Internal Noise and Visual Working Memory Deficits in Schizophrenia

By

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Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Psychology

August 7, 2020

Nashville, Tennessee

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ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my advisor, Dr. Sohee Park, for her invaluable guidance, support, and expertise that guided this work. As my academic mentor, she has been critical to my development as a scientist and clinician, and as an individual, she continues to inspire me with her passion for helping and teaching others. I am also deeply grateful for the financial support of Vanderbilt University and the National Institute of Mental Health Institutional Training Grant that allowed me to complete this work. And importantly, I would like to acknowledge the many participants who took part in these studies, without whom this research would not have been possible.

I am very grateful to each of the members of my Dissertation Committee, whom have provided critical assistance and feedback on these studies. I am especially indebted to Dr. Duje Tadin and Dr. Woon Ju Park for helping to inspire this work and providing their technical expertise. I would also like to say thank you to all the members of the Vanderbilt Park Lab, whose helpful comments and administrative assistance facilitated this research, and whose friendship made my graduate school experience so memorable.

Finally, I wish to thank my parents for their unfailing encouragement and love, my sister and brother, Michelle and Matthew, for being excellent role models and always pushing me to do my best, and Sayrge, whose unending support and thoughtfulness kept me going throughout this process.

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CHAPTER I

INTRODUCTION

Schizophrenia is a severe psychiatric disorder characterized by psychosis but also associated with persistent and impairing cognitive deficits. Such cognitive symptoms, particularly deficits in working memory, are considered to play a critical role in individuals' ultimate recovery and long-term functioning. For instance, the severity of working memory deficits predicts immediate functional behaviors, such as medication compliance and daily problem solving skills (Heinrichs et al., 2008; Revheim et al., 2006), as well as longer-term social and occupational outcomes (Cervellione et al., 2007; Smith et al., 2002).

Working memory (WM), a fundamental cognitive construct describing the mental ability to temporarily hold and manipulate information in pursuit of some goal (Baddeley, 1992; 2012), is a critical feature of human intelligence and daily functioning. WM impairment has long been considered a core feature and endophenotypic marker of schizophrenia given its prevalence, stability across the course of illness (i.e., independent of active illness state) (Park et al., 1999), and presence in first-degree relatives of those affected (Elvevåg & Goldberg, 2000; Myles-Worsley & Park, 2002; Park et al., 1995a; Silver et al., 2003). WM deficits in schizophrenia are independent of sensory modality, found across a broad range of tasks and resistant to treatments (Lee & Park, 2005; Park & Gooding, 2014). Since cognitive impairments predict vulnerability to schizophrenia as well as functional outcomes of those with schizophrenia, targeting WM deficits for intervention has emerged as a top priority in psychiatry. However, the complexity and breadth of disrupted functional and structural networks implicated in schizophrenia WM

dysfunction has precluded a clear target for treatment. Thus, specifying the etiological mechanisms underlying WM impairment in schizophrenia remains an urgent task.

Internal Noise as a Putative Mechanism of Encoding Dysfunction in Schizophrenia

Core WM processes include the accurate encoding of sensory information into memory representations, maintenance of that information in the absence of sensory input, and subsequent retrieval of that information. WM dysfunction in schizophrenia is thought to be mainly driven by deficient encoding of sensory information into memory representations (Ichinose & Park, 2019; Lee & Park, 2005; Mayer et al., 2014; Mayer & Park, 2012). Neurocomputational models of WM that take into account how neural populations are thought to encode sensory information find that limitations in WM representations are in part accounted for by internal neural noise (Murray et al., 2014; Starc et al., 2017). In the case of visuospatial WM, memory representations are encoded by sustained spiking activity across neural ensembles tuned to fire in response to certain visual features (e.g., an orientation value) (e.g., Harrison & Tong, 2009; Pasternak & Greenlee, 2005). However, noise in neural spiking activity renders memory representations unstable and prone to drift over time, leading to behavioral errors in WM tasks (Bays, 2014; Bays, 2015). Given that random noise associated with sensory encoding limits the precision with which one forms and maintains WM representations, WM encoding in schizophrenia may be inherently limited by noisier sensory processing (Javitt et al., 1997; Krystal et al., 2017). A majority of studies examining visual WM in schizophrenia focus on deficits in capacity (e.g., number of items recalled) as opposed to reduced precision of remembered sensory representations. However, the few studies which have utilized task paradigms to explicitly test visual WM in a continuous manner provide preliminary evidence that individuals with

schizophrenia may form more variable, or less precise, visuospatial WM representations (Badcock et al., 2008; Murray et al., 2014; Starc et al., 2017), potentially reflecting noisier encoding.

Noise, more broadly, is a fundamental property of neural processing that can limit the accuracy of signal transmission and contributes to variable responding. Human perception, both in terms of the sensitivity to detect and discriminate sensory stimuli as well as the observed variability associated with those behaviors, has long been characterized by sources of noise from both the external and internal environment (Bialek, 1987; Deneve et al., 2001; Faisal et al., 2008). For example, in the visual domain, external noise is driven by the quality of the stimulus and lighting conditions, such that reduced contrast sensitivity associated with dim lighting is driven by the fluctuation of photons emitted from the light source (Faisal et al., 2008). Noise in the internal environment, on the other hand, causes variability in perception even when external noise sources are held constant. This internal noise is present throughout all stages of perception, as perception involves a series of chemical, electrical, and cellular signals subject to stochastic processes at the biochemical and biophysical levels (Faisal et al., 2008). Furthermore, noise present at earlier stages is subject to amplification during typical gain processes within the perceptual system. Optimal perception is thus limited by one's ability to effectively filter out external stimulus noise as well as the baseline internal noise of the sensoriperceptual system. These various sources of noise during perception likely contribute to the collective noise impacting the quality of WM representations during encoding.

The concept of noisier neural processing in those with schizophrenia is seen across several research areas. First, individuals with schizophrenia show greater intra-individual variability in behavioral (Kaiser et al., 2008; Schwartz et al., 1989) and neural responses during

perceptual decision-making and working memory tasks (Barch et al., 2003; Elbert et al., 1992; Fernández et al., 2013; Manoach, 2003; Vinogradov et al., 1998). Influential work by Winterer and colleagues (2000, 2004, 2006; Winterer & Weinberger, 2003, 2004) also demonstrated elevated cortical noise during auditory perception in individuals with schizophrenia, unaffected siblings, and schizotypal individuals, indicating that heightened cortical noise may convey core features of schizophrenia pathophysiology. Noise, in this case, was computed as the spontaneous background activity and variability of the event-related signal. This measure was not impaired in patients with depression, providing some degree of disease specificity.

Noisy information processing in schizophrenia has also been proposed at the cellular level. For instance, improper dopaminergic functioning associated with schizophrenia has been more explicitly connected to excess noise in the prefrontal cortex via downstream dysregulation of N-methyl-D-aspartate (NMDA) and gamma-aminobutyric acid (GABA) (Rolls et al., 2008). Models that implement the hypothesized NMDA-receptor hypofunction in schizophrenia have been shown to alter synaptic plasticity and network connectivity by elevating the excitatory/inhibitory (E/I) ratio in local cortical microcircuits, ultimately leading to increased circuit noise via cortical disinhibition (Cohen et al., 2015; Kehrer et al., 2008; Krystal et al., 2003). Recent studies modeling this NMDA-mediated cortical disinhibition actually predicted noise-related drift of WM neural firing in schizophrenia, resulting in broader neural tuning of stimulus features and degraded spatial WM precision in schizophrenia patients (Murray et al., 2014; Starc et al., 2017).

Elevated noise during perception in schizophrenia is further supported by the growing body of work demonstrating abnormal basic sensory and perceptual processing in those with schizophrenia (Butler & Javitt, 2005; Javitt, 2009; Tadin et al., 2006; Yang et al. 2013) and

subclinical schizotypal traits (Cadenhead et al., 2000; Koychev et al., 2010). Indeed, individuals with schizophrenia exhibit deficits at nearly every level of sensory processing across most sensory modalities. In the visual pathway, this includes dysfunction at the retinal level as well as in primary and association visual cortices (Lavoie et al., 2014; Dorph-Peterson et al., 2007). Such deficits have been realized behaviorally in patients' heightened detection and discrimination thresholds (e.g., visual motion, spatial integration, and contrast) and in the brain as patients' reduced amplitudes of sensory event-related potentials (ERPs) (P1/N1) and evoked steady-state responses, both of which support disruption within early stages of stimulus processing (Brenner et al., 2009; Butler & Javitt, 2005; Javitt, 2009; Tadin et al., 2006; Yang et al., 2013). Such abnormalities in early sensory processing may cause higher internal noise during perception in those with schizophrenia and contribute to downstream noisy WM encoding. Interestingly, behavioral and neural indices of early sensory processing during encoding have been shown to predict subsequent visual WM performance in those with schizophrenia and those at high clinical risk (Dias et al., 2011; Haenschel et al., 2007; Haenschel et al., 2009; Zhao et al., 2011). Early sensory processing deficits have also been related to patients' community and everyday functioning (Butler et al., 2005; Light & Braff, 2005; Light et al., 2007), suggesting the importance of perceptual deficits for higher order cognitive deficits and functional outcome.

Quantifying Internal Noise During Perception

Despite the many implications of noisier perception in schizophrenia, it remains unclear whether heightened noise contributes to patients' perceptual and WM deficits. Additionally, few studies have utilized established psychophysical models that account for various sources of noise

to better understand abnormal perceptual processing in schizophrenia. Observer models based in signal detection theory are explicitly designed to address this issue. Observer models provide an alternative approach to neurophysiological models of perception by characterizing the functional relationship between external stimuli, their respective internal representations, and a human observer's decision process. Importantly, such models provide quantitative measures of perceptual noise sources (e.g., unfiltered external stimulus noise, internal baseline noise of the sensory system) to best account for the inefficiencies of human perception and predict performance on perceptual decision-making tasks (Lu & Dosher, 1999). Although observer models do not explicitly measure or map neural responding to sensory stimuli, they include established processes and principles of perception derived from physiology. Thus, this approach may help characterize possible sources of noise contributing to perceptual and WM dysfunction in schizophrenia.

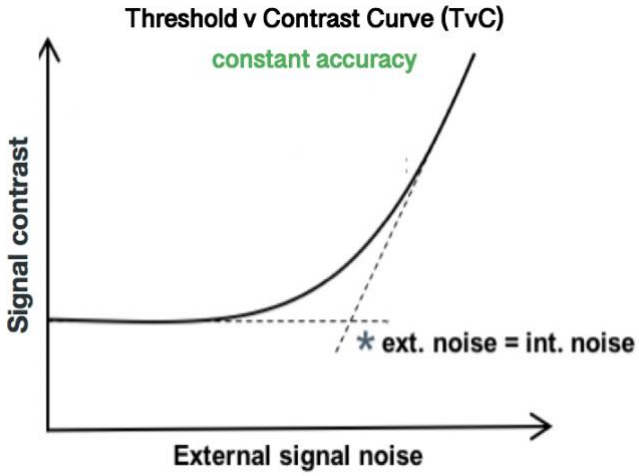
Observer models characterize noise in one's visual perceptual system by measuring the impact of adding external noise to input stimuli on the performance (e.g., perceptual discrimination) of some observer. This external noise method, termed "equivalent input noise", was first used by electrical engineers to measure the internal properties of noisy amplifiers, but has since been applied by psychologists to measure the internal properties of perceptual systems (Lu & Dosher, 1999). A given perceptual system is thus essentially treated like a noisy amplifier: by measuring the effect of added noise to an input signal and measuring the subsequent outputs, one can characterize the intrinsic limitations of that perceptual system. In a human observer model, task stimuli and their signal properties (i.e., contrast level) serve as input signals while perceptual discrimination decisions serve as system outputs. The variability of the system's output, contributing to its signal-to-noise ratio, is a function of both the known external

noise that has been added to the input stimuli as well as the unknown internal noise within the system itself.

According to external noise methods, when the known external stimulus noise is much lower than internal system noise, the variability of system output (decision variability) is driven primarily by internal noise of the system. In this scenario, a relatively constant signal level is required to maintain a given signal-to-noise ratio across external noise levels. Conversely, when external noise is much higher than the internal noise of the system, the variability of system output is driven primarily by the external noise (Lu & Dosher, 2008). In this scenario, a constant signal-to-noise ratio can only be maintained across external noise levels by increasing the signal. This relationship can be depicted graphically in a "threshold-vs-noise" (TvN) function by plotting the signal strength (contrast threshold) required to maintain a given signal-to-noise ratio across increasing levels of external noise (see Figure 1).

Figure 1

Threshold versus Contrast (Noise) Curve



Note. The signal strength (contrast) required to maintain a predetermined signal-to-noise ratio (accuracy) as external noise is added to the stimulus. The curve's inflection indicates the point at which internal noise is equivalent to the external added noise.

TvN functions have a distinctive shape that consists of a flattened slope followed by an increasing slope; the inflection point (the curve's elbow) represents the point as which threshold contrast is equally influenced by the external and internal noise; the level of added external noise is theoretically equivalent to the internal system noise. The studies outlined in this body of work utilize a prominent observer model, the Perceptual Template Model (PTM; Lu & Dosher, 1998, 1999, 2008) to estimate and compare levels of internal noise in those with schizophrenia and non-psychiatric controls, and assess the role of noise in visual WM and schizophrenia symptomology, more broadly.

The Perceptual Template Model of Visual Perception

Lu and Dosher's PTM best accounts for empirical findings in the visual domain compared to other similar human observer models (Lu & Dosher, 2008). In addition to core components shared by other observer models (e.g., a perceptual template, internal noise, a decision process), the PTM also includes unique components that account for known nonlinearities in perceptual processing. In the PTM, input stimuli (signal + external noise) are first filtered through a perceptual template. The perceptual template essentially provides a means by which stimuli with different physical characteristics can be enhanced or diminished with gain. In other words, the perceptual template is tuned for relevant stimulus features (e.g., orientation) according to task demands; it also characterizes an observer's ability to filter external noise from the stimulus. After passing through the perceptual template with some set gain, the signal is subject to a nonlinear transducer function that accounts for the nonlinear gains observed in the perceptual system. The output from this function is then combined with two noise sources:

internal additive noise and multiplicative noise. Internal additive noise represents the independent, absolute baseline level of internal noise of the system in the absence of external stimulus noise. Internal additive noise remains constant despite the strength of the signal. Multiplicative internal noise, on the other hand, is proportional to signal strength and is thought to reflect the noise resulting from contrast gain control processes in the perceptual system. Finally, the noisy signal is submitted to a probabilistic decision process determined by the type of task (e.g., two-alternative forced-choice).

The PTM ultimately predicts contrast thresholds at a given accuracy criterion (i.e., signal contrast required to obtain a given accuracy) across varying levels of added external noise. Lu and Dosher's (1998, 2008) PTM characterizes perceptual contrast thresholds by Equation 1 (derived by Park et al., 2017):

$$(1) \quad c_\tau = \frac{1}{\beta}\left[\frac{(1+N_m^2)\,N_e^{2\gamma} + N_a^2}{(\frac{1}{d'^2} - N_m^2)}\right]^{\frac{1}{2\gamma}}$$

In (1), c_τ is the contrast threshold, β is the signal gain through the perceptual template filter, d' is a threshold accuracy criterion set by the experimenter, N_e^2 is the contrast power of the external noise, N_a^2 and N_m^2 are internal additive and multiplicative noise, and γ accounts for the nonlinearity of the visual system (i.e., amplifies the signal output from the nonlinear transducer to the γth power). The particular variables related to internal noise include additive baseline noise, multiplicative noise, and external noise.

Given the earlier noted deficits in visual perception in schizophrenia, including studies which indicate poorer contrast sensitivity for orientation (Skottun & Skoyles, 2007), individuals with schizophrenia may be characterized by higher levels of all noise sources (internal additive, multiplicative, and unfiltered external noise) relative to healthy adults. Interestingly, the PTM

has been utilized to identify relations between internal noise and external noise filtering and perceptual deficits in other clinical populations, including autism spectrum disorder (Park et al., 2017), amblyopia (Huang et al., 2007; Xu et al., 2006), and cortical blindness (Cavanaugh et al., 2015). Such studies highlight the ability of the PTM to characterize perceptual differences related to underlying pathology and suggest that noise sources might differentially relate to psychiatric symptomology. The current work extends prior studies utilizing the PTM not only by determining whether internal noise levels differ in those with schizophrenia, but by additionally shedding light on the role of noise in WM. It remains unclear whether internal noise during visual perception limits the precision of WM representations, and if so, which sources of noise contribute to WM dysfunction in schizophrenia. In the context of the PTM, the tuning efficiency of the perceptual template may contribute to WM fidelity, as the template allows for task context to be maintained or updated. Thus, unfiltered external noise from the perceptual template may directly contribute to one's recall precision. However, given that internal additive noise limits perceptual detection, it may also limit WM performance to the degree that perceptual sensitivity benefits WM precision.

While the primary focus of these collective studies is to examine the role of internal noise in cognitive impairment in schizophrenia, it is notable that noise may play a broader role in schizophrenia symptomology. For instance, work by Suazo and colleagues (2012) points to a relationship between cortical noise power (power of spontaneous background electroencephalographic activity) and negative symptom severity in those with schizophrenia. Internal noise may also influence proneness to abnormal sensory and perceptual experiences (e.g., hallucinations). For instance, the severity of auditory sensory gating deficits in schizophrenia, which may contribute to higher unfiltered external noise, has been linked to

auditory hallucinations (Smith et al., 2013). Additionally, Cortes-Briones and colleagues (2015) found that the psychosis-like effects of Δ_9-THC were related to dose-dependent increases in neural noise, as measured by the level of randomness in the electroencephalogram. Therefore, these studies will additionally examine possible relations between internal noise and symptoms associated with psychosis and the schizophrenia spectrum. Study 1 examines the role of internal noise in visual perception and visual WM ability in those with schizophrenia using psychophysical and computational methods. Study 2 applies the same methods as Study 1 to determine whether individual differences in internal noise levels within a non-psychiatric population are associated with visual WM ability and subclinical schizotypal characteristics and prodromal symptoms. Study 3 tests a putative intervention for improving visual WM in schizophrenia. Specifically, we examine whether noninvasive electrical stimulation (transcranial direct current stimulation, tDCS) can be used to modulate internal noise and improve visual WM in those with schizophrenia.

CHAPTER II

STUDY 1: ESTIMATES OF INTERNAL NOISE DURING VISUAL PERCEPTION IN SZ AND RELATION TO VISUAL WORKING MEMORY ACCURACY

Introduction

Study 1 utilized the PTM to estimate and compare levels of internal noise (internal additive, multiplicative, and unfiltered external noise) in those with and without schizophrenia during visual perception. We also examined whether estimates of internal noise predicted WM variability (decreased WM precision) on a visuospatial WM task with a continuous response measure. Given the background detailed in the introduction, we hypothesized that individuals with schizophrenia would exhibit elevated levels of both internal additive noise and unfiltered external noise. A higher level of multiplicative noise in those with schizophrenia was also possible; multiplicative noise reduces the impact of signal contrast on the system similar to contrast gain control processes, and some studies interpret reduced neural indices of early visual processing as resulting from reduced contrast gain control (Butler et al., 2005; Butler et al., 2008). Regarding WM performance, we hypothesized that individuals with schizophrenia would exhibit greater variability in WM recall, and that all internal noise estimates would contribute to WM variance.

Methods

Participants

Demographic and clinical information for participants who completed Study 1 is summarized in Table 1. Twenty-seven (48% women) medicated and clinically stable outpatients with chronic schizophrenia or schizoaffective disorder (SZ) were recruited from outpatient

facilities in Nashville for participation in this study. Diagnoses were made or confirmed according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* criteria using the Structured Clinical Interview for DSM-IV (SCID-I/P; First et al, 2002). SCIDs were administered by masters-level clinical psychology graduate students.

Table 1

Demographic and Clinical Information for Participants in Study 1

	SZ (n = 27)	HC (n = 30)
M/F	14/13	16/14
Age	45.04 (8.10)	44.96 (7.55)
Years of education	13.00 (1.80)	15.53 (2.65)
IQ[a]	102.30 (9.03)	106.14 (8.41)
Handedness[b]	+60.18 (53.88)	+72.59 (43.42)
Ethnicity/Race:		
Caucasian	10	19
African American	16	9
Asian/Pacific Islander	1	2
BPRS	17.07 (6.61)	-
SAPS	18.37 (14.52)	-
SANS	28.81 (11.96)	-
CPZE[c]	380.46 (460.90)	-

Mean values are shown with *SD* in parenthesis. BPRS, Brief Psychiatric Rating Scale (Overall & Gorman, 1962); SANS, Scale for the Assessment of Negative Symptoms (Andreasen, 1983); SAPS, Scale for the Assessment of Positive Symptoms (Andreasen, 1984).
[a] National Adult Reading Test (NART; Nelson, 1982).
[b] Edinburgh Handedness Inventory (Oldfield, 1971).
[c] Chlorpromazine Equivalent Doses mg/kg/day (Woods, 2003).

Thirty (47% women) healthy controls (CO) were recruited from the same metropolitan area through advertisements. CO had no history of DSM-IV Axis I disorders or family history of psychosis. We estimated premorbid IQ using the North American Adult Reading Test (NART; Nelson, 1982). The two groups were matched on age, estimated IQ, and handedness but not on

years of education ($t(55) = 4.18$, $p < .01$). Exclusion criteria included a history of head injury, neurological disorder, or substance abuse in the 6 months preceding the study. All participants provided written informed consent to study procedures approved by the Vanderbilt University Institutional Review Board and were compensated for their participation at a rate of $20 per hour.

All SZ participants were taking medications at the time of the study; 26 were taking atypical antipsychotics, 1 was taking a typical antipsychotic, 4 were taking mood stabilizers, and 10 were taking SSRIs. Antipsychotic doses were converted to chlorpromazine equivalent dose (Woods, 2003). Symptom severity in SZ was assessed with the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983), and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). All participants were screened for normal or corrected-to-normal vision with the Snellen test of visual acuity. For the Snellen test, participants read through the chart using one eye at a time, viewed the letters from a distance of 20 feet, and read letters from the top of the chart aloud to an experimenter who scored their performance. Based on this viewing distance and the reference standard (20/20), the 8th row of letters from the top of the chart consisted of letters subtending an angle of 5° with each letter part subtending 1°.

