STIMULUS CONTEXT AS A METHOD FOR EVALUATING EARLY AUDITORY AND VISUAL SENSORY PATHWAYS

by

WILLIAM TURNER OLIVER

(Under the Direction of Brett Clementz)

ABSTRACT

Context is a critical component to all empirical research and must always be carefully considered. In early auditory and visual sensory processing, it can be employed to differentiate top-down mediated biasing signals from lower-level fundamental sensory function. Early sensory processes have been shown to deviate from normal function across dimensions of the normal aging process, pathological cases, and basic cognitive control capacity. The auditory and visual streams are complex, reciprocal in nature, and highly transient in nature. Determining where in the streams top-down control is implemented requires exceptional temporal precision and must be evaluated using the imaging modalities capable of achieving millisecond precision. In this dissertation, contextual modulation will be used as a tool to impose top-down biasing in a manner that will allow for identifying group variance across multiple group characteristics under carefully crafted semi-static auditory and visual stimuli that make clear how top-down processes mediate basic sensory cortical processing.

INDEX WORDS: Psychosis, Aging, Attention, Cognitive Control, Auditory processing, Visual Processing

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WILLIAM TURNER OLIVER

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WILLIAM TURNER OLIVER

Major Professor: Brett Clementz

Committee: Jennifer McDowell

Dean Sabatinelli

Ron Walcott

Dean of the Graduate School

The University of Georgia

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CHAPTER 1

INTRODUCTION

Context within the experimental setting is critical to all psychological research and of the utmost concern to maintaining empirical integrity. It must always be carefully considered and controlled for as some of the subtlest alterations in experimental context can have unintended consequences on the outcome of a study. The oxford definition for context is, "the circumstances that form the setting for an event, statement, or idea, and in terms of which it can be fully understood and assessed". In the empirical setting, this might include the manner with which instruction are given for a task, the order stimuli are presented, the environment where the testing is performed, and so on. In a series of experiments Stanley Milgram famously altered how much physical pain people were willing to inflict on complete strangers by simply dressing the experimenter in a lab coat or giving them a clipboard (Milgram, 1963-1974). Contextual changes in one's environment can have broad and complicated social and interpersonal implications. In the field of basic sensory perception context must also be carefully considered.

In terms of neurophysiology during processing of basic sensory stimuli, context very much matters, and can be used as tool to parse intricate and often reciprocal flow of information. For the purposes of this dissertation, I will be referring to context as alterations of relatively static stimuli, some subtle and others overt. That is, stimuli that are presented to participants will be simple in terms of lower-level sensory processing, evocative regarding the brain's processing of basic auditory and visual information, and relatively static at the point of signal transduction. Tight control of the stimuli in terms of transduction, this can be thought of as "what goes in" the eyes and ears, will allow for better measurements of what, if any, influence contextual changes

will have on basic sensory processing and what higher order biases are imposed on those basic functions. This will be done using a combination of strategies, from altering the participant's expectation of stimulus features through repetitive stimulation, to varying task demands through instruction. By altering context in the aforementioned manner, it will be determined where groups deviate from one another in both bottom-up and top-down processing of the auditory and visual stimuli.

Cognition and sensory processing are critical components to living a healthy independent lifestyle and will become a challenge for nearly everyone, whether through clinical pathology or late life aging. Identifying the interplay between the two is a cornerstone of psychological research, and arguably it's most studied subjects, as they are required to be a functional adult. Cognition and sensory processing are sometimes thought of as independent, but highly integrated brain processes, with cognition often considered a mechanism of top-down integrative control. As deficits arise in the aging and pathological, determining the root or direction of dysfunction requires a sound understanding of the interplay between cognition and basic sensory processing, but it can be difficult to render one from the other due to the highly reciprocal nature of the brain. The first step is to define basic sensory processing, top-down biasing, and cognitive control.

Differentiating between bottom-up and top-down mechanisms is critical to understanding visual and auditory streams of processing, and thorough understanding of the two is crucial to determining the role context plays in healthy non-pathological persons and how/where the pathological deviate. As stimuli begin their journey through the brain, starting at the cochlea for auditory stimuli and retina for visual, they are then passed through the thalamus and onto the primary auditory (A1) or visual (V1) cortices. At this point in the streams the stimuli are minimally influenced by higher order top-down biases, but not completely independent of bias

signaling, and at cortical registration at A1 and V1 they are processed by simplest of features (e.g. pitch, timbre, edges, contrast, etc) (Hubel & Wiesel, 1962; Merzenich et al., 1975). This level of processing is commonly referred to as bottom-up processing, and generally considered the starting point of signal processing in non-invasive neurophysiological testing in humans, namely electroencephalography (EEG) and magnetoencephalography (MEG), instrumentation that will be covered in later sections.

These simple features then continue along the auditory and visual streams, moving outward in the brain from A1 and V1 as more complex features of the stimuli are accounted for (e.g word formation, sentence structure color, motion, etc.)(Belin et al., 2000; Shapley & Hawken, 2011). As more complex features are assessed by appropriate brain regions there eventually becomes a need for integration of these features into something meaningful that makes up the perceptive experience. This is largely managed by prefrontal top-down function, commonly referred to as the "central executive" due to its management of the integrative process.

The Baddley and Hitch (1974) model of working memory proposed two different temporary stores of working memory, one specific to language and articulation, the other catered to the maintenance of visual/spatial information, with additional dimensions added into the model over the years (Baddeley, 2000). Building on the Baddley and Hitch model of working memory, working memory capacity and cognitive control were later refined into more domain specific models that relied on experimental procedures constructed in a manner that could extract variance across healthy, non-pathological individuals (Redick et al., 2012; Unsworth et al., 2005; Unsworth & Engle, 2007). This work was able to link behavioral performance across well studied visual paradigms (e.g. pro/antisacccade tasks) to performance to their working memory

evaluative procedures known as the SPAN tasks (Engle, 2010). The SPAN tasks test individuals across multiple domains, including but not exclusive to, reading, mathematics, and visual spatial orientation. Cognitive control deficits are common in both psychosis cases and the aging (Bovier et al., 2014; Camchong et al., 2006, 2008; Mewborn et al., 2018; Renzi et al., 2014; Schaeffer et al., 2015).

These procedures will evaluate contextual influence during passive perception auditory tasks and under more engaging and demanding visual perception tasks. Contextual modulation will require participants to employ selective attention , a concept closely related to cognitive control, to successfully perform as instructed. The concept of selective attention was conceptualized by William James in 1890, "It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others...". That is, one must focus one's attention to achieve the given goal, possibly at the expense of less salient stimuli/perceptions. Selective attention in terms of goal maintenance and behavioral inhibition is a function of cognitive control capability and has been shown to highly recruit top-down processing units (Engle et al., 2012; Unsworth et al., 2005; Unsworth & Engle, 2007).

CHAPTER 2

Basic sensory registration in the auditory and visual systems are widely regarded as early stream processes that occur from signal transduction in the cochlea and retina up to primary auditory and visual cortex. For auditory stimuli and the purposes of this dissertation it will be considered from thalamus forward to auditory cortex. Auditory anomalies have long been studied in those with psychosis, namely schizophrenia and schizoaffective disorders, with paired-stimulus design paradigms. Persons with psychosis show abnormal processing of basic auditory stimuli under these paired-stimulus conditions (de Wilde et al., 2007; Hamm et al., 2014). The traditional configuration for the paired-stimulus auditory paradigm is two identical clicks in close succession to one another, labeled as stimulus 1 (S1) and stimulus 2 (S2). The S1-S2 pair has a relatively short interval between the two with 500ms being the most common interval, followed by a longer interval (e.g. 10-sec) between S1-S2 pair. This groups the stimuli into pairs with 500ms between them followed by a long interval until the next S1-S2 pair. The typical neural response to this stimulus configuration is a large auditory response within 100-200ms post S1 and an attenuated response to S2 approximately 100-200ms after S2.

This attenuated response to S2 has been historically referred to as sensory “gating”, as this diminished response to S2 is seen as a type of sensory filtering and mechanism for blunting the brain’s response to less salient stimuli. Since S1 and S2 are identical in nature, other than the context in which they are presented, specifically interstimulus interval, it is believed that the redundant S2 receives some level of filtering not afforded to the initial S1. In persons with psychosis the aforementioned brain responses aren’t nearly as evident as it is in non-pathological

healthy individuals. That is the differences in auditory responses between S1-S2 isn't nearly as great in psychosis cases as it is in healthy persons and these findings have been widely replicated across the psychosis literature (de Wilde et al., 2007; Nagamato et al., 1991; Olincy et al., 2010). There are several reasons for this deviation in psychosis which will be covered in a subsequent study in more detail. The brevity of the interval between S1-S2 has been covered by previous works and optimized to show greatest S1-S2 variability in early auditory processing at the level of the cortex (Shelley et al., 1999). A question that remains, however, is what exactly makes this stimulus configuration the gold standard in studying this S2 attenuated brain response? Is there something special about this specific context that makes it necessary to elicit the desired sensory filtering that can be seen in healthy persons?

The contextual nature of the paired-stimulus paradigm could easily be changed by altering the intervals between S1 and S2, but that has been fairly-well covered and could easily become part of an alternate feature or route of auditory processing (Shelley et al., 1999; Bressler, 2002). It would also negate proper comparison to a sizeable body of "gating" and paired-stimulus literature, although this may not be a sound justification for experimental design. The better way to alter context of this procedure would be to maintain well researched and accepted stimulus intervals by locking the long and short interstimulus intervals between S1 and S2 while manipulating the broader context with which they are presented. The traditional paired-stimulus paradigm by its very nature provides the subject with an identifiable expectation.

Listening to pairs of clicks 500ms apart followed by a long interval for 10 minutes at a time takes on a natural context, or expectation, as does a constant succession of clicks separated by 500ms. By locking the interstimulus interval and altering the context or order with which the stimuli are presented, the contextual integrity of the traditional paired-stimulus paradigm can be

tested. This contextual alteration can then make clear if the traditional configuration is a necessary context and may make clear what, if any, top-down biasing could be introduced as expectation is changed. A subtle change in expectation could uncover top-down processes that are leading to irregularities seen in psychosis cases and could help disentangle top-down mediation and lower-level auditory sensory processing. If top-down biases are influencing processing in primary auditory cortex under these stimulus conditions based on changes in the contextual landscape the experimental procedures may be of use across other groups sharing similar characteristics to those with psychosis, while remaining non-pathological. It is quite possible that persons with poor cognitive functioning, but remain otherwise healthy, can be differentiated utilizing such an experimental strategy. It may also be the case that contextual alterations during basic sensory stimulus deployment, using stimuli that generate reliable and robust neural signals, can be extrapolated across multiple sensory modalities, specifically the visual systems.

Selective attention in the domain of visual processing can be difficult to disentangle early in the visual stream due to aspects of an 'attended' stimulus being assessed concurrently to another. Target detection and ongoing spatial attention allocation are in many ways reliant on one another, that is, one is highly reliant on the other to successfully detect targets in a complex visual array. As target detection demands increase visuospatial attention may narrow in a transactional manner that increases the likelihood of accurate target detection at the attended location (Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). Discerning attentional allocation in the visual field from target detection can, therefore, pose difficulty to parsing the early visual stream. One method for determining where, in a complex visual array, attention is

directed during a testing period is by implementing the steady-state visual evoked potential (ssVEP).

