

**Mechanisms of hippocampal dysfunction in psychosis**

By

Maxwell J Roeske

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Approved:

Warren D. Taylor, M.D., M.H.Sc.

Stephan Heckers, M.D., M.Sc.

Victoria Morgan, Ph.D.

Sachin Patel, M.D., Ph.D.

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For my family,  
who made this possible

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## LIST OF ABBREVIATIONS

AUD	Alcohol Use Disorder
aMCI	Amnesic Mild Cognitive Impairment
ALFF	Amplitude of Low Frequency Fluctuation
ASL	Arterial Spin Labeling
BOLD	Blood Oxygen Level-Dependent
CBD	Cannabidiol
CUD	Cannabis Use Disorder
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CHR-P	Clinical High Risk for Developing Psychosis
CNV	Copy Number Variation
CA	Cornu Ammonis
DG	Dentate Gyrus
DSM	Diagnostic and Statistical Manual of Mental Disorders
TE	Echo Time
FLIRT	FMRIB's Linear Image Registration Tool
FSL	FMRIB's Software Library
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
GW	Gestational Week

IHI	Incomplete Hippocampal Inversion
IRB	Institutional Review Board
ICV	Intracranial Volume
LEV	Levetiracetam
MRE	Magnetic Resonance Elastography
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MCD	Malformations of Cortical Development
MAM	Methazoxymethanol Acetate
MNI	Montreal Neurological Institute
NMDA	N-methyl-D-aspartate
OTS	Occipitotemporal Sulcus
PSC	Percent Signal Change
PET	Positron Emission Tomography
PANSS	Positive and Negative Symptom Scale
pCASL	Pseudo-continuous Arterial Spin Labeling
PGPP	Psychiatric Phenotype/Genotype Project
ROI	Region of Interest
rCBF	Regional Cerebral Blood Flow
TR	Repetition Time
SPT	Scene Processing Task
SENSE	Sensitivity Encoding

SNP	Single Nucleotide Polymorphism
SPECT	Single-photon Emission Computerized Tomography
SPHARM-PDM	Spherical Harmonic Point Distribution Model
SV2A	Synaptic Vesicle 2A

## CHAPTER I

### INTRODUCTION<sup>1</sup>

#### **Preface**

This introduction is designed to provide the reader with the information needed for critical evaluation of the proposed thesis. The scope is not intended to be a comprehensive review, rather, an opportunity to introduce and explore key concepts underlying the hypotheses and interpretation of the results of the original research presented. I will begin with an introduction to psychosis and schizophrenia. Second, I will examine the proposed mechanisms underlying schizophrenia, with a focus on the glutamatergic system and neurodevelopment. Third, I will introduce the hippocampus and examine its role in schizophrenia. Finally, I will unify these concepts and outline the specific aims for the thesis.

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<sup>1</sup> Parts of this chapter have been adapted from “Hippocampal volume and hippocampal neuron density, number and size in schizophrenia: a systematic review and meta-analysis of post-mortem studies”, published in *Molecular Psychiatry* and has been reproduced with the permission of the publisher and my co-authors: C Konradi, S Heckers, AS Lewis

## Introduction

Psychosis is a symptom of many psychiatric, neurologic, and medical conditions characterized by impaired reality testing. Primary psychotic disorder etiologies are psychiatric, whereas secondary psychotic disorders result from substance use or other medical conditions. There are five domains of psychopathology that define primary psychotic disorders: hallucinations, or perception that occurs without external stimulation; delusions, or fixed false beliefs despite contrary evidence; disorganized thought, often expressed in disorganized speech such as frequent derailment or incoherence; disorganized or catatonic behavior; and negative symptoms such as diminished emotional expression or avolition (American Psychiatric Association, 2013). The severity, number, and durations of psychosis are gradients that differentiate primary psychotic disorders from one another (Heckers et al., 2013).

The most severe psychotic disorder is schizophrenia (Heckers et al., 2013). In addition to the presence of psychotic symptoms (i.e., hallucinations and delusions), a diagnosis of schizophrenia can include negative symptoms, cognitive symptoms, and/or disorganization of thought and behavior (which, with hallucinations and delusions, constitute positive symptoms) (**Table 1**). A diagnosis requires the presence of two or more core symptoms, one of which must be hallucinations, delusions, or disorganized speech, for at least one month, with continuous signs of disturbance for at least 6 months to distinguish it from schizophreniform disorder (i.e., symptoms for 1-6 months) and brief psychotic disorder (i.e., symptoms for less than one month) (American Psychiatric Association, 2013). Importantly, schizophrenia is associated with several potential complications including comorbid mood symptoms (Siris, 2000), anxiety (Buckley et al., 2009), substance use disorders (Khokhar et al., 2018), and suicide (Popovic et al.,

2014). Individuals that meet criteria for schizophrenia in addition to a major mood disorder and experience psychotic symptoms for greater than 2 weeks without a major mood episode meet criteria for a diagnosis of schizoaffective disorder (American Psychiatric Association, 2013).

The lifetime prevalence of schizophrenia is between 0.3% to 0.7% of the general population (American Psychiatric Association, 2013). However, the prevalence is dependent on demographic, social, economic, and cultural factors and varies by geographic region. The World Health Organization estimates that schizophrenia affects 24 million people worldwide and is one of the greatest contributors to the global disease burden (*WHO Fact Sheet: Schizophrenia*, 2022). This contribution to the global burden of disease reflects the illness's substantial impact on social and occupational functioning and chronic natural history.

Schizophrenia typically emerges in late adolescence to early adulthood, with the highest risk in the decade between ages 20 and 30 (van der Werf et al., 2014). About 75-80% of individuals that develop schizophrenia experience a prodromal phase, marked by attenuated psychotic-like symptoms prior to the onset of psychosis (Häfner and An Der Heiden, 1999). The emergence of full psychotic symptoms, referred to as a patient's first episode, can be insidious or acute. About half of individuals experience an emergence in about a month or less (Harrison et al., 2001). The clinical course of schizophrenia varies greatly, as symptoms may remit or re-emerge at differing levels of severity. Although some patients may achieve complete remission of symptoms, the majority enter a chronic stage of illness.

The current diagnostic criteria and understanding of schizophrenia's natural course of illness were shaped by the observations of Emil Kraepelin and Eugen Bleuler in the early 1900s. In the middle of the 19<sup>th</sup> century, psychiatrists begin to characterize disorders that typically

affected the young, progressed to chronic deterioration, and had unknown causes (Jablensky, 2010). Kraepelin unified many of these concepts in the nosological term *dementia praecox*, describing a condition in which patients experienced psychosis and severe cognitive and behavioral impairments (Kraepelin, 1919). Kraepelin also noted that in most cases the course of illness was chronic and progressed towards the hallmark of disease: a terminal state of deterioration (Kendler, 2020). Bleuler modified the *dementia praecox* concept, observing that the disease does not always appear near puberty or progress as far as dementia. Bleuler coined the term *schizophrenia* to replace *dementia praecox* and introduced the concept of basic and accessory symptoms of the illness (Bleuler, 1950). Kraepelin, Bleuler, and other investigators (Cheney and Patrick H. Drewry, 1938; Rupp and Fleeter, 1940) observed that most patients progressively deteriorated, leading to impairments in capacity to independently function and interact with others.

The discovery of chlorpromazine's sedative effects in the 1950s, leading to the swift development of numerous pharmacologic interventions for schizophrenia, has profoundly impacted the clinical course of schizophrenia patients. Antipsychotic medications primarily treat positive symptoms and decrease the time to symptom remission (Leucht et al., 2018). Maintenance treatment using antipsychotic medication reduces the risk for relapse (Leucht et al., 2012; Taipale et al., 2018; Tiihonen et al., 2017). Evidence suggests that shorter duration of untreated psychosis is associated with better short-term and long-term outcomes (Perkins et al., 2005). A greater understanding of the environmental impact on schizophrenia outcomes has also informed the development of non-pharmacologic treatments that improve functional and symptomatic outcomes of patients (Kreyenbuhl et al., 2010). For example, patient age,

gender, ethnicity, migratory status, adversity, and socioeconomic status are linked to differing patient outcomes (Burns et al., 2014; Eack et al., 2012; McLean et al., 2014; Morgan and Gayer-Anderson, 2016). However, despite the advances in pharmacologic and non-pharmacologic interventions, only 20% of diagnosed individuals reach favorable outcomes receiving optimal treatment (American Psychiatric Association, 2013).

**Table 1.** *Diagnostic and Statistical Manual of Mental Disorders (DSM)-V Criteria for*

*Schizophrenia*

- 
- A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
    - 1. Delusions.
    - 2. Hallucinations.
    - 3. Disorganized speech (e.g., frequent derailment or incoherence).
    - 4. Grossly disorganized or catatonic behavior.
    - 5. Negative symptoms (i.e., diminished emotional expression or avolition).
  - B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected levels of interpersonal, academic, or occupational functioning).
  - C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual symptoms, the signs of the disturbances may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
  - D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
  - E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
  - F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).
-

---

Specify if:

The following course specifiers are only to be used after a 1-year duration of the disorder and if they are not in contradiction to the diagnostic course criteria.

**First episode, currently in acute episode:** First manifestation of the disorder meeting the defining diagnostic symptom and time criteria. An *acute episode* is a time period in which the symptom criteria are fulfilled.

**First episode, currently in partial remission:** *Partial remission* is a period of time during which an improvement after a previous episode is maintained and in which the defining criteria of the disorder are only partially fulfilled.

**First episode, currently in full remission:** *Full remission* is a period of time after a previous episode during which no disorder-specific symptoms are present.

**Multiple episodes, currently in acute episode:** Multiple episodes may be determined after a minimum of two episodes (i.e., after a first episode, a remission and a minimum of one relapse).

**Multiple episodes, currently in partial remission**

**Multiple episodes, currently in full remission**

**Continuous:** Symptoms fulfilling the diagnostic symptom criteria of the disorder are remaining for the majority of the illness course, with subthreshold symptom periods being very brief relative to the overall course.

**Unspecified**

---

Specify if:

**With catatonia:** (refer to the criteria for catatonia associated with another mental disorder, [DSM-5] pp. 119-120, for definition)

---

Specify current severity:

Severity is rated by a quantitative assessment of the primary symptoms of psychosis, including delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, and negative symptoms. Each of these symptoms may be rated for its current severity (most severe in the last 7 days) on a 5-point rating scale ranging from 0 (not present) to 4 (present and severe).

---

Reference: American Psychiatric Association, 2013.

## Schizophrenia and the brain

Improving outcomes for schizophrenia patients requires the identification of novel treatment targets, which, in turn, necessitates an understanding of an underlying pathophysiological mechanism of schizophrenia. However, one mechanism is unlikely to explain schizophrenia as a single, distinct disorder while accounting for heterogeneity in clinical presentation and epidemiology. Instead, multiple mechanisms that affect brain development

and function likely converge to produce the clinical presentation currently defined as schizophrenia. This section will review leading hypotheses suggesting neural mechanisms underlying the etiology and development of schizophrenia.

### *The dopaminergic hypothesis*

The discovery and therapeutic use of antipsychotic medications provided an opportunity to establish a biological basis for schizophrenia (Seeman, 1993). Foundational *in vivo* (Andén et al., 1970) and *in vitro* (Seeman et al., 1975) studies determined that antipsychotics primarily act as antagonists at the dopamine D<sub>2</sub> receptor. Studies showing that amphetamine, which increases synaptic dopamine levels, induce psychotic experiences in healthy individuals provided further support for dopaminergic dysfunction (Lieberman et al., 1987). Finally, in the 1970s, studies revealed that the therapeutic efficacy of antipsychotic drugs correlates with antagonist affinity at D<sub>2</sub> receptors (Creese et al., 1976; Seeman and Lee, 1975). These results led to the inception of the dopaminergic hypothesis: elevated dopamine signaling is associated with the development of schizophrenia's clinical presentation. However, early versions of this hypothesis did not link alterations in dopamine with specific dimensions of psychosis (e.g., positive vs negative symptoms) or integrate dopamine with the increasing number of other brain abnormalities rapidly being discovered in schizophrenia (Howes and Kapur, 2009).

A seminal study in the 1990s reconceptualized the dopamine hypothesis by adding regional specificity (Davis et al., 1991). Integrating evidence from imaging, post-mortem, and animal studies revealed that dopamine signaling was not ubiquitously elevated in the brain. Instead, hyperdopaminergia was localized to the striatum (Pycock et al., 1980; Scatton et al.,

1982) and linked solely to the positive symptoms of schizophrenia. This reconceptualization localized the dopaminergic hypothesis and linked altered dopamine with a specific dimension of psychosis, but it did not directly link how dopamine results in delusions or hallucinations (Howes and Kapur, 2009).

Substantial advances in genetics, imaging, and our understanding of neurodevelopment have further refined the dopaminergic hypothesis. Evidence from these converging fields suggests that multiple genetic, neural, metabolic, or developmental insults interact to result in striatal dopamine dysregulation, which is a final common pathway to psychosis (Howes and Kapur, 2009). Further, striatal dopamine dysregulation is hypothesized to alter the appraisal of stimuli through a process of aberrant salience, linking dopamine directly to the experience of psychosis for patients (Kapur, 2003). Dysregulation is linked to psychosis and not schizophrenia based on evidence indicating striatal dopamine is elevated in illnesses with psychosis other than schizophrenia (Reith et al., 1994), is not seen in other psychiatric disorders without psychosis (Martino et al., 2001; Yatham et al., 2002), and dopamine antagonism with antipsychotic treatment is effective for psychosis in neurologic and psychiatric diseases in addition to schizophrenia (Dannon et al., 2006; Zahodne and Fernandez, 2008).

Our current understanding of the dopamine hypothesis as a common pathway reveals why patients, despite receiving optimal treatment, do not achieve good outcomes. This common pathway implies that current antipsychotic drugs are not treating the primary etiology, or etiologies, of schizophrenia. Rather, they are acting “downstream” of the etiological source at the striatum to treat the positive symptoms of schizophrenia. Antipsychotics do not show significant efficacy for treating the negative symptoms and cognitive deficits of

schizophrenia that have an immense impact on one's function and outcomes. These findings suggest that to develop novel treatments, we need to focus on treatment targets that are "upstream" from striatal dopaminergic dysregulation.

### *Glutamate dysregulation*

Excitatory neurotransmission in the brain is primarily glutamatergic. Glutamate binds to several metabotropic and ionotropic receptors that differ in structure, regulation, and function (Traynelis et al., 2010). A growing body of work reports glutamatergic neurotransmission alterations in schizophrenia (Howes et al., 2015), with converging evidence on dysfunction of the ionotropic N-methyl-D-aspartate (NMDA) glutamate receptor (Stone et al., 2007). These findings have informed a unifying biochemical hypothesis for schizophrenia that complements observed alterations in the dopaminergic system: the NMDA receptor hypofunction hypothesis.

The NMDA receptor hypofunction hypothesis developed from observations that non-competitive antagonists of the NMDA receptor, such as phencyclidine and ketamine, induce symptoms observed in schizophrenia such as hallucinations, delusions, and negative symptoms in healthy individuals (Krystal et al., 1994). Further, administration of these pharmacologic agents to stable schizophrenia patients induces symptom relapse (Luby et al., 1959). Magnetic resonance spectroscopy (MRS) studies have detected elevated glutamate or glutamine (i.e., a metabolic precursor of glutamate) in healthy individuals after the administration of ketamine (Kraguljac et al., 2017; Rowland et al., 2005), in patients with schizophrenia (Merritt et al., 2016), and individuals at clinical high-risk for developing psychosis (CHR-P) (Stone et al., 2009).

Genetic studies have confirmed alterations in the glutamatergic system (Harrison and Weinberger, 2004; Ripke et al., 2014).

These findings in humans informed the development of animal models of schizophrenia using NMDA receptor antagonists. Administration of NMDA antagonists to rats causes reductions in functional connectivity (Dawson et al., 2014) and produces cognitive deficits (Featherstone et al., 2012) similar to those observed in schizophrenia patients. Animals given NMDA receptor antagonists also develop widespread structural brain deficits mimicking those observed in schizophrenia patients, suggesting that an excitotoxic effect of glutamate drives structural changes (Olney and Farber, 1995). Further, NMDA receptor antagonists reduce the function of interneurons that release gamma-aminobutyric acid (GABA) (Homayoun and Moghaddam, 2007). Reductions in parvalbumin GABAergic interneurons are frequently reported in schizophrenia (Heckers and Konradi, 2015; Zhang and Reynolds, 2002). Altogether, the findings of human and animal studies have converged on a model in which NMDA receptor antagonists bind to NMDA receptors on GABAergic interneurons (Olney and Farber, 1995). The net effect of NMDA receptor blockade would be the disinhibition of projection neurons, resulting in elevated glutamate release and excitotoxic degenerative processes (Stone et al., 2007).

A combination of both NMDA receptor hypofunction and dopamine dysfunction may provide the best mechanism for the clinical presentation of schizophrenia (Howes et al., 2015). As previously mentioned, dopaminergic abnormalities are only tightly linked to the positive symptom domains of schizophrenia. Glutamate models involving NMDA receptor hypofunction may better account for the nature of negative symptoms and cognitive deficits in schizophrenia

(Javitt, 2010). Studies in schizophrenia patients have reported correlations between NMDA receptor binding with negative, but not positive symptoms (Pilowsky et al., 2005) and temporal cortex glutamine/glutamate levels with negative symptoms (Szulc et al., 2005). Additionally, evidence suggests that dopamine dysfunction is secondary to alterations in glutamatergic function (McGuire et al., 2008). Glutamatergic projections to the midbrain dopamine nuclei regulate dopamine neurons, which are sensitive to glutamatergic function changes (Miller and Abercrombie, 1996). Evidence from preclinical models (Balla et al., 2003; Miller and Abercrombie, 1996) and human imaging studies (Breier et al., 1999; Smith et al., 1998; Vollenweider et al., 2000) demonstrating that the administration of NMDA receptor antagonists alters dopamine firing and release further supports this relationship.

The NMDA receptor hypofunction hypothesis acts as a unifying biochemical model of schizophrenia that addresses limitations of the dopaminergic hypothesis. Despite an abundance of evidence for glutamatergic abnormalities in schizophrenia, there are currently no effective treatments for schizophrenia that target the glutamatergic system. Clinical trials for novel (Patil et al., 2007; Umbricht et al., 2014a) and pre-existing pharmacologic agents (Liu et al., 2014; Tiihonen et al., 2009, 2005) report mixed results and low to moderate effects (Howes et al., 2015). These negative findings highlight our poor understanding of the molecular mechanisms underlying NMDA receptor hypofunction. A better understanding of glutamatergic dysfunction and the timing of these alterations will inform more targeted treatments for schizophrenia.

### *Neurodevelopmental hypothesis*

Despite achieving a greater understanding of the biological mechanisms underlying the clinical presentation of schizophrenia, dopaminergic and glutamatergic mechanisms do not explain other characteristic components of the diagnosis, namely the early onset and relapsing nature of the illness. Studying the timing and etiologies of brain abnormalities in schizophrenia is essential to understand the course of illness. In agreement with Emil Kraepelin's conceptualization of *dementia praecox* (Kraepelin, 1919), early studies reporting ventricular enlargement in patients with chronic schizophrenia (Johnstone et al., 1976) interpreted their findings as proof of schizophrenia as a degenerative disorder (Johnstone et al., 1978). Further reports of longitudinal changes in brain structure (Mathalon et al., 2001; Nair et al., 1997; Rapoport et al., 1999) and observational studies demonstrating increased molecular markers for cell death (Bertolino et al., 1998; Jarskog et al., 2005, 2004, 2000) in schizophrenia patients suggested that brain abnormalities result from a neurodegenerative process. The neurodegenerative hypothesis posits that clinical symptoms emerge after an accumulation of degenerative brain changes that continue into adulthood. However, findings supporting neurodegeneration have largely been refuted as artefactual (Bogerts, 1993; Harrison, 1999), due to patient heterogeneity (Harrison, 1995), or not reflective of true neurodegenerative processes (e.g., lack of gliosis) (Weinberger, 1995).

An overwhelming body of evidence points to an alternative neurodevelopmental model (Murray et al., 1987; Weinberger, 1987) in which perinatal developmental insults lead to the alteration of pathologic neural mechanisms, resulting in the emergence of clinical symptoms (Fatemi and Folsom, 2009). This neurodevelopmental hypothesis posits that genetic variation

and environmental factors contribute to abnormal brain development that can occur as early as the first trimester (Brown, 2006) or activate abnormal neural mechanisms during adolescence or early adulthood (Rapoport et al., 2005). A “two-hit” model of neurodevelopment proposes that abnormalities during these two critical time points (i.e., *in utero* brain development and adolescence) combine to produce the symptoms and timing of onset of schizophrenia (Bayer et al., 1999; Keshavan, 1999). Both epidemiological and genetic studies support this model.

Epidemiological reports describe large variations in the lifetime prevalence of schizophrenia based on differences in geography and demographic variables, suggesting an environmental risk factor for schizophrenia (McGrath et al., 2008; McGrath, 2006; Saha et al., 2005). Environmental stressors *in utero* include maternal stress (Khashan et al., 2008), infection (Khandaker et al., 2013), dietary deficiency (Xu et al., 2009), and labor and delivery complications (Brown, 2011). Environmental stressors in childhood and adolescence include psychological adversity (Varese et al., 2012), infections (Brown et al., 2004), immigration (Cantor-Graae and Pedersen, 2007), trauma (Morgan and Gayer-Anderson, 2016), and cannabis use (Manseau and Goff, 2015). Several animal models replicate brain abnormalities observed in schizophrenia by disrupting neurodevelopment, further supporting the role of early environmental risk factors (Dickerson et al., 2010; Knuesel et al., 2014; Moore et al., 2006; Tseng et al., 2009). Although numerous links are established between environmental factors and schizophrenia, estimations of environmental contributions to the risk of developing the illness are near 11% (Hilker et al., 2018).

Early twin studies reporting the high rate of schizophrenia concordance in monozygotic twins established a genetic basis of schizophrenia (Sullivan et al., 2003). Estimates of hereditary

risk range from 40 to 80% (Cannon et al., 1998; Hilker et al., 2018). Recent advances in computational genetics have demonstrated that schizophrenia is a complex, polygenic disorder through the identification of numerous, single nucleotide polymorphisms (SNPs) (Ripke et al., 2014) and rare copy number variations (CNVs) (Hoeffding et al., 2017; Malhotra and Sebat, 2012). However, the link between genetics and schizophrenia is still not clear. While many SNPs are implicated in the disease, they account for less than 4% variability of risk (Ripke et al., 2014). Conversely, CNVs and other rare mutations have a large effect on disease risk, but they have very little specificity for schizophrenia and present broadly in psychiatric disorders (Hoeffding et al., 2017; Malhotra and Sebat, 2012). Genetic loci identified by genome-wide association studies are involved in many biological functions, but it is impossible to derive a single, coherent molecular model for the illness based on genetic data.

Genetic loci identified by genome-wide association studies are involved in many biological functions, including genes related to dopamine D<sub>2</sub> receptor expression, glutamatergic neurotransmission, and immune function (Ripke et al., 2014). Interactions between these systems are integral in maturation of brain structure and function (Luján et al., 2005; Money and Stanwood, 2013; Paolicelli et al., 2011). In particular, the NMDA receptor undergoes a molecular subunit “switch” at the onset of the critical period of development that is crucial in synapse and circuit formation (Roberts et al., 2009), making it especially vulnerable to genetic and environmental risk factors (Spear, 2000). Genetic impacts on synaptic signaling trigger compensatory mechanisms to normalize neurotransmission during brain development (Snyder and Gao, 2013). However, if compensatory mechanisms are deficient, the consequences of NMDA dysfunction in perinatal development could increase the risk of an excitation-inhibition

imbalance during adolescence (Nakazawa et al., 2017). Indeed, evidence suggests that disruptions in NMDA function during different developmental windows in brain development contributes to schizophrenia risk (Nakazawa et al., 2017).

An important question is the extent to which brain dysfunction is present, and can be pharmacologically targeted, at the onset of clinically detectable symptoms, or whether the window for intervention occurs earlier in brain development (Egerton et al., 2020). Markers of congenital abnormalities indicative of neurodevelopmental insults in the first (Lloyd et al., 2008) or second (Bracha et al., 1992) trimester of development have been found in schizophrenia. Further, abnormal posturing and movement in infancy (Compton et al., 2007; Walker, 1994) and premorbid neurologic soft signs in children (Barkus et al., 2006; Walker, 1994) have been observed in individuals who later develop schizophrenia. Neuroimaging studies report structural brain deficits in individuals at first presentation of the illness (Fannon et al., 2000). These findings further support a neurodevelopmental hypothesis of schizophrenia and highlight a challenge: if brain and behavioral abnormalities are present long before the emergence of symptoms, when is the ideal therapeutic window? Studies investigating such brain and behavioral abnormalities may provide insight into the illness's developmental mechanisms, revealing novel treatment strategies.

### *Alternative mechanisms*

There is evidence for several alternative mechanisms underlying the symptoms and emergence of schizophrenia. In addition to dopamine and glutamate, molecular models suggest that the endocannabinoid system mediates responses to environmental stress and is abnormal

in patients with schizophrenia (Leweke et al., 2018). Modulation of the endocannabinoid system may provide a novel therapeutic target in treating schizophrenia (Leweke et al., 2014; Rohleder et al., 2016). Inflammation and oxidative stress pathways resulting from environmental stress during development activate microglia, stimulate the release of free radicals, and disrupt inhibitory neuron function and glutamatergic NMDA receptor signaling, resulting in abnormal excitation-inhibition imbalances (Goff et al., 2016; Steullet et al., 2016). Microglia are also involved in programmed synaptic pruning during postnatal brain development, the time when early symptoms of schizophrenia emerge. Post-mortem studies of patients with schizophrenia report reduced numbers of dendritic spines (Glausier and Lewis, 2013). Reduced synaptic density in schizophrenia may occur by a mechanism of excessive synaptic pruning by microglia (Keshavan et al., 1994). Abnormalities in several immune system markers are implicated in this process (Sekar et al., 2016; Sellgren et al., 2019).

### **Introduction to the hippocampus**

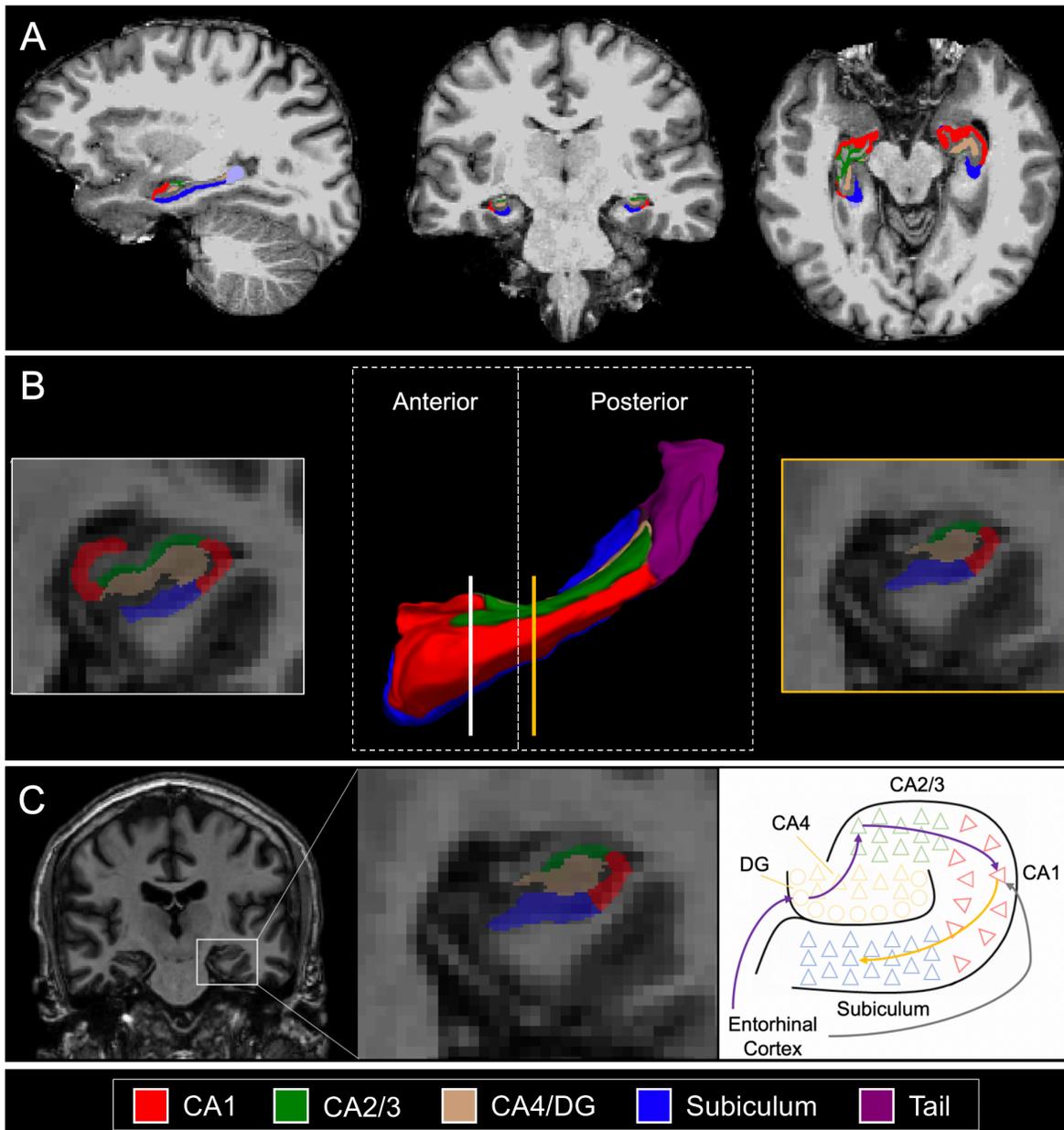
The human hippocampus is a bilateral medial temporal lobe structure (**Figure 1A**) that is essential for the encoding and retrieval of multimodal sensory information (Eichenbaum, 2004). Following the case report of H.M., a patient with epilepsy who received bilateral temporal lobe surgery and subsequently developed amnesia (Scoville and Milner, 1957), the scientific community began to link the hippocampus with many neuropsychiatric conditions. The hippocampus is one of the brain regions most consistently abnormal in structural and functional studies of patients with schizophrenia (Heckers and Konradi, 2010). The following sections will review normal and pathologic hippocampal structure and function, with a brief

overview of relevant neuroimaging methods.

### *Hippocampal structure*

#### Assessment of hippocampal structure using neuroimaging

Structural neuroimaging provides information about hippocampal volume and shape. Segmentation protocols (Dale et al., 1999; Fischl et al., 2002) generate estimates of hippocampal volume based on standard probabilistic atlases of the human brain (Despotović et al., 2015). Recent advances have allowed for the segmentation, and therefore volume estimates, of specific subfields of the hippocampus (Iglesias et al., 2015). However, subtle changes in structure cannot be detected using volumetric analyses. Instead, volumetric information is converted into hippocampal shape meshes composed of thousands of vertices that allow for the precise localization of structural deformations (Styner et al., 2006). Current neuroimaging methods cannot precisely assess cytologic information. Instead, post-mortem studies are required to assess neuronal cell number, density, size, and shape. Findings from post-mortem studies provide a contextual framework for structural findings assessed using neuroimaging.



**Figure 1. The human hippocampus.**

(A.) The hippocampus is situated in the medial temporal lobe (left hippocampus visualized here). (B.) The longitudinal axis is separated into an anterior and posterior region. The anterior hippocampus, also referred to as the hippocampal head, contains the uncus, which is defined by a folding of the hippocampus on itself. The posterior hippocampus is divided into a body and tail region. The white line and yellow line indicate coronal sections through the anterior and posterior hippocampus, respectively. (C.) The coronal axis of the hippocampus is divided into five subfields: the cornu amonis (CA) sectors 1-4 and the dentate gyrus (DG). The CA and DG form two interlocking, U-shaped laminae. The illustration of the hippocampus demonstrates projections directly from the entorhinal cortex to the CA1 subfield (grey) and indirect projections (purple) to the CA1 through the DG and CA3 subfield. The CA1 then projects out of the hippocampus through the subiculum. The triangles represent pyramidal cells and the circles represent granular cells.

## Normal hippocampal structure

The hippocampal formation consists of the hippocampus proper (hereafter referred to as *hippocampus*), the subicular complex, and the entorhinal cortex (Duvernoy et al., 2013). The hippocampus is divided into longitudinal and coronal (transverse) regions and subfields, respectively, to reflect specialization of cellular layers, circuitry, and function (Duvernoy et al., 2013; Haukvik et al., 2018). The longitudinal axis is separated into an anterior and posterior region (**Figure 1B**). The anterior hippocampus, also referred to as the hippocampal head, contains the unicus, defined by a folding of the hippocampus on itself that occurs during development. The posterior hippocampus is divided into a body and tail region. The coronal axis of the hippocampus is divided into five subfields: the cornu amonis (CA) sectors 1-4 and the dentate gyrus (DG) (Duvernoy et al., 2013). The CA and DG form two interlocking, U-shaped laminae visualized in **Figure 1C**.

While the longitudinal axis of the hippocampus can be separated using neuroimaging findings (i.e., the presence of the unicus defines the anterior hippocampus, the lack of the unicus defines the posterior), the subfields of the coronal axis are only conclusively identified through neurohistological examination of its neurons (Duvernoy et al., 2013). Pyramidal-shaped neurons are glutamatergic and comprise approximately 90% of the neurons in the hippocampus (Heckers and Konradi, 2010; Olbrich and Braak, 1985). The remaining neurons are primarily GABAergic interneurons that can be further divided into subclasses by anatomical, biochemical, and electrophysiological properties (Freund and Buzsáki, 1998). Glutamatergic, pyramidal neurons and GABAergic interneurons tightly regulate an excitation-inhibition balance that is integral for hippocampal function (Heckers and Konradi, 2010). Thus, changes in the number,

density, size, or orientation of these neurons have important implications for hippocampal pathology.

