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Neural Mechanisms of Visual Working Memory Impairment in Individuals at Clinical High Risk for Psychosis

A Dissertation submitted in partial satisfaction of the requirements
for the degree Doctor of Philosophy

in

Clinical Psychology

by

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The Dissertation of Wendy Zhang is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

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Chapters 1-4 of this dissertation, in part, are under preparation for publication with co-author Dr. Emily Kappenman. The dissertation author will be the primary author on this publication.

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ABSTRACT OF THE DISSERTATION

Neural Mechanisms of Visual Working Memory Impairment in Individuals at Clinical High Risk for Psychosis

by

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Rationale: Working memory deficits are a core feature of psychotic disorders, readily evident in the first episode and persistent throughout the illness. Whereas impaired performance on visual working memory tasks has been observed in individuals at clinical high-risk (CHR) for psychosis, the nature and underlying neural mechanisms of this impairment remain largely unknown. There is some evidence that failure to modulate brain oscillatory activities in the

alpha/beta frequency bands may constrain visual working memory capacity in schizophrenia, but it is unclear whether these potential neural processes are already implicated in the CHR stage.

Design: Using electroencephalogram (EEG), this study examined neural oscillations in the alpha (9-13 Hz) and beta (15-30 Hz) frequency bands in 48 individuals between 15-30 years of age meeting the Criteria of Prodromal Syndromes (CHR) and 47 demographically matched healthy control (HC) participants during a change localization visual working memory paradigm. Aim 1 compared behavioral visual working memory capacity between the two groups. Aim 2 examined suppression of alpha and beta neural activities during the maintenance and retrieval of visual working memory and correlated these metrics of oscillatory modulation with behaviorally measured visual working memory capacity. Aim 3 explored the associations among working memory capacity, broader measures of neurocognition, and global functioning.

Results: Working memory capacity was significantly reduced in individuals at CHR (M=3.02, SD=0.37) compared to HC (M=3.23, SD=0.40; t(93)=-5.67, p=.009). The CHR group also showed attenuated alpha and beta suppression during both retention and retrieval stages of the task (F(1,93)=4.45, p=.038), which significantly predicted working memory capacity in this group (r=-0.41, p=0.004). Further, visual working memory capacity was correlated with a range of clinical and cognitive measures in CHR (r's > 0.30, p's < 0.05).

Conclusions: This was the first study to date to directly quantify visual working memory capacity among individuals at CHR and provided evidence for a notable capacity reduction in this core cognitive ability in the at-risk state. Importantly, the EEG findings highlighted a key neural mechanism underlying such impairments and suggested that the neural architecture required for effective modulation of oscillatory activities may be critically disrupted in emerging psychosis.

I. INTRODUCTION

Schizophrenia is a serious mental illness with a lifetime prevalence of approximately 0.5% to 1% worldwide (Bhugra, 2005; McGrath et al., 2004; Saha et al., 2005; Simeone et al., 2015). Cardinal symptoms of schizophrenia can be broadly classified into three categories: positive symptoms (delusions and hallucinations), negative symptoms (blunted affect, anhedonia, diminished motivation, social withdrawal), and disorganization (disorganized thought process and behavior). The exact cause of schizophrenia is unknown, though genetic and environmental factors have both been long recognized as having major etiological contributions to its development (Birnbaum & Weinberger, 2017; Brown, 2011; Tsuang, 2000; van Os et al., 2010). Despite advancement of pharmacological and psychosocial interventions, outcomes for patients diagnosed with schizophrenia, like the clinical presentations, are heterogeneous, and they tend to run a chronic course with significant disabilities (Huxley et al., 2021; Jääskeläinen et al., 2013; Robinson et al., 2004). From a public health perspective, schizophrenia also incurs tremendous societal costs and burden to patients and their families (Jin & Mosweu, 2017; Knapp et al., 2004).

There is increasing recognition that "schizophrenia" may only represent a fraction of a multidimensional psychotic syndrome that can vary significantly in severity, duration, and disability from transient, subclinical psychotic experiences to chronic debilitating illness (Reininghaus et al., 2016; Shevlin et al., 2017). Disorders previously conceptualized as separate disease entities, most notably schizophrenia and bipolar disorder, have also been proposed as expressions of the same psychosis spectrum due to their phenomenological, biological, and genetic overlap (Keshavan et al., 2011; Potash, 2006; Potash & Bienvenu, 2009). In accordance with this movement, the Fifth Edition of the Diagnostic and Statistical Manual of Mental

Disorders (DSM-5) included dimensional assessments of eight domains of psychopathology considered relevant for psychosis, including symptoms traditionally associated with schizophrenia (hallucinations, delusions, disorganized speech), symptoms of mood disorders (depression, mania), as well as other well-characterized features of psychotic disorders (i.e., neurocognitive and psychomotor abnormalities) to aid clinical care and research on pathophysiological mechanisms of psychotic disorders (Barch et al., 2013).

The psychosis spectrum is also thought to extend temporally across the lifespan, with subclinical levels of psychotic symptoms emerging during adolescence and early childhood among those who later develop a formal psychotic disorder (Bechdolf et al., 2012; Fusar-Poli et al., 2014; Yung & McGorry, 1996). This "prodromal" phase of psychosis has attracted an explosion of research efforts in the past two decades that aim to improve early detection, assessment, and intervention of psychosis among at-risk individuals.

1.1. Clinical High Risk for Psychosis and Neurocognitive Dysfunction

The identification of individuals at risk for psychosis is currently based primarily on clinical presentations, or the presence of the clinical high risk (CHR) syndrome, characterized by subclinical levels of positive symptoms, negative symptoms, and functional impairment (McGlashan et al., 2010). Within this framework, diagnostic criteria have been developed; an individual is typically considered at CHR for psychosis if they present with subclinical psychotic symptoms, full-blown psychotic symptoms that are brief and self-limiting, or a significant decrease in functioning in the context of a family history of schizophrenia (McGlashan et al., 2010; T. J. Miller et al., n.d.; Yung et al., 2005). Based on these criteria, approximately 20% to 35% of the "at-risk" individuals develop a psychotic disorder within two to three years of initial diagnosis (Cannon et al., 2008; Fusar-Poli et al., 2012, 2015, 2015). While this rate of psychosis

conversion far exceeds the prevalence of psychotic disorders in the general population, the majority of those meeting clinical criteria for the CHR syndrome do not develop psychosis. Research efforts have thus been devoted to identifying additional "markers" of psychosis risk that may improve the sensitivity of existing tools in predicting conversion to psychotic disorders, which could in turn inform risk-stratified intervention strategies (Fusar-Poli, McGorry, et al., 2017). For example, risk calculators that combine demographic, clinical, neurocognitive, and/or functioning measures have shown promising clinical utility in predicting individual risk for psychosis (Cannon et al., 2016; Carrión et al., 2016; Fusar-Poli, Rutigliano, et al., 2017; Oliver et al., 2020). In addition to providing a clinical ground for early detection and intervention, the CHR state also presents unique opportunities for studying the pathogenesis of psychosis without the confounds of antipsychotic medication or prolonged illness duration. Indeed, many key features of schizophrenia and other psychotic disorders have been identified during the early course of the psychotic illness, including widespread cognitive disturbances that have been long recognized as a hallmark of psychotic disorders.

First conceptualized as a defining feature of schizophrenia by Kraeplin (1919) and Bleuler (1950), cognitive deficits have been subsequently observed across the psychosis spectrum and across virtually all cognitive domains (J. Giuliano et al., 2012; Lepage et al., 2014; Sheffield et al., 2018; Simonsen et al., 2011). The trajectory of cognitive functioning in psychosis across the lifespan has been well characterized: overall impairments are already evident at the prodromal phase, decline drastically at the illness onset, continue to deteriorate following the first episode, and remain relatively stable for the rest of the illness duration (Zanelli et al., 2022). In CHR, impairments have been shown on tasks measuring attention, working memory, verbal and visual memory, processing speed, verbal fluency, and executive

functions, with effect sizes ranging from small to medium compared to control groups (for meta-analyses, see Fusar-Poli et al., 2013; J. Giuliano et al., 2012). The level of cognitive functioning in CHR falls between that of healthy individuals and patients with schizophrenia or bipolar disorder (Bora et al., 2010; Kurtz & Gerraty, 2009) and is generally comparable to the level of deficits seen in unaffected first-degree relatives of patients with schizophrenia and bipolar disorder (Bora, 2017).

Understanding the neurocognitive deficits in CHR is particularly relevant because the maturation of a wide array of cognitive abilities, especially those involving higher order integrative cortices such as the prefrontal regions, coincide in time with the development of psychotic symptoms (Catts et al., 2013). The neurodevelopmental account of psychosis posits that symptoms are manifested as a result of interactions between typical neural development and early pathophysiological processes, both rapidly unfolding during adolescence and early adulthood (Bombin et al., 2013). Therefore, probing the neural mechanisms of neurocognitive deficits may elucidate the specific ways in which brain functions are impacted in this process. Further, if neurocognitive deficits prove to be a reliable vulnerability marker of psychosis (indeed, there is already some evidence that more severe neurocognitive impairment was associated with risk for conversion; see J. Giuliano et al., 2012), it could be used to inform preventive care and even serve as a treatment target for early intervention in CHR.

1.2. Working Memory Deficits in Psychosis

Working memory deficits are a hallmark of neurocognitive impairment in psychosis. Working memory describes the temporary maintenance and manipulation of information in service of ongoing goals. Expanded from the concept of short-term memory (Atkinson & Shiffrin, 1968) current models of working memory (e.g., A. Baddeley, 2010; A. D. Baddeley &

Hitch, 1974) emphasize the purposeful use of temporarily stored information based on the specific objectives or tasks in hand (thus the "working" in working memory). Dubbed the "sketchpad of consciousness" (A. Baddeley, 1993), working memory is indispensable to a wide range of cognitive tasks required for day-to-day activities. Indeed, working memory capacity has been shown to strongly predict an individual's fluid intelligence (Conway et al., 2003), mathematics and language abilities (Ashcraft & Kirk, 2001; Ashcraft & Krause, 2007), and overall academic performance (Hall et al., 2015). Across the psychosis spectrum, working memory has also been linked to functional outcomes in CHR (Broome et al., 2012), first episode psychosis (Bodnar et al., 2008; González-Ortega et al., 2013), bipolar disorder (Green, 2006), and schizophrenia (see Piskulic et al., 2007 for a review, also see Green, 2006; McGurk et al., 2004).