The steady-state paradigm method uses an oscillating stimulus to induce neural entrainment to features of the stimulus. In the visual domain this a sinusoidal or square wave oscillating of visual stimuli in an on-off manner that is perceived as flickering. This flickering of visual stimuli leads to rapid neural entrainment to the oscillatory rate of the stimulus in lower-level visual processing regions, most prominently striate and extrastriate cortex, in a manner that can be considered "frequency-tagging" of those brain regions directly involved in the processing of the stimulus (M M Müller et al., 2003). ssVEPs are characterized by robust cortical entrainment with high signal-to-noise ratios (Mast & Victor, 1991), and multiple frequencies can be presented simultaneously at different positions within a larger array, so attentional spatial position can be measured (Morgan et al., 1996; M M Müller et al., 2003; Matthias M Müller & Hübner, 2002). This frequency-tagging of spatial positions or features allows for the tracking of where/what the participants are attending during the task and can be indicative how well they are modulating their attention to different spatial locations. This method also affords the experimenter the opportunity of dissociating sustained visual attention from target detection proficiency by including deviant stimulus events (targets) in both attended and unattended regions of the stimulus array (Chen et al., 2003; Clementz et al., 2008; Wang et al., 2007).

The aforementioned studies are of importance to measuring top-down influence of basic visual elements because they also lock the gaze of the participants due to the inclusion of a central fixation point, thereby creating a static spatial image at the level of the retina, so nothing is changed as far as "what's going in". At the level of the retina the image remains the same in spatial location, degrees of visual angle, stimulus color, and luminance properties, divulging the

role of top-down biases in the visual stream as changes in power at these "driving" frequencies at the level of the cortex are altered with instructed direction to various spatial locations, each tagged at differing frequencies. By including the element of deviant target events, top-down attentional modulation and target detection can be measured concurrently during early visual processing and may prove to be a marker of poor cognitive control or pathology (Clementz et al., 2008; Wang et al., 2007). Furthermore, by locking the participant's gaze to a central fixation point, thereby fixing the stimulus at level of the retina, the only aspect of the task that is changed is task instruction. This means that the relatively static nature of the stimulus remains and the context, based on task instruction, is the only change across task.

Acquisition of these signals at the level of the cortex require exceptional temporal precision due to stimulus timing configuration and the transient neurophysiological signals to be captured. In order to successfully acquire the desired neural signal at the level of the cortex we utilized and M/EEG technologies, both of which are capable of sampling with millisecond precision. In the case of the auditory paradigm MEG was the preferred data collection method due to orientation of auditory cortex and the physical principles of A1 neuronal orientation relative to the surface of the cortex. Evoked auditory response at A1 is optimally captured by MEG making it the desired modality for studying basic sensory processing at the auditory cortex. For the visual procedures we used EEG to capture oscillatory visual activity over V1, again due to its high temporal precision and efficiency.

For the purposes of this document cognition will be deployed through experimental design in subtle, yet effective methodology, by presenting simple and largely static auditory and visual stimuli. The higher order component of cognitive processing is altered by basic changes in task context and instruction, while maintaining highly stable sensory input. Consistent sensory

input through auditory and visual systems, in well-founded experimental procedures, will replicate previous findings and isolate the higher order processes in manner that will reveal the interplay of the low-level sensory input from that of top-down processes. This will be crucial to identifying not only pathological features in people, but it will also allow for clarification of the cognitive spectrum in non-pathological persons.

Changes in context across data collection runs in each paradigm will be shown to be a useful tool in determining the role of top-down biased signals in fundamental sensory processing. It will be of use in determining group variance across age, cognition, and pathology, and play an informative role in future experimental design. This dissertation will show different ways context can be altered using semi-static basic sensory stimuli with high temporal precision across multiple imaging modalities and neurophysiological sensory modalities.

CHAPTER 3

IS A PAIRED-STIMULI CONFIGURATION NECESSARY TO OBTAIN TYPICAL EVOKED RESPONSE DIFFERENCES IN STUDIES OF PSYCHOSIS?

AN MEG STUDY[1]

[1] Oliver, W., Parker, D., Hetrick, W., & Clementz, B. A. (2021). Is a paired-stimuli configuration necessary to obtain typical evoked response differences in studies of psychosis? An MEG study. *Biomarkers in Neuropsychiatry*, *4*, 100033. Reprinted here with permission of publisher

Abstract

Paired-stimuli (S1-S2) procedures have long been used to assess auditory processing in psychosis. Such studies have shown aberrant evoked responses (ERPs) following long (S1 response) and/or short (S2 response) inter-stimulus intervals. The historical tendency from paired stimuli outcomes in the schizophrenia (SZ) literature is for (i) response to the first stimulus (S1) to be smaller among SZ, and (ii) response to the second stimulus (S2) to be larger among SZ in relation to the size of their S1. An interpretation of these two findings is that SZ have poor auditory response suppression to redundant stimuli ("poor gating"). The present study sought to determine if the reported S1 and S2 effects in SZ (smaller S1 and larger S2 in relation to S1 magnitude) require the paired-stimuli presentation format. Participants (18 schizophrenia and 17 healthy persons) were administered the equivalent of S1 (after a 4.5-sec ISI – "long ISI") and S2 (after a 500-ms ISI – "short ISI") stimuli under four conditions (traditional paired long and short, randomly interleaved long and short, block of long, block of short). Neural activity differences were consistent between-groups independent of condition: (i) schizophrenia cases had greater activity in the pre-stimulus to very early post-stimulus period, (ii) healthy persons had greater M100 activity to long ISI stimuli, and (iii) healthy persons had greater activity after the M50/M100 evoked fields (recovery phase) following short ISI stimuli. Simple early auditory processing in psychosis may be largely independent of stimulus presentation condition, an outcome that may help re-frame future translational studies. Traditional paired-stimuli auditory neural response effects may not require the paired-stimuli format.

Introduction

Paired-stimuli paradigms are used to study auditory processing abnormalities in psychosis (de Wilde et al., 2007; Hamm et al., 2014). In the typical paradigm, identical stimuli (S1-S2) are presented in close temporal proximity (500-ms), with pairs separated by long intervals (e.g. 10-sec). Normally, neural responses within the first 100 to 200-ms following S2 are smaller than those following S1. Sensory filtering or 'gating' abnormalities are presumed if response magnitudes are more similar between the two stimuli. A smaller S1-S2 difference is a historically significant and widely replicated finding among psychosis cases (de Wilde et al., 2007; Nagamoto et al., 1991; Olincy et al., 2010).

Two assumptions of sensory processing theories for interpreting differences between S1-S2 response magnitudes are: (i) S1-S2 differences are largely determined by differences at S2, not S1; and (ii) the stimulus configuration (pairing of S2 500-ms after S1) provides a necessary expectation, peculiar to the traditional paired-stimuli configuration. The available evidence, however, compels a careful consideration of these assumptions. The majority of group effects in psychosis studies are associated with three sensory neural response features. First, preparation for stimulus presentation (enhanced activity pre-stimulus) differs between healthy persons and psychosis cases (Ethridge et al., 2011). There is an elevation of background brain activity in certain psychosis cases (Rolls et al., 2008; Thomas et al., 2019), including schizophrenia (Blumenfeld & Clementz, 2001; Hamm et al., 2014), which lowers neural signal-to-noise ratio for any stimulus processed against this elevated background. Lower signal-to-noise may mean compromised signal fidelity with accompanying reduced ability to parse stimulus salience (Ethridge et al., 2011; Hudgens-Haney et al., 2017; Hudgens-Haney et al., 2018). Second, reduced amplitude M100/N100, analogous to lower S1 magnitudes in paired-stimuli paradigms, is one of the most

replicated findings in schizophrenia research (Rosburg et al., 2008). In the absence of any other effects, lower S1 amplitudes across stimulus conditions could account for the historical reports of smaller S1-S2 amplitude differences among psychosis cases in paired stimuli studies. Third, recovery from stimulation (the period after sensory registration and before the next stimulus when there is no obvious evoked response) differs between psychosis and healthy subjects (Brenner et al., 2009; Clementz & Blumenfeld, 2001; Hamm et al., 2014; Johannesen et al., 2005; Johannesen et al., 2013; Smith et al., 2010). In paired-stimuli paradigms, there is a 500-ms window between S1 and S2. Psychosis and healthy groups recovering from S1, leading up to S2, at different rates (Hamm et al., 2014; Parker et al., 2020; Popov et al., 2011). This difference could contribute to the historical report of sensory gating differences in psychosis because S2 is occurring against a different neural background in psychosis compared to healthy persons.

In this paper, we preliminarily evaluate these three neural features through manipulation of stimulus presentation conditions. Under the strongest version of the sensory gating interpretation of S1-S2 differences in psychosis, paired-stimuli pairings are required to obtain the historically reported effect. The expectation during the typical paired stimuli presentation format is a long ISI stimulus (S1) followed by a short ISI stimulus (S2), and that S2 reduction is a consequence of the irrelevance of S2 given that it is always the same as S1 (see also (Brenner et al., 2009)). To help clarify whether S1-S2 response magnitudes in psychosis are at least partially independent of the stimulus sequence expectation on the part of participants, we used the following manipulations (see Figure 1): (i) a traditional S1-S2 paired-stimuli paradigm (i.e., S1 occurred after a long temporal interval and S2 occurred after a short temporal interval, on every trial); (ii) a mixed run in which “S1” and “S2” stimuli were randomly interleaved (i.e., long and short intervals between stimuli were randomly determined for every trial); (iii) a block of stimuli with longer

interstimulus intervals (effectively all "S1"), and (iv) a block of stimuli with shorter interstimulus intervals (effectively all "S2). To the extent that background, S1, S2, and stimulus recovery magnitudes between psychosis and healthy subjects can be captured independent of the S1-S2 pairing, this will inform future theorizing and translational studies using the "sensory gating" paradigm.

Method

Participants were 18 right-handed chronic outpatients with DSM-IV (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 1994) schizophrenia (Median Age=36yrs, 25^{th}-75^{th} %tile=28-44yrs; 6 females) and 17 right-handed healthy subjects (Median Age=37yrs, 25^{th}-75^{th} %tile=28-46yrs; 10 females). Participants with schizophrenia were clinically stable on antipsychotic medications (12 on second generation; 6 on first generation). Subjects were interviewed with the SCID (First, 2004) by two Ph.D.-level psychologists to either verify their clinical diagnosis (schizophrenia) or rule out Axis I disorders (healthy subjects). Participants were absent of neurological hard signs, clinically confounding treatments, history of head trauma and current psychoactive substance use disorders. Healthy persons had no evidence, by self-report, of psychosis in either their first- or second-degree biological relatives. The project was approved by the UGA Institutional Review Board and all subjects provided written informed consent before testing. We collected neural activity data in the magnetoencephalography (MEG) environment, which is excellent for measuring cortical responses to auditory stimuli (Sams & Hari, 1991). MEG also has the advantage over EEG of measuring neural signals with minimal distortion because intervening tissues (skull, scalp) have little effect on the signals measured at the sensors in relation to the "true" response generated by activated neurons (Supek & Aine, 2014).