### Hippocampal structural abnormalities in schizophrenia

The most robust hippocampal pathology observed in schizophrenia is reduction in volume, supported by numerous magnetic resonance imaging (MRI) studies and several meta-analyses in both early and chronic stages of the illness (Adriano et al., 2012; Brugger and Howes, 2017; Haijma et al., 2013; Haukvik et al., 2018; Honea et al., 2005; Nelson et al., 1998; van Erp et al., 2016). Of all subcortical structures, reductions in hippocampal volume are the greatest (van Erp et al., 2016). Volume reductions affect all hippocampal subfields (Haukvik et al., 2018, 2015). Post-mortem studies that demonstrate reductions in total (Bogerts et al., 1990; Chen et al., 2020; Falkai and Bogerts, 1986; Fatemi et al., 2000; Rosenthal and Bigelow, 1972) and subfield-specific (Chen et al., 2020; Falkai and Bogerts, 1986; Jeste and Lohr, 1989; Walker et al., 2002) hippocampal volumes corroborate neuroimaging findings. Hippocampal shape deformations are also reported in both early (Li et al., 2015; Mamah et al., 2016) and chronic (Guimond et al., 2021; Prestia et al., 2015) stages of illness and can be localized to specific subfields.

Despite this plethora of findings, hippocampal morphology does not currently inform clinical care at diagnostic or treatment levels. First, routine neuroimaging assessments cannot use hippocampal structural deficits to establish a diagnosis of schizophrenia, as reductions in hippocampal volume are relatively subtle (typically between 2-4%) (Wright et al., 2000).

However, recent work demonstrates that early structural deficits may predict whether CHR-P

individuals (Provenzano et al., 2020) or patients with schizophreniform disorder (McHugo et al., 2020) will progress to a psychotic disorder or diagnosis of schizophrenia, respectively, at follow-up. This provides evidence that neural structure in individuals who will progress to a more severe psychotic disorder is abnormal and measurable early in the illness. Therefore, hippocampal volume may predict outcomes in schizophrenia. Second, although studies have linked psychopathology with hippocampal structural changes in CHR individuals (Dean et al., 2016) and schizophrenia patients (Antonova et al., 2004; Brambilla et al., 2013), there is no way to target and reverse the hippocampal deficit to treat the symptom. However, converging evidence from first episode patients and individuals at CHR for psychosis suggests that volumetric and shape alterations begin in the anterior hippocampus (McHugo et al., 2018), particularly in the CA1 subfield (Ho et al., 2017; Lieberman et al., 2018), and spread to involve other regions over the course of the illness (Ho et al., 2017). Therefore, studying and identifying mechanisms underlying hippocampal structural deficits may reveal treatment targets that can be engaged to halt the progression of structural changes and potentially influence psychopathology.

Alterations in neuron number, density, or size can contribute to regional brain volume and shape changes. Routine neuroimaging methods cannot determine which processes lead to morphologic changes in schizophrenia patients. Instead, the gold standard is to use hippocampal tissue in post-mortem studies to quantify cytological measures. Several post-mortem studies report modest decreases in neuron number in specific hippocampal subfields (Chen et al., 2020; Falkai et al., 2016; Konradi et al., 2011; Luts et al., 1998; Walker et al., 2002), but not in total hippocampal neuron number (Konradi et al., 2011; Walker et al., 2002).

Evidence for reductions of specific neuronal subtypes is less clear. Four studies reporting on pyramidal neuron number demonstrate either significantly reduced or statistically unchanged number of neurons in multiple subfields (Benes et al., 1998, 1991; Falkai and Bogerts, 1986; Jönsson et al., 1997). Two studies measured the number of GABAergic interneurons in the hippocampus. One did not differentiate between interneuron subtypes and reported reductions in areas CA2 and CA3 in patients (Benes et al., 1998). The other showed reductions in both somatostatin- and parvalbumin-positive inhibitory neurons in the CA1 and CA4 subfields, but not CA2/3 (Konradi et al., 2011). Thus, evidence converges on a diffuse decrease of hippocampal neurons, although this reduction does not reach the quantity observed in neurodegenerative illnesses such as Alzheimer's disease (Heckers and Konradi, 2010). This difference suggests that mechanisms of hippocampal pathology in schizophrenia differ from neurodegenerative disorders or disorders of neuronal death.

Post-mortem studies of neuron density have revealed key insights into hippocampal dysfunction in schizophrenia. The density of pyramidal cells is normal (K. M. Allen et al., 2016; Benes et al., 1998; Schreiber et al., 2011), but interneuron densities are reduced in schizophrenia (Benes et al., 1998; Konradi et al., 2011; Schreiber et al., 2011; Zhang and Reynolds, 2002). Gene expression studies complement these results by demonstrating a reduction in markers specific for GABAergic interneurons (Benes et al., 2007; Heckers et al., 2002). Evidence suggests there are regional- (Benes et al., 2007) and interneuron subclass-specific (i.e., parvalbumin-positive interneurons) (Zhang and Reynolds, 2002) abnormalities in schizophrenia (Konradi et al., 2011). Interneurons are especially vulnerable to early stress during development, as they migrate over extensive distances during neurodevelopment to the

hippocampus (Tricoire et al., 2011). Similar interneuron abnormalities, namely a loss of parvalbumin-positive interneurons, are reported in rodent models with hippocampal lesions (Berretta et al., 2009; Lodge et al., 2009). These findings suggest impaired GABAergic inhibition of hippocampal pyramidal neurons as a mechanism of psychosis.

Other cytologic findings that have implications for the pathogenesis of schizophrenia include neuron size and orientation. There are reports of hippocampal subfields with reductions in pyramidal neuron cell body size (Arnold et al., 1995; Benes et al., 1991; Jönsson et al., 1999). Cell body size is related to the volume and activity of the neuron's axonal and dendritic processes (Harrison, 2004), suggesting that size reductions are associated with abnormal synaptic connections. Altered neuronal shape (i.e., longer, thinner pyramidal neurons) in schizophrenia, which may be attributed to abnormalities at the dendrites or axonal hillock, supports this idea (Zaidel et al., 1997). Pyramidal neuron disarray (i.e., increased variability of neuronal orientation) was reported in some studies (Altshuler et al., 1987; Jönsson et al., 1997), but not replicated in others (Arnold et al., 1995; Zaidel et al., 1997). Abnormalities in orientation suggest abnormal neuronal migration during development, which could impact the formation of hippocampal synapses, circuits (Harrison, 2004) and shape (Casanova and Rothberg, 2002).

Hippocampal development has implications not only for hippocampal neurons, but also for neuroimaging measures of volume and shape. The hippocampus undergoes a morphologic inversion around the hippocampal sulcus during the second trimester of development before it is ultimately positioned in the medial temporal lobe (Bajic et al., 2010; Kier et al., 1997). The left hippocampus develops more slowly than the right hippocampus (Bajic et al., 2012), resulting in

both shape and volumetric asymmetries (i.e., right hippocampus is larger than the left hippocampus) in healthy individuals (Pedraza et al., 2004) and in individuals with schizophrenia (Gutman et al., 2021; Woolard and Heckers, 2012). Exacerbated alterations in hemispheric asymmetries of schizophrenia patients generated a “lateralization hypothesis” of schizophrenia, positing that schizophrenia is a disorder of genetic mechanisms that control the development of cerebral asymmetry (Crow et al., 1989). This hypothesis has limitations (Weinberger et al., 1991), but highlights that mechanisms of abnormal brain development may drive the illness.

In summary, there is overwhelming evidence for macro- and micro-structural abnormalities in schizophrenia. Neuroimaging studies allow for the assessment of thousands of patients over time but provide relatively poor spatial resolution. While neuroimaging methods have become increasingly effective at differentiating hippocampal subfields (Iglesias et al., 2015), post-mortem studies are required to precisely quantify structural and cytological measures. However, a major limitation of post-mortem studies is the inability to provide longitudinal information. Together, these methods have resulted in a rich body of work on hippocampal morphologic and cytologic abnormalities in schizophrenia, although their link to the symptoms and emergence of the illness is not immediately apparent. Leveraging known structural alterations with functional abnormalities provides a clearer mechanism of hippocampal dysfunction in the illness.

## *Hippocampal function*

### Assessment of hippocampal function using neuroimaging

Functional neuroimaging measures hemodynamic parameters as proxies of neural activity (Logothetis, 2008). Increased neuronal metabolic activity results in vasodilation and increases in regional blood flow and blood volume to deliver oxygen and nutrients to meet the metabolic demands of neurons and astrocytes (Buxton et al., 1998). Therefore, cerebral blood flow (CBF), cerebral blood volume (CBV), and oxygen metabolism serve as proxies of neural activity.

Many different MRI methods take advantage of these parameters. The gold standard for assessing brain function with MRI has historically been positron emission tomography (PET) imaging, which directly measures neural metabolism using exogenous radioactive agents with high resolution. Single-photon emission computerized tomography (SPECT) is a similar MRI method that measures metabolism with superior radiotracers but inferior spatial resolution. Steady state CBV imaging, generated using MRI pulse sequences, quantifies CBV and is a marker of basal brain metabolism based on its close correlation with PET (Gonzalez et al., 1995). CBV is now regarded as the gold-standard *in vivo* measure of baseline hippocampal activity (Small et al., 2011). However, CBV is not a practical method for many studies in patient populations, as it is also invasive. A popular, non-invasive, MRI pulse sequence that measures CBF is arterial spin labeling (ASL). ASL measure CBF directly, which is also coupled to glucose metabolism (Buxton et al., 1998). ASL sequences take advantage of endogenous blood water as a contrast. However, this generates a weaker signal-to-noise ratio than exogenous contrasts, resulting in lower spatial resolution. Lastly, studies will assess brain activity with the blood oxygen level-

dependent (BOLD) signal at rest or during task performance. The BOLD signal is qualitative and measures changes in and around veins secondary to direct changes in CBF and cerebral metabolic rate of oxygen (Logothetis, 2008). Therefore, in comparison to the previously mentioned imaging techniques, the BOLD signal is furthest removed from underlying neural activity. Functional connectivity and amplitude of low frequency fluctuation (ALFF) measures derive from BOLD signal contrast images acquired using T2\* weighted MRI pulse sequences.

Importantly, there is great interindividual variability in the blood supply to the hippocampus. The anterior, middle, and posterior hippocampal arteries supply the hippocampal head, body, and tail, respectively (Marinković et al., 1992). The origins of hippocampal arteries from their parent vessels differ greatly. Most often, hippocampal arteries branch from the posterior cerebral artery, although the anterior hippocampal artery may branch from the anterior choroidal artery (Spallazzi et al., 2019). There is also intra-hippocampal variability in the blood supply. The CA1 subfield is most distal in the blood supply, increasing its vulnerability to vascular or neurodegenerative diseases (T. D. Cannon et al., 2002; Duvernoy et al., 2013; Zierhut et al., 2013), whereas the CA2/3 subfield and DG only become vulnerable after severe impairments in perfusion (Kreisman et al., 2000). Differences in vascularization can affect measurements of hippocampal function.

### Normal hippocampal function

Hippocampal subfields compose a tri-synaptic pathway that is integral to the processing of sensory information. The entorhinal cortex receives multimodal sensory information from higher-order cortical areas, and sends this information to the hippocampus via excitatory,

glutamatergic fibers (Insausti, 1993). As illustrated in **Figure 1C**, inputs either project directly to the CA1 subfield (i.e., the direct pathway) or indirectly to the CA1 subfield by first synapsing at the DG and CA2/3 subfields (i.e., the indirect pathway) (Amaral and Witter, 1989). The neurons of the CA1 subfield compare novel, highly processed sensory information from the direct pathway with prior sensory experiences retrieved from higher-order cortical areas via the indirect pathway. Detections of sensory experience novelty (or the lack of detection) by the CA1 subfield is signaled out of the hippocampus to the subiculum for further processing. This circuitry is maintained through the longitudinal axis of the hippocampus.

Broadly, the hippocampus is involved in episodic memory and spatial navigation (O'Keefe, 1976; Scoville and Milner, 1957). Simpler functions have been attributed to hippocampal subfields that act as hubs to participate in tasks (Small et al., 2011). CA1 is responsible for input integration (i.e., comparing old and new stimuli in the tri-synaptic pathway) (Amaral and Witter, 1989). CA2/3 serves as a hub for pattern completion, or retrieving information based on partial cues (Fellini et al., 2009). The DG is responsible for pattern separation, or distinguishing between similar stimuli (Schmidt et al., 2012). Further, animal research suggests that there is a functional distinction between the ventral hippocampus (homolog to the human anterior hippocampus) and dorsal hippocampus (homolog to the human posterior hippocampus) (Strange et al., 2014). Functional MRI (fMRI) studies support this distinction by demonstrating that the anterior hippocampus is involved in novelty detection for faces and affective stimuli (Lee et al., 2008; Murty et al., 2010), whereas the posterior hippocampus is preferentially involved in contextual or spatial information (Awipi and Davachi, 2008; Liang et al., 2013).

Advances in neuroimaging now allow for the dissection of hippocampal function into separate regions and subfields of human participants.

### Hippocampal functional abnormalities in schizophrenia

Studies of hippocampal function primarily report two findings: resting-state activity or activity during task performance (i.e., hippocampal recruitment). Two seminal functional imaging studies of the hippocampus in schizophrenia used PET to show increases in regional cerebral blood flow (rCBF) at rest (Friston et al., 1992; Liddle et al., 1992). Increased resting-state activity of the hippocampus has been replicated using PET (Buchsbaum et al., 1992; Lahti et al., 2003; Medoff et al., 2001; Molina et al., 2005), SPECT (Kawasaki et al., 1996, 1992), CBV imaging (McHugo et al., 2019; Schobel et al., 2013, 2009; Talati et al., 2014), ASL (Scheef et al., 2010), and ALFF (Hare et al., 2017; McHugo et al., 2022, 2015; Tang et al., 2019). Increased hippocampal activity is associated with more severe psychopathology (Friston et al., 1992), specifically positive symptoms (Dierks et al., 1999; Ebmeier et al., 1993; Gur et al., 1995; Hare et al., 2017; Liddle et al., 1992; Molina et al., 2005; Schobel et al., 2009; Silbersweig et al., 1995), negative symptoms (Schobel et al., 2009), poor outcomes (Lahti et al., 2006), poor response to antipsychotic treatment (Lahti et al., 2009), and working memory performance (Tregellas et al., 2014).

CBV studies provide key insights into the relationship between resting-state hyperactivity and schizophrenia. First, CBV measurements can provide sub-millimeter spatial resolution, allowing for the dissection of hippocampal activation at the subfield level (Small et al., 2011). CBV studies show that resting-state hyperactivation is selectively increased in the

anterior CA1 subfield of chronic patients (Schobel et al., 2013; Talati et al., 2014), patients early in the illness (McHugo et al., 2019), and in CHR-P individuals (Provenzano et al., 2020; Schobel et al., 2009). Further, evidence suggests a spread of the activation pattern into the subiculum after the onset of the illness (Lieberman et al., 2018; Schobel et al., 2013). Increases in anterior, but not posterior, hippocampal resting-state activity in the illness have been replicated using other methods, although these methods do not have the spatial resolution to reveal subfield selectivity (McHugo et al., 2022). Second, increased anterior CA1 CBV functions as a predictor of illness progression in individuals at CHR for developing psychosis (Schobel et al., 2013). However, this finding has failed to replicate in more recent studies (Provenzano et al., 2020).

Assessing hippocampal activity during task performance with fMRI has revealed two abnormal functional patterns in schizophrenia patients. The hippocampus is hyperactive during tasks that are not dependent on hippocampal engagement, such as fixation on a cross (Malaspina et al., 2004, 1999), smooth pursuit eye movements (Tregellas et al., 2004), or passive listening to repeated clicks or environmental noise (Tregellas et al., 2009, 2007). This finding is consistent with the reports of increased resting-state activity of the hippocampus in studies that do not utilize behavioral tasks. Hippocampal activation decreases over time during passive attention to stimuli in healthy individuals. This habituation effect is not observed in schizophrenia (Holt et al., 2006, 2005) and is present in early stages of the illness (Avery et al., 2019; Williams et al., 2013). Conversely, the hippocampus shows abnormal recruitment (i.e., reduction in hippocampal activity) during hippocampal-dependent task performance (Hall et al., 2010; Heckers et al., 1999, 1998; Jessen et al., 2003; Öngür et al., 2006; Ragland et al., 2001; Sehatpour et al., 2010; Weiss et al., 2004, 2003). Recent studies have observed that this

phenomenon is present in the anterior, but not posterior, hippocampus during early stages of the illness (Francis et al., 2016; McHugo et al., 2021). Further, this hippocampal recruitment deficit can be measured at the individual participant level and is associated with an individual's resting-state activity of the hippocampus (McHugo et al., 2019).

## **Hippocampal hyperactivity**

### *Synthesis of hippocampal dysfunction in schizophrenia patients*

Converging evidence from studies of hippocampal structure and function, glutamatergic abnormalities, and neurodevelopment in schizophrenia suggests an excitation-inhibition imbalance of the hippocampus as a core mechanism for psychosis (Heckers and Konradi, 2015). Cellular and molecular changes of hippocampal interneurons (e.g., reduction in interneuron density, alterations at the NMDA receptor, or abnormal migration during neurodevelopment) result in a lack of inhibition on excitatory, pyramidal neurons. MRS studies that report elevated levels of hippocampal glutamate in individuals with schizophrenia (Kraguljac et al., 2019, 2013) and at CHR for psychosis (Provenzano et al., 2020) support the idea of a dysregulation of glutamatergic neurotransmission. The excitation-inhibition imbalance framework links key findings of hippocampal pathology.

First, an excitation-inhibition imbalance results in hippocampal hyperactivity, which is observed during resting-state fMRI and tasks that are not dependent on the hippocampus. When hippocampal engagement is required for memory encoding or pattern separation/completion, recruitment is limited by basal hyperactivity (Heckers et al., 1998). This “ceiling effect” has been demonstrated within individuals with schizophrenia (McHugo et al.,

2019). These data suggest that basal hippocampal hyperactivity drives hippocampal dysfunction reported in numerous fMRI studies.

Second, hippocampal hyperactivity is linked to hippocampal structural deficits. Early in the illness, anterior CA1 CBV predicts hippocampal atrophy in the anterior hippocampus (Schobel et al., 2013), which then spreads to the posterior hippocampus (McHugo et al., 2018) and across subfields (Ho et al., 2017; Lieberman et al., 2018). The mechanism by which hippocampal hyperactivity drives atrophy is likely due to excitotoxicity of excess glutamate (Plitman et al., 2014). MRS studies have also reported a correlation between glutamate and hippocampal atrophy (Kraguljac et al., 2013). These data suggest a mechanism by which hippocampal hyperactivity may explain structural changes observed using neuroimaging.

#### *Animal models of hippocampal hyperactivity*

Animal models of schizophrenia support these findings. There are three primary types of animal models used to test mechanisms of schizophrenia pathology (Lodge and Grace, 2009). The first utilizes pharmacologic intervention, such as ketamine exposure. Inhibition of NMDA receptors in the hippocampus, particularly in the CA1 subfield, decreases the activity of parvalbumin-positive interneurons, resulting in a disinhibition of hippocampal pyramidal cells (Behrens et al., 2007; Grace, 2016; Kinney et al., 2006; Lisman et al., 2008). NMDA receptor inhibition increased hippocampal activity, as measured using CBV imaging, and glutamate release, with maximal changes found in the CA1 subfield (Lieberman et al., 2018; Schobel et al., 2013). In addition to others (Gozzi et al., 2010, 2008b; Lodge and Grace, 2007), this study demonstrates that hippocampal hyperactivity can be measured directly in rodents and suggests

that this phenotype has translational utility (Tregellas, 2014). Animal models testing mechanisms of glutamatergic dysfunction with pharmacologic intervention further support a hippocampal hyperactivity model.

A second class of animal models uses genetics to model schizophrenia by manipulating genes associated with schizophrenia risk. For example, the disrupted-in-schizophrenia (*DISC1*) gene influences hippocampal volume and function (Callicott et al., 2005). Although the exact mechanisms are unclear, transgenic *DISC1* mouse models display schizophrenia-like phenotypes, a decrease in hippocampal dendritic complexity and a reduction in hippocampal synaptic transmission (W. Li et al., 2007). Mice carrying a deletion in the *DISC1* gene that model this phenotype have altered DG neuron organization and deficits in neural plasticity (Kvajo et al., 2008). Manipulation of other genes with high expression in the hippocampus that are implicated in schizophrenia including *NRG1* (B. Li et al., 2007), *DTNBP1* (Harrison and Weinberger, 2004), and *ErbB4* (Vullhorst et al., 2009), impact hippocampal neurotransmission and may affect hippocampal function.

Finally, the neurodevelopmental hypothesis of schizophrenia can be tested using developmental disruption models. One such model administers the toxin methazoxymethanol acetate (MAM) on gestational day 17, when neuronal proliferation has essentially peaked in neural development (Lodge and Grace, 2009). The effects of this toxin target parvalbumin-containing interneurons, especially in the ventral hippocampus, and leads to alterations in oscillatory activity fundamental for hippocampal function (Lodge et al., 2009; Lodge and Grace, 2009). In support of the potential role of early environmental factors, disruption of brain development by maternal immune activation *in utero*, which releases maternal inflammatory

cytokines during fetal brain development to mimic a viral infection (Knuesel et al., 2014), reduces parvalbumin-positive interneurons, increases hippocampal activity, increases striatal dopamine concentrations, and disrupts hippocampal synchrony with other brain regions (Dickerson et al., 2010). Perturbations of neurodevelopment in rodents also support a model of hippocampal hyperactivity.

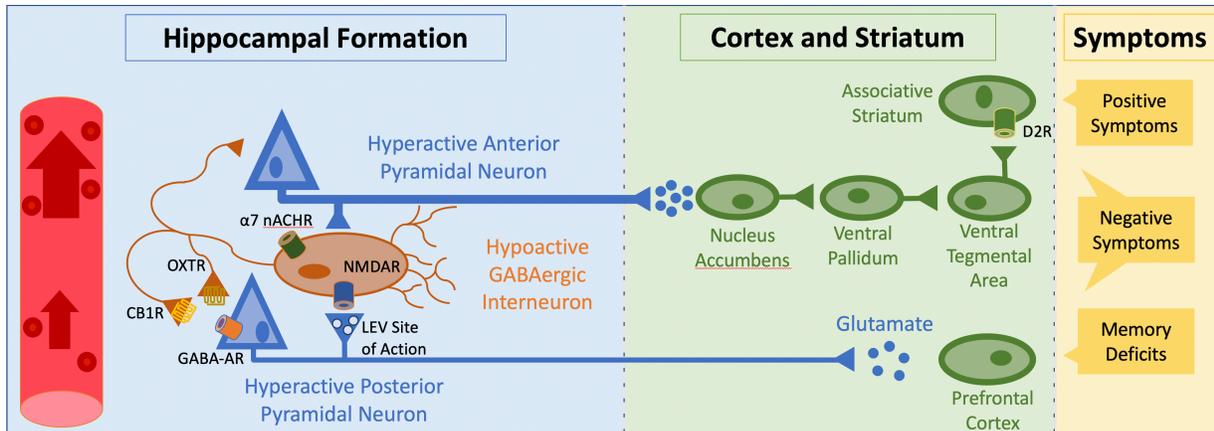
### *Circuit model of psychosis*

Hippocampal hyperactivity is linked to the dopamine hypothesis of schizophrenia. The direct evidence supporting this link in human studies is sparse, but functional imaging has revealed a link between glutamate in the hippocampus and fluorodopa uptake in dopamine terminals in the striatum in CHR-P individuals (Stone et al., 2010). Instead, the primary evidence for connecting these two systems has been established using rodent models of hippocampal hyperactivity (Grace, 2012).

Animal models of hippocampal hyperactivity demonstrate control of mesolimbic dopamine activity by the rodent ventral hippocampus. Stimulation of the ventral hippocampus triggers a hyperactive dopamine system via connections to midbrain dopamine neurons, provoking dopamine release in the striatum, which is considered to underly the positive symptoms of schizophrenia (Grace, 2012; Lisman et al., 2008; Perez and Lodge, 2014). Neurodevelopmental rodent models also demonstrate hippocampal-induced hyperactivation of the dopamine system, which are associated with schizophrenia-like behaviors (Lodge and Grace, 2007). Excessive dopamine release from the midbrain also produces thalamic burst firing, leading to the excitation of the hippocampus in a positive feedback loop (Lisman et al.,

2010). Given the extensive projections of the hippocampus to the prefrontal cortex, amygdala, and other regions involved in cognition and emotion, it is likely that the hippocampus plays a role in the negative and cognitive symptoms of schizophrenia (Herman and Mueller, 2006; Jay and Witter, 1991; Thompson et al., 2004). Thus, a hyperactive hippocampus can lead to deficits across all schizophrenia symptom domains (Grace, 2016) (**Figure 2**).

A circuit positioning the ventral hippocampus as a core dysfunction, projecting to downstream systems responsible for the psychopathology of schizophrenia, complements and supports the findings from human imaging studies. Human imaging has demonstrated that anterior hippocampal hyperactivity drives dopamine hyper-responsivity (Stone et al., 2010) and correlates with all domains of schizophrenia symptoms (Tregellas, 2014). Functional (Talati et al., 2014) and structural (Ho et al., 2017) imaging studies implicate the anterior CA1 as the subfield of origin of hippocampal dysfunction. There is also ample evidence for CA2/3 subfield molecular and cellular alterations as a driver of hippocampal pathology (Bobilev et al., 2020; Tamminga et al., 2012, 2010). Since the CA2/3 subfield is functionally upstream of the CA1 subfield in the tri-synaptic pathway, it is possible that CA2/3 dysfunction could drive CA1 hyperactivity. However, the effect of CA2/3 dysfunction on CA1 is not well understood, and high resolution CBV imaging studies have failed to demonstrate hyperactivity of the CA2/3 subfield in patients with schizophrenia (Talati et al., 2014).



**Figure 2. A circuit framework for schizophrenia positioning an excitation-inhibition imbalance of the anterior hippocampus as the core pathology.**

GABAergic interneurons in the hippocampus are driven by glutamate acting on NMDA receptors (NMDAR), providing inhibitory input to pyramidal neurons through stimulation of GABA-A receptors (GABA-AR). Hyperactivity of pyramidal neurons and hypoactivity of GABAergic interneurons lead to a relative excitation-inhibition imbalance that causes overdrive of brain circuits downstream of the hippocampus. Neuroimaging techniques such as functional MRI (fMRI) can measure altered hemodynamic signal changes in the hippocampus that provide evidence for a hippocampal hyperactivity. Animal models have shown that anterior hyperactivity leads to increased dopamine release and perturbs hippocampal-cortical network function, resulting in the psychopathology observed in schizophrenia. The associative striatum contains D2 receptors, which are antagonized by antipsychotic medications to provide relief of positive symptoms. The hippocampus is the site of many pharmacological targets that can modify neuronal activity. GABAergic interneurons possess  $\alpha$ 7-nicotinic acetylcholine receptors ( $\alpha$ 7-nAChR) that can be targeted by nicotinic compounds. Interneuron axon terminals possess cannabinoid receptor type 1 (CB1R) and oxytocin receptors (OXTR) that are engaged through retrograde signaling with cannabinoid compounds and oxytocin, respectively. Levetiracetam (LEV) affects neurotransmission of glutamate and GABA on both pyramidal cells and interneurons.

## *Hippocampal hyperactivity as a treatment target for schizophrenia*

### Excitation-inhibition imbalance is a druggable circuit

Animal treatment studies provide two lines of evidence for hippocampal hyperactivity, and the underlying excitation-inhibition imbalance, as a treatment target for schizophrenia. First, treatments targeting the ventral hippocampus directly impact the proposed circuit and modulate dopamine. Transplantation of interneuron precursors into the ventral hippocampus (Perez and Lodge, 2013) and deep brain stimulation of the ventral hippocampus rescue aberrant dopamine system function and schizophrenia-like behaviors (Perez et al., 2013). Treatment with allosteric modulators to GABA-A receptors that are spatially localized to the hippocampus releases the disinhibition of pyramidal neurons and reverses hyperactivation of the dopamine system (Gill et al., 2011). Second, targeting the excitation-inhibition imbalance has a protective effect on the hippocampus. Pretreating rodents with therapeutic glutamatergic agents that inhibit extracellular glutamate efflux prior to ketamine administration reduces or prevents hippocampal hyperactivity and hippocampal atrophy (Lieberman et al., 2018; Schobel et al., 2013). In sum, treatment of the ventral hippocampus has intra- and extra-hippocampal effects that normalize neural dysfunction associated with schizophrenia.

The ability to modulate hippocampal hyperactivity and improve phenotypes in animal models suggests that the excitation-inhibition imbalance may be a druggable circuit target for schizophrenia (Kätzel et al., 2020). Target engagement studies probing excitation-inhibition circuitry with pharmacologic interventions will advance our understanding of the neural mechanisms underlying hippocampal hyperactivity in schizophrenia patients. This section will review potential targets for pharmacologic modulation of hippocampal hyperactivity (**Figure 2**).

Epidemiologic (Olincy et al., 1997), genetic (Freedman et al., 2000; Gault et al., 2003; Leonard and Freedman, 2006; Sinkus et al., 2009; Stephens et al., 2009) and post-mortem (Guillozet-Bongaarts et al., 2014; Mexal et al., 2010) evidence suggests that nicotinic cholinergic signaling is fundamentally altered in schizophrenia (Smucny and Tregellas, 2017). A concentration of  $\alpha 7$  nicotinic receptors on hippocampal interneurons, but not pyramidal neurons (Frazier et al., 1998), indicates that pharmacologic modulation of these receptors could modulate a hippocampal excitation-inhibition imbalance. Indeed, studies have explored the effect of cholinergic agents on hippocampal activity and demonstrated a reduction in anterior hippocampal activation after the administration of nicotinic agents (Barch et al., 2016; Tanabe et al., 2006; Tregellas et al., 2011, 2010, 2005). However, numerous clinical trials using nicotinic agonists,  $\alpha 7$  partial agonists, and partial allosteric modulators demonstrate mixed results in symptom improvement of schizophrenia patients (Deutsch et al., 2013; Feuerbach et al., 2015; Haig et al., 2016; Keefe et al., 2015; Kem et al., 2018; Preskorn et al., 2014; Umbricht et al., 2014b; Winterer et al., 2013).

Evidence for alterations in the endocannabinoid system in schizophrenia is growing (Iseger and Bossong, 2015). Cannabidiol (CBD), one of over 70 cannabinoid compounds of cannabis, modulates the endocannabinoid system at the CB1 receptor (Bossong et al., 2014; Pertwee, 2008). The CB1 receptor is extremely high at specific classes of interneurons, but not pyramidal neurons, in the hippocampus, indicating that modulation of CB1 with CBD could alter a hippocampal excitation-inhibition imbalance (Kano et al., 2009). Human imaging studies have shown alterations of hippocampal activity in healthy individuals (Bhattacharyya et al., 2012) and individuals at CHR for psychosis (Bhattacharyya et al., 2018) using CBD, and mixed clinical

trial results suggest that CBD may have antipsychotic therapeutic potential in patients with schizophrenia (Boggs et al., 2018; Leweke et al., 2014; Zuardi et al., 2009, 2006).

The release of GABA results in the inhibition of the pyramidal neurons. Therefore, GABA-A receptors are an essential component in balance of hippocampal excitation-inhibition. The expression of the  $\alpha 5$  containing GABA-A receptor, which represents less than 5% of all GABA-A receptors (Quirk et al., 1996), is 25% greater in the dendrites of the pyramidal neurons of the hippocampus than the average expression of the entire brain (Sur et al., 1999). The relatively confined distribution of this receptor could provide therapeutic potential in regulating hippocampal activity. Administration of  $\alpha 5$  containing GABA-A receptor modulators in animal models of schizophrenia suggest that this class of drugs contain therapeutic potential and can modulate hippocampal activity (Costa et al., 2002; Gill et al., 2011). However, this class of drug has not been trialed in schizophrenia patients, likely owing to the severe potential side effects that may be endured after extended durations of drug administration.

Oxytocin is integral to neural development, including contributions to the excitatory-inhibitory switching of GABAergic signaling during the peri-natal period (Leonzino et al., 2016), synapse formation (Ripamonti et al., 2017), and the synchronous firing of hippocampal pyramidal neurons (Crépel et al., 2007). Abnormal oxytocin during critical periods of development could contribute to onset of schizophrenia in individuals. Rodent studies indicate oxytocin receptor modulation enhances hippocampal spike transmission (Owen et al., 2013) and inhibitory synaptic transmission (Zaninetti and Raggenbass, 2000) by modulating interneurons, suggesting that oxytocin and agonists to the oxytocin receptor can modulate a hippocampal excitation-inhibition imbalance. Human studies report modulation of hippocampal

rCBF in healthy individuals (Paloyelis et al., 2016) and CHR for psychosis individuals (Davies et al., 2019) after the administration of nasal oxytocin.

$\alpha 7$  nicotinic receptors, CB1 receptors,  $\alpha 5$  containing GABA-A receptors, and oxytocin receptors are potential pharmacologic targets for the engagement of hippocampal activity in psychosis. However, this project utilizes an anti-epileptic, levetiracetam (LEV) to target hippocampal hyperactivity. LEV has many advantages compared to other pharmacologic agents. First, LEV modulation is more feasible, or realistic and safe, to administer to patients in comparison to other agents. For example, GABA-A modulators can cause severe side effects (Rudolph and Knoflach, 2011) and nicotinic agents can activate receptors in reward circuitry, putting patients at risk of developing addiction (Smucny and Tregellas, 2013). Second, LEV is mechanistically valid, or impacts the proposed neural mechanism (i.e., excitation-inhibition imbalance) driving hippocampal hyperactivity. In comparison, oxytocin receptors are located ubiquitously in the brain (Viero et al., 2010), suggesting that any measurable changes in hippocampal hyperactivity could result from oxytocin receptor engagement outside of the hippocampus. Lastly, testing excitation-inhibition hypotheses using LEV in schizophrenia patients is novel. Many prior studies report the effects nicotinic agents and CBD on clinical psychopathology and neural targets, including hippocampal activity. Therefore, LEV is an ideal pharmacologic agent to test hypotheses to study the neural mechanisms of psychosis.

