, Heikki Laurikainen, Henri Honka, Noora Scheinin, to name just a few. Thank you for the invaluable social events during the early years of this study.

I would like to express my gratitude to Adjunct Professor Tero Taiminen for inspiring me in the field of neuromodulation, for believing in my potential in both science and clinical psychiatry, and for encouraging my clinical teaching. Also,

Assistant Professor Max Karukivi, the Director of Integrative Psychotherapy Training, I greatly appreciate your (psychological) flexibility and understanding throughout my psychotherapist training, which enabled me to successfully bring my dissertation to completion.

This written work of this thesis was financially supported by grants and stipends from Finnish Cultural Foundation, Valto Takala Foundation, Doctoral Programme in Clinical Research, Turku University Foundation, TYKS Foundation, Finnish Psychiatry Research Foundation, State Research Funding, Finnish Psychiatric Association, Finnish Medical Society Duodecim, The Finnish Medical Foundation, University of Turku Research Funding, The Alfred Kordelin Foundation, and The Maud Kuistila Memorial Foundation. I would like to thank the funders for their support and invaluable contribution to making this work possible.

It is hard to find words to express my gratitude and affection to my friends and family. I am very lucky to have parents like Pirkko Säilä and Jukka Hytönen, who always support me with love and encouragement. I am grateful to have a brother like Paulus Säilä, whose support and humor have been invaluable throughout this journey, and who has always been someone I can trust. My family have always been encouraging and understanding towards my dreams and goals. In addition, I want to thank Hanna Armio, and Heikki and Leena Armio, all of whom are the beloved grandparents of our children from the side of my husband Ville Armio. Thank you for your warm attitude towards me and understanding throughout this long project. I would also like to thank Anna Lautamäki, Katriina Lähdetie, Sandra Manninen, Emmi Hatakka, Martta Elonheimo, Veera Säilä, Arla Hillner, and 'The Turhis group', your friendship means a lot to me.

Finally, I am profoundly and endlessly grateful to my dear husband, colleague, and best friend, Ville for his unwavering support, patience, and love. Ville has supported me, most importantly during challenging times, from the very beginning of my thesis. In the end, I dedicate this book to Ville and our dear sons Frans and Volter. With you, every day is filled with happiness and a sense of purpose.

Turku, April 2025
Reetta-Liina Armio

References

Aas, M., Navari, S., Gibbs, A., Mondelli, V., Fisher, H. L., Morgan, C., Morgan, K., MacCabe, J., Reichenberg, A., Zanelli, J., Fearon, P., Jones, P. B., Murray, R. M., Pariante, C. M., & Dazzan, P. (2012). Is there a link between childhood trauma, cognition, and amygdala and hippocampus volume in first-episode psychosis? *Schizophr Res*, *137*(1-3), 73-79. https://doi.org/10.1016/j.schres.2012.01.035

Adolphs, R. (2010). What does the amygdala contribute to social cognition? *Ann N Y Acad Sci*, *1191*(1), 42-61. https://doi.org/10.1111/j.1749-6632.2010.05445.x

Agarwal, S. M., Caravaggio, F., Costa-Dookhan, K. A., Castellani, L., Kowalchuk, C., Asgariroozbehani, R., Graff-Guerrero, A., & Hahn, M. (2020). Brain insulin action in schizophrenia: Something borrowed and something new. *Neuropharmacology*, *163*, 107633. https://doi.org/10.1016/j.neuropharm.2019.05.010

Agarwal, S. M., Panda, R., Costa-Dookhan, K. A., MacKenzie, N. E., Treen, Q. C., Caravaggio, F., Hashim, E., Leung, G., Kirpalani, A., Matheson, K., Chintoh, A. F., Kramer, C. K., Voineskos, A. N., Graff-Guerrero, A., Remington, G. J., & Hahn, M. K. (2021). Metformin for early comorbid glucose dysregulation and schizophrenia spectrum disorders: a pilot double-blind randomized clinical trial. *Transl Psychiatry*, *11*(1), 219. https://doi.org/10.1038/s41398-021-01338-2

Agrawal, R., Reno, C. M., Sharma, S., Christensen, C., Huang, Y., & Fisher, S. J. (2021). Insulin action in the brain regulates both central and peripheral functions. *Am J Physiol Endocrinol Metab*, *321*(1), E156-e163. https://doi.org/10.1152/ajpendo.00642.2020

Ahmed, H., Leyrolle, Q., Koistinen, V., Kärkkäinen, O., Layé, S., Delzenne, N., & Hanhineva, K. (2022). Microbiota-derived metabolites as drivers of gut-brain communication. *Gut Microbes*, *14*(1), 2102878. https://doi.org/10.1080/19490976.2022.2102878

Aksoy-Aksel, A., Ferraguti, F., Holmes, A., Lüthi, A., & Ehrlich, I. (2024). Amygdala intercalated cells form an evolutionarily conserved system orchestrating brain networks. *Nat Neurosci*. https://doi.org/10.1038/s41593-024-01836-8

Alexander-Bloch, A. F., Shou, H., Liu, S., Satterthwaite, T. D., Glahn, D. C., Shinohara, R. T., Vandekar, S. N., & Raznahan, A. (2018). On testing for spatial correspondence between maps of human brain structure and function. *Neuroimage*, *178*, 540-551. https://doi.org/10.1016/j.neuroimage.2018.05.070

Alexandra Kredlow, M., Fenster, R. J., Laurent, E. S., Ressler, K. J., & Phelps, E. A. (2022). Prefrontal cortex, amygdala, and threat processing: implications for PTSD. *Neuropsychopharmacology*, *47*(1), 247-259. https://doi.org/10.1038/s41386-021-01155-7

Allebeck, P. (1989). Schizophrenia: a life-shortening disease. *Schizophr Bull*, *15*(1), 81-89. https://doi.org/10.1093/schbul/15.1.81

Allen, P., Azis, M., Modinos, G., Bossong, M. G., Bonoldi, I., Samson, C., Quinn, B., Kempton, M. J., Howes, O. D., Stone, J. M., Calem, M., Perez, J., Bhattacharayya, S., Broome, M. R., Grace, A. A., Zelaya, F., & McGuire, P. (2018). Increased Resting Hippocampal and Basal Ganglia Perfusion in People at Ultra High Risk for Psychosis: Replication in a Second Cohort. *Schizophr Bull*, *44*(6), 1323-1331. https://doi.org/10.1093/schbul/sbx169

Allen, P., Chaddock, C. A., Egerton, A., Howes, O. D., Bonoldi, I., Zelaya, F., Bhattacharyya, S., Murray, R., & McGuire, P. (2016). Resting Hyperperfusion of the Hippocampus, Midbrain, and Basal Ganglia in People at High Risk for Psychosis. *Am J Psychiatry*, *173*(4), 392-399. https://doi.org/10.1176/appi.ajp.2015.15040485

Alonso, Y., Miralles, C., Algora, M. J., Valiente-Palleja, A., Sanchez-Gistau, V., Muntane, G., Labad, J., Vilella, E., & Martorell, L. (2022). Risk factors for metabolic syndrome in individuals with recent-onset psychosis at disease onset and after 1-year follow-up. *Sci Rep*, *12*(1), 11386. https://doi.org/10.1038/s41598-022-15479-x

Alvarez-Herrera, S., Rosel Vales, M., Pérez-Sánchez, G., Becerril-Villanueva, E., Flores-Medina, Y., Maldonado-García, J. L., Saracco-Alvarez, R., Escamilla, R., & Pavón, L. (2024). Risperidone Decreases Expression of Serotonin Receptor-2A (5-HT2A) and Serotonin Transporter (SERT) but Not Dopamine Receptors and Dopamine Transporter (DAT) in PBMCs from Patients with Schizophrenia. *Pharmaceuticals (Basel)*, *17*(2). https://doi.org/10.3390/ph17020167

Amato, D. (2015). Serotonin in antipsychotic drugs action. *Behav Brain Res*, *277*, 125-135. https://doi.org/10.1016/j.bbr.2014.07.025

Andreasen, N. C., Carpenter, W. T., Jr., Kane, J. M., Lasser, R. A., Marder, S. R., & Weinberger, D. R. (2005). Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry*, *162*(3), 441-449. https://doi.org/10.1176/appi.ajp.162.3.441

Andreassen, O. A. (2017). Diabetes and Schizophrenia-New Findings for an Old Puzzle. *Am J Psychiatry*, *174*(7), 616-617. https://doi.org/10.1176/appi.ajp.2017.17040409

Andréasson, S., Allebeck, P., Engström, A., & Rydberg, U. (1987). Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet*, *2*(8574), 1483-1486. https://doi.org/10.1016/s0140-6736(87)92620-1

Angelo, B. C., DeFendis, A., Yau, A., Alves, J. M., Thompson, P. M., Xiang, A. H., Page, K. A., & Luo, S. (2022). Relationships between physical activity, healthy eating and cortical thickness in children and young adults. *Brain Imaging Behav*, *16*(6), 2690-2704. https://doi.org/10.1007/s11682-022-00728-4

Anthony, K., Reed, L. J., Dunn, J. T., Bingham, E., Hopkins, D., Marsden, P. K., & Amiel, S. A. (2006). Attenuation of insulin-evoked responses in brain networks controlling appetite and reward in insulin resistance: the cerebral basis for impaired control of food intake in metabolic syndrome? *Diabetes*, *55*(11), 2986-2992. https://doi.org/10.2337/db06-0376

Anticevic, A., Tang, Y., Cho, Y. T., Repovs, G., Cole, M. W., Savic, A., Wang, F., Krystal, J. H., & Xu, K. (2014). Amygdala connectivity differs among chronic, early course, and individuals at risk for developing schizophrenia. *Schizophr Bull*, *40*(5), 1105-1116. https://doi.org/10.1093/schbul/sbt165

Anticevic, A., Van Snellenberg, J. X., Cohen, R. E., Repovs, G., Dowd, E. C., & Barch, D. M. (2012). Amygdala recruitment in schizophrenia in response to aversive emotional material: a meta-analysis of neuroimaging studies. *Schizophr Bull*, *38*(3), 608-621. https://doi.org/10.1093/schbul/sbq131

Armio, R. L., Laurikainen, H., Ilonen, T., Walta, M., Salokangas, R. K. R., Koutsouleris, N., Hietala, J., & Tuominen, L. (2020). Amygdala subnucleus volumes in psychosis high-risk state and first-episode psychosis. *Schizophr Res*, *215*, 284-292. https://doi.org/10.1016/j.schres.2019.10.014

Armio, R. L., Laurikainen, H., Ilonen, T., Walta, M., Sormunen, E., Tolvanen, A., Salokangas, R. K. R., Koutsouleris, N., Tuominen, L., & Hietala, J. (2024). Longitudinal study on hippocampal subfields and glucose metabolism in early psychosis. *Schizophrenia (Heidelb)*, *10*(1), 66. https://doi.org/10.1038/s41537-024-00475-z

Arnold, S. E., & Rioux, L. (2001). Challenges, status, and opportunities for studying developmental neuropathology in adult schizophrenia. *Schizophr Bull*, *27*(3), 395-416. https://doi.org/10.1093/oxfordjournals.schbul.a006883

Astle, W. J., Elding, H., Jiang, T., Allen, D., Ruklisa, D., Mann, A. L., Mead, D., Bouman, H., Riveros-Mckay, F., Kostadima, M. A., Lambourne, J. J., Sivapalaratnam, S., Downes, K., Kundu, K., Bomba, L., Berentsen, K., Bradley, J. R., Daugherty, L. C., Delaneau, O.,…Soranzo, N. (2016).

The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. *Cell*, *167*(5), 1415-1429.e1419. https://doi.org/10.1016/j.cell.2016.10.042

Ayhan, F., Kulkarni, A., Berto, S., Sivaprakasam, K., Douglas, C., Lega, B. C., & Konopka, G. (2021). Resolving cellular and molecular diversity along the hippocampal anterior-to-posterior axis in humans. *Neuron*, *109*(13), 2091-2105.e2096. https://doi.org/10.1016/j.neuron.2021.05.003

Baglivo, V., Cao, B., Mwangi, B., Bellani, M., Perlini, C., Lasalvia, A., Dusi, N., Bonetto, C., Cristofalo, D., Alessandrini, F., Zoccatelli, G., Ciceri, E., Dario, L., Enrico, C., Francesca, P., Mazzi, F., Paolo, S., Balestrieri, M., Soares, J. C.,…Brambilla, P. (2018). Hippocampal Subfield Volumes in Patients With First-Episode Psychosis. *Schizophr Bull*, *44*(3), 552-559. https://doi.org/10.1093/schbul/sbx108

Bailey, T., Alvarez-Jimenez, M., Garcia-Sanchez, A. M., Hulbert, C., Barlow, E., & Bendall, S. (2018). Childhood Trauma Is Associated With Severity of Hallucinations and Delusions in Psychotic Disorders: A Systematic Review and Meta-Analysis. *Schizophr Bull*, *44*(5), 1111-1122. https://doi.org/10.1093/schbul/sbx161

Bang, J. Y., Zhao, J., Rahman, M., St-Cyr, S., McGowan, P. O., & Kim, J. C. (2022). Hippocampus-Anterior Hypothalamic Circuit Modulates Stress-Induced Endocrine and Behavioral Response. *Front Neural Circuits*, *16*, 894722. https://doi.org/10.3389/fncir.2022.894722

Barth, C., Nerland, S., de Lange, A. G., Wortinger, L. A., Hilland, E., Andreassen, O. A., Jørgensen, K. N., & Agartz, I. (2021). In Vivo Amygdala Nuclei Volumes in Schizophrenia and Bipolar Disorders. *Schizophr Bull*, *47*(5), 1431-1441. https://doi.org/10.1093/schbul/sbaa192

Bartlett, E. A., DeLorenzo, C., Sharma, P., Yang, J., Zhang, M., Petkova, E., Weissman, M., McGrath, P. J., Fava, M., Ogden, R. T., Kurian, B. T., Malchow, A., Cooper, C. M., Trombello, J. M., McInnis, M., Adams, P., Oquendo, M. A., Pizzagalli, D. A., Trivedi, M., & Parsey, R. V. (2018). Pretreatment and early-treatment cortical thickness is associated with SSRI treatment response in major depressive disorder. *Neuropsychopharmacology*, *43*(11), 2221-2230. https://doi.org/10.1038/s41386-018-0122-9

Başar, E., & Güntekin, B. (2008). A review of brain oscillations in cognitive disorders and the role of neurotransmitters. *Brain Res*, *1235*, 172-193. https://doi.org/10.1016/j.brainres.2008.06.103

Basavaraju, R., France, J., Sigmon, H. C., Girgis, R. R., Brucato, G., Lieberman, J. A., Small, S. A., & Provenzano, F. A. (2023). Increased parietal and occipital lobe gyrification predicts conversion to syndromal psychosis in a clinical high-risk cohort. *Schizophr Res*, *255*, 246-255. https://doi.org/10.1016/j.schres.2023.03.027

Begleiter, H., & Porjesz, B. (2006). Genetics of human brain oscillations. *Int J Psychophysiol*, *60*(2), 162-171. https://doi.org/10.1016/j.ijpsycho.2005.12.013

Bell, C., Tesli, N., Gurholt, T. P., Rokicki, J., Hjell, G., Fischer-Vieler, T., Melle, I., Agartz, I., Andreassen, O. A., Rasmussen, K., Johansen, R., Friestad, C., & Haukvik, U. K. (2022). Associations between amygdala nuclei volumes, psychosis, psychopathy, and violent offending. *Psychiatry Res Neuroimaging*, *319*, 111416. https://doi.org/10.1016/j.pscychresns.2021.111416

Belujon, P., & Grace, A. A. (2011). Hippocampus, amygdala, and stress: interacting systems that affect susceptibility to addiction. *Ann N Y Acad Sci*, *1216*, 114-121. https://doi.org/10.1111/j.1749-6632.2010.05896.x

Belvederi Murri, M., Prestia, D., Mondelli, V., Pariante, C., Patti, S., Olivieri, B., Arzani, C., Masotti, M., Respino, M., Antonioli, M., Vassallo, L., Serafini, G., Perna, G., Pompili, M., & Amore, M. (2016). The HPA axis in bipolar disorder: Systematic review and meta-analysis. *Psychoneuroendocrinology*, *63*, 327-342. https://doi.org/10.1016/j.psyneuen.2015.10.014

Benes, F. M., Sorensen, I., & Bird, E. D. (1991). Reduced neuronal size in posterior hippocampus of schizophrenic patients. *Schizophr Bull*, *17*(4), 597-608. https://doi.org/10.1093/schbul/17.4.597

Benzo, C. A. (1983). Minireview. The hypothalamus and blood glucose regulation. *Life Sci*, *32*(22), 2509-2515. https://doi.org/10.1016/0024-3205(83)90231-x

Berger, M., Gray, J. A., & Roth, B. L. (2009). The expanded biology of serotonin. *Annu Rev Med*, *60*, 355-366. https://doi.org/10.1146/annurev.med.60.042307.110802

Berger, M., Kraeuter, A. K., Romanik, D., Malouf, P., Amminger, G. P., & Sarnyai, Z. (2016). Cortisol awakening response in patients with psychosis: Systematic review and meta-analysis. *Neurosci Biobehav Rev*, *68*, 157-166. https://doi.org/10.1016/j.neubiorev.2016.05.027

Bergstrom, J. J. D., & Fu, M. M. (2024). Dysregulation of myelination-related genes in schizophrenia. *J Neurochem*, *168*(9), 2227-2242. https://doi.org/10.1111/jnc.16152

Berthelot, N., Garon-Bissonnette, J., Jomphe, V., Doucet-Beaupré, H., Bureau, A., & Maziade, M. (2022). Childhood Trauma May Increase Risk of Psychosis and Mood Disorder in Genetically High-risk Children and Adolescents by Enhancing the Accumulation of Risk Indicators. *Schizophr Bull Open*, *3*(1), sgac017. https://doi.org/10.1093/schizbullopen/sgac017

Beyeler, A., Namburi, P., Glober, G. F., Simonnet, C., Calhoon, G. G., Conyers, G. F., Luck, R., Wildes, C. P., & Tye, K. M. (2016). Divergent Routing of Positive and Negative Information from the Amygdala during Memory Retrieval. *Neuron*, *90*(2), 348-361. https://doi.org/10.1016/j.neuron.2016.03.004

Biessels, G. J., Kamal, A., Ramakers, G. M., Urban, I. J., Spruijt, B. M., Erkelens, D. W., & Gispen, W. H. (1996). Place learning and hippocampal synaptic plasticity in streptozotocin-induced diabetic rats. *Diabetes*, *45*(9), 1259-1266. https://doi.org/10.2337/diab.45.9.1259

Bighelli, I., Rodolico, A., García-Mieres, H., Pitschel-Walz, G., Hansen, W.-P., Schneider-Thoma, J., Siafis, S., Wu, H., Wang, D., Salanti, G., Furukawa, T. A., Barbui, C., & Leucht, S. (2021). Psychosocial and psychological interventions for relapse prevention in schizophrenia: a systematic review and network meta-analysis. *The Lancet Psychiatry*, *8*(11), 969-980. https://doi.org/10.1016/S2215-0366(21)00243-1

Bigot, M., De Badts, C. H., Benchetrit, A., Vicq, É., Moigneu, C., Meyrel, M., Wagner, S., Hennrich, A. A., Houenou, J., Lledo, P. M., Henry, C., & Alonso, M. (2024). Disrupted basolateral amygdala circuits supports negative valence bias in depressive states. *Transl Psychiatry*, *14*(1), 382. https://doi.org/10.1038/s41398-024-03085-6

Bingham, E. M., Hopkins, D., Smith, D., Pernet, A., Hallett, W., Reed, L., Marsden, P. K., & Amiel, S. A. (2002). The role of insulin in human brain glucose metabolism: an 18fluoro-deoxyglucose positron emission tomography study. *Diabetes*, *51*(12), 3384-3390. https://doi.org/10.2337/diabetes.51.12.3384

Bipolar disorder. Current Care Guidelines. (2024). Suomalainen Lääkäriseura Duodecim. Retrieved 22.8. from https://www.kaypahoito.fi/hoi50076

Birnbaum, R., & Weinberger, D. R. (2020). A Genetics Perspective on the Role of the (Neuro)Immune System in Schizophrenia. *Schizophr Res*, *217*, 105-113. https://doi.org/10.1016/j.schres.2019.02.005

Bleuler, E. (1911). Dementia Praecox oder Gruppe der Schizophrenien. Leipzig, Germany: Deuticke.

Bluhm, R. L., Williamson, P. C., Osuch, E. A., Frewen, P. A., Stevens, T. K., Boksman, K., Neufeld, R. W., Théberge, J., & Lanius, R. A. (2009). Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. *J Psychiatry Neurosci*, *34*(3), 187-194.

Borgan, F., Laurikainen, H., Veronese, M., Marques, T. R., Haaparanta-Solin, M., Solin, O., Dahoun, T., Rogdaki, M., Salokangas, R. K., Karukivi, M., Di Forti, M., Turkheimer, F., Hietala, J., & Howes, O. (2019). In Vivo Availability of Cannabinoid 1 Receptor Levels in Patients With First-Episode Psychosis. *JAMA Psychiatry*, *76*(10), 1074-1084. https://doi.org/10.1001/jamapsychiatry.2019.1427

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. https://doi.org/10.1016/j.psyneuen.2012.12.025

Borgmann, D., & Fenselau, H. (2024). Vagal pathways for systemic regulation of glucose metabolism. *Semin Cell Dev Biol*, *156*, 244-252. https://doi.org/10.1016/j.semcdb.2023.07.010

Bose, M., Oliván, B., & Laferrère, B. (2009). Stress and obesity: the role of the hypothalamic-pituitary-adrenal axis in metabolic disease. *Curr Opin Endocrinol Diabetes Obes*, *16*(5), 340-346. https://doi.org/10.1097/MED.0b013e32832fa137

Bremne, J. D., & Vermetten, E. (2001). Stress and development: behavioral and biological consequences. *Dev Psychopathol*, *13*(3), 473-489. https://doi.org/10.1017/s0954579401003042

Brenner, A. M., Claudino, F. C. A., Burin, L. M., Scheibe, V. M., Padilha, B. L., de Souza, G. R., Duarte, J. A., & da Rocha, N. S. (2022). Structural magnetic resonance imaging findings in severe mental disorders adult inpatients: A systematic review. *Psychiatry Res Neuroimaging*, *326*, 111529. https://doi.org/10.1016/j.pscychresns.2022.111529

Brew, B., Doris, M., Shannon, C., & Mulholland, C. (2018). What impact does trauma have on the at-risk mental state? A systematic literature review. *Early Interv Psychiatry*, *12*(2), 115-124. https://doi.org/10.1111/eip.12453

Briend, F., Nelson, E. A., Maximo, O., Armstrong, W. P., Kraguljac, N. V., & Lahti, A. C. (2020). Hippocampal glutamate and hippocampus subfield volumes in antipsychotic-naive first episode psychosis subjects and relationships to duration of untreated psychosis. *Transl Psychiatry*, *10*(1), 137. https://doi.org/10.1038/s41398-020-0812-z

Brosch, K., Stein, F., Schmitt, S., Pfarr, J. K., Ringwald, K. G., Thomas-Odenthal, F., Meller, T., Steinsträter, O., Waltemate, L., Lemke, H., Meinert, S., Winter, A., Breuer, F., Thiel, K., Grotegerd, D., Hahn, T., Jansen, A., Dannlowski, U., Krug, A.,…Kircher, T. (2022). Reduced hippocampal gray matter volume is a common feature of patients with major depression, bipolar disorder, and schizophrenia spectrum disorders. *Mol Psychiatry*, *27*(10), 4234-4243. https://doi.org/10.1038/s41380-022-01687-4

Brown, A. S., & Derkits, E. J. (2010). Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *Am J Psychiatry*, *167*(3), 261-280. https://doi.org/10.1176/appi.ajp.2009.09030361

Bruel-Jungerman, E., Lucassen, P. J., & Francis, F. (2011). Cholinergic influences on cortical development and adult neurogenesis. *Behav Brain Res*, *221*(2), 379-388. https://doi.org/10.1016/j.bbr.2011.01.021

Brugger, S. P., Angelescu, I., Abi-Dargham, A., Mizrahi, R., Shahrezaei, V., & Howes, O. D. (2020). Heterogeneity of Striatal Dopamine Function in Schizophrenia: Meta-analysis of Variance. *Biol Psychiatry*, *87*(3), 215-224. https://doi.org/10.1016/j.biopsych.2019.07.008

Bruining, H., Hardstone, R., Juarez-Martinez, E. L., Sprengers, J., Avramiea, A. E., Simpraga, S., Houtman, S. J., Poil, S. S., Dallares, E., Palva, S., Oranje, B., Matias Palva, J., Mansvelder, H. D., & Linkenkaer-Hansen, K. (2020). Measurement of excitation-inhibition ratio in autism spectrum disorder using critical brain dynamics. *Sci Rep*, *10*(1), 9195. https://doi.org/10.1038/s41598-020-65500-4

Brunner, G., Gajwani, R., Gross, J., Gumley, A. I., Krishnadas, R., Lawrie, S. M., Schwannauer, M., Schultze-Lutter, F., Fracasso, A., & Uhlhaas, P. J. (2022). Hippocampal structural alterations in early-stage psychosis: Specificity and relationship to clinical outcomes. *Neuroimage Clin*, *35*, 103087. https://doi.org/10.1016/j.nicl.2022.103087

Bryll, A., Skrzypek, J., Krzyściak, W., Szelągowska, M., Śmierciak, N., Kozicz, T., & Popiela, T. (2020). Oxidative-Antioxidant Imbalance and Impaired Glucose Metabolism in Schizophrenia. *Biomolecules*, *10*(3). https://doi.org/10.3390/biom10030384

Buchsbaum, M. S., Haznedar, M., Newmark, R. E., Chu, K. W., Dusi, N., Entis, J. J., Goldstein, K. E., Goodman, C. R., Gupta, A., Hazlett, E., Iannuzzi, J., Torosjan, Y., Zhang, J., & Wolkin, A. (2009). FDG-PET and MRI imaging of the effects of sertindole and haloperidol in the prefrontal lobe in schizophrenia. *Schizophr Res*, *114*(1-3), 161-171. https://doi.org/10.1016/j.schres.2009.07.015

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci*, *10*(3), 186-198. https://doi.org/10.1038/nrn2575

Burghy, C. A., Stodola, D. E., Ruttle, P. L., Molloy, E. K., Armstrong, J. M., Oler, J. A., Fox, M. E., Hayes, A. S., Kalin, N. H., Essex, M. J., Davidson, R. J., & Birn, R. M. (2012). Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nat Neurosci*, *15*(12), 1736-1741. https://doi.org/10.1038/nn.3257

Butler, T. R., Self, R. L., Smith, K. J., Sharrett-Field, L. J., Berry, J. N., Littleton, J. M., Pauly, J. R., Mulholland, P. J., & Prendergast, M. A. (2010). Selective vulnerability of hippocampal cornu ammonis 1 pyramidal cells to excitotoxic insult is associated with the expression of polyamine-sensitive N-methyl-D-asparate-type glutamate receptors. *Neuroscience*, *165*(2), 525-534. https://doi.org/10.1016/j.neuroscience.2009.10.018

Cai, M., Hu, J. Y., Liu, B. B., Li, J. J., Li, F., & Lou, S. (2020). The Molecular Mechanisms of Excessive Hippocampal Endoplasmic Reticulum Stress Depressing Cognition-related Proteins Expression and the Regulatory Effects of Nrf2. *Neuroscience*, *431*, 152-165. https://doi.org/10.1016/j.neuroscience.2020.02.001

Calem, M., Bromis, K., McGuire, P., Morgan, C., & Kempton, M. J. (2017). Meta-analysis of associations between childhood adversity and hippocampus and amygdala volume in non-clinical and general population samples. *Neuroimage Clin*, *14*, 471-479. https://doi.org/10.1016/j.nicl.2017.02.016

Cancel, A., Comte, M., Boutet, C., Schneider, F. C., Rousseau, P. F., Boukezzi, S., Gay, A., Sigaud, T., Massoubre, C., Berna, F., Zendjidjian, X. Y., Azorin, J. M., Blin, O., & Fakra, E. (2017). Childhood trauma and emotional processing circuits in schizophrenia: A functional connectivity study. *Schizophr Res*, *184*, 69-72. https://doi.org/10.1016/j.schres.2016.12.003

Cao, P., Chen, C., Si, Q., Li, Y., Ren, F., Han, C., Zhao, J., Wang, X., Xu, G., & Sui, Y. (2023). Volumes of hippocampal subfields suggest a continuum between schizophrenia, major depressive disorder and bipolar disorder. *Front Psychiatry*, *14*, 1191170. https://doi.org/10.3389/fpsyt.2023.1191170

Cao, Y., Ji, S., Chen, Y., Zhang, X., Ding, G., & Tang, F. (2023). Association between autoimmune diseases of the nervous system and schizophrenia: A systematic review and meta-analysis of cohort studies. *Compr Psychiatry*, *122*, 152370. https://doi.org/10.1016/j.comppsych.2023.152370

Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol*, *28*(2), 203-209.