Stimuli, tasks, and experimental procedure

All tasks and stimuli were programmed in MATLAB and Psychtoolbox and presented on a linearized monitor (20-inch Sony CRT; 1024 x 640 resolution; 120 Hz) on a gray background. A chin rest was used to maintain viewing distance at 77 cm with each pixel subtending 0.036°.

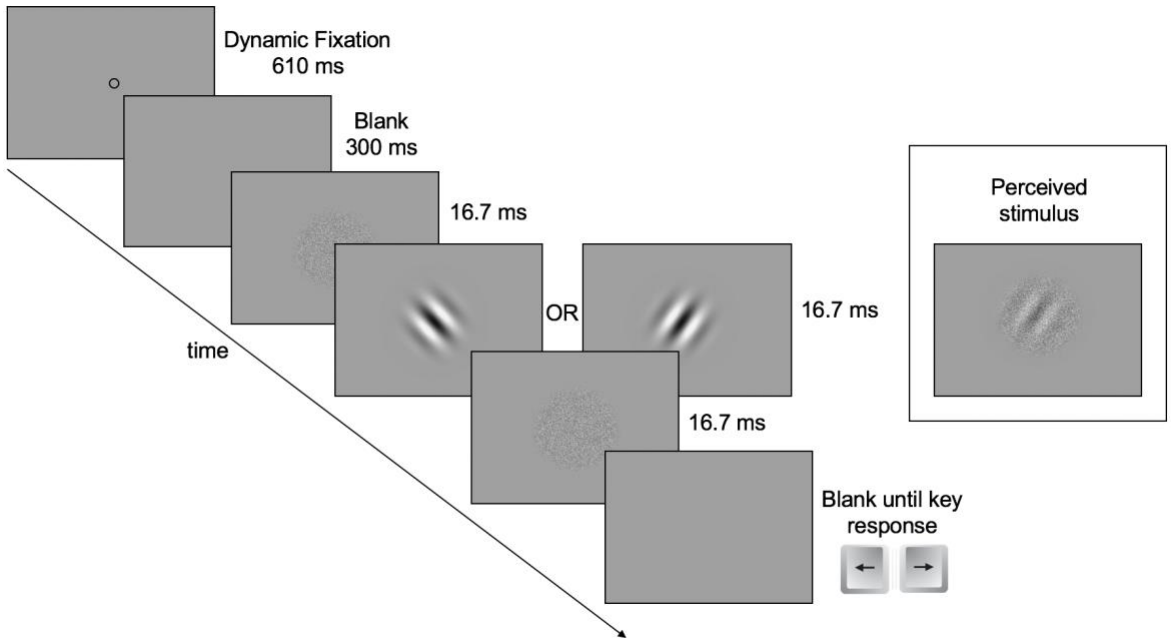
An experimenter was present in the room during both visual discrimination and working memory tasks to encourage task engagement. Task order was counterbalanced across participants.

Visual Discrimination Task

Participants performed a coarse orientation discrimination task (Park et al., 2017) where they judged the tilt of centrally presented Gabor patches (sinewave grate, 1 cycle/°, tilted ±45° from vertical) in a two-dimensional raised cosine envelope (radius = 1°). An example trial sequence is presented in Figure 2.

Figure 2

Visual Discrimination Task Trial Sequence



Note. (Figure Adapted from Park et al., 2017) Each trial started with a dynamic fixation point followed by the stimulus sequence. Stimuli were oriented Gabor patches temporally embedded in Gaussian pixel noise, perceived as a merged stimulus. Participants made an arrow key press to decide whether Gabors were oriented to the left or right.

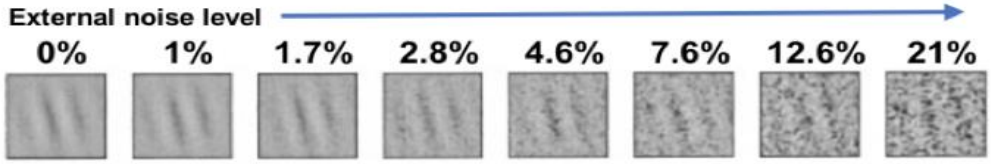
Gabors were temporally embedded in two independent external noise samples. The grey-level pixel values for external noise were sampled from a Gaussian distribution with a mean of 0 and SD that varied across trials, such that its root mean square contrast defined the external noise level to be one of 8 set levels ranging from 0-21% (0, 0.3, 0.61, 1.24, 2.51, 5.1, 10.3, or 21%). The rapid temporal succession of noise, stimulus, and noise frames (16.7 ms duration per frame) results in an intentional perceptual merging of Gabor and noise frames that is consistent with PTM experiments, as it allows for finer adjustments of stimulus contrast (e.g., Lu & Dosher, 2004). Participants indicated their response by a left or right arrow key press, and brief auditory feedback (50 ms tone) was provided after correct trials to maintain task engagement. Trials started with a dynamic, centrally-presented fixation sequence (Foss-Feig et al., 2013). Participants completed 680 trials, split equally into 8 blocks with rest periods lasting a minimum of 30 s.

The visual discrimination task utilizes the established paradigm of external noise addition, in which an adaptive staircase procedure is employed to compute the participant's contrast thresholds (the amount of contrast required to maintain a specified accuracy) across multiple levels of external visual noise added to the stimulus (Park et al., 2017). Figure 3 depicts stimuli at 8 levels of external noise with sufficient signal contrast to distinguish orientation for a sample individual. In the present task, stimulus contrast is adjusted on each trial with the Functional Adaptive Sequential Testing (FAST toolbox; Vul et al., 2010), which determines the most informative contrast levels to be sampled for estimating participants' contrast thresholds. To fully characterize the PTM, contrast threshold estimates are required for at least for two accuracy criteria. The ratio between contrast thresholds at two accuracy levels for any level of external noise added to the signal is predicted to be a constant. Thus, the present task

incorporated two FAST structures that estimate psychophysical functions reflecting the contrast level required to elicit reliable orientation discrimination at two different sensitivity levels (*d'*=1.089 and 1.634), corresponding to 70.71% and 79.37% accuracy). Accuracy levels were chosen according to prior work (Park et al., 2017) and based on recommendations to use accuracy levels below 90% so as to avoid the tails of the distribution (Lu & Dosher, 1999). Utilizing two FAST structures increases the efficiency with which signal contrasts are sampled, thus reducing the number of trials needed to estimate participants' contrast thresholds. Of note, data analyses were completed separately from the within-task FAST procedure in order to limit biased threshold estimations from potential increased accidental error responses in SZ. See Park et al. (2017) for a complete description of the psychophysical procedure.

Figure 3

Sample Gabor Stimuli at Each Level of Added External Noise



Note. To maintain perceptual discrimination performance at a given accuracy criterion, stimulus contrast increases as external noise is added to the stimulus.

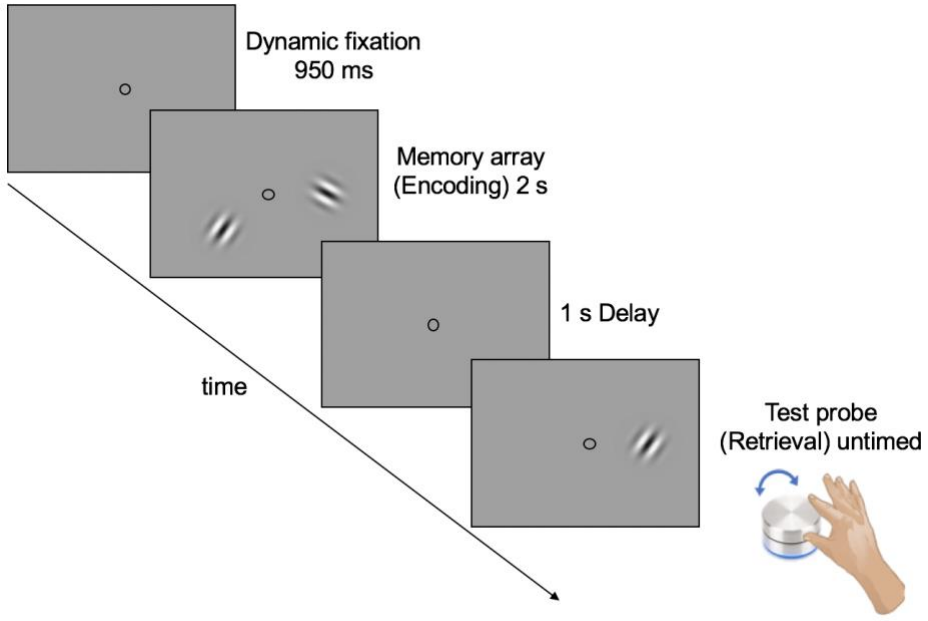
Visual Working Memory Precision Task

To assess visual WM, participants completed a WM task in which they were instructed to remember locations and orientations of Gabor patches that were the same size and spatial frequency as those in the visual discrimination task. All Gabors were presented at maximum contrast to ensure visibility. The trial procedure was as follows: first, a memory array consisting

of one, two, or four oriented Gabors was presented for 2 s. Orientations were randomly selected from all possible options [-90°, 90°] with the constraint that orientations within a given memory array were unique. Gabor locations for each trial were randomly chosen from eight positions around an invisible circle (radius 4°) centered on a fixation point. After a short delay (1 s), a new, randomly oriented [-90°, 90°] Gabor patch appeared at one of the prior locations (test probe). Participants used an input dial (PowerMate USB Mulitmedia Controller; Griffin Technology) to adjust the test probe's orientation so that it matched the orientation of the Gabor patch presented at that same location (see Figure 4).

Figure 4

Visual Working Memory Precision Task Trial Sequence



Note. Each trial started with a dynamic fixation point followed by the stimulus sequence. The memory array consisted of 1, 2, or 4 randomly oriented Gabor patches positioned at 8 possible locations around an invisible circle. After a short delay, a randomly oriented test probe Gabor was presented at one of the memory array locations. The participant was instructed to use the manual dial to orient the test probe in the same exact direction as the Gabor in that same location from the memory array.

Participants were asked to be as precise as possible when matching orientations and responses were untimed. Participants indicated their final response by pressing down on the dial, leading to a 1 s inter-trial interval. Similar to the visual discrimination task, trials began with a centrally-presented dynamic fixation sequence (Foss-Feig et al., 2013). Participants completed a total of 450 trials, split equally into 10 blocks with rest periods lasting a minimum of 30 s.

Because group differences in ability to use the manual dial may confound hypothesized group differences in WM precision, participants also completed a short motor precision task that did not tax memory. Participants completed the motor precision task prior to the WM task in order to become acclimated to using the manual dial. Trials involved presentation of a randomly oriented Gabor located at one of eight positions around an invisible circle (radius 4°) that remained on the display. A randomly oriented Gabor was then presented at the center of the display, and participants were instructed to use the manual dial to adjust the orientation of this central Gabor until it was aligned with the orientation of the first Gabor, which remained on the display until the participant's response was submitted. Consistent with instructions on the WM task, participants were asked to be as precise as possible when matching orientations and responses were untimed. Participants completed a total of 24 trials such that each of the 8 possible Gabor locations were sampled three times.

This manual recall method has been used with both healthy adults and psychiatric populations to obtain a more detailed, continuous measure of visual WM precision compared to typical binary match/non-match response paradigms (e.g., Bays, 2014; Gold et al., 2010). Importantly, this method enables WM performance to be analyzed as a distribution of recall errors (the difference between input response and target orientation) with accompanying

descriptive properties of the distribution. As number of visual features or items to be remembered increases, the decline in recall precision is captured by the increasing variance of the error distribution.

Task Analyses

Visual Discrimination Task

Data from the visual discrimination task were analyzed with two different approaches. The first involved a conventional PTM analysis to estimate model parameters at a group level, thus allowing us to test for relative groups differences in levels of noise (external noise filtering, internal additive noise, internal multiplicative noise) between SZ and CO. The second approach utilized hierarchical Bayesian model fitting to estimate each individual's model parameters. The latter thus allowed for a better understanding of individual differences in noise estimates. It also enabled us to examine how noise estimates related to WM performance. This analysis pipeline and equations 1 through 4 are consistent with those described by Park and colleagues (2017).

Conventional PTM Analysis. To examine group-level differences in noise estimates, visual discrimination performance was first analyzed using a conventional PTM fitting method. First, psychophysical contrast thresholds were estimated for each participant at each of the 8 external noise levels with data pooled across the two FAST structures. Individuals' contrast thresholds for orientation discrimination were estimated with Weibull functions at every external noise level with Equation 2:

$$(2) \quad P(c) = 1 - (1 - 0.5) \times 2^{-(\frac{\log(c)}{\alpha})^{\eta}}$$

In (2), P represents accuracy (percent correct), c is stimulus contrast, α is threshold at 75% accuracy, and η is the slope. The two free parameters, α and η, were estimated with a Bayesian

model fitting method implementing a Markov Chain Monte Carlo (MCMC) technique (See Park et al. 2017). Group averages of individuals' estimated thresholds were used to fit the conventional PTM. Coefficient indices for each noise source (external noise filtering (A_e), internal additive noise (A_a), multiplicative internal noise (A_m)), were introduced into the standard PTM (Equation 2) to account for differences in noise levels between groups with Equation 3:

$$(3) \quad c_\tau = \frac{1}{\beta}\left[\frac{(1+(A_m N_m)^2)(A_e N_e)^{2\gamma} + (A_a N_a)^2}{(\frac{1}{d'^2} - (A_m N_m)^2)}\right]^{\frac{1}{2\gamma}}$$

During PTM fitting, these three SZ coefficients (A_e, A_a, A_m) could freely vary or be fixed at one, with the latter constraining a given noise estimate to be equal across groups and the former allowing for relative group differences in a given noise estimate. The coefficients thus provide relative differences in noise estimates between groups such that a coefficient greater than one indicates a higher level of that respective noise source in SZ relative to CO. To determine if noise sources differed between groups, all possible candidate models accounting for each combination of free and fixed noise estimates were run: the null model, which assumed no group differences in any of the noise sources, the full model, which assumed group differences in all three noise sources, and six remaining models reflecting the different possible combinations of the three noise estimates. In addition to which ever noise coefficients were specified to freely vary, all candidate models included the following four free parameters: multiplicative internal noise (N_m), internal additive noise (N_a), signal gain from the perceptual template (β), and the exponent of the nonlinear transducer function (γ). Thus, the full model included 7 free parameters, the null model included 4 free parameters, and the other six models included between 5 and 6 free parameters. The eight candidate models were each fitted to average group

thresholds using a least-squares method. Candidate models were compared by evaluating differences in goodness-of-fit using r^2. The best fitting model was determined with the *F*-test for nested models using a significance level of $\alpha < 0.05$ (see Park et al., 2017 for r^2 and *F*-test equations). Specifically, the best fitting model was identified as the model with the fewest free parameters that was not significantly different from the full model, in which all parameters could freely vary.

Hierarchical Bayesian Model Analysis. A hierarchical Bayesian modeling technique was used to fit each participant's data with the PTM in order to obtain individual noise parameter estimates and examine relations between noise estimates and visual WM performance (see Park et al., 2017 for a more detailed description of Bayesian procedures). The hierarchical Bayesian approach allows for model parameters to be estimated for an individual within a population (i.e., SZ or CO), thus increasing statistical power. Unlike in the conventional PTM analysis approach described above, in which model parameters are estimated from the contrast thresholds at each level of external noise, the Bayesian approach allows for model parameters to be estimated for each participant directly from single trial data points based on the probability of participants making a correct response. The PTM used during the Bayesian analysis to compute perceptual thresholds, seen in Equation 4, was identical to that in Equation 1, with the exception of adding a coefficient (A_f) to capture the extent to which external noise was filtered from the signal. Similar to the coefficients added during the conventional PTM analysis to capture group difference, A_f allows us to capture individual differences in how well external noise is filtered from the signal.

$$(4) \quad c_{\tau ij} = \frac{1}{\beta}\left[\frac{\left(1+{N_m}^2\right)\left(A_f N_{e_{ij}}\right)^{2\gamma}+{N_a}^2}{\left(\frac{1}{{d'^2}_i}-N_m^2\right)}\right]^{\frac{1}{2\gamma}}$$

In Equation 4, the contrast threshold is estimated at a given accuracy criterion, i (either 70.71% or 79.37%), and external noise level, j. Each participant's response on a given trial (with a given external noise level and at a given difficulty level) was assumed to be drawn from a Bernoulli distribution to capture the set of possible outcomes from the 2-alternative forced-choice response in the visual discrimination task (see Park et al. 2017 for details). PTM fitting was constrained such that the gain parameter β and nonlinear power parameter γ were held constant to minimize the number of free model parameters while enabling estimation of all three noise parameters of interest (N_a, N_m, A_f) and the slope of the psychometric function (η). Values were set at β = 1 and γ = 1.27 for all individuals. Values for β and γ were based on estimates generated from the conventional PTM analysis as well as estimates that have been reported in previous studies (Cavanaugh et al. 2015; Lu & Dosher, 2008; Park et al., 2017). Importantly, modifications in the values of the gain parameter β and nonlinear power parameter γ did not change the results regarding relations between noise estimates and WM recall variance. Free model parameters were estimated for each individual with the Markov chain Monte Carlo (MCMC) method for sampling from posterior probability distributions. A given individual's model parameters were constrained by hierarchical priors in that parameters were assumed to be drawn from a group's (SZ or CO) population distribution with their own means and SDs. Priors for the two groups were set to broad uniform distributions (see Park et al., 2017 for detailed description).

Visual Working Memory Precision Task

Gabor orientations were recorded and reported in the circular parameter space of all possible line orientation values [-90°, 90°) and converted to the circular space [-π, π) radians. Recall error on each trial was calculated as the difference between the orientation of the target

Gabor and the orientation of the test probe that was reported (input with the manual dial) by the participant. Given that internal noise is hypothesized to add variability to, or destabilize, the internal representation (Bays et al., 2014; Starc et al., 2017), the primary performance metric of interest on the visual WM task was participants' recall variance. Poorer WM performance is thus reflected by higher recall variance, as demonstrated by the characteristic increase in recall variance (decline in precision) as the number of items remembered increases (Bays & Husain, 2008; Wilken & Ma, 2004). The Von Mises probability density function (circular normal distribution) with mean $\theta = 0$ (no error, such that recall is centered at the target memory location) and SD = σ was used to fit every participant's distribution of recall errors at each memory array set size. The Von Mises probability density function for a given angle x, centered at θ with a concentration κ is seen in Equation 5, where $I_0(\kappa)$ is the modified Bessel function of order 0:

$$(5) \quad f(x|\theta,\kappa) = \frac{e^{\kappa \cos(x-\theta)}}{2\pi I_0(\kappa)}.$$

The variance of the Von Mises probability density function (σ^2), which reflects the dispersion of the distribution, is analogous to the inverse of the distribution's concentration ($1/\kappa$). The concentration parameter (κ) was estimated from each participant's recall errors at every memory array set size using a maximum likelihood method. Estimates of distribution concentration were converted to variances by taking the inverse for subsequent between-group and individual differences analyses. Repeated measures ANOVAs were conducted to determine changes in recall variance with increasing WM set size and probe group differences in recall variance. Pearson correlations were conducted to examine relations between noise estimates and recall variance. Multiple linear regressions were completed to determine the contributions of internal additive, multiplicative, and unfiltered external noise to WM recall variance within each group.

Spearman correlations were conducted to examine relations between noise estimates and positive and negative symptoms.

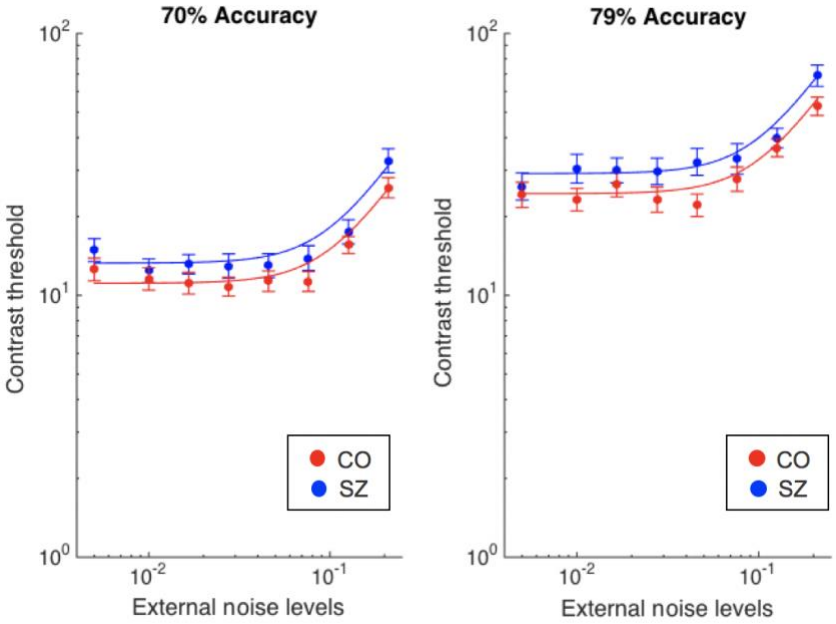
Results

Relative Group Differences in Noise Estimates

The conventional PTM analysis yielded characteristic nonlinear TvN functions for both the SZ and CO groups (See Figure 5), which reflect each group's contrast thresholds as a function of varying levels of external stimulus noise. On average, individuals with SZ performed worse than CO at every level of external noise, as seen by the SZ group's heightened contrast thresholds across nearly all levels of external noise.

Figure 5

Conventional Perceptual Template Model (PTM) Threshold vs. Noise (TvN) Curves



Note. Contrast thresholds (filled dots) estimated from the conventional PTM at each external noise level for the two accuracy criterion (left: 70.71%, right: 79.14%). CO, control group; SZ, schizophrenia group. Error bars are ±SEM.

Results from the conventional PTM indicated that these group differences were best accounted for by the model in which SZ and CO differed in levels of unfiltered external noise (A_e) and internal additive noise (A_a), but *not* internal multiplicative noise (A_m). In particular, this model specified a 24% increase in internal additive noise alongside a 23% increase in unfiltered external noise in the SZ group relative to noise levels of the CO group (R^2=98.5%). This model was significantly different from the null model, in which noise parameters were equivalent between groups, $F(2, 26) = 30.4$, $p < 0.001$, but not statistically different from the full model, in which all three noise sources were different between groups, $F(1,25) = 0.89$, $p = 0.36$. These results indicate that visual perception in those with SZ is characterized by higher levels of internal additive noise as well as a poorer ability to filter out external stimulus noise. There was no evidence of group differences in internal multiplicative noise.