## Levetiracetam

LEV has overwhelming evidence for modulating neuronal activity and has been established as a FDA-approved anti-epileptic for almost two decades (Lyseng-Williamson, 2011). While the mechanism of action of LEV continues to be evaluated, evidence shows that it binds with high affinity to the synaptic vesicle 2A (SV2A) protein to regulate synaptic exocytosis and calcium-induced neurotransmitter release (Lynch et al., 2004). Most other anti-epileptics affect neuronal ion channels. Because LEV's mechanism of action differs and is further "downstream" from ion channel modulation, LEV has a more favorable side-effect profile, a lower risk of pharmacokinetic interactions with antipsychotics, and a lower risk of cognitive side effects when compared to other anti-epileptics (Patsalos, 2000). Treatment with levetiracetam decreases excitatory transmission in the CA1 subfield of the hippocampus *in vivo* and *in vitro* (Yang et al., 2007; Yang and Rothman, 2009) and enhances GABAergic signaling (Wakita et al., 2014). Therefore, this therapeutic may normalize hippocampal activity and have cognitive or clinical therapeutic potential for patients with schizophrenia.

Studies in animal models of schizophrenia have tested the effects of LEV. Using a sensory gating paradigm, LEV treated mice demonstrated an improvement in auditory gating (Smucny et al., 2015). Importantly, the dosage of LEV used in this study is equivalent to a human dose that is lower than typically prescribed for epilepsy (Smucny et al., 2015). A second study using a ketamine-exposure rat model to test the effects of LEV given separately and concurrently with an antipsychotic, risperidone, during a hippocampal-dependent memory task. LEV, but not risperidone, improved memory performance when administered alone and remained effective when administered concurrently with risperidone. This finding supports

potential viability of adjunctive therapy with LEV to treat cognitive deficits in schizophrenia patients receiving antipsychotic therapy (Koh et al., 2018). This study also showed that LEV could attenuate amphetamine-induced augmentation of locomotor activity, a phenotype that exemplifies positive symptoms in schizophrenia (Koh et al., 2018).

No study has investigated the effects of LEV on patients with schizophrenia. However, two studies report the effect of LEV on hippocampal activity in patients with amnesic mild cognitive impairment (aMCI). During a pattern-completion task, aMCI patients demonstrated higher levels of hippocampal activation when compared to healthy individuals. Treatment with low-dose LEV reduced the excess activity in the DG and CA3 subregions of the hippocampus so that the aMCI group activity did not differ from the control group activity (Bakker et al., 2012) with a dose-dependent effect (Bakker et al., 2015). The most efficacious dosage of LEV was significantly lower than doses prescribed for patients with epilepsy, similar to the sensory gating rodent study (Smucny et al., 2015). These studies suggest that LEV may have clinical benefit in other disease populations at low doses.

#### Hippocampal hyperactivity is a biomarker for psychosis

Hippocampal hyperactivity is a proposed biomarker for schizophrenia (Tregellas, 2014) that can serve as an immediate and objective measure of the biological effects of therapeutic candidates. This concept is supported by five converging findings that have previously been introduced but will be summarized here (**Table 2**).

**Table 2. Findings in support of hippocampal hyperactivity as biomarker for schizophrenia**

Findings in support of hippocampal hyperactivity as a biomarker for schizophrenia		Representative Citations <sup>1</sup>
Measured with fMRI methods	Prodromal phase	Schobel et al., 2013
	Early illness	McHugo et al., 2019
	Chronic illness	Talati et al., 2014; Schobel et al., 2009
Correlates with clinical symptoms	Positive Symptoms	Liddle et al., 1992; Friston et al., 1992
	Negative Symptoms	Schobel et al., 2009
	Cognitive Symptoms	Tregellas et al., 2014
Translational utility in animal models	Pharmacologic models	Schobel et al., 2013; Gozzi et al., 2010
	Developmental models	Lodge and Grace, 2007
Predictive value	Progression of illness <sup>2</sup>	Schobel et al., 2009
	Structural changes	Schobel et al., 2013
Modulated with interventions	Human studies	Tregellas et al., 2010; Barch et al., 2016; Davies 2019
	Animal studies	Gill et al., 2011; Schobel et al., 2013

<sup>1</sup> Citations included here are not comprehensive

<sup>2</sup> There is recent evidence that does not replicate hippocampal hyperactivity as a predictor of progression of illness

First, an excitation-inhibition imbalance can be reliably measured with fMRI in the prodromal phase of the illness, early in the illness, and in chronic patients. Second, hyperactivity correlates with clinical symptoms and response to antipsychotic treatments, suggesting that targeting and normalizing it may alleviate symptoms. Third, there is translational utility with animal models that link hippocampal hyperactivity with the striatum, the common pathway of psychosis, and other brain regions contributing to the negative and cognitive symptoms of psychosis. Fourth, there is evidence that hyperactivity can predict hippocampal structural changes and progression to more severe stages of psychosis, indicating that early intervention of this target can have therapeutic effects. Fifth, interventions modulate hippocampal hyperactivity.

### **Conclusion and hypotheses**

Schizophrenia is a heterogenous and functionally disabling illness that impacts individuals, their families, and society at large. Despite optimal treatments, many individuals do not achieve good clinical outcomes. Poor outcomes are likely because all current FDA-approved pharmacologic treatments target the dopamine system, which human and animal studies have shown only contribute to the positive symptoms of schizophrenia. Further, glutamatergic dysfunction appears to drive dopamine hyper-responsivity, while the dopamine system itself is relatively unperturbed in schizophrenia patients. Evidence suggests that early environmental and genetic interactions have neurodevelopmental impacts on the glutamatergic system.

An excitation-inhibition imbalance in the human hippocampus results in hippocampal hyperactivity and structural deficits in schizophrenia patients. Animal models have revealed a

circuit in which a hyperactive anterior hippocampus projects downstream to the dopaminergic system and drives the positive symptoms of schizophrenia. In animal models, this circuit can be targeted and modulated, resulting in the alleviation of schizophrenia-like behaviors. Converging evidence from human and animal studies has suggested that hippocampal hyperactivity may be a potential treatment target for schizophrenia. Many studies are currently using pharmacologic agents to target hippocampal hyperactivity to test for improvements in clinical symptoms or changes in neuroimaging measures.

Despite the overwhelming evidence informing our understanding of hippocampal hyperactivity, two fundamental questions need to be clarified. First, what are the neural mechanisms driving the excitation-inhibition balance underlying hippocampal hyperactivity? Second, when does hippocampal dysfunction arise during neurodevelopment? This thesis aims to test two mechanisms of hippocampal dysfunction to address these questions and advance our understanding of hippocampal hyperactivity. First, we will examine the impact of low-dose LEV on hippocampal resting-state activity and hippocampal recruitment to better understand the neural mechanisms contributing to the excitation-inhibition underlying hippocampal hyperactivity in schizophrenia. Second, we will leverage the relationship between incomplete hippocampal inversion (IHI), an anatomic variant of the human hippocampus that arises in a specific window of neurodevelopment, and schizophrenia to better understand when hippocampal deficits arise.

## **Specific aims**

Aim 1: Test a hyperactivity mechanism of psychosis using functional neuroimaging techniques

1a. Test the impact of LEV on anterior hippocampal resting-state activity using ASL

(Chapter II)

1b. Test the impact of LEV on anterior hippocampal recruitment using BOLD signal

change during a hippocampal-dependent task (Chapter II)

Aim 2: Test a neurodevelopmental mechanism of psychosis using structural imaging techniques

2a. Assess the prevalence and severity of IHI in schizophrenia (Chapter III)

Aim 2b. Test the impact of IHI on hippocampal volume and volumetric asymmetry in

schizophrenia (Chapter IV)

Aim 2c. Test the impact of IHI on hippocampal shape in schizophrenia (Chapter IV)

## CHAPTER II

### PHARMACOLOGIC MODULATION OF HIPPOCAMPAL ACTIVITY USING LEVETIRACETAM IN SCHIZOPHRENIA: A RANDOMIZED, DOUBLE-BLIND, CROSS-OVER, PLACEBO-CONTROLLED TRIAL

#### Introduction

The lifetime prevalence of schizophrenia is about 0.7% (Saha et al., 2005), and the burden of illness is significant for patients and society at large (Lehman et al., 2004). A contribution to this disease burden is the lack of optimal treatments, as only 20% of diagnosed individuals reach favorable treatment outcomes (American Psychiatric Association, 2013). One significant challenge in developing treatments for psychotic disorders is the lack of biological treatment targets. There is compelling evidence that the hippocampus is abnormal in schizophrenia (Heckers and Konradi, 2002; Tamminga et al., 2010), and recent models have proposed hippocampal hyperactivity as a biomarker for this disease (Tregellas, 2014). This claim is supported by findings that show hyperactivity is associated with more severe psychopathology (Friston et al., 1992; Gur et al., 1995; Liddle et al., 1992), is predictive of clinical progression (Schobel et al., 2009), can function as a therapeutic target for psychosis (Gill and Grace, 2014; Gomes et al., 2016; Koh et al., 2018; Perez and Lodge, 2014; Smucny and Tregellas, 2017), and has translational utility with animal models of schizophrenia (Gozzi et al., 2010, 2008a; Stevens and Wear, 1997). Despite these findings, it has been a challenge to establish hippocampal hyperactivity as a treatment target due to a poor understanding of the underlying neural mechanisms driving this hyperactivity.

A growing body of literature indicates that the anterior hippocampus is hyperactive in patients with schizophrenia (Schobel et al., 2009; Talati et al., 2014) and individuals at clinical high-risk for developing psychosis (CHR-P) (Modinos et al., 2018; Schobel et al., 2013). Hyperactivity results from an excitation-inhibition imbalance (Heckers and Konradi, 2015; Uhlhaas, 2013) due to disruptions in hippocampal micro-circuitry (Benes, 1999; Grace and Gomes, 2018; Heckers and Konradi, 2015; Lodge et al., 2009; Stan et al., 2015). Approximately 90% of hippocampal neurons are glutamatergic pyramidal cells (Freund and Buzsáki, 1998; Olbrich and Braak, 1985). These glutamatergic neurons have a high baseline firing rate and are synchronized into oscillatory patterns by GABAergic, non-pyramidal interneurons (Freund, 2003; Klausberger and Somogyi, 2008). Evidence from human and animal models of psychosis suggests that the excitation-inhibition imbalance results from hypo-functioning NMDA receptors on fast-spiking hippocampal interneurons (Lisman et al., 2008) and abnormal glutamatergic or GABAergic neurotransmission (Briend et al., 2020; Lieberman et al., 2018; Tamminga et al., 2010). There is growing evidence that positive symptoms (Roiser et al., 2013; Wolthusen et al., 2018), negative symptoms (Makowski et al., 2017), and cognitive deficits (Achim and Lepage, 2005; Guo et al., 2019; Ranganath et al., 2008) are due to hippocampal dysfunction or the subsequent disruption of the hippocampal-cortical network.

Neuroimaging studies can measure the net activity of pyramidal cells and interneurons, and therefore test an excitation-inhibition imbalance hypothesis (Logothetis, 2008). Functional magnetic resonance imaging (fMRI) techniques that quantify cerebral blood volume (CBV) or cerebral blood flow (CBF) can measure the resting-state activity of the hippocampus. CBV has previously been regarded as the gold-standard *in vivo* measure of baseline hippocampal activity

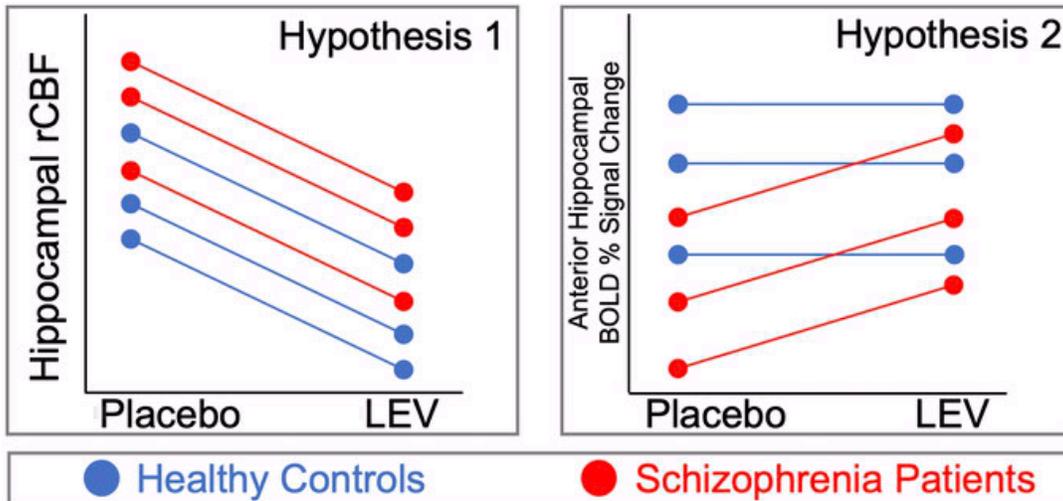
(Small et al., 2011). However, CBV is not a practical method for many studies on patient populations, as it is invasive. Three CBV studies have observed anterior hippocampal hyperactivity in individuals with schizophrenia (McHugo et al., 2019; Schobel et al., 2009; Talati et al., 2014). A popular, non-invasive measure of CBF is arterial spin labeling (ASL). ASL measures CBF directly, which is tightly coupled to glucose metabolism, an indicator of neuronal activity. ASL has also been used to study the hippocampus in schizophrenia (Kindler et al., 2015; Ota et al., 2014; Pinkham et al., 2011; Scheef et al., 2010; Walther et al., 2011). However, these studies have mixed conclusions and methodological limitations.

Neuroimaging studies also show reduced hippocampal activity in patients during hippocampal-dependent task performance (i.e., recruitment) when compared to healthy controls (Achim et al., 2007; Heckers et al., 1998; Jessen et al., 2003; Sehatpour et al., 2010; Weiss et al., 2004, 2003). Studies that use fMRI (BOLD signal) while subjects perform hippocampal-dependent tasks can measure hippocampal recruitment. The BOLD signal is qualitative and measures changes in and around veins secondary to direct changes in CBF and cerebral metabolic rate of oxygen. Critically, a recent study demonstrated that anterior hippocampal hyperactivity, as measured by CBV, correlates with the recruitment of this region during a hippocampal-dependent scene-processing task (SPT) in the same people with schizophrenia (McHugo et al., 2019). This evidence suggests elevated hippocampal resting-state activity may limit the recruitment of the hippocampus (i.e., a ceiling effect).

Levetiracetam (LEV) has overwhelming evidence for modulating neuronal activity and has been established as a FDA-approved anti-epileptic for over two decades (Lyseng-Williamson, 2011). LEV's exact mechanism of action continues to be elucidated, but evidence

suggests it normalizes glutamatergic neurotransmission (Lynch et al., 2004). A recent study showed that, in an animal model that recapitulates neural hyperactivity and cognitive symptoms similar to those seen in schizophrenia patients, LEV improved cognitive function (Koh et al., 2018). Critically, LEV remained effective when administered concurrently with an antipsychotic drug, implicating that LEV could be used as an adjunctive therapy. Two human studies have studied the effects of low-dose LEV in amnesic mild cognitive impairment (aMCI) patients with hippocampal hyperactivity and detected restoration of hippocampal hyperactivity to normal levels (Bakker et al., 2015, 2012). However, no published study investigating LEV's effect on hippocampal activity in schizophrenia patients exists. This work will perturb the neural mechanisms underlying hippocampal activity in schizophrenia patients using LEV.

In this study, we tested two main hypotheses. First, hippocampal regional cerebral blood flow (rCBF) is increased in schizophrenia under placebo conditions (group effect), and LEV treatment reduces rCBF from placebo treatment in both groups (treatment effect). Second, hippocampal BOLD percent signal change (PSC) is decreased in schizophrenia under placebo conditions (group effect), and LEV treatment increases BOLD PSC in schizophrenia patients but not healthy controls (group by treatment effect). These hypotheses are summarized in **Figure 3**. Using non-invasive, high-resolution imaging techniques to test these hypotheses will strengthen our understanding of the hippocampus's role in psychosis.



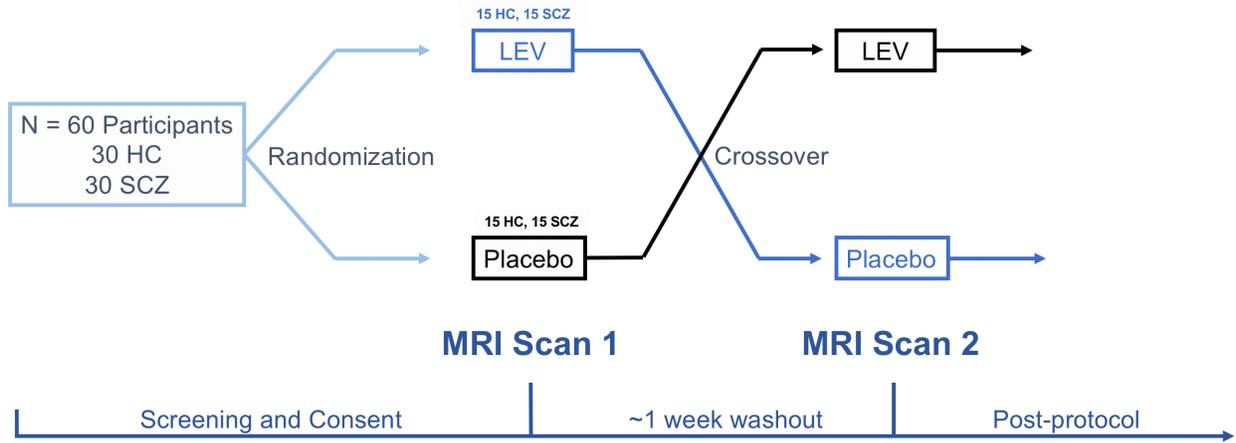
**Figure 3. Study hypotheses.**

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## Methods

### *Study procedures*

All participants completed the same study procedures with MRI scans after each of the two treatment sessions, separated by a washout period of at least one week (**Figure 4**). Both healthy control participants and schizophrenia patients were given oral placebo during one treatment session and 500mg oral LEV (Keppra, UCB Laboratories) during the other treatment session, with the order counter-balanced (randomized, double-blind). The Investigational Drug Service at Vanderbilt University Medical Center prepared placebo and LEV treatments in identical capsules. At both study visits, treatment administration occurred at participant arrival. Two hours after placebo or LEV treatment, participants completed a MRI scan and blood draw. The Investigational Drug Service controlled blinding and unblinding of all study data. The study team was blind to the treatment administered to each participant and the participant's serum drug concentration until the beginning of data analysis. Data safety was monitored by an independent study monitor in collaboration with the Vanderbilt Institutional Review Board (IRB).



**Figure 4. Study Design.**

Each participant was randomized, double-blind, in a within-crossover design, with the order of treatment on LEV and placebo counterbalanced within each cohort. *Note:* HC = Healthy controls; SCZ = Patients with schizophrenia

### *Study participants*

Participants in this study included 30 patients with schizophrenia spectrum disorder diagnoses (7 schizoaffective disorder, 23 schizophrenia; all schizoaffective disorder patients met full criteria for schizophrenia (Seldin et al., 2017) and therefore the entire patient sample is referred to here as *schizophrenia patients*) and 30 healthy control participants matched to patients on age, gender, race, and parental education (**Table 3, Figure 5**). All patients were in the chronic stage of illness (duration of illness > 2 years). All participants had previously contributed to the Psychiatric Phenotype/Genotype Project (PGPP) (NCT00762866), an ongoing data repository including schizophrenia patients recruited from the inpatient unit and outpatient clinics of the Vanderbilt University Medical Center Psychotic Disorders Program and healthy control participants recruited from the local community via advertisement. The Vanderbilt University IRB approved the study. This study was pre-registered at [clinicaltrials.gov](https://clinicaltrials.gov) (NCT04559529). All participants provided written informed consent and were compensated for their time.

Participant exclusion criteria include significant medical or neurological illness, age under 18 or over 65 years, pregnancy, head injury, meeting criteria for substance abuse within the past month, or with conditions that preclude study drug administration. Healthy control participants were excluded if they had a current or past psychiatric illness, a first degree relative with a psychotic illness, or psychotropic drug use. One schizophrenia patient did not complete the second study session.

**Table 3.** Chapter II participant demographics and clinical characteristics

	Healthy Control Participants		Schizophrenia Patients		Healthy Control Participants > Schizophrenia Patients	
	N = 30		N = 30		Statistic (t)	p
	Mean	SD	Mean	SD		
<b>Age (yrs)</b>	34.1	10.2	35.2	12.2	-0.37	0.71
<b>Parental Education (yrs)</b>	15.0	2.11	15.3	2.49	-0.58	0.56
<b>WTAR</b>	111.0	9.53	105.0	13.3	1.94	0.06
<b>CPZ Equivalents</b>			350.09	252.55		
<b>Duration of Illness (yrs)</b>			13.78	11.92		
	N	%	N	%	Statistic (X <sup>2</sup> )	p
<b>Sex (Male)</b>	21	0.70	21	0.70	0.00	1.00
<b>Race (White)</b>	21	0.70	24	0.80	0.36	0.55
<b>Tobacco Use</b>						
No	26	0.87	14	0.47	12.43	<b>0.002</b>
Yes, continued	1	0.03	11	0.37		
Yes, quit	3	0.10	5	0.17		
<b>Cannabis Use (last month)</b>	1	0.03	7	0.23	3.06	0.06
<b>Diagnosis</b>						
Schizophrenia			23	0.77		
Schizoaffective DO			7	0.23		
<b>PANSS</b>						
Positive			16.45	9.30		
Negative			15.52	8.45		
General			25.90	6.85		

Key: yrs = years; SD = standard deviation; IHI = Incomplete Hippocampal Inversion; DO = disorder

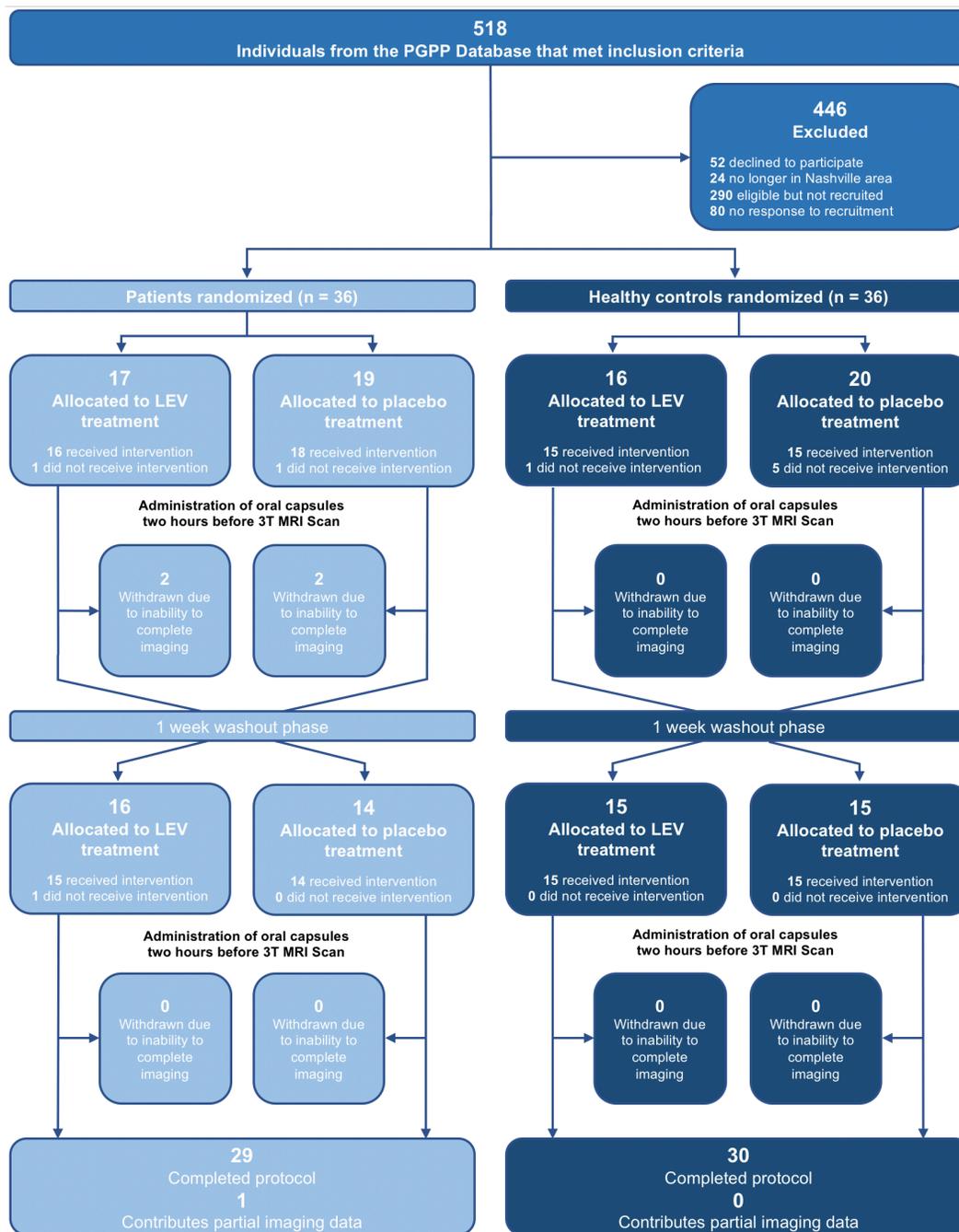


Figure 5. Consort Diagram.

Psychiatric diagnoses were assessed with the Structured Clinical Interview for DSM-IV, TR (First et al., 2002). We collected clinical data during in-person or virtual interviews during one of the study visits. Clinical symptoms at the time of scanning were characterized using the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987). The duration of psychosis was calculated as the amount of time between the date of study enrollment and onset of psychosis, as determined through the Symptom Onset in Schizophrenia Inventory (Perkins et al., 2000), a standardized measure for rating prodromal versus psychotic symptoms. Chlorpromazine equivalents were calculated using published formulas (Gardner et al., 2010; Leucht et al., 2014). Premorbid IQ was estimated using the Wechsler Test of Adult Reading (Wechsler, 2001). Clinical characteristics of the sample are described in **Table 3**.

### *Structural imaging*

#### Data acquisition

Structural MRI acquisition was completed on a 3 T Philips Intera Achieva scanner at the Vanderbilt University Institute of Imaging Sciences (Philips Healthcare, Inc.). Each participant received a 3D T1-weighted scan (voxel resolution: 1 mm<sup>3</sup>; field of view = 256<sup>2</sup>; number of slices = 170; TE = 3.7 ms; TR = 8.0 ms). Structural images were visually inspected and determined to be free from motion or other artifacts prior to inclusion in the analysis (no images were removed).

## Structural image processing

Each participant's T1 structural image was processed using the FreeSurfer 6 (Dale et al., 1999; Fischl et al., 2002) hippocampal subfield module (Iglesias et al., 2015) with standard parameters to create individual-specific hippocampal regions of interest. The anterior hippocampal region of interest was defined using the FreeSurfer segmentation of the hippocampal head. The posterior hippocampal region of interest was defined as the sum of the body and tail segmentations determined by FreeSurfer. Segmentations were visually inspected to correct those with tissue labeled outside the hippocampus or incomplete labeling of the hippocampus. Failed automated segmentations were corrected for inclusion in this study by manually deleting segmented voxels that extended outside of the hippocampal head, body, or tail into surrounding structures or by manually replacing amygdala segmentation voxels with hippocampal head segmentation voxels at the amygdala–hippocampal border. Manual voxel correction was completed using ITK-SNAP version 3.8.0 (Yushkevich et al., 2006). We constructed individual-specific masks of the left and right, and whole, anterior, and posterior hippocampal regions for pseudocontinuous ASL (pCASL) and fMRI region of interest analyses, detailed below.

## *Cerebral blood flow imaging*

### Data acquisition

A hippocampal pCASL sequence was not preceded by a functional task and was acquired with the following parameters: spatial resolution =  $3 \times 3 \times 5 \text{ mm}^3$ , TE = 18 ms, TR = 3750 ms, SENSE factor = 2.3, flip angle = 90, labeling duration = 1650 ms train of 0.5 ms Hanning pulses,

and post-labeling delay = 1600 ms. The echo-planar imaging sequence acquired 40 paired (label, unlabeled) dynamics covering 10 ascending slices, oriented at  $-15^\circ$  relative to the intercommissural plane, and utilized two background suppression pulses at 1710 and 2860 ms to suppress static tissue signal over a wide range of T1s. An additional M0 ASL scan was acquired for baseline magnetization and for coregistration to the structural image. This scan had identical geometry and parameters as the pCASL scan except the TR = 15 s, and the spin labeling pulse train was turned off.

#### ASL data processing and analysis

Control and label maps were motion-corrected to the first control image using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>) in Matlab 2018a (Mathworks, Inc.) using standard parameters. Difference images (control-label) were then averaged across dynamics and fit to Buxton's kinetic model (Buxton et al., 1998), with appropriate parameters recommended by the ISMRM perfusion study group (Alsop et al., 2015) to generate CBF maps. These maps were corrected for slice labeling delay (calculated at 26 ms). It was assumed that the gray matter to white matter CBF ratio was 2.5 (Buxton et al., 1998). The CBF maps were coregistered to the T1 structural data using FSL's FLIRT (Jenkinson et al., 2002), and the inverse transform was used to bring the hippocampal ROIs into CBF space. Two hippocampal pCASL sequences were collected. Hippocampal rCBF values were generated using the average of both pCASL sequences.

## *Task fMRI*

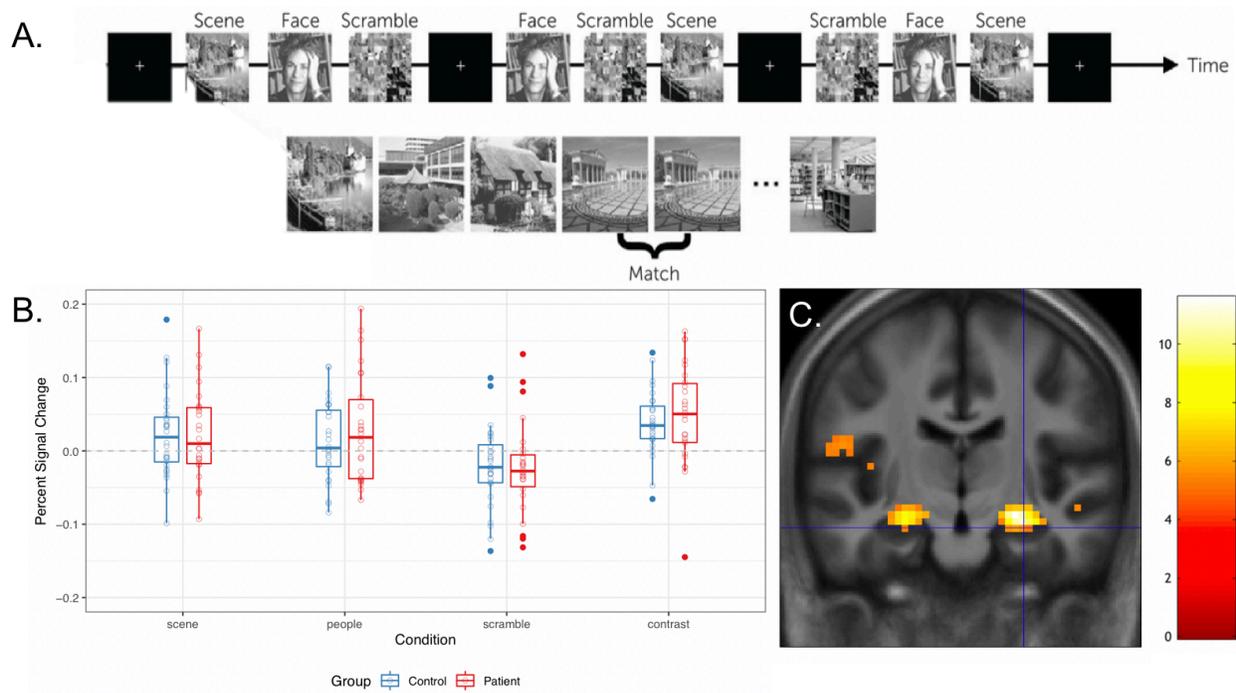
### Data acquisition

We collected 111 volumes of whole brain fMRI data during the task with an echo planar imaging sequence (38 ascending slices, oriented at  $-15^\circ$  relative to the intercommissural plane; voxel size =  $3.0 \times 3.0 \times 3.2\text{mm}$ ; TR = 2s; TE = 28.0ms; flip angle =  $90^\circ$ ). This acquisition protocol and sequence parameters were designed to maximize signal in the hippocampus (Weiskopf et al., 2006). Whole brain fMRI data acquisition occurred after pCASL sequence completion.

### fMRI scene-processing task

Participants completed a single run of a block-design 1-back task (**Figure 6**) during fMRI scanning during both visits. The run was composed of nine blocks of 16 black-and-white scenes, faces, or scrambled images, separated by fixation periods. Stimuli consisted of indoor or outdoor scenes, scenes featuring neutral male or female faces, and scrambled images of scenes. Each image was presented for 750ms with a 250ms interstimulus interval. Participants were instructed to respond by button-press if the current image was identical to the immediately preceding image. There were between 0-3 target matches per block. Different stimulus sets matched for the presence of indoor/outdoor scenes and male/female faces were used at each study visit. Task performance was measured using mean hit rate, correct rejection rate, and reaction time (**Table 4**). Participants were removed from analysis if task performance was poor (hit rate  $<50\%$  in any condition; scan 1 excluded: 1 healthy participant, 2 schizophrenia patients; scan 2 excluded: 2 healthy participants, 3 schizophrenia patients) or for

scanner-related issues (scanner failure or excessive motion; scan 1 excluded: 1 schizophrenia patient; scan 2 excluded: 1 healthy participant, 2 schizophrenia patients).



**Figure 6. Scene processing task.**

(A.) An example block of the scene processing task. Individuals respond via button press when an image repeats (“match”). (B.) Both healthy control participants and schizophrenia patients demonstrate expected percent signal change patterns by each condition (increases in percent signal change for scene, people, and contrast condition; decrease in percent signal change for scramble condition). Schizophrenia patients do not differ from healthy control participants in any condition after placebo treatment. (C.) Robust activation of the anterior hippocampus during the contrast condition (subtract scramble condition from average of scene and face conditions) in all participants in whole brain analysis without masking.