For the typical paired-stimuli task, there is a stimulus following a long interval (S1 - which here occurred after 4.5-sec because 3-sec is sufficient to obtain auditory evoked response differences in psychosis; (Shelley et al., 1999) and another stimulus following a short interval (S2 - 500 ms after S1). We tested the possibility that it is the interval between stimuli (long vs short), rather than stimulus context (paired-stimuli paradigm) that largely accounts for the traditional S1-S2 psychosis effects. Every subject completed four conditions: (i) 120 trials of a traditional **paired**-stimuli paradigm as described above; (ii) a **mixed** run with 0.5 sec and 4.5 sec ISI randomly interleaved, 120 of each ISI, (iii) 120 trials of 4.5 sec ISI (**long blocked**), and (iv) 120 trials of only 0.5 sec ISI (**short blocked**). **Figure 1** provides a schematic of the four conditions.

MEG recordings were obtained using a 143 channel CTF OMEGA whole head system (CTF/VSM Medtech Ltd., Coquitlam, BC, Canada). MEG data were recorded continuously, sampled at 600 Hz, with an analog filter bandpass of 0.6–300 Hz. An inflatable air bladder was fitted to the subject's head (like a stocking cap) to encourage head stabilization throughout. Three head localization coils (positioned at the nasion, and left and right preauricular points) and Ag–AgCl electrodes (positioned at the outer canthi of each eye, and above and below the left eye for recording of horizontal and vertical eye movements, respectively) were affixed prior to testing. Head position relative to sensor locations was measured at the beginning and end of testing, with no participant moving more than 3 mm in any plane.

Data were pre-processed following previously published procedures, including adjustment for cardiac, muscle, and ocular artifacts (Gao, 2007; Hamm et al., 2011; Hayrynen et al., 2016). Prior to analyses, each subject's evoked fields were standardized over all time points and sensors, yielding evoked fields in a common neural response space that could be compared across subjects and between groups. Evoked fields butterfly plots, averaging over conditions, along with M100

topographies, are shown in **Figure 2**, which illustrate typical signal-to-noise. Signal-to noise for short interval responses is insufficient for reliable individual source estimates (Fuchs et al., 2017; Wagner et al., 2004). Instead, we calculated magnetic global field power (mGFP), a measure of variance of signal at each point in time (Ahonen et al., 2016; Lehmann & Skrandies, 1980, 1984). Like a root mean square measure, larger mGFP (like at the time of the M100) indicates a stronger signal; smaller mGFP (like at the time of the M50) indicates a weaker signal. **Figures 3 and 4** show mGFP for long and short ISI stimuli by condition. Data were segmented into 10-ms bins from 45-ms pre-stimulus to 295-ms post-stimulus. To quantify group (healthy, SZ) by condition (paired, mixed, blocked) effects as a function of long versus short ISI we used mixed model ANOVAs on mGFP over time prior to baseline adjustment (which captures pre-stimulus and stimulus recovery activity more effectively; (Ethridge et al., 2011)) and then after baseline adjustment (the typical evoked response quantification approach). These tests were followed by source estimates (sLoreta in Brainstorm; (Tadel et al., 2011), on grand averages, at times of significant effects to illustrate the approximate distribution of brain activities that differentiated healthy and SZ groups. We selected sLoreta versus least-square minimum norm to obtain source estimates for three main reasons: (i) sLoreta has lower localization errors, (ii) we were not interested in the strength of the estimated sources, only their locations, for which sLoreta is well suited, and (iii) sLoreta works well under low signal-to-noise conditions, which is a particular concern for estimating sources in response to short ISI ("S2") stimuli (Pascual-Marqui, 2002; Pascual-Marqui et al., 2018; Wagner et al., 2004, 2007).

Results

Prior to baseline adjustment, there were two significant group main effects (see **Figure 3**): (i) in response to long ISI stimuli from just pre-stimulus up until shortly after stimulus presentation (-25-45ms) Avg $F(1,33) = 5.06$, $p<.047$; average effect size, Cohen's $d = -0.75$ and (ii) in response to short ISI stimuli in the M50 time range (45-75 ms) Avg $F(1,33) = 5.34$, $p<.049$; Avg Cohen's $d = -0.77$, SZ had greater mGFP activity in both time ranges. There were no significant interactions involving stimulus presentation condition. Magnetic fields difference plots and sLoreta solutions on the unadjusted data indicate that (i) greater SZ activity during the long ISI stimuli preparatory period was associated with sources in mostly right hemisphere frontal and parietal cortices; and (ii) greater SZ activity in response to short ISI stimuli in the M50 time range was associated with sources in mainly right auditory cortex and supramarginal gyrus.

Following baseline adjustment, there were two significant group main effects (see **Figure 4**): (i) in response to long ISI stimuli, in the M100 time range (115-135 ms), healthy had greater mGFP than SZ, Avg $F(1,33) = 4.43$, $p<.048$; avg Cohen's $d = 0.69$, and (ii) in response to short ISI stimuli, in the time range of the late part of the M200 (from 225-265 ms), healthy had greater mGFP than SZ, Avg $F(1,33) = 4.85$, $p<.045$; avg Cohen's $d = 0.80$. There were no significant interactions involving stimulus presentation condition. Magnetic fields difference plots and sLoreta solutions on the baseline adjusted data indicate that (i) in response to long ISI stimuli healthy had greater M100 activity mainly in right primary auditory and temporo-parieto-occipital junction; and (ii) in response to short ISI stimuli healthy had greater activation in the later M200 time range in temporal, inferior frontal, and parietal cortices.

Discussion

This project provides novel information about the interpretation of traditional paired-stimuli paradigm outcomes used to assess basic auditory processing in schizophrenia and psychosis syndromes. Analyses of neuromagnetic responses showed replication in the three previously mentioned time ranges: preparation, response to S1, and recovery from stimulation. The similarity of effects across context indicates they may be mostly related to fundamental auditory sensory processing functions.

First, the importance of preparatory effects was evident in two outcomes: (i) there was a baseline offset difference (SZ>healthy) in response to long ISI stimuli, replicating other studies using the same and different paradigms (Clementz & Blumenfeld, 2001; Ethridge et al., 2011; Hamm et al., 2014; Hudgens-Haney et al., 2018); and (ii) there was a difference in M50 amplitude to the short ISI stimuli (SZ>healthy) that disappeared after adjusting for pre-stimulus activity, also recapitulating previous findings (Ethridge et al., 2011; Hudgens-Haney et al., 2018). Both of these outcomes may be related to exuberant intrinsic activity observed among a subset of psychosis cases (Clementz et al., 2016). Second, the importance for group differentiation of the M100/N100 response to auditory stimuli after longer (>3 sec but not shorter stimulus delays after baseline adjustment replicates previous reports (Clementz & Blumenfeld, 2001; Johannesen et al., 2005; Johannesen et al., 2013; Shelley et al., 1999), and implicates problems with basic sensory registration of salient stimuli among at least a subset of psychosis cases (Clementz et al., 2016; Clementz et al., 2008). Third, difference in later stimulus processing, especially in recovery from stimulation has been previously reported in psychosis (Ethridge et al., 2011). Because recovery functions between psychosis and healthy subjects

differ, the interpretation of group sensory processing differences to closely spaced stimuli are especially complicated (Wang et al., 2010), and may require paradigmatic manipulations to properly parse the relevant disrupted neural operations.

It is often assumed that the invariant nature of the paired-stimuli task, with its 'condition-test' format, is essential to assessing psychosis relevant stimulus processing deviations. The outcomes of the present project, however, indicate that the ISI, rather than the specific paired-stimuli context, may be more relevant for indexing critical psychosis-relevant fundamental sensory deviations. These outcomes require replication and extension in larger and more diverse psychosis samples; we had a mixed group of schizophrenia cases here so it is uncertain whether specific neurobiological types may have unique result profiles across context. If variation in stimulus context, however, is largely irrelevant for assessing at least some aspects of basic psychosis-relevant sensory processing deviations, this would be an important advance in useful knowledge supporting novel translational investigations.

The strengths of our study include the technology used for auditory neural processing assessment (MEG), which is ideally suited for this type of investigation (Supek and Aine, 2014), and the use of multiple means for assessing auditory processing to physically identical stimuli ("S1" and "S2" in different conditions, although S1 always had the same long ISI and S2 always had the same short ISI). The only parameter that changed was the expectation on the part of the subject of when an S1 versus an S2 would occur. Among limitations, most patients were medicated, so the effect of treatment cannot be excluded. In other projects with larger samples, however, we have not found large proportions of variance in ERP responses associated with medication status (Clementz et al., 2016; see also Hamilton et al., 2019a, 2019b).

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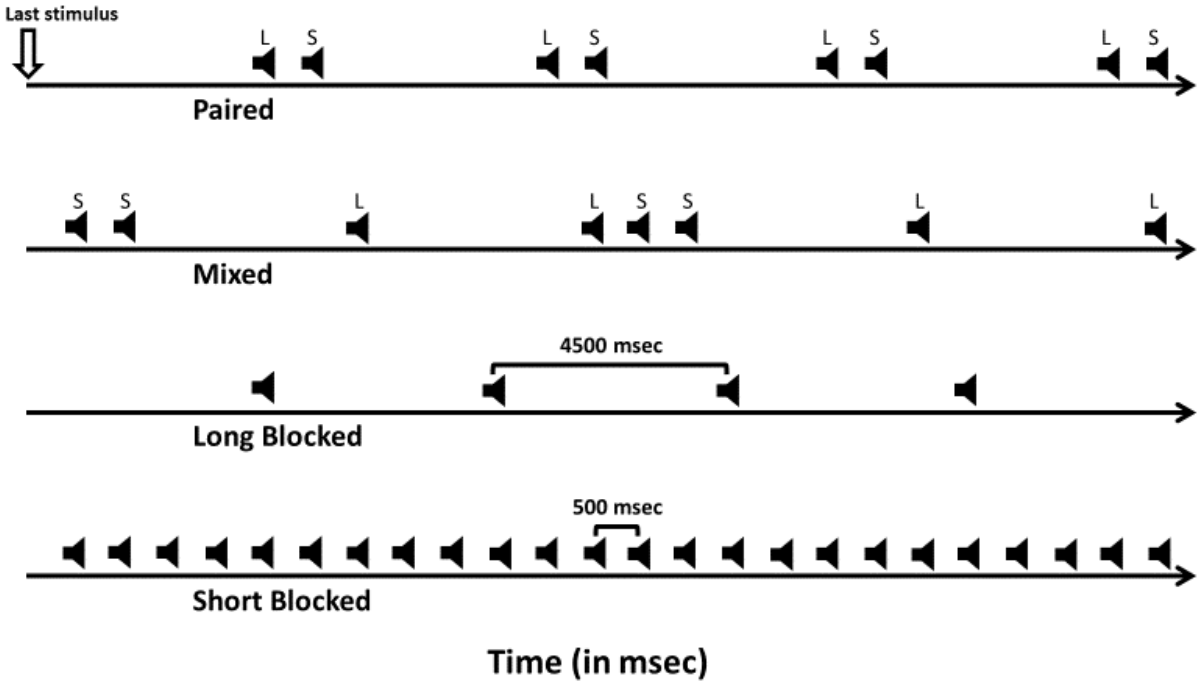

Figure 3.1 Grand averaged butterfly plots (all 143 MEG sensors; sensors have different colored lines) of the evoked magnetic fields in response to long ISI (left panels) and short ISI (right panels) stimuli. Stimuli occurred at time 0 on the x-axis. The plots have been averaged over all contexts for healthy persons (top panels) and schizophrenia subjects (bottom panels). The inserted top-down fields topography of the M100 is shown for each grand average, and they illustrate the expected dipolar configuration over left and right auditory cortices for these binaural stimuli.

