Abstract

Contrast Sensitivity and Clinical High Risk for Psychosis:

A Psychophysical Investigation

Individuals with schizophrenia exhibit visual anomalies and perceptual deficits, such as contrast detection, which is typically expressed as contrast sensitivity (CS). Visual anomalies are common among people at clinical high risk for psychosis (CHR-P). One study investigated CS in CHR-P and found increased CS compared to controls. We attempted to replicate this finding using a technique based on an iPad Pro. Also, comparisons were made with existing schizophrenia data.

Fourteen controls and 12 CHR-P participants were administered the CS task: forced-choice paradigm with gratings of five spatial frequencies (SFs, 0.41-13 cyc/deg) presented under two durations to emphasize transient (33-ms) or sustained (500-ms) pathway activity. The Audio-Visual Abnormalities Questionnaire (AVAQ) was utilized to assess perceptual disturbances.

In the 33-ms condition, all groups exhibited nearly a lowpass function, whereas in the 500-ms condition, a bandpass function was obtained, consistent with the literature. Under 33-ms, difference in logCS, peak value at 1.6 cyc/deg to 0.41 cyc/deg, is greatest for the CHR-P group. Under 500-ms, controls benefitted most from longer duration, especially at mid-SFs. Modeling of excitatory/inhibitory mechanisms demonstrated that controls had greater

excitation overall and greater increase in inhibition with increased duration. Linear mixed-effects modeling revealed a Group x Temporal Condition interaction, $F(1,234) = 5.008$, $p = .026$. Positive correlations of logCS with AVAQ scores were obtained at the lowest SF, 500-ms for the CHR-P group (AVAQ total, $r = .62$, $p = .04$; visual processing subscale, $r = .67$, $p = .03$); negative correlations were obtained for logCS at 6.5 cyc/deg, 500-ms (AVAQ total, $r = -.60$, $p = .04$; visual processing subscale, $r = -.61$, $p = .04$).

CS enhancement at low-SF in the CHR-P group was associated with perceptual disturbances, suggesting a deficit in lateral inhibition. A differential effect on CS with duration indicated possible concomitant effects on neural integration. CHR-P relative loss of CS at mid-SFs suggests dysfunction in ganglion cells tuned to mid-SFs which play a critical role in facial recognition and expression. These deficits are associated with other perceptual disturbances and psychotic-like symptoms. Additional research is needed to investigate CS in a larger sample, adjusting for medication.

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CHAPTER I: INTRODUCTION

Background and Significance

Organization of the Visual System

The visual system transforms what people view into a set of higher-order representations of several aspects of the visual world, such as color, size, edge orientation, and movement. The primary visual pathway projects from photoreceptors in the retina to the primary visual cortex in the occipital lobe via the lateral geniculate nucleus (LGN) of the thalamus, which is often referred to as the retino-geniculo-cortical pathway. When light hits the retina, it is converted by photoreceptors into electrical signals that are connected to the bipolar cells, which relay the message to the ganglion cells, whose axons form the optic nerve (Kaplan, 2004). The two major types of ganglion cells are midget and parasol cells (Polyak, 1941). Midget cells receive their input from bipolar cells that obtain input from a single cone (photoreceptor), whereas the parasol cells receive input from several dispersed bipolar cells, which in turn sample from several cones (i.e., photoreceptors; (Polyak, 1941).

Midget and parasol ganglion cells project to the LGN, which is comprised of six layers arranged in two divisions (Kaplan, 2004). The upper division of the LGN contains four layers of smaller cells (i.e., parvocellular [P] layers), while the lower division has larger cells called magnocellular (M) layers. Layers 6, 4, and 1 receive input from the contralateral eye, while Layers 5, 3, and 2 are innervated by the ipsilateral eye. Parasol cells project to the M

layers of the LGN (the lower two layers), while the midget ganglion cells innervate the upper four P layers (Perry et al., 1984). These anatomical layers gave rise to two major visual streams: M and P pathways

The information from the LGN is fed primarily into Layer 4 of the primary visual cortex, V1. Magnocellular cells synapse in Layer 4Ca, while P cells synapse in Layer 4Cb. From V1, the information is relayed to the rest of the visual system. The pattern of M/P connectivity below and above V1 has given rise to the notion of parallel systems, each handling a certain aspect of the visual system (Kaplan, 2004; Kaplan & Shapley, 1986).

Studies have shown different physiological and functional properties of M and P pathways. A review paper by Kaplan (2004) provides a summary of the properties of M and P streams. The M stream is more sensitive to phasic (i.e., moving), achromatic, and low luminance stimuli; high luminance contrast; mostly linear; and has a large receptive field and more transient light adaptation. The P stream is the opposite (Benardete & Kaplan, 1997a, 1997b; Croner & Kaplan, 1995; Gouras, 1968; Ingling & Martinez-Uriegas, 1985; Kaplan & Shapley, 1986; Lee et al., 1990; Perry et al., 1984; Purpura et al., 1990; Wiesel & Hubel, 1966). The visual system is thus divided into the “where” (i.e., dorsal) pathway corresponding to the M system and the “what” (i.e., ventral) stream matching the P system (Livingstone & Hubel, 1988; Zeki & Shipp, 1988).

Contrast and Spatial Frequency

One way to isolate and investigate these streams of activity is to manipulate the contrast and spatial frequency (SF) of images in psychophysical experiments (Demb et al., 1998). Contrast and SF are low-level aspects of visual perception that allow for perception of

the world. The ability of humans and animals to perceive the details of objects and scenes is determined by how well their visual system perceives contrasts (Jindra & Zemon, 1989). Contrast refers to the difference in luminance of an object compared to its background that makes it visible (Legge, 1978; Pelli & Bex, 2013; Slaghuis, 1998). In low-contrast images, the dark and light aspects of the image appear more similar, while high-contrast images have distinctly dark and light aspects (Legge, 1978). One's threshold contrast is the lowest contrast level required to detect a visual stimulus from the background, and objects' visibility and brightness depend mainly on the contrast of their background (Jindra & Zemon, 1989; Kaplan & Shapley, 1986). Contrast sensitivity (CS) is the inverse of threshold contrast, and greater CS means better ability to detect contrast. The neurophysiological basis for CS is "lateral inhibition," a phenomenon in which groups of photoreceptors are wired together to produce a "center-surround" arrangement where light differentially affects the center versus surrounding regions of the receptive field of a neuron (Stringham et al., 2017). This perceived difference between the center and its surround yields the visual system's ability to detect edges. The minimum difference in luminance detectable between the center versus surround regions of the receptive field determines threshold CS (Stringham et al., 2017). The visual receptive field of a retinal ganglion cell has been modeled as a sum of excitatory and inhibitory processes (Enroth-Cugell & Robson, 1966), and its shape has been described by a *difference in Gaussian* functions (Rodieck, 1965).

SF refers to the number of pairs of spatial elements (e.g., light and dark bars) that present in one degree of visual angle, and it is expressed in terms of cycles per degree (cyc/deg). Images can be broken down into SF components such that each component is a grating (i.e., bar pattern) set at a particular orientation with a sinusoidal luminance profile

and a peak contrast value (Campbell & Maffei, 1974). An image with high SF (HSF) shows more detailed content compared to one with low SF (LSF; (Kaplan & Shapley, 1986). The highest SF the human eye can see is approximately 50 cyc/deg, and high contrast is needed for this frequency to be seen (Campbell & Maffei, 1974).

The gold standard for determining a CS function (CSF) is to measure contrast thresholds to detect sinusoidal gratings across a range of SFs using robust psychophysical techniques (Campbell & Robson, 1968). Contrast detection has been studied using a wide variety of psychophysical techniques since the eighteenth century (Robson, 1993). A system analysis approach has been applied to the measurement of CS since the mid-1900s (Campbell & Green, 1965; Campbell & Robson, 1968; Jindra & Zemon, 1989; Kelly & Savoie, 1973; Schade, 1956). CS depends on the spatial pattern used, and grating patterns with a sinusoidal luminance profile are typically used for testing. Some researchers use the spatial method (Butler et al., 2008; Calderone et al., 2013; Herrera et al., 2021; Zemon et al., 2021), whereas others use a temporal method with steady or pulsed pedestal paradigms to tap into the M or P pathway activity (Keri & Benedek, 2007; Pokorny, 2011).

In the psychophysical domain, a distinction is made between two parallel channels within the human visual system (i.e., sustained and transient channels, which broadly resemble the properties of P and M pathways, respectively). Psychophysical evidence shows that sustained channels are involved in viewing colors and patterns, selective for medium and HSF, and respond to chromatic and stationary stimuli, as well as slow temporal changes. The transient channels are involved in position and space; selective for LSF; and respond to stimulus motion, flicker, and high rapid temporal changes (Breitmeyer, 1992; Breitmeyer & Ganz, 1976; Green, 1981; Kulikowski & Tolhurst, 1973; Legge, 1978; Merigan et al., 1991).

The CSF reflects a merge of transient and sustained channels, as it describes how the eye performs at all contrast levels and not solely at high contrast. In photopic luminance conditions, healthy individuals are most sensitive to contrast at an SF of approximately 4 cyc/deg and are less sensitive above and below this (Kelly, 1977). Studies have shown that the CSF varies with SF, size, brightness, motion, and temporal condition of the paradigm independently and thus is a respective choice to measure CS and tap into each visual stream (Kelly, 1977; Kulikowski & Tolhurst, 1973). To summarize, the CSF reflects a composite of transient and sustained channel, where the transient channel is sensitive to LSF, high temporal frequencies, and motion and flicker, whereas the sustained channel is sensitive to HSF, low temporal frequencies, stationary stimuli, and color and pattern.

Studies have demonstrated that CS measured by brief stimulus temporal condition (less than 100 ms) revealed a characteristic low pass function (Kelly, 1977; Legge, 1978). In healthy individuals, a low pass function is demonstrated by a peak in CS at LSF and a decrease in CS from medium to HSF, which is characteristic of the operation of the transient channel (Kelly, 1977; Legge, 1978). There is a change in the shape of CSF when the stimulus duration is greater than 100 milliseconds (ms). When the temporal condition is longer (i.e., greater than 100 ms), healthy individuals showed an overall increase in CS called a bandpass function, which is indicative of the sustained channel operation (Legge, 1978). Furthermore, an increase in temporal condition has been shown to positively affect CS at HSF (not LSF), which is consistent with the sustained channel operation (Campbell & Maffei, 1974). This function resembled an inverted U shape with a peak at 4 cyc/deg and a decrease in CS at LSF and HSF. The decrease in CS at LSF under low temporal frequency and long duration conditions is considered to reflect lateral inhibition which is controlled by the center and

surroundings of the receptive field (Burbeck & Kelly, 1980; Cornsweet, 1970; Kelly, 1973). Activity elicited in the smaller, center mechanism of the smallest neuron receiving the visual stimulus has been shown to determine the falloff in the CSF at HSF (manuscript, in preparation).

Since the visual system is the most understood part of the human brain and the most studied area in neuroscience, it provides an excellent model system for understanding neural function and circuitry (Silverstein et al., 2015). CS is impaired in ophthalmic and neurological conditions (Abrahamsson & Sjöstrand, 1986; Bodis-Wollner, 1972; Collins & Carney, 1990; Freeman & Thibos, 1975; Hess & Woo, 1978; Stamper, 1984)as well as psychiatric conditions like multiple sclerosis (Regan et al., 1981), Parkinson's disease (Bodis-Wollner & Onofrj, 1987), autism (Guy et al., 2016), and schizophrenia (SCZ; (Zemon et al., 2021)). Studies that show alterations in visual functions in SCZ and individuals at high risk of developing SCZ can inform the understanding of the development, pathophysiology, and heterogeneity of the condition. The current study reviews the literature on CS in individuals with SCZ and clinical high risk for psychosis (CHR-P) and investigate CS in these populations using a psychophysical task.

Schizophrenia

Schizophrenia is characterized by significant impairments in the way reality is perceived. Symptoms of SCZ include positive symptoms (e.g., delusions and hallucinations); negative symptoms (e.g., avolition and anhedonia); and disorganized symptoms in thinking, speech, movement, and behavior (Andreasen & Olsen, 1982; APA, 2013). Additionally, people with SCZ often experience persistent difficulties with cognitive abilities such as

memory, attention and problem solving (see the Diagnostic and Statistical Manual for Mental Disorder Version 5 (DSM-5) for a more detailed list of SCZ criteria). According to the Global Burden of Disease 2019, SCZ affects 23.4 million people worldwide and 1.5 million adults per year in the U.S. (Collaborators, 2022; NAMI, 2020). The onset of SCZ typically occurs in one's late teens to early twenties, with an earlier age of onset for males compared to females (Ochoa et al., 2012; Patel et al., 2014). Studies have shown increased numbers of females in older onset cases that occur during menopause (Howard et al., 2000; Ochoa et al., 2012). When analyzed for a family history of SCZ, those with a stronger familial loading had an earlier onset of illness in their early twenties and those with a low familial loading had a delayed onset in their late twenties (Esterberg et al., 2010).

Studies have shown that duration of untreated psychosis (DUP) has an impact on an individual's prognosis. Among individuals with first-episode psychosis (FEP), patients who previously received treatment in a specialized psychosis program had a significantly shorter average DUP compared to those who did not (Conus et al., 2017; Marshall et al., 2005; Perkins et al., 2005; Valmaggia et al., 2015). A shorter DUP is consistently associated with better outcomes, including reduced hospitalizations, positive symptoms, anxiety and depression, and better quality of life (Valmaggia et al., 2015). Early detection and treatment are thus imperative.

SCZ may arise from a combination of factors such as family history (i.e., genetics), maternal complications during pregnancy and birth, and environmental factors (e.g., trauma and minority stress; (Anglin et al., 2021; Davis et al., 2016; Maki et al., 2005). Developmental factors associated with increased risk for the development of SCZ include

family history, premorbid IQ, trait anhedonia, minority status, childhood trauma, and childhood social withdrawal (Chen et al., 2018; Howard et al., 2000; Radua et al., 2018).

Mounting evidence suggests that altered neurotransmitters might be the basis for the pathophysiology of neurodevelopmental and neuropsychiatric disorders such as SCZ. For half a century, dopamine has been linked to SCZ (Howes et al., 2015; Liu et al., 2021; Stahl, 2018). Specifically, dopamine hyperactivity at D2 dopamine receptors in the mesolimbic pathway caused positive symptoms (paranoid delusions and auditory hallucinations) of psychosis and thus antipsychotics were drugs that blocked dopamine D2 receptors (Stahl, 2018). This is called the dopamine hypothesis. In the past decade, researchers have proposed that NMDA receptor hypofunction in the prefrontal cortex can lead to psychosis. In conjunction with the dopamine hypothesis, researchers have postulated that dopamine hyperactivity is a downstream consequence of glutamate dysregulation in the prefrontal cortex (Howes et al., 2015; Kantrowitz & Javitt, 2012; Quinones et al., 2021; Stahl, 2018).