The group effect on independently estimated contrast thresholds across levels of external noise did not reach significance, $F(1,55) = 3.05$, $p = .09$. However, this is not surprising given that the conventional PTM approach utilizes a less precise means of estimating contrast thresholds in order to optimally estimate PTM parameters.

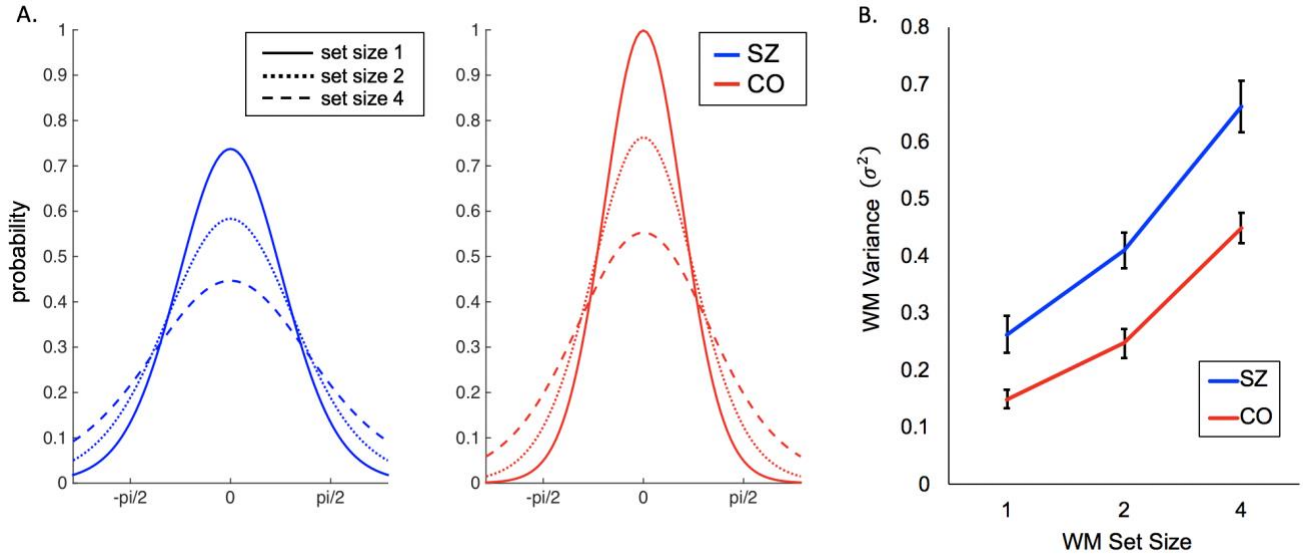
Group Differences in Visual Working Memory

Individuals' WM recall variance was estimated from participants' error distributions at each set size with the Von Mises distribution. Von Mises probability density functions, plotted by set size and group, are shown in Figure 6a. WM recall variance exhibited the expected pattern of greater variance with increasing WM set size across groups, $F(1,55) = 49.37$, $p < .001$. There was a significant group effect such that SZ exhibited higher recall variance relative to CO across set sizes, $F(1,55) = 18.04$, $p < .001$ (See Figure 6b). There was also a significant group by set

size interaction, $F(2,110) = 5.05$, $p < .05$. While SZ exhibited higher WM recall variance than CO at each set size, post-hoc group comparisons indicated that the difference between groups was greater at set size 4 ($M_{diff} = 0.213$) than that at set size 2 ($M_{diff} = 0.162$), which was greater than the group difference at set size 1 ($M_{diff} = 0.052$). SZ and CO did not exhibit significant differences in recall variance on the motor precision task, $t(55) = 1.65$, $p = 0.11$.

Figure 6

Visual Working Memory (WM) Recall Variance for SZ and CO



Note. (A) Von Mises probability density functions of visual WM recall for the schizophrenia group (SZ) and control group (CO). (B) WM recall variance at each set size, by group.

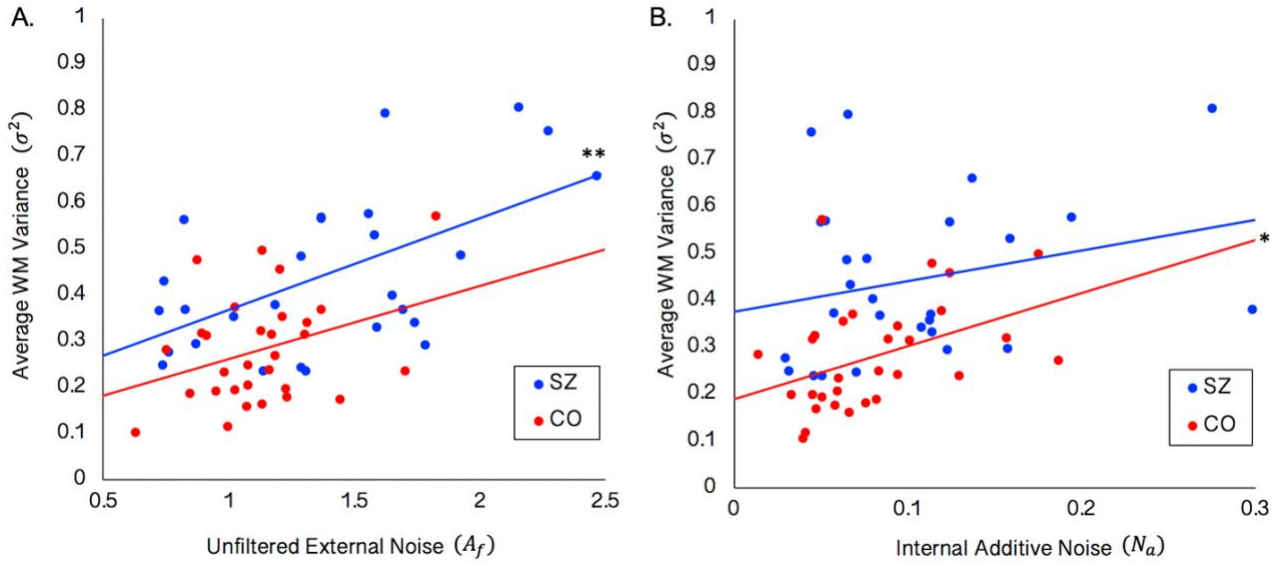
Relations between Noise Estimates and Visual Working Memory

The hierarchical Bayesian analysis resulted in estimates of the three noise parameters for each individual. There was not a significant correlation between internal additive noise and unfiltered external noise for SZ, $r(27) = .26$, $p = .19$, or CO, $r(30) = .09$, $p = .63$, which is consistent with the PTM in that these two sources of noise contribute at least somewhat

independently to perceptual inefficiencies. To limit the number of tests conducted, WM variance was averaged across set sizes for each participant. Pearson correlations indicated a significant positive relation between unfiltered external noise and average recall variance for SZ, $r(27) = .57$, $p < .01$, and a trending relationship for CO, $r(30) = .34$, $p = .06$ (See Figure 7a). A significant positive correlation between internal additive noise and recall variance was observed for CO, $r(30) = .42$, $p < .05$, but not for SZ, $r(27) = .26$, $p = .20$ (See Figure 7b). Internal multiplicative noise was not significantly correlated with WM recall variance for CO or SZ ($ps > .62$).

Figure 7

Relations Between Noise Estimates and Visual Working Memory (WM) Recall Variance for SZ and CO



Note. (A) Unfiltered external noise and average WM recall variance, plotted by group. (B) Internal additive noise and WM recall variance, plotted by group. CO, control group; SZ, schizophrenia group. *$p < .05$, **$p < .01$.

A multiple linear regression was conducted to better examine contributions of each noise source to WM recall variance in each group. In SZ, a significant regression equation ($F(3,23) = 3.90$, $p < .05$, $R^2 = .34$, $R^2_{Adj} = .25$) indicated that internal additive noise, multiplicative noise, and unfiltered external noise accounted for 33.7% of the variance in WM recall variance. However, only unfiltered external noise significantly predicted WM recall variance in this model, $\beta = .53$, $t(26) = 3.02$, $p < .01$. Neither internal additive noise ($\beta = .12$, $t(26) = .66$, n.s.) nor multiplicative noise ($\beta = .04$, $t(26) = .25$, n.s.) significantly predicted WM recall variance. In CO, a significant regression equation ($F(3,26) = 3.99$, $p < .05$, $R^2 = .32$, $R^2_{Adj} = .24$) indicated that internal additive noise, multiplicative noise, and unfiltered external noise accounted for 31.5% of the variance in WM recall variance. Both unfiltered external noise ($\beta = .45$, $t(29) = 2.31$, $p < .05$) and internal additive noise ($\beta = .38$, $t(29) = 2.31$, $p < .05$) significantly predicted WM recall variance in this model. Multiplicative noise did not significantly predict WM recall variance for CO, $\beta = -.26$, $t(29) = -1.33$, n.s.

Relations between Noise Estimates and Schizophrenia Symptoms, Medication, and Premorbid IQ

In the SZ group, none of the noise measures were significantly correlated with clinical symptoms. However, a positive relation between total negative symptoms (SANS) and internal additive noise was trending, $\rho(27) = .34$, $p = .08$. There was a significant correlation between antipsychotic medication dose (CPZE) and internal additive noise, $r(27) = .41$, $p < .05$, although upon removal of an outlier in CPZE dose (>3 SD from the mean), the correlation was no longer significant $r(26) = .08$, $p = .70$. Additionally, the results of the multiple linear regression examining contributions of noise measures on WM recall variance did not change when CPZE was included as a predictor. CPZE was not significantly correlated with WM recall variance at

any set size (*p*s > 0.6). Premorbid IQ, assessed with the NART, was not significantly correlated with any of the noise estimates in SZ (*p*s > .60) or CO (*p*s > .13).

Discussion

The present study estimated levels of internal noise in individuals with and without schizophrenia during a visual orientation discrimination task utilizing an established psychophysical paradigm of external noise addition. We also examined the relationship between internal noise estimates and visual WM variance, measured from performance on a spatial delayed response task with a continuous response measure. Consistent with our hypothesis, results indicated elevated levels of internal noise in those with schizophrenia. More specifically, the SZ group exhibited greater internal additive noise as well as unfiltered external noise relative to CO, suggesting that visual perception in schizophrenia is limited both by internal additive noise alongside a poorer ability to filter out external stimulus noise. These findings are also consistent with prior work showing reduced contrast sensitivity in those with schizophrenia (for a review, see Skottun & Skoyles, 2007).

Regarding visual WM performance, we found evidence that individuals with SZ exhibit greater WM variance and reduced precision relative to CO. Both SZ and CO exhibited the typical increase in recall variance (decreased recall precision) with increasing memory set size, and SZ recall variance was higher than CO at every set size. Greater recall variance in SZ relative to CO is consistent with established visuospatial WM deficits in SZ (Lee & Park, 2005) as well as specific studies of reduced visuospatial WM precision in SZ (Badcock et al., 2008; Starc et al., 2017). Interestingly, greater recall variability for SZ was noted even when recall was for a single item, under relatively long encoding (2 s) and short delay (1 s) conditions,

highlighting the importance of using sensitive measures of recall. Finally, results supported the hypothesis that internal noise estimates would contribute to WM variance in both groups. While only unfiltered external noise predicted WM variance in SZ, both internal additive and unfiltered external noise predicted WM variance in CO. Collectively, these findings provide additional evidence for more variable, "noisier" perception in SZ, and underscore a putative role of internal noise in patients' WM dysfunction.

Results from the conventional PTM analysis indicating greater internal additive noise in schizophrenia are also consistent with prior work demonstrating increased intra-individual variability in reaction times during perceptual detection tasks (Kaiser et al., 2008; Nuechterlein, 1977; Rentrop et al., 2010; Schwartz et al., 1991). Such increased variability has been attributed to a number of potential causes, including instability of information processing (Rentrop et al., 2010), alterations in perceptual timing (Bolbecker et al., 2014), and dysfunction in patients' facilitation of adaptive motor responses (Karantinos et al., 2014). While these various explanations may each uniquely contribute to variable visual perception in schizophrenia, limitations imposed by elevated internal additive noise during perception may provide a more comprehensive and parsimonious explanation for such variability. There is currently mixed evidence of whether patients also exhibit increased variability in underlying neural activity during visual perception as reflected by neurophysiological measures (Ergen et al., 2008; Haigh et al., 2016), with more consistent findings of variability during auditory perception (Callaway et al., 1970; Jansen et al., 2010; Shin et al., 2015). However, studies examining visual perceptual deficits in schizophrenia often capture a related weakened neural signal that may, in part, be driven by increased internal additive noise. For example, findings of reduced steady-state visual evoked potentials (ssVEPs) and ERPs that reflect early visual processing in schizophrenia (e.g.,

P1 and N1) (Brenner et al., 2009; Javitt, 2009) have been linked to increased variability, or temporal jitter, in the neural response (Ergen et al., 2008; Krishnan et al., 2005). Individuals with schizophrenia also exhibit reduced cell number and volume in primary visual cortex, suggesting an overall smaller cortical area for primary visual perception (Dorph-Petersen et al., 2007). Interestingly, damage to the primary visual cortex has been related to increased internal additive noise but not unfiltered external noise (Cavanaugh et al., 2015). Thus, greater internal additive noise may also reflect the downstream variability stemming from inherent deficits in primary visual regions.

In addition to heightened internal additive noise, the present study also points to increased unfiltered external noise in schizophrenia. Unfiltered external noise is thought to reflect the efficiency of a perceptual template tuned to task-relevant sensory information. Accordingly, noise filtering has also been described as "template tuning", in which prior information related to task goals and task feedback informs the precision of the template itself (Lu & Dosher, 1998, 2004, 2008). External noise exclusion has also been linked to improved perceptual sensitivity following perceptual training, indicating that enhanced template tuning may partly underlie mechanisms of perceptual learning (Lu & Dosher, 2004, 2009). Greater unfiltered external noise in those with schizophrenia may thus result from deficiencies in the use of task-relevant information to predict and update the perceptual template. This framework is a reformulation of an earlier theory of schizophrenia that pointed to the central role of comparing expected behavior predicted from stored regularities and observed behavior in generating context-appropriate actions (see Hemsley, 2003; Hemsley, 2005). Within the current predictive coding framework, sensory perception is constrained by predictions (priors) encoded in higher cortical levels of processing (e.g. mental representation or long-term memory), and the degree to

which incoming sensory signals are processed depend largely on the difference between the predicted and actual sensory signals (i.e., prediction error). If the magnitude of the difference surpasses the expected noise of the system, the predictive model is adjusted. Schizophrenia symptomology, including cognitive impairment, has been increasingly described as a breakdown in this prediction error mechanism (e.g., Corlett et al., 2007; Corlett et al., 2016; Hemsley, 1993; Hemsley, 2005).

Changes in external noise filtering and internal additive noise have also been linked to the impact of spatial attention (Pratte et al., 2013; Lu & Dosher, 2004; Lu et al., 2002), raising the possibility that attentional deficits account for the perceptual variability and heightened noise estimates in the SZ group. While attentional deficits are considered a core aspect of cognitive impairment in schizophrenia (Nuechterlein & Dawson, 1984), recent work indicates a more nuanced view of visuospatial attention in this population. For example, studies point to generally intact visuospatial orienting to spatial cues (Spencer et al., 2011) with more selective impairment under conditions requiring broad attentional monitoring (Hahn et al., 2013; Lubow, 2005) or those involving inhibition of task-related distractors (Demeter et al., 2013; Mayer et al., 2012). Certainly, poor filtering of external stimulus noise may lead to difficulties inhibiting task irrelevant information. However, the current perceptual discrimination task did not require broad attentional monitoring or distractor inhibition, limiting the likelihood that perceptual discrimination differences in SZ were attributable to attentional deficits alone. Additionally, prior studies have demonstrated relative independence between perceptual deficits and measures of sustained attention (Demeter et al., 2013; Stuve et al., 1997). Finally, a SZ-specific deficit in sustained attention would theoretically impact both internal and external noise estimates, which

is inconsistent with the lack of observed relationship between these two estimates in the SZ group.

Given that one's perceptual threshold is limited by both internal additive noise and unfiltered external noise, one may question whether patients' deficits in contrast sensitivity necessitate higher levels of both noise sources. However, studies utilizing external noise addition paradigms to assess reduced contrast sensitivity in other populations indicate unique patterns of noise elevations across clinical and developmental conditions. For example, spatial deficits observed in those with treated and untreated amblyopia (lazy eye) were best characterized by higher internal additive noise at lower spatial frequencies but both additive and unfiltered external noise at higher spatial frequencies (Huang et al., 2007; Xu et al., 2006). Reduced contrast sensitivity associated with aging has been primarily related to elevated internal additive noise (Fang-Fang et al., 2020). Alternatively, perceptual discrimination in autism spectrum disorder was characterized by higher internal noise and unfiltered external noise, although autism spectrum traits were only associated with internal noise levels (Park et al., 2017). While these studies argue against the specificity of internal noise elevations to any one clinical condition, they demonstrate the relatively unique contributions of noise elevations to perceptual deficits or aberrations across clinical and developmental populations.

The present study importantly expands upon the existing literature utilizing internal noise estimates to characterize clinical populations by highlighting relations between psychophysically-derived estimates of internal noise and visual WM performance in those without and with schizophrenia. This observed link between visual perception and WM is consistent with the concept of WM as involving the integration of higher-order executive processes with sensory processes (e.g., Vogel & Machizawa, 2004; Xing et al., 2013). Results

from the SZ group are further in line with work demonstrating contributions of early visual deficits to WM dysfunction in those with schizophrenia (Haenschel et al., 2007; Tek et al., 2002) and schizotypal traits (Koychev et al., 2010). As discussed earlier, heightened noise within sensory and perceptual regions, possibly resulting from underlying neuroanatomical and/or neurochemical differences, could contribute to downstream variability, "noise", in WM circuits that also involve higher-order cognitive processing.

While noise estimates accounted for a similar proportion of variance in WM recall for SZ (33.7%) as CO (31.5%), the two groups demonstrated different relations between noise sources and WM recall variance. Both internal additive and unfiltered external noise predicted WM recall variance in CO, but only unfiltered external noise significantly predicted WM recall variance in SZ. This finding raises the possibility that internal additive noise and unfiltered external noise may differentially contribute to schizophrenia pathophysiology. That is, a build-up of unfiltered external noise may contribute in a more proximal way to cognitive dysfunction, while internal additive noise may impact visual perception in a relatively constrained manner, leading to more distal effects on symptoms (e.g., negative symptoms). As discussed earlier, neurocomputational models of WM based on the NMDA receptor hypofunction hypothesis of schizophrenia show that heightened noise within prefrontal cortex (PFC) WM circuits accounts for patients' heightened WM variance (Murray et al., 2014; Starc et al., 2017). Thus, greater unfiltered external noise may more directly contribute to the inefficiency of top-down WM mechanisms that orchestrate perceptual activity during encoding and maintenance. NDMA receptor hypofunction has also been linked to aberrant predictive coding associated with schizophrenia (Corlett et al., 2011), which would theoretically impact the precision which the perceptual template (filter) is tuned to task context. Further work is needed to determine whether

this external noise filtering mechanism is engaged by frontal, top-down processes involved in WM, bottom-up, sensory-driven processes, or an integration of both.

Another possible explanation for the observed relationship between internal noise estimates and WM variance in SZ and CO is that PTM-estimates of internal and external noise index a broader measure of cortical noise beyond visual perception. Unfortunately, there is little work describing whether individual differences in psychophysically-derived internal noise estimates are stable across sensory modalities. Similarly, at a neural level, it remains unclear whether psychophysically-derived noise estimates are related to variable neural activity within a focal area that propagates more globally or vice-versa. Saville and colleagues (2012) found that intra-individual variability reflected more of a unitary construct across behavioral and neural levels of observation for both visual and auditory perception. If intra-individual variability in behavioral and neural responses contributes to PTM estimates of noise, this work potentially supports a broader role for internal noise and unfiltered external noise across cognitive functions.

While we did not observe a significant relationship between internal noise estimates and positive or negative symptoms, the current symptom measures may be too rough to capture more subtle links between internal noise and abnormal processes underlying certain symptoms (e.g., emotion perception). However, lack of relationship between noise estimates and clinical symptoms may also be consistent with a more stable underlying process of WM dysfunction as an endophenotype of schizophrenia that does not notably wax and wane with positive or negative symptoms. Because the current sample of individuals with schizophrenia were all in the middle or later stages of illness, it is unclear whether levels of internal noise are related to core features of disease pathophysiology or arise from factors associated with disease progression, such as the use of antipsychotics. Though we did not find a relation between antipsychotic dose and levels

of internal noise, the degree to which medication may affect visual processing in schizophrenia remains unresolved. While some research suggests that contrast detection thresholds are related to only typical, rather than atypical antipsychotics (Chen et al., 2003), other studies show that patients' visual deficits persist when off antipsychotic medications for short periods of time (Kéri et al., 2004) and when receiving atypical antipsychotics alone (Butler et al., 2005).

In conclusion, results from the present study suggest that visual perception in schizophrenia is limited by elevated levels of internal noise and unfiltered external noise. As predicted, individuals with schizophrenia exhibited greater WM recall variance than those without. Importantly, noise estimates predicted WM recall variance across groups, emphasizing the importance of basic perceptual processing in the encoding and maintenance of precise WM representations. In particular, findings that unfiltered external noise uniquely contributed to WM recall variance in schizophrenia further our understanding of WM dysfunction in schizophrenia by providing a more nuanced explanation of noise's role in visuospatial WM deficits. Future studies should examine whether internal noise sources (internal additive, unfiltered external) reflect core aspects of disease pathophysiology in schizophrenia or capture current cognitive state. It will also be important for future work to examine how internal noise measures related to underlying neurophysiology.

CHAPTER III

STUDY 2: ESTIMATES OF INTERNAL NOISE DURING VISUAL PERCEPTION IN YOUNG ADULTS AT PSYCHOMETRIC RISK OF PSYCHOSIS

Introduction

Results from Study 1 indicated higher levels of internal additive noise and unfiltered external noise during visual perception in individuals with schizophrenia. Additionally, levels of unfiltered external noise were related to patients' visual WM deficits – specifically, the increased variability, or reduced precision, of WM recall. Such findings presented the possibility that internal additive noise and unfiltered external noise relate to unique aspects of schizophrenia symptomology, with the latter more directly related to cognitive dysfunction. However, it remained unclear whether elevated internal noise levels reflected a stable aspect of disease pathophysiology or, alternatively, were the biproduct of factors associated with chronic illness, such as antipsychotic use, educational attainment, and level of functioning. Should internal noise contribute to the visual perceptual and WM deficits considered core to the illness, elevated noise levels should theoretically emerge at the same point in illness trajectory. Neurocognitive deficits, including WM dysfunction, have been shown to emerge prior to illness onset such that they are observed in those at high clinical risk for developing a psychotic disorder (Corigliano et al., 2014; Smith et al., 2006) and predict conversion to psychosis alongside attenuated psychotic symptoms themselves (De Herdt et al., 2013; Seidman et al., 2016).