**Table 4.** Behavioral performance after placebo and LEV treatment

	Healthy Controls				Schizophrenia Patients			
	Placebo		LEV		Placebo		LEV	
	n = 28		n = 29		n = 27		n = 26	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hit rate	0.92	0.10	0.89	0.12	0.89	0.11	0.87	0.13
Correct rejection rate	0.99	0.01	0.98	0.02	0.97	0.02	0.97	0.02
Reaction time (ms)	584.71	44.40	580.59	41.57	582.70	43.19	576.29	41.30

Key: LEV = levetiracetam; SD = standard deviation; ms = milliseconds

## SPT data processing and analysis

We analyzed structural and functional data with SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>) in Matlab 2018a (Mathworks Inc.) using standard parameters. Functional images were realigned to the mean image. The structural image was then coregistered to the mean functional image, segmented, and normalized to MNI space. The realigned functional images were normalized by applying the deformation fields derived from structural image processing, then spatially smoothed with a 6 mm full-width at half-maximum Gaussian kernel. Framewise displacement was calculated for each participant (Power et al., 2012). Participants were assessed for incomplete coverage of the hippocampus based on visual inspection of the first-level masks. Data from included participants of both groups had similar levels of motion after placebo treatment (mean framewise displacement: healthy control participants = 0.18, schizophrenia patients = 0.22;  $t_{52} = 2.00$ ,  $p = 0.05$ ) and LEV treatment (mean framewise displacement: healthy control participants = 0.22, schizophrenia patients = 0.24;  $t_{50} = 0.79$ ,  $p = 0.44$ ).

The first-level fMRI analysis included separate regressors for the scene, face, and scramble conditions, modeling the onset of each block in each condition with a stimulus duration = 16s, convolved with the canonical hemodynamic response. Realignment parameters (translation, rotation) were included as additional regressors in the first-level model. We then applied a high-pass filter with a cutoff of 128 s. Face images used in the task were composed of people presented in the context of a background scene (**Figure 6A**). As a result, we measured activation during scenes using a first-level contrast calculated as the difference in the average

response to scene and face images compared to scrambled images (hereafter referred to as 'contrast').

We completed a region of interest analysis in the anterior hippocampus. For each participant, the anterior hippocampus mask from Freesurfer was coregistered to participant's mean functional image and normalized to MNI space at the same resolution as the functional data with nearest-neighbor interpolation using the deformation fields derived from structural image segmentation described above. PSC for each condition (scene, people, scramble, contrast) was extracted from the individual-specific anterior hippocampus region of interest using MarsBar (<http://marsbar.sourceforge.net>). PSC is the signal difference between the condition and a fixation cross.

### *Statistical analysis*

We conducted all statistical analyses in R (R Core Team, 2019), unless otherwise specified. We tested all dependent variables (i.e., rCBF and BOLD PSC) in linear models or linear mixed models with the packages lme4 (Bates et al., 2015), and emmeans (Fox and Weisberg, 2011). For all models, we conducted significance tests on the fixed effects using analysis of variance (ANOVA) on the model output. We tested all main effects and interaction effects using type 2 sum of squares. Significant interactions were followed up with contrasts adjusted for multiple comparisons using Bonferroni correction.

### pCASL

To test for baseline (after placebo treatment) hippocampal rCBF group differences, we constructed models with region of interest rCBF as the dependent variable and group as a fixed effect. To test for a treatment effect, we constructed models with region of interest rCBF as the dependent variable, an interaction effect between group and treatment (placebo, LEV), and with participant as a random effect. We fitted all models by adjusting for age and gender. We also adjusted the test for a baseline group effect by adjusting for visit (visit 1, visit 2).

### Scene processing task

To confirm activation of the hippocampus was not the result of activation extending from adjacent regions, we completed a whole-brain analysis in addition to the region of interest analysis (**Figure 6C**). A one-sample whole-brain t-test of the average response to scenes and faces, minus scrambled images, was carried out in SPM12 for the healthy control participants and schizophrenia patients and thresholded at a voxelwise familywise error  $<0.05$ .

To test for baseline anterior hippocampal PSC group differences, we constructed models with PSC of each SPT condition as the dependent variable and group as a fixed effect. To test for a treatment effect, we constructed models with PSC of each SPT condition as the dependent variable, an interaction between group and treatment as a fixed effect, and participant as a random effect. We fitted all models by adjusting for age and mean framewise displacement to account for differences in motion. We also adjusted the test for a baseline group effect by adjusting for visit.

We assessed group differences in task performance using linear mixed models with hit rate, correct rejection rate, and reaction times as dependent variables, group and time as fixed

effects, and subject as a random effect. For all models, we conducted significance tests on the fixed effects using analysis of variance (ANOVA) on the model output. We conducted all analyses in R.

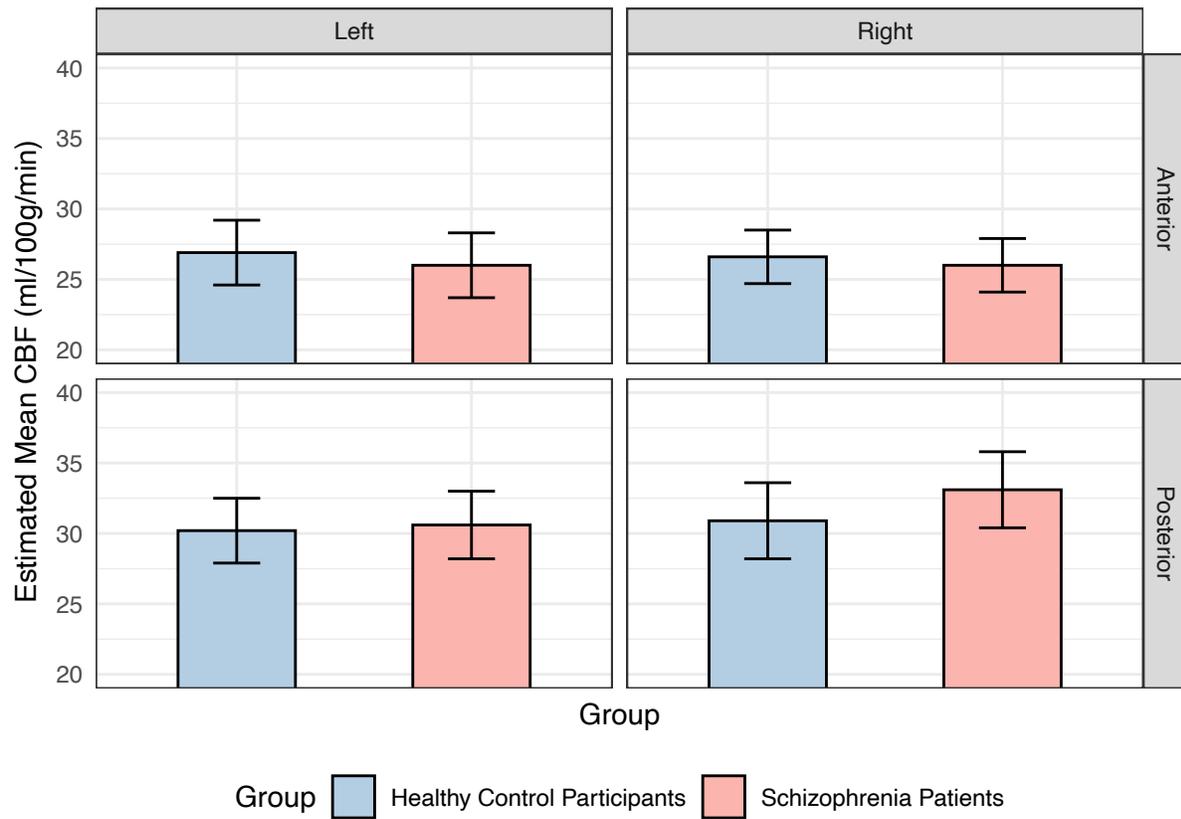
We performed additional analyses to test the association between the clinical characteristics (PANSS scores, chlorpromazine equivalents, and duration of illness) of our patient sample and hippocampal activation using Spearman correlation analyses. We tested the relationship of these variables with hippocampal PSC during the scramble condition of the SPT and hippocampal rCBF after placebo treatment and LEV treatment. We conducted all analyses in R.

## **Results**

### *Hippocampal activity*

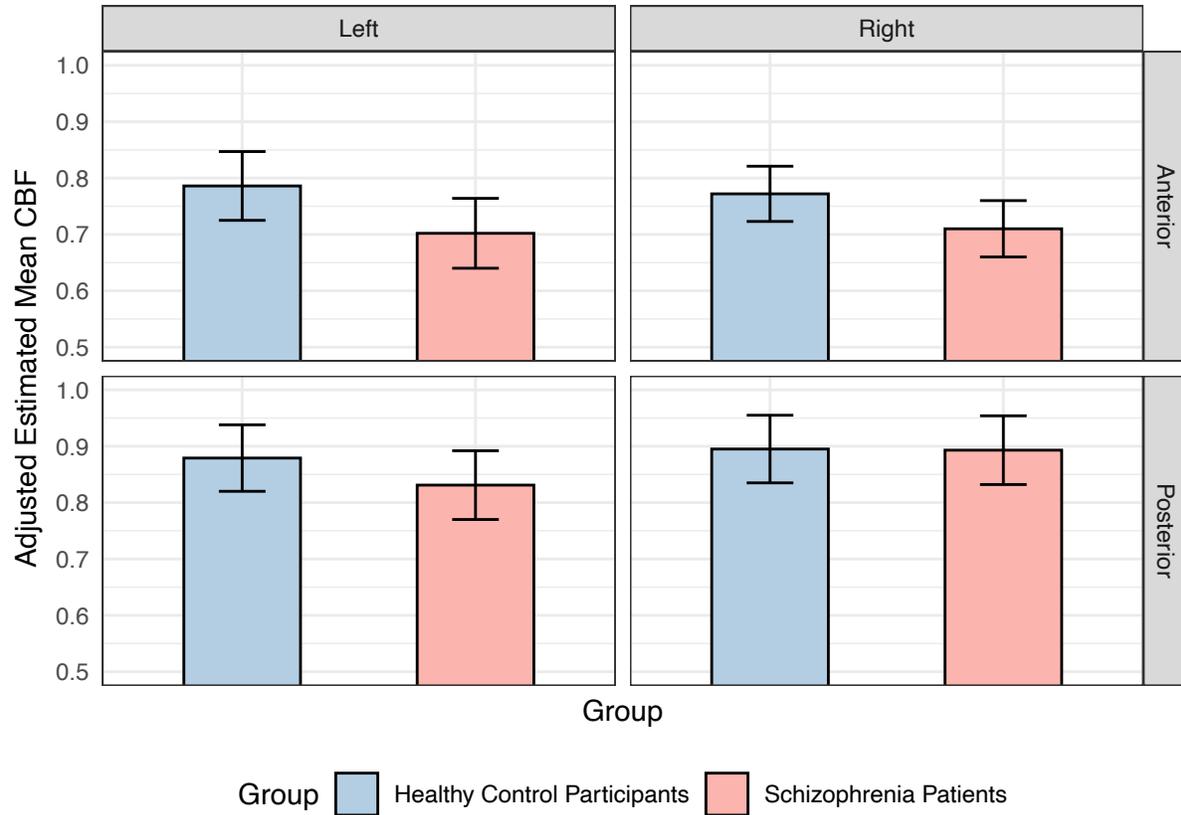
Hippocampal resting-state rCBF measurements did not differ between healthy individuals and schizophrenia patients in any subregion of the hippocampus during the placebo condition (**Figure 7**). Adjusting for gray matter rCBF did not change the results (**Figure 8**).

During the scene processing task (SPT), both healthy individuals and schizophrenia patients demonstrated the expected changes in BOLD signal (**Figure 6**). In the placebo condition, the two groups did not differ, during any condition of the SPT, in anterior hippocampal BOLD signal changes.



**Figure 7. Hippocampal rCBF does not differ between groups.**

Linear mixed models indicate no effect of group in healthy control participants (n = 28) or schizophrenia patients (n = 27) in any hippocampal subregion or hemisphere after placebo treatment. Hippocampal rCBF was measured using a hippocampal ASL sequence. Error bars represent 95% confidence intervals.



**Figure 8. Hippocampal rCBF does not differ between groups after adjusting hippocampal ASL sequence values by gray matter rCBF.**

Linear mixed models indicate no effect of group in healthy control participants (n = 28) or schizophrenia patients (n = 27) in any hippocampal subregion or hemisphere after placebo treatment. Error bars represent 95% confidence intervals.

### *Effect of levetiracetam treatment on hippocampal activity*

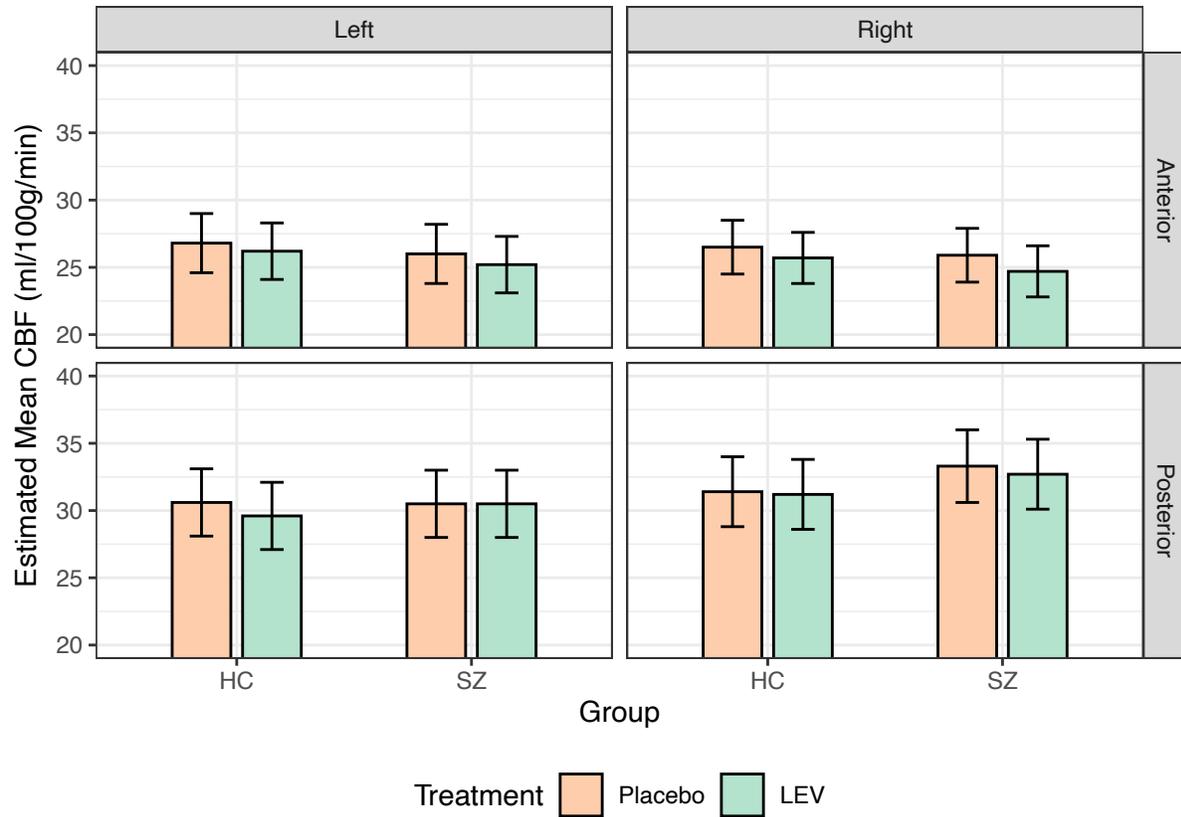
Treatment with 500mg LEV provided a serum drug level of 8.86 +/- 4.73 ug/mL.

We did not find an effect of LEV treatment on hippocampal rCBF (**Figure 9**). Adjusting for gray matter rCBF did not change the results (**Figure 10**).

We did not find a significant main effect of LEV treatment on BOLD signal change during the SPT (**Figure 11**). When we limited our analysis to the participants' first SPT session, we observed a main effect of group ( $p = 0.008$  for scramble condition) and a group by treatment interaction ( $p = 0.039$ ) for the scramble condition (**Figure 12**). Post-hoc tests demonstrated a difference in group after LEV treatment ( $t_{50} = 3.47$ ,  $p = 0.002$ ) but no difference under placebo treatment ( $t_{50} = 0.49$ ,  $p = 1.00$ ). These effects were not found in the second SPT session (**Figure 13**).

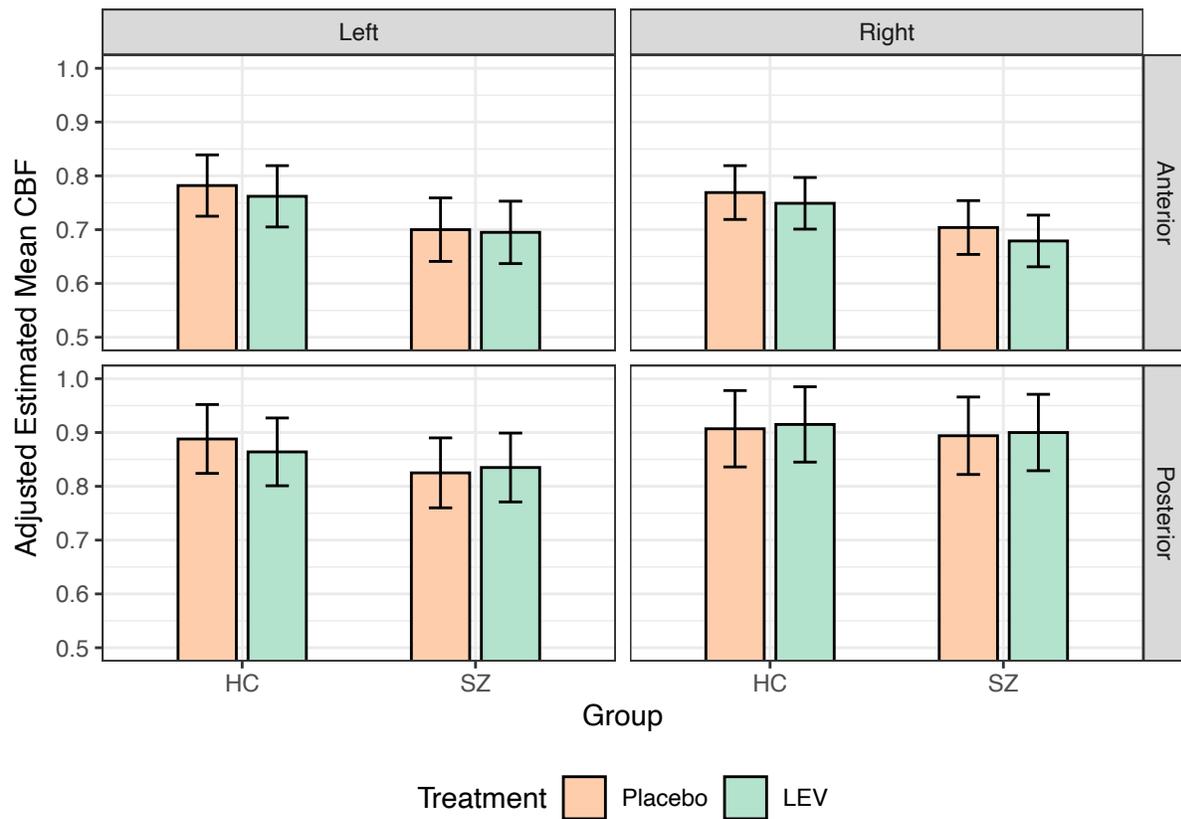
### *Behavioral task performance*

Performance was high in both groups after placebo and LEV treatment (**Table 4**). Hit rate did not differ by group (main effect of group:  $F_{1,89} = 0.49$ ,  $p = 0.48$ ) or treatment (main effect of treatment:  $F_{1,49} = 1.86$ ,  $p = 0.18$ ; group by treatment interaction:  $F_{1,51} = 0.00$ ,  $p = 0.97$ ). Correct rejection rate did not differ by group (main effect of group:  $F_{1,77} = 0.56$ ,  $p = 0.46$ ) or treatment (main effect of treatment:  $F_{1,49} = 2.76$ ,  $p = 0.10$ ; group by treatment interaction:  $F_{1,50} = 2.60$ ,  $p = 0.11$ ). Reaction time (milliseconds) did not differ by group (main effect of group:  $F_{1,73} = 0.21$ ,  $p = 0.65$ ) or treatment (main effect of treatment:  $F_{1,49} = 0.31$ ,  $p = 0.58$ ; group by treatment interaction:  $F_{1,50} = 0.18$ ,  $p = 0.67$ ).



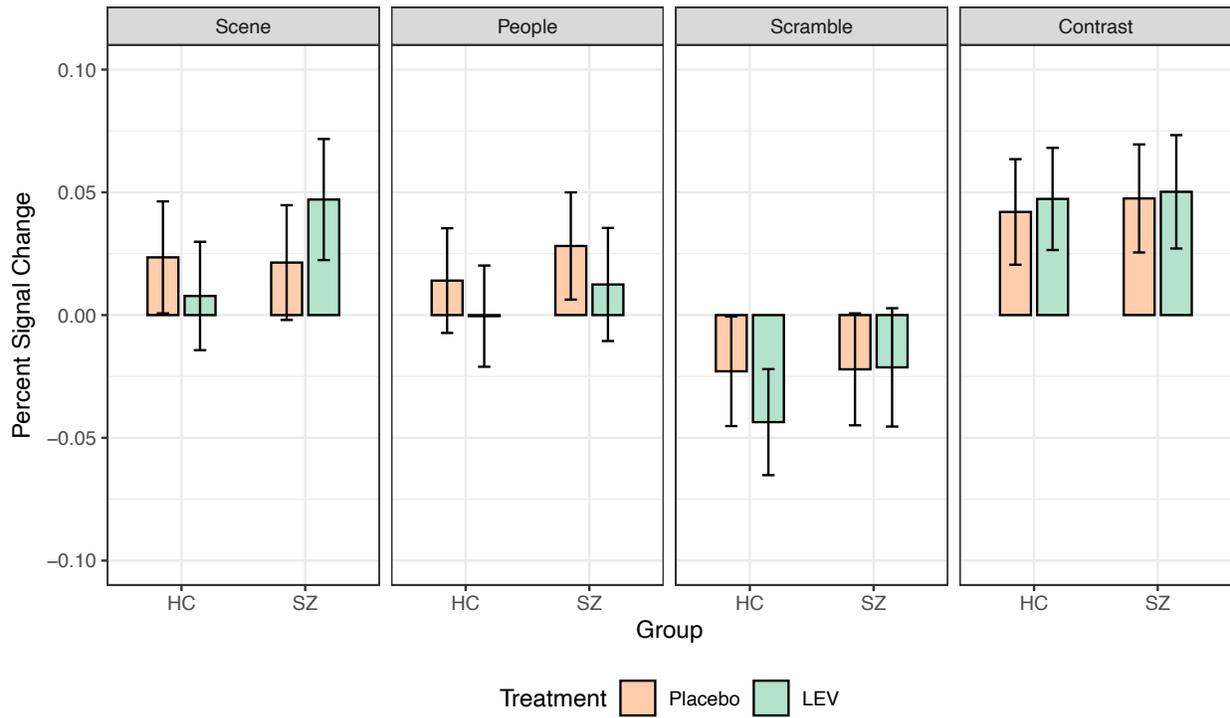
**Figure 9. Hippocampal rCBF does not change after LEV treatment.**

Linear mixed models indicate no effect of group or treatment in healthy control participants (n = 30) or schizophrenia patients (n = 29) in any hippocampal subregion or hemisphere. Hippocampal rCBF was measured using a hippocampal ASL sequence.



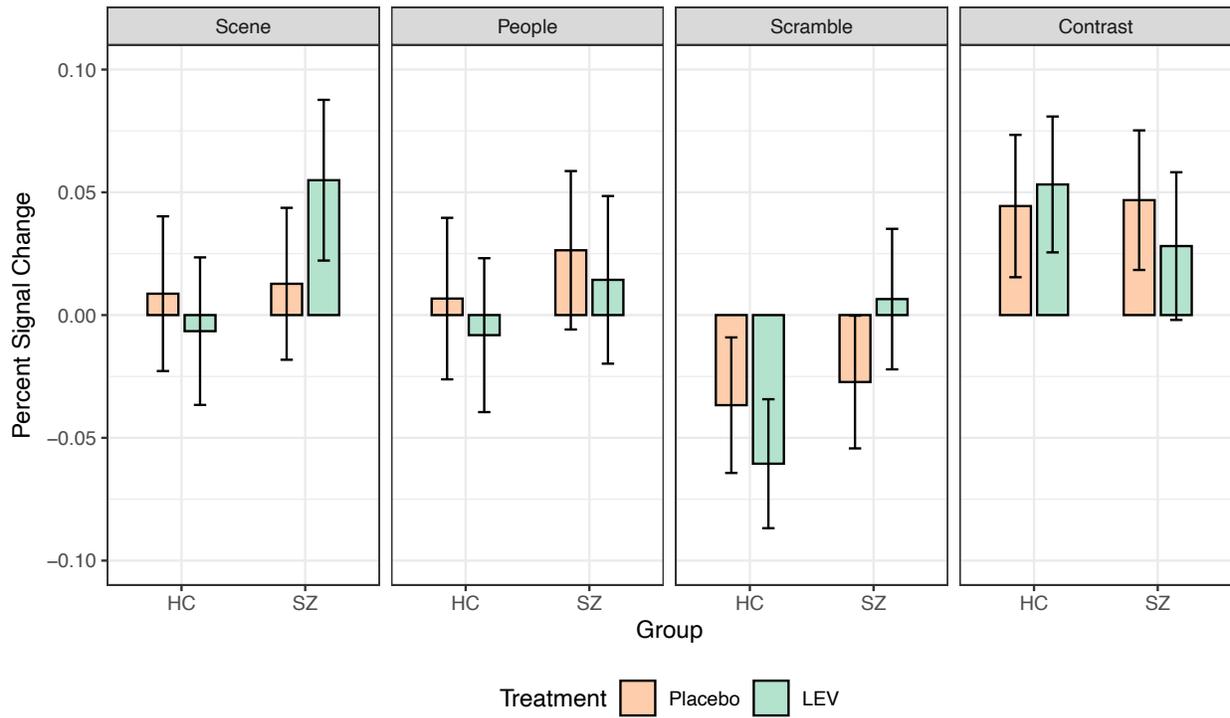
**Figure 10. Hippocampal rCBF does not change after LEV treatment after adjusting hippocampal ASL sequence values by gray matter rCBF.**

Linear mixed models indicate no effect of group or treatment in healthy control participants (n = 30) or schizophrenia patients (n = 29) in any hippocampal subregion or hemisphere. Error bars represent 95% confidence intervals.

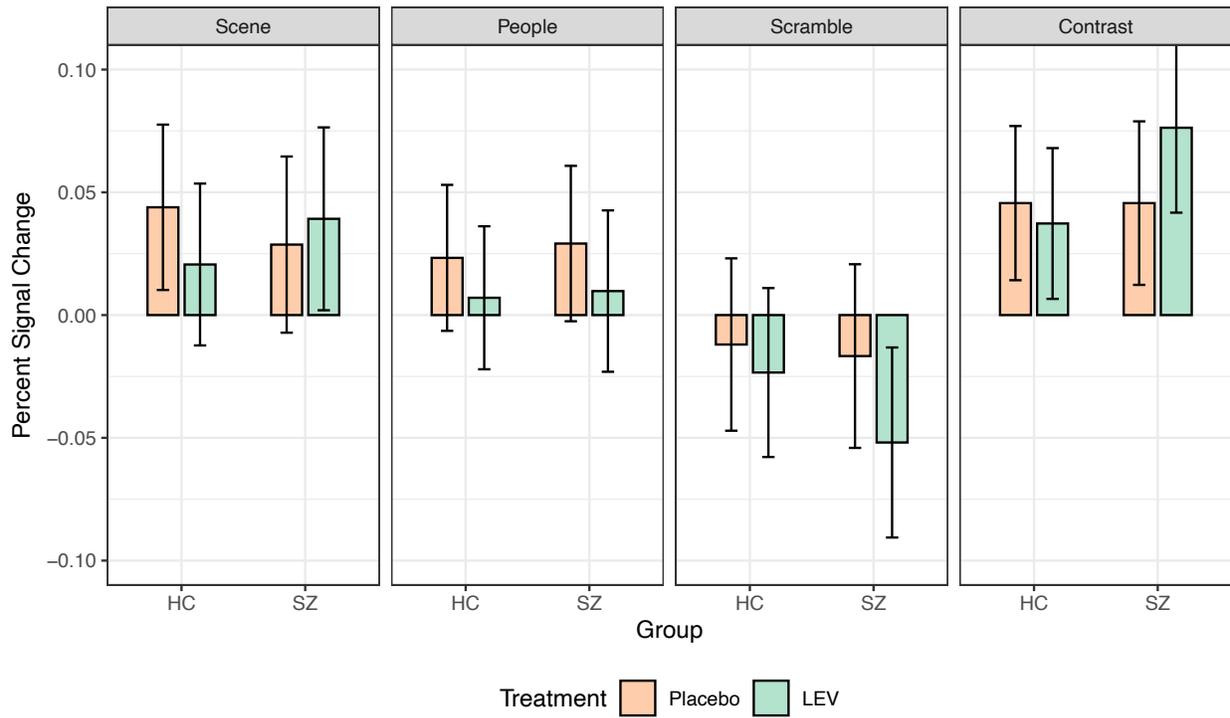


**Figure 11. Percent BOLD signal change in the anterior hippocampus is not altered by LEV treatment across both study SPT sessions.**

Linear models do not demonstrate an effect of group or group by treatment interaction in any SPT condition in healthy control participants (n = 29) and schizophrenia patients (n = 29). Error bars represent 95% confidence intervals.



**Figure 12. Percent BOLD signal change in the anterior hippocampus is altered by LEV treatment.** Linear models demonstrate an effect of group and group by treatment interaction in the scramble condition of the SPT of healthy control participants (n = 29) and schizophrenia patients (n = 27) when analysis is limited to the first SPT session.



**Figure 13. Percent BOLD signal change in the anterior hippocampus is not altered by LEV treatment during the second LEV session.**

Linear models do not demonstrate an effect of group or group by treatment interaction in any SPT condition in healthy control participants (n = 28) and schizophrenia patients (n = 23) when analysis is limited to the second SPT session. Error bars represent 95% confidence intervals.

### *Association of hippocampal cerebral blood flow and clinical factors in schizophrenia patients*

We explored whether hippocampal rCBF was associated with clinical characteristics in the patient group. We observed associations between hippocampal rCBF with positive symptoms after placebo treatment (**Table 5**). There were no associations detected after LEV treatment.

### **Discussion**

We investigated the impact of low-dose LEV on hippocampal hyperactivity, a potential treatment target for schizophrenia, using a randomized, double-blind, cross-over, placebo-controlled design and fMRI. We did not detect group differences between schizophrenia patients and healthy controls when comparing functional measures. Further, we did not identify an effect of treatment on resting-state hippocampal rCBF or recruitment during a hippocampal-dependent task after LEV treatment. This is the first published work detailing the effect of low-dose LEV on hippocampal hyperactivity in schizophrenia, although other trials are currently underway. In the following sections, we will discuss potential contributions to our negative findings and the implications of this study on hippocampal hyperactivity as a potential treatment target for schizophrenia.

**Table 5. Association of clinical characteristics with imaging measures**

	Hippocampal pCASL sequence			
	Placebo		LEV	
	r	p	r	p
PANSS				
Positive	<b>0.387</b>	<b>0.045</b>	0.324	0.092
Negative	0.073	0.718	-0.042	0.830
General	0.062	0.758	-0.067	0.736
DOI (yrs)	-0.049	0.809	-0.102	0.596
CPZE	0.273	0.168	0.209	0.276

Key: pCASL = Pseudo-continuous Arterial Spin Labeling; LEV = Levetiracetam; PANSS = Positive and Negative Syndrome Scale; DOI = Duration of illness; yrs = years; CPZE = chlorpromazine equivalents

### *Patient heterogeneity*

Several factors may have contributed to the recruitment of a patient sample that does not represent schizophrenia patients, resulting in our negative findings. First, the entirety of this cohort was recruited during the COVID-19 pandemic (between October 2020 and July 2021), restricting individuals who could participate. Second, the study design demanded that patients are relatively high functioning (e.g., organization to attend sessions during two separate weeks and arrive at strict times for treatment administration). Third, this pharmacologic intervention study was the first conducted in the PGPP cohort. Over 50 eligible PGPP participants that contributed to previous studies declined to participate in this study. Many patients declined participation because of the requirement to take a new medication, LEV. Altogether, these factors may have contributed to a selection bias in the study cohort.

Hippocampal recruitment differences during SPT performance in schizophrenia have been reported in one cross-sectional study and during the first assessment of one longitudinal study (McHugo et al., 2021, 2019). In the longitudinal study, no hippocampal recruitment differences existed at follow-up two years later. The average duration of illness was approximately eight months when recruitment differences were detected in both studies. Similarly, a recent longitudinal study investigating anterior hippocampal hyperactivity using ALFF reported hippocampal hyperactivity early in the illness (average duration of illness of 6 months) but not at two-year follow-up (McHugo et al., 2022). This pattern of results suggests that hippocampal dysfunction may be associated with an acute illness state. The current study's patient cohort was primarily composed of clinically stable individuals with chronic illness (average duration of illness of 13 years, minimum duration of 5 years) and stable antipsychotic

medication regimens. This difference in duration of illness and acuity of illness could contribute to the lack of fMRI differences. Of note, other demographic and clinical variables in this study resembled those of previous studies using the SPT to assess hippocampal recruitment.

### *Imaging methods*

Resting-state hippocampal rCBF did not differ in the anterior or posterior hippocampus. Previous ASL studies report inconsistent findings in the hippocampus of schizophrenia patients (Kindler et al., 2015; Ota et al., 2014; Pinkham et al., 2011; Scheef et al., 2010; Walther et al., 2011). Differences in acquisition parameters (e.g., using continuous or pulsed sequences instead of the preferred pCASL sequences) and low-resolution data likely result in conflicting results. In this study, we sought to overcome such limitations by following the International Society for Magnetic Resonance in Medicine's recommended sequence parameters (Alsop et al., 2015) and scanning at a higher resolution to achieve high-quality data. Despite these adjustments, our ASL methods did not replicate findings of increased resting-state activity of the hippocampus in schizophrenia patients previously reported using ASL (Scheef et al., 2010) or CBV methods (McHugo et al., 2019; Schobel et al., 2009; Talati et al., 2014).