Working memory deficits have been reliably and robustly shown among patients with schizophrenia, with meta-analyses indicating impairments of moderate-to-large effect sizes across modalities (i.e., verbal versus visual) and a diverse range of working memory tasks (Forbes et al., 2009; Lee et al., 2005), though the deficits were found to be more consistent for visual than for verbal memory (Lee et al., 2005). Importantly, the degree of the impairment has been shown to be independent of illness duration, antipsychotic medication dosage, or symptom profile, suggesting working memory deficits are a stable trait of the illness rather than the secondary consequence of prolonged exposure to psychosis or medication. Working memory deficits have also been identified in bipolar disorder across mood states, albeit with reduced severity compared to individuals with schizophrenia (see Soraggi-Frez et al., 2017 for a review). There is some evidence that visuospatial working memory is more impaired in bipolar patients with a history of psychosis than those without psychosis (Glahn et al., 2006), suggesting that

there may be a specific link between psychosis and visuospatial working memory functioning in bipolar disorder. Working memory impairments are readily evident in the prodrome. In a meta-analysis, Bora and colleagues (2014) found consistent reductions in both verbal and visual working memory performance among CHR individuals across samples, with visuospatial working memory showing a particularly robust effect ($d = 0.71$) compared to verbal working memory ($d = 0.41$). Importantly, performance on working memory tasks has been repeatedly shown to account for unique variability that separates CHR individuals from healthy controls (Bendfeldt et al., 2015; Pflueger et al., 2007), even after controlling for general intelligence and performance in other cognitive domains (Seidman et al., 2016).

Neurodevelopmentally, the maturation of working memory abilities occurs in striking parallel with the development of psychosis. Both cross-sectional and longitudinal studies of neurotypical children/adolescents have found continuous improvement in working memory abilities from early childhood to approximately age 15, leveling off between ages 15 and 22 (Gathercole et al., 2004; Ullman et al., 2014). Intriguingly, this developmental trajectory may be uniquely disrupted in psychosis. When comparing the amount of working memory improvement from age 8 to 20 across samples with and without psychosis, Mollon and colleagues (2018) found halted growth only in the group that met diagnostic criteria for a psychotic disorder as adults, whereas those with depression or nonclinical psychotic experiences showed developmental trajectories comparable to those of healthy controls. Neurobiologically, dopaminergic pathways in the prefrontal cortex have been implicated in both working memory functions and the etiology of psychosis (for a review, see Tost et al., 2010). Given the prominent working memory deficits across the psychosis spectrum, particularly in the visual domain, as well as the neurodevelopmental and neurobiological overlap between working memory and

psychosis, characterizing the nature of working memory deficits in psychosis and clarifying the underlying neural mechanisms could have significant theoretical and clinical implications.

1.3. Mechanisms of Reduced Visual Working Memory Capacity in Psychosis

Why is working memory impaired in psychosis? To answer this question, it is important to first clarify that working memory is not a unitary construct. Rather, a key feature of virtually all models of working memory is that it is a system involving interactions among multiple cognitive components. Baddeley and Hitch (1974)'s seminal multi-store model describes a "central executive" component that oversees and coordinates the operations of modality-specific temporary stores (i.e., phonological loop and visuospatial sketchpad). The model was later modified with the addition of an episodic memory buffer that is thought to bind the temporary information across modalities and interface with perception and long-term memory (A. Baddeley, 2000). Recently, Eriksson and colleges (2015) took this multi-component view one step further to suggest that working memory does not consist of a fixed set of cognitive subcomponents *per se*. Instead, the encoding/consolidation, maintenance, and retrieval of information in working memory are the results of interactions among various cognitive processes that are required to complete the specific working memory task in hand. According to this and other "component processes" views of working memory, cognitive processes that may be described differently in other contexts (e.g., selective attention, executive control, sustained attention, inhibition) could all constitute integral aspects of working memory. Therefore, to understand the nature of working memory deficits in psychosis, it is critical to examine the context in which working memory functions are measured, the cognitive processes that are activated by a given working memory task, and specific working memory subcomponent(s) that may contribute to the observed impairments.

Clinically, working memory has been predominantly assessed with neuropsychological tests theorized to tap working memory operations. Whereas these tasks do provide functionally and clinically meaningful measures of working memory performance in schizophrenia, they often recruit additional cognitive operations that are likely also compromised in psychosis, making the interpretations of impaired performance difficult (Kessels, 2019). For example, in the Wechsler Memory Scale-III Spatial Span task, one of the core working memory tasks in the MATRICS Consensus Cognitive Battery designed to measure cognition in individuals diagnosed with schizophrenia and other psychotic disorders, participants are required to touch irregularly spaced blocks in the same or reverse order as the examiner (Green et al., 2004). That is, in addition to successful encoding, maintenance, and retrieval of the visuospatial information in working memory, the task also requires learning, programming and executing complex motor sequences—an area where individuals with psychosis have shown pronounced deficits (Cuesta et al., 2018; Exner et al., 2006)—all before the working memory traces are rapidly lost (Zhang & Luck, 2009).

Further, much of the evidence of visual working memory impairment in psychosis comes from complex span tasks (e.g., the spatial span task described above) that require both the maintenance of visuospatial memoranda and a concurrent, secondary task (e.g., reversing the sequence of blocks being touched). Thus, impairments on these "storage-plus-processing" tasks could reflect reduced capacity of the temporary storage system of working memory (analogous to the "episodic memory buffer" described by Baddeley), inefficient manipulation of stored information (reflecting failure in the executive component of working memory), or a combination of both. There is abundant evidence suggesting impairment in both components of visual working memory in psychosis (Ichinose & Park, 2019). Given the likely multifactorial

nature of visual working memory impairment in psychosis, we choose to focus on one fundamental aspect of working memory—working memory capacity—and specific neural mechanisms that may serve to constrain visual working memory capacity in psychosis.

1.3.1. Reduced Visual Working Memory Capacity in Psychosis

One of the fundamental features of working memory is that its *capacity*, or the amount of information that can be held active simultaneously, is strikingly limited. In the visual domain, both behavioral and neurophysiological studies have shown that the capacity is approximately three to four simple items among neurotypical young adults (Luck & Vogel, 1997, 2013). Visual working memory capacity has been shown to stay highly stable over time once matured (Johnson et al., 2013), even after extensive practice (Xu et al., 2018), and accounts for over 40% of variance in individual differences in fluid intelligence and broad cognitive functions (Fukuda et al., 2010; Johnson et al., 2013). Inquiries into visual working memory capacity were popularized in the 1990s partially due to the development of experimental paradigms that allowed for reliable estimates of capacity using simple visual stimuli, most notably the change detection task (Luck & Vogel, 1997; Pashler, 1988). In a typical change detection task, participants first briefly view a to-be-remembered sample array of visual stimuli (e.g., colored squares). After a delay period when the array is not in view, a test array appears, and the participants are to indicate whether the two arrays are identical or if one item has changed. In a variant of the design, the change localization task, participants are informed that the test array will differ from the sample array in one or more aspects (e.g., the color of one square), and the task is instead to identify the item that changed. Visual working memory is typically estimated as a function of task performance (e.g., percent correct, hit rate) and the number of items in the memory array (i.e., set size), although additional outcome metrics can also be derived from these tasks, such as estimates of memory

strength based on signal detection models and receiver operating characteristic (ROC) analysis (Brady et al., 2023). The task is thought to provide relative "pure" measures of visual working memory capacity compared to complex span tasks and particularly suitable for isolating capacity limits from the widespread sensory, cognitive, and motor deficits in psychosis. Specifically, in a typical change detection/localization task, stimuli are simple geometric shapes (i.e., squares) presented in bright, highly discriminable colors; the simplicity of the visual stimuli minimizes the amount of sensory and perceptual processing required for encoding and recognition of individual items. The delay period is remarkably brief (usually 1-2 seconds or shorter). The response requires only a mouse click and is unspeeded, eliminating any interference from potentially impaired processing speed or motor functioning. Importantly, the attention and executive demand to complete the task is relatively low, with no dual task, task switching, or memory manipulation required.

There is mounting evidence that even when measured in these most controlled experimental settings, visual working memory capacity is significantly reduced in individuals with schizophrenia (Erickson et al., 2015, 2017; Gold et al., 2010, 2019). Consistent with findings in healthy adults, Johnson and colleagues (2013) found that visual working memory capacity, as measured by a simple change localization task, was robustly correlated with higher order cognitive abilities such as attention/vigilance, processing speed, and reasoning/problem-solving in schizophrenia, all areas in which this group showed impairment. More recently, Gold and colleagues (2019) employed the change detection and localization tasks to examine visual working memory capacity across psychotic disorders, in patients with schizophrenia, schizoaffective disorder, and bipolar disorder with psychosis. They found that as a group, patients with psychotic disorders had significantly lower visual working memory capacity

compared to healthy controls, with no systematic differences in working memory impairment across diagnostic groups. Visual working memory capacity also showed significant correlations with functional capacity and outcome among those with psychotic disorders. Together, these findings suggest that there is a robust reduction in visual working memory capacity across psychotic disorders that can be reliably isolated from more generalized working memory impairment, and reduced visual working memory capacity is functionally and clinically relevant for individuals living with psychosis.

To the best of our knowledge, no study has directly assessed visual working memory *capacity* in individuals at CHR, despite consistent evidence of impaired performance on visual working memory tasks in this group. In the second phase of North American Prodrome Longitudinal Study (NAPLS), one of the largest datasets published on neurocognitive functioning in CHR to date, Seidman and colleagues (2016) performed a factor analysis using data from 19 neuropsychological tests and 689 CHR individuals and identified an "attention and working memory" factor on which the CHR group showed significant impairment compared to control subjects. Given that factor analyses have previously shown working memory capacity to account for much of the shared variance across different working memory tasks (Wilhelm et al., 2013), it is possible that part of the impairment on this "attention and working memory" factor in CHR can be accounted for by reduced working memory capacity. However, direct assessment of visual working memory in CHR is warranted to answer this question.