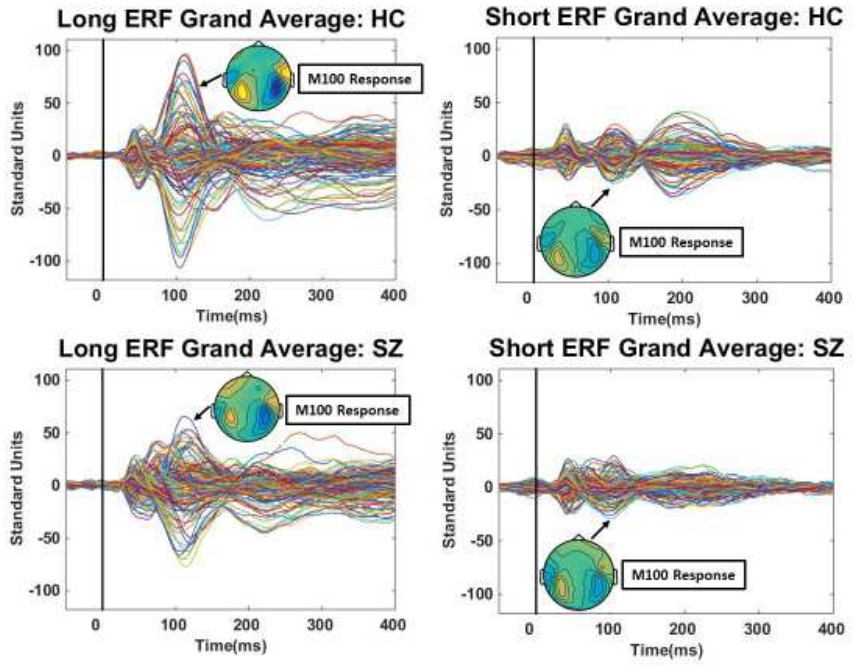

Figure 3.2 Grand averaged butterfly plots (all 143 MEG sensors; sensors have different colored lines) of the evoked magnetic fields in response to long ISI (left panels) and short ISI (right panels) stimuli. Stimuli occurred at time 0 on the x-axis. The plots have been averaged over all contexts for healthy persons (top panels) and schizophrenia subjects (bottom panels). The inserted top-down fields topography of the M100 is shown for each grand average, and they illustrate the expected dipolar configuration over left and right auditory cortices for these binaural stimuli.

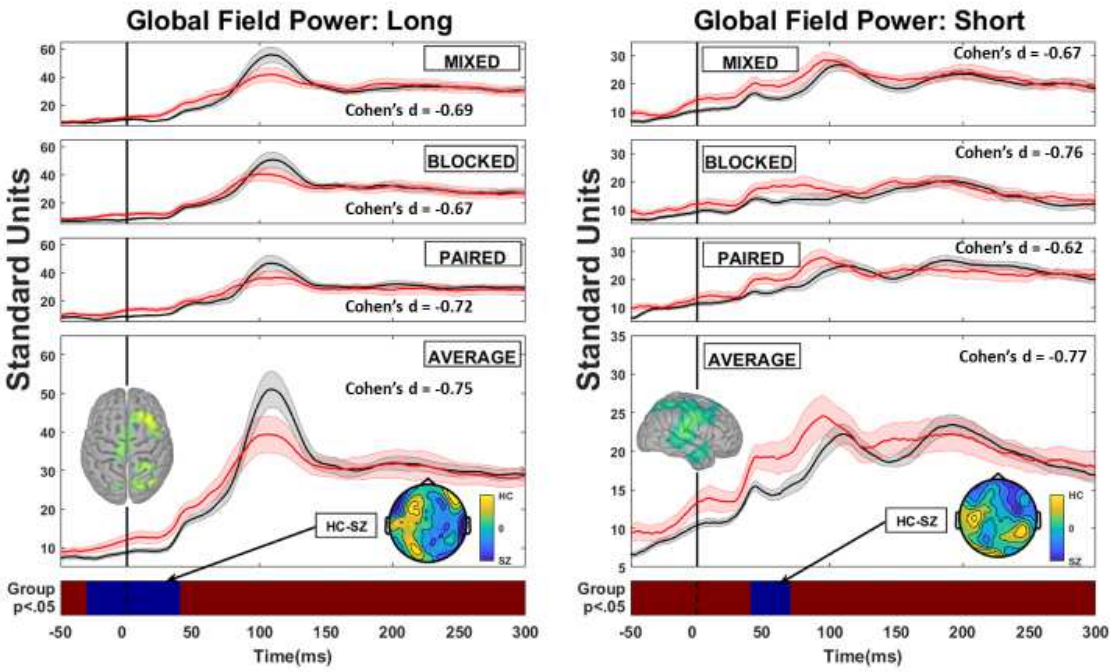

Figure 3.3 Grand average magnetic global field power plots prior to baseline adjustment for healthy (black lines) and schizophrenia cases (red lines) as a function of context (mixed condition is when ISIs were randomly interleaved; blocked condition when one ISI only is presented in series; paired condition is the typical paired-stimuli configuration with long followed by short ISI repeatedly). Long duration plots are in the left hand panels and short duration plots are in the right hand panels. The grand average over all contexts is shown in the bottom panel, along with the regions of statically significant group comparison differences (blue regions) against the non-significant red strip at the bottom (there were no significant interactions so only the main effect of group is displayed). Stimuli occurred at time 0 on the x-axis. The inserted top-down fields topographies below the grand average line plots illustrate the main effect difference between healthy and schizophrenia cases. Effect sizes are shown for the region of the statistically significant main effect for individual contexts (even though there were no significant interactions) as well as for the grand average over contexts. The inserted top-down

source topographies above the grand average line plots illustrate the source configuration for the region of statistically significant difference.

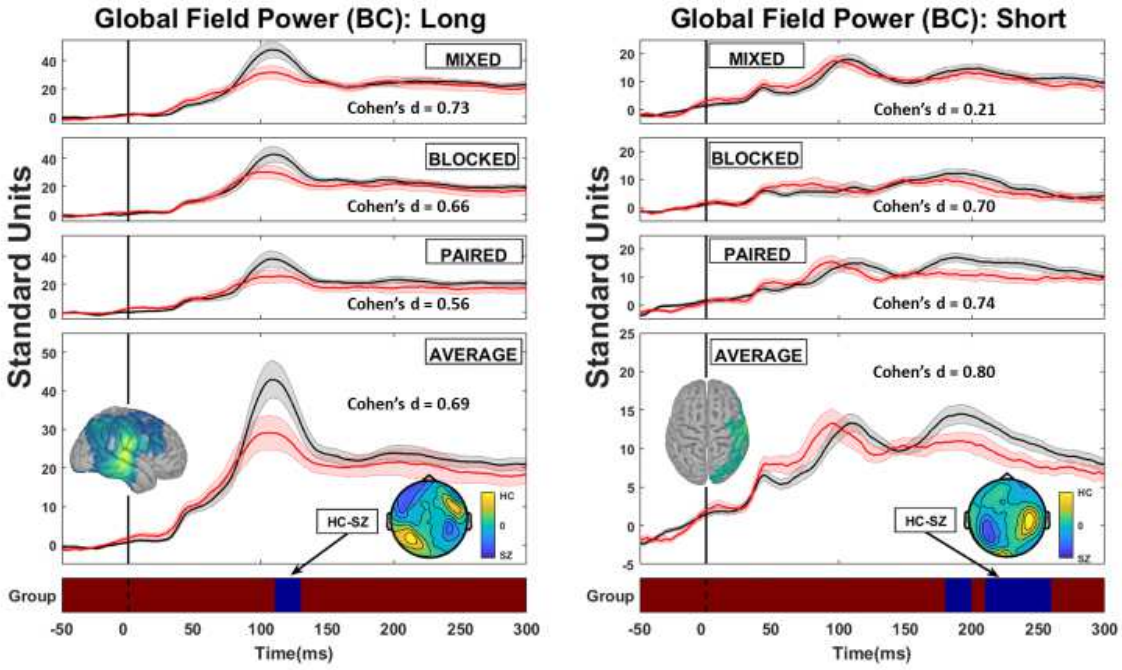

Figure 3.4 Grand average magnetic global field power plots following baseline adjustment for healthy (black lines) and schizophrenia cases (red lines) as a function of context (mixed condition is when ISIs were randomly interleaved; blocked condition when one ISI only is presented in series; paired condition is the typical paired-stimuli configuration with long followed by short ISI repeatedly). Long duration plots are in the left-hand panels and short duration plots are in the right-hand panels. The grand average over all contexts is shown in the bottom panel, along with the regions of statically significant group comparison differences (blue regions) against the non-significant red strip at the bottom (there were no significant interactions so only the main effect of group is displayed). Stimuli occurred at time 0 on the x-axis. The inserted top-down fields topographies below the grand average line plots illustrate the main effect difference between healthy and schizophrenia cases. Effect sizes are shown for the region

of the statistically significant main effect for individual contexts (even though there were no significant interactions) as well as for the grand average over contexts. The inserted top-down source topographies above the grand average line plots illustrate the source configuration for the region of statistically significant difference.

TRANSITION 1

Study 1 evaluated the traditional paired-stimulus paradigm as a necessary context to elicit the typical S1-S2 brain response in healthy and psychosis cases. The use of fixed interstimulus intervals (long and short) allowed for alterations of stimulus context by imposing an expectative element through repetitive stimulus configuration. This showed that there were no top-down signals biasing basic auditory processing of the stimuli and that group differences were more a difference in fundamental auditory processing, not a context specific to the paired-stimulus procedure.

In Study 2 context will be evaluated in the visual systems with a task designed to measure visual spatial attention in younger and older persons. Like the previous study, the visual array will be presented using a semi-static method by locking the visual stimulus with central fixation. Subjects will be instructed to attend to different spatial locations through task instruction while maintaining fixation throughout. This design utilizes a steady-state component to track where subjects are attending based on brain activation associated with spatial features of the stimulus. Contextual changes to the stimulus are introduced through instructions as to where to attend. Due to the central fixation feature of the stimulus, subjects will be required to covertly attend to alternate peripherally located stimuli. It will test top-down control of sustained visual spatial attention across the young and older groups. This study will also measure macular pigment optical density as a measure of retinal health and evaluate the ways it may affect spatial attention and processing of the visual array. Contextual modulation will allow for measurement of top-down biasing, basic sensory processing in the visual systems, and retinal health as a marker of neurophysiological mechanisms.

CHAPTER 4

NEURAL ACTIVATION DURING VISUAL ATTENTION DIFFERS IN INDIVIDUALS WITH HIGH VS. LOW MACULAR PIGMENT DENSITY[2]

[2] Oliver, W., Renzi-Hammond, L. M., Thorne, S. A., Clementz, B., Miller, L. S., & Hammond Jr, B. R. (2019). Neural activation during visual attention differs in individuals with high versus low macular pigment density. *Molecular nutrition & food research*, *63*(15), 1801052. Reprinted here with permission of publisher

Abstract

Scope: The neural efficiency hypothesis for lutein (L) and zeaxanthin (Z) suggests that higher levels of L+Z in the central nervous system (CNS) are predictive of stronger stimulus-specific brain responses. Past research suggests that supplementing L+Z can improve neural processing speed and cognitive function across multiple domains, which supports this hypothesis. The purpose of this study was to determine the extent to which CNS L+Z levels predicted brain responses using an attentionally taxing task.