The majority of neurons in the neocortex are glutamatergic excitatory pyramidal neurons while around 20% of the cortical neurons are GABAergic inhibitory interneurons (Liu et al., 2021). In a healthy brain, excitatory and inhibitory information is balanced through multiple developmental processes. Disruption of this balance has been proposed as a hypothesis providing insights into the mechanisms underlying neuropsychiatric disorders such as SCZ. Data from in vivo imaging (Kegeles et al., 2012; Rowland et al., 2013) and postmortem studies (Kim et al., 1980; van Kammen et al., 1982) in patients with SCZ provide evidence for the excitatory-inhibitory balance in SCZ such that they had altered concentrations of GABA and glutamate at levels of individual synapses, circuits and networks depending on the brain region (Liu et al., 2021). Despite more than a century of

research, the precise cause of SCZ continues to elude investigators. Prediction of psychosis could potentially be improved by incorporating neural perceptual markers that are known to reflect overall neural function and circuitry.

Perceptual Abnormalities in Schizophrenia

Altered perceptual experiences are a common feature of SCZ, specifically visual disturbances (Silverstein & Rosen, 2015). Approximately 25–30% of individuals with SCZ report visual hallucinations, and the rate of patients reporting visual distortions (i.e., in the domains of brightness, motion, form, and color) is at least double that (Silverstein & Rosen, 2015; Waters et al., 2014). Visual hallucinations are not the only form of visual perceptual anomaly experienced in SCZ. Self-reported visual abnormalities in SCZ include metachromopsia, change in facial or body perception, changes in own face perception, object pseudo movement, poor visual acuity, and double or reversed vision (see Silverstein et al. [2016] for a more detailed list; (Keane et al., 2018; Keri, Kiss, et al., 2005; Kiss et al., 2010; Klosterkotter et al., 2001; Nikitova et al., 2019; Silverstein, 2016; Silverstein et al., 2017). Additionally, visual perceptual disturbances have been found in childhood and adulthood that predict the later development of SCZ to a greater extent than other sensory anomalies (Hayes et al., 2019; Klosterkotter et al., 2001; Schubert et al., 2005). Similar visual anomalies are common in the prodrome of psychosis (i.e. the time period preceding the onset of psychosis in which symptoms begin to develop), such as larger interocular visual acuity differences (Hayes et al., 2019; Klosterkotter et al., 2001).

Studies have demonstrated that people with SCZ have difficulty with higher-level visual processing, which is characterized by an interpretation of what is seen and measured

by tasks such as object, face, and emotion recognition (Bar et al., 2006; Bortolon et al., 2016; Butler et al., 2009; Doniger et al., 2002; Edwards et al., 2002; Silverstein & Lai, 2021; Vakhrusheva et al., 2014) and depth inversion illusions (Keane et al., 2013). Since the development of neuroimaging techniques such as event-related potentials (ERPs) and functional magnetic imaging, several studies have detected higher-level visual processing abnormalities in people with SCZ (Silverstein, 2016). ERPs are changes in the brain's electrophysiological activity that occur in response to stimuli. The P300 waveform has been conceptualized as the physiological correlate of changes in working memory or an index of allocation of attentional resources that can impact performance on higher-order visual tasks (Bramon et al., 2004). In many ERP studies, P50 and P300 ERPs have been robust indicators of disease and are not influenced by the duration of illness (Bramon et al., 2004; Hamilton et al., 2019; Oribe et al., 2013).

Many studies have explored emotion perception in SCZ. Facial emotion perception deficits in SCZ are considered crucial predictors of clinical outcomes such as social functioning (Butler et al., 2009; Chan et al., 2010). Facial feature detection is captured through the N170 ERP component and has been identified to be greater during a facial stimuli presentation with emotions compared to non-face stimuli (Wynn et al., 2008). Studies have shown that individuals with SCZ have reduced N170 amplitude and latency compared to healthy controls (Chan et al., 2010; Wynn et al., 2008).

There is evidence of disruptions in mid-level visual processing described by an integration of information about visual components into higher-order representations with emergent features in examples such as figure-ground segregation (Malaspina et al., 2004); coherent motion detection (Chen, 2011); illusory contour perception (Butler et al., 2013;

Feigenson et al., 2014) ; visual context processing (e.g., Ebbinghaus illusion) (Silverstein et al., 2013; Yang et al., 2013); and perceptual organization (Keane et al., 2016; Silverstein, 2016; Silverstein et al., 2009; Silverstein & Keane, 2011; Silverstein et al., 2012; Silverstein & Lai, 2021). Over 50 studies have demonstrated reduced visual perceptual organization in SCZ across various paradigms, labs, and countries, and this dysfunction seems to be specific to SCZ (Silverstein & Keane, 2011). Furthermore, deficits in visual perceptual organization are related to illness duration, as FEP individuals showed enhanced perceptual organization compared to those with chronic SCZ (who had reduced perceptual organization) and healthy controls (Parnas et al., 2001). This finding was not accounted for by antipsychotic medication use, as deficits in perceptual organization were seen in unmedicated patients with longer illness duration (Keri, Kiss, et al., 2005; Parnas et al., 2001; Silverstein et al., 2009).

Impairments in SCZ have also been seen in both forward- and backward-masking paradigms (Braff, 1989; Butler et al., 2003; Butler et al., 1996; Cadenhead et al., 2013; Cadenhead et al., 1998; Green, Lee, et al., 2011; Green et al., 1994; Green, Wynn, et al., 2011; Herzog & Brand, 2015; Schechter et al., 2003; Slaghuis & Bakker, 1995). Masking paradigms involve presenting one visual stimulus (i.e., a "mask") immediately before (i.e., forward masking) or after (i.e., backward masking) a brief "target" visual stimulus, causing a failure to consciously perceive the stimulus (Breitmeyer & Ganz, 1976). Studies have suggested that abnormal masking functions in SCZ may reflect M pathway impairment, as the mask disrupts the P channel response necessary for target identification (Cadenhead et al., 1998; Schechter et al., 2003; Slaghuis & Curran, 1999). Schechter et al. (2003) evaluated visual-backward masking using psychophysical properties of luminance and chromatic contrast to bias processing toward the M or P pathways and found significant impairment in

M pathway function, as well as M pathway deficits correlating with negative components on the Positive and Negative Symptom Scale (PANSS; (Schechter et al., 2003). This finding is consistent with previous research showing that backward-masking deficits (which are thought to rely more on M function) are more pronounced in patients with negative symptoms or worse prognosis than in patients with positive symptoms or good prognosis (Braff, 1989; Butler et al., 2003; Slaghuis & Bakker, 1995). Similar results are found between unmedicated and medicated SCZ patients (Butler et al., 1996), high-risk populations (Green, Lee, et al., 2011), and patients with SCZ and their unaffected siblings (Keri et al., 2001) .

Lastly, studies have demonstrated low-level visual processing abnormalities in SCZ that have been defined as a representation of information produced by the retina and primary visual cortex. These deficits include sensitivity to luminance changes, edge detection, orientation tuning, vernier acuity, motion detection, and CS (Butler et al., 2005; Calderone et al., 2013; Chen, 2011; Cimmer et al., 2006; Fernandes et al., 2022; Kelemen et al., 2013; Keri, Antal, et al., 2002; Keri, Janka, et al., 2002; Keri, Kelemen, et al., 2005; Keri, Kiss, et al., 2005; Shoshina & Shelepin Iu, 2013; Silverstein & Lai, 2021; Zemon et al., 2021). CS in particular has consistently shown to be lower among individuals with SCZ compared to healthy controls, with SCZ individuals needing approximately double the contrast to detect a visual stimulus (Zemon et al., 2021).

Contrast Sensitivity in Schizophrenia

An impairment in a low-level visual process such as CS would suggest a basic visual system disturbance in SCZ, as it would be difficult to explain in terms of reduced cognitive

control. Studies indicate CS is altered in SCZ compared to healthy controls (Butler & Javitt, 2005; Butler et al., 2008) through psychophysical studies (Cadenhead et al., 2013; Calderone et al., 2013; Cimmer et al., 2006; Keri, Antal, et al., 2002; Slaghuis, 1998; Zemon et al., 2021), as well as electrophysiological (Butler et al., 2005; Schechter et al., 2005). Using visual evoke potentials (i.e. a type of ERP), SCZ show reduced amplitude of the P100 component to low-contrast conditions, an early component of the visual system that has generators in the dorsal and ventral streams (Butler et al., 2005; Schechter et al., 2005) and reduced response to contrast-versing radial patterns (Kim et al., 2005).

Most studies have demonstrated impairment of CS in SCZ, but these differ as a function of methodology, SF, symptoms, medication, and chronicity, which adds to the complexity. Some studies have investigated CS at a single SF, while others have investigated CS across various SFs (Butler et al., 2009; Butler & Javitt, 2005; Cadenhead et al., 2013; Calderone et al., 2013; Chen et al., 2003; Keri, Antal, et al., 2002; Slaghuis, 1998, 2004; Zemon et al., 2021). Some researchers have found dysfunction in LSF conditions, which they have postulated as a dysfunctional M pathway (Butler & Javitt, 2005; Butler et al., 2001; Kim et al., 2006; Kiss et al., 2006; Martinez, Hillyard, et al., 2012; Martinez et al., 2008; O'Donnell et al., 2002; Schwartz & Winstead, 1985). Other studies have found dysfunction across low, medium, and high SFs (Calderone et al., 2013; Fernandes et al., 2019; O'Donnell et al., 2006; Slaghuis, 1998, 2004; Zemon et al., 2021). Differences in methods also exist across CS studies. Some studies with unmedicated patients used a “pedestal” task and a temporal forced-choice method (Kelemen et al., 2013; Kiss et al., 2010; Sheremata & Chen, 2004), whereas studies with more chronic patients, such as those tested in our laboratory, used a spatial forced-choice method (Butler et al., 2009; Butler & Javitt, 2005; Calderone et

al., 2013). Studies have also demonstrated that patients with predominately negative symptoms have worse CS performance at all SFs, whereas those with predominately positive symptoms only present a P dysfunction (Slaghuis, 1998, 2004).

Illness chronicity and antipsychotic medication also likely play a partial role in decreased CS in people with SCZ. Shoshina and Shelepin (2013) found that people with SCZ for less than 10 years showed decreased CS for low and medium SF; whereas those who have had SCZ for more than 10 years presented decreased CS at all SFs. They probed the differences between antipsychotic medications and found that individuals who had SCZ for less than 10 years and were on atypical antipsychotic medication had decreased CS at LSF, whereas those on typical antipsychotic medication showed reduced CS at both LSF and HSF. Those who were diagnosed for over 10 years showed reductions in SF regardless of antipsychotic type (Shoshina & Shelepin Iu, 2013), which suggests that illness duration and type of antipsychotic medication influence CS in different ways.

Consistent results have demonstrated that decreased CS was related to a higher dose of antipsychotic medication and that patients on typical antipsychotics performed worse than those on atypical medication (who often were not significantly different from healthy controls; (Chen et al., 2003; Fernandes et al., 2019; Keri, Antal, et al., 2002; Zemon et al., 2021). Furthering this medication effect, researchers found that people on a combination of antipsychotics and antidepressants had lower CS than those on antipsychotics only (Sheremata & Chen, 2004).

Researchers have shown that patients with SCZ who were not taking antipsychotic medication had increased CS compared to healthy controls (Cadenhead et al., 2013; Chen et al., 2003; Kelemen et al., 2013; Kiss et al., 2010). These researchers manipulated their

paradigms to target the M pathway by having a dynamic stimulus and presenting stimuli at LSFs (0.25–.5 cyc/deg). In a study which introduced antipsychotics to SCZ patients, the increased CS was no longer seen and was reduced at follow-up compared to healthy controls (Kelemen et al., 2013). Some researchers also investigated P pathways in SCZ by adjusting color and HSF and found normal P pathway function (Kiss et al., 2010). However, this finding is mixed, as other studies have found P pathway dysfunction in unmedicated SCZ patients (Cadenhead et al., 2013; O'Donnell et al., 2006). Lastly, Shoshina et al. (2015) investigated CS in patients with FEP who had not taken antipsychotics for multiple years and those who had been exposed to antipsychotics for a few years. They found that those not taking antipsychotics for multiple years showed increased CS responses to LSF stimuli and decreased CS responses to HSF stimuli compared to controls, which suggests that the P dysfunction was observable regardless of current antipsychotic use. In contrast, those with FEP who had been exposed to long-term antipsychotics exhibited reduced CS to both LSF and HSF stimuli. The authors posit that P dysfunction is due to illness, whereas M dysfunction may be due to long-term antipsychotic use (Shoshina et al., 2015).

Antipsychotics bind to dopamine receptors, principally to the D2 receptor family. Seeman (2002) demonstrated that although both typical and atypical drugs block the D2 receptor, atypical antipsychotics (e.g., clozapine) have short occupancies. Rapid release of atypical antipsychotics allows dopamine to reoccupy the receptor, whereas the slow release of typical antipsychotics maintains the blockade of dopamine, making it less available (Seeman, 2002). These mechanisms may explain the differences in CS results observed in people taking typical versus atypical antipsychotics. Studying CS in CHR-P individuals

would allow for investigation of these visual properties without the effect of antipsychotic exposure.

Clinical High Risk for Psychosis

Identifying individuals prior to the onset of threshold psychosis provides an opportunity for early intervention that may prevent, delay, or mitigate the effects of psychosis (Fusar-Poli, 2017; Fusar-Poli & Salazar de Pablo, 2021; Salazar de Pablo et al., 2021). The prodrome of psychosis was first characterized in the 1990s. Prodrome is the time period, typically three to four years, preceding the onset of threshold psychosis when individuals begin to develop subthreshold psychotic symptoms (Yung & McGorry, 1996; Yung et al., 1996). The rationale for attempting to study the prodrome is that by the time a first episode of psychosis emerges, the illness has likely been underway for several years, with significant social and functional impairment and motivational, expressive, motor, and cognitive deficits (Corcoran et al., 2021). Retrospective studies with individuals with FEP have indicated that this prodrome occurs in ~75% of patients and is characterized by functional decline and attenuated psychotic symptoms (Hafner et al., 1998).

Efforts to identify individuals in the prodrome led to the development and use of the CHR-P construct. CHR-P individuals are identified based on having the characteristic signs of the prodrome and thus being at elevated risk for developing psychosis. CHR-P syndromes include the experience of attenuated psychotic symptoms (APS), brief intermittent psychotic symptoms (BIPS), and genetic risk for psychosis with functional decline (GRD; (Fusar-Poli, 2017; Fusar-Poli et al., 2017; Woods et al., 2001; Woods et al., 2014; Yung et al., 1996) see Woods et al. [2008] for detailed criteria). Others identify these high-risk individuals by basic

symptoms (BS), chosen from the data of the prospective Cologne early recognition study, which has a requirement of two or more cognitive disturbances (COGDIS) or at least one cognitive or perceptive basic symptom (COPER; (Klosterkotter et al., 2001; Schultze-Lutter, Klosterkötter, et al., 2007). BS refers to subjectively experienced subclinical disturbances in drive, affect, thinking, speech, and body, as well as sensory perception, motor action, central vegetative functions, and stress tolerance (Schultze-Lutter, Ruhrmann, et al., 2007). Co-occurrence of APS and BS has been related to higher transition rates to psychosis (Schultze-Lutter et al., 2014). Recently, the European Psychiatric Association recommended the APS and BIPS criteria (recommended) and COGDIS (alternative) for use in psychotic risk detection (Schultze-Lutter et al., 2015). The genetic risk and functional decline (GRD) criterion of the CHR-P approach was not recommended due to a lack of evidence of a relevant risk enhancement, and COPER was not recommended given the lack of research on its utility (Schultze-Lutter et al., 2015).