1.3.2. Neural Oscillations as a Correlate of Visual Working Memory

Neural oscillations, or the rhythmic neural activities that emerge when large ensembles of neurons fire in synchrony, have been proposed as a key neurophysiological mechanism through which information is represented and sustained in working memory. Leading computational

models of visual working memory posit that attributes of a visual scene (e.g., color, shape, and position of individual items) coded by feature-specific neuron groups are bound together by synchronized oscillations across these neuronal assemblies in the gamma frequency band (30-100 Hz; Buzsaki & Draguhn, 2004), thereby forming representations of integrated objects in visual working memory (Luck & Vogel, 1997; Wheeler & Treisman, 2002; Zhang & Luck, 2008). During the retention interval, these synchronous oscillations are sustained in the absence of external stimuli (Hebb, 1949), allowing the encoded information to be maintained in visual working memory. In the meanwhile, oscillations in the alpha (9-13 Hz) and beta (15-30 Hz) frequency bands are thought to exert top-down control over the rapid gamma bursts to allow visual working memory representations to be more robustly maintained in working memory (E. K. Miller et al., 2018). The specific mechanisms through which alpha and beta modulations facilitate visual working memory is an area of active research and heated debate in computational and cognitive neuroscience. One hypothesis posits that the high-frequency gamma oscillations containing visual working memory representations are embedded in cycles of a lower frequency oscillatory activity, such as alpha, with each gamma cycle receiving a unique "temporal code" based on the specific phase of the alpha oscillation with which it coincides. According to this "phase-code" view of visual working memory, the capacity limits exist because only a finite number of gamma cycles, each containing representations of one item held in working memory, could fit into an alpha cycle (Raffone & Wolters, 2001). In turn, alpha modulation is thought to facilitate working memory maintenance by extending the oscillatory trough during which the gamma bursts occur, thereby allowing more gamma cycles to be robustly maintained (Jensen et al., 2014). Despite its critical role in neurophysiological models of working memory, gamma activities are difficult to measure from scalp EEG recordings due to

contaminations from electromyography (EMG) and electrical line noise artifacts (Whitham et al., 2007). On the other hand, alpha and beta signals can be reliably recorded and quantified with noninvasive methods and have been used to probe the integrity of oscillatory mechanisms of working memory given their close links to gamma-band activities.

A large body of evidence suggests that this process involves the *suppression* or *desynchronization* of alpha/beta oscillations (typically quantified as the reduction of alpha/beta power). Studies of neurotypical adults have consistently shown an association between successful recall in visual working memory tasks and the magnitude of alpha/beta suppression across the parieto-occipital electrodes following the presentation of the memory array (Astrand, 2018; Bashivan et al., 2014; Foster et al., 2017). Importantly, while posterior alpha oscillations have been implicated in a wide range of cognitive processes that are closely linked to visual working memory (e.g., perception, visual attention, filtering), alpha modulation appears to serve a more memory-specific function in the context of a visual working memory task. In change detection/localization, sustained posterior alpha suppression during the delay period has been shown to parametrically increase as a function of working memory load (i.e., set size) until full capacity is reached, and such load-dependent alpha suppression was significantly associated with behavioral measures of visual working memory capacity (Fukuda et al., 2015; Fukuda & Woodman, 2017; Sauseng et al., 2009), suggesting that the modulation of alpha oscillations may be specifically linked to visual working memory capacity. More recently, Erickson and colleagues (2019) compared alpha activities during versions of the change detection task with and without a working memory component to clarify the role of alpha suppression in working memory (i.e., whether it reflects a working memory-specific cognitive subcomponent or a generic attentional control process). They found larger delay-period alpha suppression in the task

with a working memory component than those without, and importantly, alpha suppression was only significantly associated with visual working memory capacity when working memory processes were necessitated by the task, again supporting the role of alpha suppression as a neural correlate of visual working memory capacity. In addition to supporting the active maintenance of visual working memory representations in the absence of sensory input (i.e., often measured during the delay period), alpha suppression has also been linked to the retrieval processes. A load-dependent pattern of alpha suppression, analogous to the one observed during retention, has also been reported during retrieval in a capacity-limited manner (Fukuda & Woodman, 2017). The functional significance of beta oscillations in the context of visual working memory is less well understood, though there is some early evidence suggesting beta suppression may serve a similar role to alpha modulation in supporting visual working memory maintenance (Miller et al., 2018).

1.3.3. Abnormalities in Neural Oscillations and Reduced Visual Working Memory Capacity in Psychosis

A growing body of literature has identified neural oscillatory abnormalities associated with a wide range of cognitive processes in schizophrenia (see Haenschel & Linden, 2011 for a review). Given the direct links between neural oscillations and neuronal firing and synaptic connections, abnormalities in the neural oscillatory dynamics may serve to bridge known neurochemical disturbances and behaviorally measured cognitive dysfunction in psychosis (Brisch et al., 2014). Specifically, alpha suppression has been shown to be significantly reduced among patients with schizophrenia during a wide range of visual working memory tasks compared to control subjects (Bachman et al., 2008; Haenschel et al., 2009, 2010; Kang et al., 2018), suggesting the possible contribution of ineffective alpha modulation to visual working

memory impairment in psychotic disorders. Recently, Erickson and colleagues (2017) demonstrated that the magnitude of alpha suppression during the delay period among patients with schizophrenia was significantly reduced compared to control subjects, and the amount of alpha suppression predicted the number of items later recalled in both patients and controls, providing direct evidence that failure to modulate alpha oscillatory activities during consolidation and maintenance contributes to reduced visual working memory capacity in schizophrenia.

It is unclear whether inefficient alpha modulation may be readily present in CHR, and furthermore, whether it accounts for the visual working memory deficits previously reported in this group. Indeed, there is some early evidence that the neural architecture generating alpha oscillations may be already compromised in CHR. For example, the CHR state has been associated with reduced alpha suppression during an auditory oddball task (Koh et al., 2011), abnormalities in alpha functional connectivity during resting state (Liu et al., 2019), and a pattern of frontal alpha asymmetry that was correlated with negative symptoms (Bartolomeo et al., 2019). However, given the functional diversity of alpha oscillations, it remains unknown whether alpha suppression specifically pertaining to visual working memory is impaired in CHR.

1.4. Purpose of the Current Study

The current study aims to examine the behavioral and neural measures of visual working memory capacity in CHR individuals and demographically matched healthy controls (HC). Specifically, using a change localization working memory task specifically designed to minimize demands on selective attention, perceptual integration, and information manipulation as a relatively "pure" measure of visual working memory capacity, we sought to examine the neural oscillatory dynamics, particularly in the alpha and beta frequency bands, during visual working

memory operations as candidate mechanisms underlying visual working memory deficits in CHR.

Aim 1. Evaluate group differences in the behavioral and neural measures of visual working memory capacity. Hypothesis 1a. Estimates of visual working memory capacity (K), as obtained from the change localization task, will be significantly reduced in the CHR group compared to HC. Hypothesis 1b. The amount of alpha and beta suppression during the retention and retrieval intervals of the change localization task will be significantly smaller in CHR compared to HC.

Aim 2. Determine whether insufficient alpha/beta suppression during visual working memory accounts for reduced working memory capacity in CHR, if hypothesis 1a and 2b are both supported. Hypothesis 2. The amount of alpha/beta suppression will significantly predict working memory capacity in CHR.

Aim 3. Examine the relationships between visual working memory capacity and broader cognition and functional outcomes. Hypothesis 3a. Consistent with findings in neurotypical adults and individuals with psychotic disorders, estimates of visual working memory capacity in CHR will be significantly associated with performance on tasks that measure neurocognitive functioning in other domains. Hypothesis 3b. Visual working memory capacity is also expected to show a small association with measures of functioning.

Chapter 1, in part, is under preparation for publication with co-author Dr. Emily Kappenman. The dissertation author will be the primary author on this publication.

II. METHODS

2.1. Participants

Data were obtained from 50 healthy control (HC) and 50 CHR youth at the Adolescent Development and Preventative Treatment (ADAPT) program at Northwestern University. Inclusion in the CHR group required that the participants meet at least one of the Criteria of Prodromal Syndromes (COPS; Miller et al., 2013): (1) progression or recent onset of attenuated positive symptoms, (2) the presence of a first-degree relative with a psychotic disorder accompanied by a recent decline in global functioning, or (3) a decline in global functioning with the presence of schizotypal personality disorder (McGlashan et al., 2010). Exclusion criteria for both groups included history of significant head injury or neurological disorder, or any past or current psychotic disorder. In addition, any participants with a family history of a psychotic disorder in a first-degree relative were excluded from the HC group. Participants were recruited via Craigslist, community professional referrals, and advertisement postings locally and throughout the greater Chicago area. Informed consent was obtained in accordance with the protocol approved by the Institutional Review Board. Assent was obtained for individuals younger than 18 with informed consent obtained from their legal guardian.

2.2. Clinical and Neurocognitive Assessments

The Structured Interview for Psychosis Risk Syndromes (SIPS; Miller et al., 2013) was administered to diagnose a CHR syndrome and quantify attenuated positive and negative symptoms. The SIPS is a structured diagnostic interview widely used in North America and Europe that provides operational definitions for three prodromal syndromes: brief intermittent psychotic symptoms syndrome (BIPS), attenuated positive symptoms syndrome (APS), and genetic risk and deterioration syndrome (GRD). The SIPS includes a 19-item clinician-rated

scale designed to measure the severity of prodromal symptoms in the following four categories: positive symptoms, negative symptoms, disorganization symptoms, and general symptoms. Only the positive symptoms ratings are currently used for making prodromal diagnoses, but the other three subscales are useful in describing the severity of the diagnosis once established. In addition to the SIPS, the Structured Clinical Interview for DSM-V Disorders (SCID; First et al., 2016) was administered to rule out a psychotic disorder and to note the occurrence of any comorbid conditions. Clinical interviews were administered by advanced doctoral students with inter-rater reliabilities that exceeded the minimum study criterion of Kappa ≥ 0.80. Functioning was assessed with the Global Functioning Scales: Social and Role (GF:S & GF:R) (Auther et al, 2006; Niendam et al., 2006). Both scales range from 1 (severely impaired) to 10 (superior functioning). All functional evaluations were completed by advanced doctoral students.