A growing literature highlights the limitations of using ASL to study CBF in schizophrenia. Although multiple studies demonstrate increased rCBF in the striatum (Kindler et al., 2018; Pinkham et al., 2011) and decreased rCBF in the frontal lobe (Kindler et al., 2018; Oliveira et al., 2018; Pinkham et al., 2011), few report altered hippocampal rCBF. Increased perfusion has only been reported in antipsychotic-naïve patients (Scheef et al., 2010) and CHR-P individuals (Allen et al., 2018; P. Allen et al., 2016) (10 and 13% taking antipsychotic medication, respectively).

There is accumulating evidence indicating that antipsychotics reduce hippocampal rCBF, effectively normalizing rCBF to levels indistinguishable from healthy controls (Lahti et al., 2003; Medoff et al., 2001). Further, antipsychotics might drive the consistently reported striatal and frontal rCBF differences (Handley et al., 2013). Despite using optimized ASL parameters and higher resolution imaging, inherent limitations of ASL prevented us from measuring elevated hippocampal resting-state activity in our sample of chronic schizophrenia patients.

Restricting our analysis of hippocampal recruitment to the first imaging session of this study revealed a significant group and group by treatment effect in the scramble condition. The PSC during the scramble condition was elevated in schizophrenia patients, replicating previous findings using the SPT in schizophrenia patients (McHugo et al., 2019). Unlike the scene and face conditions, the scramble condition of the SPT does not elicit anterior hippocampal activation, as visualized with the negative PSC. The increase of PSC in the scramble condition for schizophrenia patients suggests a hyper-activation of this region when the hippocampus is not engaged, consistent with previous studies (McHugo et al., 2019; Ragland et al., 2017). Treatment with LEV increased PSC in patients and reduced PSC in healthy individuals. This group by treatment effect indicates that LEV may have a subtle, differential impact on hippocampal activation at rest. However, these effects are eliminated when performing an analysis across study sessions. This result suggests that there may be a practice effect during the second performance of the SPT, which affects the activation patterns of the hippocampus (Kelly and Garavan, 2005). Therefore, the SPT may not be an ideal task to assess hippocampal activation in a repeated-measures design such as in the present study.

### *LEV duration and dosage*

Two clinical trials administered LEV to normalize hippocampal activation during a hippocampal-dependent pattern-separation task in aMCI patients (Bakker et al., 2015, 2012). Comparing the study design of those trials to our current study reveals two substantial differences. First, LEV was administered for two weeks prior to assessing LEV's impact on hippocampal activity. Second, LEV effectively modulated hippocampal activity and task performance at a dosage of 125mg BID but not at 250mg BID. In this study, we tested the effect of LEV on hippocampal activity after a single administration of 500mg LEV. LEV might not have effectively engaged the hippocampus at this dosing.

### *Using fMRI to test pharmacological hypotheses*

Our results expose some of the difficulties in using fMRI to test pharmacological hypotheses in schizophrenia. First, as we have already detailed, the nature of the illness complicates this type of study. Certain fMRI methods, such as ASL, are not conducive to studying the hippocampus in schizophrenia. Further, there is patient hesitancy in taking a novel medication. Second, using fMRI to detect hippocampal hyperactivity in schizophrenia patients is difficult, evident in the small effect sizes reported (Talati et al., 2014). This difficulty is likely a combination of inconsistent fMRI signal due to the unideal positioning of the hippocampus in the skull (i.e., relative depth compared to cortices and proximity to sinuses), functional (Strange et al., 2014) and structural (Duvernoy et al., 2013) heterogeneity of the hippocampus, and limited imaging resolution. A strength of CBV imaging is hippocampal subfield-specific

resolution, but the requirement of exogenous contrast for this method introduces additional concerns for an already challenging study design.

The molecular mechanisms driving hippocampal hyperactivity are not well understood. Evidence suggests that a contributor to the excitation-inhibition imbalance driving hyperactivity is abnormal neurotransmission (Briend et al., 2020; Lieberman et al., 2018; Tamminga et al., 2010). Based on LEV's mechanism of action as a modulator of neurotransmission at the synaptic protein SV2A, we hypothesized that LEV would modulate the microcircuitry of the hippocampus and normalize the excitation-inhibition imbalance in schizophrenia patients. However, it is unclear whether LEV engaged our target, despite prior studies demonstrating hippocampal engagement in a cohort of patients with aMCI, a precursor to the development of Alzheimer's disease. There is increasing evidence (Kong et al., 2021; Romoli et al., 2021) that the mechanism by which LEV normalizes hippocampal hyperactivity in aMCI is by reducing beta-amyloid plaque deposition (Shi et al., 2013) and the corresponding beta-amyloid-induced glutamate release (Sanz-Blasco et al., 2016). Therefore, the modulation of hippocampal hyperactivity using LEV might occur via a mechanism specific to aMCI and Alzheimer's disease pathology that is not applicable to schizophrenia. Further, recent PET studies have utilized novel ligands to demonstrate alterations in SV2A receptor expression in schizophrenia patients (Onwordi et al., 2020; Radhakrishnan et al., 2021), suggesting that LEV may have altered pharmacological properties in schizophrenia. A more nuanced understanding of the molecular mechanisms underlying hippocampal hyperactivity in schizophrenia will inform the selection of potential pharmacologic agents in future clinical trials.

### *Limitations and future directions*

We have noted several limitations to this study, specifically in the patient cohort, fMRI methods, and study design. Future pharmacologic studies will need to adjust for these limitations. With increasing evidence indicating that hippocampal hyperactivity is dependent on acute illness, recruiting an early psychosis cohort may offer better target engagement. The selection of high-resolution imaging methods that are not potentially compromised by practice effects or antipsychotic use will also better capture group or treatment differences with small effect sizes. Prior clinical trials demonstrate that lower doses of LEV with longer durations of treatment may be more effective at engaging the hippocampus. Therefore, alternative treatment administrations should be considered.

Complimentary imaging methods can also provide evidence, or lack thereof, for target engagement. For example, magnetic resonance spectroscopy can test whether LEV affects hippocampal metabolites. Alterations in hippocampal glutamate after LEV administration would demonstrate target engagement and support LEV's hypothesized mechanism of action as a modulator of neurotransmission. This study presents evidence that LEV differentially affects the BOLD signal when the hippocampus is not engaged in a task during the first study visit. However, the interpretation of this group by treatment interaction is complicated by a potential practice effect during the second SPT session. Future pharmacologic fMRI studies investigating resting-state hippocampal activity using the BOLD signal, such as with ALFF, should be conducted to follow up and verify these results.

## *Conclusions*

This study is the first to test the impact of LEV on hippocampal activity. Our results suggest that at this dosage and treatment duration, LEV does not have an impact on resting-state hippocampal rCBF, as measured using ASL, or hippocampal recruitment, as measured with the BOLD signal during a hippocampal-dependent SPT. Future studies should perform alternate designs and methods in a cohort of schizophrenia patients early in the illness.

## CHAPTER III

### PREVALENCE AND SEVERITY OF INCOMPLETE HIPPOCAMPAL INVERSION IN SCHIZOPHRENIA<sup>2</sup>

#### Introduction

Neuroimaging studies demonstrate several structural and functional abnormalities of the hippocampus in schizophrenia (Brugger and Howes, 2017; Haukvik et al., 2018; Heckers and Konradi, 2010; Talati et al., 2014). The timing of these hippocampal changes is not known. The neurodevelopmental hypothesis of schizophrenia locates the origin of these abnormalities in the prenatal period (Murray et al., 1987; Weinberger, 1987). Therefore, identifying and characterizing markers of atypical hippocampal development will advance our understanding of schizophrenia.

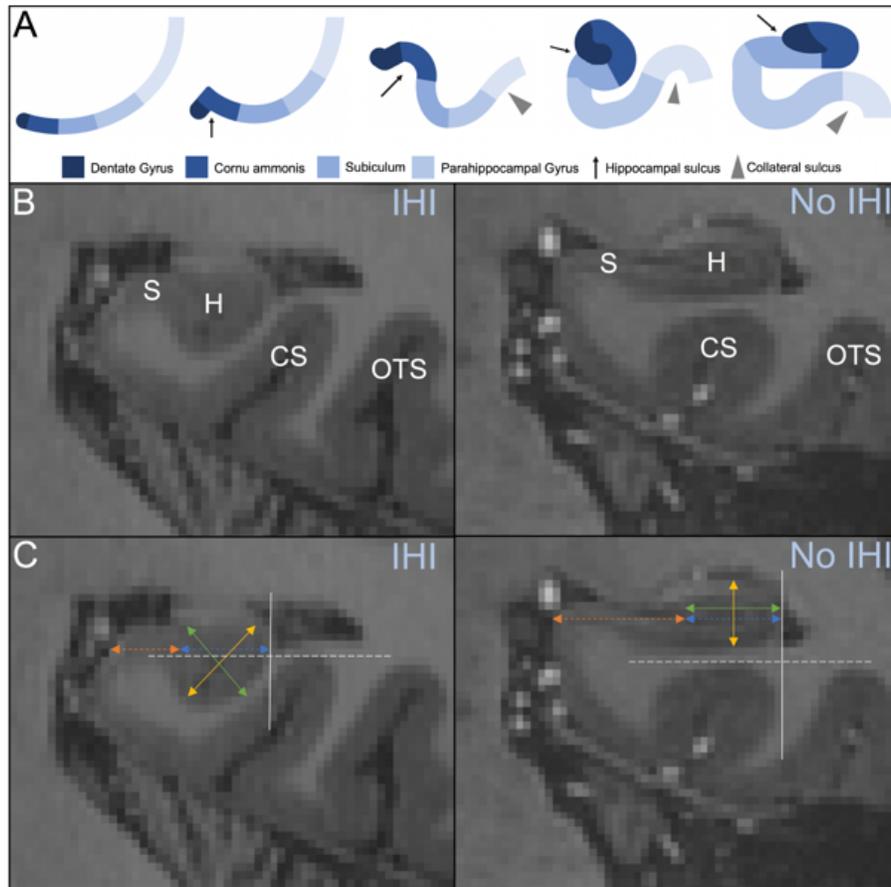
The complex development of the human hippocampus begins at gestational week (GW) 8. During GWs 10-20, the dentate gyrus (DG) and cornu ammonis (CA) are situated in the postero-medial wall of the lateral ventricles and move from the frontal to temporal lobe to surround the hippocampal sulcus (Humphrey, 1967; Kier et al., 1997). Between GWs 20-30, the DG and CA undergo a morphologic inversion around the hippocampal sulcus (Raininko and Bajic, 2010) (**Figure 14**). Failure to complete this inversion process results in an incomplete hippocampal inversion (IHI), an anatomic variant (Hennekam et al., 2013) characterized by a

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<sup>2</sup> This chapter has been adapted from “Incomplete hippocampal inversion in schizophrenia: prevalence, severity, and impact on hippocampal structure”, published in *Molecular Psychiatry* and has been reproduced with the permission of the publisher and my co-authors: M McHugo, S Vandekar, JU Blackford, ND Woodward, and S Heckers.

round, verticalized, medially positioned hippocampal body in the coronal plane and a deep collateral sulcus (Bajic et al., 2008; Baker and Barkovich, 1992; Baulac et al., 1998; Bernasconi et al., 2005; Cury et al., 2015). Prevalence of IHI is high in preterm neonates and decreases to rates comparable to adult populations by GW 25 (Bajic et al., 2010). Healthy individuals with IHI demonstrate altered sulcal patterns outside the medial temporal lobe (Cury et al., 2015). IHI is also associated with several genetic abnormalities and developmental anomalies such as 22q11.2 deletion syndrome (Andrade et al., 2013; Campbell et al., 2006) and corpus callosum agenesis (Atlas et al., 1986). A recent genome wide association study of IHI identified a genome-wide significant locus and revealed that IHI has high heritability (Cury et al., 2020). Taken together, IHI is of interest in the study of neuropsychiatric disorders with a neurodevelopmental profile, including schizophrenia (Cachia et al., 2020).

Prevalence estimates of IHI have varied greatly in previous IHI studies (Atlas et al., 1986; Bajic et al., 2009, 2008; Baker and Barkovich, 1992; Barsi et al., 2000; Baulac et al., 1998; Beker-Acay et al., 2017; Bernasconi et al., 2005; Emery et al., 1999; Fitoz et al., 2003; Lehericy et al., 1995; Montenegro et al., 2006; Riedl et al., 2002; Sato et al., 2001), largely due to inconsistency in defining hippocampal features that constitute an IHI. Recently, Cury et al. established a clear set of quantitative IHI criteria in a large healthy cohort (2015). Subsequent studies using these criteria reported consistent prevalence estimates and findings (Colenutt et al., 2018; Colle et al., 2016). Employing the Cury criteria, the prevalence of IHI can now be reliably assessed in neuropsychiatric disorders such as schizophrenia.



**Figure 14. Incomplete hippocampal inversion.**

(A.) Developmental process of the hippocampus from one layer of cortical mantle through early inversion (rounded, verticalized hippocampus with deep collateral sulcus) and late inversion (flat, horizontal hippocampus with shallow collateral sulcus). Arrest in hippocampal development (at Step 4) results in IHI. (B.) 7T MRI coronal view of an incomplete (left) and complete (right) hippocampal inversion. The hippocampus (H), subiculum (S), collateral sulcus (CS), and occipitotemporal sulcus (OTS) are used as anatomical landmarks to identify IHI. (C.) Criterion 1 is evaluated by comparing the width of the hippocampus (green, solid line) with the height of the hippocampal body (yellow, solid line). The grey, solid line indicates the lateral limit of the hippocampus, which is used for criterion 2. Criterion 3 is measured by comparing the length of the subiculum not covered by the dentate gyrus (orange, dotted line) with the ventral part of the cornu ammonis/subiculum that is covered by the dentate gyrus (blue, dotted line). Criterion 4 is measured using the thickness of the subiculum. The grey, dotted line located at the deepest portion of the CS or OTS is used to evaluate criterion 5.

Two previous studies have investigated an incomplete development of the hippocampus in schizophrenia. The first reported an increased prevalence of moderate and severe forms in familial schizophrenia patients when compared to control participants (Connor et al., 2004). Importantly, this study reported only a qualitative anomaly (hippocampus appeared rounder or more pyramidal). The second study employed Cury's IHI criteria in a schizophrenia cohort and reported that patients with visual hallucinations possessed more IHI-specific morphological patterns than patients with only auditory hallucinations and healthy control participants (Cachia et al., 2020). However, the authors only measured a single IHI criterion (i.e., criterion 1, hippocampal flatness) in a small patient sample. Therefore, the prevalence of IHI in schizophrenia is unknown.

In this study, we examined IHI in a large cohort of patients with schizophrenia spectrum disorders and healthy control participants, using comprehensive and quantitative criteria. We aimed to answer two questions. First, is the prevalence of IHI increased in schizophrenia? Second, is IHI more severe in schizophrenia?

## **Methods**

### *Participants*

Participants in this study included 199 patients with schizophrenia spectrum disorder diagnoses (86 schizophreniform disorder, 77 schizophrenia, 36 schizoaffective disorder; referred to here as *schizophrenia patients*) and 161 healthy control participants matched to patients on age, sex, race, and parental education (**Table 6**). Schizophrenia patients were recruited from the inpatient unit and outpatient clinics of the Vanderbilt University Medical

Center Psychotic Disorders Program as part of an ongoing data repository, the Psychiatric Phenotype/Genotype Project (PGPP) (NCT00762866). Healthy control participants were recruited from the local community via advertisement. The study was approved by the Vanderbilt University Institutional Review Board. All participants provided written informed consent and were compensated for their time. The Structured Clinical Interview for DSM-IV was used for diagnostic assessment (First et al., 2002). Participant exclusion criteria include significant medical or neurological illness, age under 16 or over 65 years, pregnancy, head injury, or meeting criteria for substance abuse within the past month. Healthy control participants were excluded if they had a current or past psychiatric illness, a first degree relative with a psychotic illness, or psychotropic drug use. All participants with a T1-weighted MRI scan without motion artifact were selected from the PGPP repository for inclusion in this study.

#### *MRI acquisition and processing*

Structural MRI acquisition was completed on a 3T Philips Intera Achieve MRI scanner at the Vanderbilt University Institute of Imaging Sciences (Philips Healthcare, Inc.). Each participant received a 3D T1-weighted scan (voxel resolution:  $1\text{mm}^3$ ; field of view =  $256^2$ ; number of slices = 170; TE = 3.7ms; TR = 8.0ms). Each image was visually inspected and determined to be free from motion or other artifacts prior to inclusion in the analysis. All images were reoriented toward the MNI152 atlas using FSL rigid body transformation (Jenkinson et al., 2002).

**Table 6.** Chapter III and IV participant demographics and clinical characteristics

	Healthy Control Participants N = 161		Schizophrenia Patients N = 199		Healthy Control Participants > Schizophrenia Patients	
	Mean	SD	Mean	SD	Statistic (t)	p
<b>Age (yrs)</b>	33.59	11.35	35.45	13.29	-1.41	0.16
<b>Parental Education (yrs)</b>	14.45	2.35	14.44	2.76	0.01	0.99
<b>WTAR</b>	111.02	11.30	98.94	16.28	-7.84	<b>&lt;0.001</b>
<b>CPZ Equivalents</b>			418.48	258.22		
<b>Duration of Illness (yrs)</b>			7.70	11.35		
	N	%	N	%	Statistic (X <sup>2</sup> )	p
<b>Gender (Male)</b>	106	66	143	72	1.51	0.22
<b>Race (White)</b>	114	71	126	63	2.25	0.13
<b>AUD</b>	11	7	55	28		
<b>CUD</b>	4	2	91	46		
<b>Tobacco Use</b>						
No	130	81	89	45		
Yes, continued	16	10	81	41		
Yes, quit	14	9	29	15		
Missing	1	<1	0	0		
<b>Diagnosis</b>						
Schizophreniform DO			86	43		
Schizophrenia			77	39		
Schizoaffective DO			36	18		

Key: yrs = years; WTAR = Wechsler Test of Adult Reading; CPZ = Chlorpromazine; AUD = Alcohol

Use Disorder; CUD = Cannabis Use Disorder; DO = Disorder

### *Assessment of incomplete hippocampal inversions*

The criteria used to determine the severity of IHI in this study were validated in a study by Cury et al. in 2,089 participants. The IHI score for each hippocampus ranges from 0 – 10. IHI presence was defined based on a score of  $\geq 3.75$  (Cury et al., 2015). IHI was assessed by two observers after training. Both observers were blinded to the subject group (schizophrenia patients, healthy control participants) when assessing IHI. Ten of these individuals were randomly selected to evaluate intra- and inter-observer reproducibility using the kappa statistic (Viera and Garrett, 2005). Cohen's kappa indicated very strong ( $\text{kappa} = 0.88$ ) intra-observer and substantial ( $\text{kappa} = 0.76$ ) inter-observer reliability, consistent with the findings of Cury et al. (2015). All criteria were obtained in the coronal view for both the left and right hippocampus using ITK-SNAP (Version 3.6.0). Criteria are summarized in **Figure 14B,C**.

#### Criterion 1: Verticality and roundness of the hippocampal body

Two different measurements are used to determine the roundness of the hippocampus. A segment from the medial part of the DG to the lateral part of the CA/subiculum is measured as the width of the hippocampus. Following this segment, a perpendicular segment is measured from the dorsal part of the hippocampus to the ventral part of the CA. This second segment represents the height of the hippocampus. Three levels of hippocampal roundness can then be determined: flat (width > height), round (width = height), or oval (width < height). The width segment of the hippocampus is used to determine hippocampal verticality on three levels: horizontal (segment is horizontal), vertical (segment is vertical), or oblique (neither horizontal nor vertical). After determining both roundness and verticality, a grade of 0 – 2 is assigned.

#### Criterion 2: Collateral sulcus

To assess the verticality and depth of the collateral sulcus, a grade is assigned based on its orientation (horizontal, oblique, or vertical) and whether the sulcus crosses the lateral limit of the hippocampus. A grade of 0 – 2 is assigned.

#### Criterion 3: Medial positioning

The length of the part of the subiculum that is not covered by the DG is measured relative to the ventral part of the CA/subiculum that is covered by the DG to determine how medial the hippocampus is positioned. A grade from 0 – 2 is made on five levels, where 0 is most lateral and 2 is most medial. This rating also accounts for temporal horn volume.

#### Criterion 4: Subiculum

A subiculum is abnormal if it is bulging upward, appearing thickened. It is then assigned a grade of 2. Otherwise, the subiculum is normal and is assigned a grade of 0.

#### Criterion 5: Sulci of the fusiform gyrus

The occipitotemporal sulcus (OTS) separates the occipitotemporal gyrus from the inferior temporal gyrus. Abnormal morphology of the OTS is associated with IHI, similar to the collateral sulcus (criterion 2). Criterion 5 takes both the collateral sulcus and OTS into account

by assigning a grade of 0, 1, or 2 based on the depth of each sulcus. For example, if either sulcus is deep enough to cross the level of the subiculum, a grade of 2 is assigned.

### *Statistical analyses*

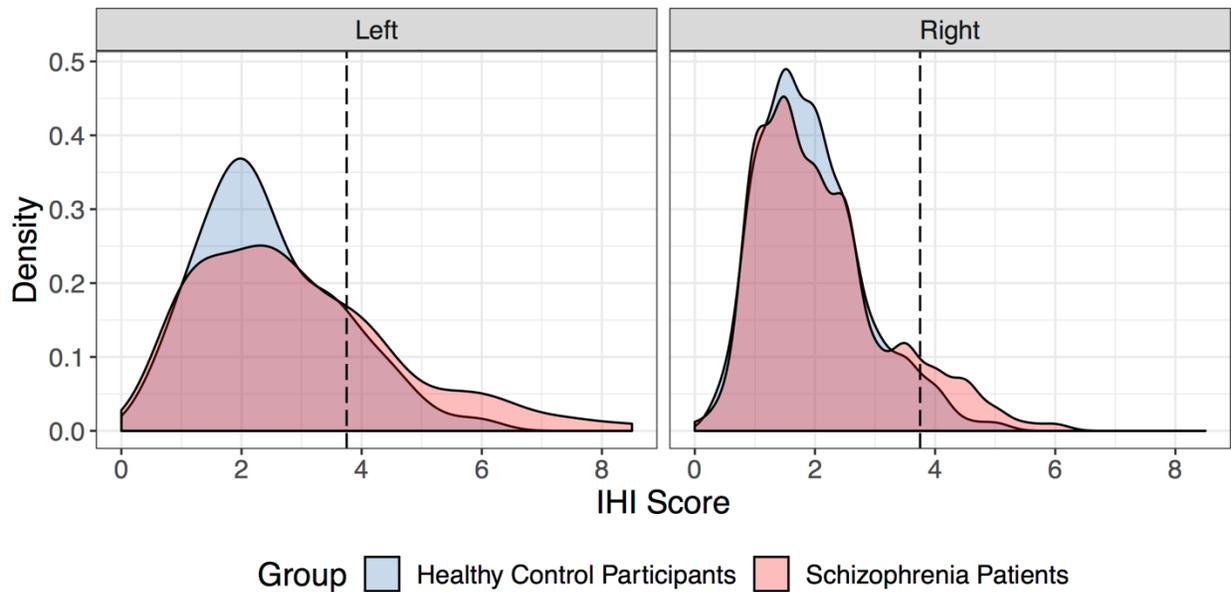
A  $\chi^2$  test was performed on the IHI threshold score ( $\geq 3.75$ ) for each hemisphere to test whether IHI is more prevalent in schizophrenia patients than healthy control participants. A t-test was performed on the continuous IHI score (0-10) for each hemisphere to test whether IHI is more severe (i.e., the total IHI score is greater) in schizophrenia patients than in healthy control participants. A sub-analysis of individual criteria was assessed with t-tests in each hemisphere, and corrected for multiple comparisons using the Bonferroni method, to test which criterion differed between schizophrenia patients and healthy control participants. For all statistical methods in this study, tests were two-sided and the significance level was defined as  $\alpha < 0.05$ . For some IHI criteria, there was a significant difference between the variance of groups being compared. Therefore, we used Welch's unequal variance t-test, due to its reliability for samples with unequal variances or unequal sample sizes, for all t-tests completed in this study.

### **Results**

In our sample of 360 individuals (199 schizophrenia patients, 161 healthy control participants), we found 57 (16% of the total sample) unilateral left IHI (38 schizophrenia patients, 19 healthy control participants), 21 (6%) bilateral IHI (16 schizophrenia patients, 5

healthy control participants), and 6 (2%) unilateral right IHI (4 schizophrenia patients, 2 healthy control participants) cases. The remaining 276 participants (77%) showed no IHI.

Schizophrenia patients had more frequent IHI in both the left ( $\chi^2 = 7.84$ ,  $p < 0.01$ ) and right ( $\chi^2 = 4.17$ ,  $p = 0.04$ ) hemisphere (**Figure 15, Table 7**). IHI severity, as measured by the total IHI score, was significantly greater in the left ( $t_{351} = 3.00$ ,  $p < 0.01$ ) but not right ( $t_{358} = 1.60$ ,  $p = 0.11$ ) hemisphere in schizophrenia. Criterion 3 scores, which reflect the medial positioning of the hippocampus, were significantly greater for schizophrenia patients in the left hemisphere ( $t_{343} = 3.28$ ,  $p < 0.01$ ) after correction for multiple comparisons. No other criteria differed between groups in either hemisphere (**Table 7**).



**Figure 15. Distribution of IHI scores based on laterality of the hippocampus in both schizophrenia patients and healthy control participants.**

The density indicates the percent of total hippocampi that have a specific score attributed to them. The dashed line at a score of 3.75 designates the threshold used to define an IHI based on Cury et al (Cury et al., 2015). The prevalence of IHI in schizophrenia patients compared to healthy control participants is greater in the left hemisphere (left panel;  $\chi^2 = 7.84$ ,  $p < 0.01$ ) and right hemisphere (right panel,  $\chi^2 = 4.17$ ,  $p = 0.04$ ).

**Table 7. IHI prevalence and severity**

	Healthy Control Participants		Schizophrenia Patients		Healthy Control Participants < Schizophrenia Patients	
	N = 161		N = 199		Statistic ( $\chi^2$ )	p
	N	%	N	%		
<b>Left IHI</b>	24	15	54	27	7.84	<b>0.005</b>
<b>Right IHI</b>	7	4	20	10	4.17	<b>0.04</b>
	Mean	SD	Mean	SD	Statistic (t)	p
<b>Left IHI Score</b>	2.46	1.17	2.91	1.68	3.00	<b>0.003</b>
C1	0.45	0.38	0.56	0.51	2.40	0.08 <sup>1</sup>
C2	1.02	0.56	1.06	0.58	0.65	1.00 <sup>1</sup>
C3	0.51	0.39	0.68	0.60	3.28	<b>0.006<sup>1</sup></b>
C4	0.00	0.00	0.04	0.28	2.02	0.23 <sup>1</sup>
C5	0.48	0.63	0.57	0.68	1.28	1.00 <sup>1</sup>
<b>Right IHI Score</b>	1.95	0.87	2.11	1.10	1.60	0.11
C1	0.38	0.31	0.37	0.36	0.25	1.00 <sup>1</sup>
C2	0.95	0.51	0.95	0.51	0.05	1.00 <sup>1</sup>
C3	0.46	0.39	0.57	0.53	2.23	0.13 <sup>1</sup>
C4	0.00	0.00	0.00	0.00	N/A	N/A
C5	0.16	0.37	0.23	0.49	1.43	0.77 <sup>1</sup>

Key: IHI = Incomplete Hippocampal Inversion; <sup>1</sup> = p-value adjusted for multiple comparisons

using Bonferroni method

## Discussion

Our study of 360 participants shows that IHI is significantly more prevalent and severe in schizophrenia. To our knowledge, this is the first analysis of IHI in schizophrenia patients using a comprehensive set of quantitative and validated criteria (Cury et al., 2015).

IHI was more prevalent in schizophrenia patients in both the left and right hemisphere. Since IHI is the result of arrested brain development (Bajic et al., 2012), our finding is consistent with the neurodevelopmental hypothesis of schizophrenia (Marenco and Weinberger, 2000; Weinberger, 1995). The right hippocampus completes inversion before the left hippocampus during GW 20-30 (Bajic et al., 2012). Therefore, our finding of left > right IHI in schizophrenia is consistent with previous IHI studies (Colenutt et al., 2018; Colle et al., 2016; Cury et al., 2015) and maps the changes in schizophrenia to a later stage in hippocampal development.

IHI was more severe in the left hemisphere of schizophrenia patients. We found that criterion 3, i.e., the medial positioning of the hippocampus, differed most significantly between the two groups. This finding suggests a reduction in the width of the hippocampal body in schizophrenia. Numerous shape analyses conducted on the hippocampus of schizophrenia patients have described inward displacements on the medial or lateral surfaces of the left hippocampal head (Csernansky et al., 2002; Lee et al., 2004; Shenton et al., 2002), body (Kalmady et al., 2017; Lee et al., 2004; Mamah et al., 2012), and tail (Mamah et al., 2012; Styner et al., 2004); however, whether IHI contributes to these findings is unknown. Future studies are needed to investigate the impact of IHI on shape differences observed between healthy control participants and schizophrenia patients.

Our study has several limitations. First, IHI criteria were only measured in the coronal view of the hippocampal body; therefore, IHI patterns located in the hippocampal head cannot be captured using the established protocol we used here (Cury et al., 2015). Second, we did not examine the prevalence of other anatomic variants within the hippocampus (Maller et al., 2013) or in other brain structures associated with IHI (Atlas et al., 1986; Cury et al., 2015). Future studies investigating the co-occurrence of IHI with other morphological variants will provide additional evidence that IHI is a marker of atypical development in schizophrenia and help determine the timing of developmental disruption. Lastly, we did not assess whether participants had a history of obstetric complications (i.e., a trigger for aberrant *in utero* development). Evidence suggests that obstetric complications may mediate hippocampal volume reductions in both healthy control participants and schizophrenia patients (Ho and Magnotta, 2010), and increase schizophrenia susceptibility (T. D. Cannon et al., 2002). Future studies should collect obstetric information to better elucidate the relationship between IHI and obstetric complications.

## **Conclusions**

In conclusion, our finding of more prevalent and more severe IHI supports the neurodevelopmental hypothesis of schizophrenia. The impact of this developmental variant deserves further exploration in studies of the hippocampus in schizophrenia.

## CHAPTER IV

### THE IMPACT OF INCOMPLETE HIPPOCAMPAL INVERSION ON HIPPOCAMPAL VOLUME AND SHAPE IN SCHIZOPHRENIA<sup>3</sup>

#### Introduction

Decades of research have revealed alterations of hippocampal structure in individuals with schizophrenia. Meta-analyses, synthesizing the results of post-mortem and neuroimaging studies, display deficits in hippocampal volume in both early and chronic stages of the illness (Adriano et al., 2012; Brugger and Howes, 2017; Haukvik et al., 2018; Roeske et al., 2021a). The hippocampus shows the largest volume reduction of all subcortical regions in schizophrenia (van Erp et al., 2016). Additionally, studies of subcortical structures consistently show hippocampal shape differences in schizophrenia (Gutman et al., 2021; Li et al., 2015; Mamah et al., 2016). Shape deformities are present in both early (Mamah et al., 2012; Narr et al., 2004; Qiu et al., 2013; Sauras et al., 2017; Tang et al., 2020) and chronic stages of the illness (Csernansky et al., 2002, 1998b; Guimond et al., 2021; Kalmady et al., 2017; Lee et al., 2004; Li et al., 2015; Mamah et al., 2016; Narr et al., 2001; Prestia et al., 2015; Qiu et al., 2010; Smith et

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<sup>3</sup> Part of this chapter has been adapted from “Incomplete hippocampal inversion in schizophrenia: prevalence, severity, and impact on hippocampal structure”, published in *Molecular Psychiatry* and has been reproduced with the permission of the publisher and my co-authors: M McHugo, S Vandekar, JU Blackford, ND Woodward, and S Heckers. This chapter has also been adapted from “Incomplete hippocampal inversion: a neurodevelopmental mechanism for hippocampal shape deformation in schizophrenia”, published in *Biological Psychiatry* and has been reproduced with the permission of the publisher and my co-authors: I Lyu, M McHugo, JU Blackford, ND Woodward, and S Heckers.

al., 2011; Styner et al., 2004; Tepest et al., 2003; Zierhut et al., 2013). These studies also report abnormalities in right > left asymmetries of hippocampal volume and shape (Shenton et al., 2002; Wang et al., 2001).

Despite the compelling evidence for hippocampal structural deformities in schizophrenia, the anatomical details are not clear. The anatomy of the hippocampus is complex, reflecting specialization of cellular layers, circuitry, and function (Haukvik et al., 2018). The hippocampal formation can be divided into three segments along the anterior-posterior axis (i.e., head, body, tail) and, using coronal sections, into the dentate gyrus (DG), the Cornu Ammonis (CA) 1-4 subfields, and the subiculum (Duvernoy et al., 2013). Several volumetric studies have reported volume reductions in the CA1 (Narr et al., 2004; Zierhut et al., 2013; Ho et al., 2017) subfield, and others have indicated deficits in the CA2/3, CA4/DG, and subiculum (Mathew et al., 2014; Haukvik et al., 2015). The majority of shape deformation studies have suggested surface deformations in the CA1 subfield (Csernansky et al., 2002; Gutman et al., 2021; Kalmady et al., 2017; Mamah et al., 2016, 2012; Narr et al., 2004; Prestia et al., 2015; Sauras et al., 2017; Tang et al., 2020; Zierhut et al., 2013), although there are reports of deformations in the CA2 (Mamah et al., 2012; Narr et al., 2004; Prestia et al., 2015; Sauras et al., 2017; Tang et al., 2020) and CA3 (Mamah et al., 2012; Prestia et al., 2015) subfields and subiculum (Gutman et al., 2021; Kalmady et al., 2017; Mamah et al., 2016, 2012; Prestia et al., 2015). Of note, shape analyses using a surface reconstruction are limited in their ability to detect changes in the CA4/DG subfields because the CA1, CA2, and CA3 subfields and subiculum dominate the topography of the hippocampal surface (Zierhut et al., 2013). Discrepancies in results are likely the result of divergent analytic methods, differences in study populations, and

small sample sizes. Converging evidence from first episode psychosis and individuals at clinical high-risk for psychosis (CHR-P) suggests that volumetric and shape alterations begin in the anterior hippocampus (McHugo et al., 2020), particularly in the CA1 subfield (Ho et al., 2017; Lieberman et al., 2018), and spread to involve other regions over the course of the illness (Ho et al., 2017; Mamah et al., 2012).