Carr, C. P., Martins, C. M., Stingel, A. M., Lemgruber, V. B., & Juruena, M. F. (2013). The role of early life stress in adult psychiatric disorders: a systematic review according to childhood trauma subtypes. *J Nerv Ment Dis*, *201*(12), 1007-1020. https://doi.org/10.1097/nmd.0000000000000049

Carvalho Silva, R., Oliva, F., Barlati, S., Perusi, G., Meattini, M., Dashi, E., Colombi, N., Vaona, A., Carletto, S., & Minelli, A. (2024). Childhood neglect, the neglected trauma. A systematic review and meta-analysis of its prevalence in psychiatric disorders. *Psychiatry Res*, *335*, 115881. https://doi.org/10.1016/j.psychres.2024.115881

Cenquizca, L. A., & Swanson, L. W. (2006). Analysis of direct hippocampal cortical field CA1 axonal projections to diencephalon in the rat. *J Comp Neurol*, *497*(1), 101-114. https://doi.org/10.1002/cne.20985

Cenquizca, L. A., & Swanson, L. W. (2007). Spatial organization of direct hippocampal field CA1 axonal projections to the rest of the cerebral cortex. *Brain Res Rev*, *56*(1), 1-26. https://doi.org/10.1016/j.brainresrev.2007.05.002

Chan, R. C., Di, X., McAlonan, G. M., & Gong, Q. Y. (2011). Brain anatomical abnormalities in high-risk individuals, first-episode, and chronic schizophrenia: an activation likelihood estimation meta-analysis of illness progression. *Schizophr Bull*, *37*(1), 177-188. https://doi.org/10.1093/schbul/sbp073

Chand, G. B., Dwyer, D. B., Erus, G., Sotiras, A., Varol, E., Srinivasan, D., Doshi, J., Pomponio, R., Pigoni, A., Dazzan, P., Kahn, R. S., Schnack, H. G., Zanetti, M. V., Meisenzahl, E., Busatto, G. F., Crespo-Facorro, B., Pantelis, C., Wood, S. J., Zhuo, C.,…Davatzikos, C. (2020). Two distinct neuroanatomical subtypes of schizophrenia revealed using machine learning. *Brain*, *143*(3), 1027-1038. https://doi.org/10.1093/brain/awaa025

Chand, G. B., Singhal, P., Dwyer, D. B., Wen, J., Erus, G., Doshi, J., Srinivasan, D., Mamourian, E., Varol, E., Sotiras, A., Hwang, G., Dazzan, P., Kahn, R. S., Schnack, H. G., Zanetti, M. V., Meisenzahl, E., Busatto, G. F., Crespo-Facorro, B., Pantelis, C.,…Davatzikos, C. (2022).

Schizophrenia Imaging Signatures and Their Associations With Cognition, Psychopathology, and Genetics in the General Population. *Am J Psychiatry*, *179*(9), 650-660. https://doi.org/10.1176/appi.ajp.21070686

Chang, M., Womer, F. Y., Edmiston, E. K., Bai, C., Zhou, Q., Jiang, X., Wei, S., Wei, Y., Ye, Y., Huang, H., He, Y., Xu, K., Tang, Y., & Wang, F. (2018). Neurobiological Commonalities and Distinctions Among Three Major Psychiatric Diagnostic Categories: A Structural MRI Study. *Schizophr Bull*, *44*(1), 65-74. https://doi.org/10.1093/schbul/sbx028

Charil, A., Laplante, D. P., Vaillancourt, C., & King, S. (2010). Prenatal stress and brain development. *Brain Res Rev*, *65*(1), 56-79. https://doi.org/10.1016/j.brainresrev.2010.06.002

Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G., McGrath, J. J., & Whiteford, H. A. (2018). Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophr Bull*, *44*(6), 1195-1203. https://doi.org/10.1093/schbul/sby058

Charron, A., Hage, C. E., Servonnet, A., & Samaha, A. N. (2015). 5-HT2 receptors modulate the expression of antipsychotic-induced dopamine supersensitivity. *Eur Neuropsychopharmacol*, *25*(12), 2381-2393. https://doi.org/10.1016/j.euroneuro.2015.10.002

Chavhan, G. B. (2022). *MRI Made Easy (for Beginners)*. Jaypee Brothers Medical Publishers Pvt Limited. https://books.google.fi/books?id=GJhUzwEACAAJ

Chen, W., Feng, J., Guo, J., Dong, S., Li, R., Ngo, J. C. K., Wang, C., Ma, Y., & Dong, Z. (2023). Obesity causally influencing brain cortical structure: a Mendelian randomization study. *Cereb Cortex*, *33*(15), 9409-9416. https://doi.org/10.1093/cercor/bhad214

Chen, Y., Qiu, C., Yu, W., Shao, X., Zhou, M., Wang, Y., & Shao, X. (2022). The relationship between brain glucose metabolism and insulin resistance in subjects with normal cognition - a study based on 18F-FDG PET. *Nucl Med Commun*, *43*(3), 275-283. https://doi.org/10.1097/mnm.0000000000001511

Chen, Y., Xu, J., & Chen, Y. (2021). Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders. *Nutrients*, *13*(6). https://doi.org/10.3390/nu13062099

Cheng, W., van der Meer, D., Parker, N., Hindley, G., O'Connell, K. S., Wang, Y., Shadrin, A. A., Alnaes, D., Bahrami, S., Lin, A., Karadag, N., Holen, B., Fernandez-Cabello, S., Fan, C. C., Dale, A. M., Djurovic, S., Westlye, L. T., Frei, O., Smeland, O. B., & Andreassen, O. A. (2022). Shared genetic architecture between schizophrenia and subcortical brain volumes implicates early neurodevelopmental processes and brain development in childhood. *Mol Psychiatry*, *27*(12), 5167-5176. https://doi.org/10.1038/s41380-022-01751-z

Cheng, X., Zhang, H., Guan, S., Zhao, Q., & Shan, Y. (2023). Receptor modulators associated with the hypothalamus -pituitary-thyroid axis. *Front Pharmacol*, *14*, 1291856. https://doi.org/10.3389/fphar.2023.1291856

Cheon, E. J., Bearden, C. E., Sun, D., Ching, C. R. K., Andreassen, O. A., Schmaal, L., Veltman, D. J., Thomopoulos, S. I., Kochunov, P., Jahanshad, N., Thompson, P. M., Turner, J. A., & van Erp, T. G. M. (2022). Cross disorder comparisons of brain structure in schizophrenia, bipolar disorder, major depressive disorder, and 22q11.2 deletion syndrome: A review of ENIGMA findings. *Psychiatry Clin Neurosci*, *76*(5), 140-161. https://doi.org/10.1111/pcn.13337

Cheslack-Postava, K., & Brown, A. S. (2022). Prenatal infection and schizophrenia: A decade of further progress. *Schizophr Res*, *247*, 7-15. https://doi.org/10.1016/j.schres.2021.05.014

Chiappelli, J., Kochunov, P., Savransky, A., Fisseha, F., Wisner, K., Du, X., Rowland, L. M., & Hong, L. E. (2017). Allostatic load and reduced cortical thickness in schizophrenia. *Psychoneuroendocrinology*, *77*, 105-111. https://doi.org/10.1016/j.psyneuen.2016.11.021

Chiapponi, C., Piras, F., Fagioli, S., Piras, F., Caltagirone, C., & Spalletta, G. (2013). Age-related brain trajectories in schizophrenia: a systematic review of structural MRI studies. *Psychiatry Res*, *214*(2), 83-93. https://doi.org/10.1016/j.pscychresns.2013.05.003

Choi, S., Kim, M., Park, H., Kim, T., Moon, S. Y., Lho, S. K., Lee, J., & Kwon, J. S. (2022). Volume deficits in hippocampal subfields in unaffected relatives of schizophrenia patients with high

genetic loading but without any psychiatric symptoms. *Schizophr Res*, *240*, 125-131. https://doi.org/10.1016/j.schres.2021.12.037

Chokhawala, K., & Stevens, L. (2025). Antipsychotic Medications. In *StatPearls*. StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC.

Chopra, S., Fornito, A., Francey, S. M., O'Donoghue, B., Cropley, V., Nelson, B., Graham, J., Baldwin, L., Tahtalian, S., Yuen, H. P., Allott, K., Alvarez-Jimenez, M., Harrigan, S., Sabaroedin, K., Pantelis, C., Wood, S. J., & McGorry, P. (2021). Differentiating the effect of antipsychotic medication and illness on brain volume reductions in first-episode psychosis: A Longitudinal, Randomised, Triple-blind, Placebo-controlled MRI Study. *Neuropsychopharmacology*, *46*(8), 1494-1501. https://doi.org/10.1038/s41386-021-00980-0

Chopra, S., Segal, A., Oldham, S., Holmes, A., Sabaroedin, K., Orchard, E. R., Francey, S. M., O'Donoghue, B., Cropley, V., Nelson, B., Graham, J., Baldwin, L., Tiego, J., Yuen, H. P., Allott, K., Alvarez-Jimenez, M., Harrigan, S., Fulcher, B. D., Aquino, K.,…Fornito, A. (2023). Network-Based Spreading of Gray Matter Changes Across Different Stages of Psychosis. *JAMA Psychiatry*, *80*(12), 1246-1257. https://doi.org/10.1001/jamapsychiatry.2023.3293

Chouinard, V. A., Henderson, D. C., Dalla Man, C., Valeri, L., Gray, B. E., Ryan, K. P., Cypess, A. M., Cobelli, C., Cohen, B. M., & Ongur, D. (2019). Impaired insulin signaling in unaffected siblings and patients with first-episode psychosis. *Mol Psychiatry*, *24*(10), 1513-1522. https://doi.org/10.1038/s41380-018-0045-1

Chung, Y., Addington, J., Bearden, C. E., Cadenhead, K., Cornblatt, B., Mathalon, D. H., McGlashan, T., Perkins, D., Seidman, L. J., Tsuang, M., Walker, E., Woods, S. W., McEwen, S., van Erp, T. G. M., & Cannon, T. D. (2018). Use of Machine Learning to Determine Deviance in Neuroanatomical Maturity Associated With Future Psychosis in Youths at Clinically High Risk. *JAMA Psychiatry*, *75*(9), 960-968. https://doi.org/10.1001/jamapsychiatry.2018.1543

Ciranna, L. (2006). Serotonin as a modulator of glutamate- and GABA-mediated neurotransmission: implications in physiological functions and in pathology. *Curr Neuropharmacol*, *4*(2), 101-114. https://doi.org/10.2174/157015906776359540

Claassen, J., Thijssen, D. H. J., Panerai, R. B., & Faraci, F. M. (2021). Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. *Physiol Rev*, *101*(4), 1487-1559. https://doi.org/10.1152/physrev.00022.2020

Clarke, G., O'Mahony, S. M., Dinan, T. G., & Cryan, J. F. (2014). Priming for health: gut microbiota acquired in early life regulates physiology, brain and behaviour. *Acta Paediatr*, *103*(8), 812-819. https://doi.org/10.1111/apa.12674

Clemens, V., Bürgin, D., Eckert, A., Kind, N., Dölitzsch, C., Fegert, J. M., & Schmid, M. (2020). Hypothalamic-pituitary-adrenal axis activation in a high-risk sample of children, adolescents and young adults in residential youth care - Associations with adverse childhood experiences and mental health problems. *Psychiatry Res*, *284*, 112778. https://doi.org/10.1016/j.psychres.2020.112778

Cole, A. B., Montgomery, K., Bale, T. L., & Thompson, S. M. (2022). What the hippocampus tells the HPA axis: Hippocampal output attenuates acute stress responses via disynaptic inhibition of CRF+ PVN neurons. *Neurobiol Stress*, *20*, 100473. https://doi.org/10.1016/j.ynstr.2022.100473

Cole, M. W., Anticevic, A., Repovs, G., & Barch, D. (2011). Variable global dysconnectivity and individual differences in schizophrenia. *Biol Psychiatry*, *70*(1), 43-50. https://doi.org/10.1016/j.biopsych.2011.02.010

Conrad, C. D. (2006). What is the functional significance of chronic stress-induced CA3 dendritic retraction within the hippocampus? *Behav Cogn Neurosci Rev*, *5*(1), 41-60. https://doi.org/10.1177/1534582306289043

Constantinides, C., Han, L. K. M., Alloza, C., Antonucci, L. A., Arango, C., Ayesa-Arriola, R., Banaj, N., Bertolino, A., Borgwardt, S., Bruggemann, J., Bustillo, J., Bykhovski, O., Calhoun, V., Carr, V., Catts, S., Chung, Y. C., Crespo-Facorro, B., Díaz-Caneja, C. M., Donohoe, G.,…Walton, E. (2023). Brain ageing in schizophrenia: evidence from 26 international cohorts via the ENIGMA

Schizophrenia consortium. *Mol Psychiatry*, *28*(3), 1201-1209. https://doi.org/10.1038/s41380-022-01897-w

Cordes, J., Bechdolf, A., Engelke, C., Kahl, K. G., Balijepalli, C., Lösch, C., Klosterkötter, J., Wagner, M., Maier, W., Heinz, A., de Millas, W., Gaebel, W., Winterer, G., Janssen, B., Schmidt-Kraepelin, C., Schneider, F., Lambert, M., Juckel, G., Wobrock, T.,…Moebus, S. (2017). Prevalence of metabolic syndrome in female and male patients at risk of psychosis. *Schizophr Res*, *181*, 38-42. https://doi.org/10.1016/j.schres.2016.09.012

Corvin, A. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, *511*(7510), 421-427. https://doi.org/10.1038/nature13595

Croft, J., Heron, J., Teufel, C., Cannon, M., Wolke, D., Thompson, A., Houtepen, L., & Zammit, S. (2019). Association of Trauma Type, Age of Exposure, and Frequency in Childhood and Adolescence With Psychotic Experiences in Early Adulthood. *JAMA Psychiatry*, *76*(1), 79-86. https://doi.org/10.1001/jamapsychiatry.2018.3155

Crump, C., Winkleby, M. A., Sundquist, K., & Sundquist, J. (2013). Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. *Am J Psychiatry*, *170*(3), 324-333. https://doi.org/10.1176/appi.ajp.2012.12050599

Cryan, J. F., O'Riordan, K. J., Cowan, C. S. M., Sandhu, K. V., Bastiaanssen, T. F. S., Boehme, M., Codagnone, M. G., Cussotto, S., Fulling, C., Golubeva, A. V., Guzzetta, K. E., Jaggar, M., Long-Smith, C. M., Lyte, J. M., Martin, J. A., Molinero-Perez, A., Moloney, G., Morelli, E., Morillas, E.,…Dinan, T. G. (2019). The Microbiota-Gut-Brain Axis. *Physiol Rev*, *99*(4), 1877-2013. https://doi.org/10.1152/physrev.00018.2018

Cullen, A. E., Labad, J., Oliver, D., Al-Diwani, A., Minichino, A., & Fusar-Poli, P. (2024). The Translational Future of Stress Neurobiology and Psychosis Vulnerability: A Review of the Evidence. *Curr Neuropharmacol*, *22*(3), 350-377. https://doi.org/10.2174/1570159x21666230322145049

Cullen, A. E., Zunszain, P. A., Dickson, H., Roberts, R. E., Fisher, H. L., Pariante, C. M., & Laurens, K. R. (2014). Cortisol awakening response and diurnal cortisol among children at elevated risk for schizophrenia: relationship to psychosocial stress and cognition. *Psychoneuroendocrinology*, *46*(100), 1-13. https://doi.org/10.1016/j.psyneuen.2014.03.010

Damme, K. S. F., Alloy, L. B., Young, C. B., Kelley, N. J., Chein, J., Ng, T. H., Titone, M. K., Black, C. L., & Nusslock, R. (2020). Amygdala subnuclei volume in bipolar spectrum disorders: Insights from diffusion-based subsegmentation and a high-risk design. *Hum Brain Mapp*, *41*(12), 3358-3369. https://doi.org/10.1002/hbm.25021

Dauvermann, M. R., Mothersill, D., Rokita, K. I., King, S., Holleran, L., Kane, R., McKernan, D. P., Kelly, J. P., Morris, D. W., Corvin, A., Hallahan, B., McDonald, C., & Donohoe, G. (2021). Changes in Default-Mode Network Associated With Childhood Trauma in Schizophrenia. *Schizophr Bull*, *47*(5), 1482-1494. https://doi.org/10.1093/schbul/sbab025

Davidson, T. L., & Stevenson, R. J. (2024). Vulnerability of the Hippocampus to Insults: Links to Blood-Brain Barrier Dysfunction. *Int J Mol Sci*, *25*(4). https://doi.org/10.3390/ijms25041991

Davies, C., Segre, G., Estradé, A., Radua, J., De Micheli, A., Provenzani, U., Oliver, D., Salazar de Pablo, G., Ramella-Cravaro, V., Besozzi, M., Dazzan, P., Miele, M., Caputo, G., Spallarossa, C., Crossland, G., Ilyas, A., Spada, G., Politi, P., Murray, R. M.,…Fusar-Poli, P. (2020). Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. *Lancet Psychiatry*, *7*(5), 399-410. https://doi.org/10.1016/s2215-0366(20)30057-2

de Bartolomeis, A., Ciccarelli, M., De Simone, G., Mazza, B., Barone, A., & Vellucci, L. (2023). Canonical and Non-Canonical Antipsychotics' Dopamine-Related Mechanisms of Present and Next Generation Molecules: A Systematic Review on Translational Highlights for Treatment Response and Treatment-Resistant Schizophrenia. *Int J Mol Sci*, *24*(6). https://doi.org/10.3390/ijms24065945

Del Re, E. C., Stone, W. S., Bouix, S., Seitz, J., Zeng, V., Guliano, A., Somes, N., Zhang, T., Reid, B., Lyall, A., Lyons, M., Li, H., Whitfield-Gabrieli, S., Keshavan, M., Seidman, L. J., McCarley, R.

W., Wang, J., Tang, Y., Shenton, M. E., & Niznikiewicz, M. A. (2021). Baseline Cortical Thickness Reductions in Clinical High Risk for Psychosis: Brain Regions Associated with Conversion to Psychosis Versus Non-Conversion as Assessed at One-Year Follow-Up in the Shanghai-At-Risk-for-Psychosis (SHARP) Study. *Schizophr Bull*, *47*(2), 562-574. https://doi.org/10.1093/schbul/sbaa127

Delavari, F., Rafi, H., Sandini, C., Murray, R. J., Latrèche, C., Van De Ville, D., & Eliez, S. (2023). Amygdala subdivisions exhibit aberrant whole-brain functional connectivity in relation to stress intolerance and psychotic symptoms in 22q11.2DS. *Transl Psychiatry*, *13*(1), 145. https://doi.org/10.1038/s41398-023-02458-7

Deschênes, S. S., Nearchou, F., McInerney, A., Schmitz, N., Pouwer, F., & Nouwen, A. (2024). Childhood maltreatment and the risk of impaired glucose metabolism or type 2 diabetes in young adults: Findings from the Lifelines Cohort Study. *J Health Psychol*, 13591053241243285. https://doi.org/10.1177/13591053241243285

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*, *31*(3), 968-980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Dickens, A. M., Borgan, F., Laurikainen, H., Lamichhane, S., Marques, T., Rönkkö, T., Veronese, M., Lindeman, T., Hyötyläinen, T., Howes, O., Hietala, J., & Orešič, M. (2020). Links between central CB1-receptor availability and peripheral endocannabinoids in patients with first episode psychosis. *NPJ Schizophr*, *6*(1), 21. https://doi.org/10.1038/s41537-020-00110-7

Dieset, I., Andreassen, O. A., & Haukvik, U. K. (2016). Somatic Comorbidity in Schizophrenia: Some Possible Biological Mechanisms Across the Life Span. *Schizophr Bull*, *42*(6), 1316-1319. https://doi.org/10.1093/schbul/sbw028

Do, K. Q., Cuenod, M., & Hensch, T. K. (2015). Targeting Oxidative Stress and Aberrant Critical Period Plasticity in the Developmental Trajectory to Schizophrenia. *Schizophr Bull*, *41*(4), 835-846. https://doi.org/10.1093/schbul/sbv065

Dorph-Petersen, K. A., Pierri, J. N., Perel, J. M., Sun, Z., Sampson, A. R., & Lewis, D. A. (2005). The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology*, *30*(9), 1649-1661. https://doi.org/10.1038/sj.npp.1300710

Dragioti, E., Radua, J., Solmi, M., Arango, C., Oliver, D., Cortese, S., Jones, P. B., Il Shin, J., Correll, C. U., & Fusar-Poli, P. (2022). Global population attributable fraction of potentially modifiable risk factors for mental disorders: a meta-umbrella systematic review. *Mol Psychiatry*, *27*(8), 3510-3519. https://doi.org/10.1038/s41380-022-01586-8

Dumbell, R. (2022). An appetite for growth: The role of the hypothalamic - pituitary - growth hormone axis in energy balance. *J Neuroendocrinol*, *34*(6), e13133. https://doi.org/10.1111/jne.13133

Duvarci, S., & Pare, D. (2014). Amygdala microcircuits controlling learned fear. *Neuron*, *82*(5), 966-980. https://doi.org/10.1016/j.neuron.2014.04.042

Dwyer, D. B., Chand, G. B., Pigoni, A., Khuntia, A., Wen, J., Antoniades, M., Hwang, G., Erus, G., Doshi, J., Srinivasan, D., Varol, E., Kahn, R. S., Schnack, H. G., Meisenzahl, E., Wood, S. J., Zhuo, C., Sotiras, A., Shinohara, R. T., Shou, H.,…Dazzan, P. (2023). Psychosis brain subtypes validated in first-episode cohorts and related to illness remission: results from the PHENOM consortium. *Mol Psychiatry*, *28*(5), 2008-2017. https://doi.org/10.1038/s41380-023-02069-0

Endicott, J., Spitzer, R. L., Fleiss, J. L., & Cohen, J. (1976). The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry*, *33*(6), 766-771. https://doi.org/10.1001/archpsyc.1976.01770060086012

Enez Darcin, A., Yalcin Cavus, S., Dilbaz, N., Kaya, H., & Dogan, E. (2015). Metabolic syndrome in drug-naïve and drug-free patients with schizophrenia and in their siblings. *Schizophr Res*, *166*(1-3), 201-206. https://doi.org/10.1016/j.schres.2015.05.004

Ersland, K. M., Skrede, S., Stansberg, C., & Steen, V. M. (2017). Subchronic olanzapine exposure leads to increased expression of myelination-related genes in rat fronto-medial cortex. *Transl Psychiatry*, *7*(11), 1262. https://doi.org/10.1038/s41398-017-0008-3

Faber, C. L., Deem, J. D., Campos, C. A., Taborsky, G. J., Jr., & Morton, G. J. (2020). CNS control of the endocrine pancreas. *Diabetologia*, *63*(10), 2086-2094. https://doi.org/10.1007/s00125-020-05204-6

Falkai, P., Steiner, J., Malchow, B., Shariati, J., Knaus, A., Bernstein, H. G., Schneider-Axmann, T., Kraus, T., Hasan, A., Bogerts, B., & Schmitt, A. (2016). Oligodendrocyte and Interneuron Density in Hippocampal Subfields in Schizophrenia and Association of Oligodendrocyte Number with Cognitive Deficits. *Front Cell Neurosci*, *10*, 78. https://doi.org/10.3389/fncel.2016.00078

Farmer, C. B., Roach, E. L., Bice, L. R., Falgout, M. E., Mata, K. G., Roche, J. K., & Roberts, R. C. (2023). Excitatory and inhibitory imbalances in the trisynaptic pathway in the hippocampus in schizophrenia: a postmortem ultrastructural study. *J Neural Transm (Vienna)*, *130*(7), 949-965. https://doi.org/10.1007/s00702-023-02650-5

Favalli, G., Li, J., Belmonte-de-Abreu, P., Wong, A. H., & Daskalakis, Z. J. (2012). The role of BDNF in the pathophysiology and treatment of schizophrenia. *J Psychiatr Res*, *46*(1), 1-11. https://doi.org/10.1016/j.jpsychires.2011.09.022

Fernandes, B. S., Steiner, J., Berk, M., Molendijk, M. L., Gonzalez-Pinto, A., Turck, C. W., Nardin, P., & Gonçalves, C. A. (2015). Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: meta-analysis and implications. *Mol Psychiatry*, *20*(9), 1108-1119. https://doi.org/10.1038/mp.2014.117

Fernandes, B. S., Steiner, J., Bernstein, H. G., Dodd, S., Pasco, J. A., Dean, O. M., Nardin, P., Gonçalves, C. A., & Berk, M. (2016). C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. *Mol Psychiatry*, *21*(4), 554-564. https://doi.org/10.1038/mp.2015.87

Figlewicz, D. P. (2016). Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat: Historical perspective. *Brain Res*, *1645*, 68-70. https://doi.org/10.1016/j.brainres.2015.12.041

Fischl, B. (2012). FreeSurfer. *Neuroimage*, *62*(2), 774-781. https://doi.org/10.1016/j.neuroimage.2012.01.021

Fisher, H. L., Craig, T. K., Fearon, P., Morgan, K., Dazzan, P., Lappin, J., Hutchinson, G., Doody, G. A., Jones, P. B., McGuffin, P., Murray, R. M., Leff, J., & Morgan, C. (2011). Reliability and comparability of psychosis patients' retrospective reports of childhood abuse. *Schizophr Bull*, *37*(3), 546-553. https://doi.org/10.1093/schbul/sbp103

Fisher, H. L., Jones, P. B., Fearon, P., Craig, T. K., Dazzan, P., Morgan, K., Hutchinson, G., Doody, G. A., McGuffin, P., Leff, J., Murray, R. M., & Morgan, C. (2010). The varying impact of type, timing and frequency of exposure to childhood adversity on its association with adult psychotic disorder. *Psychol Med*, *40*(12), 1967-1978. https://doi.org/10.1017/s0033291710000231

Frangou, S., Abbasi, F., Watson, K., Haas, S. S., Antoniades, M., Modabbernia, A., Myoraku, A., Robakis, T., & Rasgon, N. (2022). Hippocampal volume reduction is associated with direct measure of insulin resistance in adults. *Neurosci Res*, *174*, 19-24. https://doi.org/10.1016/j.neures.2021.07.006

French, L., Gray, C., Leonard, G., Perron, M., Pike, G. B., Richer, L., Séguin, J. R., Veillette, S., Evans, C. J., Artiges, E., Banaschewski, T., Bokde, A. W., Bromberg, U., Bruehl, R., Buchel, C., Cattrell, A., Conrod, P. J., Flor, H., Frouin, V.,…Paus, T. (2015). Early Cannabis Use, Polygenic Risk Score for Schizophrenia and Brain Maturation in Adolescence. *JAMA Psychiatry*, *72*(10), 1002-1011. https://doi.org/10.1001/jamapsychiatry.2015.1131

Fuller-Rowell, T. E., Homandberg, L. K., Curtis, D. S., Tsenkova, V. K., Williams, D. R., & Ryff, C. D. (2019). Disparities in insulin resistance between black and white adults in the United States: The role of lifespan stress exposure. *Psychoneuroendocrinology*, *107*, 1-8. https://doi.org/10.1016/j.psyneuen.2019.04.020

Fusar-Poli, P., Bonoldi, I., Yung, A. R., Borgwardt, S., Kempton, M. J., Valmaggia, L., Barale, F., Caverzasi, E., & McGuire, P. (2012). Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry*, *69*(3), 220-229. https://doi.org/10.1001/archgenpsychiatry.2011.1472

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., Keshavan, M., Wood, S., Ruhrmann, S., Seidman, L. J., Valmaggia, L., Cannon, T., Velthorst, E., De Haan, L., Cornblatt, B., Bonoldi, I., Birchwood, M., McGlashan, T., Carpenter, W.,…Yung, A. (2013a). The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*, *70*(1), 107-120. https://doi.org/10.1001/jamapsychiatry.2013.269

Fusar-Poli, P., & Meyer-Lindenberg, A. (2013). Striatal presynaptic dopamine in schizophrenia, part II: meta-analysis of [(18)F/(11)C]-DOPA PET studies. *Schizophr Bull*, *39*(1), 33-42. https://doi.org/10.1093/schbul/sbr180

Fusar-Poli, P., Smieskova, R., Kempton, M. J., Ho, B. C., Andreasen, N. C., & Borgwardt, S. (2013b). Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev*, *37*(8), 1680-1691. https://doi.org/10.1016/j.neubiorev.2013.06.001

Fusar-Poli, P., Tantardini, M., De Simone, S., Ramella-Cravaro, V., Oliver, D., Kingdon, J., Kotlicka-Antczak, M., Valmaggia, L., Lee, J., Millan, M. J., Galderisi, S., Balottin, U., Ricca, V., & McGuire, P. (2017). Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. *Eur Psychiatry*, *40*, 65-75. https://doi.org/10.1016/j.eurpsy.2016.09.003

Gage, S. H., Hickman, M., & Zammit, S. (2016). Association Between Cannabis and Psychosis: Epidemiologic Evidence. *Biol Psychiatry*, *79*(7), 549-556. https://doi.org/10.1016/j.biopsych.2015.08.001

Gallagher, K. E., Funaro, M. C., & Woods, S. W. (2022). Prescription Stimulants and the Risk of Psychosis: A Systematic Review of Observational Studies. *J Clin Psychopharmacol*, *42*(3), 308-314. https://doi.org/10.1097/jcp.0000000000001552

Galow, L. V., Schneider, J., Lewen, A., Ta, T. T., Papageorgiou, I. E., & Kann, O. (2014). Energy substrates that fuel fast neuronal network oscillations. *Front Neurosci*, *8*, 398. https://doi.org/10.3389/fnins.2014.00398

Gao, K., Mu, C. L., Farzi, A., & Zhu, W. Y. (2020). Tryptophan Metabolism: A Link Between the Gut Microbiota and Brain. *Adv Nutr*, *11*(3), 709-723. https://doi.org/10.1093/advances/nmz127

Gao, W. J., Yang, S. S., Mack, N. R., & Chamberlin, L. A. (2022). Aberrant maturation and connectivity of prefrontal cortex in schizophrenia-contribution of NMDA receptor development and hypofunction. *Mol Psychiatry*, *27*(1), 731-743. https://doi.org/10.1038/s41380-021-01196-w

GBD. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry*, *9*(2), 137-150. https://doi.org/10.1016/s2215-0366(21)00395-3

Gehred, M. Z., Knodt, A. R., Ambler, A., Bourassa, K. J., Danese, A., Elliott, M. L., Hogan, S., Ireland, D., Poulton, R., Ramrakha, S., Reuben, A., Sison, M. L., Moffitt, T. E., Hariri, A. R., & Caspi, A. (2021). Long-term Neural Embedding of Childhood Adversity in a Population-Representative Birth Cohort Followed for 5 Decades. *Biol Psychiatry*, *90*(3), 182-193. https://doi.org/10.1016/j.biopsych.2021.02.971

Gershon, M. D., & Tack, J. (2007). The serotonin signaling system: from basic understanding to drug development for functional GI disorders. *Gastroenterology*, *132*(1), 397-414. https://doi.org/10.1053/j.gastro.2006.11.002

Girshkin, L., Matheson, S. L., Shepherd, A. M., & Green, M. J. (2014). Morning cortisol levels in schizophrenia and bipolar disorder: a meta-analysis. *Psychoneuroendocrinology*, *49*, 187-206. https://doi.org/10.1016/j.psyneuen.2014.07.013

Glasser, M. F., & Van Essen, D. C. (2011). Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. *J Neurosci*, *31*(32), 11597-11616. https://doi.org/10.1523/jneurosci.2180-11.2011

Goff, D. C., Zeng, B., Ardekani, B. A., Diminich, E. D., Tang, Y., Fan, X., Galatzer-Levy, I., Li, C., Troxel, A. B., & Wang, J. (2018). Association of Hippocampal Atrophy With Duration of Untreated Psychosis and Molecular Biomarkers During Initial Antipsychotic Treatment of First-Episode Psychosis. *JAMA Psychiatry*, *75*(4), 370-378. https://doi.org/10.1001/jamapsychiatry.2017.4595

Goh, C., & Agius, M. (2010). The stress-vulnerability model how does stress impact on mental illness at the level of the brain and what are the consequences? *Psychiatr Danub*, *22*(2), 198-202.