Measures such as the Structured Interview for Psychosis Risk Syndromes (SIPS) and the Comprehensive Assessment of At Risk Mental States (CAARMS) have been developed to assess for the presence of CHR-P (McGlashan, 2001; Yung et al., 2005). The CAARMS and SIPS convey a comparable prevalence of CHR-P cases (Fusar-Poli et al., 2015; Oliver et al., 2018). The SIPS has a relatively higher sensitivity for the prediction of psychosis than the CAARMS, but the difference did not influence the prevalence of cases identified (Oliver et al., 2018). In a review of studies, the most frequently used CHR-P instrument was SIPS (65.7%), followed by the CAARMS (40.0%) (Salazar de Pablo et al., 2021). Using the SIPS, Lo Casio et al. (2016) noted that CHR-P individuals had significantly lower SIPS positive

symptom scores than early onset psychosis individuals but similar SIPS negative, disorganized, and general symptom scores (Lo Cascio et al., 2016).

Salazar de Pablo et al. (2021) conducted a systematic review and meta-analysis to investigate the prevalence of CHR-P in the general population and clinical samples. In their review, 35 studies were included with a total sample size of 27,135 (i.e. 26,835 in the general population and 10,300 in clinical samples). The total number of CHR-P individuals identified was 1,554 (i.e. 352 in the general population and 1,202 in clinical samples), with a median age of 19.3 and a median percentage of females of 52.2. They found that the prevalence of CHR-P in the general population of adolescents and young adults was 1.7% and 19.2% in the population entering mental health services. This high rate was also reported in a community sample study by Schultze-Lutter (2017).

While not all individuals characterized as CHR-P develop psychosis, many continue to experience subthreshold symptoms and functional impairment (Schlosser et al., 2012). In addition to attenuated psychotic symptoms, people who meet the criteria for CHR-P typically present with other clinical concerns such as anxiety, depression, and substance use disorders (Woods et al., 2009; Yung et al., 2008; Yung et al., 2004); high levels of negative symptoms (Fusar-Poli, 2017; Piskulic et al., 2012); significant impairments in academic performance and occupational functioning(Fusar-Poli et al., 2013); difficulties with interpersonal relationships (Lee et al., 2017); and substantial compromised subjective quality of life (Addington, Epstein, et al., 2008; Bechdolf et al., 2005; Lencz et al., 2004; Velthorst et al., 2011).

APS is the most common CHR-P syndrome, evident in more than 85% of all patients with CHR-P (Fusar-Poli, Schultze-Lutter, et al., 2016). In 2013, the APS diagnosis was

introduced to the DSM-5 Appendix and found to be associated with equivalent prognostic accuracy compared to the CAARMS-APS. Those diagnosed with DSM-5–APS had a five-fold probability of transitioning to psychosis compared to high-risk individuals not diagnosed with DSM-5–APS (Salazar de Pablo et al., 2020; Woods et al., 2010). The Meta-analytical risk of psychosis onset using the DSM-5 attenuated positive symptoms diagnosis was 11% at six months, 15% at 12 months, 20% at 24 months, and 23% at 36 months (Salazar de Pablo et al., 2020). In 2021, Corcoran, Mittal, and Woods (2021) argued for attenuated psychotic syndrome (APS) to be moved to the main section of the DSM-5-TR (Corcoran et al., 2021).

In the past decade, studies have focused on the content of APS in CHR-P. 15% of participants reported experiencing symptoms containing direct sexual content (Thompson et al., 2010). Falukozi and Addington (2012) found significant positive correlations between increased trauma and feeling watched or followed and grandiose ideas related to status or power (Falukozi & Addington, 2012). Examining the content of 414 CHR-P individuals who met the criteria for APS, researchers found that these individuals more frequently endorsed being perplexed by reality and having overvalued beliefs under the “unusual thought” category. They also frequently endorsed being suspicious of others speaking negatively about them and feeling guarded towards other people; being suspicious of their friends and acquaintances in the context of work or school; hearing indistinct sounds such as hissing and buzzing; hearing distinct sounds such as footsteps and knocking; and seeing vague figures or shadows (Marshall et al., 2014).

Researchers have attempted to determine early neurodevelopmental markers associated with psychotic symptoms in adolescence. They found early neurodevelopmental problems such as autism spectrum symptoms, asphyxia during birth, lower IQ, and delayed

early motor development were specifically associated with psychotic symptoms in adolescence (Kounali et al., 2014) and emotional and behavioral problems (depressive symptoms, aggressive behavior, anxiety, sleep difficulties, attention problems, and somatic complaints) at age three and six as the earliest significant predictors of psychotic symptoms at age 10 (Kooijman et al., 2016). Additionally, researchers investigated the combination of risk factors that make a CHR-P individual more likely to convert to psychosis. Yung, Philips, Yuen, and McGorry (2004) found that combining trait risk factors (e.g., family history) with state risk factors (e.g., current mental state and deterioration in functioning) predicted a higher proportion of psychotic cases over a considerably shorter follow-up period than traditional high-risk strategies that solely use family history of illness. The North American Prodrome Longitudinal Study, a consortium of nine programs focused on studying CHR-P individuals, reported three clinical predictive variables in their sample of high-risk participants: genetic risk with functional decline, high unusual thought content scores, and low social functioning (Thompson et al., 2011).

A community sample review found that the risk factors for the presence of psychosis risk were younger age, lifetime alcohol misuse, lifetime and current drug misuse, single marital status, no current partner, lower education level, unemployment, family history of mental disorders in first-or second-degree biological relatives, and lifetime traumatic events (Schultze-Lutter et al., 2018). Multiple studies have suggested that traumatic childhood experiences are associated with the development of psychotic illness (Davis et al., 2016; Fusar-Poli et al., 2017; Schultze-Lutter et al., 2018; Thompson et al., 2009). In 30 CHR-P individuals, 97% endorsed at least one general trauma experience, 83% physical abuse, 67% emotional abuse, and 27% sexual abuse. Additionally, total trauma exposure was positively

associated with the severity of attenuated positive symptoms (i.e., in particular grandiosity; (Thompson et al., 2009).

As stated above, disruption of dopaminergic and glutamatergic neurotransmission has been proposed to be central to the pathophysiology of SCZ (Howes et al., 2015). These findings raise the question of whether it predates the onset of the disorder. It is possible to investigate neurochemical changes prior to the onset of SCZ by studying CHR-P. Researchers conducted a meta-analysis of in vivo imaging studies on CHR-P to investigate this question and found no differences between controls and CHR-P (McCutcheon et al., 2021) . However, other studies found striatal dopaminergic (Egerton et al., 2013) and prefrontal glutamate hyperactivity (Bossong et al., 2019; Merritt et al., 2016; Provenzano et al., 2020) in CHR-P individuals compared to controls. These differences may be due to different samples of CHR-P that transition and those that do not.

Variability occurs in transition rates to psychosis. A meta-analysis found that the median transition rate to psychosis was 20% in two years (Salazar de Pablo et al., 2021), but individual studies have reported transition rates of 11–41% (Fusar-Poli et al., 2012; Klosterkotter et al., 2001; McGorry et al., 2002; Salazar de Pablo et al., 2021; Thompson et al., 2011; Wood et al., 2004; Yung et al., 2004). More information is needed to aid in the prediction to psychosis.

Perceptual and Visual Abnormalities in Clinical High Risk for Psychosis

To improve characterization of CHR-P and the predictive power of psychosis, researchers have begun to recognize neurobiological and physiological markers associated with the pathophysiology of SCZ. Self-reported perceptual abnormalities are included in the

CHR-P criteria, which has signified high and impending risk for psychosis. Examples include seeing shadows or vague figures out of the corner of one's eye or mis-seeing things. These perceptual abnormalities can be present at a subthreshold level (i.e., insight is maintained or the quality of the symptom is such that it is not a hallucination) or can be a full hallucination that does not occur at sufficient frequency or intensity to be considered psychosis (O' Connor et al., 2019). Perceptual abnormalities are one of the most prevalent attenuated symptoms in the CHR-P population (Cannon et al., 2008; Ruhrmann et al., 2010). Researchers found that in CHR-P individuals, the presence of a depressive disorder at baseline was associated with increased likelihood of experiencing perceptual abnormalities, particularly visual perceptual abnormalities (O' Connor et al., 2019).

Many patients have reported anomalous perceptual experiences, including abnormal intensity of environmental stimuli, feelings of being flooded and inundated, and the inability to focus attention on relevant details (Phillipson & Harris, 1985). Studies have shown that these visual symptoms are especially pronounced in the initial stage of illness before the evolution of the chronic state of SCZ (Klosterkotter et al., 2001; Parnas et al., 2001). Additionally, visual processing impairments had the highest predictive validity among all BS for conversion to a psychotic disorder (Klosterkotter et al., 2001).

Visual deficits in CHR-P have also been shown using a visuospatial task, the visual form perception of the Rorschach Comprehensive System (Kimhy et al., 2007), eye gesture tracking (Gupta et al., 2021; Millman et al., 2014), and visual oddball tasks (Cohen et al., 2006; Hamilton et al., 2019; Lee et al., 2010; Oribe et al., 2013; van der Stelt et al., 2006). Regarding the visual oddball tasks, researchers have found that compared to healthy controls, those at CHR-P show a reduced p300 amplitude (Hamilton et al., 2019; Lee et al., 2010;

Oribe et al., 2013). P300 amplitude is thought to reflect controlled attentional resource allocation, contextual updating of working memory, and stimulus salience processing (Hamilton et al., 2020; Hamilton et al., 2019). This reduction is also apparent in first episode and chronic SCZ (Bramon et al., 2004). P300 reduction has been shown to be negatively correlated with negative symptoms (Lee et al., 2010). Hamilton et al. (2019) found that both P300a (elicited by infrequent non target novel stimuli) and P300b (elicited by infrequent target stimuli) were reduced in CHR-P and those with SCZ compared to controls. Furthermore, P300b reduction was greater in 15 of the CHR-P who later converted to SCZ, compared to those who did not convert. They did not find this association in P300a in the subsample that converted. Additionally, a Cox regression demonstrated that more imminent risk for psychosis onset was predicted by greater deficits in target P300b amplitude (Hamilton et al., 2019). Oribe et al. (2013) also found a reduction in P300 with their sample of CHR-P and FEP and additionally found an intact N100 in CHR-P but reduced N100 in FEP. They suggest that this is indicative that visual processing is affected before the FEP but becomes more abnormal after the episode. Regarding perceptual organization, one study found no difference in perceptual organization abilities across CHR-P, FEP, and healthy controls. They only found deficits in chronic SCZ (Silverstein et al., 2006). Whereas, another study found increased perceptual organization in FEP compared to a control group but reduced functioning in chronic SCZ (Parnas et al., 2001).

Certain visual processes are enhanced in CHR-P individuals. A number of studies have conveyed that individuals with SCZ have impaired face recognition and processing (Bortolon et al., 2015; McCleery et al., 2015). However, Silverstein et al. (2021) found that the CHR-P group reported perceiving a greater number of faces in a task that measures facial

perception in two-tone form (i.e., threshold or black-and-white images). Additionally, male CHR-P individuals' greater number of reported faces were related to increased perceptual abnormalities (Silverstein et al., 2021). The authors suggested that heightened perceptual sensitivity may characterize individuals at CHR-P. However, this finding is inconsistent with other studies that demonstrated impaired facial affect recognition and facial perception and reduced N170 (i.e., a component known for the structural encoding of a face) amplitude in those with CHR-P (Addington, Penn, et al., 2008; Amminger et al., 2012; Osborne et al., 2022; Wolwer et al., 2012).

Several researchers have suggested susceptibility to backward masking to be a trait marker of SCZ These researchers investigated backward masking in college students prone to psychosis and found that they had significantly fewer correct identifications of target stimuli than controls subjects (Balogh & Merritt, 1985). Perez et al. (2012) furthered their research by investigating visual masking in those who met criteria for CHR-P, FEP, and healthy controls. They used stimuli in the visual-masking task to stimulate the P and M pathways with an HSF and LSF mask, respectively. The masking paradigms required participants to locate (i.e., via M transient pathways) versus identify (i.e., via P sustained pathways) target stimuli, activating cortical components (Cadenhead et al., 1998; Green et al., 1994; Slaghuis & Curran, 1999). Patients with psychosis have visual-masking deficits when required to locate target stimuli, suggesting dysfunction in the M pathway and dorsal stream (Cadenhead et al., 1998; Green et al., 1994). The researchers found that both FEP and CHR-P had similar backward-masking deficits in both location and identification tasks, which is indicative of dysfunction in both streams. They proposed that CHR-P individuals with the severest impairments in the identification tasks were more likely to convert to psychosis and more

indicative of future negative symptoms (but not at baseline; (Perez et al., 2012). In regard to forward masking, only FEP showed forward-masking deficits in the identification task (i.e., P stream), whereas CHR-P showed enhanced performance on the forward mask location task (i.e., M stream). These results demonstrate abnormalities in the two visual streams for the CHR-P group for backward masking but not for forward masking.

Contrast Sensitivity in Clinical High Risk for Psychosis

To our knowledge, the only study examining CS in CHR-P found increased CS in this group compared to healthy controls (Keri & Benedek, 2007). In 2007, Kéri and Benedek examined CS using a psychophysical paradigm of pulsed and steady pedestal paradigms and a structured interview measure of perceptual anomalies (SIAPA) in 16 CHR-P individuals compared to 20 healthy controls. They found that CHR-P participants showed elevated CS in the steady-pedestal paradigm that targets the transient pathway (i.e., respond to small luminance changes, coarse resolution of objects, and fast stimulus exposure and offset) compared to healthy controls. CHR-P showed no differences in CS in the pulsed-pedestal paradigm that targets the sustained pathway (i.e., responds to static stimuli with fine details of objects and colors) compared to healthy controls. The visual SIAPA scores were positively correlated with CS in the transient condition. The authors suggested that the high-risk state is associated with hyper-reactive transient pathways, which may be responsible for certain anomalous visual perceptual experiences (Keri & Benedek, 2007).

Studies have consistently shown that a longer duration of psychotic illness prior to the initiation of antipsychotic medication is associated with poorer treatment response and clinical outcomes (Hegelstad et al., 2012; Marshall et al., 2005; Norman & Malla, 2001;

Woods et al., 2001). To improve identification of the CHR-P state and detect who will transition to psychosis, this effort has the potential to shorten the DUP for those in crisis. Additionally, identifying individuals before the prodrome may create further opportunities for intervention to improve the course of illness or prevent illness onset (Joa et al., 2015). Given that visual perceptual abnormalities are prominent in CHR-P, and examining CS uses a brief noninvasive method to understand the pathophysiology of the brain, the goal of the present study was to identify the feasibility in testing this population and replicate and expand upon the work of Kéri and Benedek (2007). This current study is investigating CS in individuals with CHR-P compared to healthy controls as well as exploring the relationship between CS and self-reported visual abnormalities in CHR-P.