Neurocognition was assessed using the Computerized Neurocognitive Battery (CNB), a computerized cognitive battery consisting of 14 tests assessing five neurocognitive domains: Executive Control (Abstraction and Mental-Flexibility, Attention and Working-Memory tests), Episodic Memory (Verbal-Memory, Face-Memory and Spatial-Memory tests), Complex Cognition (Language, Nonverbal-Reasoning and Spatial-Processing tests), Social Cognition (Emotion Identification, Emotion-Differentiation and Age-Differentiation tests), and Sensorimotor Speed (Motor-Speed and Sensorimotor-Speed tests). The test takes approximately one hour to administer and yields measures of both accuracy (number of correct responses) and speed (median reaction time for correct responses) for each task. Primary outcome measures of the CNB are efficiency scores for each domain, calculated as the average of accuracy and speed scores for each task (Gur et al., 2010).

2.3. Visual Working Memory EEG Task Design

Visual working memory capacity was measured with a change localization task (Johnson et al., 2013). Example trial sequences are presented in Figure 1. The task was programmed in the E-prime software and presented on an LCD monitor with a gray background and a continuously visible central fixation cross at a nominal viewing distance of 70 cm. On each trial of the task, participants were first presented with a sample array of four colored squares, each measuring 0.7° x 0.7° of visual angle. The colored squares were randomly placed around an imaginary circle with a radius of 3°, with the constraints that one item appeared in each of the four screen quadrants, and each item was separated by a minimum of 30° on the circle from the next item. The sample array was displayed for 100 ms, followed by a 900-ms delay period during which only the fixation cross was shown. Next, participants were presented with a test array that was identical to the sample array except that the color of one square changed to a value not present in the sample array. The colors were selected at random without replacement from a set of six colors with the following RGB values: red (255, 0, 0), green (0, 255, 0), yellow (255, 255, 0), magenta (255, 0, 255), cyan (0, 255, 255), and bright blue (80, 60, 255). Participants were instructed to identify the item in the test array that changed color by clicking on the square with a computer mouse. They were encouraged to respond accurately with no speed pressure. The test array was visible until the response was made, and trials were separated by a 2,000-ms intertrial interval. A total of 60 trials were presented for each subject, which typically required approximately 8-10 minutes of testing time.

Visual working memory storage capacity was quantified using a variant of the Pashler/Cowan K equation, where K indicates the number of items that have been stored in working memory (Cowan et al., 2005; Pashler, 1988; Johnson et al., 2013). As all trials contain a

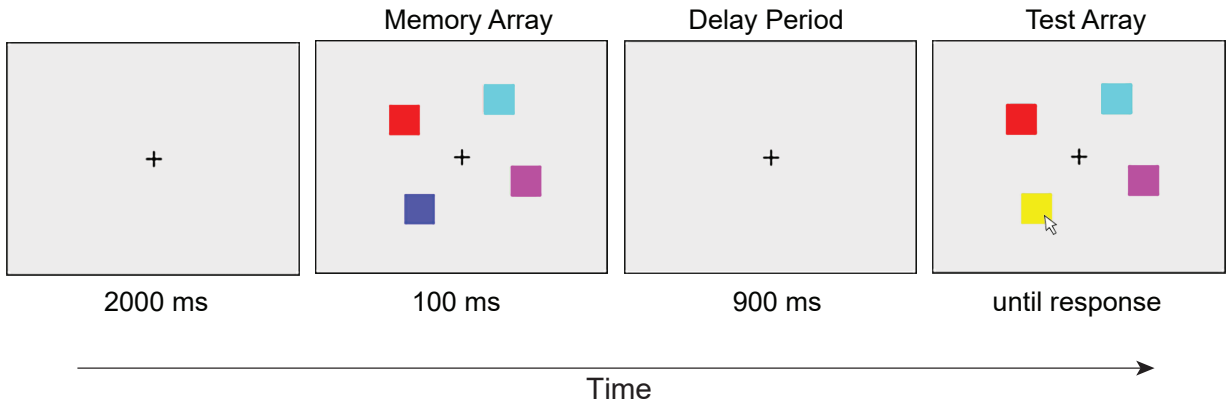

Figure 1. Example trial sequence of the change localization task. Position of cursor on the test array indicates correct localization of changed item on this trial. Note that stimuli are not to exact scale; see text for actual sizes used in the experiment.

change and the task provides no opportunities for false alarms, K will be calculated simply by multiplying each participant's proportion of trials correct by the set size 4. Of note, the quantification of working memory capacity using K is primarily based in discrete-slot models of working memory, which characterizes visual working memory as an all-or-none phenomenon where an item is either remembered or not remembered, allowing capacity limits to be numerically quantified (Alvarez & Cavanagh, 2004; Awh et al., 2007; Zhang & Luck, 2008). A competing view posits that working memory representations exist on a continuum of varying strengths; responses on a forced-choice task such as change localization is made not based on which items were remembered, but on the relative memory strengths of the target (i.e., changed item) and foils (i.e., unchanged items; see Brady et al., 2023; Williams et al., 2022). To reconcile these two views, we calculated *d'* from the signal detection theory framework using formula for multiple forced-choice tasks suggested in DeCarlo (2012), as an additional measure of working memory capacity. Specifically, in the context of the change localization task, *d'* quantifies the number of items in the memory array that had higher memory strength than the novel item in the test array.

2.4. EEG Recording Procedures

As participants completed the change localization working memory task, electroencephalogram (EEG) was recorded from 58 passive Ag/AgCl electrodes mounted in an elastic cap positioned according to the International 10-20 System. A subset of these electrodes will be selected for processing (Fp1, Fpz, Fp2, F3, Fz, F4, F7, F8, FC3, FCz, FC4, C3, Cz, C4, C5, C6, CPz, P3, Pz, P4, P7, P8, PO3, POz, PO4, PO7, PO8, O1, Oz, O2). The vertical electrooculogram (VEOG) was recorded from electrodes placed above and below the left eye (centered with the pupil), and the horizontal electrooculogram (HEOG) was recorded from electrodes placed beside each eye near the external canthi. All signals were low-pass filtered with a 100 Hz cutoff and then digitized at 500 Hz with 24 bits of resolution. Data were recorded with an online reference of the left mastoid and re-referenced to the average of left and right mastoids offline.

2.5. EEG Data Processing and Time-Frequency Analysis

Signal processing was conducted offline in MATLAB using EEGLAB (Delorme and Makeig, 2004) and ERPLAB toolboxes (Lopez-Calderon and Luck, 2014). After DC offsets were removed, the signals were high-pass filtered using a non-causal Butterworth impulse response function with a half-amplitude cut-off at 0.1 Hz and 12 dB/oct roll-off. Independent components analysis (ICA; Jung et al., 2000) was performed on each participant's continuous data to remove components clearly associated with eye blinks and horizontal eye movements. The ICA-corrected data were then segmented into 3000 ms intervals (-500 ms to 2500 ms) relative to the sample array onset and baseline-corrected for each trial to the mean prestimulus voltage. Segments of data containing artifacts were excluded from further analysis using automated ERPLAB procedures with individualized thresholds set on the basis of visual

inspection of each participant's data. All signal processing and artifact rejection procedures were performed by an individual blind to group membership. Participants were excluded from further analyses if more than 50% were rejected due to artifacts; a total of 2 CHR and 3 HC participants were excluded for this reason.

Alpha- and beta-band activities were estimated with Morlet wavelet transform (Tallon-Baudry & Bertrand, 1999; Bertrand & Pantev, 1994) conducted in MATLAB 2021b (MathWorks, Natic, MA, USA). First, artifact-free epochs of the EEG data were tapered with a cosine square window (20 samples rise/fall) to minimize edge effects. Data from each trial were transformed to time-varying spectral amplitude using a family of complex Morlet wavelets with a wavelet constant (also known as Morlet parameter, or *m*) of 7. This resulted in, for example, a frequency resolution of 1 Hz and a time resolution of 112 ms for signals at 10 Hz and a frequency resolution of 2.86 Hz and a time resolution of 56 ms for signals at 20 Hz. Wavelets were calculated for frequencies between 3 Hz and 50 Hz in linear steps of 1 Hz. The time-frequency spectra were baseline corrected to the proportional change in post-stimulus magnitude relative to the 1000 ms before the onset of the sample array on a logarithmic scale (dB) and averaged across trials. Spectral magnitude was measured from two frequency bands: alpha (9-13 Hz), beta (15-30 Hz) averaged across 11 occipital and parietal electrode sites (PO7, PO8, PO3, PO4, POZ, P3, P4, PZ, O1, O2, OZ) and two measurement windows: delay period (100-1000 ms) and retrieval period (1000-2000 ms).

2.6. Statistical Analysis Approach

Independent t-tests and Chi-square tests were used to examine group differences in demographic variables.

Hypothesis 1. Behavioral and neural measures of visual working memory capacity will be significantly reduced in CHR compared to HC. Independent t-tests were used to compare estimates of working memory capacity, K, between CHR and HC. Two (Group: CHR vs. HC) x two (Interval: retention vs. retrieval) repeated measures ANOVAs were used to examine group differences in alpha and beta suppression, as well as group-by-interval interactions.

Hypothesis 2. Insufficient alpha/beta suppression significantly will predict reduced working memory capacity in CHR. Pearson correlation analyses were conducted to examine the association between alpha/beta suppression and K in both CHR and HC.

Hypothesis 3. Visual working memory capacity will be associated with broader cognition and functioning. Pearson correlation analyses were conducted to examine the associations between K, domain scores of the CNB, and GF. Two-tailed tests with an alpha level of .05 were used for all statistical tests.

Chapter 2, in part, is under preparation for publication with co-author Dr. Emily Kappenman. The dissertation author will be the primary author on this publication.

III. RESULTS

3.1 Sample Characteristics

The final sample included 48 participants in the CHR group (Mean age = 21.1, range = 15-28, 56% female) and 47 participants in the HC group (Mean age = 21.2, range = 16-30, 57% female). Further participant demographic and clinical characteristics are presented in Table 1. Independent sample t-tests were used to examine group differences on quantitative variables of interest and chi-squared tests categorical variables. The HC and CHR groups were matched on age ($t(93) = 0.15$, $p = .88$), sex ($\chi^2_1 = 0.01$, $p = .91$), race ($\chi^2_1 = 0.51$, $p = .47$), education ($t(93) = -0.74$, $p = .46$), and parental education ($t(92) = -1.21$, $p = .23$), a proxy for socioeconomic status.