Given that both early visual sensory deficits and WM deficits have been put forward as endophenotypes of schizophrenia (Glahn et al., 2003; Kéri et al., 2005; Park & Gooding, 2014, Saperstein et al., 2006; Yeap et al., 2006), we would also expect that elevated noise levels would be observed in those who share some genetic loading or vulnerability for a schizophrenia

spectrum disorder. Such vulnerability has been termed the "extended psychosis phenotype", and is thought to reflect a group of factors (e.g., behaviors, etiology, familial factors) shared with clinical psychotic disorders but observed at subclinical levels in the nonill population (van Os & Linscott, 2012; van Os & Reininghaus, 2016). For instance, epidemiological research indicates that psychotic experiences are relatively common in the general population (Linscott & van Os, 2013). Research further shows that these experiences exist on a psychometric continuum of severity, with attenuated, subclinical psychotic experiences at one end and diagnosable psychotic disorders at the other. While the majority of individuals who experience subclinical psychotic symptoms never go on to develop a psychotic disorder, they are at higher risk for psychotic disorders relative to the general population, especially if subclinical psychotic experiences reoccur (Linscott & van Os, 2013).

Individual differences in traits associated with the extended psychosis phenotype have been well-captured with psychometric instruments measuring subclinical psychotic experiences (e.g., the Prodromal Questionnaire, PQ; Loewy et al., 2005) and schizotypal personality traits (SPQ; Raine, 1991). The PQ was primarily designed as a mental health screening measure with sensitivity for those at high clinical risk for and subsequent conversion to psychosis (Lowey et al. 2005), while the SPQ was designed to capture traits associated with underlying dimensions of schizotypal personality. Although schizotypal personality traits have been shown to reflect some independent dimensions from psychosis risk (Bedwell & Donnelly, 2005), the SPQ has also been used to identify individuals at clinical high risk (Barrantes-Vidal et al., 2013) and predict conversion to psychosis (Salokangas et al., 2013). Visual perceptual and visual WM deficits are observed in individuals at clinical high risk for psychosis (De Herdt et al., 2013; Fusar-Poli et al., 2012; Kéri & Benedek, 2007; Kimhy et al., 2007; Oribe et al., 2013; Smith et al., 2006) as well

as those high in schizotypal traits (Koychev et al., 2010; Koychev et al., 2011; Park & Holzman, 1995b; Park & McTigue, 1997), suggesting that noise estimates may also relate to the extended psychosis phenotype.

The aim of Study 2 was to determine whether internal noise reflected core aspects of schizophrenia pathophysiology consistent with the extended psychosis phenotype. Specifically, Study 2 utilized an individual differences approach to estimate levels of internal noise with the PTM in an antipsychotic-naïve sample of young adults in order to determine whether individual differences in internal noise levels related to visual WM variability, schizotypal traits, and psychosis-risk. This study thus examined internal noise and its association with visual WM within the broader, dimensional model of schizophrenia pathophysiology. Based on our findings from Study 1, young adults were hypothesized to exhibit positive relations between internal noise and visual WM recall variance. In particular, we hypothesized that internal additive noise and unfiltered external noise, but not multiplicative noise, would predict greater visual WM variance in this group, consistent with patterns observed in the adult control group in Study 1. Given substantial evidence that visual WM deficits convey some vulnerability to psychosis (as specified above), we also hypothesized that greater psychosis risk and higher levels of schizotypal traits would relate to greater visual WM variability. Because early visual processing abnormalities have also been linked to psychosis risk, we further hypothesized that greater psychosis risk and higher levels of schizotypal traits would relate to higher levels of internal and unfiltered external noise.

Methods

Participants

Demographic information for participants who completed Study 2 is summarized in Table 2. Sixty college students (73% women) between the ages of 18-21 years old voluntarily participated in Study 2. Exclusion criteria included substance or alcohol abuse or dependence during the past year, history of head injury with loss of consciousness greater than fifteen minutes, history of organic brain disease or brain lesions, and current use or history of antipsychotic medication. Five participants were prescribed SSRIs and two were prescribed stimulants.

Table 2

Demographic Information for Participants in Study 2

	Participants (n = 60)
M/F	16/44
Age	18.83 (1.03)
Years of education	12.72 (0.94)
FSIQ[a]	114.91 (9.74)
Handedness[b]	89.17 (44.24)
Ethnicity/Race	
Caucasian	29
African American	8
Asian/Pacific Islander	10
Multiple	6
Latino/Hispanic	7

Mean values are shown with *SD* in parenthesis. FSIQ, Full-Scale IQ
[a] Wechlser Abbreviated Scale of Intelligence, 2nd Edition (WASI-II; Wechsler, 2011).
[b] Edinburgh Handedness Inventory (Oldfield, 1971).

Full-scale IQ was estimated with the Wechsler Abbreviated Scale of Intelligence-2nd Edition (WASI-II; Wechsler, 2011). All participants were screened for normal or corrected-to-normal vision with the Snellen test of visual acuity. For the Snellen test, participants read through the chart using one eye at a time, viewed the letters from a distance of 20 feet, and read letters from the top of the chart aloud to an experimenter who scored their performance. Based on this viewing distance and the reference standard (20/20), the 8th row of letters from the top of the chart consisted of letters subtending an angle of 5° with each letter part subtending 1°. All participants provided written informed consent to study procedures approved by the Vanderbilt University Institutional Review Board and received course credits for participation.

Self-Report Measures

Participants completed the Schizotypal Personality Questionnaire (SPQ; Raine, 1991) to obtain psychometric estimates of schizotypal personality traits. The SPQ is a 74-item yes/no self-report questionnaire assessing schizotypal personality traits and yields a total score, 9 subscale scores (Ideas of reference, Excessive social anxiety, Odd beliefs/magical thinking, Unusual perceptual experiences, Odd/eccentric behavior, Lack of close interpersonal relationships, Odd speech, Constricted affect, and Suspiciousness), and 3 domain scores (Cognitive-perceptual, Interpersonal, and Disorganized deficits) reflecting the hypothesized 3-factor structure of schizotypal personality in the general population (Fossati et al., 2003; Raine et al., 1994; Wuthrich & Bates, 2006). The Cognitive-perceptual factor includes items probing unusual perceptual experiences, magical thinking, ideas of reference, and paranoid thinking, and thus was described as reflecting the positive symptoms of schizophrenia (Raine et al., 1994). The Interpersonal factor has been linked to negative symptoms of schizophrenia, as it includes

items about constricted affect and withdrawal (Raine et al., 1994). The Disorganized factor includes items assessing odd behavior and speech that are most consistent with the disorganized dimension of schizophrenia symptoms.

Participants completed the Prodromal Questionnaire Brief (PQ-B; Loewy et al., 2011) to obtain psychometric estimates of prodromal symptoms (psychosis risk). The PQ-B is a 21-item yes/no self-report questionnaire assessing various types of experiences similar to positive symptoms of schizophrenia (e.g., "Do familiar surroundings sometimes seem strange, confusing, threatening or unreal to you?", "Do you feel that other people are watching you or talking about you?", "Are your thoughts sometimes so strong that you can almost hear them?"). The PQ-B was developed in order to improve the efficiency and accuracy of the original 92-item Prodromal Questionnaire (PQ; Loewy et al., 2005). Importantly, the PQ-B exhibits good concurrent validity with one of the gold-standard clinical measures for assessing and diagnosing prodromal (high-risk) syndromes, similar to the original PQ (Loewy et al., 2011). Thus, the PQ-B was selected for the present study in order to reduce assessment burden on participants while maintaining sensitivity to detect underlying psychosis risk. Consistent with PQ-B administration instructions, participants were only asked to consider experiences they have had in the last month, not while under the influence of alcohol, drugs, or non-prescribed medications. If a subject endorses an item, they additionally rate how distressing the experience is ("When this happens, I feel frightened, concerned, or it causes problems for me") on a 5-choice Likert-scale ranging from strongly disagree to strongly agree (scored 1 to 5). Thus, the PQ-B yields a total raw score, consisting of the total number of items endorsed, as well as a total distress score, consisting of the summed distressed scores across items.

Undergraduate students typically endorse PQ items at moderately high rates, but fewer endorse items as distressing or impairing – key characteristics related to psychosis risk (Loewy & Cannon, 2007; Loewy et al., 2011). For instance, the distress score exhibits maximal sensitivity and specificity for identifying those with a prodromal syndrome in a help-seeking population, with a distress score cutoff of 6 or above discriminating between those with and without prodromal and psychotic syndrome diagnoses with 88% sensitivity and 68% specificity (Loewy et al., 2011). Although the SPQ was not explicitly designed to estimate psychosis risk, research examining relations between schizotypal personality traits, prodromal symptoms, and risk of conversion to psychosis indicate that the Cognitive-perceptual dimension is most strongly correlated with prodromal symptoms (Bedwell & Donnelly, 2005), while the two subscales of Ideas of reference and Lack of close interpersonal relationships predicted transition to psychosis among clinical high-risk patients (Salokangas et al., 2013). Collection of both the SPQ and PQ-B allowed a more comprehensive understanding of how internal noise and visual working memory may map onto overlapping, yet distinct constructs of schizotypal personality and psychosis risk.

Finally, participants completed the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) for a measure of current depressive symptoms. The BDI-II is a 21-item self-report questionnaire designed to estimate the severity of depressive symptoms over the past two weeks in adolescents and adults (Beck et al., 1996). Items are scored on a 4-point scale ranging from 0 to 3. We included this common measure of depressive symptoms in order to determine whether internal noise estimates were more broadly related to common psychiatric symptoms that are highly comorbid with psychosis risk (Fusar-Poli et al., 2014) and schizophrenia (Buckley et al., 2009). Depressive symptoms are common indicators of mental health, such that they may be

explained by a number of different clinical syndromes. By including the BDI-II we sought to probe whether elevations in internal noise were specific to psychosis or potentially associated with psychopathology in general, for instance a general *p*-factor (Caspi et al., 2014).

Stimuli, tasks, and experimental procedure

Participants completed study activities across two visits scheduled within one week of each other. During the first visit, participants completed the Snellen test of visual acuity, demographic and self-report questionnaires, and were administered the WASI-II by a masters-level clinical psychology graduate student. During the second visit, participants completed the experimental tasks (visual discrimination and visual WM precision tasks). Task order was counterbalanced across participants. All tasks and stimuli were programmed in MATLAB and Psychtoolbox and presented on a linearized monitor (20-inch Sony CRT; 1024 x 640 resolution; 120 Hz) on a gray background. A chin rest was used to maintain viewing distance at 77 cm with each pixel subtending 0.036°. An experimenter was present in the room during both visual discrimination and working memory tasks to encourage task engagement.

Visual Discrimination Task

Participants completed the same visual discrimination task as described in Study 1. All procedures for task administration were identical to Study 1. See page 15 for details.

Visual Working Memory Precision Task

Participants completed the same visual working memory task as described in Study 1. All procedures for task administration were identical to Study 1. See page 17 for details.

Task Analyses

Visual Discrimination Task

The hierarchical Bayesian modeling technique described in Study 1 was utilized to fit each participant's data from the visual discrimination task with the PTM in order to obtain individual noise parameter estimates and examine relations between noise estimates, visual WM performance, schizotypal personality traits, and psychosis risk. This analysis pipeline was consistent with procedures described in Study 1 (see page 22). PTM fitting was constrained such that the gain parameter β and nonlinear power parameter γ were held constant to minimize the number of free model parameters while enabling estimation of all three noise parameters of interest (N_a, N_m, A_f) and the slope of the psychometric function (η) (see Equation 4). We utilized the same values for β (β = 1) and γ (γ = 1.27) as those from Study 1, which were based on estimates generated from the conventional PTM analysis in Study 1 as well as estimates that have been reported in previous studies (Cavanaugh et al. 2015; Lu & Dosher, 2008; Park et al., 2017). Free model parameters were estimated for each individual with the Markov chain Monte Carlo (MCMC) method for sampling from posterior probability distributions.

Visual Working Memory Precision Task

The analysis pipeline for visual WM performance was consistent with that described in Study 1 (see page 23). Gabor orientations were recorded and reported in the circular parameter space of all possible line orientation values [-90°, 90°) and converted to the circular space [-π, π) radians. Recall error on each trial was calculated as the difference between the orientation of the target Gabor and the orientation of the test probe that was reported (input with the manual dial) by the participant. The Von Mises probability density function (circular normal distribution) with mean θ = 0 (no error, such that recall is centered at the target memory location) and SD = σ was used to fit every participant's distribution of recall errors at each memory array set size (see

Equation 5). The concentration parameter (κ) was estimated from each participant's recall errors at every memory array set size using a maximum likelihood method. Estimates of distribution concentration were converted to variances by taking the inverse of concentration parameters for subsequent individual differences analyses. We conducted a repeated measures ANOVA to determine changes in recall variance with increasing WM set size. Pearson correlations were run to examine relations between noise estimates and recall variance. A multiple linear regression analysis was conducted to understand the unique contributions of each type of noise (parameters reflecting internal additive, multiplicative, and external noise) to mean WM recall variance.

Relations Between Noise Estimates, Schizotypal Personality Traits, and Psychosis Risk

We conduced Spearman correlations to examine relations between noise estimates (internal additive, multiplicative, and unfiltered external noise), schizotypal personality traits (total and dimension scores), psychosis risk (total raw score and total distress scores), and depressive symptoms.

Results

Internal and External Noise Estimates and Visual Working Memory Recall Variance

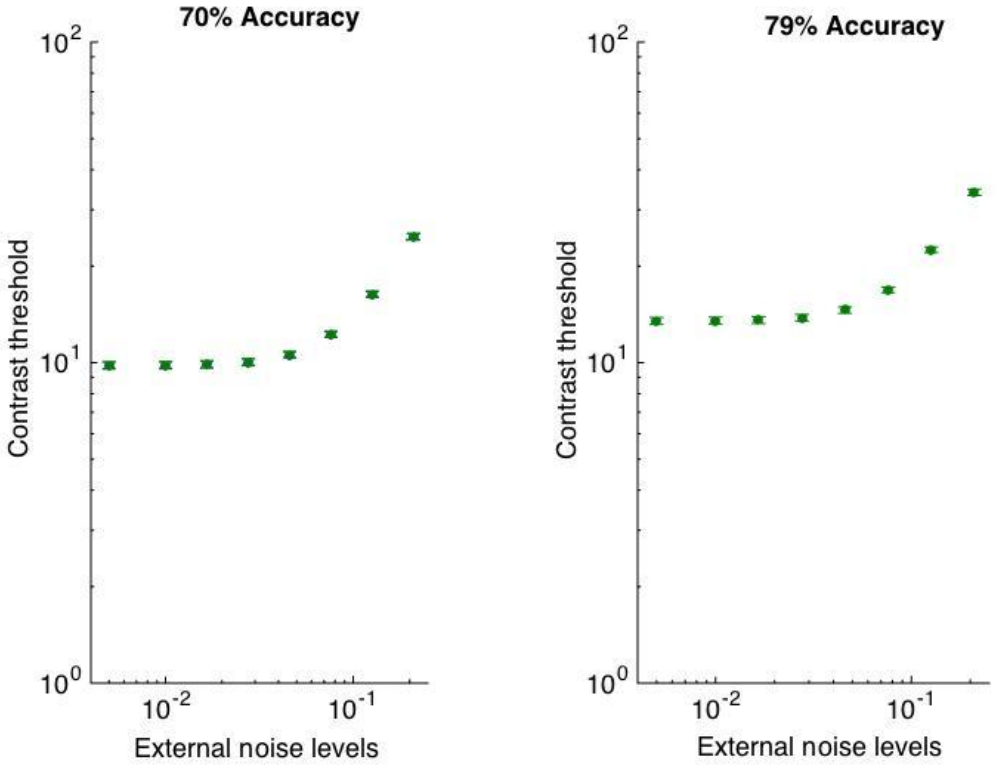
The hierarchical Bayesian analysis resulted in contrast thresholds that follow typical TvN curves (see Figure 8 for plotted group contrast thresholds). The Bayesian analysis also yielded individual parameter estimates of internal additive noise (M=0.053, SD=0.012), multiplicative noise (M=0.016, SD=.0024), and unfiltered external noise (M=1.07, SD=0.21).

Individuals' WM recall variance was estimated from participants' error distributions at each set size with the Von Mises distribution. Von Mises probability density functions, plotted

by set size, are shown in Figure 9. WM recall variance exhibited the expected pattern of greater variance with increasing WM set size, $F(2,118) = 295.02$, $p < .001$ (see Figure 9).

Figure 8

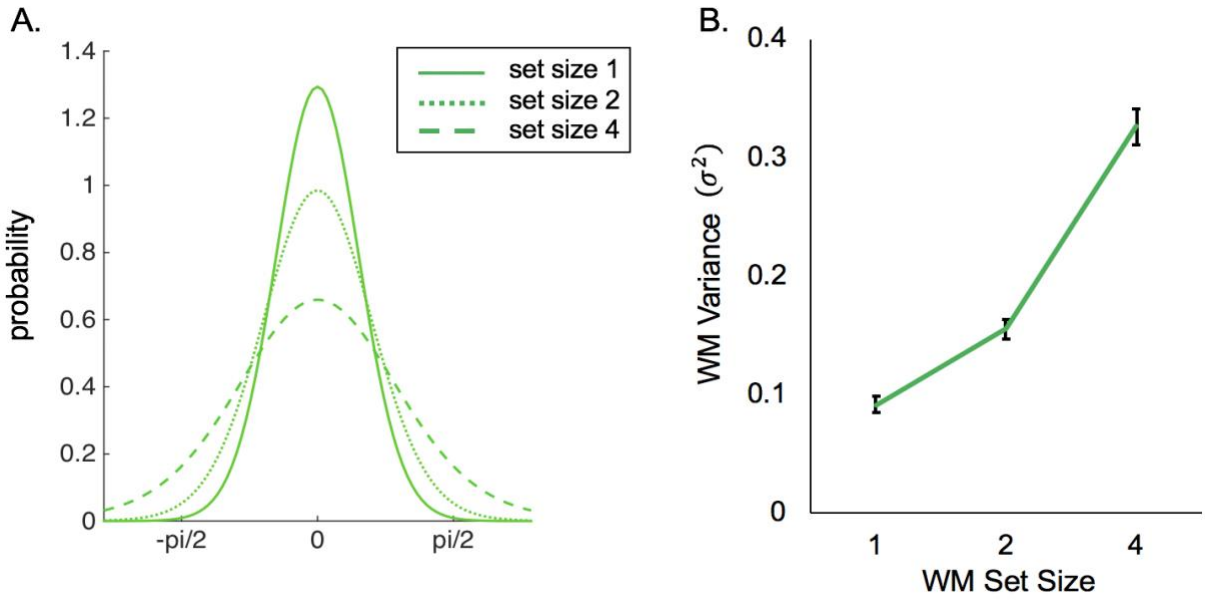
Bayesian Contrast Thresholds for College Students



Note. Contrast thresholds (filled dots) estimated from the hierarchical Bayesian analysis at each external noise level for the two accuracy criterion (left: 70.71%, right: 79.14%). Error bars are ±SEM.

Figure 9

Visual Working Memory (WM) Recall Variance for College Students



Note. (A) Von Mises Probability Density Functions of Visual WM Recall for College Students. (B) WM Variance at Each Set Size.

Self-Report Measures of Schizotypal Personality, Prodromal Symptoms, and Depression

Descriptive statistics for the self-report clinical measures are presented in Table 3. Distributions of PQ-B, SPQ, and BDI-II scores were examined for violation of normality assumptions. Consistent with prior studies utilizing these measures in college samples (Bedwell et al., 2009; Loewy et al., 2011; Whisman & Richardson, 2015), responses on the BDI-II, PQ-B, and select dimensional scores on the SPQ were positively skewed (concentrated at the low end of the possible range) and demonstrated non-normal kurtosis. Thus, the strength of the relation between schizotypal personality traits, prodromal symptoms, depressive symptoms, internal noise estimates, and WM variance were examined by computing bivariate Spearman's correlations as necessary.

Table 3

Descriptive Data for Clinical Measures Administered in Study 2

	Range	Mean (SD)	Skewness (SE)	Kurtosis (SE)
PQ-B (Total raw)	0 – 13	3.92 (3.41)	0.99 (0.31)	0.69 (0.61)
PQ-B (Total distress)	0 – 55	10.08 (11.98)	1.91 (0.31)	3.87 (0.61)
SPQ (Total)	0 – 42	18.38 (11.73)	0.38 (0.31)	-0.77 (0.61)
Cognitive-perceptual	0 – 22	6.03 (5.07)	0.95 (0.31)	0.79 (0.61)
Interpersonal	0 – 23	10.15 (6.40)	0.13 (0.31)	-0.90 (0.61)
Disorganized	0 – 14	4.05 (3.84)	1.20 (0.31)	0.87 (0.61)
BDI-II (Total score)	0 – 37	7.27 (7.83)	1.96 (0.31)	5.03 (0.61)

PQ-B, Prodromal Questionnaire - Brief (Loewy et al., 2011); SPQ, Schizotypal Personality Questionnaire (Raine, 1991); BDI-II, Beck Depression Inventory, 2nd Edition (Beck, Steer, & Brown, 1996).