Rationale

Psychophysical CS measures may be of value in demonstrating the potential for visual neural measures to yield a biomarker for psychosis and in determining if visual deficits, may, in part, underlie psychosis development (Zemon et al., 2021). Visual impairments are important because they can be found in a majority of CHR-P and psychosis cases, they predict future illness onset, and they can serve as an endophenotype, trait or episode markers, depending on the type of anomaly (Hayes et al., 2019; Silverstein, 2016). Examining these visual distortions also provides further insight into how those with SCZ perceive the world and how their perception differs from unaffected individuals. Additionally, identifying which visual impairments may be reliable indicators of clinical state could prove useful in predicting (and possibly preventing) relapse and in monitoring treatment response. Empirical evidence using psychophysical CS methods consistently

demonstrates contrast processing deficits among individuals with SCZ compared to healthy controls (Silverstein, 2016). The current study builds upon previous psychophysical CS work in healthy controls and SCZ (Calderone et al., 2013; Zemon et al., 2021) (manuscript, in preparation). As stated above, medication and illness duration effects have been shown to affect CS. Investigating CHR-P affords an opportunity to study the pathophysiology of psychosis in a developmental context with minimal medication and illness duration effects and determine if visual processing deficits may underlie behavioral characteristics (symptoms) of psychosis. The current study builds upon the only CS in CHR-P study (Keri & Benedek, 2007) by using a psychophysical CS task that has been extensively refined in our lab and used to study various psychiatric and medical conditions, including SCZ.

Innovation

The goal of the current study was to further the understanding of visual neural function in psychosis. This was achieved by measuring CS using a refined psychophysical task that has been recently validated for delivery on an iPad Pro (manuscript, *in preparation*). This is the first study to utilize this technique on an iPad Pro within a clinical population and thus this current study was also a feasibility study. This psychophysical assessment of contrast processing will provide a basis for investigating this method as a potential classification tool for those that at risk for psychosis and who may convert to psychosis. There are major findings that biological measures outperform clinical tools in diagnostic ability. The Bipolar-Schizophrenia Network on intermediate Phenotypes (B-SNI), a NIH-funded consortium of researchers, investigates biological measures in individuals with SCZ, schizoaffective disorder, and bipolar disorder with psychosis (Pearlson et al., 2016). Their findings demonstrated that clinical measures poorly discriminate these diagnoses, while

biological measures (i.e., evoked potentials, structural MRI, fMRI, cognition, and eye movements) strongly distinguish patients from controls and moderately distinguish among the three clinical diagnoses (Pearlson et al., 2016). Additionally, a review of predictive models and a meta-analysis of those with CHR-P demonstrated that the best positive predictive value for those that converted to SCZ was achieved by using a combination of clinical and biological methods such as EEG and MRI (Schmidt et al., 2017).

Furthermore, the current study explores the relationship between contrast processing, psychotic-like symptoms, and perceptual anomalies. This is the first study to utilize the validated Audio-Visual Abnormalities Questionnaire (AVAQ) (Nikitova et al., 2019) in a clinical sample. While this self-report measure, the AVAQ, was created and intended as a measure of auditory and visual sensory dysfunction in SCZ spectrum disorders, it has only been validated in a group of healthy controls thus far. Overall, the proposed study will determine if collecting CS on the CHR-P population is feasible, advance our understanding of visual processing deficits in SCZ and CHR-P, and add to the literature on the relationship between early visual processing, reported visual abnormalities and symptoms in these populations. Further investigation of these relationships will inform novel approaches to the treatment of psychosis or preventative measures of psychosis from CHR-P.

Aims and Hypotheses

Aim 1: Compare contrast sensitivity functions under short (33 ms) and long (500 ms) temporal conditions for individuals at clinical high risk for psychosis (CHR-P) versus healthy controls.

Hypothesis 1a: CHR-P participants will exhibit increased contrast sensitivity compared to healthy controls in the short-temporal condition (33 ms), designed to

emphasize the transient channel/magnocellular pathway. This finding would support the only contrast sensitivity study in CHR-P showing enhanced contrast sensitivity at low spatial frequencies (Keri & Benedek, 2007). Previous findings demonstrate decreased contrast sensitivity in those on antipsychotics and there are differences between those on typical antipsychotics vs atypical antipsychotics (Chen et al., 2003). Research has shown enhanced contrast sensitivity in first episode psychotic participants who were also unmedicated. (Keri et al., 2000; Kiss et al., 2010). Thus, we see a possible effect of illness duration and medication on contrast sensitivity.

Hypothesis 1b: There will be no significant difference in contrast sensitivity between CHR-P participants and healthy controls in the long-temporal condition (500 ms), designed to emphasize the sustained channel/parvocellular pathway. This finding would support the only contrast sensitivity study in CHR-P showing no difference in contrast sensitivity at medium spatial frequencies compared to healthy controls (Keri & Benedek, 2007).

For a basis of comparison, we utilized CS data from age-matched schizophrenia patients that were collected in a previous study with a similar but not identical paradigm and spatial frequencies (Zemon et al., 2021) to visually compare to the two groups' CSFs collected here. The CS data from the iPad Pro have been compared to data collected using this similar paradigm in a recent study which demonstrated good agreement between the two datasets (manuscript, in preparation). It is expected that the schizophrenia CS data will be reduced at all spatial frequencies compared to the CHR-P and control groups in this current study.

Aim 2: Explore relationships between contrast sensitivity, self-reported perceptual anomalies, and clinical symptoms in CHR-P individuals.

Hypothesis 2a: There will be a positive correlation between low spatial frequency (0.41 and 1.6 cyc/deg) contrast sensitivity measures under the 33 ms temporal condition and the perceptual abnormalities measure (AVAQ). This finding would support the only contrast sensitivity study in CHR-P showing a positive correlation between contrast sensitivity and perceptual anomalies, albeit measured with a different instrument (Keri & Benedek, 2007).

Hypothesis 2b: There will be no correlation between contrast sensitivity measures and clinical symptoms. No one has investigated the relationship between contrast sensitivity and clinical symptoms in CHR-P. However, using a visual backward masking task, Perez et al. (2012) found no correlation between identification or location performance and symptoms, but they did find that worsening performance on identification tasks predicted future negative symptoms (Perez et al., 2012). It is hypothesized here that there will not be a difference between contrast sensitivity and SIPS categories due to their symptoms being subthreshold psychotic symptoms.

CHAPTER II: METHODS

Participants

Clinical High Risk for Psychosis

Twelve participants, who were already diagnosed with CHR-P status, were recruited from Icahn School of Medicine's Psychosis Risk Program and Research Studies. Diagnosis for CHR-P status was obtained from a past Structured Interview for Psychosis Risk Syndrome (SIPS) on record. Eligibility included: English speaking, the ages 12-35 years, met criteria for psychosis risk syndrome on the Structured Interview for Psychosis Risk Syndromes, and must have normal or corrected-to-normal visual acuity. This study was approved by the Icahn School of Medicine Mount Sinai Review Board.

Healthy Controls

Deidentified CS data from age and gender-matched healthy controls were obtained from a study conducted at Hunter College, which used identical CS methods to the proposed study (manuscript, *in preparation*). Participants were recruited from outreach at Hunter College and friends and family of Hunter college students. Participants were also recruited at Icahn School of Medicine Mount Sinai for additional age- and gender-matched healthy controls. The sample consisted of 14 healthy participants. Criteria for healthy control

participants were as follows: English speaking, ages 16-35 years, no current or past history of DSM-5 disorders, and normal or corrected-to-normal visual acuity. This study was approved by the Hunter College Institutional Review Board and the Icahn School of Medicine Mount Sinai Review Board.

Schizophrenia

Eleven deidentified CS data from individuals with SCZ were obtained from a previous study in our laboratory, collected using a research system, and for purposes of comparison were age-matched to our CHR-P group and healthy control group (Zemon et al., 2021). These patients were recruited from the Nathan Kline Institute for Psychiatric Research CREF in Orangeburg, NY, and the County of Rockland Department of Mental Health. Diagnoses were obtained using the Structured Clinical Interview for DSM-IV (SCID) and available clinical information. Participants were excluded if they had any neurological or ophthalmological disorders that might affect performance or met the criteria for alcohol or substance dependence within the last six months or abuse within the last month. All participants had normal or corrected-to-normal visual acuity of 20/30 or better on the Logarithmic Visual Acuity Chart (Precision Vision, La Salle, IL). This study was approved by the Nathan Kline Institute Review Board and all participants provided informed consent.

Measures and Procedures

Psychophysical contrast sensitivity task

The stimuli (grating patterns) were presented in an appearance/disappearance mode from a uniform luminance screen of equal space-average luminance to the pattern on an iPad

Pro (frame rate = 60 frames/s) in two separate tests under two temporal conditions (33.33 [2 frames] and 500.00 ms temporal condition) in random order on the left or right side of the screen (see Figure 1). The fixation mark was centered on the screen. Participants sat at a viewing distance of 114 cm and the full display (mean luminance = 100 nits) had a visual angle of 9.84 x 9.84 degrees (2048 x 2048 pixels). SF refers to the number of cycles (pairs of light and dark bars) in one degree of visual angle (cycles/degree, cyc/deg). Horizontal sinusoidal gratings were presented to obtain CSFs at SFs of 0.406, 1.626, 3.251, 6.502, and 13.005 cyc/deg.

Using a two-alternative spatial forced-choice paradigm, the participants indicated to the experimenter which side of the screen the grating stimulus appeared by raising their right or left hand. The experimenter recorded the response by pressing buttons on the keypad. An up-down staircase procedure was used to track the 70.7% correct point on the psychometric function (Levitt, 1971; Wetherill & Levitt, 1965; Zwislocki & Relkin, 2001). Staircases for each SF tested were interleaved randomly. The contrast was set initially at 50% for each grating pattern and then changed up or down in 6 decibel (dB) steps (0.3 log units) based on the correctness or incorrectness of the response until two incorrect responses were recorded for the presenting pattern. Afterward, an up-down transformed response rule was applied with 3 dB steps (0.15 log units) such that the contrast was decreased following two consecutive correct responses while the contrast was increased following one incorrect response. This step size appears to be near optimal for efficiency and reliability based on previous work and earlier studies (Tom N. Cornsweet, 1962; Kelly & Savoie, 1973; Zemon et al., 2021); (manuscript, *in preparation*). The staircase procedure for each SF condition terminated after 10 reversals in contrast and the median $\log_{10}$ contrast of the last six reversals

(three peaks and three troughs) was determined to yield an estimate of contrast threshold. The algorithm was set to have an absolute minimum contrast of 0.2%, and the contrast was maintained at that value regardless of whether more than one correct response was obtained until an error was recorded. This technique on an iPad Pro was validated against an established research system (*manuscript, in preparation*). The data from the SCZ group collected with the research system were obtained using a similar psychophysical paradigm and similar stimulus conditions to that on the iPad Pro, but the SF tested were not identical on the two systems, especially for the highest SF condition (13 cyc/deg on the iPad Pro vs. 21 cyc/deg on the research system). The SCZ group was tested under the following five SF conditions: 0.5, 1, 4, 7, 21 cyc/deg.

All participants were tested on two separate conditions in which the gratings appeared for either a short temporal condition (33 ms) or a long temporal condition (500 ms). Short-temporal condition presentations of LSF patterns and long-temporal condition presentations of moderate to HSF patterns are thought to bias processing toward the *transient* and *sustained* psychophysical mechanisms, respectively (Legge, 1978; Zemon et al., 2021).

Symptom Severity

The Structured Interview for Psychosis-Risk Syndromes (SIPS) was administered to the CHR-P group to characterize psychotic-like symptoms. The SIPS aims to identify symptoms of the SCZ prodrome (the phase before the onset of threshold psychosis), which resemble those of SCZ but are often milder. The SIPS demonstrates strong psychometric properties, including good internal consistency, test-retest reliability, and validity (McGlashan, 2001; Woods et al., 2009). The SIPS is a 19-item instrument that uses a 7-point

severity scale to assess positive, negative, disorganization, and general prodromal symptoms (ranging from 0-absent to 6-severe and psychotic). There are five positive (total score up to 30), six negative (total score up to 36), four disorganization (total score up to 24), and four general symptoms (total score up to 24) items.

In the SCZ group, the Positive and Negative Syndrome Scale (PANSS), a medical scale used for measuring symptom severity of individuals with schizophrenia, was administered. The PANSS is a 30-item scale that combines the 18-item Brief Psychotic Rating Scale and 12 items from the Psychopathology Rating Schedule (Kay et al., 1987). The PANSS demonstrates strong psychometric properties, including good internal consistency, test-retest reliability, and validity (Kay et al., 1988). Ratings are summed scores on a 1-7-point scale for the following subscales: seven positive (total score= 49), seven negative (total score = 49), and 16 general psychopathology symptoms (total score = 112).

The Audio-Visual Abnormalities Questionnaire (AVAQ) was administered to the CHR-P group to characterize self-reported visual and auditory perception anomalies. The 85-item AVAQ was validated in an online sample of 355 healthy participants to establish the instrument's factorial structure, internal consistency, and reliability (Nikitova et al., 2019). The questionnaire uses a 4-point severity scale (*never*, *sometimes*, *often*, *nearly always*) and has three subscales: Visual, Audio-Visual, and Auditory Processing. The range of total scores is between 0-255. The AVAQ demonstrates strong psychometric properties, including good internal consistency for the total score ($\alpha = .99$) as well as its visual, auditory, and audio-visual subscales ($\alpha = .98, .96, .83$, respectively). Additionally, the AVAQ was positively correlated with the Schizotypal Personality Questionnaire ($r = .69$, $p < .001$) as well as the Autism-Spectrum Questionnaire ($r = .38$, $p < .001$). The questionnaire was intended to

characterize sensory dysfunction in the schizophrenia spectrum disorders and the current study is the first to use it in a psychotic-like sample.

Data Analysis

Power Analysis

G*power 3.1 (Faul et al., 2009) was used for *a priori* power analyses. In order to test the primary aim, based on a study by Kéri and Benedek (2007), which states that logCS will be elevated in CHR-P compared to controls under the short-temporal condition over all SFs, but not under the long-temporal condition. A large effect size ($d = 0.8$) for the short-temporal condition was utilized based on Kéri and Benedek's result (Cohen, 1988). The mean difference between two groups was utilized and a total proposed sample size of 42 in a balanced design (controls and CHR-P) is required to yield 80% power at the .05 level of significance to detect the hypothesized effect. Unfortunately, due to COVID-19 pandemic and the rare disease population, the current study was only able to recruit 12 CHR-P participants. This project is therefore properly considered a feasibility and acceptability study and it will be addressed in the Limitations section of Discussion.

Psychophysical contrast sensitivity

Contrast thresholds obtained from the psychophysical task were converted to CS by taking the reciprocal of the contrast threshold. Greater CS indicated better performance. CS was converted to $\log_{10}$CS (logCS) because discrimination thresholds for contrast are scaled approximately logarithmically and it is common practice (Abramov et al., 2012; T. N.

Cornsweet, 1962; Kelly, 1977; Kelly & Savoie, 1973; Patel, 1966). All analyses were performed using logCS.

Model fits to psychophysical data

A *difference of Gaussian* model, based on receptive field profiles of retinal ganglion cells (Enroth-Cugell & Robson, 1966; Rodieck, 1965) was applied to fit the logCS data as a function of SF (Kelly, 1977; Patel, 1966) (*manuscript, in preparation)*. Gaussian model fits enabled the ability to interpolate logCS values between collected data points across SFs. The mean of the distribution for this model was always set to zero. The four parameters that the study utilized were the standard deviations and strengths for the excitatory (center-mechanism) and inhibitory (surround-mechanism) functions. The standard deviation determines the width of the curve. When the standard deviation is large, the curve is wide/broad; when the standard deviation is small the curve is narrow. The strength parameter determines the height of the curve and the area under it.