Furthermore, it is not clear whether hippocampal volume and shape abnormalities in schizophrenia are a sign of disease progression or an antecedent risk factor. Some studies have suggested that CA1 structural alterations result from localized hyperactivity present before the onset of illness, leading to a neurotoxic effect (Lieberman et al., 2018; Schobel et al., 2009; Zierhut et al., 2013). However, structural abnormalities of the hippocampus in schizophrenia could also result from atypical brain development, possibly due to pathological events during the perinatal period (Marenco and Weinberger, 2000).

Incomplete hippocampal inversion (IHI) is more prevalent and severe in individuals with schizophrenia (Roeske et al., 2021b). IHI is the result of an arrest in brain development, primarily during the second trimester, when the DG and CA undergo a morphologic inversion around the hippocampal sulcus (Bajic et al., 2010). Therefore, IHI serves as a neurodevelopmental marker that can be traced to a specific perinatal window. IHI is characterized by a round, verticalized, medially positioned hippocampal body in the coronal plane and a deep collateral sulcus (Cury et al., 2015). Whether IHI affects hippocampal volume and shape in the healthy brain or contributes to structural differences between healthy control participants and patient groups (e.g., schizophrenia) needs to be explored further.

Two studies have investigated the effect of IHI on hippocampal volume using recently established criteria (Cury et al., 2015). The first study characterized IHI in 60 participants with a major depressive episode and 60 matched healthy control participants and reported no significant volume differences between groups (Colle et al., 2016). Additionally, the hippocampal volumes of participants with IHI did not differ from those without the variant. In a second study analyzing a healthy, aging cohort, the authors reported that participants with IHI do not differ in whole hippocampal volume, but show decreased subfield volumes, namely CA1 (Colenutt et al., 2018). IHI is more frequent in the left (17%) than the right (6%) hemisphere (Cury et al., 2015) in healthy control participants. The left hippocampus develops more slowly than the right hippocampus, making it more likely for a developmental arrest to result in a unilateral left IHI (Bajic et al., 2012). The increased prevalence of IHI in the left hemisphere may be related to some of the hemispheric asymmetries in the human brain (Bernasconi et al., 2005; Geschwind and Galaburda, 1985), including the right > left hippocampal volume difference that is most prominent in the anterior hippocampus (Pedraza et al., 2004; Shi et al., 2009; Woolard and Heckers, 2012).

No study has investigated the effect of IHI on hippocampal shape. Shape analyses are well suited to explore questions about hippocampal neurodevelopment and the neurobiology of schizophrenia (Ho and Magnotta, 2010; Sauras et al., 2017). Evidence suggests that the physical tension of brain growth during neurodevelopment is associated with shape deformations (van Essen, 1997), and that resulting developmental abnormalities can be characterized using shape measures (Thompson et al., 2000). This is particularly relevant for the shapes of anisotropic brain structures such as the hippocampus, which are thought to be

influenced by physical properties of neural tissue and patterns of neural activity (Csernansky et al., 1998b). Indeed, reports of hippocampal shape deformations in cohorts of schizophrenia patients have been hypothesized to result from neurodevelopmental disruptions (Ho and Magnotta, 2010; Shenton et al., 2002). Sibling studies have also indicated that hippocampal shape deformations may be trait markers (Johnson et al., 2013), as unaffected siblings or young relatives of schizophrenia patients demonstrate anterior hippocampal inward deformations (Ho and Magnotta, 2010; Tepest et al., 2003).

Here we aimed to answer four questions to advance a neurodevelopmental explanation of hippocampal structural differences in schizophrenia. First, does IHI contribute to hippocampal volume differences in schizophrenia, including right > left volume asymmetry? Second, can we replicate well-documented shape differences in a large cohort of patients with schizophrenia spectrum disorders and healthy control participants, particularly in the anterolateral hippocampus, where the CA1 subfield is located? Third, does IHI have an impact on hippocampal shape? Fourth, can we use IHI, a neurodevelopmental variant established *in utero*, to explain shape differences reported in schizophrenia?

## **Methods**

### *Participants*

Participants in this study included 199 patients with schizophrenia spectrum disorder diagnoses (86 schizophreniform disorder, 77 schizophrenia, 36 schizoaffective disorder; referred to here as *schizophrenia patients*) and 161 healthy control participants matched to patients on age, sex, race, and parental education (**Table 6**). The majority of the 86

schizophreniform disorder patients were followed for 2 years and final diagnoses were: 38 schizophreniform disorder (44.2% of the original diagnoses), 41 schizophrenia (47.7%), and 7 schizoaffective disorder (8.1%). Therefore, our schizophrenia spectrum disorder sample is primarily a schizophrenia cohort (118 out of 199, 59.3%). IHI prevalence and severity differed in both groups (**Table 7**). Schizophrenia patients were recruited from the inpatient unit and outpatient clinics of the Vanderbilt University Medical Center Psychotic Disorders Program as part of an ongoing data repository, the Psychiatric Phenotype/Genotype Project (PGPP) (NCT00762866). Healthy control participants were recruited from the local community via advertisement. The study was approved by the Vanderbilt University Institutional Review Board. All participants provided written informed consent and were compensated for their time. The Structured Clinical Interview for DSM-IV was used for diagnostic assessment (First et al., 2002). Participant exclusion criteria include significant medical or neurological illness, age under 16 or over 65, pregnancy, head injury, or meeting criteria for substance abuse within the past month. Healthy control participants were excluded if they had a current or past psychiatric illness, a first degree relative with a psychotic illness, or psychotropic drug use. All participants with a T1-weighted MRI scan without motion artifact were selected from the PGPP repository for inclusion in this study.

### *MRI acquisition and processing*

Structural MRI acquisition was completed on a 3T Philips Intera Achieve scanner at the Vanderbilt University Institute of Imaging Sciences (Philips Healthcare, Inc.). Participants received a 3D T1-weighted scan (voxel resolution: 1mm<sup>3</sup>; field of view = 256<sup>2</sup>; number of slices

= 170; TE = 3.7ms; TR = 8.0ms). All images were visually inspected and determined to be free from motion or other artifacts prior to inclusion in the analysis.

Each image was processed using the Freesurfer 6 (Dale et al., 1999; Fischl et al., 2002) hippocampal subfield module (Iglesias et al., 2015) with standard parameters. Segmentations were visually inspected to correct those with tissue labeled outside the hippocampus or incomplete labeling of the hippocampus. Automated segmentation failed because of two major errors: 1) hippocampal segmentation extending beyond the border of the hippocampus into surrounding structures and 2) amygdala segmentation extending into the hippocampal head. To maximize study inclusion, automated segmentation failures were corrected by manually deleting segmented voxels extending outside of the hippocampus or by manually replacing amygdala segmentation voxels with hippocampal head segmentation voxels at the amygdala-hippocampal border. Manual voxel correction was completed using ITK-SNAP version 3.8.0 (Yushkevich et al., 2006). Volume data from all participants were included in a previous study (McHugo et al., 2018).

### *Hippocampal surface processing*

Shape analysis was completed using the SPHARM-PDM toolkit (Brechtbuhler et al., 1995; Styner et al., 2004) to generate hippocampal surfaces and their initial spherical mapping and correspondence. A detailed description of this methodology is available in Styner et al. (Styner et al., 2004). We then adapted spherical surface registration proposed in Lyu et al. (Lyu et al., 2019) to further refine the initial shape correspondence in a group-wise manner that estimates an unbiased representative (average) surface of the cohort. High-resolution hippocampal

surfaces were generated with 40,962 vertices per hemisphere via a standard icosahedral subdivision (Baumgardner and Frederickson, 1985). The local shape variation of each participant's hippocampal surface was calculated from the cohort average of all participants by quantifying the perpendicular distance between surfaces at a vertex-to-vertex level. The quantification of perpendicular change between surfaces was assigned a positive (outward displacement from cohort average) or negative (inward displacement from cohort average) value.

#### *Volumetric statistical analyses*

A  $\chi^2$  test was performed on the IHI threshold score ( $\geq 3.75$ ) for each hemisphere to test whether IHI is more prevalent in schizophrenia patients than healthy control participants. A t-test was performed on the continuous IHI score (0-10) for each hemisphere to test whether IHI is more severe (i.e., the total IHI score is greater) in schizophrenia patients than in healthy control participants. A sub-analysis of individual criteria was assessed with t-tests in each hemisphere, and corrected for multiple comparisons using the Bonferroni method, to test which criterion differed between schizophrenia patients and healthy control participants. These statistical tests were replicated to examine differences between participants with successful and failed automated segmentations. For all statistical methods in this study, tests were two-sided and the significance level was defined as  $\alpha < 0.05$ . For some IHI criteria, there was a significant difference between the variance of groups being compared. Therefore, we used Welch's unequal variance t-test, due to its reliability for samples with unequal variances or unequal sample sizes, for all t-tests completed in this study.

To examine the effect of IHI on hippocampal volume and asymmetry group differences, a two-step sensitivity analysis was conducted using linear mixed models in R (R Core Team, 2019) with the packages lme4 (Bates et al., 2015), emmeans (Lenth, 2018), car (Fox and Weisberg, 2011), and MuMIn (Barton, 2020). In Step 1, models comparing schizophrenia patient and healthy control groups were fitted by adjusting for estimated intracranial volume (ICV), Age, and Sex, with Participant as a random effect. To test whether there is a difference in hippocampal volume in the schizophrenia patient cohort versus healthy participant cohort, a model was constructed with Volume as the dependent variable and interaction between Group (schizophrenia patient, healthy control participant) and Hemisphere (left, right) as fixed effects (Volume Model, Step 1:  $\text{Volume} \sim \text{Group} * \text{Hemisphere} + \text{Age} + \text{Sex} + \text{ICV} + (1 | \text{Participant})$ ). The Group by Hemisphere interaction and main effect of Group was tested using Type 2 sum of squares. To test the hypothesis that there is an asymmetry difference in the anterior or posterior regions of the hippocampus in the schizophrenia patient cohort, a separate model was constructed with Asymmetry Index as the dependent variable and the interaction between Group (schizophrenia patient, healthy control participant) and Region (anterior, posterior) as fixed effects (Asymmetry Index Model, Step 1:  $\text{Asymmetry Index} \sim \text{Group} * \text{Region} + \text{Age} + \text{Sex} + \text{ICV} + (1 | \text{Participant})$ ). The Group by Region interaction and main effect of Group was tested using Type 2 sum of squares. The volume asymmetry index was calculated using the equation:  $\text{Asymmetry Index} = (\text{Right} - \text{Left}) / (0.5 * (\text{Right} + \text{Left}))$ .

In Step 2, IHI was added as a fixed effect to both models to test whether IHI contributes to volume or the asymmetry index (Volume Model, Step 2:  $\text{Volume} \sim \text{Group} * \text{Hemisphere} + \text{IHI} + \text{Age} + \text{Sex} + \text{ICV} + (1 | \text{Participant})$ ; Asymmetry Index Model, Step 2:  $\text{Asymmetry Index} \sim$

Group\*Region + IHI + Age + Sex + ICV + (1 | Participant)). Exploratory analyses including a Group by IHI interaction were conducted to investigate whether IHI has a different effect on Volume or Asymmetry Index in each group (Volume Model:  $\text{Volume} \sim \text{Group} * \text{Hemisphere} + \text{Group} * \text{IHI} + \text{Age} + \text{Sex} + \text{ICV} + (1 | \text{Subject})$ ; Asymmetry Index Model:  $\text{Asymmetry Index} \sim \text{Group} * \text{Region} + \text{Group} * \text{IHI} + \text{Age} + \text{Sex} + \text{ICV} + (1 | \text{Subject})$ ). Significance tests were conducted on the fixed effects using analysis of variance (ANOVA) with Type 2 sum of squares so that the main effects were tested in the absence of the interaction terms. Significant interactions were followed up with contrasts adjusted for multiple comparisons using Bonferroni correction. Marginal  $R^2$  and AIC were calculated for models in Step 1 and Step 2 to assess model fit.

### *Shape statistical analyses*

To test our hypotheses, shape variation of hippocampal surfaces was examined in surface-based analyses performed using SurfStat (Worsley et al., 2009) implemented in MATLAB (MatLab 2019a). The left and right hippocampus were analyzed separately. Random field theory (RFT) was applied using SurfStat to account for multiple comparisons. To identify significant clusters using RFT, an initial height threshold of  $p \leq 0.01$  was implemented at the vertex level, and a corrected family-wise error ( $p \leq 0.05$ ) was subsequently applied. T-values generated from SurfStat analyses were converted to effect sizes (Cohen's  $d$ ) using R (R Core Team, 2019) package `compute.es` (Del Re, 2013).

To replicate previous findings demonstrating hippocampal shape differences between schizophrenia patients and healthy control participants, displacement values were regressed

onto Group (schizophrenia patient, healthy participant) using a general linear model adjusted for estimated ICV, Age, and Gender (Displacement  $\sim$  Group + ICV + Age + Gender).

To determine whether hippocampal shape is impacted by IHI, displacement values were regressed onto IHI severity scores using a general linear model fitted by adjusting for ICV, Age, and Gender (Displacement  $\sim$  IHI + ICV + Age + Gender). To determine whether hippocampal shape of healthy control participants is impacted by IHI, displacement values were regressed onto IHI severity scores using a general linear model fitted by adjusting for ICV, Age, and Gender (Displacement  $\sim$  IHI + ICV + Age + Gender) after restricting the shape analysis to the 161 healthy individuals included in the study.

To test the contribution of IHI to shape differences between schizophrenia patients and healthy control participants, displacement values were regressed onto Group and IHI score using a general linear model fitted by adjusting for ICV, Age, and Gender (Displacement  $\sim$  Group + IHI + ICV + Age + Gender).

We collected the lifetime history of substance use disorders for individuals included in this study. To eliminate potential confounds of substance use disorder on our hippocampal shape results, we repeated our analyses using a history of alcohol use disorder (AUD) and cannabis use disorder (CUD) as covariates in our general linear models. We first tested for hippocampal shape differences between healthy participants and schizophrenia patients by regressing displacement values onto Group using a linear model adjusted for ICV, Age, Gender, AUD, and CUD (Displacement  $\sim$  Group + ICV + Age + Gender + AUD + CUD). We then tested the contribution of IHI to shape differences between healthy participants and schizophrenia patients, regressing displacement values onto Group and IHI score using a linear model fitted by

adjusting for ICV, Age, Gender, AUD, and CUD (Displacement ~ Group + IHI + ICV + Age + Gender + AUD + CUD).

## Results

### *Hippocampal segmentation*

Automated segmentation of the hippocampus failed in 48 individuals (30 schizophrenia patients, 18 healthy control participants), of which 30 participants had IHI (16 unilateral left, 11 bilateral, 3 unilateral right) (**Table 8**). The prevalence of IHI in segmentation failure was significantly greater in both the left ( $\chi^2 = 39.03$ ,  $p < 0.001$ ) and right ( $\chi^2 = 37.48$ ,  $p < 0.001$ ) hemispheres (**Table 9**). Participants with failed segmentations had higher total left ( $t_{52} = 6.09$ ,  $p < 0.001$ ) and right IHI scores ( $t_{55} = 4.08$ ,  $p < 0.001$ ) than participants with successful segmentations. Multiple criteria contributed to the total score group differences. Criterion 1 ( $t_{58} = 2.74$ ,  $p = 0.04$ ), 2 ( $t_{65} = 3.99$ ,  $p < 0.001$ ), 3 ( $t_{54} = 5.56$ ,  $p < 0.001$ ), and 5 ( $t_{58} = 5.08$ ,  $p < 0.001$ ) significantly differed between segmentation successes and failures in the left hemisphere. Criterion 3 ( $t_{55} = 4.25$ ,  $p < 0.001$ ) and 5 ( $t_{54} = 3.20$ ,  $p < 0.001$ ) differed in the right hemisphere. Participants with failed segmentations also had higher parental education ( $t_{61} = 2.34$ ,  $p = 0.02$ ) and higher estimated premorbid intellectual functioning ( $t_{66} = 2.37$ ,  $p = 0.02$ ), but did not differ with respect to diagnosis (i.e., schizophrenia patient vs healthy control participant) ( $\chi^2 = 1.17$ ,  $p = 0.28$ ), age ( $t_{66} = -1.39$ ,  $p = 0.17$ ), sex ( $\chi^2 = 3.79$ ,  $p = 0.05$ ), or race ( $\chi^2 = 0.11$ ,  $p = 0.74$ ). All failed segmentations were manually corrected for inclusion in the following volumetric analyses.

### *Volumetric analyses*

We used a linear mixed model to test whether IHI contributes to the well-known hippocampal volume differences in schizophrenia (**Table 10**). Without IHI in the model, we found overall smaller hippocampal volume in schizophrenia patients (main effect of Group:  $F_{1,355} = 13.72$ ,  $p < 0.001$ ). Including IHI in the model showed that volume decreases with overall IHI severity (main effect of IHI:  $F_{1,560} = 50.81$ ,  $p < 0.001$ ) and revealed a Group by Hemisphere interaction (Group x Hemisphere interaction:  $F_{1,358} = 4.42$ ,  $p = 0.04$ ). Follow-up tests showed a significantly greater effect of IHI on volume reductions of the right ( $t_{443} = -3.79$ ,  $p < 0.001$ ) than the left ( $t_{448} = -2.37$ ,  $p = 0.04$ ) hippocampus in schizophrenia patients. Including IHI as a fixed effect improved the Volume model fit (Step 1  $R^2 = 0.47$ , AIC = 9777.27; Step 2  $R^2 = 0.49$ , AIC = 9724.85; estimated marginal means of hippocampal volume are in **Figure 16A**). Our exploratory analysis investigating whether IHI has a different effect on volume in each group did not find evidence for an interaction (Group X IHI interaction:  $F_{1,560} = 1.21$ ,  $p = 0.27$ ).

**Table 8.** Demographic information of participants with automated segmentation failures

	Segmentation Successes		Segmentation Failures		Segmentation Successes < Segmentation Failures	
	N = 312		N = 48			
	Mean	SD	Mean	SD	Statistic (t)	p
<b>Age (yrs)</b>	34.95	12.60	32.44	11.52	-1.39	0.17
<b>Parental Education (yrs)</b>	14.31	2.57	15.26	2.53	2.34	<b>0.02</b>
<b>WTAR</b>	103.65	15.68	108.78	13.33	2.37	<b>0.02</b>
	N	%	N	%	Statistic ( $\chi^2$ )	p
<b>Gender (Male)</b>	210	67	39	81	3.79	0.05
<b>Race (White)</b>	207	66	33	69	0.11	0.74
<b>Schizophrenia Patients</b>	169	54	30	63	1.17	0.28

Key: yrs = years; WTAR = Wechsler Test of Adult Reading

**Table 9.** IHI prevalence and severity in automated segmentation failures

	Segmentation Successes N = 312		Segmentation Failures N = 48		Segmentation Successes < Segmentation Failures	
	N	%	N	%	Statistic ( $\chi^2$ )	p
<b>Left IHI</b>	51	16	27	56	39.03	< 0.001
<b>Right IHI</b>	13	4	14	29	37.48	< 0.001
	Mean	SD	Mean	SD	Statistic (t)	p
<b>Left IHI Score</b>	2.47	1.22	4.30	2.03	6.09	< 0.001
C1	0.48	0.44	0.70	0.51	2.74	0.04 <sup>1</sup>
C2	1.00	0.57	1.32	0.52	3.99	< 0.001 <sup>1</sup>
C3	0.53	0.45	1.09	0.68	5.56	< 0.001 <sup>1</sup>
C4	0.00	0.00	0.17	0.56	2.07	0.22 <sup>1</sup>
C5	0.46	0.62	1.02	0.73	5.08	< 0.001 <sup>1</sup>
<b>Right IHI Score</b>	1.93	0.91	2.72	1.28	4.08	< 0.001
C1	0.38	0.34	0.33	0.30	-0.92	1.00 <sup>1</sup>
C2	0.93	0.51	1.09	0.51	2.11	0.19 <sup>1</sup>
C3	0.47	0.43	0.85	0.60	4.25	< 0.001 <sup>1</sup>
C4	0.00	0.00	0.00	0.00	N/A	N/A
C5	0.16	0.40	0.44	0.58	3.20	0.01 <sup>1</sup>

Key: IHI = Incomplete Hippocampal Inversion; <sup>1</sup> = p-value adjusted for multiple comparisons

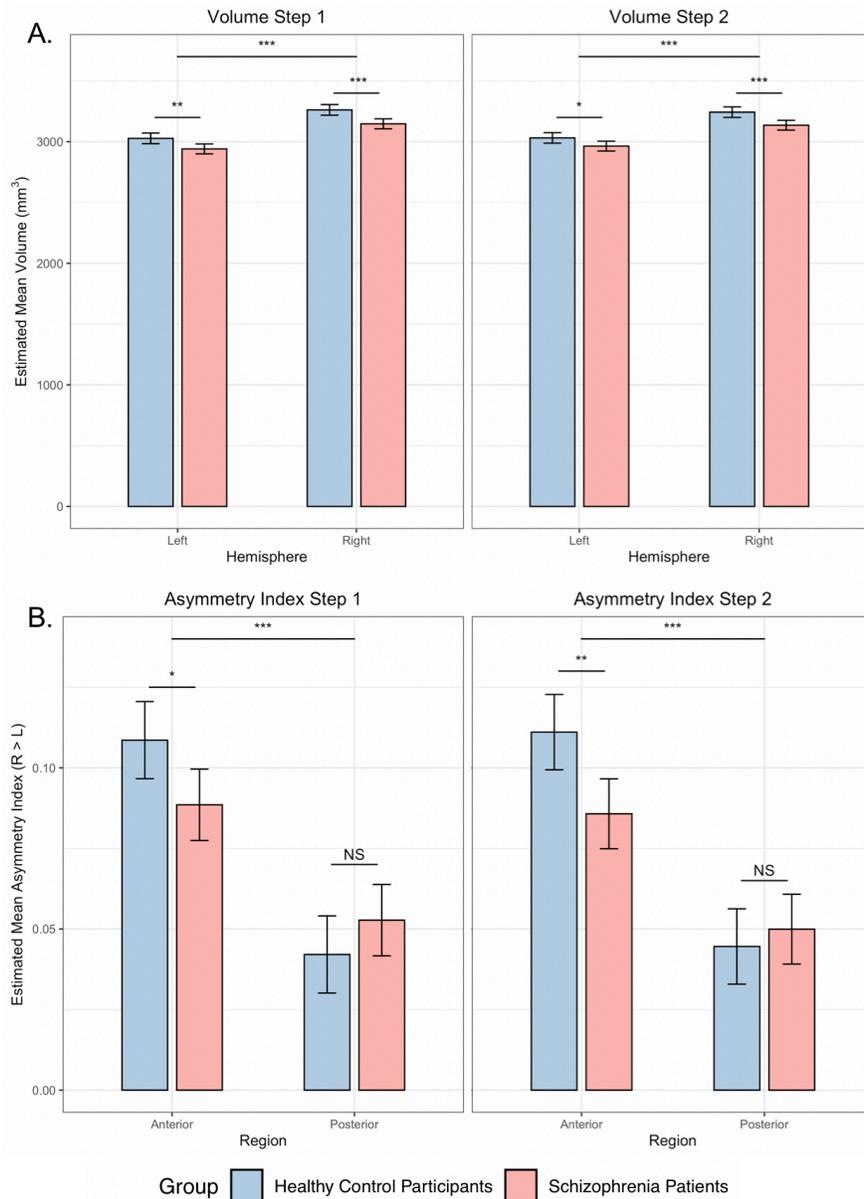
using Bonferroni method.

**Table 10.** Sensitivity analysis of hippocampal volume and asymmetry index

Volume (mm <sup>3</sup> )							
Predictor	Coefficient	Coeff SD	df	F	p-value	R <sup>2</sup>	AIC
<b>Step 1: Model without IHI</b>						0.47	9777.3
Group	-86.89	28.96	1, 355	13.72	<b>&lt;0.001</b>		
Hemisphere	234.31	14.83	1, 358	487.49	<b>&lt;0.001</b>		
ICV	0.00	0.00	1, 355	188.41	<b>&lt;0.001</b>		
Age	-0.25	1.13	1, 355	0.05	0.82		
Sex	-30.62	36.47	1, 355	0.70	0.40		
Group:Hemisphere	-27.64	19.95	1, 358	1.92	0.17		
<b>Step 2: Model with IHI</b>						0.49	9724.9
Group	-67.40	28.49	1, 357	10.74	<b>0.001</b>		
Hemisphere	211.85	14.46	1, 385	342.62	<b>&lt;0.001</b>		
IHI	-43.57	6.10	1, 560	50.81	<b>&lt;0.001</b>		
ICV	1.37	0.10	1, 355	201.52	<b>&lt;0.001</b>		
Age	-0.28	1.11	1, 355	0.06	0.80		
Sex	-29.66	35.85	1, 355	0.68	0.41		
Group:Hemisphere	-40.10	19.06	1, 358	4.42	<b>0.04</b>		
Asymmetry Index (R > L)							
Predictor	Coefficient	Coeff SD	df	F	p-value	R <sup>2</sup>	AIC
<b>Step 1: Model without IHI</b>						0.13	-1629.3
Group	-2.01E-02	7.99E-03	1, 355	0.54	0.46		
Region	-6.65E-02	7.05E-03	1, 355	110.35	<b>&lt;0.001</b>		
ICV	3.52E-08	2.33E-08	1, 355	2.29	0.13		
Age	-8.67E-04	2.68E-04	1, 355	10.48	<b>0.001</b>		
Sex	-5.51E-03	8.63E-03	1, 355	0.41	0.52		
Group:Region	3.07E-02	9.48E-03	1, 358	10.49	<b>0.001</b>		
<b>Step 2: Model with IHI</b>						0.17	-1646.2
Group	-2.53E-02	7.85E-02	1, 354	2.54	0.11		
Region	-6.65E-02	7.05E-03	1, 358	110.35	<b>&lt;0.001</b>		
IHI	1.15E-02	2.09E-03	1, 354	30.52	<b>&lt;0.001</b>		
ICV	2.35E-08	2.24E-08	1, 354	1.10	0.30		
Age	-8.65E-04	2.57E-04	1, 354	11.29	<b>&lt;0.001</b>		
Sex	-3.26E-03	8.30E-03	1, 354	0.15	0.69		
Group:Region	3.07E-02	9.48E-03	1, 358	10.49	<b>0.001</b>		

Key: AIC = Akaike Information Criterion; ICV = Intracranial Volume; IHI = Incomplete

Hippocampal Inversion



**Figure 16. Estimated mean volume and asymmetry index in healthy control participants and schizophrenia patients.**

(A.) Schizophrenia patients have reduced volume in both the left and right hemisphere compared to control participants, based on estimated marginal means generated from a linear mixed model analyzing volume without IHI included as a fixed effect (Step 1) and with IHI included (Step 2). (B.) Schizophrenia patients have a reduced asymmetry index in the anterior hippocampus compared to control participants, based on estimated marginal means generated from a linear mixed model analyzing the asymmetry index without IHI included as a fixed effect (Step 1) and with IHI included (Step 2). Error bars represent 95% confidence intervals. \* =  $p < 0.05$ ; \*\* =  $p < 0.01$ ; \*\*\* =  $p < 0.001$ ; NS = Non-significant.

We conducted a similar analysis for hippocampal right > left volume asymmetry (**Table 10**). Without IHI in the model, we found volume asymmetry to be greater in healthy control participants (main effect of Group:  $F_{1,355} = 0.54$ ,  $p = 0.46$ ), but only in the anterior region (Group X Region interaction:  $F_{1,358} = 10.49$ ,  $p < 0.01$ ; anterior region:  $t_{654} = -2.51$ ,  $p = 0.02$ ; posterior region:  $t_{654} = 1.33$ ,  $p = 0.37$ ). Including IHI did not change these effects. Asymmetry index increases with overall IHI severity (main effect of IHI:  $F_{1,354} = 30.52$ ,  $p < 0.001$ ) and including IHI as a fixed effect improved the Asymmetry Index model (Step 1  $R^2 = 0.13$ ,  $AIC = -1643.13$ ; Step 2  $R^2 = 0.17$ ,  $AIC = -1659.98$ ) (estimated marginal means of hippocampal volume are in (**Figure 16B**)). Our exploratory analysis investigating whether IHI has a different effect on asymmetry index in each group did not find evidence for an interaction (Group X IHI interaction:  $F_{1,353} = 1.25$ ,  $p = 0.26$ ).

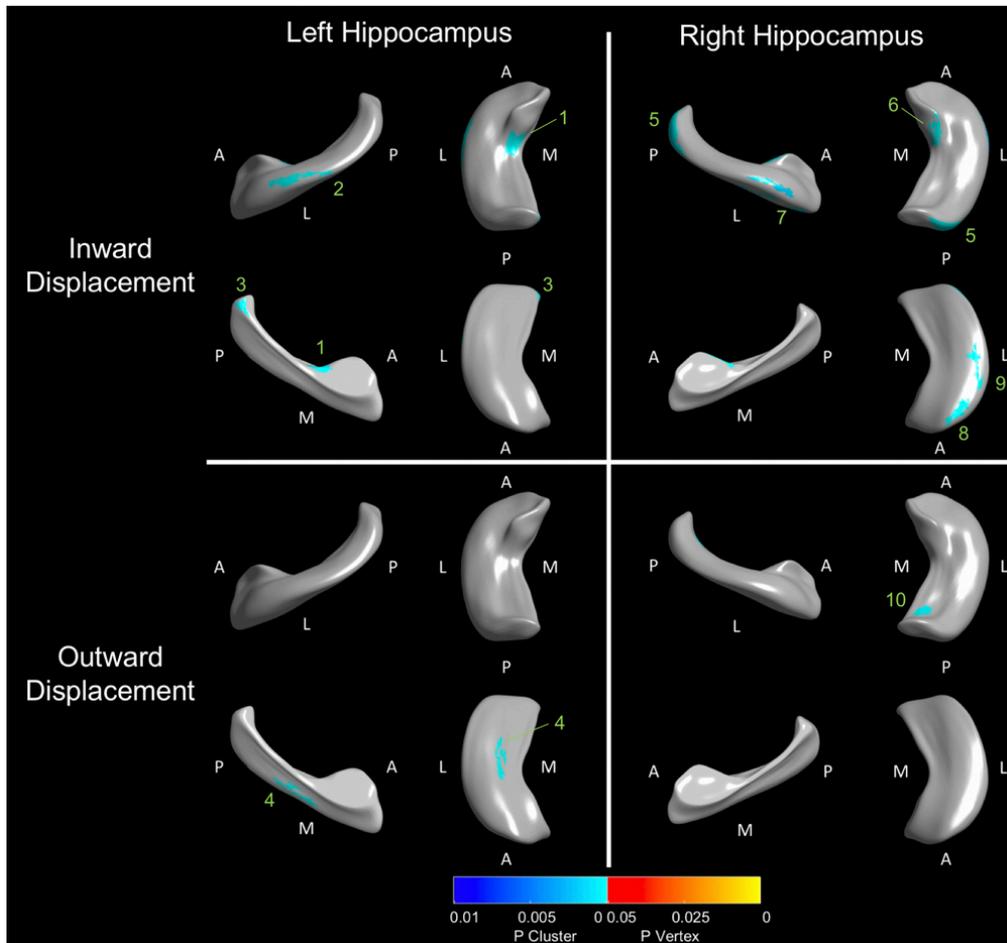
#### *Between-group hippocampal shape analysis*

A comparison of hippocampal shape between healthy control participants and patients with schizophrenia revealed significant differences in both hemispheres. Significant clusters are visualized on hippocampal surfaces in **Figure 17**. In the left hippocampus, inward shape displacements are located at the uncus (cluster 1 in **Figure 17**), anterolateral body (cluster 2), and posterior-most surface of the medial tail (cluster 3). Outward shape displacement is restricted to the ventral body (cluster 4). In the right hippocampus, inward shape displacements are clustered at the lateral tail (cluster 5), uncus (cluster 6), anterolateral body (cluster 7), ventrolateral tail (cluster 8), and ventrolateral body (cluster 9). Outward shape displacement is limited to the dorsal tail (cluster 10). Peak t-values, effect sizes (Cohen's d), the number of

significant vertices, and RFT corrected p-values for all significant clusters are summarized in **Table 11**. Additional hippocampal surface maps in **Figure 18** illustrate the mean difference in vertex displacement in our patient cohort (Panel A) and t-values for the between-group analysis (Panel C).

#### *Effect of IHI on hippocampal shape*

IHI severity is associated with outward displacements in the dorsal and ventral hippocampal surfaces and inward displacements in the medial and lateral hippocampal surfaces bilaterally. Areas of significance contain both clusters and individual vertices. There are more significant vertices and larger clusters of significance on the left than the right hippocampal surface. Significant clusters are visualized on hippocampal surfaces in **Figure 19**, and the peak t-values, effect sizes (Cohen's d), the number of significant vertices, and RFT corrected p-values for all significant clusters are summarized in **Table 12**. Surface maps demonstrating the t-values of this analysis are found in **Supplemental Figure 18B**. We found a similar main effect of IHI in the healthy control sample (**Figure 20**).



**Figure 17. Hippocampal shape deformations in schizophrenia patients.**

Hippocampal surface maps showing structural differences between patients with schizophrenia ( $n = 199$ ) and healthy individuals ( $n = 161$ ), controlling for the effects of ICV, age, and gender in a linear model. The figure is shown at  $P \leq 0.01$  with RFT correction. Blue coloration indicates areas significant at the cluster level. No individual vertex reached statistical significance. Green numbers indicate clusters of significance described in Table 2. *Note:* A, anterior; P, posterior; L, lateral; M, medial.