Methods and results: Macular pigment optical density (MPOD) was measured at baseline in 85 participants ranging in age from 18-92 years. Brain activation was measured using dense array electroencephalography (EEG). Stimuli evoking the signal included a grating array of vertical bars, oscillating at four driving frequencies. Significant stimulus-specific interactions were detected between attend condition, location, and age ($p < .002$) for unattended image locations, and between age and location ($p < .008$) for attended locations. Although no differences were found across age by MPOD, this measure was found to be predictive of neural power at parafoveal bar locations (R^2 .080).

Conclusion: CNS L+Z status is related to differences in brain activation in conditions designed to stress visual attention. These differences were strongest for older subjects.

Introduction

One prominent view of cognitive aging focuses on sensory decrements: as sensory systems decline, the cognitive systems that depend on their input diminish as well (Baltes & Lindenberger, 1997). There is little doubt that sensory loss is accompanied by a loss in saliency (e.g., (Tsvetanov, Mevorach, Allen, & Humphreys, 2013)) and a reduction in the amount of information processed at any given time (Myerson, Hale, Wagstaff, Poon, & et Al, 1990): a typical 80 year old will perceive only about half of what a young person would in a similar circumstance (Schneider & Pichora-Fuller, 2000). Sensory loss both drives and accompanies cognitive loss. There is high comorbidity between sensory and cognitive decline (e.g., (Chung et al., 2015; Gurgel et al., 2014)) and both share similar risk factors (e.g., (Kaarniranta, Salminen, Haapasalo, Soininen, & Hiltunen, 2011)). It could be argued that the human brain is a vision-dominated organ (e.g., (Posner, Nissen, & Klein, 1976)), but loss and/or alteration of even less dominant senses, such as olfaction, is a reliable indicator of cognitive loss and dementia (e.g., (Velayudhan, Pritchard, Powell, Proitsi, & Lovestone, 2013)).

The close correspondence between sensory and cognitive development and loss implies a similar parallel with improvement. This has been shown, compellingly, in studies looking at the cognitive benefits that follow cataract surgery (e.g., (Ishii, Kabata, & Oshika, 2008; Jefferis, Clarke, & Taylor, 2015; Tamura et al., 2004)) and the use of hearing aids (e.g., (Dawes et al., 2015)). On the developmental side, sensory maturation both drives and accompanies cognitive development. For instance, strabismus drives amblyopia and alterations in somatosensation accompany many forms of autism spectrum disorders (e.g., (Marco et al., 2012)) and cognitive ability in younger individuals (perhaps due to areas such as the insula which integrate affect, cognition, and somatosensation; (Chang, Yarkoni, Khaw, & Sanfey, 2012)). Even subtle sensory

issues, such as uncorrected refractive errors or hearing loss are often linked to problems with academic performance (e.g., (Dudovitz, Izadpanah, Chung, & Slusser, 2015; Narayanasamy, Vincent, Sampson, & Wood, 2015; Orlansky et al., 2015)).

The purpose of this study is to examine a factor that has been shown to influence both sensory and cognitive systems, the dietary xanthophlls. In retina, the xanthophyll lutein (L) and its isomers, zeaxanthin (Z) and meso-zeaxanthin (MZ) accumulate in the inner layers of the macula and there are referred to as macular pigment (MP). Macular pigment levels (quantified as optical density, OD) can be measured non-invasively (MPOD) and measures in retina correlate strongly with brain cortical levels in humans (Rohini Vishwanathan, Schalch, & Johnson, 2015). The macular xanthophylls have antioxidant and anti-inflammatory properties and protect the retina against degenerative disease, particularly macular degeneration (Chew et al., 2014). L has also been linked to preventing dementia through some of the same mechanisms (Akbaraly, Faure, Gourlet, Favier, & Berr, 2007; Feart et al., 2015; Rinaldi, 2003). MPOD, however, has also been linked to improving normal visual function (Emily R Bovier & Hammond, 2015) and, lately, has been linked to improving cognition as well (E R Bovier, Renzi, & Hammond, 2014; Feeney et al., 2013; Hammond et al., 2017; Johnson et al., 2008, 2013; Lindbergh et al., 2016; Renzi-Hammond et al., 2017; L M Renzi, Dengler, Puente, Miller, & Hammond, 2014; R Vishwanathan et al., 2014; Walk et al., 2017).

What do these parallels imply? Perhaps the most straightforward interpretation is simply that increased MPOD reflects a healthier brain accompanied by less retinal and central neural degeneration. Another interpretation is that by improving visual function, visual (and even auditory (Wong, Kaplan, & Hammond, 2016)) saliency could also be improved and cognition would benefit. Yet another interpretation would be that L at the level of the brain is associated

with specific neural changes that underlie cognitive abilities (the neural efficiency hypothesis, e.g., (E R Bovier et al., 2014; Lisa M Renzi & Hammond, 2010; Walk et al., 2017). To explore these possibilities, we tested a sample of younger and older adults with a range of MPOD, as part of a larger study on the relation between L+Z status and cognitive function. Brain activity was measured directly via high-density electroencephalography, with high temporal precision, while participants performed a visual attention task. Importantly, this task was derived from a paradigm by Clementz et al (Clementz, Wang, & Keil, 2008) designed to tax attentional resources in cognitively vulnerable patients with high levels of underlying neural noise by using the steady-state visual evoked potential method (ssVEP). The ssVEP is observed when participants are presented with oscillating (flickering) visual stimuli. The electro-cortical brain response will entrain itself to the frequency of the stimulus being attended by the participant. When visual stimuli are presented at multiple frequencies, with each stimulus maintaining its own static frequency, it allows the researcher to "frequency tag" what is being attended, whether the subject's attention is direct or covert (Clementz et al., 2008; Muller, Malinowski, Gruber, & Hillyard, 2003). The amplitude at which these neural populations oscillate is quantified using a frequency transformation and measured as power at the frequencies of interest.

1. Experimental Section

As part of a larger study on MPOD and cognitive and neurological function (Hammond et al., 2017; Lindbergh et al., 2017; Renzi-Hammond et al., 2017), data from 85 right-handed community-dwelling adults were analyzed in this sub-study. The young adult study group (n = 43) was composed of male and female participants aged 18-30 years (M = 20.79 ± 2.16 years; 46.5 % female). The older adult study group (n = 42) was composed of male and female adults aged 65-92 years (M = 72.36 ± 6.58 years; 61.9 % female) (see **Table 1**). All participants were

recruited from the local Athens-Clarke County population and from the University of Georgia student population. Past research suggests that xanthophyll carotenoids are not effective in improving cognitive function in participants with Alzheimer's disease (e.g., (Nolan et al., 2015)). Consequently, the Clinical Dementia Rating Scale (CDR) (Morris, 1993) was administered prior to participation to exclude participants with possible dementia (CDR global score > 0.5) . The University of Georgia Institutional Review Board approved all study materials and procedures, and the tenets of the Declaration of Helsinki were adhered to at all times while this study was conducted. All participants issued written and verbal informed consent prior to participation.

MPOD

At baseline, MPOD was measured at 30-minutes of retinal eccentricity using customized heterochromatic flicker photometry (Stringham et al., 2008) with a table-top device described by Wooten et al (Wooten, Hammond, Land, & Snodderly, 1999). Measurement in young participants was described in Renzi-Hammond et al (Renzi-Hammond et al., 2017), and measurement in older participants was described in Hammond et al (Hammond et al., 2017). Briefly, a visual stimulus array consisting of 460 nm and 570 nm light-emitting diodes (LED) was used to create the perception of flicker. The difference in energy of the 460 nm portion of the stimulus required to eliminate flicker in the fovea (where MP accumulates), compared to the parafovea (where MP is low or absent), was used to derive MPOD. This method is the most common method of measuring MP and has been extensively validated for these groups (e.g., see (Hammond et al., 2005)).

Visual Attention

Stimuli and Procedure

Visual stimuli consisted of two superimposed square images (originally described by (Clementz et al., 2008), both of which consisted of five equally spaced bars. In the first image, hereafter referred to as the "to be attended" image, the bars were vertical and red in color. In the second image, the bars were horizontal and green in color (see **Figure 1**). In both images, bars of 1 deg visual angle were isoluminant (5.5 cd/m^2 against a 0.1 cd/m^2 background) and were designed to activate V1 simple cells (Hubel & Wiesel, 1962). The superimposed square stimulus was presented on a 21" high resolution, flat surface color monitor with a 100 Hz refresh rate, presented 60 cm from participants' eyes, to subtend nine total degrees of visual angle.

A dim, grey fixation dot was presented at the center of the stimulus array. Participants were instructed to maintain fixation on the dot during two attentional manipulations: attend-mid, and attend-peripheral. In the attend-mid condition, participants were instructed to maintain gaze on the fixation dot, but pay attention to width changes (50-75% increase in width) in the middle (foveal) bar, which flickered at 7.69 Hz. In the attend-peripheral condition, participants were instructed to maintain gaze on the fixation dot, but pay attention to width changes (50-75% increase) in the two peripheral (parafoveal) bars that bordered the middle bar. The peripheral bars flickered at 7.14 Hz. In both the attend-mid and attend-peripheral conditions, participants were instructed to press a button each time they noticed the width change. Participants were not instructed to attend to the outside bars, which flickered at 6.67 Hz, or the red horizontal bars, which flickered at 8.33 Hz. Trial blocks lasted a total of two minutes. Each participant completed four total trial blocks for each condition (attend-mid and attend-peripheral).

EEG Recording

EEG data were recorded using a 256-channel Geodesic Sensor Net and NetAmps 200 amplifiers (Electrical Geodesics, Inc.). Recordings were vertex referenced (sensor Cz). As is standard with high impedance amplifiers like those from EGI, sensor impedance values were less than 50 kΩ. Data were analog filtered from 0.1-100 Hz, digitized at 500 Hz and recorded continuously throughout the two-minute trial blocks.

Analysis

Raw data were visually inspected for bad sensors (<5% for any participant), which were replaced using a spherical spline interpolation method (as implemented in BESA 5.3). Data were transformed to an average reference and digitally filtered from 2 to 40 Hz (12 db/octave rolloff, zero-phase). To ensure that steady state had been adequately established, we used only the last 100 s of each 120 s trial block. The 100 s window yields 0.01 Hz resolution, which was necessary to quantify neural response magnitudes at the specific oscillation frequencies used in the present study. Eye blink artifact, heart rate, and muscle tension were removed by visual inspection using the ICA toolbox in EEGLAB 12.0.2 (Delorme & Makeig, 2004) under Matlab (version 8.4, MathWorks) under previously established protocols (Clementz et al., 2008; Ethridge et al., 2012; Hamm et al., 2013; Hamm, Gilmore, Picchetti, Sponheim, & Clementz, 2012). Artifact corrected data were then transformed to the frequency domain using a fast Fourier transform (FFT). These spectral data show power across the frequency spectrum, power representing the strength with which neural populations are oscillating at frequencies of interest. FFT power, which at the frequency of stimulation averaged over 36 EEG sensors that captured

the maximal signal, was used to quantify strength of sustained visual selective attention (for example, see also [47], **Figures 2 and 3)**.