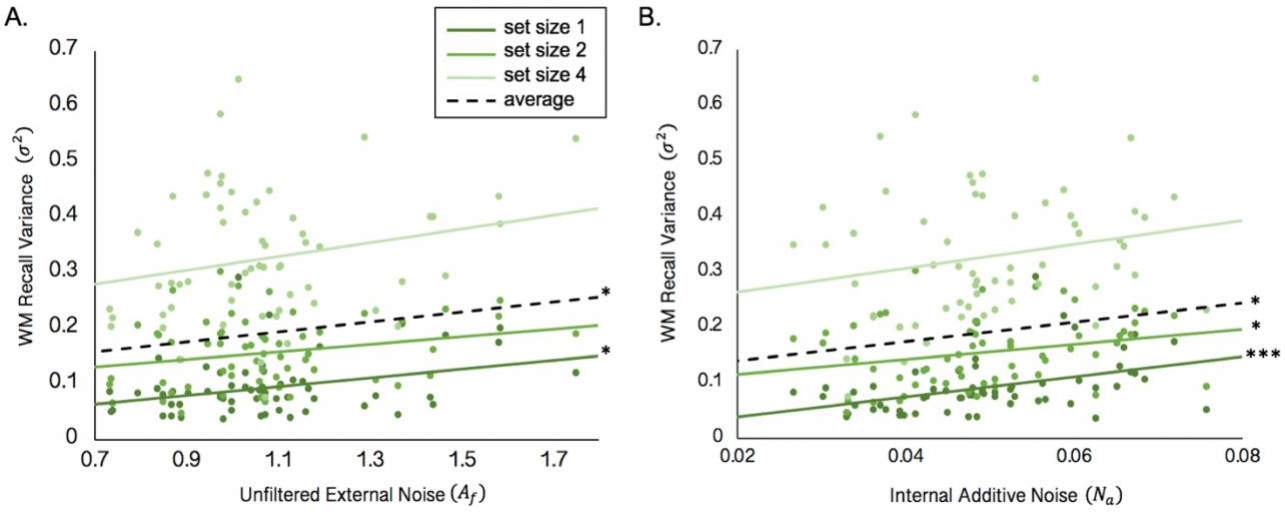
Relations between Internal Noise and Visual WM

There was a significant correlation between internal additive noise and multiplicative noise, $r(60) = .28$, $p < .05$, as well as between internal additive noise and unfiltered external noise, $r(60) = .48$, $p < .05$, suggesting substantial overlap between noise sources in the college student sample. To limit the number of initial tests conducted, WM variance was averaged across set sizes for each participant. Pearson correlations indicated a significant positive relation between internal additive noise and WM recall variance, $r(60) = .30$, $p < .05$. Unfiltered external noise was also significantly correlated with WM recall variance, $r(60) = .29$, $p < .05$. Internal multiplicative noise was not significantly correlated with WM recall variance, $r(60) = .03$, $p = .85$. Simple regressions were conducted to better examine contributions of each noise source to WM recall variance. Separate regressions were conducted for internal additive noise and unfiltered external noise given the moderate correlation between internal additive noise and unfiltered external noise. Internal additive noise accounted for 9.2% of the variance in WM recall variance, $F(1,59) = 5.90$, $p < .05$, $R2 = .092$, $R2_{Adj} = .077$, while unfiltered external noise

accounted for 8.3% variance in WM recall variance, $F(1,59) = 5.26$, $p < .05$, $R2 = .083$, $R2_{Adj} = .067$. See Figure 10 for plotted relations between internal additive noise, unfiltered external noise, and WM recall variance.

Figure 10

Relations Between Noise Estimates and Visual Working Memory (WM) Recall Variance for College Students



Note. (A) Unfiltered external noise and WM variance, plotted by set size. (B) Internal additive noise and WM variance, plotted by set size. *$p < .05$, **$p < .01$, ***$p < .001$.

In order to better understand the role of internal additive noise and unfiltered external noise estimates in WM recall variance in this sample of college students, we completed post-hoc correlations between noise estimates and WM variance at each set size. Pearson correlations indicated that the relation between internal additive noise and WM recall variance was strongest at lower set sizes, such that a significant correlation was observed at set size 1, $r(60) = .41$, $p < .001$, and set size 2, $r(60) = .26$, $p < .05$, but not at set size 4, $r(60) = .22$, $p = .10$. Pearson correlations between unfiltered external noise and WM recall variance exhibited a similar

pattern, with a significant correlation at set size 1, $r(60) = .34$, $p < .01$, but weaker relations at set size 2, $r(60) = .24$, $p = 0.06$, and set size 4, $r(60) = .23$, $p = 0.08$. Surprisingly, we did not find significant correlations between visual WM variance at any set size and total schizotypal personality traits ($p = .51$) or prodromal symptoms ($p = .39$).

Relations between Internal Noise, Schizotypal Personality, and Prodromal Symptoms

See Table 4 for Spearman rank correlations between internal noise estimates and clinical measures. There was a weak but significant positive correlation between internal additive noise and total prodromal symptoms endorsed and a trending relation with the total PQ-B distress score ($p = .07$) (See Figure 11a). An additional significant weak positive correlation was observed between internal additive noise and scores on the Disorganized domain of the SPQ (See Figure 11b). Neither multiplicative noise nor unfiltered external noise exhibited relations with schizotypal traits or prodromal symptoms. None of the three noise estimates were significantly correlated with depressive symptom severity on the BDI-II. We found a significant strong positive correlation between the PQ-B and SPQ, which is consistent with prior studies finding moderate to strong relations between these similar constructs (Kline et al., 2012a; Kline et al., 2012b). We also found moderately-sized significant correlations between the extended psychosis phenotype measures and BDI-II that are similar to those found in prior studies (Andorko et al., 2017; Kline et al., 2012a).

Table 4

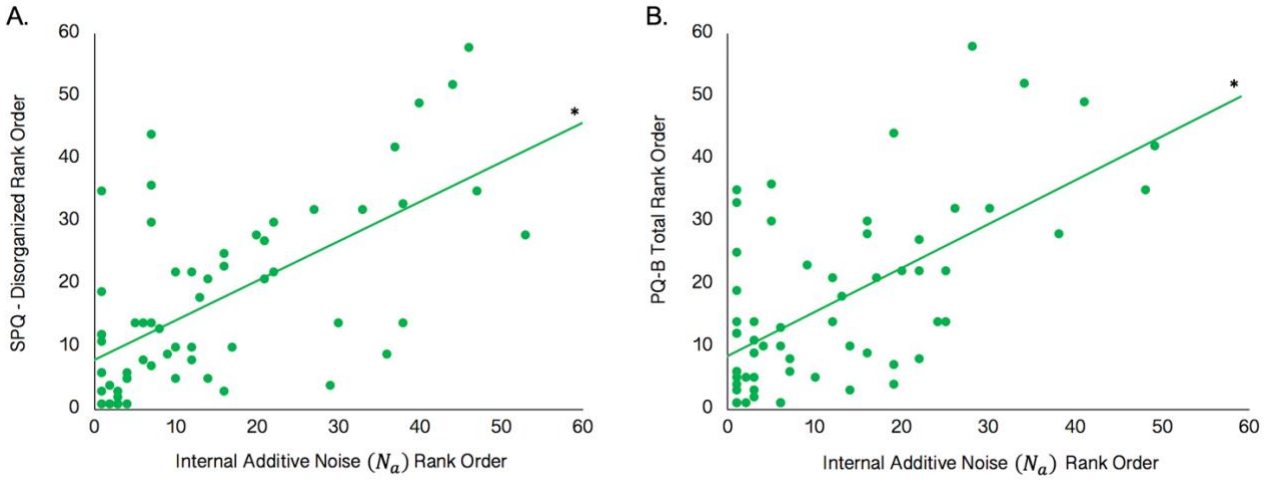
Spearman Correlations between Internal Noise Estimates and Clinical Measures

	N_a	N_m	A_f	PQ-B$_{Tot}$	PQ-B$_{Dis}$	SPQ$_{Tot}$	BDI-II
PQ-B$_{Tot}$	0.27*	0.11	-0.01	1			
PQ-B$_{Dis}$	0.24	0.06	0.06	0.92***	1		
SPQ$_{Tot}$	0.11	0.12	-0.03	0.75***	0.68***	1	
Cognitive-Perceptual	0.07	0.05	-0.02	0.73***	0.71***	0.88***	0.49***
Interpersonal	0.00	0.11	-0.12	0.58***	0.51***	0.90***	0.38**
Disorganized	0.26*	0.17	0.10	0.67***	0.59***	0.79***	0.23
BDI-II	0.17	-0.03	0.02	0.41**	0.40**	0.41**	1

N_a, Internal additive noise; N_m, Internal multiplicative noise; A_f, Unfiltered external noise. PQ-B$_{Tot}$, Total items endorsed from the Prodromal Questionnaire - Brief (Loewy et al., 2011); PQ-B$_{Dis}$, Total distress score from the PQ-B; SPQ$_{Tot}$, Total score from the Schizotypal Personality Questionnaire (Raine, 1991); BDI-II, Beck Depression Inventory, 2nd Edition (Beck, Steer, & Brown, 1996). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Figure 11

Relations between Internal Additive Noise, Schizotypal, and Prodromal Symptoms in College Students



Note. (A) Relation between internal additive noise and SPQ-Disorganized symptoms (B) Relation between internal additive noise and total items endorsed on the PQ-B. Scores are plotted as rank orders due to non-normality of SPQ-Disorganized and PQ-B scores. *$p < .05$.

Discussion

The present study utilized the same combination of psychophysical and computational approaches as in Study 1 in order to estimate levels of internal noise in a non-clinical sample of college students and examine whether individual differences in internal noise were related to the psychometric measures of schizotypy and prodromal symptoms. Additionally, we tested whether the relationships between internal noise estimates and visual WM variance found in Study 1 were replicated in this sample by utilizing the same spatial delayed response task. We found that level of internal additive noise, but not unfiltered external noise, was weakly related to prodromal symptoms and disorganized symptoms on the SPQ, suggesting that elevated internal additive noise may contribute to subtle perceptual processing differences across the broader schizophrenia spectrum. Consistent with findings from Study 1, both internal additive noise and unfiltered external noise were related to WM variance, highlighting the importance of basic visual perception in visual WM precision across age groups (Peich et al., 2013). Contrary to our hypothesis, we did not find that higher levels of prodromal symptoms (psychosis risk) or schizotypal traits were related to greater WM recall variance. Overall, results replicate Study 1 relations between internal noise and visual WM variability in a second sample of healthy adults and further suggest that elevated internal noise may contribute to perceptual differences underlying sub-psychotic experiences and vulnerability for a schizophrenia spectrum disorder.

An interesting finding from the present study was that both internal additive and unfiltered external noise were most related to WM performance when the memory array was small; noise estimates did not relate to WM performance at the highest set size of 4 items. These results suggest that WM variance in this sample is primarily limited by noise somewhat specific to visual perceptual processing, rather than noise associated with top-down control processes

during WM or even a more global measure of cortical noise. In other words, internal noise and unfiltered external noise may limit individuals' visual WM performance to the extent that visual perception enables precise WM encoding, for instance under low-burden memory conditions. At higher set sizes or other conditions that burden the WM system (e.g., longer delays, inclusion of distractor items), WM performance may be primarily limited by noise within more top-down cognitive processes. Sims and colleagues (2012) outline two such noise sources in their ideal observer model of visual WM, specifically referring to the sensory noise of a stimulus prior to entering WM and the WM-specific noise that further limits memory capacity and precision. Theoretically, when noise specific to WM processing or attentional control is relatively low, sensory noise may govern the precision (or conversely, variability) of a given WM representation. In this sample of college students, WM processing may have been relatively unburdened at low set sizes, resulting in a more prominent role of sensory noise in limiting WM precision.

Consistent with our hypothesis, individual differences in noise estimates were related to prodromal symptoms and aspects of schizotypal personality. In particular, we found that internal additive noise was weakly correlated with total scores on the PQ-B and the Disorganized domain of the SPQ. The total PQ-B score reflects the number of psychotic-like experiences one has had, independent of the distress they cause. Because internal additive noise reflects the visual processing deficiencies that limit contrast sensitivity in the absence of external stimulus noise, elevated internal additive noise may contribute to inherent perceptual processing deficits that make one more susceptible to psychotic-like experiences. These results are consistent with prior work capturing reduced visual contrast sensitivity in those at clinical high risk for psychosis (Kéri & Benedek, 2007) and contribute to a growing literature identifying early visual processing

deficits in this population, including disrupted visual form perception (Kimhy et al., 2007), smooth pursuit eye tracking (Gooding et al., 2000), visual context processing (Mittal et al., 2015), and reductions in early and late visual ERPs (Lee et al., 2010; Oribe et al. 2013). While the relationship between internal additive noise and the PQ-B total distress score was trending, internal additive noise may be primarily related to the underlying unusual perceptual and/or cognitive experiences themselves, while the degree to which these experiences cause distress may be mediated by additional risk factors, for instance attributional style (An et al., 2010).

Interestingly, internal additive noise was only related to the Disorganized domain of the SPQ and not the Cognitive-perceptual or Interpersonal domains, which are thought to roughly comprise positive and negative symptom clusters, respectively. This finding may be coherent with prior work demonstrating a consistent link between perceptual organization deficits and disorganized symptomology in those with schizophrenia (Silverstein et al., 1998; Silverstein et al., 2000, Uhlhaas et al., 2005). Such studies hypothesize that the disorganization syndrome in schizophrenia reflects deficits in the organization and coordination of stimulus processing (i.e., contextual processing) across multiple domains, including visual perception, thought processes, and language (Silverstein et al., 2000). Thus, elevations in internal noise during perception may contribute to or at least partially reflect existing deficiencies in the processing of perceptual context.

Another possible explanation for the observed relation between disorganized SPQ traits and internal noise is that elevations in Disorganized SPQ traits may reflect an overlap with autism spectrum traits. Adults high in autism traits and adolescents with autism exhibit high levels of disorganized symptoms (Barneveld et al., 2011; Hurst et al., 2007), while individuals with autism have been shown to exhibit higher levels of PTM-estimated internal noise relative to

typically developing peers (Park et al., 2017). Although we did not collect a measure of autism traits in the present study, elevated internal noise may reflect a possible area of overlap or shared vulnerability between schizophrenia and autism spectrum disorders that contribute to both populations' perceptual deficits. These two disorders, while considered distinct, are also thought to share some genetic vulnerability and exhibit phenotypic similarities (for a review, see Chisholm et al. 2015). Despite moderate correlations between BDI-II, PQ-B, and SPQ scores, we did not find that noise estimates were related to depressive symptoms, casting doubt on the possibility that internal noise reflects a more nonspecific risk factor common amongst psychiatric populations.

Contrary to our hypothesis, unfiltered external noise was not related to schizotypal traits or prodromal symptoms in this study. One possible explanation for the absence of this relation in this college sample is that greater unfiltered external noise may be specific to the cognitive deficits accompanying schizophrenia that become more pronounced after illness onset. Additionally, the current sample of college students was skewed for above-average intelligence, with a mean FSIQ approximately one standard deviation above the general population (M = 114.91, SD = 9.74, Range = 96-137), suggesting an absence of cognitive dysfunction relative to the general population. Furthermore, we did not find a relationship between WM variance and prodromal symptoms or schizotypal traits, which was surprising given that visual WM deficits are often captured in those at clinical high-risk for psychosis (De Herdt et al., 2013; Fusar-Poli et al., 2012; Smith et al., 2006) and those with high schizotypal personality trait scores (Koychev et al., 2011; Park & Holzman, 1995b; Park & McTigue, 1997; Xie et al., 2018). Because WM is highly related to intelligence (Colom et al., 2008; Oberauer et al., 2005), our current sample may not have exhibited the typical WM vulnerability associated with psychosis risk given this

group's relatively intact and even superior cognitive abilities, resulting in an absence of notable WM dysfunction.

The lack of relation between WM variance and schizotypal traits may also be accounted for by the restricted range of schizotypal traits observed in the current sample. Past studies examining the relation between schizotypy and WM have compared WM performance between a high schizotypy and low schizotypy group (Koychev et al., 2011; Park & McTigue, 1997). SPQ cut-off scores for high schizotypy groups are consistently above 43 (Koychev et al., 2011; Park & McTigue, 1977), which is beyond the maximum score in our current sample. Raine's (1994) paper on the SPQ indicated that this cutoff score represented the top 10% scores and was relatively sensitive to a diagnosis of schizotypal personality disorder. Thus, we may not have obtained sufficient scores at the upper extreme to capture significant elevations in schizotypal personality traits and observe subclinical deficits in working memory. Similarly, because this sample was not help-seeking (non-clinical), psychometrically-measured prodromal symptoms that are relatively common in the general population may not be sufficient to capture a WM impairment that accompanies those diagnosed with a clinical high-risk syndrome. While the restricted range in schizotypal personality traits remains a possible limitation of the present study, it may also be the case that internal noise conveys risk for subsequent WM deficits at a later stage in illness progression.

In conclusion, this study found that computational estimates of internal noise during visual perception were related to aspects of the extended psychosis phenotype, including subclinical prodromal and disorganized symptoms. These results support the theory that early visual processing deficits may be a useful marker of psychosis-proneness, but also extend the literature by highlighting a possible mechanism underlying visual processing abnormalities

specific to sub-psychotic experiences. Similar to the control group in Study 1, both internal additive and unfiltered external noise levels related to visual WM variance in this college sample. Future work should clarify how internal noise maps onto neural processes, and additionally whether such mechanisms contributing to noise can serve as targets for treatment.

CHAPTER IV

STUDY 3: MODULATING INTERNAL NOISE WITH TRANSCRANIAL DIRECT CURRENT STIMULATION

Introduction

Results from Study 1 suggest that estimates of internal noise during visual perception are elevated in those with schizophrenia, and that internal noise levels are further related to visual WM variance in those with and without schizophrenia. However, while unfiltered external noise and internal additive noise were related to WM in adults without schizophrenia, only unfiltered external noise was related to WM variance in those with schizophrenia. Thus, unfiltered external noise (i.e., the failure to filter external stimulus noise) may be a promising target for treatment of WM dysfunction, such that improvements in patients' ability to filter external noise during visual perception may also help ameliorate their visual WM deficits. While the PTM implies separable noise mechanisms during visual perception, how these noise concepts map onto neural activity and brain regions remains unclear, as does how to target such mechanisms for treatment.

One possible technique for exploring and possibly modifying the neural underpinnings of internal noise is transcranial direct current stimulation (tDCS) – a noninvasive brain stimulation technique which has been increasingly used to transiently alter both lower level perceptual processes (e.g., Antal & Paulus, 2008; Antal et al., 2004; Reinhart et al., 2016) as well as higher order cognitive functions (e.g., Hill et al., 2016; Plewnia et al., 2015; Reinhart et al., 2015a, 2015b; Reinhart & Woodman, 2014; Reinhart et al., 2019). tDCS involves the application of low amplitude direct current to the scalp, which has been shown to modulate the underlying excitability of cortical neurons in a polarity-specific manner, such that anodal stimulation increases and cathodal stimulation decreases cortical excitability during and after stimulation

(Nitsche & Paulus, 2000; 2001; Wagner et al., 2007). While the neurobiological mechanisms by which tDCS affects cognition are not fully understood, ongoing research implicates stimulation-related molecular and cellular changes, causing shifts in membrane potential, neuronal depolarization, and post-stimulation synaptic modification (Filmer et al., 2014; Reinhart et al., 2017; Stagg & Nitsche, 2011). Importantly, tDCS seems to modify underlying neural measures of signal processing, including ERPs and neural oscillations critical to visual perception and cognition (Antal et al., 2004; Filmer et al., 2014; Reinhart et al., 2016; Reinhart et al., 2015b). Oscillatory activity, in particular, may reflect sources of internal noise, as oscillatory activity is thought to reflect dynamic fluctuations in cortical excitability contributing to ongoing variability in stimulus processing (Bates et al., 2009; Becker et al., 2011; Coon et al., 2016; Ergenoglu et al., 2004). It is also worth mentioning that ERPs indexing visual perception may actually be generated by evoked oscillations (Klimesch et al., 2004), thus ERP amplitudes may also indirectly reflect levels of internal noise. Thus, tDCS provides one potential method by which to target elevations in internal noise and underlying oscillatory activity during visual perception.

There is growing evidence that anodal tDCS over visual cortex can improve visual processing in healthy adults, including visual detection thresholds (Kraft et al., 2010; Olma et al., 2011; Reinhart et al., 2016). Reinhart and colleagues (2016) found that 20 minutes of anodal tDCS over occipitoparietal visual cortex improved subjects' visual acuity, which was also related to increases in early visual evoked potentials P1 and N1. This group also found that anodal stimulation over occipitoparietal cortex improved contrast sensitivity for gratings presented contralateral to stimulation placement (Reinhart et al., 2016). Similarly, Kraft and colleagues (2010) found that 15 minutes of anodal tDCS over visual cortex improved contrast sensitivity relative to sham and cathodal stimulation, while Olma and colleagues (2011) found that 15

minutes of anodal tDCS over occipital cortex improved perceptual sensitivity for centrally presented stimuli. While there are no studies to our knowledge examining tDCS's impact on early visual perception in those with schizophrenia, anodal tDCS has been shown to improve select visual deficits in adults with amblyopia (Ding et al., 2016; Spiegel et al., 2013) and visual field loss (Plow et al., 2012). These findings suggest that anodal tDCS is a promising tool for remediating visual deficits and may also improve visual contrast sensitivity in those with schizophrenia. Additionally, given that the PTM's internal noise sources limit contrast sensitivity, anodal tDCS over occipitoparietal cortex may improve contrast sensitivity in those with schizophrenia by reducing such noise sources.

Several studies that have examined changes in oscillatory activity following anodal tDCS over visual regions show that stimulation increased local baseline levels of alpha (8-12 Hz) (Heinrichs-Graham et al., 2017; Wiesman et al., 2018; Wilson et al., 2018). Alpha activity has been highlighted as critical to visual perception, with several studies finding that reduced alpha band activity over visual areas prior to stimulus onset is related to perceptual sensitivity (Hanslmayr et al., 2007; Lange et al., 2013; van Dijk et al., 2008). Interestingly, alpha abnormalities have been frequently documented in those with schizophrenia (Boutros et al., 2008; Moran & Hong, 2011), of which reduced resting alpha power is perhaps the most replicated (Abeles & Gomez-Ramirez, 2014; Clementz et al., 1994; Itil et al., 1972; Sponheim et al., 1994). These findings somewhat conflict with those showing that lower pre-stimulus and resting alpha activity relate to improved near-threshold perception (Hanslmayr et al., 2007) and better performance on visual tasks in healthy adults (Romei et al., 2008). One possibility is that lower resting alpha in those with schizophrenia does not reflect the same optimized brain state for visual detection as in healthy adults – rather, it may reflect poorer modulation of alpha during

functional tasks (Abeles & Gomez-Ramirez, 2014; Bachman et al., 2008; Erickson et al., 2017; Haenschel et al., 2009). For instance, alpha exhibits a characteristic post-stimulus event-related desynchronization (ERD) that has been interpreted as both the suppression or inhibition of task-irrelevant stimulus processing during spatial attention tasks (Foxe & Snyder, 2011) as well as ability to maintain WM representations during the delay of visual WM tasks (Fukuda et al., 2015; Fukuda et al., 2017). Individuals with schizophrenia exhibit reduced alpha ERD over posterior regions during the visual WM delay (Bachman et al., 2008; Erkison et al., 2017) as well as during visual discrimination, the latter of which was related to reductions in pre-stimulus alpha (Abeles & Gomez-Ramirez, 2014).