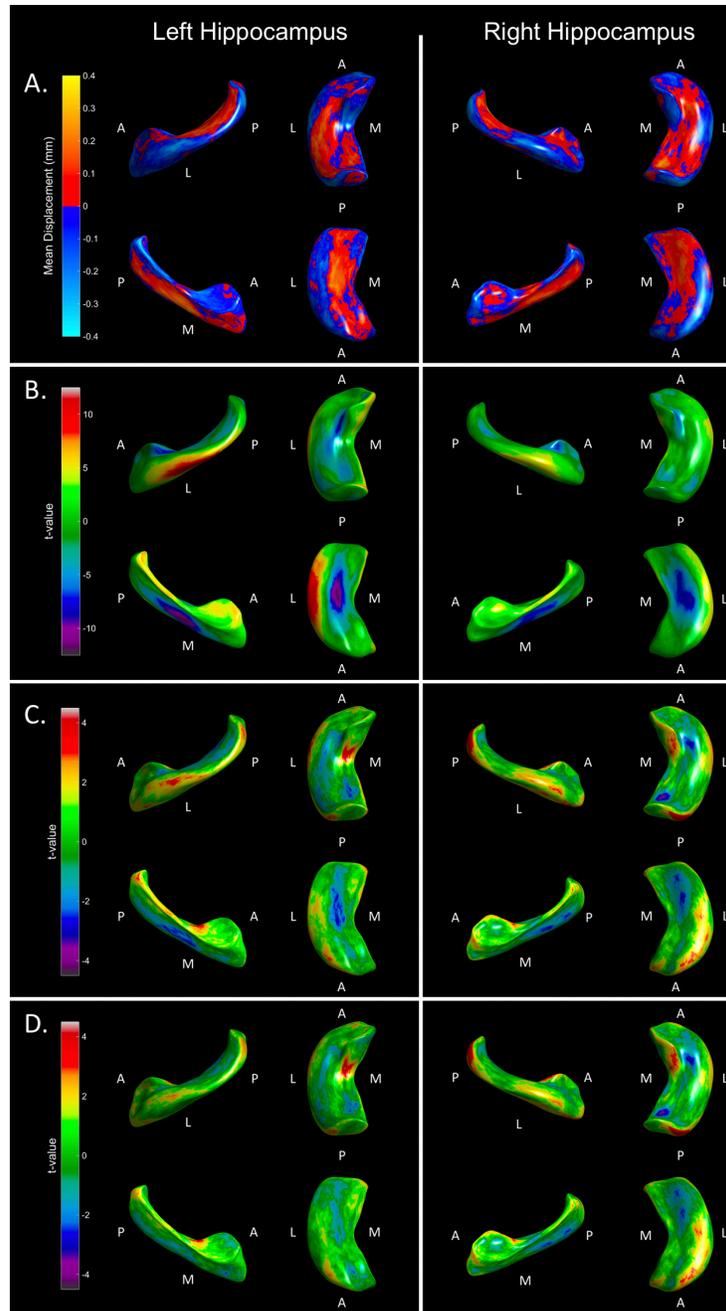
**Table 11.** Significant clusters in between-group shape analyses without and including IHI

LEFT HIPPOCAMPUS									
Hippocampal Surface		Model without IHI				Model including IHI			
Cluster	Location	Peak $t_{358}$	ES	Vertices	p-value	Peak $t_{358}$	ES	Vertices	p-value
<u>Inward Displacement</u>									
1	Uncus	4.19	0.44	550	1.24E-06	4.19	0.44	476	1.29E-06
2	<i>Anterolateral body</i>	3.73	<i>0.40</i>	533	<i>1.34E-06</i>	2.96	<i>0.31</i>	38	<i>0.99</i>
3	Medial tail	3.79	0.40	193	7.63E-06	2.89	0.31	117	0.77
<u>Outward Displacement</u>									
4	Ventral body	3.46	0.37	448	7.96E-06	2.61	0.28	4	1.00
RIGHT HIPPOCAMPUS									
Hippocampal Surface		Model without IHI				Model including IHI			
Cluster	Location	Peak $t_{358}$	ES	Vertices	p-value	Peak $t_{358}$	ES	Vertices	p-value
<u>Inward Displacement</u>									
5	Lateral tail	4.23	0.45	967	1.24E-06	4.06	0.43	858	1.27E-06
6	Uncus	3.48	0.37	413	1.27E-06	3.45	0.37	451	1.27E-06
7	<i>Anterolateral body</i>	<i>3.15</i>	<i>0.33</i>	<i>346</i>	<i>2.01E-05</i>	<i>2.81</i>	<i>0.30</i>	<i>53</i>	<i>0.87</i>
8	Ventrolateral tail	3.27	0.35	313	2.35E-05	3.27	0.35	335	1.65E-05
9	Ventrolateral body	3.04	0.32	245	8.43E-03	3.08	0.33	194	7.03E-03
<u>Outward Displacement</u>									
10	Dorsal tail	4.08	0.43	282	6.85E-06	3.88	0.41	243	3.71E-05

Key: Peak t = Greatest t-value for an individual vertex in the cluster; ES = effect size (Cohen's d)

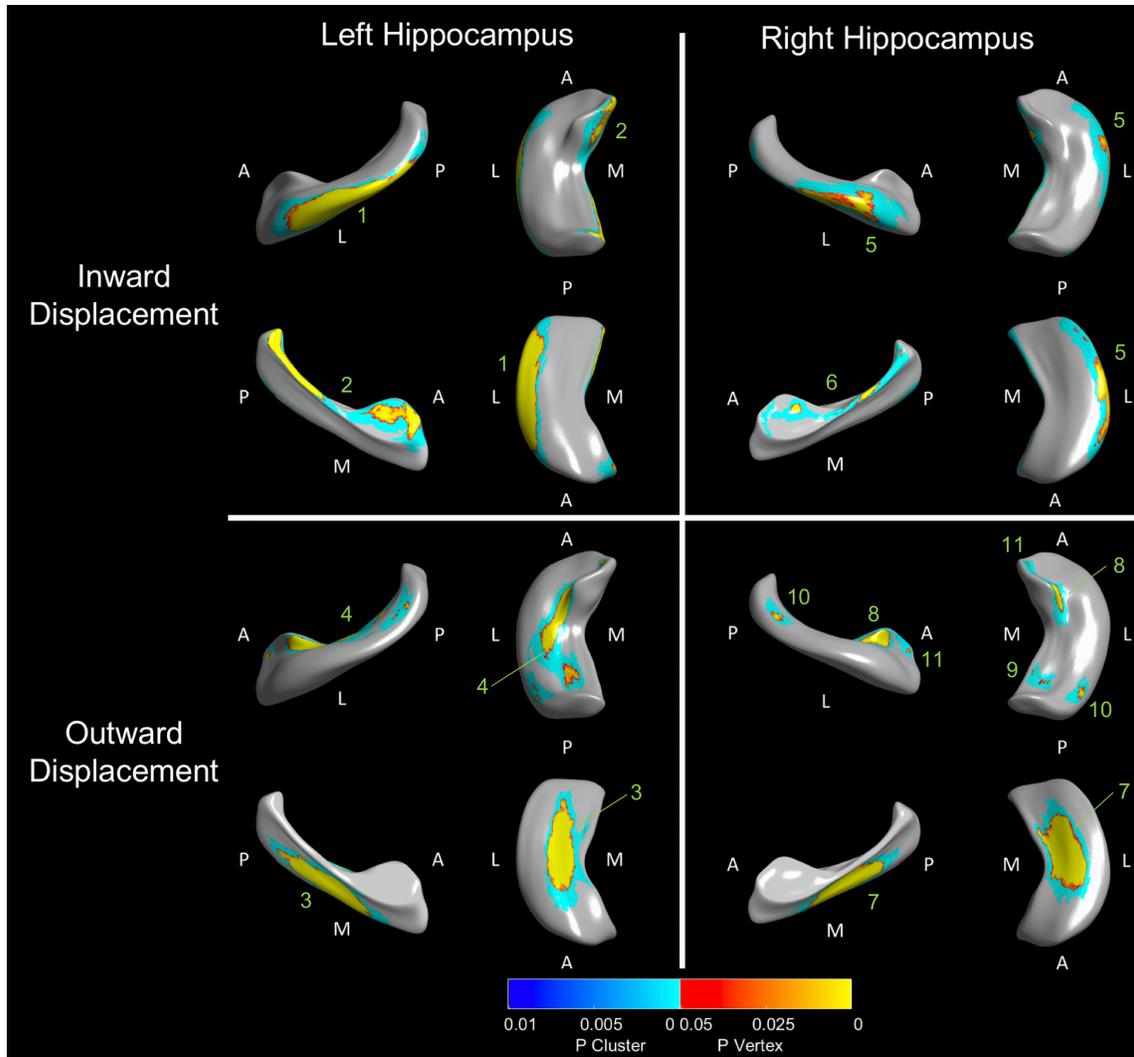
corresponding to the individual vertex with greatest t-value; IHI = incomplete hippocampal

inversion. Italicized text indicates the location of the CA1 subfield



**Figure 18. Mean displacement and t-value maps of schizophrenia patients.**

(A.) Surface maps showing the magnitude of inward (blue) and outward (red) displacement (mm) of patients with schizophrenia when compared to the average shape. (B.) Surface maps for the entire cohort showing the magnitude of t-values generated in the linear model testing the main effect of IHI on hippocampal shape. (C.) Surface maps for patients with schizophrenia showing the magnitude of t-values generated in the linear model comparing shape differences between groups. (D.) Surface maps for patients with schizophrenia showing the magnitude of t-values generated in the linear model, including IHI as a fixed effect, comparing shape differences between groups. *Note:* A, anterior; P, posterior; L, lateral; M, medial.



**Figure 19. Association of IHI with hippocampal shape variation in entire study cohort.**

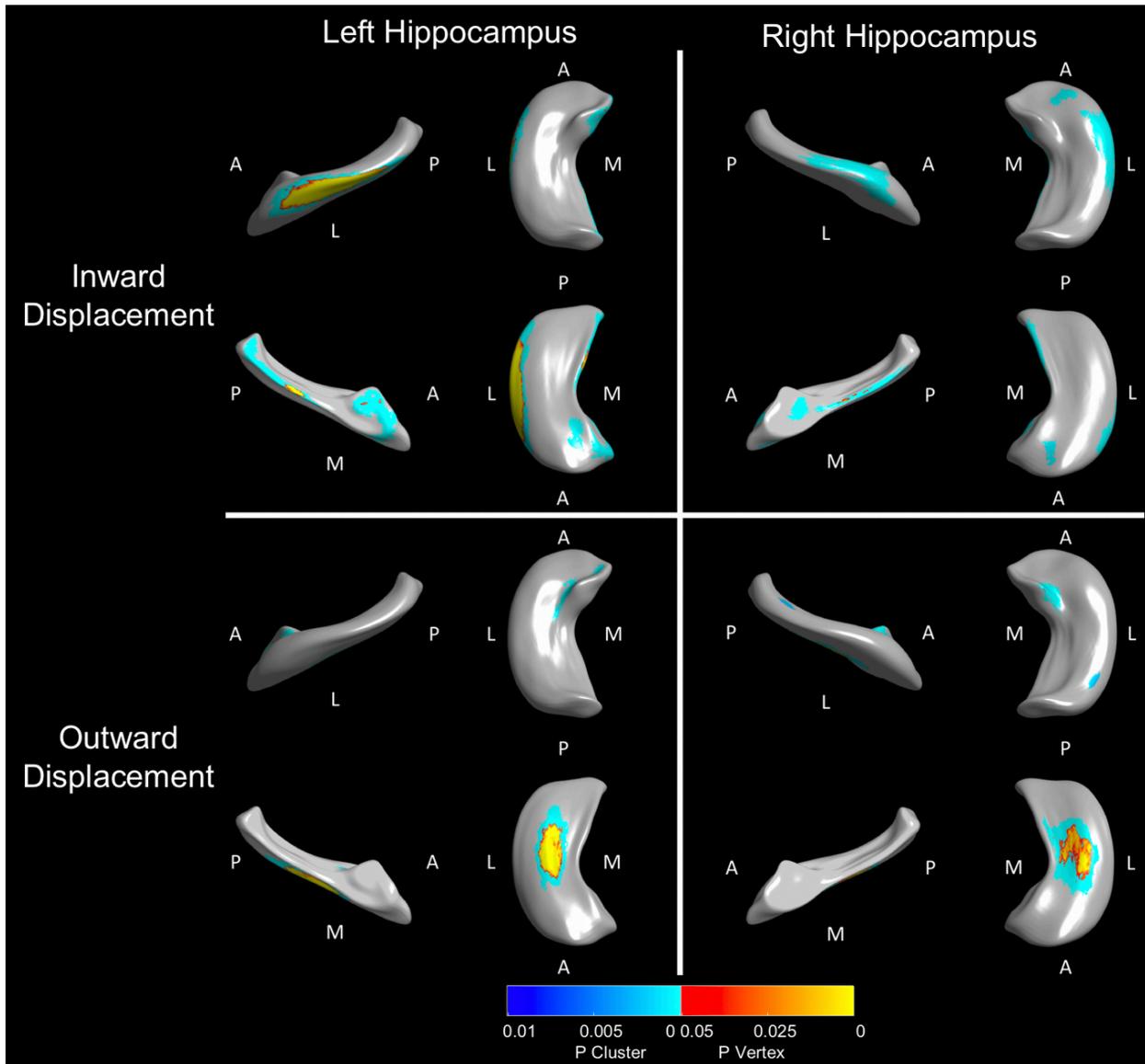
Hippocampal surface maps where local shape variation is associated with IHI in a linear model, controlling for the effects of ICV, age, and gender (N = 360). The figure is shown at  $P \leq 0.01$  with RFT correction. Blue coloration indicates areas significant at the cluster level and red coloration indicates areas significant at the vertex level. Green numbers indicate clusters of significance described in Table 3. *Note:* A, anterior; P, posterior; L, lateral; M, medial.

**Table 12.** Significant clusters in shape analysis of IHI effect on shape

<b>LEFT HIPPOCAMPUS</b>					
<b>Cluster</b>	<b>Location</b>	<b>Peak <math>t_{358}</math></b>	<b>ES</b>	<b>Vertices</b>	<b>p-value</b>
<u>Inward Displacement</u>					
1	Lateral hippocampus	12.88	1.37	8016	1.29E-06
2	Medial hippocampus	7.86	0.83	5156	1.29E-06
<u>Outward Displacement</u>					
3	Ventral hippocampus	12.26	1.30	4570	1.29E-06
4	Dorsal hippocampus	8.08	0.86	3655	1.29E-06
<b>RIGHT HIPPOCAMPUS</b>					
<b>Cluster</b>	<b>Location</b>	<b>Peak <math>t_{358}</math></b>	<b>ES</b>	<b>Vertices</b>	<b>p-value</b>
<u>Inward Displacement</u>					
5	Lateral hippocampus	7.04	0.75	7371	1.26E-06
6	Medial hippocampus	6.21	0.66	2567	1.26E-06
<u>Outward Displacement</u>					
7	Ventral hippocampus	9.35	0.99	4675	1.26E-06
8	Dorsal posterior uncus	6.80	0.72	1027	1.26E-06
9	Dorsomedial tail	4.89	0.52	597	1.26E-06
10	Dorsolateral tail	5.70	0.60	448	1.26E-06
11	Dorsal anterior uncus	4.49	0.48	279	3.90E-06

Key: Peak t = Greatest t-value for an individual vertex in the cluster; ES = effect size (Cohen's d)

corresponding to the individual vertex with greatest t-value

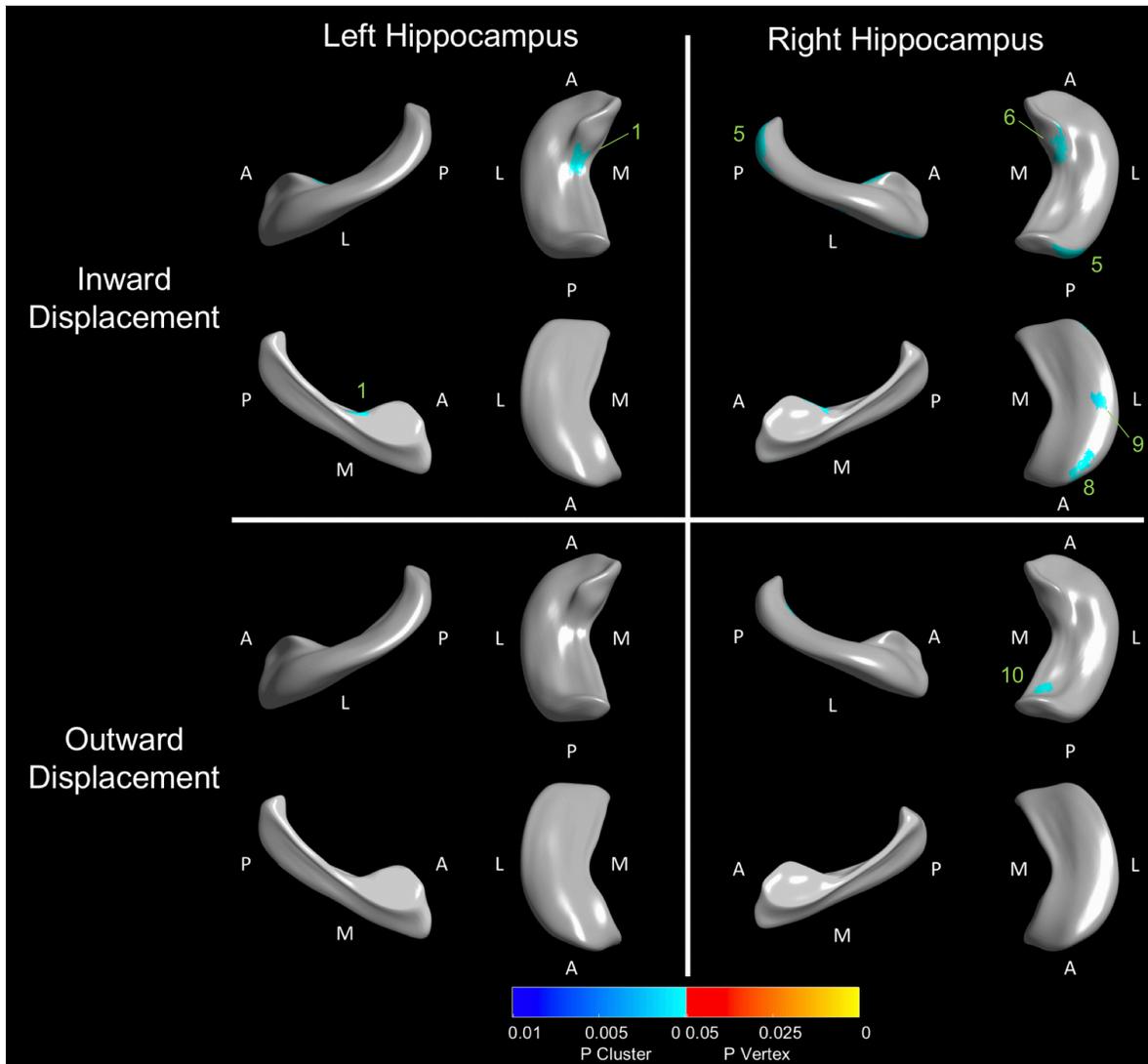


**Figure 20. Association of IHI with local shape variation in healthy individuals.**

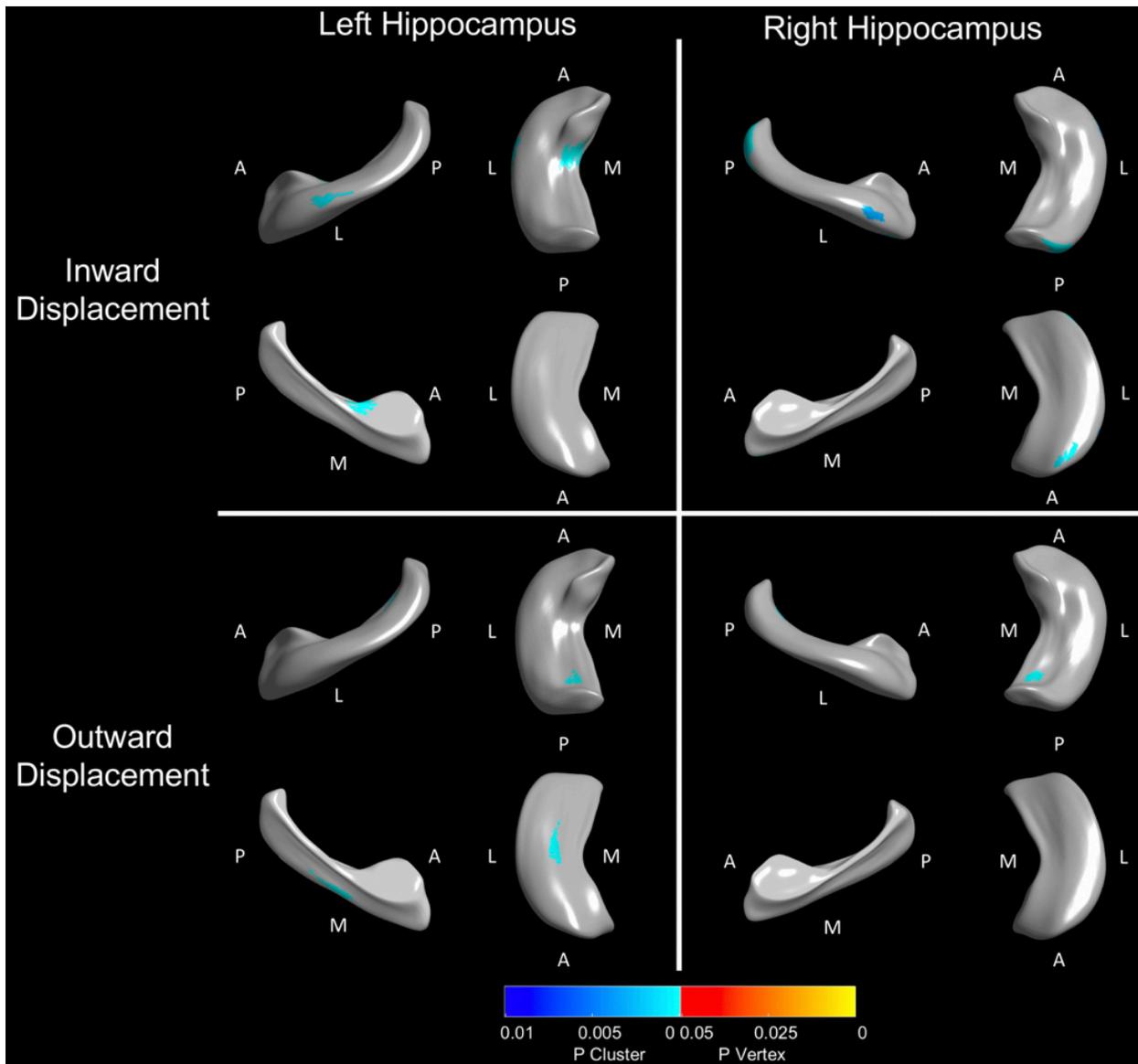
Hippocampal surface maps where local shape variation is associated with IHI in a linear model, controlling for the effects of ICV, age, and gender (N = 161). The figure is shown at  $P \leq 0.01$  with RFT correction. Blue coloration indicates areas significant at the cluster level and red coloration indicates areas significant at the vertex level. *Note:* A, anterior; P, posterior; L, lateral; M, medial.

*Between-group hippocampal shape analysis including IHI as a main effect*

Including IHI as a main effect in our linear model results in the elimination of significant clusters of shape variation in the left and right hippocampus. In the left hippocampus, the inward displacements located at the anterolateral body (cluster 2) and medial tail (cluster 3) no longer reach statistical significance. The significant outward displacement in the ventral body is also no longer significant (cluster 4). In the right hippocampus, the inward displacement visualized at the anterolateral body (cluster 7) is no longer significant. All other clusters in our previous between-group model remained significant after including IHI in the model. The impact of IHI on significant clusters is visualized on hippocampal surfaces in **Figure 21**. The changes in all clusters are summarized in **Table 11**. Surface maps demonstrating the t-values of this analysis are found in **Supplemental Figure 18** (Panel D). Covarying for alcohol and cannabis use disorder in our models did not change the impact of IHI on hippocampal shape differences (**Figures 22-23**).

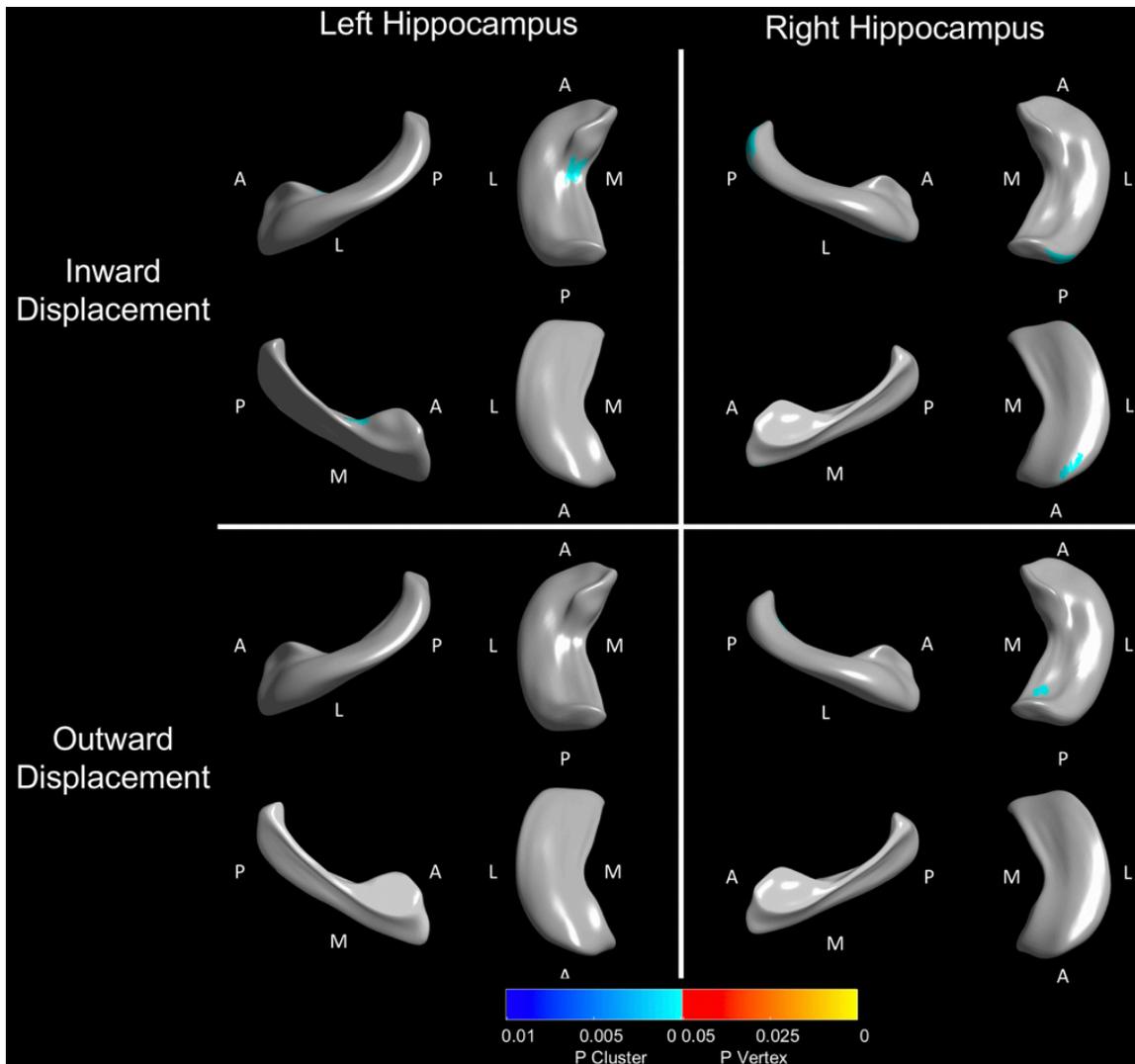


**Figure 21. Hippocampal shape deformation in schizophrenia patients, adjusting for the effect of IHI.** Hippocampal surface maps showing structural differences between patients with schizophrenia ( $n = 199$ ) and healthy individuals ( $n = 161$ ), including IHI in a linear model and controlling for the effects of ICV, age, and gender. The figure is shown at  $P \leq 0.01$  with RFT correction. Blue coloration indicates areas significant at the cluster level. No individual vertex reached statistical significance. Green numbers indicate clusters of significance described in Table 2. *Note:* A, anterior; P, posterior; L, lateral; M, medial.



**Figure 22. Hippocampal shape deformation in schizophrenia patients, adjusting for the effect of AUD and CUD.**

Hippocampal surface maps showing structural differences between patients with schizophrenia ( $n = 199$ ) and healthy individuals ( $n = 161$ ), controlling for the effects of ICV, age, gender, AUD, and CUD in a linear model. The figure is shown at  $P \leq 0.01$  with RFT correction. Blue coloration indicates areas significant at the cluster level. No individual vertex reached statistical significance. *Note:* A, anterior; P, posterior; L, lateral; M, medial.

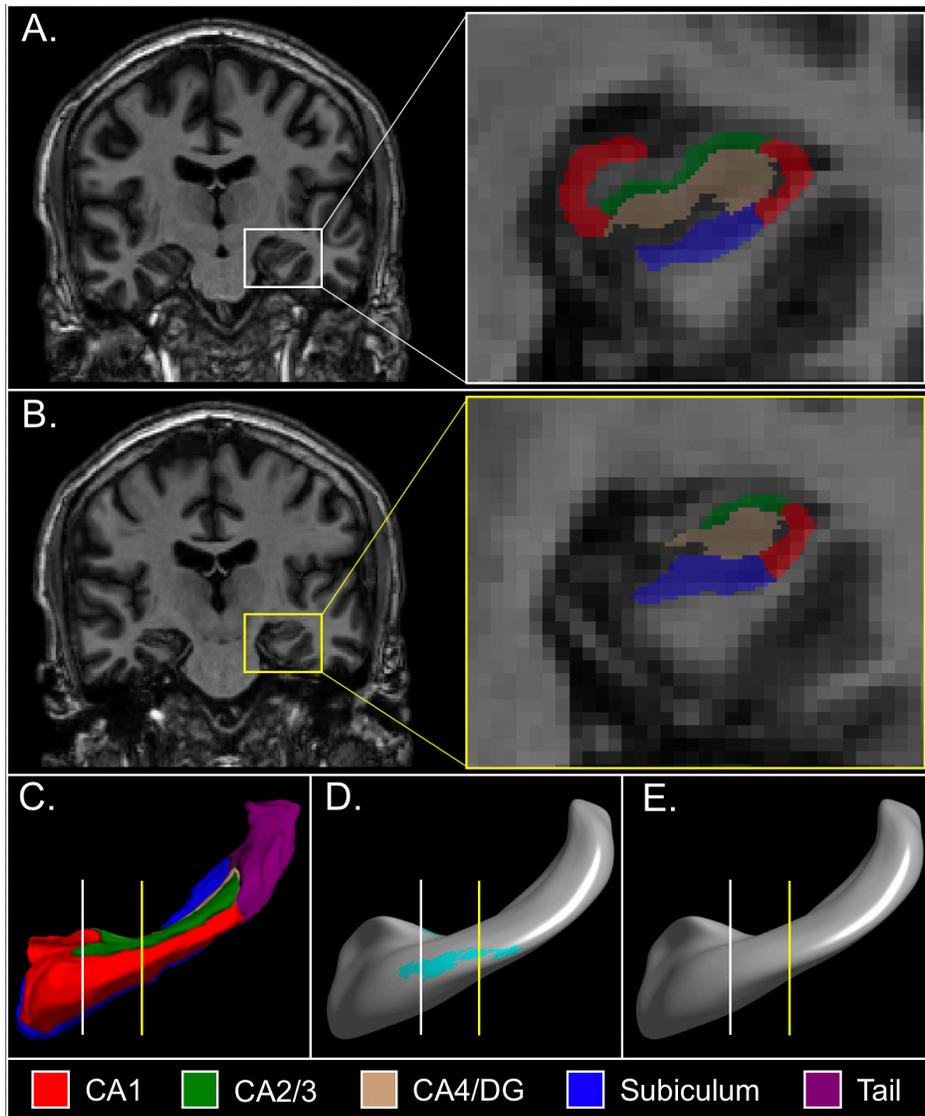


**Figure 23. Hippocampal shape deformation in schizophrenia patients, adjusting for the effect of IHI, AUD, and CUD.**

Hippocampal surface maps showing structural differences between patients with schizophrenia ( $n = 199$ ) and healthy individuals ( $n = 161$ ), including IHI in a linear model and controlling for the effects of ICV, age, gender, AUD, and CUD. The figure is shown at  $P \leq 0.01$  with RFT correction. Blue coloration indicates areas significant at the cluster level. No individual vertex reached statistical significance. Green numbers indicate clusters of significance described in Table 2. *Note:* A, anterior; P, posterior; L, lateral; M, medial.

## Discussion

Our study of 360 participants showed significant hippocampal volume deficits and shape variations in schizophrenia patients. We demonstrate that IHI is strongly correlated with hippocampal volume, increases the right > left anterior hippocampal volume asymmetry, and contributes to hippocampal volume differences between schizophrenia patients and healthy control participants, particularly in the left hemisphere. We also illustrate that IHI is associated with extensive rounding of the hippocampal formation. Lastly, including IHI in our shape analysis explains significant variance in shape differences in the anterolateral hippocampus, which corresponds with the CA1 subfield (**Figure 24**). To our knowledge, this is the first study that links hippocampal morphologic differences to a neurodevelopmental variant established *in utero*.



**Figure 24. IHI eliminates CA1 surface deformation differences in schizophrenia patients.**

Enlarged T1 image detail and overlay of Freesurfer hippocampal segmentation demonstrating anatomical location of CA1-4, DG, and subiculum in the (A., in white) left hippocampal head (B., in yellow) and anterior body. (C.) Left hippocampal surface with subfields. (D.) Left hippocampal surface generated using SPHARM-PDM toolkit and left anterolateral hippocampal shape differences (Table 2: cluster 2) generated using SurfStat in our between-group analysis. (E.) Elimination of left anterolateral hippocampal shape differences after including IHI as a main effect in our between-group analysis. In C.-E., the white line indicates the location of the coronal section through the hippocampal head in A., and the yellow line indicates the location of the coronal section through the hippocampal anterior body in B.