We quantified nonspecific brain activity in the region spanned by the driving frequencies (6.5– 8.5 Hz, excluding the driving frequencies themselves). In addition, to adjust for possible nonspecific brain activity differences between groups, we subtracted the mean power of 20 bins (0.1 Hz) around the unique driving frequencies (6.67, 7.14, 7.69, and 8.33 Hz) from steady-state visual evoked potentials (ssVEP) for each subject before making group comparisons on sustained visual selective attention [48]. Thus, we have a measure of nonspecific brain activity and a measure of stimulus-specific brain activity.

Statistical Analyses

Statistical analysis was completed using SPSS, version 25 (IBM). The neural efficiency hypothesis (Hammond & Wooten, 2005; Lisa M Renzi & Hammond, 2010) predicts a positive relationship between MPOD and effective attentional modulation, and a negative relationship between MPOD and neural noise. Due to the novel approach of this study using these EEG measurements there were no data available to conduct a proper power analysis to determine sample size. There was, however, a power analysis calculation based on previous samples that have supplemented LZ and measured changed in macular pigment optical density. In a similar study using a case-control design, the same sample size, LZ dose and duration, there were noted significant MP and visual function changes (Hammond, Fletcher, Roos, Wittwer, & Schalch, 2014). These analyses concluded that if an effect size for the MPOD increase of 0.16 ± 0.21 (SD) and a 20% drop-out rate were assumed, the study with 50 subjects per group would have a power of 92% (at $\alpha = 0.05$, two sided). Given the fact that this study represents one of the first times that this hypothesis has been tested in adult participants, in an EEG environment with

induced noise, we used a non-directional (two-tailed) testing approach. An alpha = .05 was used as the criterion for statistical significance. When applicable, correction was applied for multiple comparisons.

2. Results

Non-Specific Activation

A repeated-measures analysis of variance was applied to the non-specific activation surrounding the driving frequencies. This was the range of 6-9 Hz but excluding the driving frequencies ± .01 Hz. Participants did not differ by age or by MPOD in non-specific brain activity surrounding the driving frequencies ($F[1,83] = .80, p = 0.37$). There were also no significant interactions between MPOD and age on non-specific activation ($F[1,83] = .003, p = 0.96$). (**Figure 4**).

Stimulus Specific Activation

1. Age Effects

<u>Unattended Images</u>

Younger participants showed reduced power to the outside bar location and increased power to the horizontal background during the attend peripheral condition. A repeated-measures ANOVA was applied to the unattended outside bars and background image. This statistical method yielded a significant interaction between attend condition, unattended image location, and age ($F[2,82] = 10.358$, $p = 0.002$) (**Figure 5**). These group differences to unattended images were only present during the attend peripheral condition. During the attend middle condition, the only group effects are those seen at the attended, middle bar location (see below).

Attended Images

There was a significant interaction for a repeated-measures ANOVA between age and location attended ($F[1,83] = 7.48, p = 0.008$), with young participants showing greater ability to modulate attention to the middle bar location between attend conditions. (**Figure 5**). Although older adults were able to modulate attention between the attend middle and attend peripheral conditions, the shift in power was greatly augmented in younger adults. Across the two attend conditions the primary differences in power at the driving frequencies are seen at only the middle bar frequency, with all other locations remaining relatively steady across conditions. Older adults, on the other hand, show an inversion of power at the attended frequencies between conditions.

2. MPOD Effects

T-tests were applied to MPOD measures in order to determine if group differences in MPOD would be a possible determining factor if any significance was observed when a regression model was applied to the data. MPOD was not significantly different between older and younger adult participants ($t,(83) = 1.813, p = .073$). To determine whether MPOD related to specific activation, it was used as the dependent variable in a predictive regression model, comparing power at each driving frequency across both attend conditions. MPOD significantly predicted power at the peripheral bar, independent of age ($F[4,80] = 1.74$, $p = .016$), with an R^2 of .080 (**Figure 6**).

3. Discussion

In this study, visual attention was measured by having subjects maintain visual fixation while conducting a task that required attending to various portions of a flickering visual stimulus. This task kept the visual stimulus constant at the retina but required top-down control, sourced from brain regions upstream from visual cortex (Clementz et al., 2008), to accommodate specific task demands. Our hypothesis was based on the premise that if the macular carotenoids were influencing this outcome that it would then, perforce, be post-retinal. This was a unique approach in the sense that at least some of the variance in past assessments (E R Bovier et al., 2014)(Emily R Bovier & Hammond, 2015) could always be influenced by the input side of the task. Our finding that MP covaried with visual attention in this EEG study, specifically at the parafoveal stimulus location, supports the hypothesis that the macular carotenoids are affecting visual processing in the brain itself. If that is so, then how might the pigments effect such change?

One possible mechanism is simply prophylactic: L and Z could prevent the cumulative deleterious effects of oxidative and/or inflammatory damage in the brain, as they do in retina. Recent research investigating this hypothesis using a rhesus macaque model found associations between membrane L levels and docosahexaenoic acid oxidative byproducts in prefrontal cortex myelin and striatal myelin, as well as mitochondria in prefrontal cortex, cerebellum and striatum (Mohn et al., 2017), which certainly supports this hypothesis. There are a number of other antioxidants that accumulate in cortical tissues (Craft, Haitema, Garnett, & Fitch, 2004),

however, so it is unlikely that even if L and Z are serving this function, they are uniquely or exclusively serving this function.

Another possibility, linked to protection, is based on improving vasculature. Early work on the macular carotenoids suggested they might help prevent neovascularization in the progression of macular degeneration (Izumi-Nagai et al., 2007). Lutein has also been linked to preventing atherosclerosis (Dwyer et al., 2001). The brain, like the retina, is highly vascularized and lutein, either localized in cells or circulation, might be expected to affect that vasculature. Recent research using the same participants as tested in this study suggests that supplementing L and Z can also change cortical blood flow, measured during a word recall test in an fMRI testing environment (Lindbergh et al., 2017), which would be consistent with vascular effects.

The idea that L and Z (particularly L) directly influence lipid peroxidation and, hence, myelin is intriguing and may provide at least part of the explanation for how they influence neural efficiency. Loss of white matter integrity and subsequent breakdown of information transmission within neural networks is known to reduce processing speed, which, in turn, influences executive function (Bennett & Madden, 2014; Madden, Bennett, & Song, 2009; Madden, Spaniol, et al., 2009; Satlhouse, Timothy A.; Madden, 2008). White matter loss tends to be exacerbated in older age; hence, processing speed tends to slow in older age. In this study, we also found differences in processing power by age, with younger adults better able to mediate covert attention than older adults. Research from our laboratories, using the same subjects tested in this study, suggests that L and Z are related to markers of white matter integrity, such as whole brain diffusivity and diffusivity in specific regions of interest associated with dementia (Mewborn, Terry, Renzi-Hammond, Hammond, & Miller, 2017). Corticothalamic pathways, specifically the lateral geniculate nucleus (LGN) and cortex, may also play a role in the

peripheral condition and the attended peripheral location lending predictive value to MPOD. The parafoveal location of these stimuli would place them in the visual stream passing through magnocellular processing pathways of the LGN and proceeding to the dorsal visual stream. Failure of top-down integration over lower level visual processing units, such as LGN, primary visual cortex, and dorsal visual stream, will lead to a reduced response to changes in environment. The dorsal visual stream's role is critical for navigating the environment and deficient top-down input in this stream causes improper attentional modulation during a demanding visual attention task. Other research from our laboratory, on the same sample of participants, suggests that supplementing L and Z can improve cognitive function in both the younger and older adult populations (Hammond et al., 2017; Renzi-Hammond et al., 2017). The current study is the first study of its kind that has attempted to "close the loop" on the neural efficiency hypothesis by using a paradigm that manipulates neural noise and measures power directly, to investigate these relationships.

There are a number of limitations that should be addressed in future studies aimed at understanding the role of L and Z in cognition and neural efficiency, with generalizability of the current sample being chief among them. With respect to baseline status, all of the participants tested in this study were well educated and relatively well nourished. The older adult sample that we tested did not contain any ethnic or racial diversity, despite attempts to recruit a generalizable sample. Consequently, we essentially tested the population *least* likely to benefit from L and Z supplementation, and the *least* likely to show an effect. The fact that an effect was seen is noteworthy. Future studies should attempt to sample from a more diverse population, including those individuals who may benefit from xanthophyll supplementation and dietary change.

Author Contributions

Per ICMJE guidelines, author contributions are as follows:

Study design: LRH, BH, WO, BC, LSM

Data acquisition: AT, WO, LSM, BH, LRH

Data analysis: WO, BC, LRH

Drafting and manuscript revision: BH, LRH, WO, BC

Final approval: all authors

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Conflicts of Interest Disclosure: During a portion of the data collection period, author LRH was an employee of Abbott Laboratories. Author LRH has been solely employed by the University of Georgia for the past three years, as of submission. No other authors have conflicts of interest to report.

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Table 4.1 Characteristics of younger and older participants analyzed in this study. Values are expressed as mean ± standard deviation, unless otherwise indicated.

Group	**Age (years)**	**Gender**	**Race / Ethnicity**	**CDR Global***	**Years of Education****	**MPOD**
Younger adults	20.79 ± 2.16	46.5% Female	89% Caucasian 8% Asian 3% Hispanic	N/A	12+	0.43 ± 0.17
Older adults	72.36 ± 6.58	61.9% Female	100% Caucasian	90.5% = 0 9.5% = 0.5	16.24 ± 2.87	0.50 ± 0.19

* Clinical Dementia Rating Scale global score.