Taken together, these findings suggest two possible effects of inefficient alpha modulation in those individuals with schizophrenia on PTM noise estimates. First, inefficient alpha modulation in response to visual stimuli may result in a poorer ability to detect the visual signal even in zero-noise or low-noise conditions, which Lu & Dosher (1998) describe as computationally indistinguishable from heightened internal additive noise. Thus, anodal tDCS may offer a way to enhance alpha modulation by boosting signal detection (equivalent to reducing internal additive noise) in visual regions. Second, failure to modulate and suppress alpha during visual perception and visual WM may lead to poorer top-down external noise filtering. In line with these hypothesized effects, at least two studies have found that anodal tDCS over posterior visual regions improved subsequent visual WM performance in healthy adults (Hsu et al., 2014; Makovski & Lavidor, 2014), suggesting that stimulation of visual regions may improve both visual perception and visual WM through mechanisms of reducing internal additive noise, improving external noise filtering, or both. Hsu and colleagues (2014) found that visual WM improvement following anodal tDCS over posterior parietal cortex was

specific to low performers, who exhibited a unique decline in pre-stimulus alpha power with anodal stimulation. The authors interpreted these results as evidence that anodal stimulation can modulate alpha power and subsequent visual WM performance in those with reduced WM capacity. Given the lack of correlation between internal additive noise and visual WM variance in those with schizophrenia, it remains unclear whether a reduction in internal additive noise would result in an improvement in visual WM in those with schizophrenia. However, these study results are more broadly consistent with the hypothesized link between posterior alpha modulation, internal additive noise reduction, external noise filtering, and improved visual WM.

Another possible point of intervention for reducing unfiltered external noise more specifically in those with schizophrenia may be targeting top-down regions implicated in attention and executive control. For instance, spatial attention has been shown to enhance contrast detection at the target location by improving external noise filtering (Lu et al., 2002). Observed elevations in unfiltered external noise in those with schizophrenia may reflect a failure in top-down, attentional or executive control mechanisms, which then contribute to deficits in visual WM. Reinhart and colleagues (2019) found that anodal tDCS of medial frontal cortex improved visual attention deficits in schizophrenia. Interestingly, this group proposes that such attentional deficits schizophrenia are due to a failure in transitioning from top-down attentional control, associated with WM, to more long-term memory (LTM) processing across a given task (Reinhart et al., 2019). This interpretation followed the observed remediation of a LTM-associated ERP after stimulation in patients, although of note, stimulation also improved a neural index of visual WM (Reinhart et al., 2019). Anodal tDCS of medial frontal cortex may thus reduce the burden of WM circuitry in those with schizophrenia, potentially by facilitating LTM, providing efficient access to task context.

More broadly, medial frontal stimulation may result in enhanced executive functioning, which is consistent with findings of improved adaptive control in those with schizophrenia following stimulation to the same region (Reinhart et al., 2015b). Of note, anodal medial frontal stimulation in the latter study was related to a normalization of theta (4-8 Hz) synchrony amongst medial frontal and frontolateral sites in patients. Theta oscillations are widely thought to coordinate neural communication across distributed brain regions to support cognitive control and adjust processing given ongoing feedback (Cavanagh et al., 2009; Cavanagh & Frank, 2014). Given this hypothesized function of theta, it is thus unsurprising that theta has also been implicated in the control mechanisms of WM processing (Kawasaki et al., 2010; Sauseng et al., 2010). This top-down mediated processing required for efficient executive control may thus also be critical to the context guided template-tuning mechanism that contributes to external noise filtering during visual perception. Poor theta modulation in those with schizophrenia (e.g., Griesmayr et al., 2014; Schmiedt et al., 2005; Reinhart et al., 2015b) may contribute to observed insufficiencies in external noise filtering.

The current literature on the cognitive-enhancing effects of tDCS in schizophrenia is relatively small and faces significant methodological heterogeneity. Past studies have tested the impact of anodal tDCS on WM by stimulating dorsolateral prefrontal cortex (DLPFC) – a prominent region implicated in WM circuitry (e.g., Barbey et al., 2013), but such work has yielded mixed results in both healthy adults (for reviews, see Brunoni & Vanderhasselt, 2014, Mancuso et al., 2016) and those with schizophrenia (for a review, see Mervis et al., 2017). Indeed, there is not currently a consistent montage that seems to elicit visual WM improvement in those with schizophrenia. While DLPFC is considered a core hub within the WM network, it may exhibit a highly variable response to stimulation in schizophrenia, potentially due to the

heterogeneity regarding both findings of under- and over-activation during WM processing in this population (Henseler et al., 2010). By stimulating regions functionally implicated in visual perception and executive control that may contribute to underlying noise elevations in schizophrenia, the current study seeks to extend the literature and test novel targets for intervention, while improving the understanding of how PTM noise sources may map onto neural processing.

In summary, studies examining the enhancing effects of tDCS on perception and cognition point to associated changes in underlying oscillatory activity, such that anodal stimulation seems to enhance the efficient modulation or synchronization of specific frequency-band activity (Hsu et al., 2014; Reinhart et al., 2015b). tDCS thus offers a technique by which to reduce sources of internal noise during visual perception and WM, both via increased temporal synchrony and modulation of underlying functional oscillations. Because little is known about the neural correlates of PTM-derived noise sources, tDCS also offers a way to probe the role of regional involvement in such noise mechanisms. As discussed above, two promising options for stimulation include occipitoparietal and medial frontal regions. Thus, Study 3 tests the effects of anodal tDCS over these two regions of interest (occipitoparietal and medial frontal) on PTM-estimates of internal noise (additive noise, external noise, and multiplicative noise) and visual WM performance in adults with schizophrenia.

Through the lens of the PTM, tDCS may improve contrast sensitivity through enhancement of the signal, the PTM equivalent of internal additive noise suppression (Dosher & Lu, 1998), or external noise exclusion, in which external noise is better filtered via more narrow tuning of the perceptual template (Dosher & Lu, 1999). Signal enhancement would result in improved signal detection under low, but not high, external noise conditions, while external

noise exclusion would result in improved signal detection under high, but not low, external noise conditions. Given the background discussed above, anodal stimulation of occipitoparietal cortex is hypothesized to improve internal additive noise and possibly unfiltered external noise during visual perception, leading to downstream improvements in WM performance (reduced WM variance). Anodal stimulation of medial frontal cortex is hypothesized to improve unfiltered external noise by enhancing attentional and control networks that tune the perceptual template, also leading to reduced WM variance. Given its impact on underlying cortical excitability, anodal tDCS may increase the noise alongside with the signal. However, the perceptually-enhancing effects of anodal tDCS have been hypothesized to occur by increasing the stochastic resonance of the visual system, thereby boosting the signal-to-noise ratio and making visual perception more sensitive (McDonnell & Ward, 2011, Reinhart et al., 2016). Supporting this explanation, Reinhart and colleagues (2016) found that cathodal stimulation (which reduces overall activity levels) over occipitoparietal lobe reduced visual sensitivity. Because the current work is focused on the perceptually-enhancing effects of tDCS, the proposed study only included anodal stimulation.

Methods

Participants

Demographic and clinical information for participants who completed Study 3 is summarized in Table 5. Twenty (45% women) medicated and clinically stable outpatients with chronic schizophrenia or schizoaffective disorder (SZ) were recruited from outpatient facilities in Nashville for participation in this study. Diagnoses were made or confirmed according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-*

TR) criteria using the Structured Clinical Interview for DSM-IV (SCID-I/P; First et al., 2002). SCIDs were administered by masters-level clinical psychology graduate students. We estimated premorbid IQ using the North American Adult Reading Test (NART; Nelson, 1982). Exclusion criteria included a history of head injury, neurological disorder, or substance abuse in the 6 months preceding the study. All participants provided written informed consent to study procedures approved by the Vanderbilt University Institutional Review Board and were compensated for their participation at a rate of $20 per hour.

Table 5

Demographic and Clinical Information for Participants in Study 3

	Participants (n = 20)
M/F	11/9
Age	48.60 (9.84)
Years of education	13.00 (2.08)
IQ[a]	102.25 (8.11)
Handedness[b]	+66.00 (53.87)
Ethnicity/Race:	
Caucasian	6
African American	13
Asian/Pacific Islander	1
Latino/Hispanic	0
BPRS	20.7 (10.95)
SAPS	28.25 (15.92)
SANS	29.85 (17.90)
CPZE[c]	394.94 (271.43)

Mean values are shown with *SD* in parenthesis. BPRS, Brief Psychiatric Rating Scale (Overall & Gorman, 1962); SANS, Scale for the Assessment of Negative Symptoms (Andreasen, 1983); SAPS, Scale for the Assessment of Positive Symptoms (Andreasen, 1984).
[a] National Adult Reading Test (NART; Nelson, 1982).
[b] Edinburgh Handedness Inventory (Oldfield, 1971).
[c] Chlorpromazine Equivalent Doses mg/kg/day (Woods, 2003).

All participants were taking medications at the time of the study; 19 were taking atypical antipsychotics, 1 was taking a typical antipsychotic, 1 was taking a mood stabilizer, and 10 were taking SSRIs. Antipsychotic doses were converted to chlorpromazine equivalent dose (Woods, 2003). Symptom severity in SZ was assessed with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorman, 1962), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983), and the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984). All participants were screened for normal or corrected-to-normal vision with the Snellen test of visual acuity. For the Snellen test, participants read through the chart using one eye at a time, viewed the letters from a distance of 20 feet, and read letters from the top of the chart aloud to an experimenter who scored their performance. Based on this viewing distance and the reference standard (20/20), the 8th row of letters from the top of the chart consisted of letters subtending an angle of 5° with each letter part subtending 1°.

Stimuli and Tasks

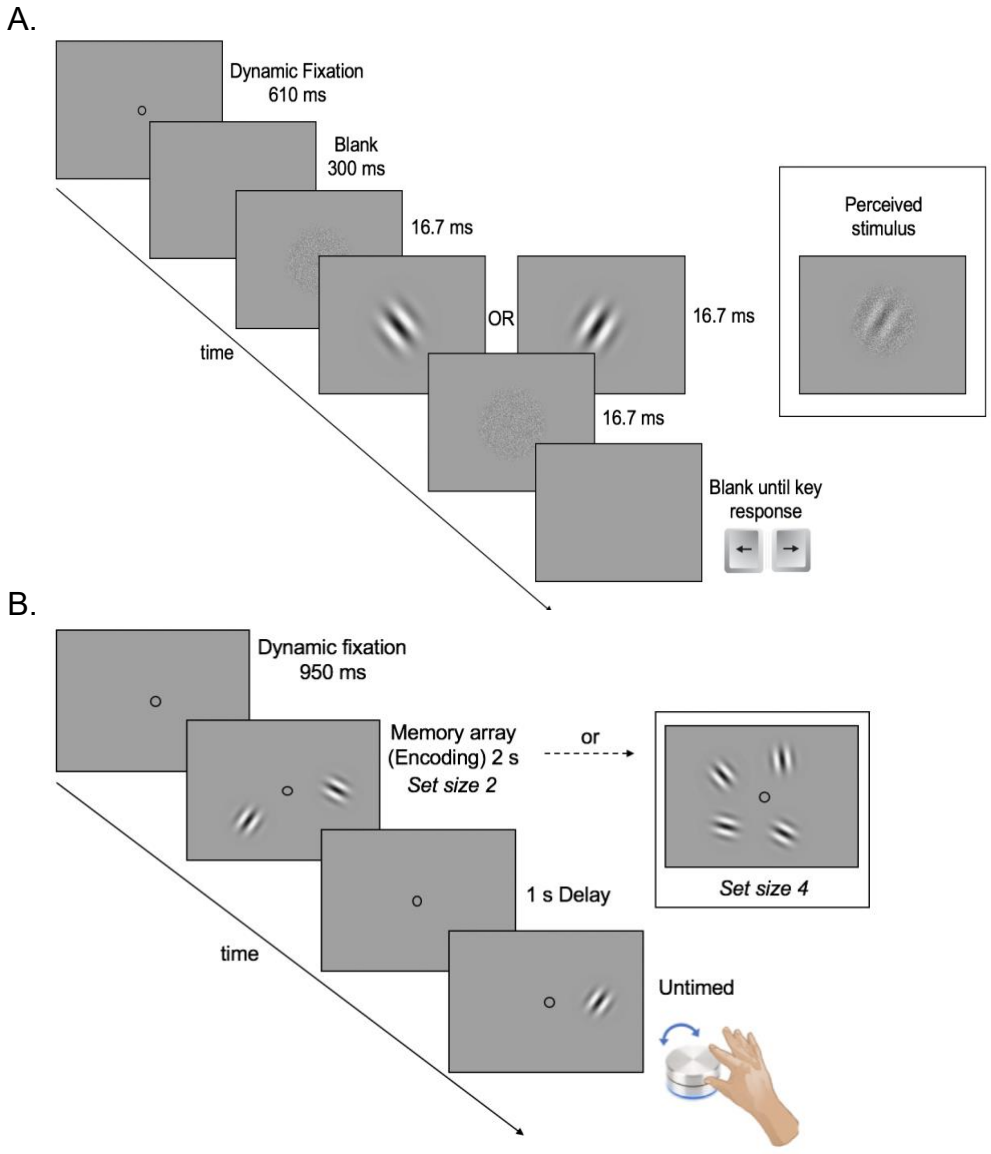
All tasks and stimuli were programmed in MATLAB and Psychtoolbox and presented on a linearized monitor (20-inch Sony CRT; 1024 x 640 resolution; 120 Hz) on a gray background. A chin rest was used to maintain viewing distance at 77 cm with each pixel subtending 0.036°. An experimenter was present in the room during both visual discrimination and working memory tasks to encourage task engagement.

Visual Discrimination Task

Participants completed the same visual discrimination task as described in Studies 1 and 2 (See page 15 for details and Figure 12a). All procedures for task administration were identical to those described in Studies 1 and 2.

Figure 12

Experimental Tasks for Study 3



Note. (A) Visual Discrimination Task (Adapted from Park et al., 2017) from Studies 1 and 2. (B) Visual Working Memory Task adapted from Studies 1 and 2. Trials included memory arrays with either 2 or 4 Gabors. Participants completed 60 total trials.

Visual Working Memory Precision Task

Participants completed a shortened version of the visual WM task described in Studies 1 and 2 (See page 17 for details) in order to reduce task duration and cognitive burden on participants. Participants completed a total of 60 trials, split equally into 3 blocks with rest periods lasting a minimum of 30 s. While the trial procedure was identical, memory arrays only consisted of two of four oriented Gabors (See Figure 12b).

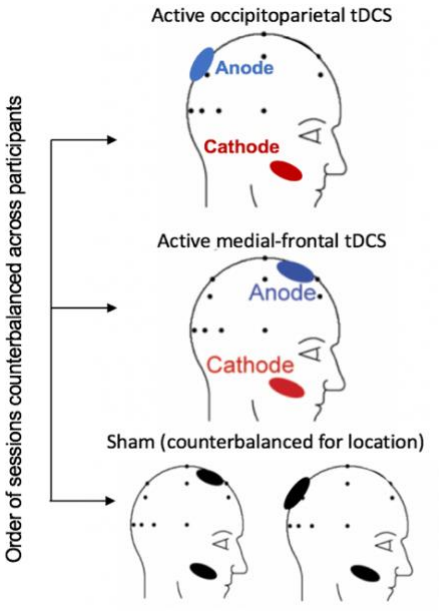
Experimental Design

The present study followed a within-subjects design, such that each participant completed the three stimulation conditions (anodal active over medial-frontal, anodal active over occipitoparietal, and sham) on three separate days. Session order was counterbalanced across participants, and the location of sham (medial frontal/occipitoparietal) was randomly assigned (See Figure 13). Participants were blinded to stimulation type (active or sham). The time interval between session visits was at least 48 hours to minimize potential task practice effects or carryover effects related to the previous session's brain stimulation (M=6.60 days between sessions, SD=4.11 days) (Monte-Silva et al., 2013).

All study sessions began with 20 minutes of active or sham tDCS applied over medial frontal or occipitoparietal cortex. Immediately after tDCS, participants completed the visual WM precision task (20-30 minutes), followed by the visual discrimination task (40-60 minutes). In total, the two tasks lasted approximately 90 minutes, which is within the time window in which tDCS effects have been shown to last in comparable stimulation procedures (Reinhart & Woodman, 2014).

Figure 13

The Transcranial Direct-Current Stimulation (tDCS) Montage and Experimental Design



Note. (Adapted from Reinhart et al., 2018) Anodal electrode placed at site Pz for occipitoparietal stimulation and at site FCz for medial-frontal stimulation, according to the International 10-20 system. Cathode placed over the right cheek (reference).

Transcranial Direct Current Stimulation

The tDCS was administered using a battery driven, constant current stimulator (MindAlive Inc., Alberta, Canada) and a pair of conductive rubber electrodes (active: 19.25 cm^2, reference: 52 cm^2). The electrodes were placed over saline-soaked sponges and each held in place with elastic cloth headbands. In the active anodal conditions, current is applied for 20 minutes. Stimulation intensity is fixed at 2.0 mA, as this intensity demonstrated improvement in visual acuity in a prior study (Reinhart et al., 2016). For medial frontal stimulation, the anodal electrode was placed over the medial frontal lobe at midline (site FCz of the International 10-20 System) and the cathodal electrode as placed over the right cheek to avoid confounding effects from other brain regions. For occipitoparietal stimulation, the anodal electrode was placed over

occipitoparietal cortex at midline (site Pz of the International 10-20 System), with the cathodal electrode again placed over the right cheek. Consistent with tDCS montages in related work, the placement of the cheek electrode is on a diagonal, parallel to the jaw line, 3 cm from the lip corner (cheilion) above the jaw (Reinhart & Woodman, 2014; Reinhart et al., 2016). Location of anodal electrode placement over FCz or Pz was determined with individual scalp measurements.

The tDCS sham condition involves similar administration as that for the active condition, except the stimulation only lasts 30 seconds, which ramps up and down at the beginning and end of the 20-minute period. This sham procedure results in the same physical sensations (e.g., tingling, itching) that are reported with active tDCS (Reinhart et al., 2016). Following each session, participants completed a questionnaire and visual analog scale that included questions regarding attention, concentration, mood, vision, headache, fatigue, and skin sensations during tDCS. Participants were additionally asked to rate whether they had received active versus sham stimulation and the degree of confidence associated with those ratings. Participants tended to overestimate the presence of stimulation, leading to an accuracy rate of detecting the correct stimulation condition of 57%. However, the hit rate for detecting sham stimulation was 15%, well below chance, suggesting that participants were blind to the sham versus active conditions. Additionally, confidence ratings did not differ across stimulus condition ($p > .23$). Scores across all questionnaire ratings did not significantly differ between stimulation conditions ($ps > .092$).

Task Analyses

Visual Discrimination Task

Data from the visual discrimination task were analyzed with two different approaches. The first involved a conventional PTM analysis to estimate model parameters between

stimulation conditions. Specifically, we examined relative differences in noise estimates (external noise filtering, internal additive noise, internal multiplicative noise) between medial frontal versus sham conditions, and occipitoparietal versus sham conditions. The second approach utilized hierarchical Bayesian model fitting to estimate each individual's model-generated noise estimates. Repeated-measures ANOVAs were conducted to examine the effect of stimulation condition (anodal medial frontal/anodal occipitoparietal/sham) on the Bayesian noise parameters (internal additive noise, external noise) and visual WM recall variance at each set size.

Conventional PTM Analysis. To examine differences in noise estimates across stimulation conditions, visual discrimination performance was first analyzed using the conventional PTM fitting method described in Study 1 (see page 20), with stimulation condition being treated similar to group comparisons in Study 1. Two conventional PTM analyses were completed to compare relative differences in noise parameters between (1) medial frontal versus sham stimulation and (2) occipitoparietal stimulation versus sham. Within each PTM analysis, coefficients for external noise filtering (A_e), internal additive noise (A_a), and multiplicative internal noise (A_m) were introduced into the standard PTM equation (see Equation 3) to account for differences in noise levels between active stimulation and sham conditions, such that a coefficient less than one indicates *lower* noise in the active stimulation. To determine if noise sources differed between the active and sham conditions, all possible candidate models accounting for each combination of free and fixed noise estimates were run: the null model, which assumed no group differences in any of the noise sources, the full model, which assumed group differences in all three noise sources, and six remaining models reflecting the different possible combinations of the three noise estimates. In addition to which ever noise coefficients

were specified to freely vary, all candidate models included the following four free parameters: multiplicative internal noise (N_m), internal additive noise (N_a), signal gain from the perceptual template (β), and the exponent of the nonlinear transducer function (γ). The eight candidate models were each fitted to average thresholds for the active and sham conditions using a least-squares method. Candidate models were compared by evaluating differences in goodness-of-fit using r^2. The best fitting model was determined with the *F*-test for nested models using a significance level of $\alpha < 0.05$ (See Park et al., 2017 for r^2 and *F*-test equations). Specifically, the best fitting model was identified as the model with the fewest free parameters that was not significantly different from the full model, in which all parameters could freely vary between conditions (active, sham).

Hierarchical Bayesian Model Analysis. Because the conventional PTM examines relative differences in noise between stimulation conditions at a group level, it may not be as sensitive an approach for capturing within-subject changes across stimulation conditions. Thus, we additionally completed a hierarchical Bayesian modeling technique to fit each participant's data with the PTM at each stimulation condition (occipitoparietal, medial-frontal, sham) in order to obtain individual noise parameter estimates across conditions. Similar to Studies 1 and 2, the hierarchical Bayesian approach allows for model parameters to be estimated for each participant directly from single trial data points based on the probability of participants' making a correct response. The computational procedures for estimating perceptual thresholds are identical to those described in Study 1 (see page 22). PTM fitting was constrained such that the gain parameter β and nonlinear power parameter γ were held constant to minimize the number of free model parameters while enabling estimation of all three noise parameters of interest (N_a, N_m, A_f) and the slope of the psychometric function (η). Values were set at $\beta = 1$ and $\gamma = 1.5$ for all

individuals, both which were based on estimates generated from the conventional PTM analysis for this group. Free model parameters were estimated for each individual with the Markov chain Monte Carlo (MCMC) method for sampling from posterior probability distributions, and participants' model parameters were constrained by hierarchical priors such that parameters were assumed to be drawn from the group's population distribution, a broad uniform distribution, with its own mean and SD. We conducted repeated-measures ANOVAs to examine the effect of stimulation condition (medial frontal, occipitoparietal, sham) on the three noise parameters (internal additive noise, multiplicative noise, unfiltered external noise).