Gold, A. L., Sheridan, M. A., Peverill, M., Busso, D. S., Lambert, H. K., Alves, S., Pine, D. S., & McLaughlin, K. A. (2016). Childhood abuse and reduced cortical thickness in brain regions involved in emotional processing. *J Child Psychol Psychiatry*, *57*(10), 1154-1164. https://doi.org/10.1111/jcpp.12630

Goldsmith, D. R., Haroon, E., Miller, A. H., Addington, J., Bearden, C., Cadenhead, K., Cannon, T., Cornblatt, B., Mathalon, D., McGlashan, T., Seidman, L., Tsuang, M., Woods, S. W., Walker, E. F., & Perkins, D. O. (2019). Association of baseline inflammatory markers and the development of negative symptoms in individuals at clinical high risk for psychosis. *Brain Behav Immun*, *76*, 268-274. https://doi.org/10.1016/j.bbi.2018.11.315

Goldsmith, D. R., Rapaport, M. H., & Miller, B. J. (2016). A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Mol Psychiatry*, *21*(12), 1696-1709. https://doi.org/10.1038/mp.2016.3

Goldstein, J. M., Seidman, L. J., Makris, N., Ahern, T., O'Brien, L. M., Caviness, V. S., Jr., Kennedy, D. N., Faraone, S. V., & Tsuang, M. T. (2007). Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. *Biol Psychiatry*, *61*(8), 935-945. https://doi.org/10.1016/j.biopsych.2006.06.027

Gómez-Apo, E., Mondragón-Maya, A., Ferrari-Díaz, M., & Silva-Pereyra, J. (2021). Structural Brain Changes Associated with Overweight and Obesity. *J Obes*, *2021*, 6613385. https://doi.org/10.1155/2021/6613385

González-Pinto, A., Mosquera, F., Palomino, A., Alberich, S., Gutiérrez, A., Haidar, K., Vega, P., Barbeito, S., Ortiz, A., & Matute, C. (2010). Increase in brain-derived neurotrophic factor in first episode psychotic patients after treatment with atypical antipsychotics. *Int Clin Psychopharmacol*, *25*(4), 241-245. https://doi.org/10.1097/yic.0b013e328338bc5a

Goodman, G. S., Ghetti, S., Quas, J. A., Edelstein, R. S., Alexander, K. W., Redlich, A. D., Cordon, I. M., & Jones, D. P. (2003). A prospective study of memory for child sexual abuse: new findings relevant to the repressed-memory controversy. *Psychol Sci*, *14*(2), 113-118. https://doi.org/10.1111/1467-9280.01428

Goozée, R., Handley, R., Kempton, M. J., & Dazzan, P. (2014). A systematic review and meta-analysis of the effects of antipsychotic medications on regional cerebral blood flow (rCBF) in schizophrenia: association with response to treatment. *Neurosci Biobehav Rev*, *43*, 118-136. https://doi.org/10.1016/j.neubiorev.2014.03.014

Gottesman, II, Laursen, T. M., Bertelsen, A., & Mortensen, P. B. (2010). Severe mental disorders in offspring with 2 psychiatrically ill parents. *Arch Gen Psychiatry*, *67*(3), 252-257. https://doi.org/10.1001/archgenpsychiatry.2010.1

Grace, A. A. (2016). Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nat Rev Neurosci*, *17*(8), 524-532. https://doi.org/10.1038/nrn.2016.57

Grace, A. A. (2017). Dopamine System Dysregulation and the Pathophysiology of Schizophrenia: Insights From the Methylazoxymethanol Acetate Model. *Biol Psychiatry*, *81*(1), 5-8. https://doi.org/10.1016/j.biopsych.2015.11.007

Gralle, M., Labrecque, S., Salesse, C., & De Koninck, P. (2021). Spatial dynamics of the insulin receptor in living neurons. *J Neurochem*, *156*(1), 88-105. https://doi.org/10.1111/jnc.14950

Greenhalgh, A. M., Gonzalez-Blanco, L., Garcia-Rizo, C., Fernandez-Egea, E., Miller, B., Arroyo, M. B., & Kirkpatrick, B. (2017). Meta-analysis of glucose tolerance, insulin, and insulin resistance in antipsychotic-naïve patients with nonaffective psychosis. *Schizophr Res*, *179*, 57-63. https://doi.org/10.1016/j.schres.2016.09.026

Grinevich, V. P., Papke, R. L., Lippiello, P. M., & Bencherif, M. (2009). Atypical antipsychotics as noncompetitive inhibitors of alpha4beta2 and alpha7 neuronal nicotinic receptors. *Neuropharmacology*, *57*(2), 183-191. https://doi.org/10.1016/j.neuropharm.2009.05.003

Grover, S., Varadharajan, N., & Venu, S. (2024). Urbanization and psychosis: an update of recent evidence. *Curr Opin Psychiatry*, *37*(3), 191-201. https://doi.org/10.1097/yco.0000000000000931

Grozeva, D., Kirov, G., Ivanov, D., Jones, I. R., Jones, L., Green, E. K., St Clair, D. M., Young, A. H., Ferrier, N., Farmer, A. E., McGuffin, P., Holmans, P. A., Owen, M. J., O'Donovan, M. C., & Craddock, N. (2010). Rare copy number variants: a point of rarity in genetic risk for bipolar disorder and schizophrenia. *Arch Gen Psychiatry*, *67*(4), 318-327. https://doi.org/10.1001/archgenpsychiatry.2010.25

Gueddouri, D., Caüzac, M., Fauveau, V., Benhamed, F., Charifi, W., Beaudoin, L., Rouland, M., Sicherre, F., Lehuen, A., Postic, C., Boudry, G., Burnol, A. F., & Guilmeau, S. (2022). Insulin resistance per se drives early and reversible dysbiosis-mediated gut barrier impairment and bactericidal dysfunction. *Mol Metab*, *57*, 101438. https://doi.org/10.1016/j.molmet.2022.101438

Guimond, S., Gu, F., Shannon, H., Kelly, S., Mike, L., Devenyi, G. A., Chakravarty, M. M., Sweeney, J. A., Pearlson, G., Clementz, B. A., Tamminga, C., & Keshavan, M. (2021). A Diagnosis and Biotype Comparison Across the Psychosis Spectrum: Investigating Volume and Shape Amygdala-Hippocampal Differences from the B-SNIP Study. *Schizophr Bull*, *47*(6), 1706-1717. https://doi.org/10.1093/schbul/sbab071

Guimond, S., Mothi, S. S., Makowski, C., Chakravarty, M. M., & Keshavan, M. S. (2022). Altered amygdala shape trajectories and emotion recognition in youth at familial high risk of schizophrenia who develop psychosis. *Transl Psychiatry*, *12*(1), 202. https://doi.org/10.1038/s41398-022-01957-3

Guma, E., Rocchetti, J., Devenyi, G. A., Tanti, A., Mathieu, A., Lerch, J. P., Elgbeili, G., Courcot, B., Mechawar, N., Chakravarty, M. M., & Giros, B. (2018). Regional brain volume changes following chronic antipsychotic administration are mediated by the dopamine D2 receptor. *Neuroimage*, *176*, 226-238. https://doi.org/10.1016/j.neuroimage.2018.04.054

Gunduz-Bruce, H., Szeszko, P. R., Gueorguieva, R., Ashtari, M., Robinson, D. G., Kane, J. M., & Bilder, R. M. (2007). Cortisol levels in relation to hippocampal sub-regions in subjects with first episode schizophrenia. *Schizophr Res*, *94*(1-3), 281-287. https://doi.org/10.1016/j.schres.2007.03.025

Gunnell, D., & Holly, J. M. (2004). Do insulin-like growth factors underlie associations of birth complications, fetal and pre-adult growth with schizophrenia? *Schizophr Res*, *67*(2-3), 309-311. https://doi.org/10.1016/s0920-9964(03)00180-4

Gyawali, U., & James, M. H. (2022). Orexin (Hypocretin) Signaling in the Basolateral Amygdala Contributes to Individual Differences in Stress Sensitivity. *Biol Psychiatry*, *91*(9), 775-777. https://doi.org/10.1016/j.biopsych.2022.02.957

Haas, S. S., Ge, R., Agartz, I., Amminger, G. P., Andreassen, O. A., Bachman, P., Baeza, I., Choi, S., Colibazzi, T., Cropley, V. L., de la Fuente-Sandoval, C., Ebdrup, B. H., Fortea, A., Fusar-Poli, P., Glenthøj, B. Y., Glenthøj, L. B., Haut, K. M., Hayes, R. A., Heekeren, K.,…Frangou, S. (2024). Normative Modeling of Brain Morphometry in Clinical High Risk for Psychosis. *JAMA Psychiatry*, *81*(1), 77-88. https://doi.org/10.1001/jamapsychiatry.2023.3850

Habeck, C., Gazes, Y., Razlighi, Q., & Stern, Y. (2020). Cortical thickness and its associations with age, total cognition and education across the adult lifespan. *PLoS One*, *15*(3), e0230298. https://doi.org/10.1371/journal.pone.0230298

Hackett, R. A., & Steptoe, A. (2017). Type 2 diabetes mellitus and psychological stress - a modifiable risk factor. *Nat Rev Endocrinol*, *13*(9), 547-560. https://doi.org/10.1038/nrendo.2017.64

Hagi, K., Nosaka, T., Dickinson, D., Lindenmayer, J. P., Lee, J., Friedman, J., Boyer, L., Han, M., Abdul-Rashid, N. A., & Correll, C. U. (2021). Association Between Cardiovascular Risk Factors and Cognitive Impairment in People With Schizophrenia: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *78*(5), 510-518. https://doi.org/10.1001/jamapsychiatry.2021.0015

Haidl, T. K., Schneider, N., Dickmann, K., Ruhrmann, S., Kaiser, N., Rosen, M., Seves, M., Lichtenstein, T., Upthegrove, R., Salokangas, R. K. R., Pantelis, C., Meisenzahl, E., Wood, S. J., Brambilla, P., Borgwardt, S., Rebekka, L., Kambeitz, J., Koutsouleris, N., & Schultze-Lutter, F. (2020). Validation of the Bullying Scale for Adults - Results of the PRONIA-study. *J Psychiatr Res*, *129*, 88-97. https://doi.org/10.1016/j.jpsychires.2020.04.004

Haijma, S. V., Van Haren, N., Cahn, W., Koolschijn, P. C., Hulshoff Pol, H. E., & Kahn, R. S. (2013). Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophr Bull*, *39*(5), 1129-1138. https://doi.org/10.1093/schbul/sbs118

Halff, E. F., Cotel, M. C., Natesan, S., McQuade, R., Ottley, C. J., Srivastava, D. P., Howes, O. D., & Vernon, A. C. (2021). Effects of chronic exposure to haloperidol, olanzapine or lithium on SV2A and NLGN synaptic puncta in the rat frontal cortex. *Behav Brain Res*, *405*, 113203. https://doi.org/10.1016/j.bbr.2021.113203

Hall, J., Whalley, H. C., McKirdy, J. W., Romaniuk, L., McGonigle, D., McIntosh, A. M., Baig, B. J., Gountouna, V. E., Job, D. E., Donaldson, D. I., Sprengelmeyer, R., Young, A. W., Johnstone, E. C., & Lawrie, S. M. (2008). Overactivation of fear systems to neutral faces in schizophrenia. *Biol Psychiatry*, *64*(1), 70-73. https://doi.org/10.1016/j.biopsych.2007.12.014

Hansen, J. Y., Shafiei, G., Markello, R. D., Smart, K., Cox, S. M. L., Nørgaard, M., Beliveau, V., Wu, Y., Gallezot, J. D., Aumont, É., Servaes, S., Scala, S. G., DuBois, J. M., Wainstein, G., Bezgin, G., Funck, T., Schmitz, T. W., Spreng, R. N., Galovic, M.,…Misic, B. (2022). Mapping neurotransmitter systems to the structural and functional organization of the human neocortex. *Nat Neurosci*, *25*(11), 1569-1581. https://doi.org/10.1038/s41593-022-01186-3

Hansen, T., Ingason, A., Djurovic, S., Melle, I., Fenger, M., Gustafsson, O., Jakobsen, K. D., Rasmussen, H. B., Tosato, S., Rietschel, M., Frank, J., Owen, M., Bonetto, C., Suvisaari, J., Thygesen, J. H., Pétursson, H., Lönnqvist, J., Sigurdsson, E., Giegling, I.,…Werge, T. (2011). At-risk variant in TCF7L2 for type II diabetes increases risk of schizophrenia. *Biol Psychiatry*, *70*(1), 59-63. https://doi.org/10.1016/j.biopsych.2011.01.031

Hanson, J. L., Nacewicz, B. M., Sutterer, M. J., Cayo, A. A., Schaefer, S. M., Rudolph, K. D., Shirtcliff, E. A., Pollak, S. D., & Davidson, R. J. (2015). Behavioral problems after early life stress: contributions of the hippocampus and amygdala. *Biol Psychiatry*, *77*(4), 314-323. https://doi.org/10.1016/j.biopsych.2014.04.020

Hao, L., Li, Q., Zhao, X., Li, Y., & Zhang, C. (2019). A long noncoding RNA LOC103690121 promotes hippocampus neuronal apoptosis in streptozotocin-induced type 1 diabetes. *Neurosci Lett*, *703*, 11-18. https://doi.org/10.1016/j.neulet.2019.03.006

Hardi, F. A., Beltz, A. M., McLoyd, V., Brooks-Gunn, J., Huntley, E., Mitchell, C., Hyde, L. W., & Monk, C. S. (2024). Latent Profiles of Childhood Adversity, Adolescent Mental Health, and Neural Network Connectivity. *JAMA Netw Open*, *7*(8), e2430711. https://doi.org/10.1001/jamanetworkopen.2024.30711

Haris, E. M., Bryant, R. A., Williamson, T., & Korgaonkar, M. S. (2023). Functional connectivity of amygdala subnuclei in PTSD: a narrative review. *Mol Psychiatry*, *28*(9), 3581-3594. https://doi.org/10.1038/s41380-023-02291-w

Haro, J. M., Novick, D., Bertsch, J., Karagianis, J., Dossenbach, M., & Jones, P. B. (2011). Cross-national clinical and functional remission rates: Worldwide Schizophrenia Outpatient Health Outcomes (W-SOHO) study. *Br J Psychiatry*, *199*(3), 194-201. https://doi.org/10.1192/bjp.bp.110.082065

Haukvik, U. K., Gurholt, T. P., Nerland, S., Elvsåshagen, T., Akudjedu, T. N., Alda, M., Alnaes, D., Alonso-Lana, S., Bauer, J., Baune, B. T., Benedetti, F., Berk, M., Bettella, F., Bøen, E., Bonnín, C. M., Brambilla, P., Canales-Rodríguez, E. J., Cannon, D. M., Caseras, X.,…Agartz, I. (2022). In

vivo hippocampal subfield volumes in bipolar disorder-A mega-analysis from The Enhancing Neuro Imaging Genetics through Meta-Analysis Bipolar Disorder Working Group. *Hum Brain Mapp*, *43*(1), 385-398. https://doi.org/10.1002/hbm.25249

Haukvik, U. K., Tamnes, C. K., Söderman, E., & Agartz, I. (2018). Neuroimaging hippocampal subfields in schizophrenia and bipolar disorder: A systematic review and meta-analysis. *J Psychiatr Res*, *104*, 217-226. https://doi.org/10.1016/j.jpsychires.2018.08.012

Haukvik, U. K., Westlye, L. T., Mørch-Johnsen, L., Jørgensen, K. N., Lange, E. H., Dale, A. M., Melle, I., Andreassen, O. A., & Agartz, I. (2015). In vivo hippocampal subfield volumes in schizophrenia and bipolar disorder. *Biol Psychiatry*, *77*(6), 581-588. https://doi.org/10.1016/j.biopsych.2014.06.020

Heckers, S., & Konradi, C. (2015). GABAergic mechanisms of hippocampal hyperactivity in schizophrenia. *Schizophr Res*, *167*(1-3), 4-11. https://doi.org/10.1016/j.schres.2014.09.041

Heni, M., Wagner, R., Kullmann, S., Veit, R., Mat Husin, H., Linder, K., Benkendorff, C., Peter, A., Stefan, N., Häring, H. U., Preissl, H., & Fritsche, A. (2014). Central insulin administration improves whole-body insulin sensitivity via hypothalamus and parasympathetic outputs in men. *Diabetes*, *63*(12), 4083-4088. https://doi.org/10.2337/db14-0477

Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Prog Neuropsychopharmacol Biol Psychiatry*, *29*(8), 1201-1213. https://doi.org/10.1016/j.pnpbp.2005.08.006

Herrera Moro Chao, D., Kirchner, M. K., Pham, C., Foppen, E., Denis, R. G. P., Castel, J., Morel, C., Montalban, E., Hassouna, R., Bui, L. C., Renault, J., Mouffle, C., García-Cáceres, C., Tschöp, M. H., Li, D., Martin, C., Stern, J. E., & Luquet, S. H. (2022). Hypothalamic astrocytes control systemic glucose metabolism and energy balance. *Cell Metab*, *34*(10), 1532-1547.e1536. https://doi.org/10.1016/j.cmet.2022.09.002

Herringa, R. J., Birn, R. M., Ruttle, P. L., Burghy, C. A., Stodola, D. E., Davidson, R. J., & Essex, M. J. (2013). Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. *Proc Natl Acad Sci U S A*, *110*(47), 19119-19124. https://doi.org/10.1073/pnas.1310766110

Herweg, N. A., Solomon, E. A., & Kahana, M. J. (2020). Theta Oscillations in Human Memory. *Trends Cogn Sci*, *24*(3), 208-227. https://doi.org/10.1016/j.tics.2019.12.006

Herzog, J. I., Thome, J., Demirakca, T., Koppe, G., Ende, G., Lis, S., Rausch, S., Priebe, K., Müller-Engelmann, M., Steil, R., Bohus, M., & Schmahl, C. (2020). Influence of Severity of Type and Timing of Retrospectively Reported Childhood Maltreatment on Female Amygdala and Hippocampal Volume. *Sci Rep*, *10*(1), 1903. https://doi.org/10.1038/s41598-020-57490-0

Hides, L., Lubman, D. I., Buckby, J., Yuen, H. P., Cosgrave, E., Baker, K., & Yung, A. R. (2009). The association between early cannabis use and psychotic-like experiences in a community adolescent sample. *Schizophr Res*, *112*(1-3), 130-135. https://doi.org/10.1016/j.schres.2009.04.001

Hietala, J., Syvälahti, E., Vuorio, K., Räkköläinen, V., Bergman, J., Haaparanta, M., Solin, O., Kuoppamäki, M., Kirvelä, O., Ruotsalainen, U., & et al. (1995). Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. *Lancet*, *346*(8983), 1130-1131. https://doi.org/10.1016/s0140-6736(95)91801-9

Hietala, J., & Tuulio-Henriksson, A. (2021). Mitä tiedetään skitsofrenian etiologiasta? In *Kliininen Neuropsykiatria*. Kustannus Oy Duodecim. https://www.oppiportti.fi/opk04642

Hinney, B., Walter, A., Aghlmandi, S., Andreou, C., & Borgwardt, S. (2020). Does Hippocampal Volume Predict Transition to Psychosis in a High-Risk Group? A Meta-Analysis. *Front Psychiatry*, *11*, 614659. https://doi.org/10.3389/fpsyt.2020.614659

Hirano, Y., Oribe, N., Kanba, S., Onitsuka, T., Nestor, P. G., & Spencer, K. M. (2015). Spontaneous Gamma Activity in Schizophrenia. *JAMA Psychiatry*, *72*(8), 813-821. https://doi.org/10.1001/jamapsychiatry.2014.2642

Hiroi, N., & White, N. M. (1991). The lateral nucleus of the amygdala mediates expression of the amphetamine-produced conditioned place preference. *J Neurosci*, *11*(7), 2107-2116. https://doi.org/10.1523/jneurosci.11-07-02107.1991

Hjorthøj, C., Stürup, A. E., McGrath, J. J., & Nordentoft, M. (2017). Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *Lancet Psychiatry*, *4*(4), 295-301. https://doi.org/10.1016/s2215-0366(17)30078-0

Ho, B. C., Andreasen, N. C., Ziebell, S., Pierson, R., & Magnotta, V. (2011). Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry*, *68*(2), 128-137. https://doi.org/10.1001/archgenpsychiatry.2010.199

Ho, N. F., Holt, D. J., Cheung, M., Iglesias, J. E., Goh, A., Wang, M., Lim, J. K., de Souza, J., Poh, J. S., See, Y. M., Adcock, A. R., Wood, S. J., Chee, M. W., Lee, J., & Zhou, J. (2017a). Progressive Decline in Hippocampal CA1 Volume in Individuals at Ultra-High-Risk for Psychosis Who Do Not Remit: Findings from the Longitudinal Youth at Risk Study. *Neuropsychopharmacology*, *42*(6), 1361-1370. https://doi.org/10.1038/npp.2017.5

Ho, N. F., Iglesias, J. E., Sum, M. Y., Kuswanto, C. N., Sitoh, Y. Y., De Souza, J., Hong, Z., Fischl, B., Roffman, J. L., Zhou, J., Sim, K., & Holt, D. J. (2017b). Progression from selective to general involvement of hippocampal subfields in schizophrenia. *Mol Psychiatry*, *22*(1), 142-152. https://doi.org/10.1038/mp.2016.4

Ho, N. F., Li Hui Chong, P., Lee, D. R., Chew, Q. H., Chen, G., & Sim, K. (2019). The Amygdala in Schizophrenia and Bipolar Disorder: A Synthesis of Structural MRI, Diffusion Tensor Imaging, and Resting-State Functional Connectivity Findings. *Harv Rev Psychiatry*, *27*(3), 150-164. https://doi.org/10.1097/hrp.0000000000000207

Holmes, A., Levi, P. T., Chen, Y. C., Chopra, S., Aquino, K. M., Pang, J. C., & Fornito, A. (2023). Disruptions of Hierarchical Cortical Organization in Early Psychosis and Schizophrenia. *Biol Psychiatry Cogn Neurosci Neuroimaging*, *8*(12), 1240-1250. https://doi.org/10.1016/j.bpsc.2023.08.008

Holper, L., Ben-Shachar, D., & Mann, J. J. (2019). Multivariate meta-analyses of mitochondrial complex I and IV in major depressive disorder, bipolar disorder, schizophrenia, Alzheimer disease, and Parkinson disease. *Neuropsychopharmacology*, *44*(5), 837-849. https://doi.org/10.1038/s41386-018-0090-0

Holt, D. J., Coombs, G., Zeidan, M. A., Goff, D. C., & Milad, M. R. (2012). Failure of neural responses to safety cues in schizophrenia. *Arch Gen Psychiatry*, *69*(9), 893-903. https://doi.org/10.1001/archgenpsychiatry.2011.2310

Holt, D. J., Lebron-Milad, K., Milad, M. R., Rauch, S. L., Pitman, R. K., Orr, S. P., Cassidy, B. S., Walsh, J. P., & Goff, D. C. (2009). Extinction memory is impaired in schizophrenia. *Biol Psychiatry*, *65*(6), 455-463. https://doi.org/10.1016/j.biopsych.2008.09.017

Hong, C. J., Yu, Y. W., Lin, C. H., & Tsai, S. J. (2003). An association study of a brain-derived neurotrophic factor Val66Met polymorphism and clozapine response of schizophrenic patients. *Neurosci Lett*, *349*(3), 206-208. https://doi.org/10.1016/s0304-3940(03)00828-0

Hopkins, D. F., & Williams, G. (1997). Insulin receptors are widely distributed in human brain and bind human and porcine insulin with equal affinity. *Diabet Med*, *14*(12), 1044-1050. https://doi.org/10.1002/(sici)1096-9136(199712)14:12<1044::Aid-dia508>3.0.Co;2-f

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophr Bull*, *35*(3), 549-562. https://doi.org/10.1093/schbul/sbp006

Hsiang, H. L., Epp, J. R., van den Oever, M. C., Yan, C., Rashid, A. J., Insel, N., Ye, L., Niibori, Y., Deisseroth, K., Frankland, P. W., & Josselyn, S. A. (2014). Manipulating a "cocaine engram" in mice. *J Neurosci*, *34*(42), 14115-14127. https://doi.org/10.1523/jneurosci.3327-14.2014

Hu, H., Liu, F., Liu, L., Mei, Y., Xie, B., Shao, Y., & Qiao, Y. (2023). Smaller amygdala subnuclei volume in schizophrenia patients with violent behaviors. *Brain Imaging Behav*, *17*(1), 11-17. https://doi.org/10.1007/s11682-022-00736-4

Huang, T. L. (2013). Effects of antipsychotics on the BDNF in schizophrenia. *Curr Med Chem*, *20*(3), 345-350. https://doi.org/10.2174/092986713804870729

Huang, Z., Liu, L., Zhang, J., Conde, K., Phansalkar, J., Li, Z., Yao, L., Xu, Z., Wang, W., Zhou, J., Bi, G., Wu, F., Seeley, R. J., Scott, M. M., Zhan, C., Pang, Z. P., & Liu, J. (2022). Glucose-sensing glucagon-like peptide-1 receptor neurons in the dorsomedial hypothalamus regulate glucose metabolism. *Sci Adv*, *8*(23), eabn5345. https://doi.org/10.1126/sciadv.abn5345

Hughes, K., Bellis, M. A., Hardcastle, K. A., Sethi, D., Butchart, A., Mikton, C., Jones, L., & Dunne, M. P. (2017). The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health*, *2*(8), e356-e366. https://doi.org/10.1016/s2468-2667(17)30118-4

Iatcu, C. O., Steen, A., & Covasa, M. (2021). Gut Microbiota and Complications of Type-2 Diabetes. *Nutrients*, *14*(1). https://doi.org/10.3390/nu14010166

Iglesias, J. E., Augustinack, J. C., Nguyen, K., Player, C. M., Player, A., Wright, M., Roy, N., Frosch, M. P., McKee, A. C., Wald, L. L., Fischl, B., & Van Leemput, K. (2015). A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: Application to adaptive segmentation of in vivo MRI. *Neuroimage*, *115*, 117-137. https://doi.org/10.1016/j.neuroimage.2015.04.042