Descriptive statistics

Preliminary analyses included an examination of participant demographics and all visual and clinical variables using univariate descriptive statistics and frequency distributions to inspect the data. Box plots were applied to visually investigate parametric and group differences. Correlation coefficients and scatterplots were used to examine bivariate associations between psychophysical measures, self-report measures of perceptual disturbances, and clinical variables in the psychotic and psychotic-like samples.

Linear mixed-effects modeling

Linear mixed-effects modeling (LMM) was used to examine group differences in logCS. Models were applied to the data using maximum-likelihood estimation with a variance components covariance matrix structure. Initially, a null model with a random intercept for participant was run to compute the intraclass correlation coefficient (ICC) to determine the level of correlation within individuals' data, and therefore, the necessity for using LMM. This primary analysis included only individuals tested on the iPad system, and therefore, only the CHR-P group and the control group tested on that system. Subsequently, fixed effects were added to account for group (CHR-P and controls), SF, temporal condition, and all possible interaction terms. Age was explored as a covariate based on its effect on CSFs (Abramov et al., 2012; Owsley et al., 1983) . Acuity was not included in the LMM because of its association with the HSF limb of the CSF (Jindra & Zemon, 1989; Riggs, 1965; Zemon et al., 2021). Main effects and all possible interaction terms were added hierarchically to build a full model.

CHAPTER III: RESULTS

Group Demographics

Table 1 displays the demographics and clinical characteristics of the sample. Controls and the CHR-P participants were matched in age and sex (16-33 and 15-32 years of age, respectively; individuals in the comparison SCZ group (18-34 years of age) were only matched on age given they were all males. Additionally, only individuals with SCZ who were not on typical antipsychotics were included in the SCZ group as typical antipsychotics have been shown to affect CS (Fernandes et al., 2019). In the CHR-P group, only one participant was on an antipsychotic medication. The SCZ group's median total score on the PANSS indicates a moderately ill Clinical Global Impressions classification (Leucht et al., 2005). The CHR-P sample's SIPS scores are similar to a larger CHR-P sample (n = 68) in a study conducted by Osborne and Mittal (2019), which supports the good reliability of the SIPS and the representativeness of the current sample (Osborne & Mittal, 2019).

All participants who enrolled into the study completed it. There were no issues using the iPad Pro. While participants participated despite not being paid, they did comment on their boredom throughout the task, which took 30 minutes to complete. It took on average 10 minutes to complete the Audio-Visual Abnormalities Questionnaire. There were no adverse effects or protocol deviations.

Contrast Sensitivity

Box plots of logCS vs. SF are depicted in Figures 2 and 3. Corresponding median values and semi-interquartile ranges are reported in Table 2. CS depends on the stimulus temporal condition, as reported previously for a range of temporal conditions (Kelly, 1977; Legge, 1978; Zemon et al., 2021), and so data are shown for both the short (33 ms) and long (500 ms) temporal conditions. Data for the SCZ group are displayed only for the four lower SFs that are similar to those tested on the iPad Pro for the primary groups under investigation as a basis of comparison (Figure 3). Note that the value labels for SF correspond to the actual SFs tested on the iPad Pro system with the CHR-P and control groups.

In the 33-ms condition, all groups exhibit nearly a lowpass function (in this dataset, a reduction after 1.6 cyc/deg), with the SCZ group decreasing more rapidly with increases in SF. (Note again that no data are displayed for the SCZ group at the highest SF condition because the SCZ data collected previously differed considerably from the current study's data in SF for the highest value condition, 21 vs. 13 cyc/deg). In the 500-ms condition, however, we see an inverted U-shape/bandpass function with a peak at 3.25 cyc/deg, which is consistent with the literature (lowpass function and bandpass functions are defined in the Introduction). With the exception of the lowest SF condition for the SCZ group, median logCS values are greater under the 500- as compared to the 33-ms condition. CSs under the 33-ms condition exhibit the highest values at 0.41–1.6 cyc/deg, and CSs under the 500-ms condition exhibit the highest values at 3.25 cyc/deg. Under the 33-ms condition, the difference in median logCS between the peak value at 1.6 cyc/deg and that obtained at 0.41 cyc/deg is greatest for the CHR-P group (0.3 log units, a doubling in CS), whereas under the

500-ms condition, the difference in median logCS between the peak at 3.25 cyc/deg and that at 0.41 cyc/deg is similar for all groups at about 0.4 log units.

Interestingly, the CHR-P group under the 33-ms condition shows the clearest bandpass function for this temporal condition (even though this condition typically yields a lowpass function) and this group has the highest logCS at 1.6 cyc/deg compared to the other two groups; the highest logCS for the SCZ group is at the lowest SF. This enhanced logCS at a LSF under the 33-ms temporal condition is consistent with Kéri and Bendek's 2007 finding of enhanced logCS at LSFs for this population. Under the 500-ms condition, the CHR-P group has a peak at 3.25 cyc/deg, but the peak for controls at 3.25 cyc/deg is more robust and logCS does not fall as rapidly with increases in SF for controls as it does for the other two groups. After the lowest SF, those with SCZ show the most reduced logCS of all the groups.

Duration of stimulus is known to affect CS by increasing it. An exception to this is that CS does not increase at low SFs beyond a duration of 100 ms (Legge, 1978). When comparing the 33-ms temporal condition versus the 500-ms temporal condition, it appears as if the controls are benefiting more from the longer duration of the stimulus, especially in the middle SFs compared to those in the CHR-P group as the controls' logCS is practically doubled from 2.1 to 2.4 log units. Likewise, the SCZ group is also benefiting more from the longer duration. At 13 cyc/deg while the control group and CHR-P individuals are about equal again, when comparing the 3-3 vs 500-ms conditions there is a factor of four enhancement for both groups. Thus, we only see the larger difference in enhancement in the middle SFs for the control and SCZ groups.

Parameter values for each model fit are in Table 3. Graphs of each excitatory, inhibitory, and sum (actually *difference*, *excitatory - inhibitory*) models are in Figures 4 and

5. As can be seen for the sum model in Figure 4, in all groups, what dominates the model function is the excitatory input as the inhibitory input is weak and falling off even before 1.6 cyc/deg. When examining these responses by group (Figure 5), they appear similar, however, the excitatory input for controls is a bit stronger than for the CHR-P and SCZ groups overall. The largest difference observed is with regard to the inhibitory mechanisms and between temporal conditions. For the control group, the difference of inhibition between 33 vs. 500 ms temporal conditions is stronger than for the CHR-P and SCZ groups (*SD* difference = 0.7 cyc/deg; strength difference = 1.19).

Linear mixed-effects modeling (LMM) was used to examine group differences in logCS given repeated measures over SFs and temporal condition and within-individual correlated data. The null model yielded an ICC = .05, indicating correlated data within individuals and the need for LMM. In the full model, including group (CHR-P and control), SF, temporal condition, and all interaction terms with age as a covariate, age was not significant and was excluded from the final model $F(1,26) = 1.530$, $p = .227$. The fixed effects in the final model were as follows: group, $F(1,26) = 1.359$, $p = .254$; SF, ($F(4,234) = 146.101$, $p < .001$); temporal condition, $F(1,234) = 101.455$, $p < .001$; Spatial Frequency x Temporal Condition, $F(4,234) = 7.987$, $p < .001$; Group x Spatial Frequency, $F(4,234) = 0.705$, $p = .589$; Group x Temporal Condition, $F(1,234) = 5.008$, $p = .026$; and Group x Spatial Frequency x Temporal Condition, $F(4,234) = 0.959$, $p = .431$. Interestingly, the interaction between group and temporal condition was significant which demonstrates that there is a differential effect between groups with respect to logCS for different temporal conditions.

Correlational Analysis

Zeroth-order bivariate correlations were computed for the CHR-P group for logCS with SIPS scores and AVAQ scores, split by temporal condition (Tables 4 and 5). One CHR-P individual had to be excluded from analyses with the AVAQ due to being an outlier. Under the long temporal condition (500 ms), logCS to the lowest SF (0.41 cyc/deg) was positively and moderately correlated with the AVAQ total and AVAQ visual processing subscale scores (Table 5). Whereas logCS to the middle SF (6.5 cyc/deg) was negatively and moderately correlated with the AVAQ total and AVAQ visual processing subscale. For corresponding scatterplots of these bivariate relations see Figure 6. These results indicate that higher logCS to LSF is associated with higher self-reported perceptual disturbances, especially visual disturbances. Whereas lower logCS to HSF is associated with higher self-reported perceptual disturbances, especially visual disturbances. Additionally, logCS at 1.6 cyc/deg was negatively correlated with the SIPS total score, indicating lower logCS is associated with more SIPS symptoms at this SF (see Figure 7).

CHAPTER IV: DISCUSSION

Empirical evidence using psychophysical CS methods consistently demonstrates contrast processing deficits among individuals with SCZ compared to healthy controls (Cadenhead et al., 2013; Calderone et al., 2013; Keri, Antal, et al., 2002; Silverstein, 2016; Skottun & Skoyles, 2007; Slaghuis, 1998). The current study builds upon previous psychophysical CS work in healthy controls and SCZ (Calderone et al., 2013; Zemon et al., 2021) (manuscript, in preparation). As stated in the Introduction, medication and illness duration effects have been shown to affect CS leading to conflicting results. Investigating CHR-P affords an opportunity to study the pathophysiology of psychosis in a developmental context with minimal medication and illness duration effects and determine if visual processing deficits may underlie behavioral characteristics (symptoms) of SCZ. This study builds upon the one CS in CHR-P study (Keri & Benedek, 2007) by investigating the transient/M and sustained/P visual pathways in this clinical population using a CS task programmed on an iPad Pro. In addition, the current study explored the relationships between CS and visual anomalies as measured by the AVAQ. CS results were compared to those from a previous study that analyzed logCS in aged-matched individuals with SCZ (Zemon et al., 2021). This is only the second known study to examine contrast processing in CHR-P and the first study to use the self-reported perceptual anomalies questionnaire (AVAQ) (Nikitova et al., 2019), which was intended to characterize perceptual abnormalities in those with SCZ. Group differences between the three groups were visually inspected using box plots and the

difference of Gaussian model. Additionally, group differences in logCS between CHR-P and healthy controls were analyzed using linear mixed effects modeling. Lastly, bivariate correlational analyses were utilized in order to investigate associations between logCS, perceptual abnormalities, and psychotic-like symptoms from the SIPS in the CHR-P group.

Interpretation

Aim 1: Compare contrast sensitivity functions under short (33 ms) and long (500 ms) temporal conditions for individuals at clinical high risk for psychosis (CHR-P) versus healthy controls to investigate the transient/magnocellular and sustained/parvocellular pathways.

This is the first study to utilize these psychophysical techniques on an iPad Pro with a clinical sample. In the current study, we were able to replicate the lowpass and bandpass characteristics of the CSF functions in psychophysical literature obtained from healthy observers with transient and sustained pathway paradigms, respectively (Burbeck & Kelly, 1980; Kelly, 1977; Legge, 1978). See Figures 2 and 3 for box plots. Specifically, in the short temporal condition (33 ms), a peak around 1 cyc/deg was observed, followed by CS declining rapidly as SF increases. In the long temporal condition (500 ms), a bandpass function was obtained with a peak at 3.25 cyc/deg. This demonstrates replication of psychophysical findings without the requirement of complex, research equipment. These basic characteristics of the CSFs under short- and long-duration conditions were also found for the CHR-P group.

The only CS CHR-P study published found enhanced logCS for all five SFs tested (0.25, 0.5, 1, 2 and 4 cyc/deg) under the steady-pedestal paradigm (biasing the

transient/magnocellular pathway). On the other hand, they found no differences compared to healthy controls with the pulsed-pedestal paradigm (biasing the sustained/parvocellular pathway). When examining the median logCS values in Figure 3 and Table 2, a slight enhancement of logCS is observed for the CHR-P group compared to controls and SCZ at 1.6 cyc/deg under the short temporal condition. This is in partial support of Hypothesis 1a which posits enhanced logCS under the LSFs in the short temporal condition for the CHR-P group. This may be due to a deficit in lateral inhibition which will be explained later. Under the 500-ms temporal condition, the control group yielded elevated logCS at 6.5 cyc/deg compared to the CHR-P group which the opposite of what we hypothesized in Hypothesis 1b.

There are a few explanations that could account for the differences between the current results and those of Kéri and Benedek (2007). One possible explanation is the use of a different CS psychophysical paradigm. There are several differences in the paradigms of the two studies that might be critical for conflicting results. In their steady-pedestal paradigm condition, in order to bias the response to magnocellular pathway activity, Kéri and Benedek (2007) used a target Gabor patch of 2.5 deg extent presented for 45 ms in the center of a luminance pedestal decrement (7.6 deg square) continuously present, surrounded by a larger adapting field (12 deg square) of about twice the luminance of the pedestal. In the pulsed-pedestal paradigm designed to bias the response to parvocellular activity, the pedestal decrement was presented only during the 45 ms test period, together with the target Gabor patch for the same duration. Apparently, the Gabor patch had a space-average luminance above that of the pedestal field which varied depending on the contrast of the pattern within the Gaussian envelope. This confounded simple luminance change with contrast change, and therefore there were brief luminance flashes of 45 ms (albeit relatively small changes at low

contrasts) even in the steady-pedestal condition. Furthermore, the limited extent of the Gabor patch (2.5 deg) prevented a proper representation of a grating pattern within its enveloping function when the center SF was low (e.g., 0.25, 0.5, 1 cyc/deg). For example, a 0.25 cyc/deg grating requires 4 deg of visual angle to present a single cycle (two bars, one light and one dark) which is inadequate mathematically to define a grating pattern (Kelly, 1965, 1975). Thus, the actual SF content of the Gabor patch was not well specified under most of the spatial conditions tested. In fact, they did not test a HSF condition – the highest SF tested was only 4 cyc/deg, and it was presented only for 45 ms which is typical for a transient but not sustained condition. Thus, the Kéri and Benedek (2007) study does not have the same HSF fall off that is attributable to parvocellular/sustained channel pathways that is seen in the current study and in the literature and may not be tapping into the sustained mechanism (Legge, 1978). More evidence that the paradigm may have desensitized the parvocellular pathway and thus the researchers do not see any difference between groups is the low CS results that they received from the paradigm. Lastly, the task was different as the participants were asked to judge whether the Gabor patch was horizontal or vertical by pressing two different keys on the keyboard. Thus, instead of just detection of horizontal bars, their task utilized detection of different orientations. Research has shown that there is a difference in reliability with horizontal versus vertical bars (Pointer, 1996; Zemon et al., 1983).

Furthermore, the CHR-P samples in the two studies may be different due to different clinical characteristics. All high-risk participants in the current study fulfilled the criteria of Attenuated Psychotic Symptoms (APS) according to the SIPS, whereas in the Kéri and Benedek (2007) sample, half of the sample fulfilled criteria of APS and the other half met criteria for Brief Limited Intermittent Psychotic Symptoms (BLIPS) according to the

CAARMS criteria. There is a higher risk of psychosis if one meets criteria for BLIPS rather than APS at 24, 36, and 48 or more months of follow-up (Fusar-Poli, Cappucciati, et al., 2016). Furthermore, in their sample, they stated that the 16 individuals were already in the prodromal phase of psychosis. Often prodrome and CHR-P criteria are not differentiated. Studies of duration of untreated illness (DUI) and help seeking in the prodromal phase fail to differentiate between a prodromal state and the simple presence of clinical high-risk symptoms. Previous retrospective studies of the duration of untreated illness have not distinguished between prodromal states with and without CHR symptoms. Investigators that were interested in this distinction examined the occurrence of CHR symptoms and help seeking-patients retrospectively. They found that 109 patients reported a prodrome and that 58 of those people had CHR symptoms before that state (Schultze-Lutter et al., 2015). Therefore, the level of psychosis is unclear in Kéri and Benedek's (2007) paper.