Compared to HC, the CHR group was rated significantly lower on the GSF for both social functioning ($t(91) = -5.75$, $p < .001$, Cohen's $d = -1.19$) and role functioning ($t(91) = -4.13$, $p < .001$, Cohen's $d = -0.86$).

3.2 Task Performance

Visual working memory capacity (K) was significantly lower in CHR (M = 3.02, SD = 0.37) compared to HC (M = 3.23, SD = 0.40; $t(93) = -2.67$, $p = .009$, Cohen's $d = -0.55$), with an average capacity reduction of 0.21 in the CHR group. Like K, *d'* was significantly lower in CHR (M = 1.75, SD = 0.39) than HC (2.03, SD = 0.53; $t(93) = -2.91$, $p = .005$, Cohen's $d = -0.60$). Given that K and *d'* were strongly correlated in our sample ($r = .97$, $p < .001$), we only included K for all subsequent analyses involving behavioral measures of working memory to limit the number of statistical tests conducted in the study.

Although reaction time (RT) was not a primary outcome metric of the change localization task, as responses were unspeeded in this task, we examined how RT differed between CHR and HC. RT, quantified as the average latency between the onset of the test array and the mouse click

Table 1. Demographics and Clinical Characteristics for the Clinical-High Risk and Healthy Control Participants

	CHR	HC
Demographics		
Age	21.10 (2.85)	21.19 (2.75)
Sex		
Male	21	20
Female	27	27
Race and ethnicity (percentage)		
American Indian or Alaska Indian	0 (0%)	1 (2.13%)
Asian	3 (6.25%)	13 (27.66%)
Black	10 (28.83%)	2 (4.25%)
Hispanic	6 (12.50%)	1 (2.13%)
White	26 (54.17%)	22 (44.81%)
Multiple races	2 (4.17%)	8 (17.02%)
Unknown	1 (2.08%)	0 (0%)
Education (yr.)	14.14 (1.85)	14.45 (2.20)
Parent education (yr.)	15.37 (3.56)	16.20 (2.97)
Symptoms		
SIPS Positive	10.85 (3.51)	--
SIPS Negative	6.79 (4.86)	--
Functioning		
GFS: Social	7.57 (1.25)	8.80 (0.75)
GFS: Role	7.89 (1.29)	8.80 (0.73)

Note: Descriptive statistics reflect means and standard deviations (in parentheses) unless otherwise specified. CH*R* = Clinical high-risk participants; HC = Healthy control participants; SIPS = Structure Interview for Psychosis-Risk Syndromes; GFS: Social = Global Functioning Scale: Social; GFS: Role = Global Functioning Scale: Role. Positive and negative symptoms were quantified using the Structure Interview for Psychosis-Risk Syndromes (SIPS). Years of education was unavailable for 1 HC participant.

response across correct trials, was numerically longer in CHR (M = 1346.46 ms, SD = 243.84) compared to HC (M = 1302.33, SD = 238.60). However, this difference was not statistically significant ($t(93) = 0.89$, $p = .375$, Cohen's $d = 0.18$).

3.3 Time-Frequency Analysis

3.3.1. Baseline Alpha and Beta Activities

To characterize the magnitude of baseline alpha and beta activities in the CHR and HC groups, we calculated the alpha and beta amplitudes averaged across the 1000 ms pre-stimulus interval prior to the onset of the memory array on each trial. These values are provided in Table 2. Note that this was measured from the "raw" time-frequency transformation of the EEG signals without baseline correction to the pre-stimulus interval. Compared to HC, the CHR group had significantly lower levels of baseline activity in both alpha ($t(93) = -2.79$, $p = .006$) and beta frequency bands ($t(93) = -2.40$, $p = .018$). This was expected, as diminished resting-state alpha activity has been implicated in both psychosis risk (Trajkovic et al., 2021) and schizophrenia (Sponheim et al., 2000). Given our interest in examining task-related changes in alpha/beta amplitude and their relation to working memory capacity (K), we first tested whether there was any association between baseline alpha/beta amplitude and K. None of the correlations were significant (all p's > .13).

3.3.2. Alpha/Beta Suppression

We next examined whether the amount of alpha and beta modulation during the change localization task was impaired in CHR. The baseline-corrected time-frequency spectrum, time-locked to the onset of the memory array and averaged across trials and electrode sites, are shown separately for CHR and HC in Figure 2A. The time courses of posterior alpha and beta are shown in Figure 2B. In both groups, there was a clear reduction in alpha and beta amplitude that started approximately 100 ms after the onset of the memory array and sustained throughout the delay period (100 – 1000 ms), reaching maximum suppression at around 300 to 400 ms after the memory array onset and returning to near-baseline level at the end of the delay period. The

Table 2. Alpha and Beta Amplitude During Prestimulus Interval, Delay Period, and Retrieval Period

	CHR	HC
Prestimulus Interval (μV)		
Alpha Magnitude	4.85 (2.25)	6.55 (3.55)
Beta Magnitude	1.95 (0.46)	2.23 (0.64)
Delay Period (dB)		
Alpha Suppression	-2.44 (1.98)	-3.36 (2.46)
Beta Suppression	-1.20 (0.72)	-1.60 (0.97)
Retrieval Period (dB)		
Alpha Suppression	-3.73 (2.38)	-5.12 (2.93)
Beta Suppression	-2.00 (1.08)	-2.64 (1.24)

Note: Baseline alpha (9-13 Hz) and beta (15-30 Hz) amplitudes were measured from the 1000 ms prestimulus interval without baseline correction. Alpha and beta amplitudes during the delay period (100 – 1000 ms) and retrieval period (1000 – 2000 ms) were measured from baseline-corrected time-frequency spectrum. Descriptive statistics reflect means and standard deviations (in parentheses). CHR = Clinical high-risk participants; HC = Healthy control participants.

retrieval phase began with the onset of the test array (1000 ms after the memory array onset), where a second round of alpha/beta suppression was observed, which started approximately 100 ms into the retrieval period and lasted for at least a full second, notably surpassing the initial delay-period alpha/beta suppression in magnitude. The group difference in the baseline-corrected time-frequency spectrum (calculated as CHR minus HC) is shown in Figure 2A. The CHR group showed reduced suppression of both alpha and beta band activities from around 100 to 1000 ms and again starting at around 1100 ms and lasting through the end of the trial, with a particularly prominent reduction in alpha suppression around 1600 ms to 2000 ms at the end of the retrieval period.

The baseline-corrected alpha and beta amplitudes for the delay and retrieval intervals are shown in Table 2, separately for CHR and HC. To statistically compare the magnitudes of alpha

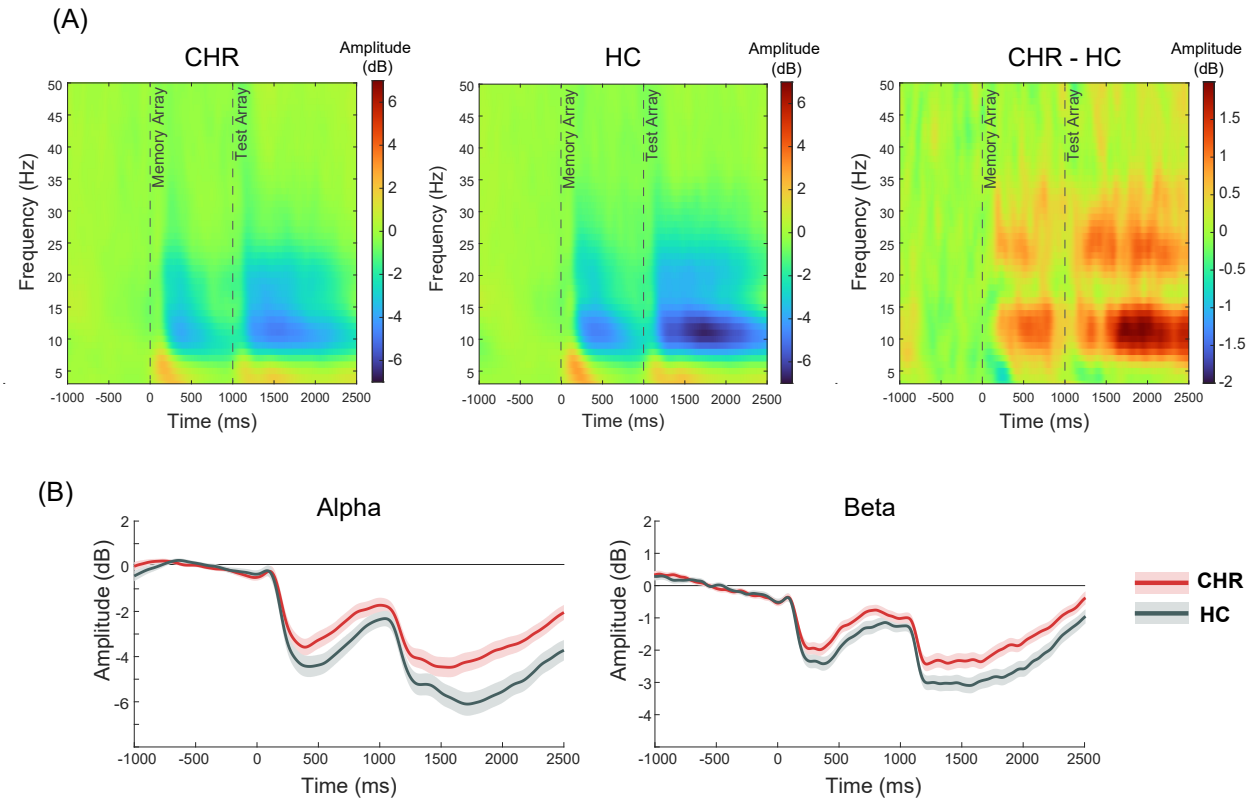

Figure 2. (A) Time-frequency spectrum averaged across posterior electrodes and all artifact-free trials, time-locked to the memory array onset and corrected to the prestimulus baseline period, shown separately for clinical high risk (CHR) participants (left), health control participants (middle), and CHR-HC group comparison (right; calculated as CHR minus HC). (B) Time course of alpha (9-13 Hz; left panel) and beta (15-30 Hz; right panel) modulation relative to the prestimulus baseline in CHR (red line) and HC (green line). Shaded areas indicate +/- 1 standard error.