Jaffe, A. E., Straub, R. E., Shin, J. H., Tao, R., Gao, Y., Collado-Torres, L., Kam-Thong, T., Xi, H. S., Quan, J., Chen, Q., Colantuoni, C., Ulrich, W. S., Maher, B. J., Deep-Soboslay, A., Cross, A. J., Brandon, N. J., Leek, J. T., Hyde, T. M., Kleinman, J. E., & Weinberger, D. R. (2018). Developmental and genetic regulation of the human cortex transcriptome illuminate schizophrenia pathogenesis. *Nat Neurosci*, *21*(8), 1117-1125. https://doi.org/10.1038/s41593-018-0197-y

Jalbrzikowski, M., Hayes, R. A., Wood, S. J., Nordholm, D., Zhou, J. H., Fusar-Poli, P., Uhlhaas, P. J., Takahashi, T., Sugranyes, G., Kwak, Y. B., Mathalon, D. H., Katagiri, N., Hooker, C. I., Smigielski, L., Colibazzi, T., Via, E., Tang, J., Koike, S., Rasser, P. E.,…Hernaus, D. (2021). Association of Structural Magnetic Resonance Imaging Measures With Psychosis Onset in Individuals at Clinical High Risk for Developing Psychosis: An ENIGMA Working Group Mega-analysis. *JAMA Psychiatry*, *78*(7), 753-766. https://doi.org/10.1001/jamapsychiatry.2021.0638

Janak, P. H., & Tye, K. M. (2015). From circuits to behaviour in the amygdala. *Nature*, *517*(7534), 284-292. https://doi.org/10.1038/nature14188

Janiri, D., Sani, G., Rossi, P., Piras, F., Iorio, M., Banaj, N., Giuseppin, G., Spinazzola, E., Maggiora, M., Ambrosi, E., Simonetti, A., & Spalletta, G. (2017). Amygdala and hippocampus volumes are differently affected by childhood trauma in patients with bipolar disorders and healthy controls. *Bipolar Disord*, *19*(5), 353-362. https://doi.org/10.1111/bdi.12516

Janssen, J. (2022). New Insights into the Role of Insulin and Hypothalamic-Pituitary-Adrenal (HPA) Axis in the Metabolic Syndrome. *Int J Mol Sci*, *23*(15). https://doi.org/10.3390/ijms23158178

Jiménez-Trejo, F., Jiménez-García, K. L., & Canul-Medina, G. (2024). Serotonin and schizophrenia: what influences what? *Front Psychiatry*, *15*, 1451248. https://doi.org/10.3389/fpsyt.2024.1451248

Jo, Y. H., & Chua, S. C., Jr. (2013). The brain-liver connection between BDNF and glucose control. *Diabetes*, *62*(5), 1367-1368. https://doi.org/10.2337/db12-1824

Jung, W. H., Kim, J. S., Jang, J. H., Choi, J. S., Jung, M. H., Park, J. Y., Han, J. Y., Choi, C. H., Kang, D. H., Chung, C. K., & Kwon, J. S. (2011). Cortical thickness reduction in individuals at ultra-high-risk for psychosis. *Schizophr Bull*, *37*(4), 839-849. https://doi.org/10.1093/schbul/sbp151

Kaar, S. J., Angelescu, I., Marques, T. R., & Howes, O. D. (2019). Pre-frontal parvalbumin interneurons in schizophrenia: a meta-analysis of post-mortem studies. *J Neural Transm (Vienna)*, *126*(12), 1637-1651. https://doi.org/10.1007/s00702-019-02080-2

Kaar, S. J., Natesan, S., McCutcheon, R., & Howes, O. D. (2020). Antipsychotics: Mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. *Neuropharmacology*, *172*, 107704. https://doi.org/10.1016/j.neuropharm.2019.107704

Kahhale, I., Buser, N. J., Madan, C. R., & Hanson, J. L. (2023). Quantifying numerical and spatial reliability of hippocampal and amygdala subdivisions in FreeSurfer. *Brain Inform*, *10*(1), 9. https://doi.org/10.1186/s40708-023-00189-5

Kalantar-Hormozi, H., Patel, R., Dai, A., Ziolkowski, J., Dong, H. M., Holmes, A., Raznahan, A., Devenyi, G. A., & Chakravarty, M. M. (2023). A cross-sectional and longitudinal study of human brain development: The integration of cortical thickness, surface area, gyrification index, and cortical curvature into a unified analytical framework. *Neuroimage*, *268*, 119885. https://doi.org/10.1016/j.neuroimage.2023.119885

Kamal, A., Biessels, G. J., Urban, I. J., & Gispen, W. H. (1999). Hippocampal synaptic plasticity in streptozotocin-diabetic rats: impairment of long-term potentiation and facilitation of long-term depression. *Neuroscience*, *90*(3), 737-745. https://doi.org/10.1016/s0306-4522(98)00485-0

Kamali, A., Milosavljevic, S., Gandhi, A., Lano, K. R., Shobeiri, P., Sherbaf, F. G., Sair, H. I., Riascos, R. F., & Hasan, K. M. (2023). The Cortico-Limbo-Thalamo-Cortical Circuits: An Update to the Original Papez Circuit of the Human Limbic System. *Brain Topogr*, *36*(3), 371-389. https://doi.org/10.1007/s10548-023-00955-y

Kapur, S., & Remington, G. (1996). Serotonin-dopamine interaction and its relevance to schizophrenia. *Am J Psychiatry*, *153*(4), 466-476. https://doi.org/10.1176/ajp.153.4.466

Karanikas, E., Ntouros, E., Oikonomou, D., Floros, G., Griveas, I., & Garyfallos, G. (2017). Evidence for Hypothalamus-Pituitary-Adrenal Axis and Immune Alterations at Prodrome of Psychosis in Males. *Psychiatry Investig*, *14*(5), 703-707. https://doi.org/10.4306/pi.2017.14.5.703

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. *Dev Psychopathol*, *20*(4), 1297-1327. https://doi.org/10.1017/s095457940800062x

Kaufman, J., & Torbey, S. (2019). Child maltreatment and psychosis. *Neurobiol Dis*, *131*, 104378. https://doi.org/10.1016/j.nbd.2019.01.015

Kaul, I., Sawchak, S., Correll, C. U., Kakar, R., Breier, A., Zhu, H., Miller, A. C., Paul, S. M., & Brannan, S. K. (2024a). Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline-trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomised, double-blind, placebo-controlled, flexible-dose phase 3 trial. *Lancet*, *403*(10422), 160-170. https://doi.org/10.1016/s0140-6736(23)02190-6

Kaul, I., Sawchak, S., Walling, D. P., Tamminga, C. A., Breier, A., Zhu, H., Miller, A. C., Paul, S. M., & Brannan, S. K. (2024b). Efficacy and Safety of Xanomeline-Trospium Chloride in Schizophrenia: A Randomized Clinical Trial. *JAMA Psychiatry*, *81*(8), 749-756. https://doi.org/10.1001/jamapsychiatry.2024.0785

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*, *13*(2), 261-276. https://doi.org/10.1093/schbul/13.2.261

Keinänen, J., Mantere, O., Markkula, N., Partti, K., Perälä, J., Saarni, S. I., Härkänen, T., & Suvisaari, J. (2018). Mortality in people with psychotic disorders in Finland: A population-based 13-year follow-up study. *Schizophr Res*, *192*, 113-118. https://doi.org/10.1016/j.schres.2017.04.048

Kelsey, M. M., & Zeitler, P. S. (2016). Insulin Resistance of Puberty. *Curr Diab Rep*, *16*(7), 64. https://doi.org/10.1007/s11892-016-0751-5

Keshavan, M. S., Tandon, R., Boutros, N. N., & Nasrallah, H. A. (2008). Schizophrenia, "just the facts": what we know in 2008 Part 3: neurobiology. *Schizophr Res*, *106*(2-3), 89-107. https://doi.org/10.1016/j.schres.2008.07.020

Keshavarzi, S., Sullivan, R. K., Ianno, D. J., & Sah, P. (2014). Functional properties and projections of neurons in the medial amygdala. *J Neurosci*, *34*(26), 8699-8715. https://doi.org/10.1523/jneurosci.1176-14.2014

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., Aguilar-Gaxiola, S., Alhamzawi, A. O., Alonso, J., Angermeyer, M., Benjet, C., Bromet, E., Chatterji, S., de Girolamo, G., Demyttenaere, K., Fayyad, J., Florescu, S., Gal, G., Gureje, O.,…Williams, D. R. (2010). Childhood adversities and adult psychopathology in the WHO World

Mental Health Surveys. *Br J Psychiatry*, *197*(5), 378-385. https://doi.org/10.1192/bjp.bp.110.080499

Keyvanfard, F., Schmid, A. K., & Nasiraei-Moghaddam, A. (2023). Functional Connectivity Alterations of Within and Between Networks in Schizophrenia: A Retrospective Study. *Basic Clin Neurosci*, *14*(3), 397-409. https://doi.org/10.32598/bcn.2022.3928.2

Khandaker, G. M., Zimbron, J., Lewis, G., & Jones, P. B. (2013). Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. *Psychol Med*, *43*(2), 239-257. https://doi.org/10.1017/s0033291712000736

Khashan, A. S., Abel, K. M., McNamee, R., Pedersen, M. G., Webb, R. T., Baker, P. N., Kenny, L. C., & Mortensen, P. B. (2008). Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. *Arch Gen Psychiatry*, *65*(2), 146-152. https://doi.org/10.1001/archgenpsychiatry.2007.20

Kiemes, A., Gomes, F. V., Cash, D., Uliana, D. L., Simmons, C., Singh, N., Vernon, A. C., Turkheimer, F., Davies, C., Stone, J. M., Grace, A. A., & Modinos, G. (2022). GABA(A) and NMDA receptor density alterations and their behavioral correlates in the gestational methylazoxymethanol acetate model for schizophrenia. *Neuropsychopharmacology*, *47*(3), 687-695. https://doi.org/10.1038/s41386-021-01213-0

Kim, J., Tashjian, S. M., & Mobbs, D. (2024). The human hypothalamus coordinates switching between different survival actions. *PLoS Biol*, *22*(6), e3002624. https://doi.org/10.1371/journal.pbio.3002624

Kim, J. H., Son, Y. D., Kim, H. K., & Kim, J. H. (2021). Association Between Lack of Insight and Prefrontal Serotonin Transporter Availability in Antipsychotic-Free Patients with Schizophrenia: A High-Resolution PET Study with [(11)C]DASB. *Neuropsychiatr Dis Treat*, *17*, 3195-3203. https://doi.org/10.2147/ndt.S336126

Kim, J. J., & Diamond, D. M. (2002). The stressed hippocampus, synaptic plasticity and lost memories. *Nat Rev Neurosci*, *3*(6), 453-462. https://doi.org/10.1038/nrn849

Kim, W. S., Shen, G., Liu, C., Kang, N. I., Lee, K. H., Sui, J., & Chung, Y. C. (2020). Altered amygdala-based functional connectivity in individuals with attenuated psychosis syndrome and first-episode schizophrenia. *Sci Rep*, *10*(1), 17711. https://doi.org/10.1038/s41598-020-74771-w

Király, B., Domonkos, A., Jelitai, M., Lopes-Dos-Santos, V., Martínez-Bellver, S., Kocsis, B., Schlingloff, D., Joshi, A., Salib, M., Fiáth, R., Barthó, P., Ulbert, I., Freund, T. F., Viney, T. J., Dupret, D., Varga, V., & Hangya, B. (2023). The medial septum controls hippocampal supra-theta oscillations. *Nat Commun*, *14*(1), 6159. https://doi.org/10.1038/s41467-023-41746-0

Kirkbride, J. B., Hameed, Y., Ioannidis, K., Ankireddypalli, G., Crane, C. M., Nasir, M., Kabacs, N., Metastasio, A., Jenkins, O., Espandian, A., Spyridi, S., Ralevic, D., Siddabattuni, S., Walden, B., Adeoye, A., Perez, J., & Jones, P. B. (2017). Ethnic Minority Status, Age-at-Immigration and Psychosis Risk in Rural Environments: Evidence From the SEPEA Study. *Schizophr Bull*, *43*(6), 1251-1261. https://doi.org/10.1093/schbul/sbx010

Kishi, T., Tsumori, T., Ono, K., Yokota, S., Ishino, H., & Yasui, Y. (2000). Topographical organization of projections from the subiculum to the hypothalamus in the rat. *J Comp Neurol*, *419*(2), 205-222. https://doi.org/10.1002/(sici)1096-9861(20000403)419:2<205::aid-cne5>3.0.co;2-0

Kleinridders, A., Ferris, H. A., Cai, W., & Kahn, C. R. (2014). Insulin action in brain regulates systemic metabolism and brain function. *Diabetes*, *63*(7), 2232-2243. https://doi.org/10.2337/db14-0568

Klimesch, W. (2012). α-band oscillations, attention, and controlled access to stored information. *Trends Cogn Sci*, *16*(12), 606-617. https://doi.org/10.1016/j.tics.2012.10.007

Knezevic, E., Nenic, K., Milanovic, V., & Knezevic, N. N. (2023). The Role of Cortisol in Chronic Stress, Neurodegenerative Diseases, and Psychological Disorders. *Cells*, *12*(23). https://doi.org/10.3390/cells12232726

Knight, S., McCutcheon, R., Dwir, D., Grace, A. A., O'Daly, O., McGuire, P., & Modinos, G. (2022). Hippocampal circuit dysfunction in psychosis. *Transl Psychiatry*, *12*(1), 344. https://doi.org/10.1038/s41398-022-02115-5

Koen, J. D., Lewis, L., Rugg, M. D., Clementz, B. A., Keshavan, M. S., Pearlson, G. D., Sweeney, J. A., Tamminga, C. A., & Ivleva, E. I. (2023). Supervised machine learning classification of psychosis biotypes based on brain structure: findings from the Bipolar-Schizophrenia network for intermediate phenotypes (B-SNIP). *Sci Rep*, *13*(1), 12980. https://doi.org/10.1038/s41598-023-38101-0

Kohen, D. (2004). Diabetes mellitus and schizophrenia: historical perspective. *Br J Psychiatry Suppl*, *47*, S64-66. https://doi.org/10.1192/bjp.184.47.s64

Konradi, C., & Heckers, S. (2001). Antipsychotic drugs and neuroplasticity: insights into the treatment and neurobiology of schizophrenia. *Biol Psychiatry*, *50*(10), 729-742. https://doi.org/10.1016/s0006-3223(01)01267-7

Konttajärvi, T., Haapea, M., Huhtaniska, S., Björnholm, L., Miettunen, J., Isohanni, M., Penttilä, M., Murray, G. K., Koponen, H., Vernon, A. C., Jääskeläinen, E., & Lieslehto, J. (2024). The contribution of first-episode illness characteristics and cumulative antipsychotic usage to progressive structural brain changes over a long-term follow-up in schizophrenia. *Psychiatry Res Neuroimaging*, *339*, 111790. https://doi.org/10.1016/j.pscychresns.2024.111790

Kowalski, J., Aleksandrowicz, A., Dąbkowska, M., & Gawęda, Ł. (2021). Neural Correlates of Aberrant Salience and Source Monitoring in Schizophrenia and At-Risk Mental States-A Systematic Review of fMRI Studies. *J Clin Med*, *10*(18). https://doi.org/10.3390/jcm10184126

Kraan, T., Velthorst, E., Smit, F., de Haan, L., & van der Gaag, M. (2015). Trauma and recent life events in individuals at ultra high risk for psychosis: review and meta-analysis. *Schizophr Res*, *161*(2-3), 143-149. https://doi.org/10.1016/j.schres.2014.11.026

Kraepelin, E. (1893). Lehrbuch der Psychiatrie (4th ed.). Barth Verlag.

Kraszpulski, M., Dickerson, P. A., & Salm, A. K. (2006). Prenatal stress affects the developmental trajectory of the rat amygdala. *Stress*, *9*(2), 85-95. https://doi.org/10.1080/10253890600798109

Krieckhaus, E. E., Donahoe, J. W., & Morgan, M. A. (1992). Paranoid schizophrenia may be caused by dopamine hyperactivity of CA1 hippocampus. *Biol Psychiatry*, *31*(6), 560-570. https://doi.org/10.1016/0006-3223(92)90242-r

Kudinova, A. Y., Kulak, M. J., Daniels, T. E., Angeles, W. L. L., de la Monte, S., Mathis, K. J., Beck, Q. M., Laumann, L. E., & Tyrka, A. R. (2024). Increased plasminogen activator inhibitor-1 (PAI-1) and its associations with metabolic risk in healthy young adults with early life stress. *Psychoneuroendocrinology*, *166*, 107071. https://doi.org/10.1016/j.psyneuen.2024.107071

Kullmann, S., Kleinridders, A., Small, D. M., Fritsche, A., Häring, H. U., Preissl, H., & Heni, M. (2020). Central nervous pathways of insulin action in the control of metabolism and food intake. *Lancet Diabetes Endocrinol*, *8*(6), 524-534. https://doi.org/10.1016/s2213-8587(20)30113-3

Kumar, J. S., & Mann, J. J. (2014). PET tracers for serotonin receptors and their applications. *Cent Nerv Syst Agents Med Chem*, *14*(2), 96-112. https://doi.org/10.2174/1871524914666141030124316

Kung, L., & Roberts, R. C. (1999). Mitochondrial pathology in human schizophrenic striatum: a postmortem ultrastructural study. *Synapse*, *31*(1), 67-75. https://doi.org/10.1002/(sici)1098-2396(199901)31:1<67::Aid-syn9>3.0.Co;2-#

Large, M., Sharma, S., Compton, M. T., Slade, T., & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Arch Gen Psychiatry*, *68*(6), 555-561. https://doi.org/10.1001/archgenpsychiatry.2011.5

Lasztóczi, B., & Klausberger, T. (2017). Distinct gamma oscillations in the distal dendritic fields of the dentate gyrus and the CA1 area of mouse hippocampus. *Brain Struct Funct*, *222*(7), 3355-3365. https://doi.org/10.1007/s00429-017-1421-3

Laurikainen, H., Vuorela, A., Toivonen, A., Reinert-Hartwall, L., Trontti, K., Lindgren, M., Keinänen, J., Mäntylä, T., Paju, J., Ilonen, T., Armio, R. L., Walta, M., Tuisku, J., Helin, S., Marjamäki, P., Hovatta, I., Therman, S., Vaarala, O., Linnaranta, O.,…Suvisaari, J. (2020). Elevated serum chemokine CCL22 levels in first-episode psychosis: associations with symptoms, peripheral

immune state and in vivo brain glial cell function. *Transl Psychiatry*, *10*(1), 94. https://doi.org/10.1038/s41398-020-0776-z

Laursen, T. M., Nordentoft, M., & Mortensen, P. B. (2014). Excess early mortality in schizophrenia. *Annu Rev Clin Psychol*, *10*, 425-448. https://doi.org/10.1146/annurev-clinpsy-032813-153657

Lawson, G. M., Camins, J. S., Wisse, L., Wu, J., Duda, J. T., Cook, P. A., Gee, J. C., & Farah, M. J. (2017). Childhood socioeconomic status and childhood maltreatment: Distinct associations with brain structure. *PLoS One*, *12*(4), e0175690. https://doi.org/10.1371/journal.pone.0175690

Le, L., R, K., B, M., & Mj, G. (2020). Risk of schizophrenia in relatives of individuals affected by schizophrenia: A meta-analysis. *Psychiatry Res*, *286*, 112852. https://doi.org/10.1016/j.psychres.2020.112852

LeDoux, J. (2007). The amygdala. *Curr Biol*, *17*(20), R868-874. https://doi.org/10.1016/j.cub.2007.08.005

Lee, E. E., Martin, A. S., Tu, X., Palmer, B. W., & Jeste, D. V. (2018). Childhood Adversity and Schizophrenia: The Protective Role of Resilience in Mental and Physical Health and Metabolic Markers. *J Clin Psychiatry*, *79*(3). https://doi.org/10.4088/JCP.17m11776

Lee, J., Xue, X., Au, E., McIntyre, W. B., Asgariroozbehani, R., Tseng, G. C., Papoulias, M., Panganiban, K., Agarwal, S. M., McCullumsmith, R., Freyberg, Z., Logan, R. W., & Hahn, M. K. (2024). Central insulin dysregulation in antipsychotic-naïve first-episode psychosis: In silico exploration of gene expression signatures. *Psychiatry Res*, *331*, 115636. https://doi.org/10.1016/j.psychres.2023.115636

Lee, S. H., Ripke, S., Neale, B. M., Faraone, S. V., Purcell, S. M., Perlis, R. H., Mowry, B. J., Thapar, A., Goddard, M. E., Witte, J. S., Absher, D., Agartz, I., Akil, H., Amin, F., Andreassen, O. A., Anjorin, A., Anney, R., Anttila, V., Arking, D. E.,…Wray, N. R. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*, *45*(9), 984-994. https://doi.org/10.1038/ng.2711

Lee, Y., & Davis, M. (1997). Role of the hippocampus, the bed nucleus of the stria terminalis, and the amygdala in the excitatory effect of corticotropin-releasing hormone on the acoustic startle reflex. *J Neurosci*, *17*(16), 6434-6446. https://doi.org/10.1523/jneurosci.17-16-06434.1997

Leucht, S., Rothe, P., Davis, J. M., & Engel, R. R. (2013). Equipercentile linking of the BPRS and the PANSS. *Eur Neuropsychopharmacol*, *23*(8), 956-959. https://doi.org/10.1016/j.euroneuro.2012.11.004

Leucht, S., Samara, M., Heres, S., & Davis, J. M. (2016). Dose Equivalents for Antipsychotic Drugs: The DDD Method. *Schizophr Bull*, *42 Suppl 1*(Suppl 1), S90-94. https://doi.org/10.1093/schbul/sbv167

Lewis, R., Kapur, S., Jones, C., DaSilva, J., Brown, G. M., Wilson, A. A., Houle, S., & Zipursky, R. B. (1999). Serotonin 5-HT2 receptors in schizophrenia: a PET study using [18F]setoperone in neuroleptic-naive patients and normal subjects. *Am J Psychiatry*, *156*(1), 72-78. https://doi.org/10.1176/ajp.156.1.72

Li, C., Liu, Y., Yin, S., Lu, C., Liu, D., Jiang, H., & Pan, F. (2015). Long-term effects of early adolescent stress: dysregulation of hypothalamic-pituitary-adrenal axis and central corticotropin releasing factor receptor 1 expression in adult male rats. *Behav Brain Res*, *288*, 39-49. https://doi.org/10.1016/j.bbr.2015.04.007

Li, J., Liu, B., Banaschewski, T., Bokde, A. L. W., Quinlan, E. B., Desrivières, S., Flor, H., Frouin, V., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Martinot, J. L., Artiges, E., Nees, F., Papadopoulos Orfanos, D., Paus, T., Poustka, L., Hohmann, S.,…Jiang, T. (2022). Orbitofrontal cortex volume links polygenic risk for smoking with tobacco use in healthy adolescents. *Psychol Med*, *52*(6), 1175-1182. https://doi.org/10.1017/s0033291720002962

Li, L., Garvey, W. T., & Gower, B. A. (2017). Childhood Maltreatment Is an Independent Risk Factor for Prediabetic Disturbances in Glucose Regulation. *Front Endocrinol (Lausanne)*, *8*, 151. https://doi.org/10.3389/fendo.2017.00151

Li, Z., & Chen, X. (2022). Comprehensive analysis of shared genetic loci between hippocampal volume and schizophrenia. *Psychiatry Res*, *316*, 114795. https://doi.org/10.1016/j.psychres.2022.114795

Lieberman, J. A., Girgis, R. R., Brucato, G., Moore, H., Provenzano, F., Kegeles, L., Javitt, D., Kantrowitz, J., Wall, M. M., Corcoran, C. M., Schobel, S. A., & Small, S. A. (2018). Hippocampal dysfunction in the pathophysiology of schizophrenia: a selective review and hypothesis for early detection and intervention. *Mol Psychiatry*, *23*(8), 1764-1772. https://doi.org/10.1038/mp.2017.249

Lim, L., Radua, J., & Rubia, K. (2014). Gray matter abnormalities in childhood maltreatment: a voxel-wise meta-analysis. *Am J Psychiatry*, *171*(8), 854-863. https://doi.org/10.1176/appi.ajp.2014.13101427

Limongi, R., Jeon, P., Mackinley, M., Das, T., Dempster, K., Théberge, J., Bartha, R., Wong, D., & Palaniyappan, L. (2020). Glutamate and Dysconnection in the Salience Network: Neurochemical, Effective Connectivity, and Computational Evidence in Schizophrenia. *Biol Psychiatry*, *88*(3), 273-281. https://doi.org/10.1016/j.biopsych.2020.01.021

Lipska, B. K., Jaskiw, G. E., & Weinberger, D. R. (1993). Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: a potential animal model of schizophrenia. *Neuropsychopharmacology*, *9*(1), 67-75. https://doi.org/10.1038/npp.1993.44

Lisman, J. (2012). Excitation, inhibition, local oscillations, or large-scale loops: what causes the symptoms of schizophrenia? *Curr Opin Neurobiol*, *22*(3), 537-544. https://doi.org/10.1016/j.conb.2011.10.018

Liu, J., Fan, W., Jia, Y., Su, X., Wu, W., Long, X., Sun, X., Liu, J., Sun, W., Zhang, T., Gong, Q., Shi, H., Zhu, Q., & Wang, J. (2020). Altered Gray Matter Volume in Patients With Type 1 Diabetes Mellitus. *Front Endocrinol (Lausanne)*, *11*, 45. https://doi.org/10.3389/fendo.2020.00045

Liu, Y., Li, Z., Zhang, M., Deng, Y., Yi, Z., & Shi, T. (2013). Exploring the pathogenetic association between schizophrenia and type 2 diabetes mellitus diseases based on pathway analysis. *BMC Med Genomics*, *6 Suppl 1*(Suppl 1), S17. https://doi.org/10.1186/1755-8794-6-s1-s17

Lodge, D. J., Behrens, M. M., & Grace, A. A. (2009). A loss of parvalbumin-containing interneurons is associated with diminished oscillatory activity in an animal model of schizophrenia. *J Neurosci*, *29*(8), 2344-2354. https://doi.org/10.1523/jneurosci.5419-08.2009

Lodge, D. J., & Grace, A. A. (2008). Hippocampal dysfunction and disruption of dopamine system regulation in an animal model of schizophrenia. *Neurotox Res*, *14*(2-3), 97-104. https://doi.org/10.1007/bf03033801

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. *Schizophr Res*, *205*, 10-14. https://doi.org/10.1016/j.schres.2018.05.003

Loh, J. S., Mak, W. Q., Tan, L. K. S., Ng, C. X., Chan, H. H., Yeow, S. H., Foo, J. B., Ong, Y. S., How, C. W., & Khaw, K. Y. (2024). Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases. *Signal Transduct Target Ther*, *9*(1), 37. https://doi.org/10.1038/s41392-024-01743-1

Lopez Vicchi, F., Luque, G. M., Brie, B., Nogueira, J. P., Garcia Tornadu, I., & Becu-Villalobos, D. (2016). Dopaminergic drugs in type 2 diabetes and glucose homeostasis. *Pharmacol Res*, *109*, 74-80. https://doi.org/10.1016/j.phrs.2015.12.029

Lowry, C. A. (2002). Functional subsets of serotonergic neurones: implications for control of the hypothalamic-pituitary-adrenal axis. *J Neuroendocrinol*, *14*(11), 911-923. https://doi.org/10.1046/j.1365-2826.2002.00861.x

Mably, A. J., & Colgin, L. L. (2018). Gamma oscillations in cognitive disorders. *Curr Opin Neurobiol*, *52*, 182-187. https://doi.org/10.1016/j.conb.2018.07.009

MacQueen, G. M., Yucel, K., Taylor, V. H., Macdonald, K., & Joffe, R. (2008). Posterior hippocampal volumes are associated with remission rates in patients with major depressive disorder. *Biol Psychiatry*, *64*(10), 880-883. https://doi.org/10.1016/j.biopsych.2008.06.027

Madrid-Gambin, F., Föcking, M., Sabherwal, S., Heurich, M., English, J. A., O'Gorman, A., Suvitaival, T., Ahonen, L., Cannon, M., Lewis, G., Mattila, I., Scaife, C., Madden, S., Hyötyläinen, T., Orešič, M., Zammit, S., Cagney, G., Cotter, D. R., & Brennan, L. (2019). Integrated Lipidomics and Proteomics Point to Early Blood-Based Changes in Childhood Preceding Later Development of Psychotic Experiences: Evidence From the Avon Longitudinal Study of Parents and Children. *Biol Psychiatry*, *86*(1), 25-34. https://doi.org/10.1016/j.biopsych.2019.01.018

Madsen, M. K., Fisher, P. M., Burmester, D., Dyssegaard, A., Stenbæk, D. S., Kristiansen, S., Johansen, S. S., Lehel, S., Linnet, K., Svarer, C., Erritzoe, D., Ozenne, B., & Knudsen, G. M. (2019). Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. *Neuropsychopharmacology*, *44*(7), 1328-1334. https://doi.org/10.1038/s41386-019-0324-9