Visual Working Memory Precision Task

The analysis pipeline for visual WM performance was consistent with that described in Studies 1 and 2 (see page 23). Gabor orientations were recorded and reported in the circular parameter space of all possible line orientation values [-90°, 90°) and converted to the circular space [-π, π) radians. Recall error on each trial was calculated as the difference between the orientation of the target Gabor and the orientation of the test probe that was reported (input with the manual dial) by the participant. The Von Mises probability density function (circular normal distribution) with mean $\theta = 0$ (no error, such that recall is centered at the target memory location) and SD = σ was used to fit every participant's distribution of recall errors at each memory array set size. The concentration parameter (κ) was estimated from each participant's recall errors at every memory array set size using a maximum likelihood method. Estimates of distribution concentration were converted to variances by taking the inverse of concentration parameters for subsequent individual differences analyses. We conducted repeated-measures ANOVAs to examine the effect of stimulation condition (medial frontal, occipitoparietal, sham) on mean WM recall variance at each set size. Pearson correlations were conducted to examine

relations between noise estimates and WM recall variance at each of the three stimulation conditions.

Results

Relative Differences in Noise Estimates Across Stimulation Conditions

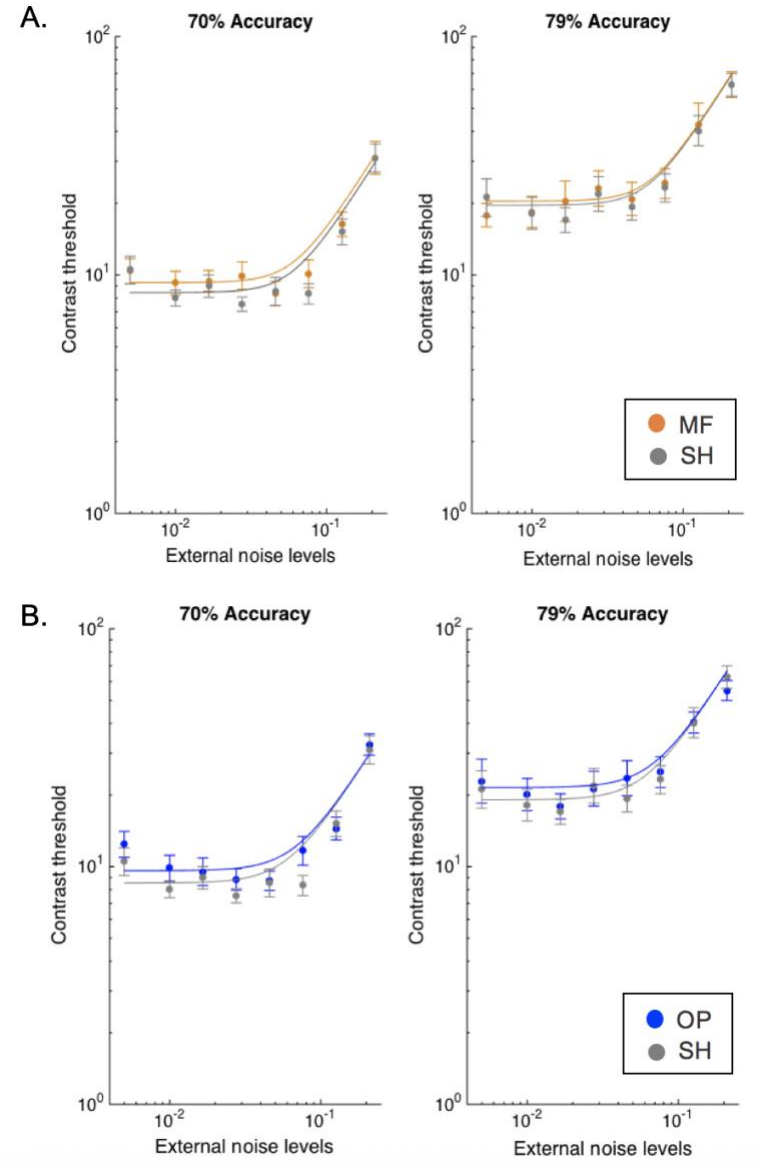
Upon inspection of data from the visual discrimination task at each condition, we identified 2 participants who appeared to exhibit random responding across all 3 sessions, and 1 participant who appeared to exhibit random responding during 1 session (medial frontal stimulation), such that performance was close to chance. Due to concerns that these participants were unable to complete the task, we excluded their data from analyses, leaving 18 participants in analyses comparing occipitoparietal versus sham stimulation and 17 participants in analyses comparing medial frontal versus sham stimulation.

The conventional PTM analyses yielded characteristic nonlinear threshold versus noise (TvN) functions, which reflect contrast thresholds as a function of varying levels of external stimulus noise during each stimulation condition (See Figure 14). Results from the conventional PTM examining differences in noise estimates between medial frontal stimulation and sham did not indicate significant differences in levels of unfiltered external noise (A_e), internal additive noise (A_a), or internal multiplicative noise (A_m) between the active medial frontal or sham conditions. In particular, no model with any combination of varying noise parameters was significantly different from the null model in which all three noise parameters were held constant across active medial frontal and sham conditions (all Fs < 2.54, ps > .13). Results from the conventional PTM examining differences in noise estimates between occipitoparietal stimulation and sham indicated that stimulation differences were accounted for by a model in which active

occipitoparietal and sham differed in levels of internal additive noise (A_a), but not unfiltered external noise (A_e) or internal multiplicative noise (A_m). In particular, this model specified a 19% *increase* in internal noise with occipitoparietal stimulation relative to sham (R_2 = 96.39%). This model was significantly different from the null model, in which noise parameters were equivalent across stimulation conditions, $F(1, 27) = 5.31$, $p < .05$, but not statistically different from the full model, in which all three noise sources were different between groups, $F(2, 25) = 0.39$, $p = .68$. These results indicate that visual perception was characterized by a relatively higher level of internal additive noise during occipitoparietal stimulation relative to the sham condition. We did not find evidence that medial frontal stimulation significantly impacted noise levels relative to sham.

Figure 14

Conventional PTM Threshold vs. Noise (TvN) Curves Across Stimulation Conditions



Note. Conventional PTM Threshold vs. Noise (TvN) Curves. Contrast thresholds (filled dots) estimated from the conventional PTM at each external noise level at both accuracy criteria (70.71, 79.14%) for (A) Anodal medial frontal (MF) stimulation versus sham (SH), and (B) Anodal occipitoparietal (OP) stimulation versus sham (SH). Error bars are ±SEM.

Within-Subject Differences in Noise Estimates Across Stimulation Conditions

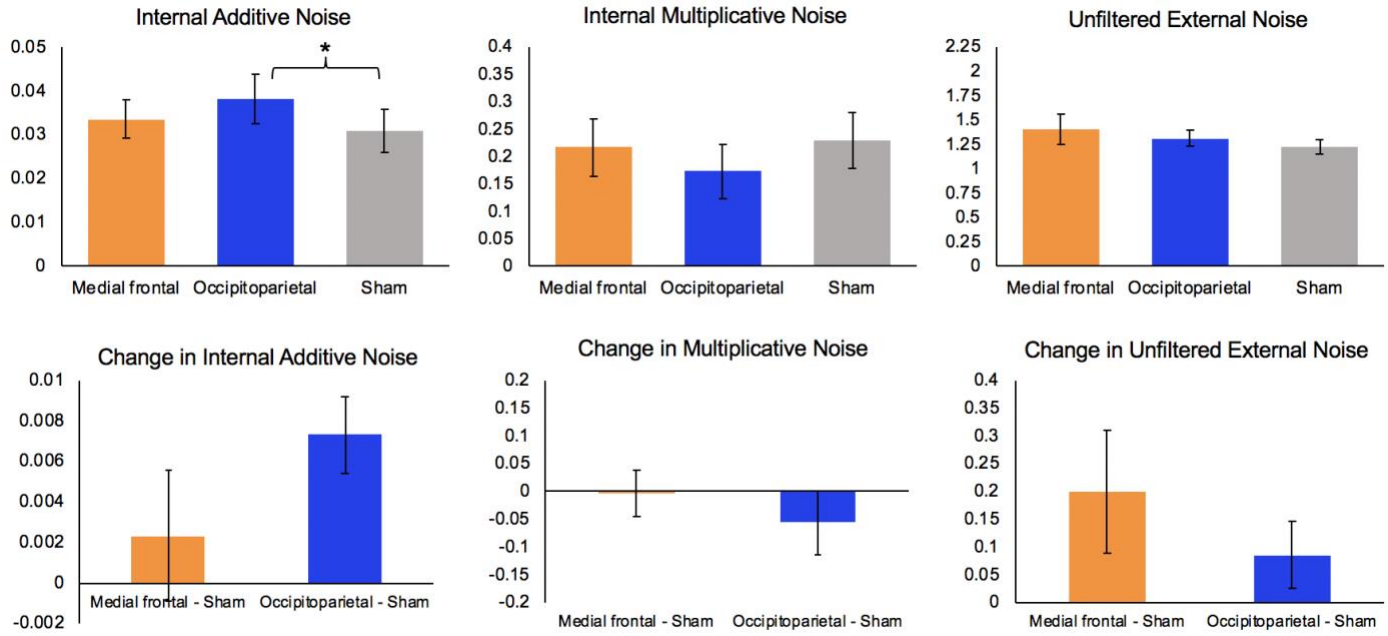
We did not find a significant main effect of stimulation type on contrast thresholds (across 8 levels of added external stimulus noise) in a repeated measures ANOVA examining the

impact of active medial frontal versus sham, $F(1, 16) = .78$, $p = .39$, or for active occipitoparietal versus sham, $F(1,17) = 1.52$, $p = .24$ on contrast thresholds. However, there was a significant interaction between stimulation type and level of external stimulus noise on contrast thresholds for active occipitoparietal versus sham, $F(7,119) = 2.80$, $p < .05$, such that occipitoparietal stimulation resulted in higher contrast thresholds at low, but not high, levels of added external stimulus noise relative to sham. Because internal noise is thought to best characterize contrast sensitivity at low but not high levels of external noise (Lu & Dosher, 1998, 2008), this finding is consistent with results from the conventional PTM analysis indicating that occipitoparietal stimulation resulted in a higher level of internal additive noise relative to sham.

Repeated measures ANOVAs directly examining the effect of stimulation condition (occipitoparietal, medial frontal, sham) on noise levels were also largely consistent with the conventional PTM analyses. Specifically, we found a trending effect of stimulation condition on internal additive noise, $F(2, 32) = 3.21$, $p = .07$. Post-hoc comparisons indicated higher internal additive noise during occipitoparietal stimulation relative to sham, $t(17) = 3.92$, $p < .01$, but no differences between other stimulation conditions (ps > .18). We did not find a significant effect of stimulation condition on multiplicative noise, $F(2, 32) = .92$, $p = .41$, or unfiltered external noise, $F(2, 32) = 2.37$, $p = .12$. See Figure 15 for mean noise estimates across stimulation conditions.

Figure 15

Mean Noise Estimates Across Stimulation Conditions



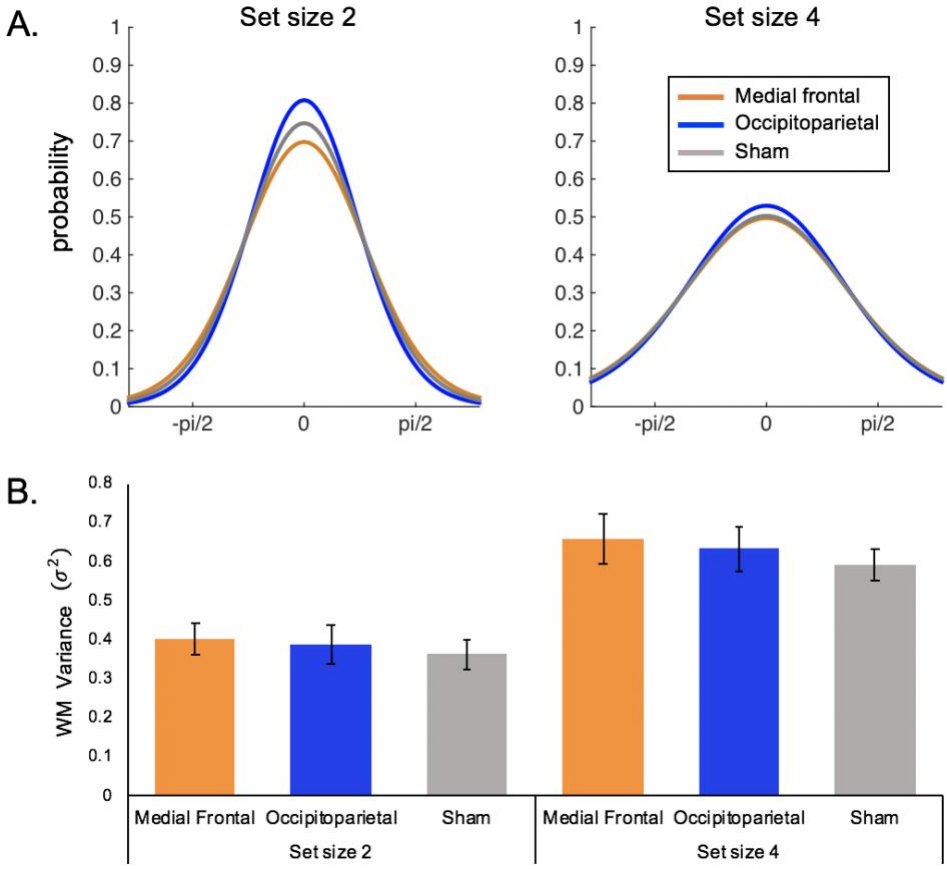
Note. Top panel: Mean Bayesian model estimates for internal additive noise, multiplicative noise, and unfiltered external noise at each stimulation condition. Bottom panel: Mean change score of internal additive noise, multiplicative noise, and unfiltered external noise estimates between active and sham conditions. Error bars are ±SEM. *$p < .05$

Differences in Visual Working Memory Across Stimulation Conditions

Individuals' WM recall variances were estimated from their error distributions at each stimulation condition and at each set size with the Von Mises distribution. Von Mises probability density functions, plotted by stimulation condition and set size, are shown in Figure 16. WM recall variance exhibited the expected pattern of greater variance with increasing WM set size across stimulation conditions, $F(1,19) = 61.52$, $p < .001$. We did not find a significant main effect of stimulation on WM recall variance, $F(2,38) = 1.26$, $p = .30$, or significant interaction between stimulation condition and WM set size, $F(2,38) = .17$, $p = .84$.

Figure 16

Visual Working Memory (WM) Recall Variance Across Stimulation Conditions



Note. (A) Von Mises probability density functions of visual WM recall across stimulation conditions. (B) WM recall variance at each stimulation condition, displayed by set size (Left: Set size 2, Right: Set size 4). No significant effect of stimulation on WM recall variance.

Relations between Noise Estimates and Visual Working Memory Across Stimulation Conditions

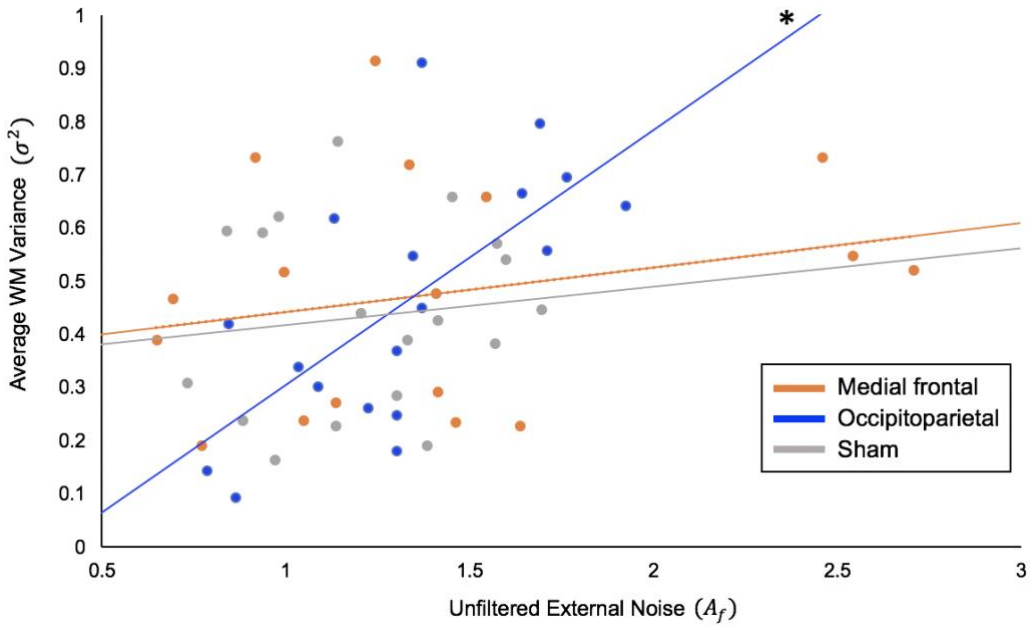
We did not find significant correlations between internal additive noise and unfiltered external noise at the sham condition, $r(18) = .20$, $p = .42$, or active occipitoparietal condition, $r(18) = .27$, $p = .28$, which is consistent with the idea that PTM in that these two sources of noise contribute at least somewhat independently to perceptual inefficiencies. However, internal additive noise was significantly correlated with unfiltered external noise, $r(17) = .50$, $p < .05$ for

the medial frontal condition, suggesting that internal additive and unfiltered external noise sources may share some variance in this condition.

WM variance was averaged across set sizes for each participant at every stimulation condition to limit the number of tests conducted. Pearson correlations indicated a significant positive relation between unfiltered external noise and average WM recall variance only for the active occipitoparietal condition, $r(18) = .68$, $p < .01$, but not the active medial frontal or sham conditions ($ps > .35$) (See Figure 17). Consistent with findings from Study 1, average WM recall variance was not significantly correlated with internal additive or multiplicative noise at any of the stimulation conditions ($ps > .21$).

Figure 17

Unfiltered External Noise and Working Memory Recall Variance Across Stimulation Conditions



Note. Relations between unfiltered external noise and average visual working memory (WM) recall variance at each stimulation condition. *$p < .01$.

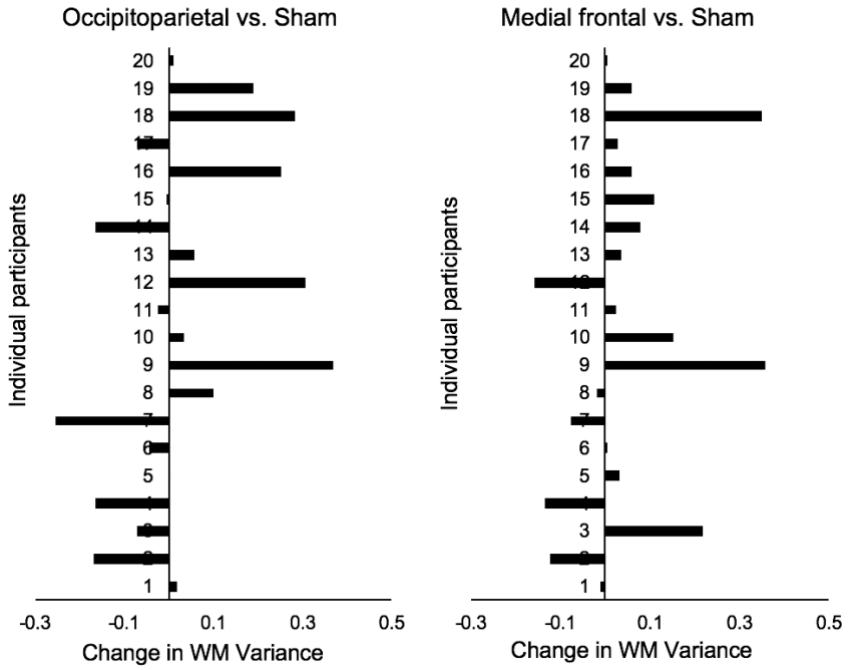
Contributions to Changes in Noise and Working Memory Variance with Active Stimulation

Given that anodal stimulation of occipitoparietal cortex resulted in an increase in internal additive noise, we completed post-hoc correlation analyses to determine whether certain participant characteristics were related to the change in internal additive noise. We did not find significant correlations between the change in internal additive noise and age, symptom level (BPRS, SAPS, or SANS), antipsychotic dose, estimated IQ, or education level (*ps* > .13).

We did not find that anodal stimulation of medial frontal cortex or occipitoparietal cortex resulted in consistent increases or decreases in WM recall variance relative to sham. However, further inspection of changes in WM variance between active and sham conditions suggested that individuals exhibited significant variability in direction of change (see Figure 18). Thus, to examine whether changes in noise levels (internal additive, multiplicative, and unfiltered external noise) between active stimulation and sham predicted changes in WM recall variance, we completed stepwise linear regressions for the two stimulation comparisons (medial frontal versus sham, occipitoparietal versus sham). For each stepwise regression, the three noise change scores were entered as independent variables, with the WM variance change score as the dependent variable. Change scores were computed by subtracting individuals' noise estimates and average WM variances at sham from those at active stimulation conditions, resulting in change scores for medial frontal stimulation versus sham and occipitoparietal stimulation versus sham. Thus, a positive value indicated an increase in noise or WM variance from active to sham while a negative value indicated a decrease in noise or WM variance.