** Younger adults were all students enrolled at the University of Georgia.

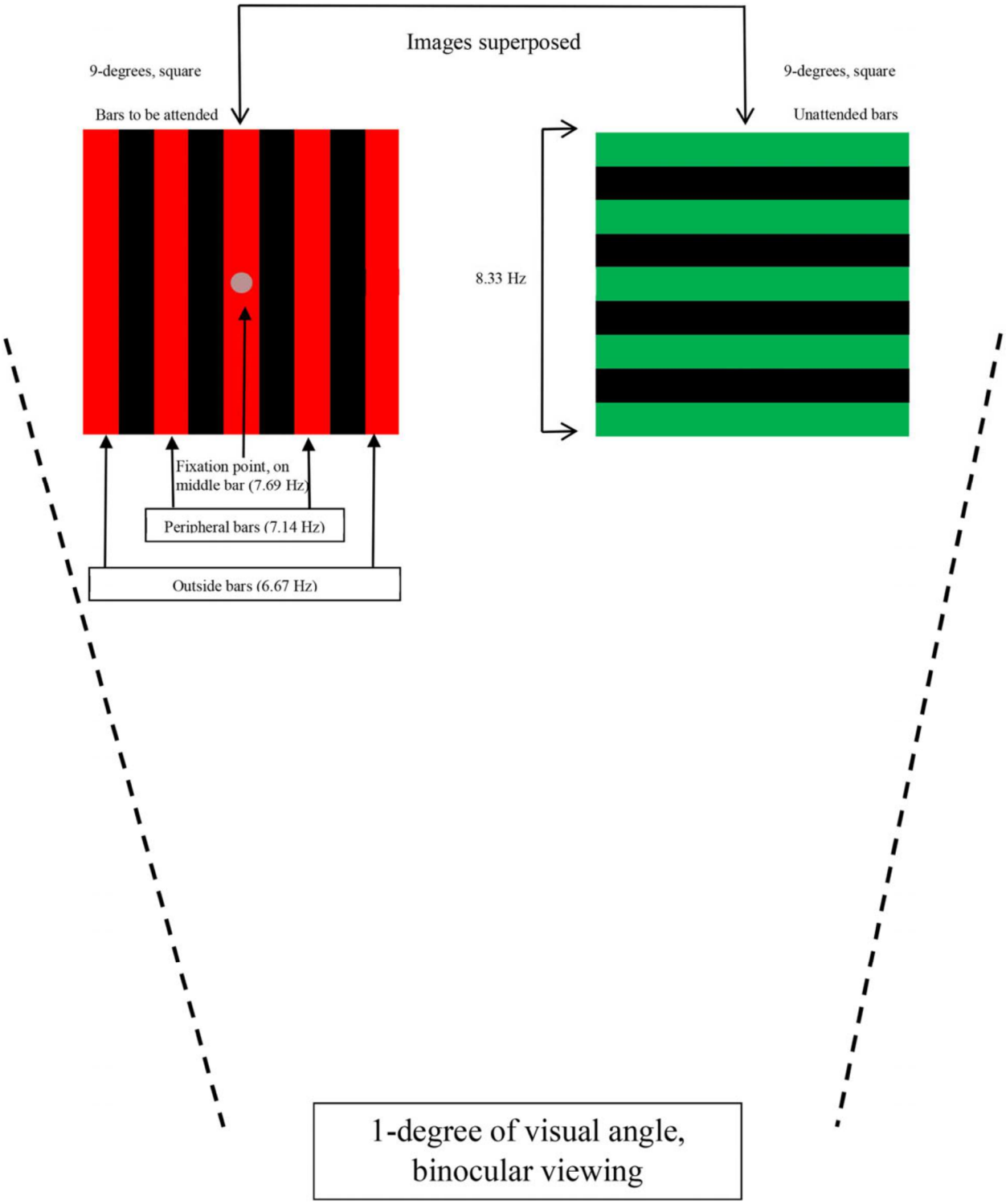

Figure 4.1 Stimulus array used to generate steady-state responses, adapted from Clementz et al., 2008

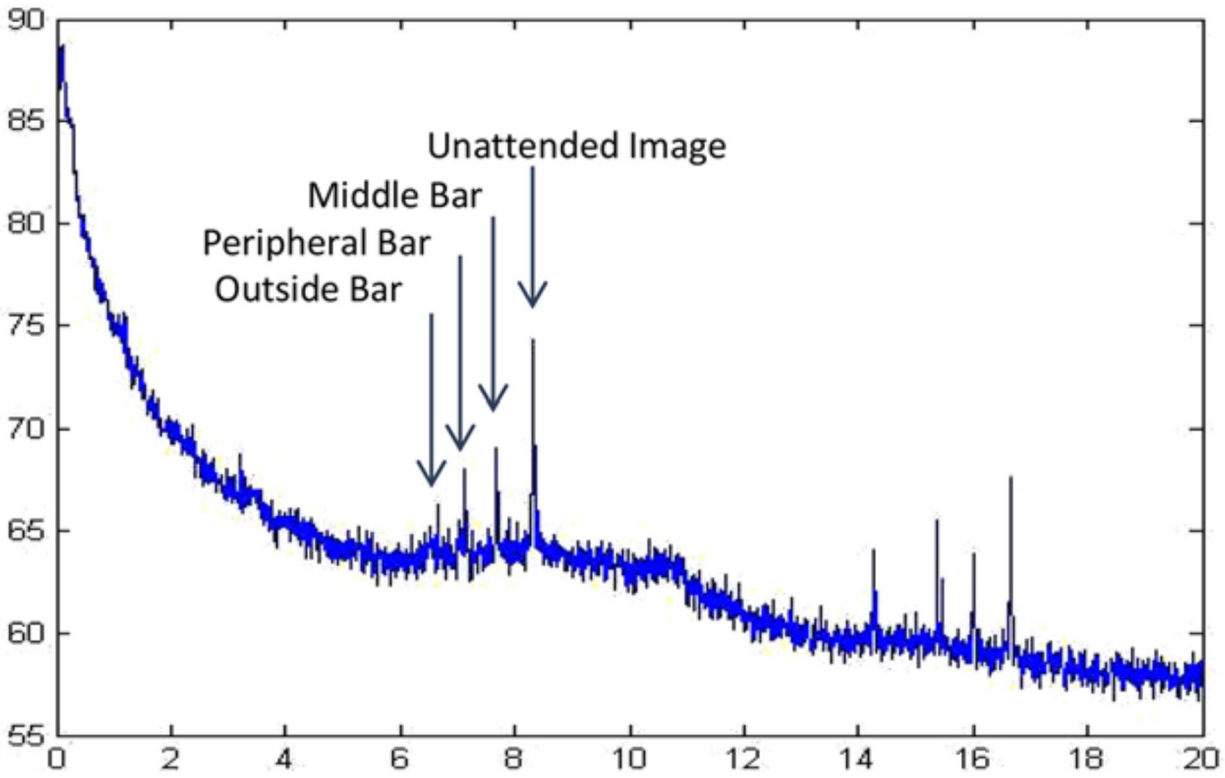

Figure 4.2 Fast Fourier transform showing driving frequencies for each bar position.

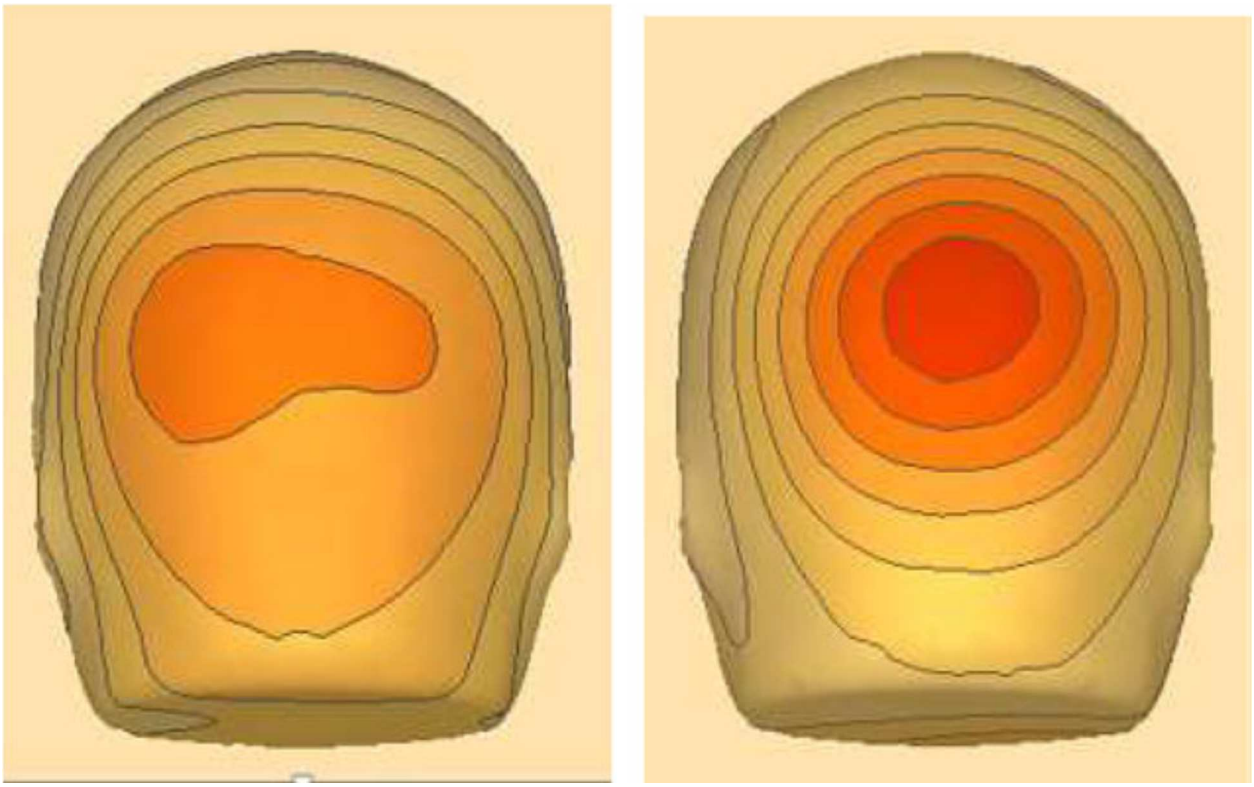

Figure 4.3 Topographies of the steady-state signal at the back of the head in young adults (left) and older adults (right). These topographies were used to determine the sensors that capture maximal at the driving frequencies of interest.

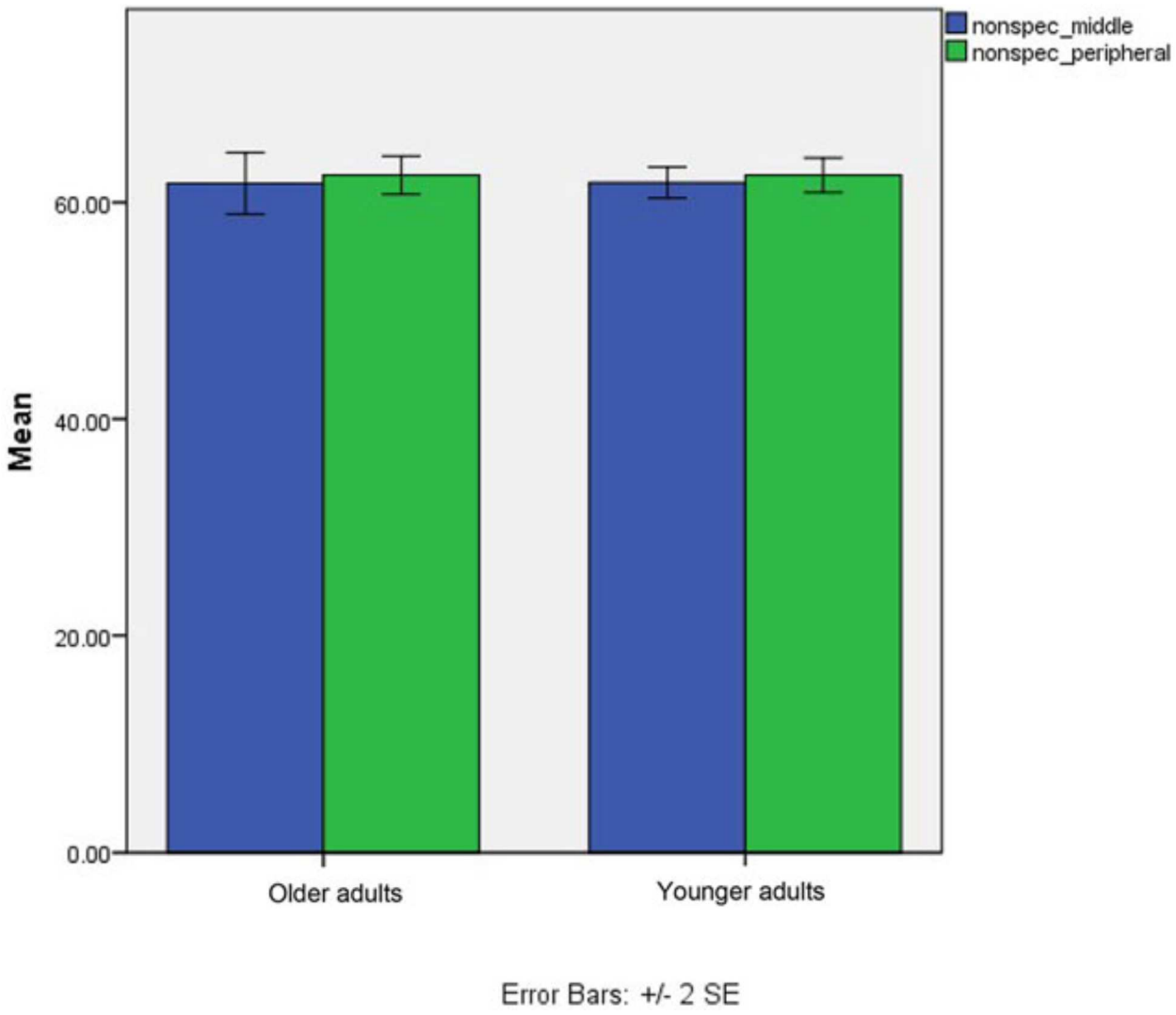

Figure 4.4 Nonspecific activity in the 6.5-8.5 Hz range, excluding driving frequencies. These graphs depict brain activity that is not specific to the attended images and intrinsic to these groups. The nonspecific activation is shown here across each group, across each attend condition. No significant differences were found between groups in this range of intrinsic activity.