Magwai, T., Shangase, K. B., Oginga, F. O., Chiliza, B., Mpofana, T., & Xulu, K. R. (2021). DNA Methylation and Schizophrenia: Current Literature and Future Perspective. *Cells*, *10*(11). https://doi.org/10.3390/cells10112890

Mahon, P. B., Eldridge, H., Crocker, B., Notes, L., Gindes, H., Postell, E., King, S., Potash, J. B., Ratnanather, J. T., & Barta, P. E. (2012). An MRI study of amygdala in schizophrenia and psychotic bipolar disorder. *Schizophr Res*, *138*(2-3), 188-191. https://doi.org/10.1016/j.schres.2012.04.005

Mahon, P. B., Lee, D. S., Trinh, H., Tward, D., Miller, M. I., Younes, L., Barta, P. E., & Ratnanather, J. T. (2015). Morphometry of the amygdala in schizophrenia and psychotic bipolar disorder. *Schizophr Res*, *164*(1-3), 199-202. https://doi.org/10.1016/j.schres.2015.02.011

Maita, I., Bazer, A., Blackford, J. U., & Samuels, B. A. (2021). Functional anatomy of the bed nucleus of the stria terminalis-hypothalamus neural circuitry: Implications for valence surveillance, addiction, feeding, and social behaviors. *Handb Clin Neurol*, *179*, 403-418. https://doi.org/10.1016/b978-0-12-819975-6.00026-1

Makowski, C., Bodnar, M., Shenker, J. J., Malla, A. K., Joober, R., Chakravarty, M. M., & Lepage, M. (2017). Linking persistent negative symptoms to amygdala-hippocampus structure in first-episode psychosis. *Transl Psychiatry*, *7*(8), e1195. https://doi.org/10.1038/tp.2017.168

Malaspina, D., Harlap, S., Fennig, S., Heiman, D., Nahon, D., Feldman, D., & Susser, E. S. (2001). Advancing paternal age and the risk of schizophrenia. *Arch Gen Psychiatry*, *58*(4), 361-367. https://doi.org/10.1001/archpsyc.58.4.361

Maleki Balajoo, S., Eickhoff, S. B., Masouleh, S. K., Plachti, A., Waite, L., Saberi, A., Bahri, M. A., Bastin, C., Salmon, E., Hoffstaedter, F., Palomero-Gallagher, N., & Genon, S. (2023). Hippocampal metabolic subregions and networks: Behavioral, molecular, and pathological aging profiles. *Alzheimers Dement*, *19*(11), 4787-4804. https://doi.org/10.1002/alz.13056

Maller, J. J., Broadhouse, K., Rush, A. J., Gordon, E., Koslow, S., & Grieve, S. M. (2018). Increased hippocampal tail volume predicts depression status and remission to anti-depressant medications in major depression. *Mol Psychiatry*, *23*(8), 1737-1744. https://doi.org/10.1038/mp.2017.224

Manoliu, A., Riedl, V., Zherdin, A., Mühlau, M., Schwerthöffer, D., Scherr, M., Peters, H., Zimmer, C., Förstl, H., Bäuml, J., Wohlschläger, A. M., & Sorg, C. (2014). Aberrant dependence of default mode/central executive network interactions on anterior insular salience network activity in schizophrenia. *Schizophr Bull*, *40*(2), 428-437. https://doi.org/10.1093/schbul/sbt037

Marangoni, C., Hernandez, M., & Faedda, G. L. (2016). The role of environmental exposures as risk factors for bipolar disorder: A systematic review of longitudinal studies. *J Affect Disord*, *193*, 165-174. https://doi.org/10.1016/j.jad.2015.12.055

Markello, R. D., Hansen, J. Y., Liu, Z. Q., Bazinet, V., Shafiei, G., Suárez, L. E., Blostein, N., Seidlitz, J., Baillet, S., Satterthwaite, T. D., Chakravarty, M. M., Raznahan, A., & Misic, B. (2022). neuromaps: structural and functional interpretation of brain maps. *Nat Methods*, *19*(11), 1472-1479. https://doi.org/10.1038/s41592-022-01625-w

Matheson, S. L., Shepherd, A. M., Pinchbeck, R. M., Laurens, K. R., & Carr, V. J. (2013). Childhood adversity in schizophrenia: a systematic meta-analysis. *Psychol Med*, *43*(2), 225-238. https://doi.org/10.1017/s0033291712000785

Mathew, I., Gardin, T. M., Tandon, N., Eack, S., Francis, A. N., Seidman, L. J., Clementz, B., Pearlson, G. D., Sweeney, J. A., Tamminga, C. A., & Keshavan, M. S. (2014). Medial temporal lobe structures and hippocampal subfields in psychotic disorders: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *JAMA Psychiatry*, *71*(7), 769-777. https://doi.org/10.1001/jamapsychiatry.2014.453

Maudsley, H. (1879). The Pathology of Mind. London: Macmillan and co.

Mazer, C., Muneyyirci, J., Taheny, K., Raio, N., Borella, A., & Whitaker-Azmitia, P. (1997). Serotonin depletion during synaptogenesis leads to decreased synaptic density and learning deficits in the adult rat: a possible model of neurodevelopmental disorders with cognitive deficits. *Brain Res*, *760*(1-2), 68-73. https://doi.org/10.1016/s0006-8993(97)00297-7

McCutcheon, R. A., Krystal, J. H., & Howes, O. D. (2020). Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. *World Psychiatry*, *19*(1), 15-33. https://doi.org/10.1002/wps.20693

McCutcheon, R. A., Merritt, K., & Howes, O. D. (2021a). Dopamine and glutamate in individuals at high risk for psychosis: a meta-analysis of in vivo imaging findings and their variability compared to controls. *World Psychiatry*, *20*(3), 405-416. https://doi.org/10.1002/wps.20893

McCutcheon, R. A., Pillinger, T., Mizuno, Y., Montgomery, A., Pandian, H., Vano, L., Marques, T. R., & Howes, O. D. (2021b). The efficacy and heterogeneity of antipsychotic response in schizophrenia: A meta-analysis. *Mol Psychiatry*, *26*(4), 1310-1320. https://doi.org/10.1038/s41380-019-0502-5

McDermott, E., & de Silva, P. (2005). Impaired neuronal glucose uptake in pathogenesis of schizophrenia - can GLUT 1 and GLUT 3 deficits explain imaging, post-mortem and pharmacological findings? *Med Hypotheses*, *65*(6), 1076-1081. https://doi.org/10.1016/j.mehy.2005.06.022

McEwen, B. S. (2017). Neurobiological and Systemic Effects of Chronic Stress. *Chronic Stress (Thousand Oaks)*, *1*. https://doi.org/10.1177/2470547017692328

McGlashan, T. H., Zipursky, R. B., Perkins, D., Addington, J., Miller, T., Woods, S. W., Hawkins, K. A., Hoffman, R. E., Preda, A., Epstein, I., Addington, D., Lindborg, S., Trzaskoma, Q., Tohen, M., & Breier, A. (2006). Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry*, *163*(5), 790-799. https://doi.org/10.1176/ajp.2006.163.5.790

McGorry, P. D., Yung, A. R., Phillips, L. J., Yuen, H. P., Francey, S., Cosgrave, E. M., Germano, D., Bravin, J., McDonald, T., Blair, A., Adlard, S., & Jackson, H. (2002). Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Arch Gen Psychiatry*, *59*(10), 921-928. https://doi.org/10.1001/archpsyc.59.10.921

McHugo, M., Armstrong, K., Roeske, M. J., Woodward, N. D., Blackford, J. U., & Heckers, S. (2020). Hippocampal volume in early psychosis: a 2-year longitudinal study. *Transl Psychiatry*, *10*(1), 306. https://doi.org/10.1038/s41398-020-00985-1

McHugo, M., Roeske, M. J., Vandekar, S. N., Armstrong, K., Avery, S. N., & Heckers, S. (2024). Smaller anterior hippocampal subfields in the early stage of psychosis. *Transl Psychiatry*, *14*(1), 69. https://doi.org/10.1038/s41398-023-02719-5

McKay, M. T., Cannon, M., Chambers, D., Conroy, R. M., Coughlan, H., Dodd, P., Healy, C., O'Donnell, L., & Clarke, M. C. (2021). Childhood trauma and adult mental disorder: A systematic review and meta-analysis of longitudinal cohort studies. *Acta Psychiatr Scand*, *143*(3), 189-205. https://doi.org/10.1111/acps.13268

Meehl, P. E. (1989). Schizotaxia revisited. *Arch Gen Psychiatry*, *46*(10), 935-944. https://doi.org/10.1001/archpsyc.1989.01810100077015

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci*, *15*(10), 483-506. https://doi.org/10.1016/j.tics.2011.08.003

Menon, V. (2023). 20 years of the default mode network: A review and synthesis. *Neuron*, *111*(16), 2469-2487. https://doi.org/10.1016/j.neuron.2023.04.023

Menon, V., Palaniyappan, L., & Supekar, K. (2023). Integrative Brain Network and Salience Models of Psychopathology and Cognitive Dysfunction in Schizophrenia. *Biol Psychiatry*, *94*(2), 108-120. https://doi.org/10.1016/j.biopsych.2022.09.029

Merritt, K., Luque Laguna, P., Irfan, A., & David, A. S. (2021). Longitudinal Structural MRI Findings in Individuals at Genetic and Clinical High Risk for Psychosis: A Systematic Review. *Front Psychiatry*, *12*, 620401. https://doi.org/10.3389/fpsyt.2021.620401

Miller, B. J., Buckley, P., Seabolt, W., Mellor, A., & Kirkpatrick, B. (2011). Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry*, *70*(7), 663-671. https://doi.org/10.1016/j.biopsych.2011.04.013

Miller, B. J., Gassama, B., Sebastian, D., Buckley, P., & Mellor, A. (2013). Meta-analysis of lymphocytes in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry*, *73*(10), 993-999. https://doi.org/10.1016/j.biopsych.2012.09.007

Miller, C. H., Fleischhacker, W. W., Ehrmann, H., & Kane, J. M. (1990). Treatment of neuroleptic induced akathisia with the 5-HT2 antagonist ritanserin. *Psychopharmacol Bull*, *26*(3), 373-376.

Miller, T. J., McGlashan, T. H., Woods, S. W., Stein, K., Driesen, N., Corcoran, C. M., Hoffman, R., & Davidson, L. (1999). Symptom assessment in schizophrenic prodromal states. *Psychiatr Q*, *70*(4), 273-287. https://doi.org/10.1023/a:1022034115078

Millhouse, O. E. (1986). The intercalated cells of the amygdala. *J Comp Neurol*, *247*(2), 246-271. https://doi.org/10.1002/cne.902470209

Milne, N. T., Bucks, R. S., Davis, W. A., Davis, T. M. E., Pierson, R., Starkstein, S. E., & Bruce, D. G. (2018). Hippocampal atrophy, asymmetry, and cognition in type 2 diabetes mellitus. *Brain Behav*, *8*(1), e00741. https://doi.org/10.1002/brb3.741

Mirzadeh, Z., Faber, C. L., & Schwartz, M. W. (2022). Central Nervous System Control of Glucose Homeostasis: A Therapeutic Target for Type 2 Diabetes? *Annu Rev Pharmacol Toxicol*, *62*, 55-84. https://doi.org/10.1146/annurev-pharmtox-052220-010446

Misiak, B., & Frydecka, D. (2016). A History of Childhood Trauma and Response to Treatment With Antipsychotics in First-Episode Schizophrenia Patients: Preliminary Results. *J Nerv Ment Dis*, *204*(10), 787-792. https://doi.org/10.1097/nmd.0000000000000567

Misiak, B., Łoniewski, I., Marlicz, W., Frydecka, D., Szulc, A., Rudzki, L., & Samochowiec, J. (2020). The HPA axis dysregulation in severe mental illness: Can we shift the blame to gut microbiota? *Prog Neuropsychopharmacol Biol Psychiatry*, *102*, 109951. https://doi.org/10.1016/j.pnpbp.2020.109951

Misiak, B., Pruessner, M., Samochowiec, J., Wisniewski, M., Reginia, A., & Stanczykiewicz, B. (2021). A meta-analysis of blood and salivary cortisol levels in first-episode psychosis and high-risk individuals. *Front Neuroendocrinol*, *62*, 100930. https://doi.org/10.1016/j.yfrne.2021.100930

Misra, S., Gelaye, B., Koenen, K. C., Williams, D. R., Borba, C. P. C., Quattrone, D., Di Forti, M., La Cascia, C., La Barbera, D., Tarricone, I., Berardi, D., Szöke, A., Arango, C., Tortelli, A., de Haan, L., Velthorst, E., Bobes, J., Bernardo, M., Sanjuán, J.,…Morgan, C. (2019). Early Parental Death and Risk of Psychosis in Offspring: A Six-Country Case-Control Study. *J Clin Med*, *8*(7). https://doi.org/10.3390/jcm8071081

Mitchell, A. J., Vancampfort, D., De Herdt, A., Yu, W., & De Hert, M. (2013a). Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. *Schizophr Bull*, *39*(2), 295-305. https://doi.org/10.1093/schbul/sbs082

Mitchell, A. J., Vancampfort, D., Sweers, K., van Winkel, R., Yu, W., & De Hert, M. (2013b). Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related

disorders--a systematic review and meta-analysis. *Schizophr Bull*, *39*(2), 306-318. https://doi.org/10.1093/schbul/sbr148

Mondelli, V., Pariante, C. M., Navari, S., Aas, M., D'Albenzio, A., Di Forti, M., Handley, R., Hepgul, N., Marques, T. R., Taylor, H., Papadopoulos, A. S., Aitchison, K. J., Murray, R. M., & Dazzan, P. (2010). Higher cortisol levels are associated with smaller left hippocampal volume in first-episode psychosis. *Schizophr Res*, *119*(1-3), 75-78. https://doi.org/10.1016/j.schres.2009.12.021

Monereo-Sanchez, J., Jansen, J. F. A., Kohler, S., van Boxtel, M. P. J., Backes, W. H., Stehouwer, C. D. A., Kroon, A. A., Kooman, J. P., Schalkwijk, C. G., Linden, D. E. J., & Schram, M. T. (2023). The association of prediabetes and type 2 diabetes with hippocampal subfields volume: The Maastricht study. *Neuroimage Clin*, *39*, 103455. https://doi.org/10.1016/j.nicl.2023.103455

Morais, L. H., Schreiber, H. L. t., & Mazmanian, S. K. (2021). The gut microbiota-brain axis in behaviour and brain disorders. *Nat Rev Microbiol*, *19*(4), 241-255. https://doi.org/10.1038/s41579-020-00460-0

Moran, L. V., Masters, G. A., Pingali, S., Cohen, B. M., Liebson, E., Rajarethinam, R. P., & Ongur, D. (2015). Prescription stimulant use is associated with earlier onset of psychosis. *J Psychiatr Res*, *71*, 41-47. https://doi.org/10.1016/j.jpsychires.2015.09.012

Morella, I. M., Brambilla, R., & Morè, L. (2022). Emerging roles of brain metabolism in cognitive impairment and neuropsychiatric disorders. *Neurosci Biobehav Rev*, *142*, 104892. https://doi.org/10.1016/j.neubiorev.2022.104892

Morosini, P. L., Magliano, L., Brambilla, L., Ugolini, S., & Pioli, R. (2000). Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand*, *101*(4), 323-329.

Morton, G. J., Meek, T. H., & Schwartz, M. W. (2014). Neurobiology of food intake in health and disease. *Nat Rev Neurosci*, *15*(6), 367-378. https://doi.org/10.1038/nrn3745

Moulton, C. D., Costafreda, S. G., Horton, P., Ismail, K., & Fu, C. H. (2015). Meta-analyses of structural regional cerebral effects in type 1 and type 2 diabetes. *Brain Imaging Behav*, *9*(4), 651-662. https://doi.org/10.1007/s11682-014-9348-2

Mu, C., Dang, X., & Luo, X. J. (2024). Mendelian randomization analyses reveal causal relationships between brain functional networks and risk of psychiatric disorders. *Nat Hum Behav*, *8*(7), 1417-1428. https://doi.org/10.1038/s41562-024-01879-8

Murphy, F., Nasa, A., Cullinane, D., Raajakesary, K., Gazzaz, A., Sooknarine, V., Haines, M., Roman, E., Kelly, L., O'Neill, A., Cannon, M., & Roddy, D. W. (2022). Childhood Trauma, the HPA Axis and Psychiatric Illnesses: A Targeted Literature Synthesis. *Front Psychiatry*, *13*, 748372. https://doi.org/10.3389/fpsyt.2022.748372

Myers, M. G., Jr., Affinati, A. H., Richardson, N., & Schwartz, M. W. (2021). Central nervous system regulation of organismal energy and glucose homeostasis. *Nat Metab*, *3*(6), 737-750. https://doi.org/10.1038/s42255-021-00408-5

Myran, D. T., Pugliese, M., Xiao, J., Kaster, T. S., Husain, M. I., Anderson, K. K., Fabiano, N., Wong, S., Fiedorowicz, J. G., Webber, C., Tanuseputro, P., & Solmi, M. (2024). Emergency Department Visits Involving Hallucinogen Use and Risk of Schizophrenia Spectrum Disorder. *JAMA Psychiatry*. https://doi.org/10.1001/jamapsychiatry.2024.3532

Najjar, S., Pahlajani, S., De Sanctis, V., Stern, J. N. H., Najjar, A., & Chong, D. (2017). Neurovascular Unit Dysfunction and Blood-Brain Barrier Hyperpermeability Contribute to Schizophrenia Neurobiology: A Theoretical Integration of Clinical and Experimental Evidence. *Front Psychiatry*, *8*, 83. https://doi.org/10.3389/fpsyt.2017.00083

Nakahara, S., Matsumoto, M., & van Erp, T. G. M. (2018). Hippocampal subregion abnormalities in schizophrenia: A systematic review of structural and physiological imaging studies. *Neuropsychopharmacol Rep*, *38*(4), 156-166. https://doi.org/10.1002/npr2.12031

Nash, A. I. (2017). Crosstalk between insulin and dopamine signaling: A basis for the metabolic effects of antipsychotic drugs. *J Chem Neuroanat*, *83-84*, 59-68. https://doi.org/10.1016/j.jchemneu.2016.07.010

Nekovarova, T., Fajnerova, I., Horacek, J., & Spaniel, F. (2014). Bridging disparate symptoms of schizophrenia: a triple network dysfunction theory. *Front Behav Neurosci*, *8*, 171. https://doi.org/10.3389/fnbeh.2014.00171

Newson, J. J., & Thiagarajan, T. C. (2018). EEG Frequency Bands in Psychiatric Disorders: A Review of Resting State Studies. *Front Hum Neurosci*, *12*, 521. https://doi.org/10.3389/fnhum.2018.00521

Nietola, M., Heiskala, A., Nordström, T., Miettunen, J., Korkeila, J., & Jääskeläinen, E. (2018). Clinical characteristics and outcomes of psychotic depression in the Northern Finland Birth Cohort 1966. *Eur Psychiatry*, *53*, 23-30. https://doi.org/10.1016/j.eurpsy.2018.05.003

Nogovitsyn, N., Muller, M., Souza, R., Hassel, S., Arnott, S. R., Davis, A. D., Hall, G. B., Harris, J. K., Zamyadi, M., Metzak, P. D., Ismail, Z., Downar, J., Parikh, S. V., Soares, C. N., Addington, J. M., Milev, R., Harkness, K. L., Frey, B. N., Lam, R. W.,…MacQueen, G. M. (2020). Hippocampal tail volume as a predictive biomarker of antidepressant treatment outcomes in patients with major depressive disorder: a CAN-BIND report. *Neuropsychopharmacology*, *45*(2), 283-291. https://doi.org/10.1038/s41386-019-0542-1

O'Hare, J. D., Zielinski, E., Cheng, B., Scherer, T., & Buettner, C. (2011). Central endocannabinoid signaling regulates hepatic glucose production and systemic lipolysis. *Diabetes*, *60*(4), 1055-1062. https://doi.org/10.2337/db10-0962

O'Hare, J. D., & Zsombok, A. (2016). Brain-liver connections: role of the preautonomic PVN neurons. *Am J Physiol Endocrinol Metab*, *310*(3), E183-189. https://doi.org/10.1152/ajpendo.00302.2015

O'Mahony, S. M., Clarke, G., Borre, Y. E., Dinan, T. G., & Cryan, J. F. (2015). Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behav Brain Res*, *277*, 32-48. https://doi.org/10.1016/j.bbr.2014.07.027

Obata, Y., & Pachnis, V. (2016). The Effect of Microbiota and the Immune System on the Development and Organization of the Enteric Nervous System. *Gastroenterology*, *151*(5), 836-844. https://doi.org/10.1053/j.gastro.2016.07.044

Ogle, C. M., Rubin, D. C., & Siegler, I. C. (2013). The impact of the developmental timing of trauma exposure on PTSD symptoms and psychosocial functioning among older adults. *Dev Psychol*, *49*(11), 2191-2200. https://doi.org/10.1037/a0031985

Ohi, K., Ishibashi, M., Torii, K., Hashimoto, M., Yano, Y., & Shioiri, T. (2022). Differences in subcortical brain volumes among patients with schizophrenia and bipolar disorder and healthy controls. *J Psychiatry Neurosci*, *47*(2), E77-e85. https://doi.org/10.1503/jpn.210144

Ohi, K., Nemoto, K., Kataoka, Y., Sugiyama, S., Muto, Y., Shioiri, T., & Kawasaki, Y. (2021). Alterations in hippocampal subfield volumes among schizophrenia patients, their first-degree relatives and healthy subjects. *Prog Neuropsychopharmacol Biol Psychiatry*, *110*, 110291. https://doi.org/10.1016/j.pnpbp.2021.110291

Olfson, M., Gerhard, T., Huang, C., Crystal, S., & Stroup, T. S. (2015). Premature Mortality Among Adults With Schizophrenia in the United States. *JAMA Psychiatry*, *72*(12), 1172-1181. https://doi.org/10.1001/jamapsychiatry.2015.1737

Olney, J. W., & Farber, N. B. (1995). Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry*, *52*(12), 998-1007. https://doi.org/10.1001/archpsyc.1995.03950240016004

Onwordi, E. C., Halff, E. F., Whitehurst, T., Mansur, A., Cotel, M. C., Wells, L., Creeney, H., Bonsall, D., Rogdaki, M., Shatalina, E., Reis Marques, T., Rabiner, E. A., Gunn, R. N., Natesan, S., Vernon, A. C., & Howes, O. D. (2020). Synaptic density marker SV2A is reduced in schizophrenia patients and unaffected by antipsychotics in rats. *Nat Commun*, *11*(1), 246. https://doi.org/10.1038/s41467-019-14122-0

Orliac, F., Naveau, M., Joliot, M., Delcroix, N., Razafimandimby, A., Brazo, P., Dollfus, S., & Delamillieure, P. (2013). Links among resting-state default-mode network, salience network, and

symptomatology in schizophrenia. *Schizophr Res*, *148*(1-3), 74-80. https://doi.org/10.1016/j.schres.2013.05.007

Ouyang, L., Li, D., Li, Z., Ma, X., Yuan, L., Fan, L., Yang, Z., Zhang, Z., Li, C., He, Y., & Chen, X. (2022). IL-17 and TNF-β: Predictive biomarkers for transition to psychosis in ultra-high risk individuals. *Front Psychiatry*, *13*, 1072380. https://doi.org/10.3389/fpsyt.2022.1072380

Overall, J. E. (1974). The Brief Psychiatric Rating Scale in Psychopharmacology Research. In P. Pichot & R. Olivier-Martin (Eds.), *Psychological Measurements in Psychopharmacology* (Vol. 7, pp. 0). S.Karger AG. https://doi.org/10.1159/000395069

Paksarian, D., Eaton, W. W., Mortensen, P. B., Merikangas, K. R., & Pedersen, C. B. (2015). A population-based study of the risk of schizophrenia and bipolar disorder associated with parent-child separation during development. *Psychol Med*, *45*(13), 2825-2837. https://doi.org/10.1017/s0033291715000781

Palaniyappan, L., White, T. P., & Liddle, P. F. (2012). The concept of salience network dysfunction in schizophrenia: from neuroimaging observations to therapeutic opportunities. *Curr Top Med Chem*, *12*(21), 2324-2338. https://doi.org/10.2174/156802612805289881

Palma-Gudiel, H., Prather, A. A., Lin, J., Oxendine, J. D., Guintivano, J., Xia, K., Rubinow, D. R., Wolkowitz, O., Epel, E. S., & Zannas, A. S. (2021). HPA axis regulation and epigenetic programming of immune-related genes in chronically stressed and non-stressed mid-life women. *Brain Behav Immun*, *92*, 49-56. https://doi.org/10.1016/j.bbi.2020.11.027

Pan, S., Worker, C. J., & Feng Earley, Y. (2023). The hypothalamus as a key regulator of glucose homeostasis: emerging roles of the brain renin-angiotensin system. *Am J Physiol Cell Physiol*, *325*(1), C141-c154. https://doi.org/10.1152/ajpcell.00533.2022

Pan, Y., Pu, W., Chen, X., Huang, X., Cai, Y., Tao, H., Xue, Z., Mackinley, M., Limongi, R., Liu, Z., & Palaniyappan, L. (2020). Morphological Profiling of Schizophrenia: Cluster Analysis of MRI-Based Cortical Thickness Data. *Schizophr Bull*, *46*(3), 623-632. https://doi.org/10.1093/schbul/sbz112

Pantelis, C., Velakoulis, D., McGorry, P. D., Wood, S. J., Suckling, J., Phillips, L. J., Yung, A. R., Bullmore, E. T., Brewer, W., Soulsby, B., Desmond, P., & McGuire, P. K. (2003). Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet*, *361*(9354), 281-288. https://doi.org/10.1016/s0140-6736(03)12323-9

Paolicelli, R. C., Bolasco, G., Pagani, F., Maggi, L., Scianni, M., Panzanelli, P., Giustetto, M., Ferreira, T. A., Guiducci, E., Dumas, L., Ragozzino, D., & Gross, C. T. (2011). Synaptic pruning by microglia is necessary for normal brain development. *Science*, *333*(6048), 1456-1458. https://doi.org/10.1126/science.1202529

Papasilekas, T., Themistoklis, K. M., Melanis, K., Patrikelis, P., Spartalis, E., Korfias, S., & Sakas, D. (2021). A Brief Review of Brain's Blood Flow-Metabolism Coupling and Pressure Autoregulation. *J Neurol Surg A Cent Eur Neurosurg*, *82*(3), 257-261. https://doi.org/10.1055/s-0040-1721682

Papazoglou, I., Lee, J. H., Cui, Z., Li, C., Fulgenzi, G., Bahn, Y. J., Staniszewska-Goraczniak, H. M., Piñol, R. A., Hogue, I. B., Enquist, L. W., Krashes, M. J., & Rane, S. G. (2022). A distinct hypothalamus-to-β cell circuit modulates insulin secretion. *Cell Metab*, *34*(2), 285-298.e287. https://doi.org/10.1016/j.cmet.2021.12.020

Pape, H. C., & Pare, D. (2010). Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. *Physiol Rev*, *90*(2), 419-463. https://doi.org/10.1152/physrev.00037.2009

Paquola, C., Bennett, M. R., & Lagopoulos, J. (2016). Understanding heterogeneity in grey matter research of adults with childhood maltreatment-A meta-analysis and review. *Neurosci Biobehav Rev*, *69*, 299-312. https://doi.org/10.1016/j.neubiorev.2016.08.011

Park, M. T. M., Jeon, P., Khan, A. R., Dempster, K., Chakravarty, M. M., Lerch, J. P., MacKinley, M., Théberge, J., & Palaniyappan, L. (2021). Hippocampal neuroanatomy in first episode psychosis:

A putative role for glutamate and serotonin receptors. *Prog Neuropsychopharmacol Biol Psychiatry*, *110*, 110297. https://doi.org/10.1016/j.pnpbp.2021.110297

Patel, Y., Parker, N., Shin, J., Howard, D., French, L., Thomopoulos, S. I., Pozzi, E., Abe, Y., Abé, C., Anticevic, A., Alda, M., Aleman, A., Alloza, C., Alonso-Lana, S., Ameis, S. H., Anagnostou, E., McIntosh, A. A., Arango, C., Arnold, P. D.,…Paus, T. (2021). Virtual Histology of Cortical Thickness and Shared Neurobiology in 6 Psychiatric Disorders. *JAMA Psychiatry*, *78*(1), 47-63. https://doi.org/10.1001/jamapsychiatry.2020.2694

Paul, S. M., Yohn, S. E., Popiolek, M., Miller, A. C., & Felder, C. C. (2022). Muscarinic Acetylcholine Receptor Agonists as Novel Treatments for Schizophrenia. *Am J Psychiatry*, *179*(9), 611-627. https://doi.org/10.1176/appi.ajp.21101083

Peh, O. H., Rapisarda, A., & Lee, J. (2019). Childhood adversities in people at ultra-high risk (UHR) for psychosis: a systematic review and meta-analysis. *Psychol Med*, *49*(7), 1089-1101. https://doi.org/10.1017/s003329171800394x

Percie du Sert, O., Unrau, J., Gauthier, C. J., Chakravarty, M., Malla, A., Lepage, M., & Raucher-Chéné, D. (2023). Cerebral blood flow in schizophrenia: A systematic review and meta-analysis of MRI-based studies. *Prog Neuropsychopharmacol Biol Psychiatry*, *121*, 110669. https://doi.org/10.1016/j.pnpbp.2022.110669

Perez, J. M., Berto, S., Gleason, K., Ghose, S., Tan, C., Kim, T. K., Konopka, G., & Tamminga, C. A. (2021). Hippocampal subfield transcriptome analysis in schizophrenia psychosis. *Mol Psychiatry*, *26*(6), 2577-2589. https://doi.org/10.1038/s41380-020-0696-6

Perry, B. I., Bowker, N., Burgess, S., Wareham, N. J., Upthegrove, R., Jones, P. B., Langenberg, C., & Khandaker, G. M. (2022). Evidence for Shared Genetic Aetiology Between Schizophrenia, Cardiometabolic, and Inflammation-Related Traits: Genetic Correlation and Colocalization Analyses. *Schizophr Bull Open*, *3*(1), sgac001. https://doi.org/10.1093/schizbullopen/sgac001

Perry, B. I., Burgess, S., Jones, H. J., Zammit, S., Upthegrove, R., Mason, A. M., Day, F. R., Langenberg, C., Wareham, N. J., Jones, P. B., & Khandaker, G. M. (2021a). The potential shared role of inflammation in insulin resistance and schizophrenia: A bidirectional two-sample mendelian randomization study. *PLoS Med*, *18*(3), e1003455. https://doi.org/10.1371/journal.pmed.1003455

Perry, B. I., Stochl, J., Upthegrove, R., Zammit, S., Wareham, N., Langenberg, C., Winpenny, E., Dunger, D., Jones, P. B., & Khandaker, G. M. (2021b). Longitudinal Trends in Childhood Insulin Levels and Body Mass Index and Associations With Risks of Psychosis and Depression in Young Adults. *JAMA Psychiatry*, *78*(4), 416-425. https://doi.org/10.1001/jamapsychiatry.2020.4180

Perälä, J., Saarni, S. I., Ostamo, A., Pirkola, S., Haukka, J., Härkänen, T., Koskinen, S., Lönnqvist, J., & Suvisaari, J. (2008). Geographic variation and sociodemographic characteristics of psychotic disorders in Finland. *Schizophr Res*, *106*(2-3), 337-347. https://doi.org/10.1016/j.schres.2008.08.017

Perälä, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsä, E., Pirkola, S., Partonen, T., Tuulio-Henriksson, A., Hintikka, J., Kieseppä, T., Härkänen, T., Koskinen, S., & Lönnqvist, J. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry*, *64*(1), 19-28. https://doi.org/10.1001/archpsyc.64.1.19

Pesarico, A. P., Carceller, H., Guirado, R., Coviello, S., & Nacher, J. (2022). Long term effects of 24-h-restraint stress on the connectivity and structure of interneurons in the basolateral amygdala. *Prog Neuropsychopharmacol Biol Psychiatry*, *115*, 110512. https://doi.org/10.1016/j.pnpbp.2022.110512

Petrikis, P., Tigas, S., Tzallas, A. T., Papadopoulos, I., Skapinakis, P., & Mavreas, V. (2015). Parameters of glucose and lipid metabolism at the fasted state in drug-naive first-episode patients with psychosis: Evidence for insulin resistance. *Psychiatry Res*, *229*(3), 901-904. https://doi.org/10.1016/j.psychres.2015.07.041

Petrovich, G. D., Canteras, N. S., & Swanson, L. W. (2001). Combinatorial amygdalar inputs to hippocampal domains and hypothalamic behavior systems. *Brain Res Brain Res Rev*, *38*(1-2), 247-289. https://doi.org/10.1016/s0165-0173(01)00080-7

Pignatelli, M., & Beyeler, A. (2019). Valence coding in amygdala circuits. *Curr Opin Behav Sci*, *26*, 97-106. https://doi.org/10.1016/j.cobeha.2018.10.010

Pikkarainen, M., Rönkkö, S., Savander, V., Insausti, R., & Pitkänen, A. (1999). Projections from the lateral, basal, and accessory basal nuclei of the amygdala to the hippocampal formation in rat. *J Comp Neurol*, *403*(2), 229-260.