and beta modulations during the delay and retrieval intervals between CHR and HC participants, we analyzed baseline-corrected alpha and beta amplitudes in separate 2x2 repeated measures ANOVA tests with time interval (retention vs. retrieval) as a within-subject factor and group (CHR vs. HC) as a between-subject factor. For alpha-band activity, the CHR showed reduced alpha suppression compared to HC, leading to a significant main effect of group ($F(1,93) = 5.59$, $p = .020$, $\eta_p^2 = 0.06$). The magnitude of alpha suppression was larger during the retrieval interval than during the delay period, leading to a significant main effect of time interval ($F(1,93) = 160.95$, $p < .001$, $\eta_p^2 = 0.63$). The increased alpha suppression during the retrieval interval was slightly more pronounced in HC than for CHR, leading to a marginally significant group x time

interval interaction ($F(1,93) = 3.77$, $p = .055$, $\eta_p^2 = 0.04$). To explore the nature of this marginal interaction, we conducted follow-up *t* tests to compare the magnitude of alpha suppression between CHR and HC separately for the delay period and the retrieval phase. CHR showed significantly reduced alpha suppression compared to HC during both the delay ($t(93) = -2.02$, $p = 0.047$, Cohen's $d = -0.41$) and the retrieval intervals ($t(93) = -2.55$, $p = 0.013$, Cohen's $d = -0.52$), with the impairment slightly more pronounced in the retrieval phase.

For beta-band modulation, CHR showed reduced beta suppression compared to HC, leading to a significant main effect of group ($F(1,93) = 7.02$, $p = .009$, $\eta_p^2 = 0.07$). Similar to alpha-band suppression, the magnitude of beta suppression was larger for both groups during the retrieval interval than the delay interval, leading to a significant main effect of time interval ($F_{1,93} = 172.95$, $p < .001$, $\eta_p^2 = 0.65$) but no group x time interval interaction ($F(1,93) = 2.82$, $p = .096$, $\eta_p^2 = 0.03$).

3.3.3. Correlations Between Alpha/Beta Suppression and WM Capacity

We next examined the associations between the magnitude of alpha/beta suppression and visual working memory capacity; the scatter plots are presented in Figure 3. In CHR, alpha suppression was negatively associated with visual working memory capacity, with more alpha suppression (i.e., a larger decrease in alpha amplitude) associated with larger K. This association did not reach statistical significance for the delay period ($r = -.23$, $p = .118$), but was significant for the retrieval phase ($r = -.30$, $p = .039$). Beta suppression was significantly and negatively correlated with K in CHR during both the delay period ($r = -.42$, $p = .003$) and the retrieval phase ($r = -.30$, $p = .007$), with larger magnitudes of beta suppression predicting higher visual working

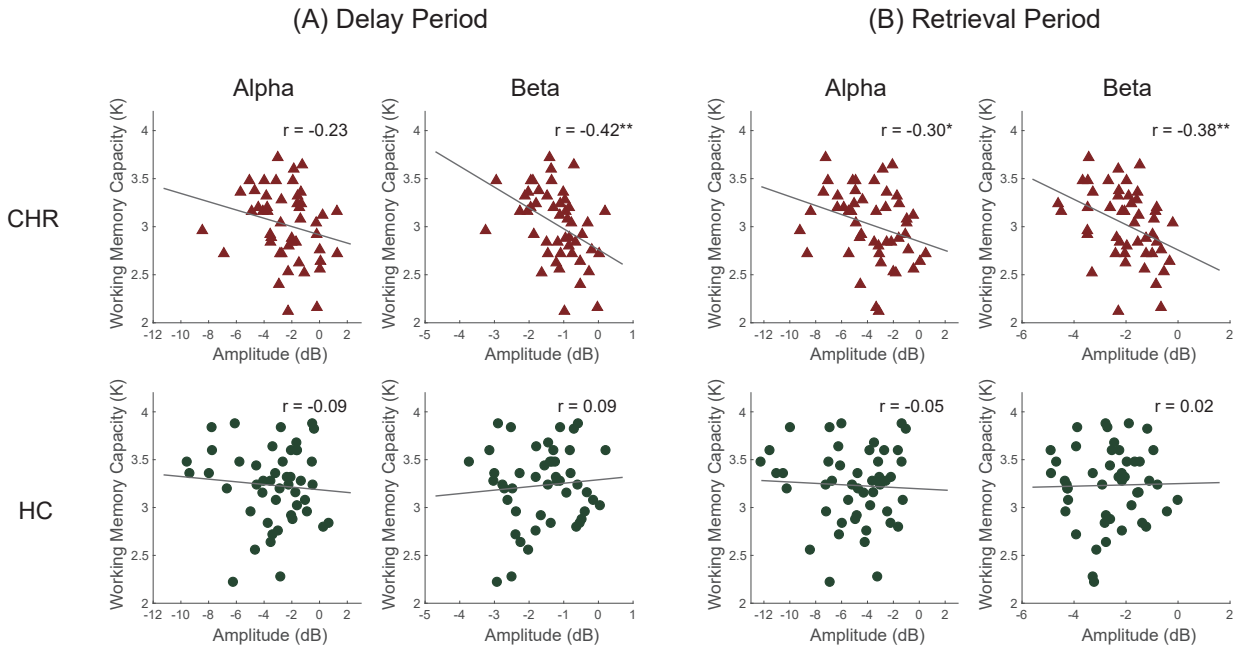

Figure 3. Scatterplot depicting the relationship between visual working memory capacity (K) and alpha and beta suppression during delay period (left panel) and retrieval period (right panel), shown separately for participants at clinical high risk (CHR) for psychosis (top; red triangles) and healthy control (HC) participants (bottom; green circles).
*p < .05, **p < .01

memory capacity. For the HCs, no significant correlations were observed between K and alpha/beta suppression (*r*'s < .09, *p*'s > .055'; see Figure 3).

3.4. Correlation Between Working Memory and Symptoms, Cognition, and Functioning

To explore the clinical and functional significance of these impairments in behavioral and neural measures of working memory in CHR, we conducted two sets of exploratory correlation analyses. First, we examined whether prodromal symptoms of psychosis (positive and negative symptoms scales on the SIPS) were associated with working memory capacity (K) and alpha/beta suppression in the CHR group. Next, we correlated measures of cognitive and global functioning (using domain scores on the CNB and role and social functioning subscales of the GFS, respectively) with measures of visual working memory (K and alpha and beta suppression); these analyses were done separately for CHR and HC. To reduce the number of exploratory

analyses, we collapsed alpha/beta amplitudes across task phases (i.e., delay period and retrieval phase) so that only one index of alpha suppression and one index of beta suppression were included. Associations with broader cognitive functioning were only examined for a subset of the sample (i.e., 33 CHR and 36 HC participants), as not all participants completed the CNB test battery.

The associations between K, alpha/beta suppression, and prodromal symptoms in CHR are shown in Figure 4. Visual working memory capacity was significantly negatively correlated with positive symptoms on the SIPS, with individuals reporting higher levels of positive symptomology having a lower K. By contrast, we observed no association between K and negative symptoms. Alpha/beta modulation was not significantly correlated with either positive or negative symptoms in CHR.

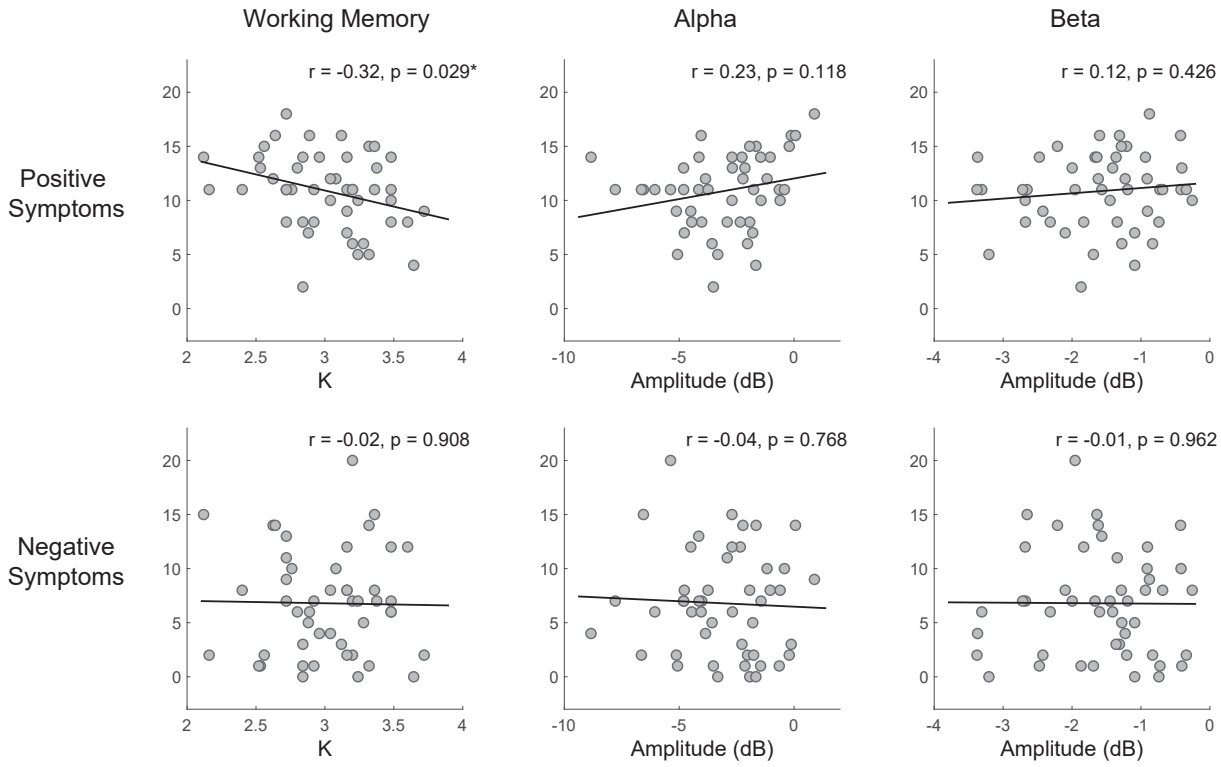

Figure 4. Scatterplot depicting the relationship between behavioral and neural measures of visual working memory (K, alpha and beta suppression) and positive symptoms (top panel) and negative symptoms (bottom panel) ratings on the Structural Interview for Prodromal Syndromes (SIPS) in the clinical high risk (CHR) group.
*p < .05