Lastly, Kéri and Benedek (2007) stated that all participants received toxicological screening for psychoactive substances but did not report if any of them were on medication. Thus, it is not known if medication had any effect on their results. In the current sample, more than half were on medication (n = 7; 4 were only on one SSRI, one was on an SSRI and a psychostimulant, one was on an anticonvulsant, and the other was on a combination of SSRI, SNRI, psychostimulant, and an atypical antipsychotic). One study looked at the effect of coadministration of atypical antipsychotics and antidepressants versus just atypical antipsychotics on CS in SCZ (Sheremata & Chen, 2004). They found that the coadministration group had poorer performance on a contrast detection task compared to those just on atypical antipsychotics. These authors suggested that antidepressants interfere with the effect of antipsychotics, i.e., activation of D1 receptors which leads to poorer

performance on these types of contrast tasks (Sheremata & Chen, 2004). It is not known how solely antidepressants affect CS. However, it has been suggested that D1 receptors in the receptive field organization of large ganglion cells with dominant surrounds mediate the response to LSF, whereas the essential role of D2 receptors in smaller 'center' dominated neurons mediate the response to middle and HSF (Bodis-Wollner et al., 1993). Research has shown that the effect of SSRIs produce an increase in D1 receptor availability and a decrease in D2 receptor availability (Shuto et al., 2020; Smith et al., 2009). Taken together, this increase in D1 receptor availability which mediates the response to LSF may be the reason why we see enhanced logCS to LSF. Accordingly, this decrease in D2 receptor availability due to SSRIs which mediate the response to middle and HSFs may be why we see decreased logCS to middle SFs. One study looked at the mechanisms underlying differential D1 vs D2 dopamine receptor regulation of inhibition in the prefrontal cortex. They found that the level of dopamine has differential effects depending upon receptors and concentration of dopamine (Trantham-Davidson et al., 2004). Specifically, lower dopamine concentrations enhance inhibitory postsynaptic currents via D1 receptors, whereas higher dopamine concentrations decrease inhibitory postsynaptic currents via D2 receptors. Due to many comorbid disorders in those with CHR-P, as shown in this current study's sample, more research is needed to investigate the effect of different medications other than antipsychotics on CS.

According to the linear mixed-effects modeling, there was no overall group difference in logCS between healthy controls and those with CHR-P, collapsing over all stimulus conditions. However, when looking at specific effects there were significant differences. As expected and consistent with the literature, SF, temporal condition, and the interaction between Spatial Frequency x Temporal Condition were significant: research shows that

temporal parameters influence CSFs (Kelly & Savoie, 1973). CS to moderate and high SFs benefit more from increases in exposure duration than CS to LSFs (Breitmeyer & Ganz, 1977; Nachmias, 1967). Interestingly, the Group x Temporal Condition interaction was significant, and this indicates that the increase in CS with an increase in duration (33 vs 500) resulted in differential effects on (increases in) contrast sensitivity in the two groups. This finding shows that the role of temporal condition was more impactful than that of SF in distinguishing CHR-P individuals from controls here. As shown in Table 2, when looking at the middle SFs (3.25 and 6.5 cyc/deg), the control group and the SCZ group are benefitting more than the CHR-P group from an increase in exposure duration, even though logCS is still reduced overall SFs for the SCZ group. This is consistent with research that found both those with SCZ (regardless of symptom classification) and controls benefited from increased exposure duration, however, a significant Group x Temporal Condition interaction effect was not found (Slaghuis, 1998).

Temporal integration involves combining information over time to improve detection or discrimination. Elevation of CS with 500-ms duration vs. 33-ms duration is indicative of temporal integration over a period greater than 33 ms (Breitmeyer & Ganz, 1977), which has been observed with healthy observers in the SF range tested here. Sensitivity measurements can also benefit from probability summation (Harris & Georgeson, 1986). The significant Group x Temporal Condition interaction effect found in the current study demonstrates greater temporal integration in controls as compared to individuals at CHR-P, especially at middle SFs. In the current CHR-P group, only a small enhancement in logCS from 33 to 500 ms is seen at middle SFs. CS to these middle SFs are likely governed by ganglion cells of mid-size dendritic fields (Dacey, 1993; Dacey & Petersen, 1992) with corresponding sized

receptive fields in the foveal/parafoveal region of the retina (Croner & Kaplan, 1995). In the CHR-P group, there may be a dysfunction in the middle-sized ganglion cells with medium extent receptive fields that are expected to respond best to the middle SFs and since there is a dysfunction, there is difficulty with neural integration at these middle SFs. This may be an important finding because we view the world predominantly through this filter between coarse (LSF) and fine (HSF) information. Thus, it would be key to know if the CHR-P group had difficulty processing the world around them and what visual remediation treatments if any would be beneficial.

Results also demonstrate a differential effect of temporal condition as well within the *Gaussian models* (Figures 4 and 5; Table 3). The data were fitted with *Gaussian models* to plot a continuous curve through the five data points collected across SF and to yield parameter estimates to capture the breadth of the CSF in SF (measured by standard deviation of each Gaussian function) for both an excitatory and inhibitory mechanism and to measure the strength of each mechanism (area under the Gaussian curve). The modeling results demonstrate that the SF extent of the excitatory mechanism was similar across groups regardless of temporal condition, but the control group exhibited overall greater strength.

Parameter estimates for the inhibitory mechanism, however, revealed a differential effect of temporal condition across groups. The changes in standard deviation and strength parameters seen under the 33 to 500 ms conditions are greater for the control as compared to the CHR-P group, with increases in both parameters with increased duration. Thus, it appears as if there is a dysfunction in the surround suppression and a lack of inhibition for the CHR-P group (which is consistent with the lack of inhibition that we previously saw in LSF). Retinal ganglion cells are broadly tuned for SF because of the center-surround organization of their

receptive fields (excitatory centers and inhibitory surrounds) (Enroth-Cugell & Robson, 1966; Rodieck, 1965). A low SF grating has bars of a width that extends into the inhibitory surround of these cells generating greater inhibitory activity while the excitatory center mechanism is already maximally stimulated (Croner & Kaplan, 1995). This results in the characteristic bandpass shape of a respective CSF. A medium SF grating has bars of a width that could match the size of the center mechanism a typical ganglion cell in the foveal-parafoveal region of the retina without extending beyond that area into the inhibitory surround. A loss of function in this cell type, which is likely part of the parvocellular pathway based on receptive field size, could result in deficits in perception that depend on neural functioning in this region of SF space. Altogether, more research is needed to investigate the LSF effect of enhanced CS in the CHR-P group, as well as the differential effect of duration on CS at middle SFs and neurophysiology behind these results. In SCZ, despite their overall CS being reduced, a temporal integration benefit on CS was found. Lastly, it is unclear if medication effects of antipsychotics or antidepressants play a role.

Aim 2: Explore relationships between contrast sensitivity, self-reported perceptual anomalies, and clinical symptoms in CHR-P individuals.

This study was the first study to utilize the self-reported perceptual anomalies questionnaire, AVAQ, in a clinical setting. Kéri and Benedek (2007) found a positive correlation between their steady-pedestal paradigm (biasing the M pathway) log CS values at 0.5, 1, and 2 cyc/deg and the visual Structured Interview for Assessing Perceptual Anomalies (SIAPA) scores. When comparing logCS at each SF and temporal condition with the AVAQ total and subscale scores, the only significant associations were found for the long temporal

condition (500 ms) at the LSF (0.41 cyc/deg) and middle SF (6.5 cyc/deg) with the total and visual subscale scores. These results indicate that higher logCS to LSF (0.41 cyc/deg) is associated with higher self-reported perceptual disturbances, especially visual disturbances. The fact that an association was observed with the LSF under the long temporal condition and not the short temporal condition, is not surprising for two reasons. As is known, longer exposure times lead to increases in CS. Additionally, Zemon et al. (2021)'s study which used a similar paradigm and SFs, found with principal component analysis that logCSs to 0.5 cyc/deg grouped close to one another given short or long temporal conditions. This demonstrated that regardless of temporal condition, the transient mechanism appeared to dominate this psychophysical performance. Thus, it is possible that finding a positive correlation between logCS to LSF (0.41 cyc/deg) and AVAQ total score as well as the visual subscale score supports Kéri and Benedek's (2007) finding. Perhaps this relation is indicative of a small deficit in lateral inhibition which may result in an imbalance in excitation/inhibition with the consequence of perceptual disturbances. This is consistent with the research mentioned in the introduction of increased glutamate found in CHR-P individuals (Bossong et al., 2019; Merritt et al., 2016). This could account for the "flooding" of environmental stimuli that those with CHR-P often report. Additionally, this M/transient pathway deficit can also explain reported visual abnormalities, specifically in global motion perception, as this is what the pathway is known for (Martinez et al., 2008). Lastly, this is consistent with the finding that the CHR-P group produced weaker overall excitatory strength and loss in inhibition when duration was increased, compared to controls.

It was also found that lower logCS to the middle SF grating (6.5 cyc/deg) is associated with higher self-reported perceptual disturbances, especially visual disturbances.

This may be due to a loss of critical spatial information required for functioning in the visual world. Spatial contrast sensitivity predicts whether people are likely to have difficulty in seeing visual targets typical of everyday experience (Owsley & Sloane, 1987). Owsley and Sloane (1987) found that if a patient had decreased sensitivity at middle SFs, that patient was also likely to have a decreased ability to see faces, road signs, and commonplace objects. Additionally, research on recognition of facial identity and facial expression has revealed that adults use a critical range of middle SFs (Collin et al., 2004; Costen et al., 1994; Fiorentini et al., 1983; Gao & Maurer, 2011). This provides stronger evidence for the finding that demonstrated impaired facial affect recognition and facial perception and reduced N170 (i.e., a component known for the structural encoding of a face) amplitude in those with CHR-P (Addington, Penn, et al., 2008; Amminger et al., 2012; Osborne et al., 2022; Wolwer et al., 2012). Taken together, one could understand how having decreased logCS at middle SFs could result in difficulty viewing the world with a broad range of perceptual abnormalities. Lastly, logCS at 1.6 cyc/deg was negatively correlated with the SIPS total score, indicating lower logCS is associated with more SIPS/psychotic-like symptoms at this SF (Figure 7). LSF information has been associated with an object's overall shape and layout and if someone is having difficulty seeing shapes and layouts, they may perceive the world around them to be dangerous/threatening and thus become suspicious of others and unable to discern what is real around them (Zhu et al., 2021). Being out of touch with reality, seeing shadows, and being suspicious of others and things around you are items highlighted on the SIPS. Another explanation for these significant associations could be the effect of antidepressants on logCS as stated above.

Clinical Implications

Prevention

Schizophrenia is among the world's leading causes of disability and is associated with substantial health-related and economic costs (Murray et al., 2012; Neil et al., 2014). As stated above, in most patients, a first episode of psychosis is preceded by a prodromal period. In recent decades, this CHR construct has been characterized by subclinical psychotic symptoms and/or a genetic predisposition and, most importantly, by functional decline and social withdrawal (Yung et al., 2008; Yung et al., 2005). Because 31.5% of people at CHR-P have been found to develop first-episode psychosis within three years (Fusar-Poli et al., 2012), this allows us to apply targeted prevention of a first episode of psychosis. Prevention may help to maintain quality of life, reduce the risk of onset, and reduce the downstream costs of intensive treatment and productivity losses. Research has shown the feasibility and effectiveness of cognitive behavior therapy on reducing the risk of transition from CHR-P to psychosis by about 50% and that it was cost saving (van der Gaag et al., 2012). In a recent long-term follow-up study with CBT in this population, no transitions to psychosis took place in the first five years (Ising et al., 2017). This suggests that the risk of developing psychosis took place in the first five years signifying that the risk of developing psychosis is confined to a critical period and is not a lifelong threat, whereas psychosis is a chronic and life-long disabling condition. Thus, identification of those in this CHR-P status is imperative.

Classification

There are increasing efforts to identify those that are in the CHR-P window, though current efforts focus on subjective measures. Self-report and behavioral observations are used

to provide a diagnosis of CHR-P. However, symptoms, especially the ones attributable in the CHR-P window overlap across diagnostic categories and there is significant heterogeneity within disorders (Fusar-Poli, Cappucciati, et al., 2016). Perceptual processes are one avenue to consider when striving for a risk indicator for schizophrenia. Psychophysical or electrophysiological methods may be utilized in conjunction with current diagnostic measures to capture information from neurobiochemical differences in psychiatric illnesses. Low-level visual processing is a promising avenue for aiding in strong classification accuracy. Since unique visual abnormalities are reported in CHR-P (Klosterkotter et al., 2001), visual dysfunction may serve as an endophenotype for transitioning to psychosis and allow for early detection and intervention. Additionally, this partial support for enhanced CS at LSFs for those with CHR-P is promising. Together, with the result of their weakened excitation, inhibition and temporal integration compared to controls, there is a case to be made that there is something going on with this population that is different from neurotypical controls.

Feasibility

Despite its acknowledged value, CS is not often evaluated in clinical settings due to the limitations of currently available psychophysical methods. Additionally, all psychophysical measures require cognitive and functional abilities to attend to the stimuli and produce verbal and/or action-oriented responses. While these factors make it difficult to measure CS regularly in healthy populations, it makes it even more difficult in many medical/psychiatric populations. CS measurement can be especially difficult to obtain for individuals with neurological impairment as there are often deficits in motor functioning,

verbal and nonverbal communication, and attentional and cognitive processing necessary to participate in standard behavioral and psychophysical tests of visual function. However, this current study has shown that it is feasible, reliable, and valid. Furthermore, mental health or primary care professionals could refer their patients to psychophysical CS testing as it is noninvasive, cost and time efficient, low risk, and does not cause any side effects. Lastly, with the task on an iPad Pro, there is the space to do it.

Limitations

There are several limitations in the current study. The small sample sizes, specifically in the CHR-P group, represent a significant limitation. Another limitation is that while the CHR-P sample's SIPS scores were similar to a larger CHR-P sample (n = 68) in a study conducted by Osborne and Mittal (2019), which supports the good reliability of the SIPS and the representativeness of the current sample (Osborne & Mittal, 2019), it may not be indicative of the true CHR-P population as these individuals were help-seeking. Additionally, no formal statistical analyses were possible with the SCZ data due to the CS data being collected on a different system with slightly different SFs. Furthermore, this is a cross-sectional study. Natural history studies examining this group longitudinally would be particularly interesting to explore whether these individuals transition to psychosis or just have attenuated positive symptoms throughout their life. Importantly, this study cannot rule out the potential effects of medication, mostly antidepressants on CS due to the small sample size. Lastly, CS data were only compared to healthy controls (and partially to those with schizophrenia). It is unknown whether similar CS deficits exist across psychiatric disorders or which psychotic symptoms may arise as secondary symptoms (e.g., major depression with psychotic features). This is important to acknowledge since many individuals with CHR-P

have comorbid psychiatric disorders. Future research should expand to include other psychiatric disorders to determine if there are unique deficits across psychiatric disorders.