Pillinger, T., Beck, K., Gobjila, C., Donocik, J. G., Jauhar, S., & Howes, O. D. (2017). Impaired Glucose Homeostasis in First-Episode Schizophrenia: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *74*(3), 261-269. https://doi.org/10.1001/jamapsychiatry.2016.3803

Pillinger, T., D'Ambrosio, E., McCutcheon, R., & Howes, O. D. (2019). Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models. *Mol Psychiatry*, *24*(6), 776-794. https://doi.org/10.1038/s41380-018-0058-9

Pillinger, T., McCutcheon, R. A., & Howes, O. D. (2023). Variability of glucose, insulin, and lipid disturbances in first-episode psychosis: a meta-analysis. *Psychol Med*, *53*(7), 3150-3156. https://doi.org/10.1017/S0033291721005213

Pillinger, T., McCutcheon, R. A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., Beck, K., Natesan, S., Efthimiou, O., Cipriani, A., & Howes, O. D. (2020). Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry*, *7*(1), 64-77. https://doi.org/10.1016/s2215-0366(19)30416-x

Poldrack, R. A., Kittur, A., Kalar, D., Miller, E., Seppa, C., Gil, Y., Parker, D. S., Sabb, F. W., & Bilder, R. M. (2011). The cognitive atlas: toward a knowledge foundation for cognitive neuroscience. *Front Neuroinform*, *5*, 17. https://doi.org/10.3389/fninf.2011.00017

Praharaj, S. K., Kongasseri, S., Behere, R. V., & Sharma, P. S. (2015). Mirtazapine for antipsychotic-induced acute akathisia: a systematic review and meta-analysis of randomized placebo-controlled trials. *Ther Adv Psychopharmacol*, *5*(5), 307-313. https://doi.org/10.1177/2045125315601343

Prakash, J., Chatterjee, K., Srivastava, K., & Chauhan, V. S. (2021). First-episode psychosis: How long does it last? A review of evolution and trajectory. *Ind Psychiatry J*, *30*(2), 198-206. https://doi.org/10.4103/ipj.ipj_38_21

Provenzano, F. A., Guo, J., Wall, M. M., Feng, X., Sigmon, H. C., Brucato, G., First, M. B., Rothman, D. L., Girgis, R. R., Lieberman, J. A., & Small, S. A. (2020). Hippocampal Pathology in Clinical High-Risk Patients and the Onset of Schizophrenia. *Biol Psychiatry*, *87*(3), 234-242. https://doi.org/10.1016/j.biopsych.2019.09.022

Pruessner, M., Lepage, M., Collins, D. L., Pruessner, J. C., Joober, R., & Malla, A. K. (2015). Reduced hippocampal volume and hypothalamus-pituitary-adrenal axis function in first episode psychosis: evidence for sex differences. *Neuroimage Clin*, *7*, 195-202. https://doi.org/10.1016/j.nicl.2014.12.001

Puig, M. V., & Gulledge, A. T. (2011). Serotonin and prefrontal cortex function: neurons, networks, and circuits. *Mol Neurobiol*, *44*(3), 449-464. https://doi.org/10.1007/s12035-011-8214-0

Puig, M. V., Watakabe, A., Ushimaru, M., Yamamori, T., & Kawaguchi, Y. (2010). Serotonin modulates fast-spiking interneuron and synchronous activity in the rat prefrontal cortex through 5-HT1A and 5-HT2A receptors. *J Neurosci*, *30*(6), 2211-2222. https://doi.org/10.1523/jneurosci.3335-09.2010

Pycock, C. J., Kerwin, R. W., & Carter, C. J. (1980). Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. *Nature*, *286*(5768), 74-76. https://doi.org/10.1038/286074a0

Qi, W., Blessing, E., Li, C., Ardekani, B. A., Hart, K. L., Marx, J., Freudenreich, O., Cather, C., Holt, D., Bello, I., Diminich, E. D., Tang, Y., Worthington, M., Zeng, B., Wu, R., Fan, X., Troxel, A.,

Zhao, J., Wang, J., & Goff, D. C. (2021). Effect of citalopram on hippocampal volume in first-episode schizophrenia: Structural MRI results from the DECIFER trial. *Psychiatry Res Neuroimaging*, *312*, 111286. https://doi.org/10.1016/j.pscychresns.2021.111286

Quednow, B. B., Geyer, M. A., & Halberstadt, A. L. (2020). Chapter 39 - Serotonin and schizophrenia. In C. P. Müller & K. A. Cunningham (Eds.), *Handbook of Behavioral Neuroscience* (Vol. 31, pp. 711-743). Elsevier. https://doi.org/https://doi.org/10.1016/B978-0-444-64125-0.00039-6

Quidé, Y., Watkeys, O. J., Tonini, E., Grotegerd, D., Dannlowski, U., Nenadić, I., Kircher, T., Krug, A., Hahn, T., Meinert, S., Goltermann, J., Gruber, M., Stein, F., Brosch, K., Wroblewski, A., Thomas-Odenthal, F., Usemann, P., Straube, B., Alexander, N.,…Green, M. J. (2024). Childhood trauma moderates schizotypy-related brain morphology: analyses of 1182 healthy individuals from the ENIGMA schizotypy working group. *Psychol Med*, *54*(6), 1215-1227. https://doi.org/10.1017/s0033291723003045

R Core Team. (2017). A language and environment for statistical computing. .

R Core Team. (2022). R Core Team: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria. . https://www.R-project.org/.

Rabinowitz, J. A., Campos, A. I., Ong, J. S., García-Marín, L. M., Alcauter, S., Mitchell, B. L., Grasby, K. L., Cuéllar-Partida, G., Gillespie, N. A., Huhn, A. S., Martin, N. G., Thompson, P. M., Medland, S. E., Maher, B. S., & Rentería, M. E. (2022). Shared Genetic Etiology between Cortical Brain Morphology and Tobacco, Alcohol, and Cannabis Use. *Cereb Cortex*, *32*(4), 796-807. https://doi.org/10.1093/cercor/bhab243

Read, J., van Os, J., Morrison, A. P., & Ross, C. A. (2005). Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatr Scand*, *112*(5), 330-350. https://doi.org/10.1111/j.1600-0447.2005.00634.x

Rempel-Clower, N. L., & Barbas, H. (1998). Topographic organization of connections between the hypothalamus and prefrontal cortex in the rhesus monkey. *J Comp Neurol*, *398*(3), 393-419. https://doi.org/10.1002/(sici)1096-9861(19980831)398:3<393::aid-cne7>3.0.co;2-v

Remschmidt, H., & Theisen, F. (2012). Early-onset schizophrenia. *Neuropsychobiology*, *66*(1), 63-69. https://doi.org/10.1159/000338548

Repovs, G., Csernansky, J. G., & Barch, D. M. (2011). Brain network connectivity in individuals with schizophrenia and their siblings. *Biol Psychiatry*, *69*(10), 967-973. https://doi.org/10.1016/j.biopsych.2010.11.009

Reppucci, C. J., & Petrovich, G. D. (2016). Organization of connections between the amygdala, medial prefrontal cortex, and lateral hypothalamus: a single and double retrograde tracing study in rats. *Brain Struct Funct*, *221*(6), 2937-2962. https://doi.org/10.1007/s00429-015-1081-0

Riem, M. M., Alink, L. R., Out, D., Van Ijzendoorn, M. H., & Bakermans-Kranenburg, M. J. (2015). Beating the brain about abuse: Empirical and meta-analytic studies of the association between maltreatment and hippocampal volume across childhood and adolescence. *Dev Psychopathol*, *27*(2), 507-520. https://doi.org/10.1017/s0954579415000127

Roalf, D. R., Vandekar, S. N., Almasy, L., Ruparel, K., Satterthwaite, T. D., Elliott, M. A., Podell, J., Gallagher, S., Jackson, C. T., Prasad, K., Wood, J., Pogue-Geile, M. F., Nimgaonkar, V. L., Gur, R. C., & Gur, R. E. (2015). Heritability of subcortical and limbic brain volume and shape in multiplex-multigenerational families with schizophrenia. *Biol Psychiatry*, *77*(2), 137-146. https://doi.org/10.1016/j.biopsych.2014.05.009

Roberts, R. C. (2017). Postmortem studies on mitochondria in schizophrenia. *Schizophr Res*, *187*, 17-25. https://doi.org/10.1016/j.schres.2017.01.056

Rochfort, K. D., & Cummins, P. M. (2015). The blood-brain barrier endothelium: a target for pro-inflammatory cytokines. *Biochem Soc Trans*, *43*(4), 702-706. https://doi.org/10.1042/bst20140319

Rodríguez-Toscano, E., Alloza, C., Fraguas, D., Durán-Cutilla, M., Roldán, L., Sánchez-Gutiérrez, T., López-Montoya, G., Parellada, M., Moreno, C., Gayer-Anderson, C., Jongsma, H. E., Di Forti, M., Quattrone, D., Velthorst, E., de Haan, L., Selten, J. P., Szöke, A., Llorca, P. M., Tortelli, A.,…Arango, C. (2023). Differences in Patterns of Stimulant Use and Their Impact on First-

Episode Psychosis Incidence: An Analysis of the EUGEI Study. *Schizophr Bull*, *49*(5), 1269-1280. https://doi.org/10.1093/schbul/sbad013

Roh, E., Song, D. K., & Kim, M. S. (2016). Emerging role of the brain in the homeostatic regulation of energy and glucose metabolism. *Exp Mol Med*, *48*(3), e216. https://doi.org/10.1038/emm.2016.4

Roozendaal, B., McEwen, B. S., & Chattarji, S. (2009). Stress, memory and the amygdala. *Nat Rev Neurosci*, *10*(6), 423-433. https://doi.org/10.1038/nrn2651

Ruggeri, A., Nerland, S., Mørch-Johnsen, L., Jørgensen, K. N., Barth, C., Wortinger, L. A., Andreou, D., Andreassen, O. A., & Agartz, I. (2024). Hypothalamic Subunit Volumes in Schizophrenia and Bipolar Spectrum Disorders. *Schizophr Bull*, *50*(3), 533-544. https://doi.org/10.1093/schbul/sbad176

Ruiz-Torras, S., Gudayol-Ferré, E., Fernández-Vazquez, O., Cañete-Massé, C., Peró-Cebollero, M., & Guàrdia-Olmos, J. (2023). Hypoconnectivity networks in schizophrenia patients: A voxel-wise meta-analysis of Rs-fMRI. *Int J Clin Health Psychol*, *23*(4), 100395. https://doi.org/10.1016/j.ijchp.2023.100395

Russo, D. A., Stochl, J., Painter, M., Dobler, V., Jackson, E., Jones, P. B., & Perez, J. (2014). Trauma history characteristics associated with mental states at clinical high risk for psychosis. *Psychiatry Res*, *220*(1-2), 237-244. https://doi.org/10.1016/j.psychres.2014.08.028

Rutigliano, G., Valmaggia, L., Landi, P., Frascarelli, M., Cappucciati, M., Sear, V., Rocchetti, M., De Micheli, A., Jones, C., Palombini, E., McGuire, P., & Fusar-Poli, P. (2016). Persistence or recurrence of non-psychotic comorbid mental disorders associated with 6-year poor functional outcomes in patients at ultra high risk for psychosis. *J Affect Disord*, *203*, 101-110. https://doi.org/10.1016/j.jad.2016.05.053

Rürup, L., Mathes, B., Schmiedt-Fehr, C., Wienke, A. S., Özerdem, A., Brand, A., & Basar-Eroglu, C. (2020). Altered gamma and theta oscillations during multistable perception in schizophrenia. *Int J Psychophysiol*, *155*, 127-139. https://doi.org/10.1016/j.ijpsycho.2020.06.002

Saarinen, A. I. L., Huhtaniska, S., Pudas, J., Björnholm, L., Jukuri, T., Tohka, J., Granö, N., Barnett, J. H., Kiviniemi, V., Veijola, J., Hintsanen, M., & Lieslehto, J. (2020). Structural and functional alterations in the brain gray matter among first-degree relatives of schizophrenia patients: A multimodal meta-analysis of fMRI and VBM studies. *Schizophr Res*, *216*, 14-23. https://doi.org/10.1016/j.schres.2019.12.023

Saha, S., Chant, D., & McGrath, J. (2007). A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry*, *64*(10), 1123-1131. https://doi.org/10.1001/archpsyc.64.10.1123

Saha, S., Chant, D. C., Welham, J. L., & McGrath, J. J. (2006). The incidence and prevalence of schizophrenia varies with latitude. *Acta Psychiatr Scand*, *114*(1), 36-39. https://doi.org/10.1111/j.1600-0447.2005.00742.x

Sahin, S., Yüksel, Ç., Güler, J., Karadayı, G., Akturan, E., Göde, E., Özhan, A. A., & Üçok, A. (2013). The history of childhood trauma among individuals with ultra high risk for psychosis is as common as among patients with first-episode schizophrenia. *Early Interv Psychiatry*, *7*(4), 414-420. https://doi.org/10.1111/eip.12022

Salokangas, R. K., Schultze-Lutter, F., Patterson, P., von Reventlow, H. G., Heinimaa, M., From, T., Luutonen, S., Hankala, J., Kotimaki, M., & Tuominen, L. (2016). Psychometric properties of the Trauma and Distress Scale, TADS, in an adult community sample in Finland. *Eur J Psychotraumatol*, *7*, 30062. https://doi.org/10.3402/ejpt.v7.30062

Salokangas, R. K. R. (2022). Emotional neglect in childhood is common and associates with adult mental ill health. *Nord J Psychiatry*, 1. https://doi.org/10.1080/08039488.2021.2019939

Salokangas, R. K. R., Hietala, J., Armio, R. L., Laurikainen, H., From, T., Borgwardt, S., Riecher-Rossler, A., Brambilla, P., Bonivento, C., Meisenzahl, E., Schultze-Lutter, F., Haidl, T., Ruhrmann, S., Upthegrove, R., Wood, S. J., Pantelis, C., Kambeitz-Ilankovic, L., Ruef, A., Dwyer, D. B.,…Koutsouleris, N. (2021). Effect of childhood physical abuse on social anxiety is mediated

via reduced frontal lobe and amygdala-hippocampus complex volume in adult clinical high-risk subjects. *Schizophr Res*, *227*, 101-109. https://doi.org/10.1016/j.schres.2020.05.041

Salokangas, R. K. R., Schultze-Lutter, F., Schmidt, S. J., Pesonen, H., Luutonen, S., Patterson, P., Graf von Reventlow, H., Heinimaa, M., From, T., & Hietala, J. (2020). Childhood physical abuse and emotional neglect are specifically associated with adult mental disorders. *J Ment Health*, *29*(4), 376-384. https://doi.org/10.1080/09638237.2018.1521940

Salvatore, P., Baldessarini, R. J., Khalsa, H. K., & Tohen, M. (2021). Prodromal features in first-psychotic episodes of major affective and schizoaffective disorders. *J Affect Disord*, *295*, 1251-1258. https://doi.org/10.1016/j.jad.2021.08.099

Samann, P. G., Iglesias, J. E., Gutman, B., Grotegerd, D., Leenings, R., Flint, C., Dannlowski, U., Clarke-Rubright, E. K., Morey, R. A., van Erp, T. G. M., Whelan, C. D., Han, L. K. M., van Velzen, L. S., Cao, B., Augustinack, J. C., Thompson, P. M., Jahanshad, N., & Schmaal, L. (2022). FreeSurfer-based segmentation of hippocampal subfields: A review of methods and applications, with a novel quality control procedure for ENIGMA studies and other collaborative efforts. *Hum Brain Mapp*, *43*(1), 207-233. https://doi.org/10.1002/hbm.25326

Samartzis, L., Dima, D., Fusar-Poli, P., & Kyriakopoulos, M. (2014). White matter alterations in early stages of schizophrenia: a systematic review of diffusion tensor imaging studies. *J Neuroimaging*, *24*(2), 101-110. https://doi.org/10.1111/j.1552-6569.2012.00779.x

Samplin, E., Ikuta, T., Malhotra, A. K., Szeszko, P. R., & Derosse, P. (2013). Sex differences in resilience to childhood maltreatment: effects of trauma history on hippocampal volume, general cognition and subclinical psychosis in healthy adults. *J Psychiatr Res*, *47*(9), 1174-1179. https://doi.org/10.1016/j.jpsychires.2013.05.008

Santos-Silva, T., Dos Santos Fabris, D., de Oliveira, C. L., Guimarães, F. S., & Gomes, F. V. (2024). Prefrontal and Hippocampal Parvalbumin Interneurons in Animal Models for Schizophrenia: A Systematic Review and Meta-analysis. *Schizophr Bull*, *50*(1), 210-223. https://doi.org/10.1093/schbul/sbad123

Sasabayashi, D., Yoshimura, R., Takahashi, T., Takayanagi, Y., Nishiyama, S., Higuchi, Y., Mizukami, Y., Furuichi, A., Kido, M., Nakamura, M., Noguchi, K., & Suzuki, M. (2021). Reduced Hippocampal Subfield Volume in Schizophrenia and Clinical High-Risk State for Psychosis. *Front Psychiatry*, *12*, 642048. https://doi.org/10.3389/fpsyt.2021.642048

Saygin, Z. M., Kliemann, D., Iglesias, J. E., van der Kouwe, A. J. W., Boyd, E., Reuter, M., Stevens, A., Van Leemput, K., McKee, A., Frosch, M. P., Fischl, B., & Augustinack, J. C. (2017). High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: manual segmentation to automatic atlas. *Neuroimage*, *155*, 370-382. https://doi.org/10.1016/j.neuroimage.2017.04.046

Scatton, B., Worms, P., Lloyd, K. G., & Bartholini, G. (1982). Cortical modulation of striatal function. *Brain Res*, *232*(2), 331-343. https://doi.org/10.1016/0006-8993(82)90277-3

SCHARRER, E. (1940). VASCULARIZATION AND VULNERABILITY OF THE CORNU AMMONIS IN THE OPOSSUM. *Archives of Neurology & Psychiatry*, *44*(3), 483-506. https://doi.org/10.1001/archneurpsyc.1940.02280090002001

Schenkel, L. S., Spaulding, W. D., DiLillo, D., & Silverstein, S. M. (2005). Histories of childhood maltreatment in schizophrenia: relationships with premorbid functioning, symptomatology, and cognitive deficits. *Schizophr Res*, *76*(2-3), 273-286. https://doi.org/10.1016/j.schres.2005.03.003

Schizophrenia. Current Care Guidelines. (2024). Retrieved 23.8. from https://www.kaypahoito.fi/hoi35050

Schmidt, C. J., Sorensen, S. M., Kehne, J. H., Carr, A. A., & Palfreyman, M. G. (1995). The role of 5-HT2A receptors in antipsychotic activity. *Life Sci*, *56*(25), 2209-2222. https://doi.org/10.1016/0024-3205(95)00210-w

Schobel, S. A., Chaudhury, N. H., Khan, U. A., Paniagua, B., Styner, M. A., Asllani, I., Inbar, B. P., Corcoran, C. M., Lieberman, J. A., Moore, H., & Small, S. A. (2013). Imaging patients with psychosis and a mouse model establishes a spreading pattern of hippocampal dysfunction and

implicates glutamate as a driver. *Neuron*, *78*(1), 81-93. https://doi.org/10.1016/j.neuron.2013.02.011

Schobel, S. A., Lewandowski, N. M., Corcoran, C. M., Moore, H., Brown, T., Malaspina, D., & Small, S. A. (2009). Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. *Arch Gen Psychiatry*, *66*(9), 938-946. https://doi.org/10.1001/archgenpsychiatry.2009.115

Schoonover, K. E., Farmer, C. B., Morgan, C. J., Sinha, V., Odom, L., & Roberts, R. C. (2021). Abnormalities in the copper transporter CTR1 in postmortem hippocampus in schizophrenia: A subregion and laminar analysis. *Schizophr Res*, *228*, 60-73. https://doi.org/10.1016/j.schres.2020.12.016

Schreier, A., Wolke, D., Thomas, K., Horwood, J., Hollis, C., Gunnell, D., Lewis, G., Thompson, A., Zammit, S., Duffy, L., Salvi, G., & Harrison, G. (2009). Prospective study of peer victimization in childhood and psychotic symptoms in a nonclinical population at age 12 years. *Arch Gen Psychiatry*, *66*(5), 527-536. https://doi.org/10.1001/archgenpsychiatry.2009.23

Schwartz, M. W., Sipols, A., Kahn, S. E., Lattemann, D. F., Taborsky, G. J., Jr., Bergman, R. N., Woods, S. C., & Porte, D., Jr. (1990). Kinetics and specificity of insulin uptake from plasma into cerebrospinal fluid. *Am J Physiol*, *259*(3 Pt 1), E378-383. https://doi.org/10.1152/ajpendo.1990.259.3.E378

Schwarz, E., Maukonen, J., Hyytiäinen, T., Kieseppä, T., Orešič, M., Sabunciyan, S., Mantere, O., Saarela, M., Yolken, R., & Suvisaari, J. (2018). Analysis of microbiota in first episode psychosis identifies preliminary associations with symptom severity and treatment response. *Schizophr Res*, *192*, 398-403. https://doi.org/10.1016/j.schres.2017.04.017

Shao, L. X., Liao, C., Gregg, I., Davoudian, P. A., Savalia, N. K., Delagarza, K., & Kwan, A. C. (2021). Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. *Neuron*, *109*(16), 2535-2544.e2534. https://doi.org/10.1016/j.neuron.2021.06.008

Shao, T., Huang, J., Zhao, Y., Wang, W., Tian, X., Hei, G., Kang, D., Gao, Y., Liu, F., Zhao, J., Liu, B., Yuan, T. F., & Wu, R. (2023). Metformin improves cognitive impairment in patients with schizophrenia: associated with enhanced functional connectivity of dorsolateral prefrontal cortex. *Transl Psychiatry*, *13*(1), 315. https://doi.org/10.1038/s41398-023-02616-x

Sharon, G., Sampson, T. R., Geschwind, D. H., & Mazmanian, S. K. (2016). The Central Nervous System and the Gut Microbiome. *Cell*, *167*(4), 915-932. https://doi.org/10.1016/j.cell.2016.10.027

Shin, J., Pelletier, S., Richer, L., Pike, G. B., Gaudet, D., Paus, T., & Pausova, Z. (2020). Adiposity-related insulin resistance and thickness of the cerebral cortex in middle-aged adults. *J Neuroendocrinol*, *32*(12), e12921. https://doi.org/10.1111/jne.12921

Sima, A. A., Kamiya, H., & Li, Z. G. (2004). Insulin, C-peptide, hyperglycemia, and central nervous system complications in diabetes. *Eur J Pharmacol*, *490*(1-3), 187-197. https://doi.org/10.1016/j.ejphar.2004.02.056

Simon, A. E., Velthorst, E., Nieman, D. H., Linszen, D., Umbricht, D., & de Haan, L. (2011). Ultra high-risk state for psychosis and non-transition: a systematic review. *Schizophr Res*, *132*(1), 8-17. https://doi.org/10.1016/j.schres.2011.07.002

Simon, L., & Admon, R. (2023). From childhood adversity to latent stress vulnerability in adulthood: the mediating roles of sleep disturbances and HPA axis dysfunction. *Neuropsychopharmacology*, *48*(10), 1425-1435. https://doi.org/10.1038/s41386-023-01638-9

Singh, T., Poterba, T., Curtis, D., Akil, H., Al Eissa, M., Barchas, J. D., Bass, N., Bigdeli, T. B., Breen, G., Bromet, E. J., Buckley, P. F., Bunney, W. E., Bybjerg-Grauholm, J., Byerley, W. F., Chapman, S. B., Chen, W. J., Churchhouse, C., Craddock, N., Cusick, C. M.,…Daly, M. J. (2022). Rare coding variants in ten genes confer substantial risk for schizophrenia. *Nature*, *604*(7906), 509-516. https://doi.org/10.1038/s41586-022-04556-w

Sklar, P. (2008). Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature*, *455*(7210), 237-241. https://doi.org/10.1038/nature07239

Slifstein, M., van de Giessen, E., Van Snellenberg, J., Thompson, J. L., Narendran, R., Gil, R., Hackett, E., Girgis, R., Ojeil, N., Moore, H., D'Souza, D., Malison, R. T., Huang, Y., Lim, K., Nabulsi, N., Carson, R. E., Lieberman, J. A., & Abi-Dargham, A. (2015). Deficits in prefrontal cortical and extrastriatal dopamine release in schizophrenia: a positron emission tomographic functional magnetic resonance imaging study. *JAMA Psychiatry*, *72*(4), 316-324. https://doi.org/10.1001/jamapsychiatry.2014.2414

Soeters, M. R., & Soeters, P. B. (2012). The evolutionary benefit of insulin resistance. *Clin Nutr*, *31*(6), 1002-1007. https://doi.org/10.1016/j.clnu.2012.05.011