Figure 18

Change Scores in Average Working Memory (WM) Variance Between Active Stimulation and Sham



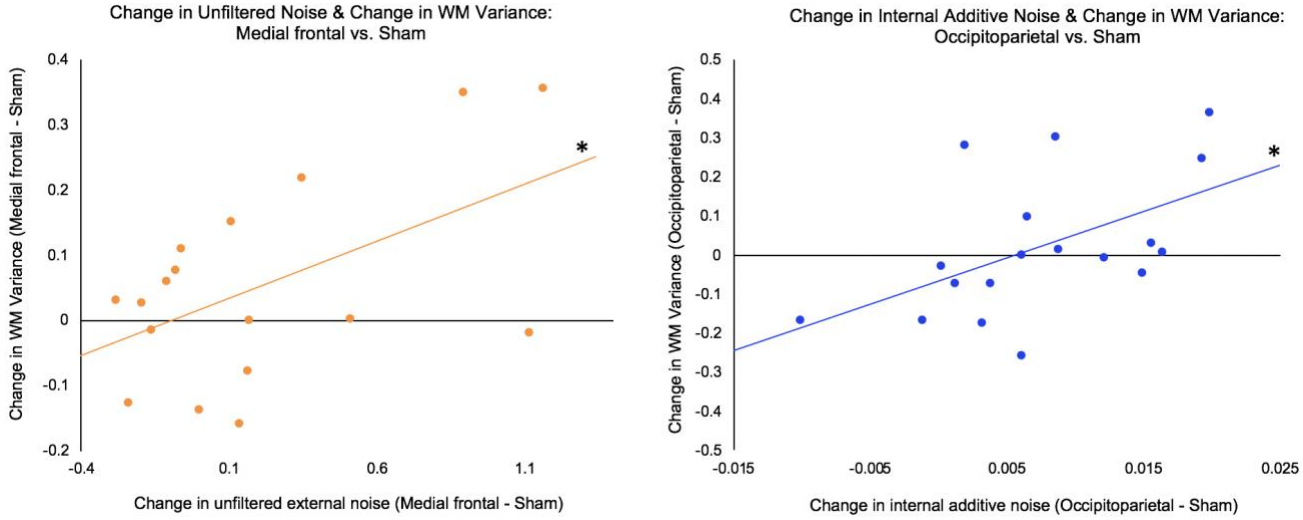
Note. Left: Change in WM variance between occipitoparietal anodal stimulation and sham. Right: Change in WM variance between medial frontal anodal stimulation and sham.

When examining predictors of change in WM with medial frontal stimulation relative to sham, a significant regression equation ($F(1,16) = 5.86$, $p < .05$, $R2 = .28$, $R2_{Adj} = .23$.) for a model including just unfiltered external noise indicated that only the change in unfiltered external noise (not internal additive or multiplicative noise) significantly predicted the change in WM variance, $\beta = .18$, $t(17) = 2.42$, $p < .05$ (See Figure 19). When examining predictors of change in WM with occipitoparietal stimulation relative to sham, a significant regression equation ($F(1,17) = 6.20$, $p < .05$, $R2 = .28$, $R2_{Adj} = .23$) for a model including just internal additive noise indicated that only the change in internal additive noise (not multiplicative noise or unfiltered external noise) significantly predicted the change in WM variance, $\beta = 11.89$, $t(18)$

= 2.49, $p < .05$ (See Figure 19). In summary, an increase in unfiltered external noise with medial frontal stimulation was related to an increase in WM variance, while an increase in internal additive noise with occipital parietal stimulation was related to an increase in WM variance.

Figure 19

Change in Noise Estimates and Working Memory (WM) Variance Between Active Stimulation and Sham



Note. Left: Change in unfiltered external noise is positively related to change in WM variance between medial frontal stimulation and sham conditions. Right: Change in internal additive noise is positively related to change in WM variance between occipitoparietal stimulation and sham conditions. *$p < .05$.

Given the variability of responses to tDCS, we conducted exploratory analyses to further examine whether any factors may characterize those who exhibited worse performance (increased WM variance) across both active tDCS conditions relative to sham stimulation. Understanding individuals' differences in response to anodal tDCS may allow us to personalize brain stimulation strategies in the future, thereby increasing potential efficacy. We explored potential group differences between those whose WM variance increased with active stimulation

in both occipitoparietal and medial frontal conditions relative to sham (n=7), and those did not (n=13). The latter group thus consisted of individuals who exhibited WM improvement in one or both active conditions. In particular, we examined group differences in symptom levels, duration of illness, age, premorbid IQ, and antipsychotic medication dose. Results showed that individuals whose WM variance was higher at both active stimulation conditions compared to sham could be characterized by a higher level of negative symptoms (SANS) relative to the group that did not show a consistent decline in performance with tDCS, $t(18) = 2.21$, $p < .05$. Group differences between the other variables examined were not significant ($ps > .20$). Given the exploratory nature of this analysis, results should be interpreted with caution.

Discussion

The present study examined the effects of 20 minute anodal tDCS over medial frontal cortex and occipitoparietal cortex on PTM-estimates of internal noise and visual WM performance in individuals with schizophrenia. Contrary to our hypothesis, we found that anodal tDCS of occipitoparietal cortex resulted in a small increase in internal additive noise (~19%), but not unfiltered external noise or multiplicative noise, relative to sham stimulation. Neither stimulation montage resulted in significant or consistent changes in visual WM variance. However, the degree to which one's WM variance changed between active and sham conditions was related to the degree of change in PTM-estimated noise levels, which is consistent with the hypothesis that changes in internal noise would lead to changes in visual WM. These results hold important implications for utilizing anodal tDCS as a means of visual or cognitive remediation in this population, as they suggest that anodal tDCS does not always have similar

enhancing effects on perception or cognition in those with schizophrenia as observed in non-patient populations.

In the current study, anodal stimulation over occipitoparietal cortex mildly increased internal additive noise levels in those with schizophrenia. The direction of stimulation's effect on internal noise and visual performance was unexpected given past work showing visual perceptual enhancement following anodal stimulation over the same region in a non-clinical population (e.g., Reinhart et al., 2016). At the same time, these results are consistent with the hypothesized mechanism of anodal tDCS as boosting underlying cortical excitability, leading to an addition of background noise to the system (Filmer et al., 2014). One possible explanation for this discrepancy in our findings is that anodal tDCS may have differential effects on perception (or cognition) based on baseline level of internal noise. For those with low or typical levels of internal noise in the visual system, an addition of random noise may result in stochastic resonance, such that the background noise boosts the signal in a nonlinear system to a point that exceeds perceptual thresholds and improves detection (Moss et al., 2004; McDonnell & Ward, 2011). When baseline levels of noise are low, this increase in internal additive noise still allows for noise to reach an optimal level and avoid signal diminution. For those with higher baseline levels of internal noise, such as those with schizophrenia (given findings from Study 1), stimulation may exceed optimal levels, such that any increase in signal is obscured by an exacerbation of background noise. In summary, individuals who have low or typical levels of baseline noise may have more of a buffer to experience an increase in internal noise without interference on signal detection, and exhibit optimal noise levels for stochastic resonance with stimulation (Moss et al., 2004).

Interestingly, occipitoparietal stimulation did not increase levels of unfiltered external noise or multiplicative noise, suggesting that internal additive noise may be particularly sensitive to cortical excitability in visual regions. This selective impact of occipitoparietal stimulation on additive noise supports Lu & Dosher's (2008) description of internal additive noise as reflecting the collective impact of intrinsic noise sources in the perceptual (visual) system. It remains unclear which neural regions or networks are responsible for visual external noise filtering during perception. However, some describe the efficient adaptation of the perceptual system to visual stimuli changes (e.g., luminance, gain, noise) as a change in neural filtering (Sharpee et al., 2006), and this sensory adaptation has been linked to multiple levels of the visual system, including retina (e.g., Hosoya et al., 2005; Smirnakis et al., 1997), lateral geniculate nucleus (Solomon et al., 2004), and primary visual cortex (Sharpee et al., 2006). Thus, cortical effects of occipitoparietal stimulation may not have impacted earlier stages of visual processing that may contribute more directly to noise filtering.

Although occipitoparietal stimulation resulted in a small increase in internal additive noise, it did not significantly affect visual WM variance. These findings are not surprising considering both the relatively small effect of stimulation on internal additive noise and the relative contribution of internal additive noise to visual WM performance, with Study 1 suggesting that all noise sources accounted for approximately 30% variance in patients' WM performance. However, the change in one's internal additive noise level between sham and occipitoparietal stimulation was related to change in visual WM variance in the hypothesized direction. That is, the degree to which internal additive noise increased with occipital stimulation predicted the degree to which WM variance also increased. These results are consistent with the hypothesis that internal additive noise reflects noise during more bottom-up

sensory processing in visual cortical areas, and that these perceptual inefficiencies (sensory noise) contribute to variability, or imprecision, in visual WM (Ester et al., 2013; Sims et al. 2012).

We did not find an effect of medial frontal anodal stimulation on noise levels or visual WM variance, which may have been due to a number of theoretical and experimental reasons that are difficult to disentangle. For example, anodal tDCS with this montage may have yielded greater individual variability in underlying cortical current flow and density relative to the occipitoparietal montage, which is somewhat consistent with increased variability of functional organization in frontal versus sensory regions (Tahmasebi et al., 2012). The functional heterogeneity of medial frontal cortex (de la Vega et al., 2016) may also contribute to more variable effects of medial frontal stimulation across individuals. Alternatively, since past work has shown cognitive enhancement in individuals with schizophrenia following anodal stimulation of this same region (Reinhart et al., 2019; Reinhart et al., 2015a; 2015b), the null effects in the present study may be driven by methodological differences. For instance, all participants completed the visual WM task immediately following stimulation, leaving open the possibility that stimulation effects were not fully realized at the time of task completion. Some studies examining patients' post-stimulation changes in WM at different time points found that WM improvement was observed at 20 minutes and 40 minutes post-stimulation, but not immediately following stimulation (Hoy et al., 2014; Hoy et al., 2015).

While speculative, another possible explanation for the lack of effect is that stimulation of this medial frontal region had a more distant, diffuse impact (very small effect) on visual perception and visual WM relative to tasks more directly assessing adaptive control, predictive coding, and spatial attention. While we targeted these top-down executive processes with the

hypothesis that they were also implicated in poor visual noise filtering and WM dysfunction in schizophrenia (Kim et al., 2004; Oram et al., 2005; Silver & Feldman, 2005), the degree to which these processes contribute to WM ability might be highly variable across individuals. Interestingly, upon further inspection of what predicted individual differences in change in WM variance between medial frontal stimulation and sham, we found that change in one's unfiltered external noise level predicted change in visual WM variance in the hypothesized direction. These results were consistent with our hypothesis that unfiltered external noise (poorer external noise filtering) in those with schizophrenia, potentially introduced through inefficient top-down control processes, limits visual WM performance. This relationship is also in line with studies showing that top-down frontal and parietal processes such as spatial attention impact perceptual processing partly through enhanced external noise exclusion (Lu et al., 2002; Dosher & Lu, 2000).

There are several methodological limitations of our study that should be considered. First, we were unable to include a control group comparison in order to probe whether individuals with schizophrenia exhibited different effects of tDCS than those without schizophrenia. While past studies show that anodal tDCS over occipitoparietal cortex enhances contrast sensitivity in non-clinical samples (Kraft et al., 2010; Olma et al., 2011; Reinhart et al., 2016), the lack of control sample in the present study makes it more challenging to determine whether the increase in internal additive noise (increase in contrast thresholds at low external noise levels) observed in the schizophrenia group truly reflects a unique response to tDCS compared to those without schizophrenia. Second, the nature of the experimental tasks did not allow us to test changes in performance following stimulation in an immediate pre- and post-test design, which is typically more sensitive to detecting stimulation-specific changes as it

eliminates some performance variability due to factors other than the stimulation. While we attempted to limit confounds associated with testing across different session days (e.g., diurnal effects, learning effects), numerous individual variables that may fluctuate daily (e.g., diet, exercise) and impact cognitive performance (Chang et al., 2012; Hoyland et al., 2008) may have limited our ability to detect effects of tDCS.

Another methodological constraint is that we did not record neural activity during task performance, limiting our understanding of whether or how tDCS impacted the hypothesized neural oscillations (e.g., alpha, theta) contributing to contrast sensitivity and visual WM. Several prior studies suggest that anodal tDCS over visual regions in healthy adults increases resting alpha power in frontal (Spitoni et al., 2013) and posterior regions (Spitoni et al., 2013; Wiesman et al., 2018; Wilson et al., 2018) following stimulation, though this finding is not universal (Marshall et al., 2016). Although many studies find that anodal stimulation enhances visual performance in health adults, Wiesman and colleagues (2018) found that increased basal alpha power following anodal tDCS was related to poorer performance (longer reaction times, lower accuracy) on a visuospatial discrimination task. These results are consistent with our findings of reduced contrast sensitivity at low external noise levels following anodal stimulation, implicating a role of altered alpha power in contributing to increases in internal additive noise. Future work is needed to better map the relationship between stimulation, resting and task-induced alpha, and behavioral performance in both healthy adults and psychiatric populations.

Results from the present study suggest that the degree to which tDCS exacts change on underlying neural activity and subsequent behavior may vary significantly by individual factors, as we observed variability in both the direction and magnitude of change in noise estimates and WM variance between active and sham conditions. As research on tDCS's ability to modulate

perception and cognition continues to expand, more of these individual factors will likely be identified. Exploratory analyses in the present study found that those with higher negative symptoms exhibited poorer WM performance following active tDCS independent of stimulation location, suggesting that individuals characterized by greater negative symptoms may not show cognitive enhancement with anodal tDCS. This finding has implications for research examining the therapeutic effects of repeated anodal tDCS over DLPFC on negative symptoms (e.g., Palm et al., 2016). Interestingly, negative symptoms have also been linked to higher levels of frontal cortical noise (Suazo et al., 2012), raising the possibility that those with higher negative symptoms may be characterized by greater internal noise, making them more susceptible to noise exacerbation with anodal tDCS. Other work has found that the direction and strength of tDCS effects and resulting electrical field characteristics are linked to individual differences in anatomical features, such as skull and cerebrospinal fluid thickness (Kim et al., 2014; Laakso et al., 2015; Opitz et al., 2015), severity of neural impairment or deficit (Bradnam et al., 2012, Marquez et al., 2013), and even genetic factors (Plewnia et al., 2013; Nieratschker et al., 2014). For example, both Plewnia and colleagues (2013) and Nieratschker and colleagues (2014) found that differences in the polymorphism of the catechol-O-methyltransferase (COMT) gene influenced the behavioral effects of tDCS on executive function. COMT is critical to dopamine neurotransmission in prefrontal cortex and related neurocognitive function (Chen et al., 2004) and has been further implicated in genetic liability for schizophrenia (Egan et al., 2001; Ira et al., 2013).

Some propose that effects of tDCS also depend on baseline levels of neurochemicals such as GABA (Li et al., 2015) given work finding that anodal tDCS reduces local GABA (Stagg et al., 2009). Such findings are relevant to schizophrenia, as GABAergic neurotransmission is

altered in schizophrenia and has been linked to this group's differences in oscillatory activity (Gonzalez-Burgos & Lewis, 2008) and neurocognition, including WM dysfunction (Hashimoto et al., 2008). Yoon and colleagues (2010) also found that individuals with schizophrenia exhibit reduced GABA concentration in visual cortex, which was related to a measure of visual inhibition (surround suppression). These findings suggest that the effect of anodal tDCS could differ in those with schizophrenia relative to controls given group-level differences in GABA concentration, which may further vary individually across cortical regions and contribute to inter-individual variability in tDCS effects at different stimulation sites.

In summary, we found that anodal tDCS over occipitoparietal cortex increased PTM-estimates of internal additive noise in those with schizophrenia, reflecting reduced contrast sensitivity under conditions of low stimulus noise. tDCS over medial frontal cortex did not affect PTM-noise levels, and neither stimulation montage impacted visual WM performance. However, we found that individual changes in internal noise and external noise filtering as a result of active occipitoparietal and medial frontal stimulation, respectively, predicted changes in visual WM. These findings provide evidence in support our hypothesis that internal additive noise and unfiltered external noise may relate to patients' inefficiencies in more bottom-up sensory processes and top-down control-related processes, respectively. Results further demonstrate the role of perceptual inefficiencies, captured by levels of internal noise, on visual WM variance. Future studies should explore the potential utility of cathodal stimulation for suppressing internal noise levels and delineating the neural impact of stimulation in those with schizophrenia.

CHAPTER V

CONCLUSION

The WM deficit in schizophrenia is considered a core feature of the illness and predictive of functional outcome. Visual processing impairments have also been extensively studied in those with schizophrenia and characterized as critical to understanding the nature of this condition (Silverstein & Thompson, 2015). Despite rich literatures in each of these areas, few research groups have examined how inefficiencies in early visual processing contribute to the widely observed visual WM deficits associated with schizophrenia. An initial goal of this dissertation was to determine whether a known visual processing deficit in schizophrenia, contrast sensitivity, was characterized by higher levels of internal noise in the visual perceptual system measured with established psychophysical and computational methods. Namely, the current series of studies utilized the Perceptual Template Model (PTM; Lu & Dosher, 1998, 1999, 2008) to estimate and compare levels of theoretical noise sources in the visual system in those with and without schizophrenia. A second goal was to examine whether such perceptual inefficiencies, captured by elevations in internal noise, were related to the visual WM deficit in those with schizophrenia.

The first behavioral study described in Chapter II provided evidence of higher PTM-estimated levels of internal noise during visual perception in individuals with schizophrenia relative to control subjects, which was the first study to report this type of analysis in those with schizophrenia to our knowledge. Importantly, this first study also documented a positive relationship between internal noise levels and variance in visual WM recall in those with and without schizophrenia, suggesting that the visual WM deficit in this population can partly be

accounted for by disruptions in visual processing. Specifically, greater visual WM recall variance in those with schizophrenia was uniquely predicted by individuals' level of unfiltered external noise, implicating that patients' WM dysfunction may at least partly be due to failures in processes governing noise-filtering. Because our sample in Study 1 largely consisted of those with chronic schizophrenia who had been taking psychotropic medications for many years with possible effects on perception and cognition, the follow-up study presented in Chapter III sought to better understand how elevations in internal noise related to underlying schizophrenia pathophysiology in a medication-naïve sample of college students. Results showed that individual differences in internal noise estimates in this non-clinical group were positively related to traits associated with the extended psychosis phenotype, including disorganized schizotypy and prodromal symptoms. Results from this study also replicated Study 1 findings of relations between internal noise levels and visual WM variability. Collectively, these first two behavioral studies uphold the theory that schizophrenia pathology involves abnormalities in visual processing, characterized here as noisier perceptual processing, while extending the existing literature to show that internal noise during visual perception contributes to patients' visual working memory dysfunction.

The final experiment presented in Chapter IV explored whether levels of internal noise could be modified in those with schizophrenia with transcranial direct current stimulation (tDCS). Ultimately, we sought to test whether downstream effects of stimulation on internal noise would also improve visual WM deficits in those with schizophrenia. Contrary to our hypothesis, results revealed that anodal tDCS over visual (occipitoparietal cortex) but not frontal regions (medial frontal cortex) mildly increased levels of internal additive noise in those with schizophrenia. While active anodal stimulation over visual or frontal regions did not result in

significant changes in visual WM performance across participants, results indicated that individual changes in internal noise with active stimulation predicted change in visual WM variance. Thus, Study 3 findings were consistent with the idea that alterations of internal noise levels can result in changes in visual WM performance, leaving open the possibility that mechanisms involved in internal noise could serve as promising targets for improving WM dysfunction in those with schizophrenia. For example, occipitoparietal cortex remains a potential point of intervention for cathodal stimulation, as the latter may actually suppress baseline noise in the visual system given its hypothesized ability to inhibit cortical excitability (Nitsche & Paulus, 2000, 2001). Findings that medial frontal stimulation failed to modulate noise levels or visual WM are more challenging to interpret given the number of possible causes outlined in the discussion, but point more broadly to the often-inconsistent effects of tDCS on perception and cognition (Horvath et al., 2015). Future work is not only needed to clarify how anodal and cathodal stimulation across regions alters underlying neural processing and subsequent behavior in those with schizophrenia, but also identify how individual differences contribute to differential effects of stimulation.

The studies outlined in this dissertation offer novel yet complimentary findings to the existing literature on neural noise in schizophrenia. For instance, noisier neural processing in those with schizophrenia has been implicated across multiple levels of analysis: greater intra-individual variability in the timing of behavioral responses (Kaiser et al., 2008) and latency of stimulus-evoked electrophysiological responses (Callaway et al., 1970; Zouridakis et al., 1997), greater variability in stimulus-induced brain oscillations (Winterer et al., 2004; Winterer et al., 2000), and findings of heightened circuit noise within biophysical computational models of glutamatergic and dopaminergic dysfunction in schizophrenia (Braver & Cohen, 1999; Murray et

al., 2012; Rolls et al., 2008; Starc et al. 2017). The current work thus provides further evidence of heightened neural noise in those with schizophrenia in yet another methodological domain, and is moreover consistent with select findings that such various measures of noise relate to patients' cognitive impairment (e.g., Winterer et al., 2000; 2004; Starc et al., 2017; Braver et al., 1999). While the latter studies focus on noise within prefrontal regions, the current work highlights the importance of noisy processing in earlier sensory regions that may have a downstream impact on WM performance. Indeed, the visual system has been proposed as a promising region for examining local circuit and feedback modulation abnormalities in those with schizophrenia given that visual paradigms can be strategically designed to isolate the role of top-down processes like attention on sensory processing and even induce changes in glutamate and GABA modulation (Yoon et al., 2013).

Finally, results across these studies point to several interesting future research directions. For instance, do individuals with schizophrenia exhibit noisier perception in other sensory modalities where early processing abnormalities are also observed, and does this noise contribute similarly to WM impairment in the same modality? Cognitive remediation programs targeting basic auditory processing deficits have been found to improve verbal WM in first-episode (Fisher et al., 2014) and chronic patients with schizophrenia (Adcock et al., 2009; Dale et al., 2015; Fisher et al., 2009), suggesting that this link between early sensory inefficiencies and WM dysfunction may not be unique to visual perception. Another intriguing line of work is how noise may contribute to other hallmark cognitive deficits associated with schizophrenia. Although we found little evidence that visual inefficiencies directly related to overall psychiatric symptoms, supporting the notion that noisier visual perception is not simply a consequence of fluctuating symptoms, internal noise may have more proximal effects on processes involved in

social cognition (e.g., affect discrimination) that contribute more distally to negative symptoms (Strauss et al., 2010). If this is the case, improving measures of internal noise may result in subtle improvements in interpersonal functioning. Given the importance of patients' visual deficits and WM impairment to functional outcome, work that further illuminates how these areas are connected and interact with each other will hopefully advance research efforts to ultimately improve the prognosis and well-being of individuals with schizophrenia.

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