Future Directions

Future directions for the current project can capitalize on the study's limitations delineated above, as well as expand upon research in this area overall. Replicating the findings with psychophysical methods used in the current study in a larger sample size would be important to assess the robustness and generalizability of these results. With more people, more analyses can be done, such as Principal Component Analysis, ROC (receiver operating characteristic) curve analysis and stratifying different groups in CHR-P based on clinical symptoms and/or comorbid psychiatric disorders. Breaking down the components of ROC curve analyses may lead to identifying a single, specific condition that best improves classification accuracy, which would be easier to implement as a clinical tool. Additionally, adding electrophysiological and fMRI measures would complement the psychophysical results. Calderone et al. (2013) compared these three measures of visual contrast responses in schizophrenia and found that they complemented each other, and each added new details to the neural underpinnings of visual dysfunction. As research has shown that there is dysfunction in the P300 electrophysiological measure in those with CHR-P (Hamilton et al., 2020; Hamilton et al., 2019), it would be interesting to follow up this finding with fMRI and VEPs that our laboratory has created. Future research should test age- and gender-matched individuals with schizophrenia with the same psychophysical CS task on the iPad Pro to be able to formally compare data.

Lastly, neurocognition in this population should be explored. The literature states that lower CS was associated with deficits in IQ, attention, working memory, reading, facial

emotion recognition, and function outcome in SCZ (Butler et al., 2009; Martinez, Revheim, et al., 2012; Revheim et al., 2014). The current study found that CHR-P individuals have decreased CS at middle SFs compared to controls and research suggests that decreased sensitivity at middle SFs is associated with decreased ability to see faces (Owsley & Sloane, 1987). Past research has reported impaired facial affect recognition, facial perception and reduced N170 (i.e., a component known for the structural encoding of a face) amplitude in those with CHR-P (Addington, Penn, et al., 2008; Amminger et al., 2012; Osborne et al., 2022; Wolwer et al., 2012). Thus, it would be interesting to assess facial affect recognition and perception together with psychophysical and electrophysiological tasks within our sample.

Herrera et al. (2021), who utilized a similar CS task in those with schizophrenia found that cognition mediated the relationship between CS and independent living. Additionally, Revheim et al. (2014) found that those with CHR-P had rapid naming scores and visual reading scores statistically similar to those with schizophrenia (Herrera et al., 2021). This suggests that visual deficits may pre-exist illness onset and may predispose to development of later functional reading impairments. Thus, it is important to investigate in hopes of remediating reading impairments and increase quality of life through independent living.

Overall, this study supports impaired CS in those with CHR-P using a psychophysical paradigm. This is the first CS study in a clinical sample conducted on an iPad Pro and results show feasibility, reliability, and validity. This is only the second CS study to investigate contrast processing in those with CHR-P. More research is needed to investigate CS differences with regard to spatial frequency, temporal condition, and medication. Future

research should also investigate these paradigms against clinical tools currently used for diagnosis to test their predictive power in this population. Also, further characterization of visual deficits and their impact on higher-level deficits and functional impairment in psychosis may inform targets for treatment and or prevention.

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Tables

Table 1. *Median Values and Semi- Interquartile Ranges (SIQR) of Demographics and Clinical Variables by Group*

Demographics	Controls (n = 14)	Clinical High Risk (n = 12)	Schizophrenia (n = 11)
Age	21.50 (5.75)	23 (5.50)	24 (4.85)
Sex	9 males	7 males	11 males
Medication	------	4 = none, 7 = meds but not antipsychotics, 1 = meds + antipsychotics	8 on atypical and 3 on a combination
Age of first hospitalization	-----	-----	14 (3.53)
Illness duration	-----	-----	8.42 (8.34)
PANSS Total Score	-----	-----	67 (11)
PANSS Positive Score	-----	-----	15 (4)
PANSS Negative Score	-----	-----	17 (3.50)
PANSS General Score	-----	-----	34 (6)
SIPS Total Score	-----	36 (6.75)	-----
SIPS Positive Score	-----	12 (3.25)	-----
SIPS Negative Score	-----	10.50 (4.38)	-----
SIPS Disorganized Score	-----	4.50 (2.63)	-----
SIPS General Score	-----	9 (1.75)	-----
AVAQ Total Score	-----	148.50 (33.50)	-----
AVAQ Visual Processing Score	-----	103 (25.25)	-----
AVAQ Auditory Processing Score	-----	40 (8)	-----
AVAQ Audio-Visual Processing Score	-----	4 (1.38)	-----

Table 2. *Median Values and Semi-Interquartile Ranges (SIQR) of LogCS by Group and Temporal Condition*

Spatial Frequency by Temporal Condition	Controls (n = 14)	Clinical High Risk (n =12)	Schizophrenia (n = 11)
0.41 cyc/deg 33 ms	2.02 (0.09)	1.91 (0.08)	2.00 (0.20)
0.41 cyc/deg 500 ms	2.11 (0.12)	1.91 (0.05)	1.94 (0.21)
1.6 cyc/deg 33 ms	2.10 (0.15)	2.21 (0.14)	1.92 (0.12)
1.6 cyc/deg 500 ms	2.40 (0.08)	2.32 (0.08)	2.09 (0.11)
3.25 cyc/deg 33 ms	2.06 (0.20)	2.02 (0.14)	1.74 (0.18)
3.25 cyc/deg 500 ms	2.47 (0.15)	2.35 (0.19)	2.31 (0.19)
6.5 cyc/deg 33 ms	1.81 (0.22)	1.80 (0.29)	1.53 (0.17)
6.5 cyc/deg 500 ms	2.26 (0.27)	2.10 (0.16)	2.09 (0.13)
13 cyc/deg 300 ms	1.17 (0.42)	0.99 (0.26)	0.40 (0.07)
13 cyc/deg 500 ms	1.69 (0.31)	1.62 (0.27)	0.86 (0.33)

Note. Spatial frequencies tested with SCZ group are 0.5, 1, 4, 7, and 21 cyc/deg.

Table 3. *Inhibitory and Excitatory Model Parameter Values by Temporal Condition and Group*

Parameter Values	Controls	Clinical High Risk	Schizophrenia
SD Excitatory 33 ms	11.93	10.65	11.79
SD Excitatory 500 ms	13.61	13.67	14.26
SD Inhibitory 33 ms	0.38	0.39	0.71
SD Inhibitory 500 ms	1.06	0.60	0.70
Strength Excitatory 33 ms	63.38	58.11	56.98
Strength Excitatory 500 ms	87.28	80.36	83.78
Strength Inhibitory 33 ms	0.17	0.36	0.00
Strength Inhibitory 500 ms	1.36	0.81	1.08

Note. Standard deviation (*SD)* units are in cycles/degree.

Table 4. *Pearson Correlation Coefficients Between LogCS at Five Spatial Frequencies/33 ms and SIPS, AVAQ scores in CHR-P Group.*

LogCS – SF (cyc/deg)	0.41	1.6	3.25	6.5	13
AVAQ Total[1]	.13 (.70)	-.30 (.37)	-.18 (.60)	-.30 (.37)	-.33 (.32)
AVAQ Visual[1]	.18 (.60)	-.29 (.40)	-.15 (.65)	-.34 (.31)	-.32 (.34)
AVAQ Auditory[1]	-.06 (.87)	-.39 (.24)	-.33 (.33)	-.20 (.57)	-.33 (.33)
AVAQ Audio-Visual[1]	.24 (.49)	.18 (.60)	.29 (.38)	.08 (.81)	-.20 (.56)
SIPS Total	.41 (.18)	-.06 (.87)	-.14 (.68)	-.08 (.80)	-.08 (.80)
SIPS Positive	.34 (.28)	.07 (.84)	-.21 (.51)	.20 (.54)	.28 (.39)
SIPS Disorganized	.39 (.41)	.17 (.60)	.01 (.99)	.06 (.87)	-.08 (.80)
SIPS General	.48 (.12)	-.40 (.20)	-.34 (.28)	-.48 (.11)	-.41 (.18)
SIPS Negative	.26 (.41)	.17 (.60)	.01 (.99)	.06 (.87)	-.08 (.80)

p values < .05, 2-tailed, are bolded; one CHR-P outlier was excluded from AVAQ analyses.

Table 5. *Pearson Correlation Coefficients Between LogCS at Five Spatial Frequencies/500 ms and SIPS, AVAQ scores for CHR-P Group.*

LogCS – SF (cyc/deg)	0.41	1.6	3.25	6.5	13
AVAQ Total[1]	**.62 (.04)**	-.42 (.20)	-.30 (.37)	**-.60 (.04)**	-.34 (.31)
AVAQ Visual[1]	**.67 (.03)**	-.43 (.19)	-.31 (.36)	**-.61 (.04)**	-.35 (.29)
AVAQ Auditory[1]	.46 (.16)	-.41 (.21)	-.32 (.34)	-.59 (.06)	-.31 (.36)
AVAQ Audio-Visual[1]	.06 (.85)	.08 (.81)	.12 (.73)	-.12 (.73)	-.08 (.83)
SIPS Total	.50 (.10)	**-.61 (.04)**	.15 (.64)	-.02 (.96)	.03 (.94)
SIPS Positive	.24 (.45)	-.50 (.10)	.17 (.60)	-.05 (.89)	.12 (.70)
SIPS Disorganized	.51 (.09)	-.50 (.10)	-.06 (.86)	-.08 (.80)	-.08 (.81)
SIPS General	.55 (.07)	-.53 (.08)	-.08 (.80)	-.30 (.35)	-.33 (.30)
SIPS Negative	.42 (.17)	-.55 (.07)	.36 (.25)	.23 (.47)	.25 (.44)

p values < .05, 2-tailed, are bolded; one CHR-P outlier was excluded from AVAQ analyses.

Figures

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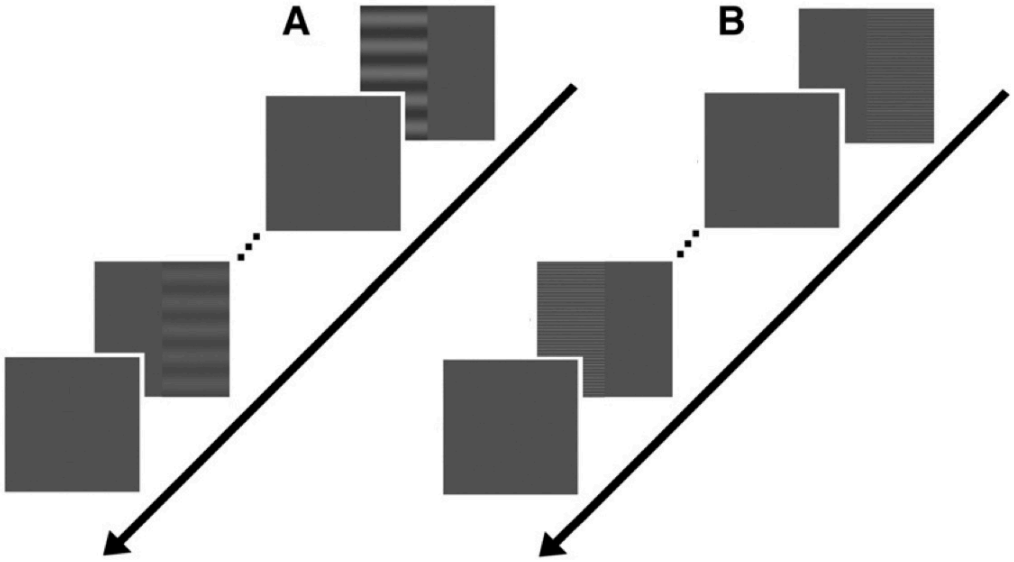
Figure 1. *Psychophysical Contrast Sensitivity Task*



Note. A) example of low spatial frequency stimuli at 33 ms; B) example of high spatial frequency stimuli at 500 ms.

Figure 2. *Box Plots of Log CS vs. Spatial Frequency Split by Temporal Condition (33 and 500 ms)*

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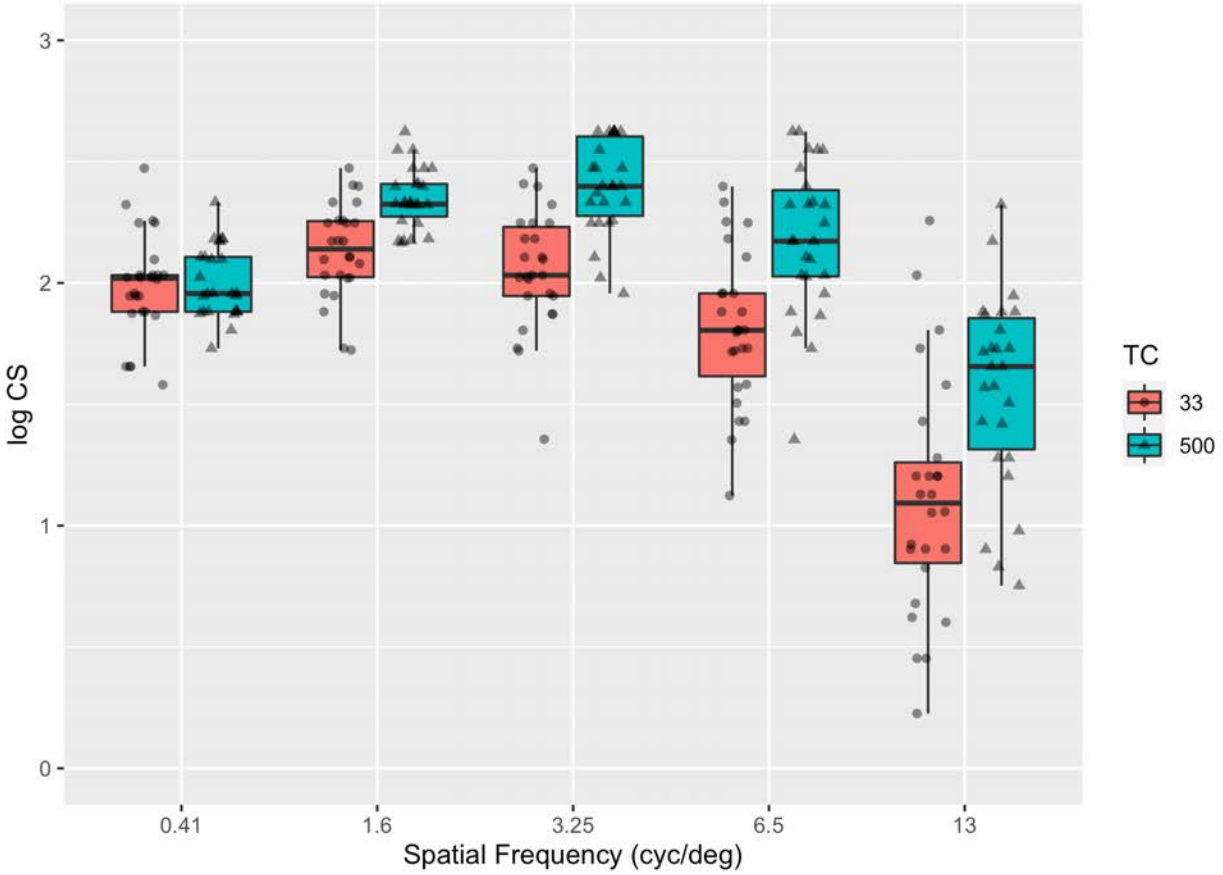
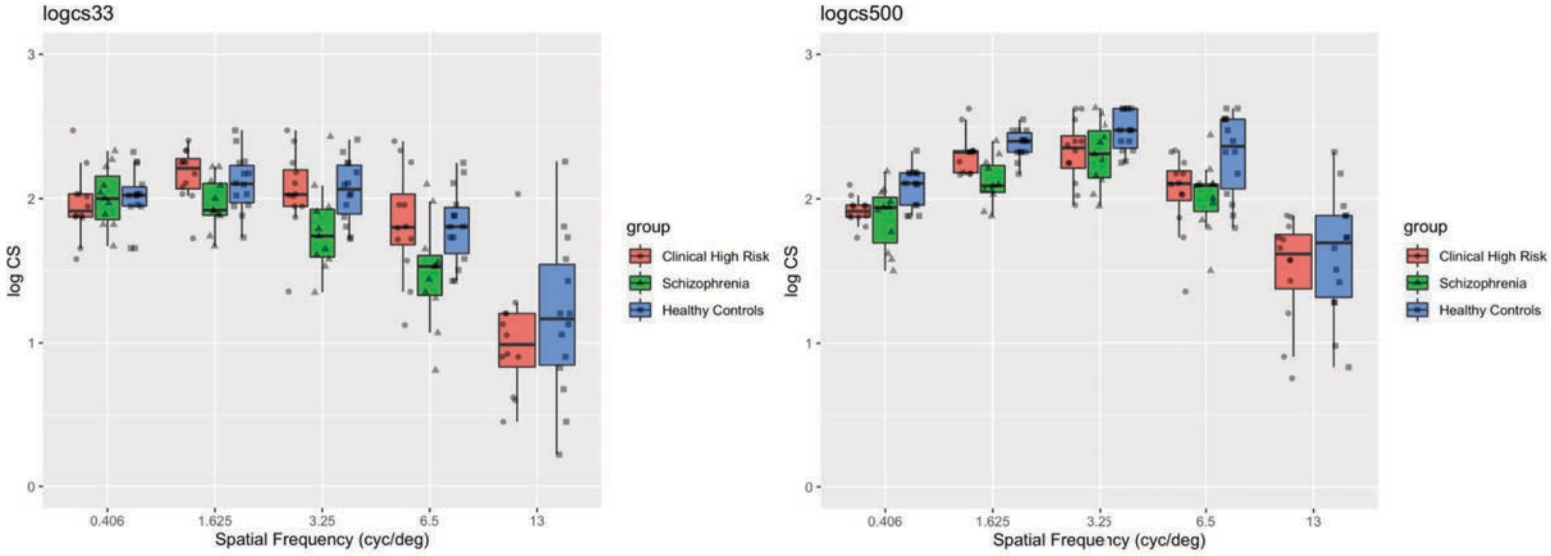