Solmi, M., Croatto, G., Piva, G., Rosson, S., Fusar-Poli, P., Rubio, J. M., Carvalho, A. F., Vieta, E., Arango, C., DeTore, N. R., Eberlin, E. S., Mueser, K. T., & Correll, C. U. (2023a). Efficacy and acceptability of psychosocial interventions in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. *Mol Psychiatry*, *28*(1), 354-368. https://doi.org/10.1038/s41380-022-01727-z

Solmi, M., Seitidis, G., Mavridis, D., Correll, C. U., Dragioti, E., Guimond, S., Tuominen, L., Dargél, A., Carvalho, A. F., Fornaro, M., Maes, M., Monaco, F., Song, M., Il Shin, J., & Cortese, S. (2023b). Incidence, prevalence, and global burden of schizophrenia - data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. *Mol Psychiatry*, *28*(12), 5319-5327. https://doi.org/10.1038/s41380-023-02138-4

Soltani Zangbar, H., Ghadiri, T., Seyedi Vafaee, M., Ebrahimi Kalan, A., Fallahi, S., Ghorbani, M., & Shahabi, P. (2020). Theta Oscillations Through Hippocampal/Prefrontal Pathway: Importance in Cognitive Performances. *Brain Connect*, *10*(4), 157-169. https://doi.org/10.1089/brain.2019.0733

Song, Y. S., Hwang, Y. C., Ahn, H. Y., & Park, C. Y. (2016). Comparison of the Usefulness of the Updated Homeostasis Model Assessment (HOMA2) with the Original HOMA1 in the Prediction of Type 2 Diabetes Mellitus in Koreans. *Diabetes Metab J*, *40*(4), 318-325. https://doi.org/10.4093/dmj.2016.40.4.318

Sormunen, E., Saarinen, M. M., Salokangas, R. K. R., Hutri-Kahonen, N., Viikari, J., Raitakari, O. T., & Hietala, J. (2022). Metabolic trajectories in childhood and adolescence: Effects on risk for schizophrenia. *Schizophrenia (Heidelb)*, *8*(1), 82. https://doi.org/10.1038/s41537-022-00282-4

Sormunen, E., Saarinen, M. M., Salokangas, R. K. R., Telama, R., Hutri-Kähönen, N., Tammelin, T., Viikari, J., Raitakari, O., & Hietala, J. (2017). Effects of childhood and adolescence physical activity patterns on psychosis risk-a general population cohort study. *NPJ Schizophr*, *3*, 5. https://doi.org/10.1038/s41537-016-0007-z

Soto, M., Cai, W., Konishi, M., & Kahn, C. R. (2019). Insulin signaling in the hippocampus and amygdala regulates metabolism and neurobehavior. *Proc Natl Acad Sci U S A*, *116*(13), 6379-6384. https://doi.org/10.1073/pnas.1817391116

Souama, C., Milaneschi, Y., Lamers, F., Vinkers, C. H., Giltay, E. J., Lieburg, E. J., & Penninx, B. (2024). Metabolic syndrome after childhood trauma: a 9-year longitudinal analysis. *Psychol Med*, *54*(7), 1373-1381. https://doi.org/10.1017/s0033291723003264

Spallazzi, M., Dobisch, L., Becke, A., Berron, D., Stucht, D., Oeltze-Jafra, S., Caffarra, P., Speck, O., & Düzel, E. (2019). Hippocampal vascularization patterns: A high-resolution 7 Tesla time-of-flight magnetic resonance angiography study. *Neuroimage Clin*, *21*, 101609. https://doi.org/10.1016/j.nicl.2018.11.019

Spellman, T. J., & Gordon, J. A. (2015). Synchrony in schizophrenia: a window into circuit-level pathophysiology. *Curr Opin Neurobiol*, *30*, 17-23. https://doi.org/10.1016/j.conb.2014.08.009

Sporns, O. (2013). Structure and function of complex brain networks. *Dialogues Clin Neurosci*, *15*(3), 247-262. https://doi.org/10.31887/DCNS.2013.15.3/osporns

Stahl, S. M. (2018). Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: dopamine, serotonin, and glutamate. *CNS Spectr*, *23*(3), 187-191. https://doi.org/10.1017/s1092852918001013

Stamatakis, A. M., Sparta, D. R., Jennings, J. H., McElligott, Z. A., Decot, H., & Stuber, G. D. (2014). Amygdala and bed nucleus of the stria terminalis circuitry: Implications for addiction-related

behaviors. *Neuropharmacology*, *76 Pt B*(0 0), 320-328. https://doi.org/10.1016/j.neuropharm.2013.05.046

Stedehouder, J., & Kushner, S. A. (2017). Myelination of parvalbumin interneurons: a parsimonious locus of pathophysiological convergence in schizophrenia. *Mol Psychiatry*, *22*(1), 4-12. https://doi.org/10.1038/mp.2016.147

Steen, N. E., Rahman, Z., Szabo, A., Hindley, G. F. L., Parker, N., Cheng, W., Lin, A., O'Connell, K. S., Sheikh, M. A., Shadrin, A., Bahrami, S., Karthikeyan, S., Hoseth, E. Z., Dale, A. M., Aukrust, P., Smeland, O. B., Ueland, T., Frei, O., Djurovic, S., & Andreassen, O. A. (2023). Shared Genetic Loci Between Schizophrenia and White Blood Cell Counts Suggest Genetically Determined Systemic Immune Abnormalities. *Schizophr Bull*, *49*(5), 1345-1354. https://doi.org/10.1093/schbul/sbad082

Stefansson, H., Ophoff, R. A., Steinberg, S., Andreassen, O. A., Cichon, S., Rujescu, D., Werge, T., Pietiläinen, O. P., Mors, O., Mortensen, P. B., Sigurdsson, E., Gustafsson, O., Nyegaard, M., Tuulio-Henriksson, A., Ingason, A., Hansen, T., Suvisaari, J., Lonnqvist, J., Paunio, T.,…Collier, D. A. (2009). Common variants conferring risk of schizophrenia. *Nature*, *460*(7256), 744-747. https://doi.org/10.1038/nature08186

Stepan, J., Dine, J., & Eder, M. (2015). Functional optical probing of the hippocampal trisynaptic circuit in vitro: network dynamics, filter properties, and polysynaptic induction of CA1 LTP. *Front Neurosci*, *9*, 160. https://doi.org/10.3389/fnins.2015.00160

Steullet, P., Cabungcal, J. H., Kulak, A., Kraftsik, R., Chen, Y., Dalton, T. P., Cuenod, M., & Do, K. Q. (2010). Redox dysregulation affects the ventral but not dorsal hippocampus: impairment of parvalbumin neurons, gamma oscillations, and related behaviors. *J Neurosci*, *30*(7), 2547-2558. https://doi.org/10.1523/jneurosci.3857-09.2010

Strandwitz, P. (2018). Neurotransmitter modulation by the gut microbiota. *Brain Res*, *1693*(Pt B), 128-133. https://doi.org/10.1016/j.brainres.2018.03.015

Strandwitz, P., Kim, K. H., Terekhova, D., Liu, J. K., Sharma, A., Levering, J., McDonald, D., Dietrich, D., Ramadhar, T. R., Lekbua, A., Mroue, N., Liston, C., Stewart, E. J., Dubin, M. J., Zengler, K., Knight, R., Gilbert, J. A., Clardy, J., & Lewis, K. (2019). GABA-modulating bacteria of the human gut microbiota. *Nat Microbiol*, *4*(3), 396-403. https://doi.org/10.1038/s41564-018-0307-3

Strubbe, J. H., Porte, D., Jr., & Woods, S. C. (1988). Insulin responses and glucose levels in plasma and cerebrospinal fluid during fasting and refeeding in the rat. *Physiol Behav*, *44*(2), 205-208. https://doi.org/10.1016/0031-9384(88)90139-4

Suárez, L. E., Markello, R. D., Betzel, R. F., & Misic, B. (2020). Linking Structure and Function in Macroscale Brain Networks. *Trends Cogn Sci*, *24*(4), 302-315. https://doi.org/10.1016/j.tics.2020.01.008

Sullivan, C. R., O'Donovan, S. M., McCullumsmith, R. E., & Ramsey, A. (2018). Defects in Bioenergetic Coupling in Schizophrenia. *Biol Psychiatry*, *83*(9), 739-750. https://doi.org/10.1016/j.biopsych.2017.10.014

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry*, *60*(12), 1187-1192. https://doi.org/10.1001/archpsyc.60.12.1187

Sullivan, R. M., & Gratton, A. (2002). Prefrontal cortical regulation of hypothalamic-pituitary-adrenal function in the rat and implications for psychopathology: side matters. *Psychoneuroendocrinology*, *27*(1-2), 99-114. https://doi.org/10.1016/s0306-4530(01)00038-5

Sun, S., Xiao, S., Guo, Z., Gong, J., Tang, G., Huang, L., & Wang, Y. (2023). Meta-analysis of cortical thickness reduction in adult schizophrenia. *J Psychiatry Neurosci*, *48*(6), E461-e470. https://doi.org/10.1503/jpn.230081

Sun, Y., Hu, N., Wang, M., Lu, L., Luo, C., Tang, B., Yao, C., Sweeney, J. A., Gong, Q., Qiu, C., & Lui, S. (2023). Hippocampal subfield alterations in schizophrenia and major depressive disorder: a systematic review and network meta-analysis of anatomic MRI studies. *J Psychiatry Neurosci*, *48*(1), E34-e49. https://doi.org/10.1503/jpn.220086

Suokas, K., Kurkela, O., Nevalainen, J., Suvisaari, J., Hakulinen, C., Kampman, O., & Pirkola, S. (2024). Geographical variation in treated psychotic and other mental disorders in Finland by region and urbanicity. *Soc Psychiatry Psychiatr Epidemiol*, *59*(1), 37-49. https://doi.org/10.1007/s00127-023-02516-x

Supekar, K., Cai, W., Krishnadas, R., Palaniyappan, L., & Menon, V. (2019). Dysregulated Brain Dynamics in a Triple-Network Saliency Model of Schizophrenia and Its Relation to Psychosis. *Biol Psychiatry*, *85*(1), 60-69. https://doi.org/10.1016/j.biopsych.2018.07.020

Sutterland, A. L., Fond, G., Kuin, A., Koeter, M. W., Lutter, R., van Gool, T., Yolken, R., Szoke, A., Leboyer, M., & de Haan, L. (2015). Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. *Acta Psychiatr Scand*, *132*(3), 161-179. https://doi.org/10.1111/acps.12423

Sykes, D. A., Moore, H., Stott, L., Holliday, N., Javitch, J. A., Lane, J. R., & Charlton, S. J. (2017). Extrapyramidal side effects of antipsychotics are linked to their association kinetics at dopamine D(2) receptors. *Nat Commun*, *8*(1), 763. https://doi.org/10.1038/s41467-017-00716-z

Szatkiewicz, J. P., O'Dushlaine, C., Chen, G., Chambert, K., Moran, J. L., Neale, B. M., Fromer, M., Ruderfer, D., Akterin, S., Bergen, S. E., Kähler, A., Magnusson, P. K., Kim, Y., Crowley, J. J., Rees, E., Kirov, G., O'Donovan, M. C., Owen, M. J., Walters, J.,…Sullivan, P. F. (2014). Copy number variation in schizophrenia in Sweden. *Mol Psychiatry*, *19*(7), 762-773. https://doi.org/10.1038/mp.2014.40

Tam, G. W., Redon, R., Carter, N. P., & Grant, S. G. (2009). The role of DNA copy number variation in schizophrenia. *Biol Psychiatry*, *66*(11), 1005-1012. https://doi.org/10.1016/j.biopsych.2009.07.027

Tamminga, C. A., Southcott, S., Sacco, C., Wagner, A. D., & Ghose, S. (2012). Glutamate dysfunction in hippocampus: relevance of dentate gyrus and CA3 signaling. *Schizophr Bull*, *38*(5), 927-935. https://doi.org/10.1093/schbul/sbs062

Tamminga, C. A., Stan, A. D., & Wagner, A. D. (2010). The hippocampal formation in schizophrenia. *Am J Psychiatry*, *167*(10), 1178-1193. https://doi.org/10.1176/appi.ajp.2010.09081187

Tanaka-Koshiyama, K., Koshiyama, D., Miyakoshi, M., Joshi, Y. B., Molina, J. L., Sprock, J., Braff, D. L., & Light, G. A. (2020). Abnormal Spontaneous Gamma Power Is Associated With Verbal Learning and Memory Dysfunction in Schizophrenia. *Front Psychiatry*, *11*, 832. https://doi.org/10.3389/fpsyt.2020.00832

Tauscher, J., Kapur, S., Verhoeff, N. P., Hussey, D. F., Daskalakis, Z. J., Tauscher-Wisniewski, S., Wilson, A. A., Houle, S., Kasper, S., & Zipursky, R. B. (2002). Brain serotonin 5-HT(1A) receptor binding in schizophrenia measured by positron emission tomography and [11C]WAY-100635. *Arch Gen Psychiatry*, *59*(6), 514-520. https://doi.org/10.1001/archpsyc.59.6.514

Teicher, M. H., & Samson, J. A. (2013). Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *Am J Psychiatry*, *170*(10), 1114-1133. https://doi.org/10.1176/appi.ajp.2013.12070957

Teicher, M. H., Samson, J. A., Anderson, C. M., & Ohashi, K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. *Nat Rev Neurosci*, *17*(10), 652-666. https://doi.org/10.1038/nrn.2016.111

Tendilla-Beltrán, H., Sanchez-Islas, N. D. C., Marina-Ramos, M., Leza, J. C., & Flores, G. (2021). The prefrontal cortex as a target for atypical antipsychotics in schizophrenia, lessons of neurodevelopmental animal models. *Prog Neurobiol*, *199*, 101967. https://doi.org/10.1016/j.pneurobio.2020.101967

Ter Horst, K. W., Lammers, N. M., Trinko, R., Opland, D. M., Figee, M., Ackermans, M. T., Booij, J., van den Munckhof, P., Schuurman, P. R., Fliers, E., Denys, D., DiLeone, R. J., la Fleur, S. E., & Serlie, M. J. (2018). Striatal dopamine regulates systemic glucose metabolism in humans and mice. *Sci Transl Med*, *10*(442). https://doi.org/10.1126/scitranslmed.aar3752

Tesli, N., van der Meer, D., Rokicki, J., Storvestre, G., Røsæg, C., Jensen, A., Hjell, G., Bell, C., Fischer-Vieler, T., Tesli, M., Andreassen, O. A., Melle, I., Agartz, I., & Haukvik, U. K. (2020).

Hippocampal subfield and amygdala nuclei volumes in schizophrenia patients with a history of violence. *Eur Arch Psychiatry Clin Neurosci*, *270*(6), 771-782. https://doi.org/10.1007/s00406-020-01098-y

Thomas, C., Hyppönen, E., & Power, C. (2008). Obesity and type 2 diabetes risk in midadult life: the role of childhood adversity. *Pediatrics*, *121*(5), e1240-1249. https://doi.org/10.1542/peds.2007-2403

Thomas, S., Höfler, M., Schäfer, I., & Trautmann, S. (2019). Childhood maltreatment and treatment outcome in psychotic disorders: a systematic review and meta-analysis. *Acta Psychiatr Scand*, *140*(4), 295-312. https://doi.org/10.1111/acps.13077

Tishler, T. A., Bartzokis, G., Lu, P. H., Raven, E. P., Khanoyan, M., Kirkpatrick, C. J., Pyle, M. H., Villablanca, J. P., Altshuler, L. L., Mintz, J., Ventura, J., Casaus, L. R., Subotnik, K. L., Nuechterlein, K. H., & Ellingson, B. M. (2018). Abnormal Trajectory of Intracortical Myelination in Schizophrenia Implicates White Matter in Disease Pathophysiology and the Therapeutic Mechanism of Action of Antipsychotics. *Biol Psychiatry Cogn Neurosci Neuroimaging*, *3*(5), 454-462. https://doi.org/10.1016/j.bpsc.2017.03.007

Tosato, S., Bonetto, C., Tomassi, S., Zanardini, R., Faravelli, C., Bruschi, C., D'Agostino, A., Minelli, A., Scocco, P., Lasalvia, A., Furlato, K., Imbesi, M., Preti, A., Ruggeri, M., Gennarelli, M., Get Up, G., & Bocchio-Chiavetto, L. (2020). Childhood trauma and glucose metabolism in patients with first-episode psychosis. *Psychoneuroendocrinology*, *113*, 104536. https://doi.org/10.1016/j.psyneuen.2019.104536

Townsend, L., Pillinger, T., Selvaggi, P., Veronese, M., Turkheimer, F., & Howes, O. (2023). Brain glucose metabolism in schizophrenia: a systematic review and meta-analysis of (18)FDG-PET studies in schizophrenia. *Psychol Med*, *53*(11), 4880-4897. https://doi.org/10.1017/S003329172200174X

Trauelsen, A. M., Bendall, S., Jansen, J. E., Nielsen, H. G., Pedersen, M. B., Trier, C. H., Haahr, U. H., & Simonsen, E. (2015). Childhood adversity specificity and dose-response effect in non-affective first-episode psychosis. *Schizophr Res*, *165*(1), 52-59. https://doi.org/10.1016/j.schres.2015.03.014

Trotta, A., Murray, R. M., & Fisher, H. L. (2015). The impact of childhood adversity on the persistence of psychotic symptoms: a systematic review and meta-analysis. *Psychol Med*, *45*(12), 2481-2498. https://doi.org/10.1017/s0033291715000574

Trotti, R. L., Parker, D. A., Sabatinelli, D., Keshavan, M. S., Keedy, S. K., Gershon, E. S., Pearlson, G. D., Hill, S. K., Tamminga, C. A., McDowell, J. E., & Clementz, B. A. (2023). Emotional scene processing in biotypes of psychosis. *Psychiatry Res*, *324*, 115227. https://doi.org/10.1016/j.psychres.2023.115227

Trubetskoy, V., Pardinas, A. F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T. B., Bryois, J., Chen, C. Y., Dennison, C. A., Hall, L. S., Lam, M., Watanabe, K., Frei, O., Ge, T., Harwood, J. C., Koopmans, F., Magnusson, S., Richards, A. L., Sidorenko, J.,…Schizophrenia Working Group of the Psychiatric Genomics, C. (2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature*, *604*(7906), 502-508. https://doi.org/10.1038/s41586-022-04434-5

Tuominen, L., Armio, R.-L., Hansen Y. J., Walta, M., Koutsouleris N., Laurikainen H., Salokangas R.K.R., Misic, B., Hietala, J. (2024). Molecular, physiological and functional features underlying cortical thinning related to antipsychotic medication use. *bioRxiv*.

Turkheimer, F. E., Selvaggi, P., Mehta, M. A., Veronese, M., Zelaya, F., Dazzan, P., & Vernon, A. C. (2020). Normalizing the Abnormal: Do Antipsychotic Drugs Push the Cortex Into an Unsustainable Metabolic Envelope? *Schizophr Bull*, *46*(3), 484-495. https://doi.org/10.1093/schbul/sbz119

Uhlhaas, P. J., & Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci*, *11*(2), 100-113. https://doi.org/10.1038/nrn2774

Uliana, D. L., Gomes, F. V., & Grace, A. A. (2021). Stress impacts corticoamygdalar connectivity in an age-dependent manner. *Neuropsychopharmacology*, *46*(4), 731-740. https://doi.org/10.1038/s41386-020-00886-3

Uliana, D. L., Resstel, L. B. M., & Grace, A. A. (2018). Fear extinction disruption in a developmental rodent model of schizophrenia correlates with an impairment in basolateral amygdala-medial prefrontal cortex plasticity. *Neuropsychopharmacology*, *43*(12), 2459-2467. https://doi.org/10.1038/s41386-018-0128-3

Unschuld, P. G., Buchholz, A. S., Varvaris, M., van Zijl, P. C., Ross, C. A., Pekar, J. J., Hock, C., Sweeney, J. A., Tamminga, C. A., Keshavan, M. S., Pearlson, G. D., Thaker, G. K., & Schretlen, D. J. (2014). Prefrontal brain network connectivity indicates degree of both schizophrenia risk and cognitive dysfunction. *Schizophr Bull*, *40*(3), 653-664. https://doi.org/10.1093/schbul/sbt077

van Bussel, F. C., Backes, W. H., Hofman, P. A., van Boxtel, M. P., Schram, M. T., Stehouwer, C. D., Wildberger, J. E., & Jansen, J. F. (2016). Altered Hippocampal White Matter Connectivity in Type 2 Diabetes Mellitus and Memory Decrements. *J Neuroendocrinol*, *28*(3), 12366. https://doi.org/10.1111/jne.12366

van Dam, D. S., van der Ven, E., Velthorst, E., Selten, J. P., Morgan, C., & de Haan, L. (2012). Childhood bullying and the association with psychosis in non-clinical and clinical samples: a review and meta-analysis. *Psychol Med*, *42*(12), 2463-2474. https://doi.org/10.1017/s0033291712000360

van der Meer, D., Cheng, W., Rokicki, J., Fernandez-Cabello, S., Shadrin, A., Smeland, O. B., Ehrhart, F., Gülöksüz, S., Pries, L. K., Lin, B., Rutten, B. P. F., van Os, J., O'Donovan, M., Richards, A. L., Steen, N. E., Djurovic, S., Westlye, L. T., Andreassen, O. A., & Kaufmann, T. (2024). Clustering Schizophrenia Genes by Their Temporal Expression Patterns Aids Functional Interpretation. *Schizophr Bull*, *50*(2), 327-338. https://doi.org/10.1093/schbul/sbad140

van der Meer, D., Rokicki, J., Kaufmann, T., Cordova-Palomera, A., Moberget, T., Alnaes, D., Bettella, F., Frei, O., Doan, N. T., Sonderby, I. E., Smeland, O. B., Agartz, I., Bertolino, A., Bralten, J., Brandt, C. L., Buitelaar, J. K., Djurovic, S., van Donkelaar, M., Dorum, E. S.,…Genetics, S. (2020). Brain scans from 21,297 individuals reveal the genetic architecture of hippocampal subfield volumes. *Mol Psychiatry*, *25*(11), 3053-3065. https://doi.org/10.1038/s41380-018-0262-7

van der Vegt, E. J., van der Ende, J., Kirschbaum, C., Verhulst, F. C., & Tiemeier, H. (2009). Early neglect and abuse predict diurnal cortisol patterns in adults A study of international adoptees. *Psychoneuroendocrinology*, *34*(5), 660-669. https://doi.org/10.1016/j.psyneuen.2008.11.004

van Erp, T. G., Hibar, D. P., Rasmussen, J. M., Glahn, D. C., Pearlson, G. D., Andreassen, O. A., Agartz, I., Westlye, L. T., Haukvik, U. K., Dale, A. M., Melle, I., Hartberg, C. B., Gruber, O., Kraemer, B., Zilles, D., Donohoe, G., Kelly, S., McDonald, C., Morris, D. W.,…Turner, J. A. (2016). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Mol Psychiatry*, *21*(4), 547-553. https://doi.org/10.1038/mp.2015.63

van Erp, T. G. M., Walton, E., Hibar, D. P., Schmaal, L., Jiang, W., Glahn, D. C., Pearlson, G. D., Yao, N., Fukunaga, M., Hashimoto, R., Okada, N., Yamamori, H., Bustillo, J. R., Clark, V. P., Agartz, I., Mueller, B. A., Cahn, W., de Zwarte, S. M. C., Hulshoff Pol, H. E.,…Turner, J. A. (2018). Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. *Biol Psychiatry*, *84*(9), 644-654. https://doi.org/10.1016/j.biopsych.2018.04.023

van Haren, N. E., Schnack, H. G., Cahn, W., van den Heuvel, M. P., Lepage, C., Collins, L., Evans, A. C., Hulshoff Pol, H. E., & Kahn, R. S. (2011). Changes in cortical thickness during the course of illness in schizophrenia. *Arch Gen Psychiatry*, *68*(9), 871-880. https://doi.org/10.1001/archgenpsychiatry.2011.88

Van Voorhees, E., & Scarpa, A. (2004). The effects of child maltreatment on the hypothalamic-pituitary-adrenal axis. *Trauma Violence Abuse*, *5*(4), 333-352. https://doi.org/10.1177/1524838004269486

van Vugt, M. K., Schulze-Bonhage, A., Litt, B., Brandt, A., & Kahana, M. J. (2010). Hippocampal gamma oscillations increase with memory load. *J Neurosci*, *30*(7), 2694-2699. https://doi.org/10.1523/jneurosci.0567-09.2010

Vancampfort, D., Stubbs, B., Mitchell, A. J., De Hert, M., Wampers, M., Ward, P. B., Rosenbaum, S., & Correll, C. U. (2015). Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry*, *14*(3), 339-347. https://doi.org/10.1002/wps.20252

Vancampfort, D., Vansteelandt, K., Correll, C. U., Mitchell, A. J., De Herdt, A., Sienaert, P., Probst, M., & De Hert, M. (2013). Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. *Am J Psychiatry*, *170*(3), 265-274. https://doi.org/10.1176/appi.ajp.2012.12050620

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., van Os, J., & Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr Bull*, *38*(4), 661-671. https://doi.org/10.1093/schbul/sbs050

Vargas, T., Dean, D. J., Osborne, K. J., Gupta, T., Ristanovic, I., Ozturk, S., Turner, J., van Erp, T. G. M., & Mittal, V. A. (2018). Hippocampal Subregions Across the Psychosis Spectrum. *Schizophr Bull*, *44*(5), 1091-1099. https://doi.org/10.1093/schbul/sbx160

Váša, F., & Mišić, B. (2022). Null models in network neuroscience. *Nat Rev Neurosci*, *23*(8), 493-504. https://doi.org/10.1038/s41583-022-00601-9

Vassos, E., Pedersen, C. B., Murray, R. M., Collier, D. A., & Lewis, C. M. (2012). Meta-analysis of the association of urbanicity with schizophrenia. *Schizophr Bull*, *38*(6), 1118-1123. https://doi.org/10.1093/schbul/sbs096

Vaucher, J., Keating, B. J., Lasserre, A. M., Gan, W., Lyall, D. M., Ward, J., Smith, D. J., Pell, J. P., Sattar, N., Pare, G., & Holmes, M. V. (2018). Cannabis use and risk of schizophrenia: a Mendelian randomization study. *Mol Psychiatry*, *23*(5), 1287-1292. https://doi.org/10.1038/mp.2016.252

Velakoulis, D., Pantelis, C., McGorry, P. D., Dudgeon, P., Brewer, W., Cook, M., Desmond, P., Bridle, N., Tierney, P., Murrie, V., Singh, B., & Copolov, D. (1999). Hippocampal volume in first-episode psychoses and chronic schizophrenia: a high-resolution magnetic resonance imaging study. *Arch Gen Psychiatry*, *56*(2), 133-141. https://doi.org/10.1001/archpsyc.56.2.133

Velakoulis, D., Wood, S. J., Wong, M. T., McGorry, P. D., Yung, A., Phillips, L., Smith, D., Brewer, W., Proffitt, T., Desmond, P., & Pantelis, C. (2006). Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Arch Gen Psychiatry*, *63*(2), 139-149. https://doi.org/10.1001/archpsyc.63.2.139

Vernon, A. C., Natesan, S., Modo, M., & Kapur, S. (2011). Effect of chronic antipsychotic treatment on brain structure: a serial magnetic resonance imaging study with ex vivo and postmortem confirmation. *Biol Psychiatry*, *69*(10), 936-944. https://doi.org/10.1016/j.biopsych.2010.11.010

Vieira, S., Gong, Q., Scarpazza, C., Lui, S., Huang, X., Crespo-Facorro, B., Tordesillas-Gutierrez, D., de la Foz, V. O., Setien-Suero, E., Scheepers, F., van Haren, N. E. M., Kahn, R., Reis Marques, T., Ciufolini, S., Di Forti, M., Murray, R. M., David, A., Dazzan, P., McGuire, P., & Mechelli, A. (2021). Neuroanatomical abnormalities in first-episode psychosis across independent samples: a multi-centre mega-analysis. *Psychol Med*, *51*(2), 340-350. https://doi.org/10.1017/s0033291719003568

Vitolo, E., Tatu, M. K., Pignolo, C., Cauda, F., Costa, T., Ando, A., & Zennaro, A. (2017). White matter and schizophrenia: A meta-analysis of voxel-based morphometry and diffusion tensor imaging

studies. *Psychiatry Res Neuroimaging*, *270*, 8-21. https://doi.org/10.1016/j.pscychresns.2017.09.014

Voineskos, A. N., Mulsant, B. H., Dickie, E. W., Neufeld, N. H., Rothschild, A. J., Whyte, E. M., Meyers, B. S., Alexopoulos, G. S., Hoptman, M. J., Lerch, J. P., & Flint, A. J. (2020). Effects of Antipsychotic Medication on Brain Structure in Patients With Major Depressive Disorder and Psychotic Features: Neuroimaging Findings in the Context of a Randomized Placebo-Controlled Clinical Trial. *JAMA Psychiatry*, *77*(7), 674-683. https://doi.org/10.1001/jamapsychiatry.2020.0036

Vonnegut, M. (1975). The Eden Express: *A memoir*. Dial Press.