The associations between K and cognitive and global functioning measures are shown in Table 3, separately for CHR and HC. In CHR, K showed a significant and positive correlation with CNB scores in the Executive Control and Complex Cognition domains; CHR participants with a more pronounced working memory capacity reduction tended to demonstrate weaker executive functioning and verbal and non-verbal reasoning on the CNB. There was also a positive association between K and Episodic Memory that was approaching statistical significance in CHR, suggesting a possible link between reduced working memory capacity and difficulty with episodic memory in this group. In HC, we also found a significant and positive correlation between K and Executive Control domain score, paralleling the findings in the CHR group and indicating a consistent association between working memory and executive functioning across both groups. In addition, K was also significantly and positively correlated

Table 3. Correlations Between Behavioral Working Memory Capacity (K) and Cognitive and Functional Measures

Measure	CHR	HC
CNB	(n = 33)	(n = 36)
Executive Control	$r = .37, p = .04$*	$r = .36, p = .03$*
Episodic Memory	$r = .31, p = .08^{+}$	$r = .10, p = .56$
Complex Cognition	$r = .40, p = .02$*	$r = .10, p = .58$
Social Cognition	$r = -.01, p = .98$	$r = .41, p = .01$*
Sensorimotor Speed	$r = -.01, p = .96$	$r = .15, p = .40$
GFS	(n = 47)	(n = 45)
GFS: Social	$r = .20, p = .16$	$r = .17, p = .27$
GFS: Role	$r = .11, p = .45$	$r = .32, p = .03$*

Note: CNB data were only available for a subset of the participants. GFS ratings were unavailable for 1 CHR participant and 2 HC participants. Resulting sample sizes for each set of correlational analyses are shown in parentheses. CNB = Computerized Neurocognitive Battery, GFS: Social = Global Functioning Scale: Social; GFS: Role = Global Functioning Scale: Role.
$^{+}p < 0.1$, *$p < 0.05$

with Social Cognition in HC; this association may reflect, in part, possible involvement of visual working memory in Social Cognitive tasks in the CNB, which required participants to hold mental representations of multiple visual stimuli (i.e., faces) to make task-relevant comparisons or judgements (of age or emotion). Regarding the relationship between working memory and global functioning, K was not significantly associated with social or role functioning in CHR. In HC, K was significantly and positively correlated with role functioning (i.e., fulfillment of occupational and/or educational roles) but not social functioning.

The associations between alpha/beta suppression and cognitive and global functioning measures are shown in Table 4, separately for CHR and HC. In CHR, both alpha and beta amplitude was significantly and negatively correlated with Sensorimotor Speed; attenuated alpha/beta suppression (i.e., larger, less negative amplitude) during visual working memory was associated with poorer performance on tasks requiring efficient coordination of the sensory and motor systems in CHR. This association was not significant in HC. It is possible that the impairment in top-down modulation of perceptual and memory representations in CHR, as indexed by insufficient alpha/beta suppression during the change localization task, also interfered with efficient completion of sensorimotor tasks in this group. Lastly, in HC, beta amplitude was negatively associated with Episodic Memory, with lower levels of suppression linked to weaker episodic memory tasks in the CNB. No other correlations between alpha/beta suppression and cognitive/functional measures reached statistical significance.

Importantly, due to the small sample size and large number of comparisons, no associations revealed in the above exploratory analyses would have survived correction for multiple comparisons. Although these exploratory analyses provided some useful insight into the potential clinical, cognitive, and functional relevance of the behavioral and neural measures of

working memory that may warrant further investigations, they should not be considered confirmatory without external replication.

Table 4. Correlations Between Alpha/Beta Suppression and Cognitive and Functional Measures

Measure	CHR		HC	
	Alpha	Beta	Alpha	Beta
CNB	(n = 33)		(n = 36)	
Executive Control	$r = 0.09$, $p = 0.61$	$r = 0.08$, $p = 0.65$	$r = -0.14$, $p = 0.44$	$r = -0.13$, $p = 0.47$
Episodic Memory	$r = 0.07$, $p = 0.72$	$r = 0.11$, $p = 0.55$	$r = -0.25$, $p = 0.15$	$r = -0.34$, $p = 0.05$*
Complex Cognition	$r = -0.06$, $p = 0.74$	$r = 0.18$, $p = 0.33$	$r = 0.00$, $p = 0.99$	$r = 0.21$, $p = 0.24$
Sensorimotor Speed	$r = -0.40$, $p = 0.02$*	$r = -0.40$, $p = 0.02$*	$r = 0.03$, $p = 0.88$	$r = 0.07$, $p = 0.71$
Social Cognition	$r = -0.20$, $p = 0.27$	$r = 0.12$, $p = 0.53$	$r = 0.08$, $p = 0.67$	$r = 0.19$, $p = 0.29$
GFS	(n = 47)		(n = 45)	
GFS: Social	$r = -0.03$, $p = 0.86$	$r = 0.00$, $p = 0.99$	$r = 0.02$, $p = 0.92$	$r = -0.09$, $p = 0.54$
GFS: Role	$r = 0.08$, $p = 0.62$	$r = 0.11$, $p = 0.44$	$r = 0.06$, $p = 0.71$	$r = 0.12$, $p = 0.44$

Note: Sample sizes for each set of correlational analyses are shown in parentheses. CNB = Computerized Neurocognitive Battery, GFS: Social = Global Functioning Scale: Social; GFS: Role = Global Functioning Scale: Role.

*$p < 0.05$

Chapter 3, in part, is under preparation for publication with co-author Dr. Emily Kappenman. The dissertation author will be the primary author on this publication.

IV. DISCUSSION

The current study investigated the neural mechanisms underlying visual working memory deficits in individuals at CHR for psychosis. We built on previous studies of working memory in CHR by using a change localization paradigm designed to minimize demands on selective attention, perceptual integration, and information manipulation and yield a "pure" measure of visual working memory capacity. We found a moderate reduction (d = 0.55) in working memory capacity in CHR compared to HC using behavioral measures. Using EEG and time-frequency analyses, we observed attenuated suppression in the alpha (9-13 Hz) and beta (15-30 Hz) frequency bands in CHR relative to HC participants during both the delay period and the retrieval period. Importantly, the magnitude of alpha/beta suppression significantly predicted behavioral working memory capacity in CHR, with lower levels of suppression associated with lower working memory capacity. Note that this was not true for baseline alpha/beta, which was reduced in CHR but not associated with working memory capacity. Further, in a set of exploratory correlational analyses, we found significant associations between these behavioral and neural measures of visual working memory and a number of clinical and cognitive measures in CHR, converging with the larger literature highlighting the real-world significance of working memory capacity and its neural correlates across stages of the psychotic illness.

4.1. Working Memory Capacity Reduction in CHR

One of the most striking findings of the study is the size of visual working memory capacity impairment the CHR group showed on the change localization task. For comparison, previous studies employing similar change localization/detection designs have shown that in full-blown psychotic disorder, predominantly schizophrenia, working memory capacity is reduced by approximately 0.4 – 0.6 compared to control participants with a medium-to-large effect size (d =

0.5 to 1.1; Gold et al., 2019; Johnson et al., 2013). In the present study, we observed a reduction in capacity in the CHR participants (M = 0.21, *d* = 0.55) that was about half the size of the impairment previously observed in schizophrenia both in terms of capacity estimate and effect size. Importantly, considering only approximately 20% to 35% of those identified as CHR are expected to develop a psychotic disorder, and those ultimately converting to psychosis have typically shown poorer baseline cognitive functioning than "non-converters" (Seidman et al., 2016), the amount of working memory capacity reduction in the true prodromal stage of psychosis likely far exceeds what was observed in the current study.

These findings also contribute to the rapidly growing literature on working memory in early psychosis by isolating and quantifying one key aspect of working memory—storage capacity—that has been shown to account for variations in broader cognitive functioning in both neurotypical individuals and those diagnosed with psychotic disorders. Whereas previous studies of working memory in CHR have primarily relied on neuropsychological span tasks that tend to be susceptible to variations in perceptual processes, attention selection and inhibition, executive control, and motivation (all domains where CHR individuals show impairment), thereby providing only a coarse estimate of working memory abilities, the current study demonstrated a notable reduction specifically in the storage capacity of visual working memory in CHR by minimizing task demands on these cognitive processes that may interfere with, but are not central to, working memory. Importantly, even on this simple task, the capacity reduction the CHR showed was nearly as large in effect size as the task performance impairment found in previous studies using visual working memory tasks recruiting a wider array of cognitive resources (see Bora & Murray, 2014 for a meta-analysis showing an overall moderate impairment on visual working tasks in CHR, *d* = 0.71, CI = [0.39 1.04]). This again highlights

the central role of working memory *capacity* in the working memory system and related cognitive operations.

In the CHR group, working memory capacity estimate, K, was significantly correlated with positive symptoms and performance on a number of CNB tasks measuring cognitive abilities that are theorized to be subserved by basic working memory functions, in particular executive control and complex cognition. These findings not only demonstrate excellent convergent validity of K as a working memory capacity measure, but also underscore the clinical and functional relevance of the core cognitive trait it captures.

4.2. Impaired Alpha/Beta Suppression as A Neural Mechanism of Reduced Working Memory Capacity in CHR

This study took advantage of the temporal resolution of EEG recordings and the time-frequency analytical approaches to track rapid changes in neural oscillatory activities in the alpha and beta frequency bands across stages of working memory, with the goal of identifying factors that may account for the reduced visual working memory capacity in CHR. In both CHR and HC, we observed two distinct phases of alpha/beta suppression that coincided temporally with the delay period and retrieval phase of the change localization task, respectively. During each of these two phases, the CHR group showed attenuated alpha/beta suppression compared to HC, which in turn predicted behaviorally measured working memory capacity reduction in CHR.