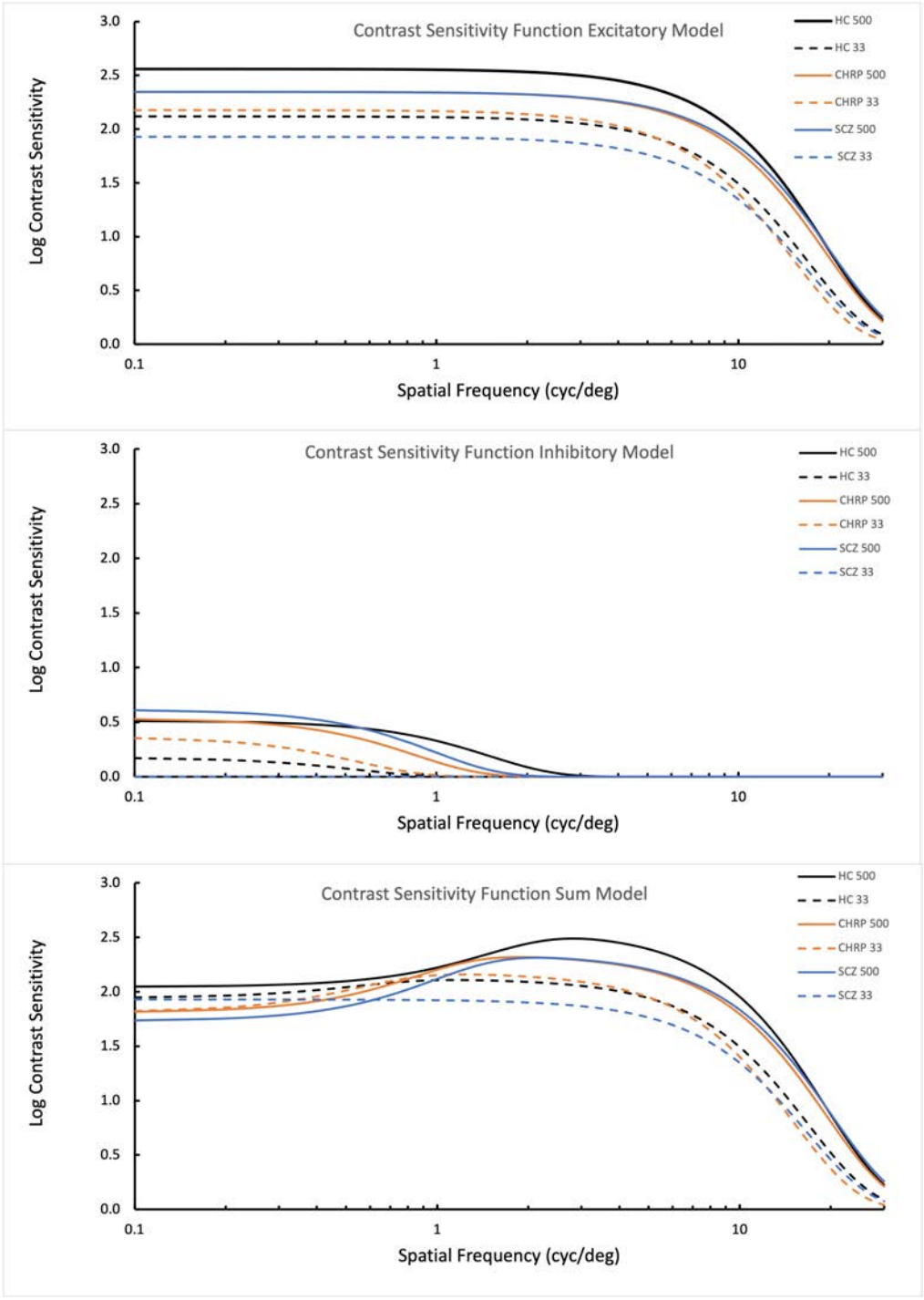
Note. TC = temporal condition; data is only shown for controls and CHR-P combined.

Figure 3. *Box Plots of LogCS vs. Spatial Frequency Split by Group and Temporal Condition (33 and 500 ms)*



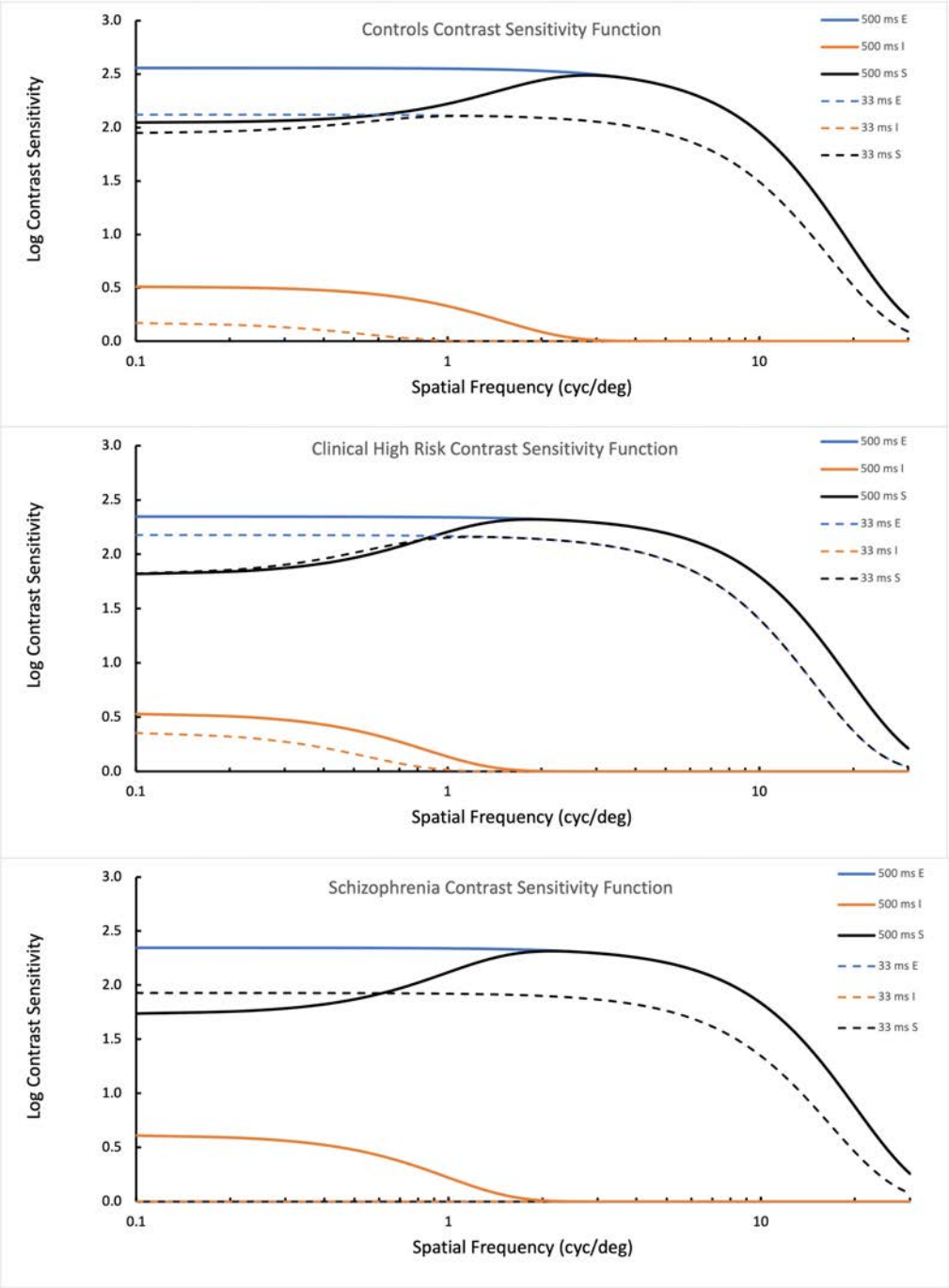
Note. Lower four spatial frequencies tested with SCZ group are 0.5, 1, 4, and 7 cyc/deg (21 cyc/deg was not included).

Figure 4. *Difference of Gaussian Models by Mechanism Split by Group and Temporal Condition*



Note. HC = Healthy Controls, CHR-P = Clinical High Risk for Psychosis, SCZ = Schizophrenia; Temporal condition – short duration, 33 ms; long duration, 500 ms.

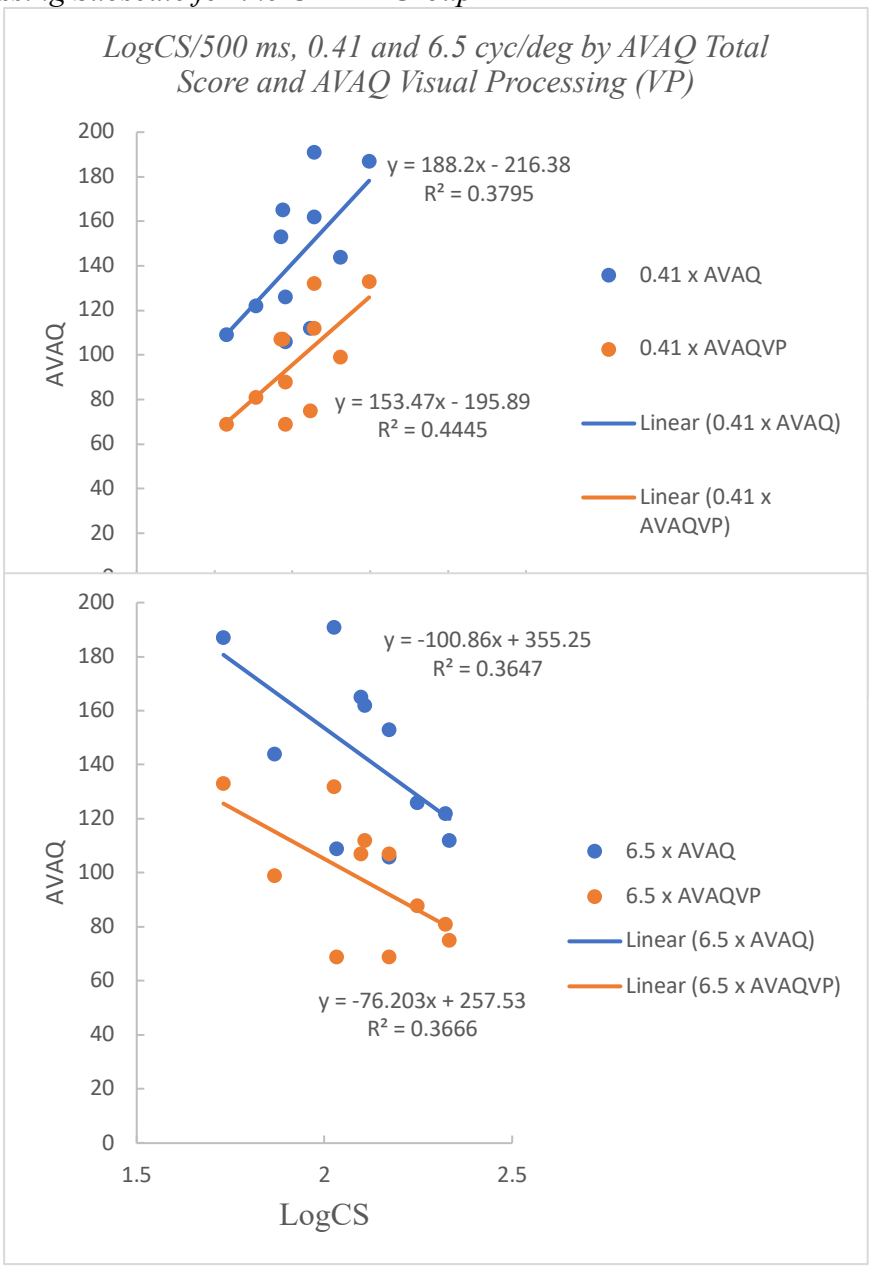
Figure 5. *Difference of Gaussian Models Split by Group and Temporal Condition*



Note. E = Excitatory Response, I = Inhibitory Response, S = Sum (Excitatory - Inhibitory).

Temporal condition – short duration, 33 ms; long duration, 500 ms.

Figure 6. *Scatterplots of LogCS/500 ms (0.41 and 6.5 cyc/deg) by AVAQ Total Score and AVAQ Visual Processing Subscale for the CHR-P Group*



Note. One CHR-P outlier was excluded from AVAQ analyses.

Figure 7. *Scatterplots of LogCS/500 ms (1.6 cyc/deg) by SIPS Total Score for the CHR-P Group*