Wagner, E., Siafis, S., Fernando, P., Falkai, P., Honer, W. G., Röh, A., Siskind, D., Leucht, S., & Hasan, A. (2021). Efficacy and safety of clozapine in psychotic disorders-a systematic quantitative meta-review. *Transl Psychiatry*, *11*(1), 487. https://doi.org/10.1038/s41398-021-01613-2

Wahlberg, K. E., Wynne, L. C., Oja, H., Keskitalo, P., Pykäläinen, L., Lahti, I., Moring, J., Naarala, M., Sorri, A., Seitamaa, M., Läksy, K., Kolassa, J., & Tienari, P. (1997). Gene-environment interaction in vulnerability to schizophrenia: findings from the Finnish Adoptive Family Study of Schizophrenia. *Am J Psychiatry*, *154*(3), 355-362. https://doi.org/10.1176/ajp.154.3.355

Walker, C. P., Buse, J. B., & Frohlich, F. (2021). Experimental increase of blood glucose alters resting state EEG measures of excitation-inhibition balance. *Exp Physiol*, *106*(4), 803-811. https://doi.org/10.1113/ep089211

Walker, E. F., Trotman, H. D., Pearce, B. D., Addington, J., Cadenhead, K. S., Cornblatt, B. A., Heinssen, R., Mathalon, D. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Cannon, T. D., McGlashan, T. H., & Woods, S. W. (2013). Cortisol levels and risk for psychosis: initial findings from the North American prodrome longitudinal study. *Biol Psychiatry*, *74*(6), 410-417. https://doi.org/10.1016/j.biopsych.2013.02.016

Wallace, T. M., Levy, J. C., & Matthews, D. R. (2004). Use and abuse of HOMA modeling. *Diabetes Care*, *27*(6), 1487-1495. https://doi.org/10.2337/diacare.27.6.1487

Walter, A., Suenderhauf, C., Harrisberger, F., Lenz, C., Smieskova, R., Chung, Y., Cannon, T. D., Bearden, C. E., Rapp, C., Bendfeldt, K., Borgwardt, S., & Vogel, T. (2016). Hippocampal volume in subjects at clinical high-risk for psychosis: A systematic review and meta-analysis. *Neurosci Biobehav Rev*, *71*, 680-690. https://doi.org/10.1016/j.neubiorev.2016.10.007

Wang, A. K., & Miller, B. J. (2018). Meta-analysis of Cerebrospinal Fluid Cytokine and Tryptophan Catabolite Alterations in Psychiatric Patients: Comparisons Between Schizophrenia, Bipolar Disorder, and Depression. *Schizophr Bull*, *44*(1), 75-83. https://doi.org/10.1093/schbul/sbx035

Wang, B., Irizar, H., Thygesen, J. H., Zartaloudi, E., Austin-Zimmerman, I., Bhat, A., Harju-Seppänen, J., Pain, O., Bass, N., Gkofa, V., Alizadeh, B. Z., van Amelsvoort, T., Arranz, M. J., Bender, S., Cahn, W., Stella Calafato, M., Crespo-Facorro, B., Di Forti, M., Giegling, I.,…Bramon, E. (2023). Psychosis Endophenotypes: A Gene-Set-Specific Polygenic Risk Score Analysis. *Schizophr Bull*, *49*(6), 1625-1636. https://doi.org/10.1093/schbul/sbad088

Wang, C., Tishler, T. A., Nuechterlein, K. H., & Ellingson, B. M. (2023). Cortical thickness, gray-white matter contrast, and intracortical myelin in first-episode schizophrenia patients treated with long-acting paliperidone palmitate versus oral antipsychotics. *Psychiatry Res*, *326*, 115364. https://doi.org/10.1016/j.psychres.2023.115364

Wang, K., Li, X., Wang, X., Hommel, B., Xia, X., Qiu, J., Fu, Y., & Zhou, Z. (2023). In vivo analyses reveal hippocampal subfield volume reductions in adolescents with schizophrenia, but not with major depressive disorder. *J Psychiatr Res*, *165*, 56-63. https://doi.org/10.1016/j.jpsychires.2023.07.012

Wang, Y. C., Ho, U. C., Ko, M. C., Liao, C. C., & Lee, L. J. (2012). Differential neuronal changes in medial prefrontal cortex, basolateral amygdala and nucleus accumbens after postweaning social isolation. *Brain Struct Funct*, *217*(2), 337-351. https://doi.org/10.1007/s00429-011-0355-4

Wang, Z., Yuan, X., Zhu, Z., Pang, L., Ding, S., Li, X., Kang, Y., Hei, G., Zhang, L., Zhang, X., Wang, S., Jian, X., Li, Z., Zheng, C., Fan, X., Hu, S., Shi, Y., & Song, X. (2024). Multiomics Analyses

Reveal Microbiome-Gut-Brain Crosstalk Centered on Aberrant Gamma-Aminobutyric Acid and Tryptophan Metabolism in Drug-Naïve Patients with First-Episode Schizophrenia. *Schizophr Bull*, *50*(1), 187-198. https://doi.org/10.1093/schbul/sbad026

Wannan, C. M. J., Cropley, V. L., Chakravarty, M. M., Van Rheenen, T. E., Mancuso, S., Bousman, C., Everall, I., McGorry, P. D., Pantelis, C., & Bartholomeusz, C. F. (2019). Hippocampal subfields and visuospatial associative memory across stages of schizophrenia-spectrum disorder. *Psychol Med*, *49*(14), 2452-2462. https://doi.org/10.1017/s0033291718003458

Waszczuk, K., Rek-Owodziń, K., Tyburski, E., Mak, M., Misiak, B., & Samochowiec, J. (2021). Disturbances in White Matter Integrity in the Ultra-High-Risk Psychosis State-A Systematic Review. *J Clin Med*, *10*(11). https://doi.org/10.3390/jcm10112515

Watson, S., Gallagher, P., Ritchie, J. C., Ferrier, I. N., & Young, A. H. (2004). Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. *Br J Psychiatry*, *184*, 496-502. https://doi.org/10.1192/bjp.184.6.496

Whalen, P., & Phelps, E. (2009). The human amygdala. Japanese Edition ed. In: Guilford Publications, Guilford County, North Carolina, Inc.

Whelan, C. D., Hibar, D. P., van Velzen, L. S., Zannas, A. S., Carrillo-Roa, T., McMahon, K., Prasad, G., Kelly, S., Faskowitz, J., deZubiracay, G., Iglesias, J. E., van Erp, T. G. M., Frodl, T., Martin, N. G., Wright, M. J., Jahanshad, N., Schmaal, L., Samann, P. G., Thompson, P. M., & Alzheimer's Disease Neuroimaging, I. (2016). Heritability and reliability of automatically segmented human hippocampal formation subregions. *Neuroimage*, *128*, 125-137. https://doi.org/10.1016/j.neuroimage.2015.12.039

White, T., Su, S., Schmidt, M., Kao, C. Y., & Sapiro, G. (2010). The development of gyrification in childhood and adolescence. *Brain Cogn*, *72*(1), 36-45. https://doi.org/10.1016/j.bandc.2009.10.009

Whitehurst, T., & Howes, O. (2022). The role of mitochondria in the pathophysiology of schizophrenia: A critical review of the evidence focusing on mitochondrial complex one. *Neurosci Biobehav Rev*, *132*, 449-464. https://doi.org/10.1016/j.neubiorev.2021.11.047

Wierenga, L., Langen, M., Ambrosino, S., van Dijk, S., Oranje, B., & Durston, S. (2014). Typical development of basal ganglia, hippocampus, amygdala and cerebellum from age 7 to 24. *Neuroimage*, *96*, 67-72. https://doi.org/10.1016/j.neuroimage.2014.03.072

Winterburn, J. L., Pruessner, J. C., Chavez, S., Schira, M. M., Lobaugh, N. J., Voineskos, A. N., & Chakravarty, M. M. (2013). A novel in vivo atlas of human hippocampal subfields using high-resolution 3 T magnetic resonance imaging. *Neuroimage*, *74*, 254-265. https://doi.org/10.1016/j.neuroimage.2013.02.003

Wittemann, M., Brielmaier, J., Rubly, M., Kennel, J., Werler, F., Schmitgen, M. M., Kubera, K. M., Hirjak, D., Wolf, N. D., Reith, W., & Wolf, R. C. (2021). Cognition and Cortical Thickness in Heavy Cannabis Users. *Eur Addict Res*, *27*(2), 115-122. https://doi.org/10.1159/000509987

Wolkowitz, O. M. (2018). Accelerated biological aging in serious mental disorders. *World Psychiatry*, *17*(2), 144-145. https://doi.org/10.1002/wps.20546

Wood, S. J., Velakoulis, D., Smith, D. J., Bond, D., Stuart, G. W., McGorry, P. D., Brewer, W. J., Bridle, N., Eritaia, J., Desmond, P., Singh, B., Copolov, D., & Pantelis, C. (2001). A longitudinal study of hippocampal volume in first episode psychosis and chronic schizophrenia. *Schizophr Res*, *52*(1-2), 37-46. https://doi.org/10.1016/s0920-9964(01)00175-x

Woodward, T. S., Leong, K., Sanford, N., Tipper, C. M., & Lavigne, K. M. (2016). Altered balance of functional brain networks in Schizophrenia. *Psychiatry Res Neuroimaging*, *248*, 94-104. https://doi.org/10.1016/j.pscychresns.2016.01.003

Woon, F. L., & Hedges, D. W. (2008). Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. *Hippocampus*, *18*(8), 729-736. https://doi.org/10.1002/hipo.20437

Xia, C., Alliey-Rodriguez, N., Tamminga, C. A., Keshavan, M. S., Pearlson, G. D., Keedy, S. K., Clementz, B., McDowell, J. E., Parker, D., Lencer, R., Kristian Hill, S., Bishop, J. R., Ivleva, E.

I., Wen, C., Dai, R., Chen, C., Liu, C., & Gershon, E. S. (2024). Genetic Analysis of Psychosis Biotypes: Shared Ancestry-Adjusted Polygenic Risk and Unique Genomic Associations. *medRxiv*. https://doi.org/10.1101/2024.12.05.24318404

Xiao, J., Buka, S. L., Cannon, T. D., Suzuki, Y., Viscidi, R. P., Torrey, E. F., & Yolken, R. H. (2009). Serological pattern consistent with infection with type I Toxoplasma gondii in mothers and risk of psychosis among adult offspring. *Microbes Infect*, *11*(13), 1011-1018. https://doi.org/10.1016/j.micinf.2009.07.007

Xu, J., Liang, J., Yan, H., Zhang, C., Zhang, X., Li, X., Huang, W., Guo, H., Yang, Y., Ye, J., Ou, Y., Deng, W., Xu, J., Li, X., Xie, G., & Guo, W. (2024). Alterations in amygdala subregions-Default mode network connectivity after treatment in patients with schizophrenia. *J Neurosci Res*, *102*(8), e25376. https://doi.org/10.1002/jnr.25376

Yang, A. C., & Tsai, S. J. (2017). New Targets for Schizophrenia Treatment beyond the Dopamine Hypothesis. *Int J Mol Sci*, *18*(8). https://doi.org/10.3390/ijms18081689

Yaribeygi, H., Maleki, M., Butler, A. E., Jamialahmadi, T., & Sahebkar, A. (2022). Molecular mechanisms linking stress and insulin resistance. *Excli j*, *21*, 317-334. https://doi.org/10.17179/excli2021-4382

Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nat Methods*, *8*(8), 665-670. https://doi.org/10.1038/nmeth.1635

Yeung, M. K., Han, Y. M. Y., Sze, S. L., & Chan, A. S. (2016). Abnormal frontal theta oscillations underlie the cognitive flexibility deficits in children with high-functioning autism spectrum disorders. *Neuropsychology*, *30*(3), 281-295. https://doi.org/10.1037/neu0000231

Yoon, N. A., & Diano, S. (2021). Hypothalamic glucose-sensing mechanisms. *Diabetologia*, *64*(5), 985-993. https://doi.org/10.1007/s00125-021-05395-6

Yuan, X., Li, X., Kang, Y., Pang, L., Hei, G., Zhang, X., Wang, S., Zhao, X., Zhang, S., Tao, Q., Zhang, L., Zhu, Q., Lv, L., Fan, X., Hu, S., & Song, X. (2022). Gut mycobiota dysbiosis in drug-naïve, first-episode schizophrenia. *Schizophr Res*, *250*, 76-86. https://doi.org/10.1016/j.schres.2022.10.011

Zaki, J. K., Lago, S. G., Rustogi, N., Gangadin, S. S., Benacek, J., van Rees, G. F., Haenisch, F., Broek, J. A., Suarez-Pinilla, P., Ruland, T., Auyeung, B., Mikova, O., Kabacs, N., Arolt, V., Baron-Cohen, S., Crespo-Facorro, B., Drexhage, H. A., de Witte, L. D., Kahn, R. S.,…Tomasik, J. (2022). Diagnostic model development for schizophrenia based on peripheral blood mononuclear cell subtype-specific expression of metabolic markers. *Transl Psychiatry*, *12*(1), 457. https://doi.org/10.1038/s41398-022-02229-w

Zeni-Graiff, M., Rizzo, L. B., Mansur, R. B., Maurya, P. K., Sethi, S., Cunha, G. R., Asevedo, E., Pan, P., Zugman, A., Yamagata, A. S., Higuchi, C., Bressan, R. A., Gadelha, A., & Brietzke, E. (2016). Peripheral immuno-inflammatory abnormalities in ultra-high risk of developing psychosis. *Schizophr Res*, *176*(2-3), 191-195. https://doi.org/10.1016/j.schres.2016.06.031

Zhan, N., Sham, P. C., So, H. C., & Lui, S. S. Y. (2023). The genetic basis of onset age in schizophrenia: evidence and models. *Front Genet*, *14*, 1163361. https://doi.org/10.3389/fgene.2023.1163361

Zhang, J., Luo, W., Huang, P., Peng, L., & Huang, Q. (2018). Maternal C-reactive protein and cytokine levels during pregnancy and the risk of selected neuropsychiatric disorders in offspring: A systematic review and meta-analysis. *J Psychiatr Res*, *105*, 86-94. https://doi.org/10.1016/j.jpsychires.2018.09.002

Zhang, L., Verwer, R. W. H., Zhao, J., Huitinga, I., Lucassen, P. J., & Swaab, D. F. (2021). Changes in glial gene expression in the prefrontal cortex in relation to major depressive disorder, suicide and psychotic features. *J Affect Disord*, *295*, 893-903. https://doi.org/10.1016/j.jad.2021.08.098

Zhang, S., Lachance, B. B., Mattson, M. P., & Jia, X. (2021). Glucose metabolic crosstalk and regulation in brain function and diseases. *Prog Neurobiol*, *204*, 102089. https://doi.org/10.1016/j.pneurobio.2021.102089

Zhang, W., Gao, C., Qing, Z., Zhang, Z., Bi, Y., Zeng, W., & Zhang, B. (2021). Hippocampal subfields atrophy contribute more to cognitive impairment in middle-aged patients with type 2 diabetes rather than microvascular lesions. *Acta Diabetol*, *58*(8), 1023-1033. https://doi.org/10.1007/s00592-020-01670-x

Zhang, W., & Rosenkranz, J. A. (2016). Effects of Repeated Stress on Age-Dependent GABAergic Regulation of the Lateral Nucleus of the Amygdala. *Neuropsychopharmacology*, *41*(9), 2309-2323. https://doi.org/10.1038/npp.2016.33

Zhang, W. H., Zhang, J. Y., Holmes, A., & Pan, B. X. (2021). Amygdala Circuit Substrates for Stress Adaptation and Adversity. *Biol Psychiatry*, *89*(9), 847-856. https://doi.org/10.1016/j.biopsych.2020.12.026

Zhang, Z. J., & Reynolds, G. P. (2002). A selective decrease in the relative density of parvalbumin-immunoreactive neurons in the hippocampus in schizophrenia. *Schizophr Res*, *55*(1-2), 1-10. https://doi.org/10.1016/s0920-9964(01)00188-8

Zhao, G., Lau, W. K. W., Wang, C., Yan, H., Zhang, C., Lin, K., Qiu, S., Huang, R., & Zhang, R. (2022). A Comparative Multimodal Meta-analysis of Anisotropy and Volume Abnormalities in White Matter in People Suffering From Bipolar Disorder or Schizophrenia. *Schizophr Bull*, *48*(1), 69-79. https://doi.org/10.1093/schbul/sbab093

Zhao, Q., Cao, H., Zhang, W., Li, S., Xiao, Y., Tamminga, C. A., Keshavan, M. S., Pearlson, G. D., Clementz, B. A., Gershon, E. S., Hill, S. K., Keedy, S. K., Ivleva, E. I., Lencer, R., Sweeney, J. A., Gong, Q., & Lui, S. (2022). A subtype of institutionalized patients with schizophrenia characterized by pronounced subcortical and cognitive deficits. *Neuropsychopharmacology*, *47*(12), 2024-2032. https://doi.org/10.1038/s41386-022-01300-w

Zhao, Q., Guo, T., Li, Y., Zhang, L., Lyu, N., Wilson, A., Zhu, X., & Li, X. (2021). Clinical characteristic of prodromal symptoms between bipolar I and II disorder among Chinese patients: a retrospective study. *BMC Psychiatry*, *21*(1), 275. https://doi.org/10.1186/s12888-021-03295-y

Zhou, X., Tian, B., & Han, H. B. (2021). Serum interleukin-6 in schizophrenia: A system review and meta-analysis. *Cytokine*, *141*, 155441. https://doi.org/10.1016/j.cyto.2021.155441

Zhu, Y., Maikusa, N., Radua, J., Sämann, P. G., Fusar-Poli, P., Agartz, I., Andreassen, O. A., Bachman, P., Baeza, I., Chen, X., Choi, S., Corcoran, C. M., Ebdrup, B. H., Fortea, A., Garani, R. R., Glenthøj, B. Y., Glenthøj, L. B., Haas, S. S., Hamilton, H. K.,…Koike, S. (2024). Using brain structural neuroimaging measures to predict psychosis onset for individuals at clinical high-risk. *Mol Psychiatry*, *29*(5), 1465-1477. https://doi.org/10.1038/s41380-024-02426-7

Zierhut, K. C., Graßmann, R., Kaufmann, J., Steiner, J., Bogerts, B., & Schiltz, K. (2013). Hippocampal CA1 deformity is related to symptom severity and antipsychotic dosage in schizophrenia. *Brain*, *136*(Pt 3), 804-814. https://doi.org/10.1093/brain/aws335

Zipursky, R. B., Reilly, T. J., & Murray, R. M. (2013). The myth of schizophrenia as a progressive brain disease. *Schizophr Bull*, *39*(6), 1363-1372. https://doi.org/10.1093/schbul/sbs135

Zorowitz, S., & Tuominen, T. (2022). Confirmatory factor analysis of the Maltreatment and Abuse Chronology of Exposure (MACE) scale: Evidence for essential unidimensionality. *PsyArXiv Preprints*. https://doi.org/10.31234/osf.io/uexgy

Zubin, J., & Spring, B. (1977). Vulnerability--a new view of schizophrenia. *J Abnorm Psychol*, *86*(2), 103-126. https://doi.org/10.1037//0021-843x.86.2.103

Appendices

Statistical methods

Study I

Differences in amygdala subnuclei between FEP, CHR and CTR

The subnuclei volumes were averaged across both hemispheres in further analyses to avoid unnecessary multiple comparisons, since there were no significant differences in subnuclei volumes between the left and right hemispheres, nor any group by hemisphere by subnuclei interactions. First, we tested overall group differences in the total amygdala volume using ANCOVA, controlling for age, sex, and total intracranial volume. After which, a linear mixed-effects model was used to examine whether there was a group by subnucleus interaction: volume ~ intercept + β1 (group) + β2 (subnucleus) + β3 (group by subnucleus interaction) + β4 (age) + β5 (sex) + β6 (total intracranial volume) + random (subject) + error (ε). The subnucleus was treated as a repeated measure within subjects, with volume as the dependent variable, and group, subnucleus, their interaction, age, sex, and intracranial volume as the independent variables. The model also included a random intercept for each subject to account for subject-specific effects.

Effect of childhood maltreatment on amygdala subnuclei

We then tested whether the TADS total score was linearly associated with subnuclei volumes. The models were fit separately for each group and limited to the subnuclei that were smaller in either FEP or CHR. We used the following linear model, fitted with robust regression using the MM-estimation method: volume ~ intercept + β1 (TADS total score) + β2 (age) + β3 (sex) + β4 (total intracranial volume) + error (ε), where β values represent the regression coefficients, and ε represents the residual error. In all statistical analyses, p-values < 0.05 were considered statistically significant. Multiple comparisons were corrected using the false discovery rate (FDR) correction at p-value < 0.05. All analyses were carried out with R version 3.5.2 (Eggshell Igloo) (R Core Team, 2017).

Study II

Analyses of hippocampal volumetry and glucose parameters in clinical groups of FEP, CHR and CTR

Cross-sectional analyses

The differences in hippocampal subfield volumes across FEP, CHR, and CTR groups were analyzed using a linear mixed-effects model: volume ~ intercept + β1 (group) + β2 (subfield) + β3 (group by subfield interaction) + β4 (age) + β5 (sex) + β6 (TIV) + β7 (BMI) + random (subject) + error (ε). Subfields were treated as a repeated measure within subjects, with volume as the dependent variable. Group status, subfield, their interaction, and the covariates (age, sex, BMI, and TIV) were the independent variables. Post-hoc pairwise comparisons of subfield volumes between groups were performed using estimated marginal means, with the false discovery rate correction applied.

Pairwise group differences of measured fasting plasma glucose and insulin, and calculated insulin resistance (HOMA2-IR) were tested using Student's t-test in FEP, CHR and CTR both the baseline and follow-up time points. The relationships between glucose metabolism parameters and hippocampal volumes (both subfield and total) were tested separately for the FEP, CHR, and control groups. This analysis was done for all metabolic indexes and volumes, as well as at both time points, using a linear model: volume ~ intercept + β1 (glucose parameter) + β2 (age) + β3 (sex) + β4 (BMI) + β5 (total intracranial volume) + error (ε).

Analyses of the longitudinal data

We used a linear mixed-effects model to analyze baseline and one-year follow-up data, aiming to detect longitudinal changes in hippocampal subfield volumes, total hippocampal volumes, and glucose parameter values over time across the FEP, CHR, and CTR groups. These models also included participants who did not have measurements at both time points. Separate linear mixed-effects models were used for each volume and glucose parameter, with the subject ID as a random effects variable. Post-hoc comparisons of volume or glucose parameter changes within each group between the baseline and one-year follow-up were conducted using estimated marginal means.

The model included a binary independent variable that indicated the time point and its interaction with the group variable. The model used for the volume changes in time was: volume ~ intercept + β_1 (group by time) + β_2 (time) + β_3 (group) + β_4 (sex) + β_5 (age) + β_6 (total intracranial volume) + β_7 (BMI) + random (subject) + ε. For glucose parameter changes in time, the model was: glucose parameter value ~ intercept + β_1 (group by time) + β_2 (time) + β_3 (group) + β_4 (sex) + β_5 (age) + β_7 (BMI) + random (subject) + ε.

Analyses of hippocampal volumetry, glucose parameters and clinical outcomes

As above, a mixed-effects linear model was used to assess whether reductions in subfield volumes at the baseline, baseline glucose parameter levels, or longitudinal changes in volumes and glucose parameters during the follow-up were linked to clinical outcomes, such as the transition to psychosis, level of functioning, or remission status at the follow-up. Additionally, we used a linear model to test whether the associations between glucose metabolism parameters and volumes were influenced by clinical outcome trajectories.

The effect of lifetime antipsychotic exposure at each MRI scan time point was controlled by using it as a covariate for each test of this study separately. In all statistical analyses, two-tailed p-values < 0.05 were considered statistically significant. Baseline pairwise multiple comparisons of volumetric differences and analyses on the associations between volumes and glucose parameters were corrected using the false discovery rate (FDR) correction at p-value < 0.05. Exploratory analyses are presented in the original publication. All analyses were carried out with R version 4.2.1 (2022-06-23) "Funny-Looking Kid" (R Core Team, 2022).

Study III

Early psychosis – Turku Discovery sample

Effect of antipsychotic drugs on cortical thickness

We started by estimating how lifetime antipsychotic use affects the overall thickness of the brain's cortex. The average cortical thickness across the whole cortical mantle was used as the outcome measure and lifetime antipsychotic exposure, age, sex, and group as explanatory variables in a linear regression model: mean cortical thickness ~ intercept + β1 (lifetime antipsychotic exposure) + β2 (age) + β3 (sex) + β4 (group)+ ε. The Robust MM-estimation method from the "robustbase" library in R (v4.2.2) was employed due to its resistance to the influence of outliers, ensuring more reliable results in the presence of possible atypical data points (R Core Team, 2017). Because illness severity might explain both increased antipsychotic use and reduced cortical thickness, we performed a series of sensitivity analyses. In these, we added measures of overall symptom or illness severity as additional variables in the regression model to account for this potential influence. The sensitivity analyses involved adding one of the following measures at a time as an extra variable in the regression analyses: total symptom score, GAF, SOFAS, total number of days spent in a mental health hospital, or the number of hospital admissions.

The regional effects of lifetime antipsychotic exposure on cortical thickness were assessed using vertex-wise analyses, performed with the glm-fit function in Freesurfer 7.1.1. In this analysis, vertex-wise cortical thickness was predicted using lifetime antipsychotic exposure with age, sex and group as covariates. We conducted 1,000 permutations to adjust for multiple comparisons, using a cluster-wise p-value significance level of 0.05 and cluster-forming p-values of 0.05 and 0.01 for a more stringent analysis. Additionally, Bonferroni correction was applied to adjust for the multiple comparisons conducted across both hemispheres.

NeuroMaps: The association between cortical structure or function and antipsychotic-related cortical thinning

For the discovery sample, the vertex-wise map of the effects of lifetime antipsychotic exposure on cortical thickness from the Turku sample was first parcellated using the Desikan-Killiany cortical atlas (Desikan et al., 2006). This choice of parcellation was made to ensure consistency with the ENIGMA data, which is available solely in this parcellation format. The selected feature annotations from the NeuroMaps were parcellated using the same Desikan-Killiany cortical atlas for consistency. Pairwise Pearson's correlation r between the parcellated lifetime antipsychotic exposure effect on cortical thinning and parcellated brain features were calculated, and statistical significance was assessed using a conservative null model that preserves the spatial-autocorrelation of brain maps ("spin test") (Alexander-Bloch et al., 2018; Váša & Mišić, 2022). In the spin test, for each pairwise comparison, the coordinates of the parcels are projected onto a sphere and then randomly rotated. The original parcels are reassigned the value of the nearest

rotated parcel, and this process is repeated 10,000 times. Next, correlations are calculated between the original non-rotated pair and each of the permuted maps. The original Pearson's correlation coefficient (r) is then compared to this distribution of values to determine the permutation p-value (p_{spin}). In the spin test, a null distribution of correlations is created by randomly rotating one of the brain maps used in a pairwise correlation and repeating the correlation (10,000 repetitions). The empirical correlation is compared against this null distribution to calculate a permutation p-value (p_{spin}). All associations were corrected for multiple comparisons using false discovery rate correction.

NeuroSynth: Post-hoc analyses on the associations between underlying cognitive features and antipsychotic-related cortical thinning

As a follow-up analysis to investigate the functional relevance of our primary findings, we examined potential associations between antipsychotic-related cortical thinning and various cognitive functions, hypothesizing that such thinning would be more pronounced in cortical regions that are involved in higher cognitive functions. For this purpose, we utilized the NeuroSynth database (neurosynth.org), which contains probabilistic maps of brain activation and deactivation derived from over 14,000 fMRI studies. We conducted voxel-wise meta-analyses for 123 cognitive terms from the Cognitive Atlas, as previously described. The probabilistic meta-analytical maps were parcellated using the Desikan-Killiany atlas, and their association with antipsychotic-related cortical thinning was studied in both the discovery sample using spin tests, as described earlier. To determine if the categories were generally linked to cortical thinning related to antipsychotic use, we performed a two-sided permutation test. This involved comparing the average correlation of each category to a null distribution created by randomly permuting category memberships 10,000 times. Additionally, to gain more insight into the relationship between antipsychotic-related cortical thinning and cognitive functions, we analyzed the top and bottom 10% of individual term correlations.

Schizophrenia – ENIGMA replication sample

Effect of antipsychotic effect on cortical thickness

To replicate the findings from the discovery sample, we used data from an ENIGMA consortium study to study correlations between the current chlorpromazine equivalent dose and cortical thickness. As before, we calculated the correlations for each Desikan-Killiany parcel while controlling for age and sex in up to 2175 individuals, depending on the parcel.

NeuroMaps and NeuroSynth: The association between underlying cortical structural, functional or cognitive features and antipsychotic-related cortical thinning

In the replication sample, we examined the relationships between antipsychotic-related cortical thinning and the selected structural and functional brain organization features, that were statistically significant in the discovery sample, using NeuroMaps. Further, based on the fundings from NeuroMaps we explored potential links between antipsychotic-related cortical thinning and various cognitive functions as described above.

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Painosalama, Turku, Finland 2025

ISBN 978-952-02-0158-6 (PRINT)
ISBN 978-952-02-0159-3 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)