### *IHI impacts hippocampal volume*

We explored whether this variant could contribute to the well-established hippocampal structural differences in schizophrenia (Brugger and Howes, 2017; Haijma et al., 2013; Woolard and Heckers, 2012). In our patient sample, we replicate findings of reduced left and right hippocampal volumes and demonstrate a reduced asymmetry index in the anterior hippocampus. Including IHI as a fixed effect in our statistical model revealed that it significantly contributes to the reduced hippocampal volume and increased right > left volume asymmetry in schizophrenia. Furthermore, including IHI as a fixed effect improved the quality of our models and accounted for more variability in our data. Lastly, inclusion of IHI in our model predicting hippocampal volume revealed a Group by Hemisphere interaction. Follow-up t-tests indicated that the inclusion of IHI decreased the between-group differences in the left but not the right hippocampus. Taken together, IHI is a significant contributor to both overall and right > left hippocampal volume in healthy control participants and schizophrenia patients.

### *IHI impacts automated segmentation*

Of the 360 participants in this study, automated hippocampal segmentation failed in 48 participants. Automated segmentation was more likely to fail with hippocampi that met more severe IHI criteria. Additionally, partitioning individual IHI criteria revealed that participants with failed segmentations have hippocampi with wide-spread IHI-like features. These findings indicate automated segmentation can successfully segment mild IHI, but fails when there are extensive changes to hippocampal structure. In studies using automated hippocampal segmentation to measure hippocampal volume, IHI can be a potential confound (Kim et al.,

2012). Specifically, if IHI is more severe or more frequent in a patient population and individuals with failed segmentations are excluded from the analysis, then the mean volume estimates may be biased and may underestimate the true volume difference. Here, we manually corrected automated segmentation failures, which allowed us to include all IHI cases, as we investigated the relationship of this anatomical variant with hippocampal structure.

### *Hippocampal shape is abnormal in schizophrenia*

Our analysis replicates significant shape deformation findings reported in previous studies of patients with schizophrenia spectrum disorders. Inward displacements of the uncus (Guimond et al., 2021; Ho and Magnotta, 2010; Johnson et al., 2013; Qiu et al., 2010; Smith et al., 2011; Tang et al., 2020; Zierhut et al., 2013), anterolateral body (Csernansky et al., 1998b; Guimond et al., 2021; Gutman et al., 2021; Kalmady et al., 2017; Li et al., 2015; Mamah et al., 2016, 2012; Narr et al., 2004; Prestia et al., 2015; Qiu et al., 2010; Sauras et al., 2017; Zierhut et al., 2013), lateral tail (Guimond et al., 2021; Li et al., 2015; Styner et al., 2004), medial tail (Kalmady et al., 2017; Lee et al., 2004; Prestia et al., 2015; Qiu et al., 2013; Smith et al., 2011), and ventrolateral areas (Guimond et al., 2021; Li et al., 2015) and outward displacements of the ventral body (Johnson et al., 2013; Smith et al., 2011) and dorsal tail (Csernansky et al., 2002; Mamah et al., 2012; Narr et al., 2004; Smith et al., 2011) have been reported previously.

Our analysis benefits from a large cohort, high-fidelity surface reconstructions with 40,962 vertices, and a conservative statistical approach to allow for the precise localization of significant clusters throughout the hippocampus. There is some evidence that hippocampal shape deformities begin in the CA1 subfield and progress over time (Mamah et al., 2012; Wang

et al., 2008) in individuals with schizophrenia. The mean duration of illness in our patient cohort is 7.70 years, indicating that progressive shape changes may have occurred across the hippocampus.

#### *IHI impacts hippocampal shape*

IHI has a significant impact on hippocampal shape regardless of diagnosis. This is evident by the number of significant individual vertices and large effect sizes of some clusters. As expected, the severity of IHI is associated with an outward displacement of the dorsal and ventral surfaces and inward displacement of the medial and lateral surfaces of the hippocampus. This pattern matches the rounded anatomy described in IHI grading criteria and visualized in coronal sections of IHI cases (Cury et al., 2015). These results also confirm qualitative descriptions that IHI primarily affects hippocampal anatomy in the head and body (Cury et al., 2015) as opposed to the tail (Connor et al., 2004). The greater impact of IHI on left hippocampal shape is likely due to the higher prevalence and greater severity of IHI in the left hippocampus.

We conclude from our findings that IHI should be included in future studies of hippocampal morphology. Furthermore, shape analyses should be added to studies of hippocampal volume, as shape deformations suggestive of neurodevelopmental anomalies may have higher sensitivity for detecting small changes in brain morphology (Csernansky et al., 1998b). For example, previous studies of IHI in major depressive disorder (Colle et al., 2016) and in an aging cohort (Colenutt et al., 2018) did not find any whole hippocampal volume differences, but shape analyses might have revealed group differences.

Our recommendation to include IHI in future studies of hippocampal morphology raises two concerns. First, the grading of IHI is a manual, time-intensive process that will be difficult to sustain in the study of large datasets. Automated methods to identify IHI based on hippocampal shape will facilitate reporting on IHI in morphological studies. Second, shape differences attributable to IHI might still be informative of schizophrenia pathophysiology. For example, localized hippocampal surface differences (that are removed after inclusion of IHI in the analysis) might be related to clinical features.

#### *IHI contributes to CA1 subfield shape deformations in schizophrenia*

Incorporating IHI as a main effect in our shape analysis model eliminated the significant group difference in the anterolateral hippocampus in the right (p-value increase from 2.01E-05 to 0.87) and left (p-value increase from 1.34E-06 to 0.99) hemisphere. This hippocampal region consists primarily of the CA1 subfield. Results of an omnibus test analysis reiterate that IHI score is the main predictor of shape differences in schizophrenia. CA1 subfield deformations, particularly in the anterolateral region of the hippocampus, have been extensively reported in patients with schizophrenia (Gutman et al., 2021; Kalmady et al., 2017; Mamah et al., 2016, 2012; Narr et al., 2004; Prestia et al., 2015; Sauras et al., 2017; Tang et al., 2020; Zierhut et al., 2013). In the only study to date to investigate the effect of IHI on hippocampal subfield volumes, IHI was correlated with the volume of CA1, but not other hippocampal subfields, in 60 healthy subjects (Colenutt et al., 2018). Here, we show for the first time that IHI contributes to CA1 shape deformation in schizophrenia.

The location of CA1 shape deformations in schizophrenia is inconsistently reported in the literature. As highlighted in Gutman et al. (2021), the use of Freesurfer, such as in this study, to generate gray matter boundaries may account for CA1 shape differences that are more posterior than the anterior CA1 shape deformities reported by groups using diffeomorphic surface mapping methods (Csernansky et al., 2002). However, our CA1 shape deformities replicate the results of a recent meta-analysis of hippocampal shape, including 2,833 patients with schizophrenia and 3,929 healthy volunteers in the ENIGMA consortium (Gutman et al., 2021), and the largest individual shape deformation study of the hippocampus in schizophrenia (Guimond et al., 2021). Both studies localize areas of significant shape deformation to the anterolateral CA1 hippocampus, which is consistent with our findings.

#### *Limitations and future directions*

Our study has several limitations. First, a recent study has shown a smaller CA1 volume in healthy participants with IHI (Colenutt et al., 2018), but our segmentation methods did not allow us to investigate hippocampal volumes at the subfield level because of manual corrections to the segmentations.

Second, the majority of schizophrenia patients in this study received antipsychotic medications, which may affect hippocampal structural measures (Goff et al., 2017). However, in a recent shape analysis study of patients with schizophrenia spectrum disorders, medication dose did not affect the shape of the hippocampus (Guimond et al., 2021). Of note, this analysis demonstrated anterolateral inward deformations, which the authors attribute to the CA1

subfield. Additionally, shape analyses of antipsychotic-naive patients also show CA1 shape inward deformations (Kalmady et al., 2017) in addition to other widespread shape differences.

Third, we could not assess the cumulative exposure of substances, including cannabis and alcohol, to hippocampal shape deformations. Shape analyses illustrate the additive effects of alcohol (Smith et al., 2011) and cannabis (Solowij et al., 2013) on hippocampal pathology in schizophrenia. Although participants with concurrent diagnoses of alcohol or cannabis use disorder were excluded from participation in this study, we collected the lifetime history of substance use disorders in this cohort (**Table 6**). Covarying for alcohol and cannabis use disorder in our shape analysis model does not change the results of our between-group analyses, suggesting that a history of substance use disorder does not contribute to the shape deformations in schizophrenia we report.

Fourth, we did not assess whether participants had a history of obstetric complications (i.e., a trigger for aberrant *in utero* development). Evidence suggests that obstetric complications may mediate hippocampal volume reductions in both healthy control participants and schizophrenia patients (Ho and Magnotta, 2010), and increase schizophrenia susceptibility (T. D. Cannon et al., 2002). Future studies should collect obstetric information to better elucidate the relationship between IHI, hippocampal structure, and obstetric complications.

Lastly, we did not investigate whether there is a relationship between clinical measures and IHI in the context of hippocampal structure. To date, one study has investigated the link between IHI and clinical outcomes, reporting that patients with visual hallucinations possess more IHI-specific morphological patterns (Cachia et al., 2020). Additional work should attempt

to link clinical measures with shape changes and IHI, similar to previous shape analysis studies relating clinical outcomes and cognitive features with shape deformations (Csernansky et al., 2002; Kalmady et al., 2017; Mamah et al., 2016; Prestia et al., 2015; Zierhut et al., 2013).

## **Conclusions**

This is the first study to report the impact of IHI on hippocampal structure. Our results suggest that IHI has a significant effect on hippocampal morphology and contributes to CA1 shape deformations in schizophrenia. This provides evidence that hippocampal shape differences in schizophrenia can be attributed to an anatomical variant arising during the perinatal period, long before the emergence of the clinical phenotype.

## CHAPTER V

### SUMMARY AND CONCLUSION

#### **Summary**

Schizophrenia affects millions of individuals and contributes a substantial burden to individuals, the families of those affected, the health care system, and society (WHO Fact Sheet: Schizophrenia, 2022). In part, schizophrenia has such devastating consequences because of limited treatment options. Even following treatment, many individuals report poor outcomes. All FDA-approved pharmacologic treatment options currently target the dopaminergic system despite this system being relatively unperturbed (Howes et al., 2015). Findings from human and animal studies instead suggest that abnormalities in other neural systems, resulting from altered neurodevelopment, drive schizophrenia psychopathology. However, the neural mechanisms underlying these abnormalities are not well understood. Understanding the brain regions contributing to these altered neural systems could help identify novel treatment targets for schizophrenia.

The hippocampus is a brain region implicated in schizophrenia pathophysiology. Studies report structural, functional, and neurometabolic abnormalities in schizophrenia patients at all stages of the illness. Studies in rodent models of schizophrenia have identified a neural circuit linking the anterior hippocampus to downstream brain regions that drive symptoms observed in schizophrenia, suggesting that the hippocampus can serve as a potential treatment target.

However, hippocampal pathology's development and underlying neural mechanisms are poorly understood.

The results presented here describe the effect of pharmacologic modulation with a low-dose anti-epileptic, LEV, on hippocampal resting-state activity and recruitment during a hippocampal-dependent SPT (Chapter II). Despite a substantial body of prior literature reporting hippocampal hyperactivity and abnormal hippocampal recruitment in schizophrenia patients, these findings did not replicate after placebo treatment (i.e., at baseline). Further, LEV did not demonstrate a treatment effect on hippocampal hyperactivity or hippocampal recruitment or differentiate between healthy control and patient groups. However, an analysis of hippocampal recruitment only during the first study session revealed a group by treatment effect, suggesting that the hippocampus habituates to the SPT during the second study session. Negative results in this study are likely the result of patient heterogeneity, limitations of imaging methods employed in the study, and the study design.

In addition to assessing hippocampal function, this project also investigated the prevalence of a neurodevelopmental variant of the hippocampus, IHI, (Chapter III), its impact on hippocampal structure, and impact structural neuroimaging methods (Chapter IV). IHI is more prevalent and severe in individuals with schizophrenia. Prevalence and severity are more significant in the left hemisphere than in the right, corresponding with the faster development of the right hippocampus. The IHI criterion measuring the medial positioning of the hippocampus contributed most to the difference in prevalence rates. IHI affects hippocampal volume, asymmetries, and shape, regardless of diagnosis. Further, IHI contributes to shape differences localized to the CA1 subfield of the hippocampus, providing support for a

neurodevelopmental impact on well-documented shape differences. Lastly, IHI is associated with a greater failure rate for automated segmentation methods that are widely implemented in many fields for structural investigation of the hippocampus. Altogether, IHI is a significant contributor to hippocampal morphology and may explain schizophrenia-specific structural alterations.

### **Future directions**

Below is a review of relevant future directions for research. First, I will consider the limitations to hippocampal hyperactivity as a biomarker for schizophrenia. Second, I will hypothesize IHI's role in increasing vulnerability for the development of psychotic disorders. Third, I will explore novel methods by which IHI can be used to further understand hippocampal pathology in schizophrenia. Finally, I will discuss the clinical implications of this work.

#### *Limitations to hippocampal hyperactivity as a biomarker for schizophrenia*

Previously, I identified five core findings from multiple studies to support hippocampal hyperactivity's role as a potential treatment target and biomarker for schizophrenia (**Table 1**). As demonstrated by the results of this project (Chapter II), there are many methodological and neurobiological limitations to the assessment of hippocampal hyperactivity in schizophrenia. This section will integrate lessons learned from this work and recent studies to identify challenges to the core findings established in the Introduction (summarized in **Table 13**).

**Table 13.** *Challenges and future directions for establishing hippocampal hyperactivity as a biomarker for schizophrenia*

<b>Findings in support of hippocampal hyperactivity as a biomarker for schizophrenia</b>	<b>Challenges</b>	<b>Future Directions</b>
Measured with fMRI methods	Poor reliability, difficulty in measuring hippocampal signal Population-specific fMRI challenges (e.g., ASL in patients treated with APs)	Improve spatial and temporal resolution of imaging Design study with conducive designs and imaging techniques
Correlates with clinical symptoms	No casual inference testing	Confirm circuits observed in animal models Intervention studies showing causal inference between hippocampal activity and symptoms
Translational utility in animal models	No true rodent model of schizophrenia	Development of novel, predictive animal models of schizophrenia
Predictive value	Failure to replicate studies	Moderation analyses using hippocampal structure
Modulated with interventions	Pharmacologic agents with ubiquitous brain targets	Identification of valid and feasible targets

## Hippocampal hyperactivity can be measured with routine fMRI methods

Studies in CHR-P individuals (Schobel et al., 2013), in the early stages of the illness (McHugo et al., 2019), and in chronic stages of the illness (Talati et al., 2014) report hippocampal hyperactivity using varying methods including CBV imaging (Schobel et al., 2009), ASL (Scheef et al., 2010), PET (Heckers et al., 1998), and the BOLD signal (McHugo et al., 2022). Each method has inherent limitations that constrain its usefulness in consistently and reliably measuring hippocampal activation. PET and CBV imaging require exogenous tracers that can be difficult to administer, particularly to actively psychotic patients. As discussed in Chapter II, antipsychotic medication use affects hippocampal rCBF, severely restricting the utility of ASL methods for measuring hippocampal activation unless the patient population of interest is antipsychotic naïve. Measuring hippocampal activity using the BOLD signal is limited by intrinsic reliability concerns (Bennett and Miller, 2010), likely resulting from the fact that the BOLD signal is qualitative and that it measures changes in and around veins secondary to direct changes in CBF and cerebral metabolic rate of oxygen (Logothetis, 2008). Therefore, compared to the other imaging techniques, the BOLD signal is further removed from underlying neural activity. Reliability concerns of all imaging methods can be further exaggerated by tasks that do not reliably engage brain structures (Elliott et al., 2020).

Measuring hippocampal hyperactivity is challenging, as evidenced in studies that report small effects (Talati et al., 2014). This challenge is likely due to a combination of limited fMRI resolution, the presence of field inhomogeneities and inconsistent fMRI signal due to the positioning of the hippocampus in the skull, and functional (Strange et al., 2014), structural (Duvernoy et al., 2013), and vascular (Spallazzi et al., 2019) heterogeneity of the hippocampus.

Further, recent evidence suggests that hippocampal hyperactivity is not a consistent signal throughout the course of illness, but rather a signal of acute illness or psychosis vulnerability (McHugo et al., 2022). If this hypothesis is confirmed, it would further elucidate difficulties in capturing hippocampal hyperactivity using fMRI. However, since this suggests that patients with schizophrenia undergo periods without measurable hippocampal hyperactivity, a validation of this hypothesis also questions the concept of hippocampal hyperactivity as a potential biomarker for schizophrenia.

As imaging technology progresses, the human hippocampus will be probed with increasing spatial and temporal resolution. Future studies investigating hippocampal hyperactivity should carefully craft study designs before implementation. Further, there is a need for a meticulous selection of fMRI assessments and the characteristics of the patient cohort to be examined, as methodological and clinical variables can impact the ability to measure the already elusive hippocampal signal.

#### Hippocampal hyperactivity correlates with clinical symptoms

Increased hippocampal activity is associated with more severe psychopathology (Friston et al., 1992), specifically positive symptoms (Dierks et al., 1999; Ebmeier et al., 1993; Gur et al., 1995; Hare et al., 2017; Liddle et al., 1992; Molina et al., 2005; Schobel et al., 2009; Silbersweig et al., 1995), negative symptoms (Schobel et al., 2009), poor outcomes (Lahti et al., 2006), and working memory performance (Tregellas et al., 2014). However, these correlations are not consistently reported across studies assessing clinical symptoms and outcomes. Further, the

evidence for associations between hippocampal hyperactivity and positive symptoms is substantially greater than for negative and cognitive symptoms.

There are two types of human studies that will be critical to strengthening the link between the hippocampus and clinical symptoms and outcomes. First, there is a need for clinical trials that perturb hippocampal activation using novel, targeted interventions. Demonstration of changes in hippocampal activity and simultaneous improvements in clinical assessments after intervention will provide necessary, causal inference testing to link hippocampal pathology with psychopathology. Second, there is a need for human trials to probe hippocampal connectivity with other brain regions involved in the expression of clinical symptoms. Recent animal models have provided a framework for hippocampal circuits that drive symptoms and behaviors observed in schizophrenia patients. Confirming this framework and establishing these circuits in humans will further strengthen the link between the brain and schizophrenia.

#### Hippocampal hyperactivity is translatable from animal models

Hippocampal hyperactivity is observed in rodent models of schizophrenia (Tregellas, 2014), suggesting that this finding has translational utility. However, there is currently no established, all-encompassing rodent model of schizophrenia. Most models have behavioral phenotypes that resemble positive symptoms of schizophrenia but lack alterations in social interactions and learning and memory impairment, corresponding with negative and cognitive symptoms, respectively (Jones et al., 2011). The heterogeneity of patients' presentations and individual variance in the domains of psychopathology further complicate the feasibility of an

all-encompassing rodent model of schizophrenia. Therefore, the direct translation of hippocampal hyperactivity in rodents to patients must be cautiously inferred. Developing reliable and predictive animal models is crucial to advance our understanding of the neural basis of the illness and for the development of novel, efficacious therapeutics (Jones et al., 2011).

#### Hippocampal hyperactivity as a predictor of illness progression and structural change

Currently, no established biological markers for schizophrenia can predict illness progression. In a longitudinal study using CBV imaging, baseline hippocampal hyperactivity in the CA1 subfield differentially predicted clinical progression to psychosis from a prodromal state (Schobel et al., 2009). However, a second cohort did not replicate this finding (Provenzano et al., 2020). Instead, this study reported that focal hippocampal atrophy predicted progression to psychosis. This finding is similar to a recent volumetric longitudinal study demonstrating that baseline volumetric deficits differentiated individuals with schizophreniform disorder that would progress to a diagnosis of schizophrenia from those that would not progress (McHugo et al., 2020). There is also evidence that baseline hippocampal hyperactivity predicts hippocampal morphological changes (Schobel et al., 2013). Future studies need to test for replications of these predictions to clarify the relationship between hippocampal hyperactivity, hippocampal volume, and illness progression. Further, hippocampal volume may complement statistical tests using hippocampal hyperactivity to test for progression of illness. Including volumetric or shape measures as tertiary variables in moderation analyses could reveal a reliable linkage between hippocampal activity and illness progression.

### Pharmacologic modulation of hippocampal hyperactivity

Rodent studies demonstrate modulation of hippocampal activity using a variety of pharmacologic agents, suggesting that their pharmacological sites of action could translate to targets to modify hippocampal activity in humans. Despite a growing understanding of the neural mechanisms underlying hippocampal hyperactivity in humans, this translation has not led to identifying novel treatments or molecular treatment targets. Several obstacles are preventing the translation of treatment targets from animal models for the modulation of hippocampal hyperactivity in humans. One such obstacle is mechanistic validity, or whether the intervention impacts the molecular or cellular contributors to the excitation-inhibition underlying hippocampal hyperactivity. For example, oxytocin has been postulated as a potential modulator of hippocampal hyperactivity (Davies et al., 2019), although its role in the mechanism is unclear. The oxytocin receptor's widespread location in the brain (Viero et al., 2010) will result in many effects outside of the hippocampus, decreasing the mechanistic validity of the intervention. Similarly, multiple studies have explored nicotinic agents as a modulator of hippocampal activity (Tanabe et al., 2006; Tregellas et al., 2010, 2005). A well-documented limitation of interventions affecting the cholinergic system is target engagement outside of the hippocampus (Tregellas and Wylie, 2019). Despite encouraging evidence from rodent studies, the non-specific engagement of the micro-circuitry underlying hippocampal hyperactivity suggests that these interventions and their targets are not ideal.

Another obstacle is feasibility, or whether novel treatments can realistically be administered to patients. For example, rodent studies have suggested that  $\alpha 5$  containing

GABA-A receptor modulators may be a potential treatment for schizophrenia (Gill et al., 2011).  $\alpha 5$  containing GABA-A receptors are regionally confined to the hippocampus in comparison to other GABA-A receptors (Sur et al., 1999). Further, their activation would hypothetically increase inhibitory control of pyramidal neurons, normalizing the excitation-inhibition imbalance underlying hippocampal hyperactivity. Therefore, interventions targeting  $\alpha 5$  containing GABA-A receptors have high mechanistic validity. However, there are well-documented, severe side effects of GABA-A modulators that may prevent the administration of specific dosages or duration of treatment to schizophrenia patients (Rudolph and Knoflach, 2011). While interventions that are not clinically feasible can still test hypotheses to elucidate the excitation-inhibition imbalance underlying hippocampal hyperactivity, they must be carefully considered if the goal is to advance the intervention to a clinical treatment option.

#### *The role of IHI in increasing vulnerability to psychotic disorders*

The results in this project do not suggest that IHI predicts the development of psychosis or specific symptom domains of schizophrenia. Instead, IHI is relatively common in healthy individuals (Cury et al., 2015). IHI is likely a neurodevelopmental marker for underlying neural alterations that increase vulnerability for the development of psychosis. This hypothesis is consistent with the “two-hit” model of schizophrenia (Bayer et al., 1999; Keshavan, 1999), in which altered neurodevelopment (hit one) primes neural systems for dysfunction in adolescence after a “second hit” (e.g., environmental insults, neuroinflammation). Whether IHI directly leads to increased vulnerability or functions as a marker for increased vulnerability is unknown. This section will explore this vulnerability hypothesis.

The mechanism by which IHI affects hippocampal structure and function in schizophrenia is unclear. IHI might indicate abnormal migration and development of interneurons, which occurs in the second trimester (Tricoire et al., 2011). Alterations in interneurons causing an excitation-inhibition imbalance might later result in hippocampal hyperactivity in the early stage of psychosis. A recent study reported that the genetically predicted expression of the brain complement component *C4A* correlates with hippocampal shape deformations that co-localize with the CA1 findings reported in this project (Da Silva et al., 2021). There is an increased risk of schizophrenia associated with genetically predicted *C4A* brain expression, and preclinical models have demonstrated that *C4A* promotes synapse elimination by microglia (Sekar et al., 2016). These findings support a hypothesis of aberrant synaptic pruning in schizophrenia and suggest an interplay between synaptic pruning and changes in hippocampal morphology that could result in IHI.

Alternatively, IHI may serve as an indicator for other abnormalities in neurodevelopment that affect hippocampal morphology. For example, an arrest in development resulting in IHI could be a marker of a systemic obstetric complication (i.e., a trigger for aberrant *in utero* development) such as hypoxia or infection, which are associated with smaller hippocampal volumes (DeLisi et al., 1988) in schizophrenia patients and elevate the risk for schizophrenia 2-5 fold (M. Cannon et al., 2002). The CA1 subfield is especially susceptible to hypoxia (T. D. Cannon et al., 2002; Zierhut et al., 2013) in comparison to other hippocampal subfields (Csernansky et al., 1998a).

Studying the perinatal information associated with individuals with IHI can test this hypothesis. A limitation of this project is that the PGPP does not collect obstetric and

developmental information. Therefore, studying IHI in openly available databases that collect rich developmental information would be ideal for testing for associations between IHI and abnormalities in development that affect hippocampal morphology. Several large-scale population neuroscience studies collect brain imaging in children and adolescents and perinatal, developmental, and parental information (Karcher and Barch, 2020; Kooijman et al., 2017; Satterthwaite et al., 2016). Studying IHI in these datasets may reveal new links between this neurodevelopmental variant and developmental pathways.

One challenge to studying IHI in large datasets will be the manual, time-intensive scoring of IHI criteria. Scoring IHI in hundreds or thousands of images will require ratings from multiple individuals, increasing the risk for inter-rater variability in scoring and therefore potential biases in IHI prevalence and severity results. Developing novel automated methods of IHI scoring addresses this problem. Novel machine learning approaches such as deep convolutional neural networks (Huo et al., 2019) can automatically generate IHI scores from raw or minimally processed structural images. Since this project has established that IHI affects hippocampal volume, asymmetries, and shape, automation of IHI will be critical for the adoption of integrating IHI measures into future hippocampal morphological studies.

A recent meta-analysis of studies documenting IHI reported increased prevalence rates of IHI in patients with epilepsy and malformations of cortical development (MCD) (Mutti et al., 2021). Commonalities between these illnesses and schizophrenia may reveal information about the mechanism of IHI. The association between epilepsy, particularly temporal lobe epilepsy, and schizophrenia is well documented (Nakahara et al., 2018). Individuals with epilepsy have an 8.5-fold higher risk of developing schizophrenia (Clarke et al., 2012). Evidence suggests that

aberrant excitatory synaptic transmission resulting in an excitation-inhibition imbalance drives psychosis and seizure activity (Nakahara et al., 2018). The most common MCD associated with IHI is periventricular nodular heterotopia (Mutti et al., 2021), a condition characterized by abnormal neuronal migration during fetal brain development resulting in seizures (Lu and Sheen, 2005). Altogether, the pathophysiologic similarities between these illnesses support a mechanism of IHI characterized by abnormal neuronal development and migration, resulting in aberrant hippocampal activity.

#### *IHI as a marker to understand hippocampal pathology in schizophrenia*

IHI is a valuable marker to study neurodevelopment. First, it can be assessed using routine structural neuroimaging methods. Second, IHI results from abnormalities in a short, specific window of neurodevelopment (i.e., the second trimester). Third, it is not exceedingly rare in a schizophrenia population, indicating it is a feasible marker to study in moderate-sized groups. This project linked IHI to several hippocampal structural measures in schizophrenia and leveraged IHI's effectiveness as a neurodevelopmental marker to better understand the effect of neurodevelopment on hippocampal shape. Similar approaches exploring the role of this variant in other domains of hippocampal pathology deserve further exploration.

This project reports the effect of IHI on hippocampal subfields in the context of a shape analysis. Shape analyses provide limited structural information, as it only allows for the assessment of hippocampal surfaces. Therefore, the effect of IHI on hippocampal subfield volumes is unknown. The conclusions of this project suggest that IHI contributes to volumetric deficits in the CA1 subfield of schizophrenia patients. Future studies should test this hypothesis

to further support the neurodevelopmental conclusions suggested by this project. Additional studies assessing the impact of IHI on hippocampal subfield volumes are necessary to fully understand the impact of IHI on hippocampal structure.

Morphologic abnormalities characteristic of IHI (i.e., verticalized, medial, rounded hippocampal shape) may be associated with alterations of hippocampal neuron structure. The link between IHI and abnormalities of neuronal development or migration reviewed above support this idea. The ideal methodological approach to test this hypothesis would require post-mortem analysis. Despite IHI's relatively common prevalence in schizophrenia, the rarity of post-mortem samples challenges the feasibility of a post-mortem study of IHI. However, recent advances in neuroimaging provide alternative methods to assess hippocampal microstructure. Specifically, magnetic resonance elastography (MRE) imaging allows for the noninvasive assessment of microstructural composition and organization of neural tissue. This method is strongly suited to studying developmental changes in mechanical properties of the brain (Johnson and Telzer, 2018). Shape abnormalities of the hippocampus, such as IHI, are ideal for measuring with MRE, as physical properties of neural tissue likely influence the shapes of anisotropic brain structures such as the hippocampus (van Essen, 1997). Future studies should utilize MRE to determine whether differences in neural tissue or microstructure composition are associated with the presence of IHI. If these differences exist, exploring their relationship with other structural abnormalities of the hippocampus in schizophrenia may reveal novel insight into hippocampal structural pathology.

Studies investigating IHI have primarily focused on the hippocampal parenchyma and surrounding sulcal patterns. No study has investigated the impact of IHI on hippocampal white

matter or structural connectivity to other brain regions. There is post-mortem evidence for white matter volumetric deficits in the hippocampus of schizophrenia patients (Heckers et al., 1991). Further, neuroimaging studies report alterations in white matter integrity (Hao et al., 2009) and connectivity (Qiu et al., 2010; White et al., 2007) of the hippocampus. Of note, one study reported hippocampal-cortical structural connectivity alterations in a cohort of patients that also demonstrated anterior, bilateral hippocampal shape deformations consistent with the results reported in this project (Qiu et al., 2010). Future studies should test whether differences in white matter are associated with the presence or severity of IHI. Exploring the relationship between white matter changes and other structural or functional abnormalities of the hippocampus can aid in the understanding of brain or circuit abnormalities in schizophrenia.

No study to date has explored the effect of IHI on hippocampal function. Structure-function relationships are a fundamental principle of naturally occurring systems, including the brain (Suárez et al., 2020). Detecting hippocampal cytoarchitectural or structural connectivity differences would suggest potential effects of IHI on hippocampal activity or functional connectivity to other brain regions. Ideally, automated grading methods will allow for assessing IHI in extensive studies collecting a variety of hippocampal structural and functional measures in both healthy individuals and schizophrenia patients to reveal further neurodevelopmental insights into hippocampal pathology.

### *Clinical implications*

Several therapeutics with novel mechanisms of action are under development and testing to treat individuals with schizophrenia (Brannan et al., 2021; Kantrowitz et al., 2020;

Koblan et al., 2020). Despite numerous trials of novel and repurposed pharmacologic agents, mechanisms of antagonizing the D<sub>2</sub> receptor have been the only proven therapeutic mechanism for schizophrenia (Miyamoto et al., 2012). Many challenges limit the development of effective treatments and the identification of their targets. First, new pharmacologic agents identified via medicinal chemistry or pharmacologic screening platforms may not have established mechanisms of action or lack target engagement studies that test whether the experimental agent binds to its molecular target in the brain in sufficient concentrations to exert its therapeutic effects. Second, despite having novel mechanisms of action or neural targets, new treatments may only suppress clinical symptoms instead of modifying the illness. Lastly, proposed therapeutics might not demonstrate comparable or superior efficacy and side-effect profiles compared to existing antipsychotic treatments. This project addresses these challenges by informing our understanding of hippocampal hyperactivity as a treatment target for schizophrenia.

There needs to be evidence for target engagement in intervention studies to establish hippocampal hyperactivity as a treatment target for schizophrenia. This work reports the results of a target engagement study designed to pharmacologically modulate hippocampal hyperactivity in patients with schizophrenia. LEV's mechanism of action suggests it may be a modulator of the excitation-inhibition imbalance driving hippocampal hyperactivity (Wakita et al., 2014; Yang et al., 2007; Yang and Rothman, 2009) and therefore is an appropriate pharmacologic agent to engage the target of interest (i.e., hippocampal activity). This project's results indicate that the dosage and duration of LEV administered to schizophrenia patients were insufficient to engage the target of interest. This negative finding does not preclude

hippocampal hyperactivity as a potential treatment target. Instead, as previously emphasized, it has highlighted many difficulties in modulating the neural mechanisms of the hippocampus. Future studies using alternate study designs, imaging methods, or clinical cohorts of patients will improve on this project for more appropriate assessments of hippocampal activity to demonstrate target engagement.

Identifying treatment targets that will be illness-modifying is challenging. Current antipsychotic medications suppress symptoms of schizophrenia by targeting the dopaminergic system but do not modify the underlying illness. Studies have identified abnormalities in neural systems and brain regions that project to the dopaminergic system (Howes et al., 2015). Targeting these upstream neural mechanisms, such as the hyperactive hippocampus, will ideally modify the illness. However, the neurodevelopmental hypothesis speculates that these altered neural mechanisms result from abnormal brain development (Murray et al., 1987; Weinberger, 1987). Therefore, even if the neural mechanisms driving dopaminergic hyper-responsivity are identified, the window for illness prevention is long before the emergence of clinical symptoms. Studying neurodevelopmental alterations such as IHI can address this conundrum. The presence of IHI locates the timing of altered neurodevelopment in the second trimester. Identifying hippocampal neural dysfunction that arises during the second trimester may provide insight into neural markers of vulnerability that can be targeted with protective pharmacologic agents, potentially preventing the emergence of the illness.

## **Conclusion**

This thesis tested mechanisms of hippocampal dysfunction to answer two fundamental questions to advance our understanding of hippocampal hyperactivity in schizophrenia. First, what are the neural mechanisms driving the excitation-inhibition imbalance underlying hippocampal hyperactivity? Second, when does hippocampal dysfunction arise during neurodevelopment? This work demonstrates the difficulty of modulating hippocampal hyperactivity, and making inferences about its underlying neural mechanisms, in human neuroimaging studies. Future target engagement studies with pharmacologic agents are necessary to establish hippocampal hyperactivity as a treatment target for schizophrenia. Additionally, this project establishes the increased prevalence of a hippocampal neurodevelopmental variant in schizophrenia and demonstrates its impact on hippocampal structure. The developmental window in which this variant arises provides new insight into potential neural abnormalities that may contribute to hippocampal dysfunction and increased susceptibility for developing the illness. Further exploration of this variant with structural and functional imaging studies will increase our understanding of hippocampal pathology and when it develops in schizophrenia.

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