The delay period begins with the offset of the memory array and marks a critical phase of working memory operations when the viewers continue to consolidate perceptual representations into working memory representations (Vogel et al., 2006) and maintain these fast-decaying memory traces without ongoing sensory input. This process is thought to be facilitated by recurrent feedback loops between neuron populations functionally connected to support the same

working memory representation, forming neuronal assemblies that fire in synchrony at given frequencies (Raffone & Wolters, 2001). While specific roles of alpha suppression in working memory remains a topic of heated debate (for example, see Woodman et al., 2022), there is strong evidence that alpha suppression constitutes an integral aspect of this neural network at work during the delay period by supporting continued representations of visuospatial information in working memory (Foster et al., 2016) and/or protecting such representations from potential interference (Schroeder et al., 2018). Our findings of sustained attenuation in alpha/beta suppression in CHR that started early (i.e., within the first 100 ms) in the delay period and persisted throughout it suggested that consolidation and maintenance visual working memory representations may be critically impaired in this group.

We also found significant impairment in alpha/beta suppression during the retrieval phase of the change localization task. Compared to neural activity in the delay period, the role of alpha/beta suppression during retrieval is less well understood. However, there is evidence that the same capacity-limited alpha modulation that supports consolidation and maintenance of visual working memory during the delay period may be reenacted during retrieval (Fukuda & Woodman, 2017), as working memory representations are being brought "back online." Therefore, our findings suggest that retrieval deficits may also contribute to limited visual working memory capacity in CHR.

Importantly, whereas we also noted group difference in baseline alpha/beta activities, they were not predictive of working memory capacity, suggesting that it is not the absolute levels of alpha/beta activities *per se*, but rather the relative changes of these neural activities in response to working memory demands, that was associated with successful consolidation, maintenance, and retrieval of visual working memory.

4.3. Pathophysiological and Clinical Implications

Our findings in the current CHR sample were highly consistent with those from Erickson et al., (2019), which demonstrated impaired delay-period alpha/beta suppression and its association with working memory capacity in adults living with schizophrenia (Mean age = 36.47, SD = 11.06). As a cross-sectional comparison, the current study provided evidence that this pathophysiological underpinning of working memory deficits in schizophrenia is readily underway in the CHR stage approximately 15 years prior during adolescence/early adulthood. That is, the neural architecture required for effective modulation of oscillatory activities supporting successful working memory operations may already be critically disrupted in emerging psychosis.

The neural generation of posterior alpha suppression has been intensively investigated for decades (Andersen & Andersson, 1968) yet still remains an open question. An emerging consensus is that while alpha oscillations are generated in the neocortex, successful alpha modulation likely involves much broader and anatomically distributed brain regions, including both frontoparietal and thalamocortical networks (Andersen & Andersson, 1968; Reinhart & Woodman, 2014; Sadaghiani et al., 2012). Importantly, not only do these brain networks undergo rapid development and maturation during adolescence and early adulthood (Lebel et al., 2008; Shaw et al., 2008), they have also been directly linked to the development trajectory of working memory capacity in typically developing children and youths. In a longitudinal functional magnetic resonance imaging (fMRI) study following a cohort of participants aged between 6 and 20, Ullman and colleges (2014) found that cortical activities in the frontal and parietal lobes predicted current working memory capacity, and structure and activity in the basal ganglia and thalamus predicted working memory capacity measured two years later. Therefore, alpha

modulations may serve to probe the structural and functional integrity of neural networks that are strongly implicated in working memory maturation in the developing brain. Findings of the current study added to previous behavioral studies demonstrating interrupted growth of working memory abilities in youths who later developed a psychotic disorder (Mollon et al., 2018) by providing a neurophysiological snapshot of working memory functioning in the CHR stage and illustrating one specific neural mechanism through which typical neurodevelopment is disrupted by the psychosis pathophysiology.

The CHR stage and the ensuing years mark a critical period that witnesses rapid, often times life altering, neurobiological, developmental, psychological, cognitive, physical and social changes in adolescents and young adults labelled as "at risk" for psychosis. While the field has made tremendous headway in early detection of psychosis risk with the development and dissemination of clinical diagnostic tools such as the SIPS, the false positive rate remains high. As such, there is an urgent need to enhance and diversify assessment tools for predicting and characterizing the development of psychosis by incorporating well understood features of psychotic illness across levels of measurement (e.g., genetic, neurobiological, behavioral, and self-reported assessments). Importantly, given the heterogeneity of the CHR group and the wide variety of domains where the CHR individuals may deviate from individuals not at risk for psychosis, assessments tools with strong reliability and validity that can be widely adopted are needed. The current study provided an example of such a tool: the change localization paradigm is a brief (8 to 10 minutes) task that is relatively easy to implement (it only requires the presentation of color squares on a regular computer monitor and a computer mouse as a response device) and yields highly reliable (Zhao et al., 2022) measures of a well-defined cognitive construct with both theoretical and clinical significance in psychosis development.

The study also highlighted a promising neural mechanism (i.e., ineffective alpha and beta modulation) that may underly behaviorally observed visual working memory capacity deficits in CHR, which is known to cascade to other domains of cognitive functioning and have real-world implications for at-risk individuals. As such, findings of the study may serve to inform intervention strategies aiming to alter the neurodevelopmental trajectory of at-risk individuals by either directly targeting behavioral and neural correlates of working memory deficits or using these measures as markers of target engagement for treatment.

4.4. Limitations and Future Directions

The current study quantified visual working memory capacity based exclusively on accuracy (i.e., percent correct) in a change localization task. Although this task paradigm has been shown to provide highly reliable and sensitive measures of visual working memory capacity (Zhao et al., 2022), there are limitations to this method. For example, performance in this task may have been confounded by within- and between-participant variations in factors such as lapsing of attention and response bias or strategy, which were not directly assessed in this study. Further, our implementation of the change localization task and use of K as an index of working memory capacity are primarily couched in discrete-slot models of visual working memory. A competing view, coined "resource" models, proposes that working memory consists of a pool of resources that can be distributed flexibly to multiple representations at various resolutions (Frick, 1988). In light of the ongoing debate in basic cognitive neuroscience regarding the nature of visual working memory representation (see Suchow et al., 2014) and the complexity of working memory operations that is far greater than a single task could capture, more studies are needed to probe additional aspects of working memory representations (e.g., resolution or strength of memory) and subcomponents of the working memory system (e.g., the

"central executive") in both neurotypical individuals and those at-risk for psychosis to better understand the nature of working memory impairment in psychosis development.

Second, the time-frequency analyses of the EEG data revealed a very similar pattern of modulations and associations with working memory capacity for both alpha and beta band activities. Namely, we found suppression of alpha and beta signals during both delay and retrieval phases of the task, and impaired modulation in the CHR group for both frequency bands. The magnitude of alpha and beta modulations was also similarly correlated with behavioral working memory capacity. The extent to which neural oscillations in these two frequency bands support shared or distinct mechanisms in visual working memory remains unclear. A recent meta-analysis of oscillatory activities in working memory maintenance found generally consistent patterns of power modulations for alpha and beta frequency bands within and across studies (Pavlov & Kotchoubey, 2022), suggesting potential functional overlap of the two signals. The functional significance of these two oscillatory signals in working memory consolidation, maintenance, and retrieval needs to be further clarified. Moreover, this study did not examine activities in other frequency ranges that have been linked to working memory. In particular, frontal theta (1-8 Hz) activities, especially in the context of frequency coupling with posterior alpha, have been implicated in the top-down control of working memory-related processes (de Vries et al., 2019; Reinhart & Woodman, 2014; Woodman et al., 2022). Due to the event-related design of the current paradigm and the overlap in frequency between early visual and attentional event-related potentials (ERPs) and theta oscillations in frequency, theta activities were difficult to assess within the current experimental design. Gamma (30-100 Hz) oscillations have also gained increasing attention in schizophrenia literature as a marker of cognitive deficits, including working memory impairment, in psychosis (Chen et al., 2014; Haenschel et al., 2009;

Kissler et al., 2000; Singh et al., 2020). There is compelling evidence from human intracranial recordings (Howard, 2003; Mainy et al., 2007) that gamma-band oscillations may represent the neural coding of working memory. However, recording and interpreting gamma signals from the human scalp are highly challenging due to contamination from muscle artifact, which overlaps almost entirely in frequency with gamma neural activity (Muthukumaraswamy, 2013; Whitham et al., 2007), and electrical line noise (60 Hz in North America). As it was not an original goal of the current study to examine gamma oscillations, the experimental environment was not designed to mitigate these confounding factors, and the current data set would not allow for measurement of true gamma signals with enough signal-to-noise ratio. Nevertheless, with well-validated experimental paradigms, controlled laboratory recording environment, and optimal data analytical approaches (Muthukumaraswamy, 2013), gamma signals may be reliably recorded with noninvasive methods and present an exciting window into the neuronal representation of working memory in psychosis and healthy biology alike.

Lastly, the CHR population is a remarkably heterogeneous group with a wide range of symptom presentation, developmental trajectory, and clinical and functional outcome (Fusar-Poli et al., 2013; Ruhrmann et al., 2010). Whereas previous studies have provided strong evidence that the maturation of working memory may be uniquely disrupted in individuals who are at true prodromal stage of psychosis (Mollon et al., 2018), the extent to which the behavioral and neural mechanisms underlying visual working memory identified in this study is unique to the psychosis pathophysiology is unclear. Indeed, working memory deficits have also been reported, albeit to a much lesser degree, in other forms of psychopathology commonly reported by individuals at CHR for psychosis, such as depression (Rock et al., 2014) and anxiety (Moran, 2016). Longitudinal follow-up assessments of clinical and functional outcomes in CHR

individuals, including assessment of psychosis conversion, are needed to further elucidate the relationship between ineffective oscillatory modulation underlying working memory deficits and the development of psychosis. The current study is part of an ongoing longitudinal investigation that will continue to evaluate the neurophysiological, cognitive, and clinical functioning in the current sample. At this time, none of the CHR participants who have completed a 12-month follow-up (N=21) has met diagnostic criteria for a psychotic disorder. Once additional data are obtained from this sample, future studies will fully assess the association between behavioral and neural markers of working memory impairment and clinical outcomes in CHR.

Chapter 4, in part, is under preparation for publication with co-author Dr. Emily Kappenman. The dissertation author will be the primary author on this publication.

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