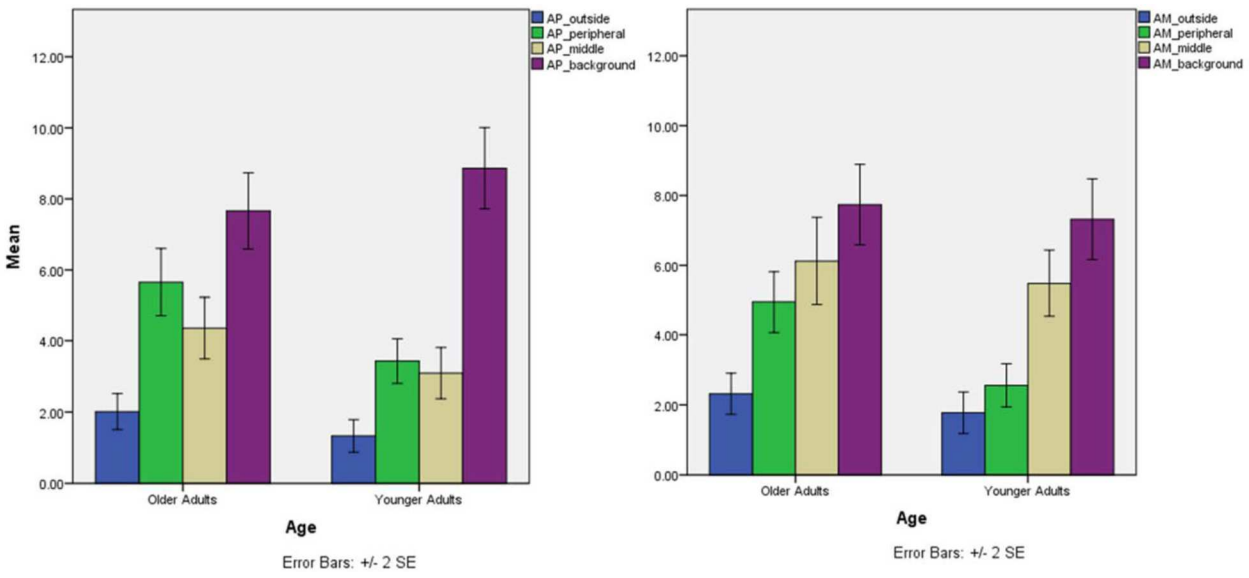

Figure 4.5 Power at each bar location during the attend peripheral (left) and attend middle (right) conditions is shown here, green (peripheral bar location) and tan (middle bar location) were attended stimuli. Attentional modulation is shown as inversion in power at middle and peripheral locations dependent upon instructed attend locations.

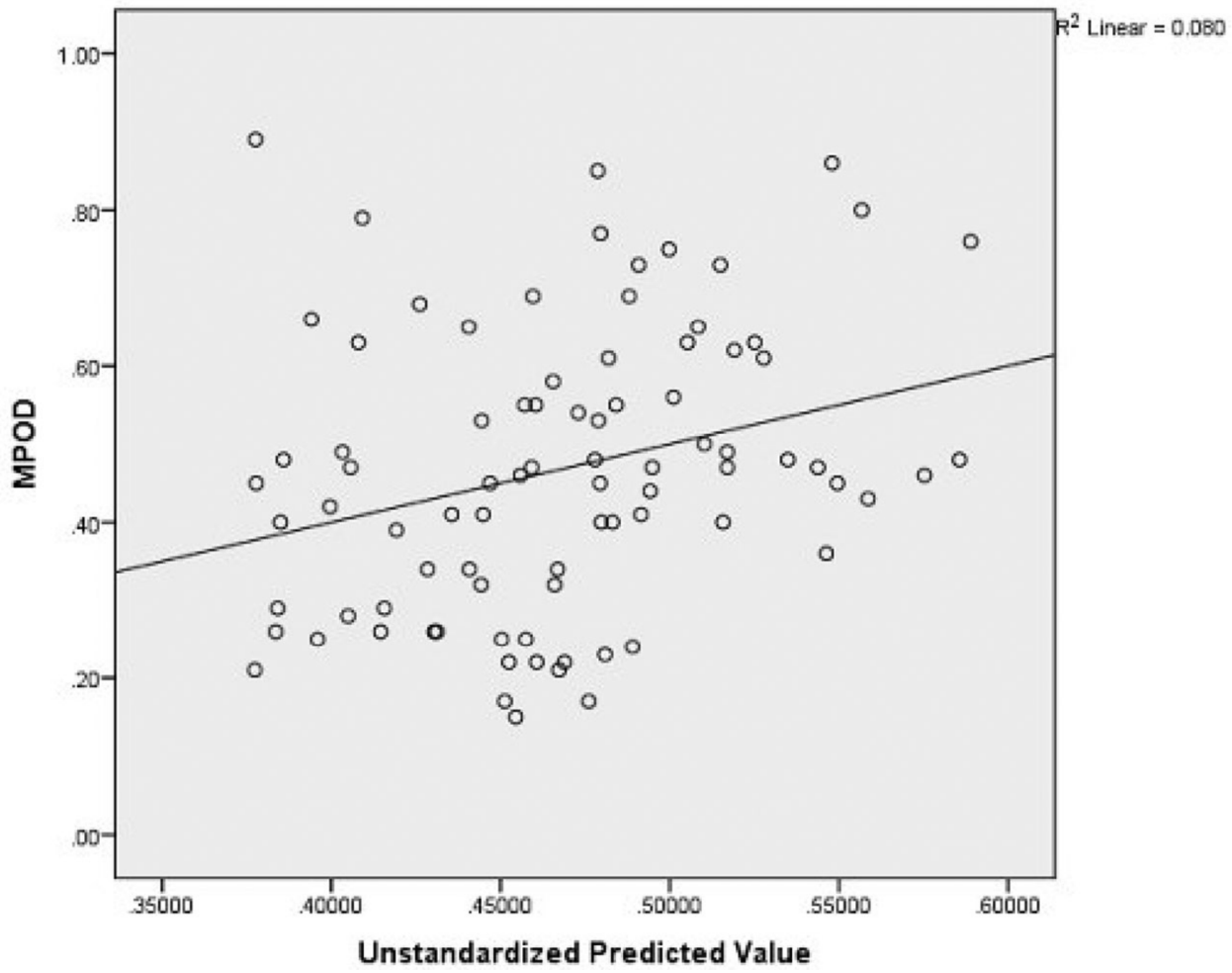

Figure 4.6 Regression analysis plot shown here for MPOD and peripheral bar power under the attend middle condition.

TRANSITION 2

Study 2 introduced a method that utilized a semi-static complex visual array in a way that allowed for altering the context of the stimulus through task instruction. This method was useful in showing top-down control over sustained visual attention without altering general stimulus properties at the level of the retina. Brain activation to specific stimulus features is adjusted through top-down biasing and shows how well subject can employ cognitive control to spatial features in the visual stream.

Study 3 will use a near identical stimulus array but will introduce an additional element in deviant stimulus features by altering the magnitude of the visual targets. Due to the characteristics of the stimulus that provide useful information in how well subjects can deploy cognitive control mechanisms to properly modulate visual spatial attention, this study will focus on the psychosis pathology and cognitive control capacity. On average persons with psychosis show poor performance in tasks requiring goal maintenance and behavioral inhibition, but it is possible that this is not specific to pathology and may be a function of cognitive control. In order evaluate the role of cognitive control during visual sustained attention healthy non-pathological subjects were recruited based on high cognitive control and low cognitive control capacity. Grouping subjects in this manner will show what aspects of the visual stimulus might be specific to cognition and which may be indicative of pathology.

The contextual alterations require top-down related cognitive control mechanisms to properly modulate attention and accurately identify targets of varying magnitudes. The complex visual stimulus array will allow for evaluation of models of selective attention and feature filtering mechanisms across psychosis and cognition by including unattended features to compare against attended stimulus locations. Context will again show use in evaluation of visual processing systems.

CHAPTER 5

TARGET DETECTION PROFICIENCY DURING SUSTAINED VISUAL SPATIAL ATTENTION[3]

[3] Oliver, W., Parker, D., Hamm, J., Edge, E., McDowell, J., & Clementz, B. A. (2021). Target Detection Proficiency During Sustained Visual Spatial Attention. *To Be Submitted to Schizophrenia Research*

Abstract

Attentional deficits are often evaluated using visuospatial target identification tasks in psychosis cases. These tasks require proper spatial allocation of attentional resources and the ability to detect targets within the instructed location. In order to successfully complete the task participants must deploy basic cognitive control mechanisms for goal maintenance and behavioral inhibition. Deficiencies in cognitive control are a common feature in those with psychosis, but are not specific to the pathology. A subset of non-pathological persons have cognitive control capacity similar to that seen in psychosis cases when tested on working memory function and goal maintenance, and may share similar neurophysiological features during sustained visual attention. To assess the role of cognitive control in visual spatial attention we recruited 78 healthy subjects, based on high cognitive control (HCC) and low cognitive control (LCC) capacity, and 47 subjects with schizophrenia (SZ). Subjects were tested on visual attention tasks using a superimposed array of horizontal and vertical bars, with bar features flickering at different frequencies. The steady-state visual evoked potential (ssVEP) was used to quantify spatial attention as enhanced brain activation to specific bar features. Behavioral responses and event related potentials (ERPs) to target bar width changes, varying in magnitude, were used to quantify target detection proficiency. Activity related to attended spatial locations were unaffected in SZ and LCC groups, and activity to unattended stimulus features were shown to be a function of cognitive control and pathology. Target detection performance was highest in the HCC group and deteriorated as a function of width change magnitude, cognitive control, and pathology. These findings indicate that some aspects of visual spatial attention are specific to the pathology of SZ, while others may be due to poor cognitive control capacity.

Introduction

The mechanism by which higher order brain regions influence behavioral requirements during cognitive operations is termed top-down or cognitive control. Top-down biases during task performance support attentional selection mechanisms (Beck & Kastner, 2009) and are related to what (Desimone & Duncan, 1995) called the "attentional template." Frontal and parietal cortical regions are consistently activated during tasks requiring top-down control, with reasonable evidence that cognitive control is initiated in higher order brain regions and influence sensory, including visual, cortices (Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Brett A. Clementz, Wang, & Keil, 2008; Geng et al., 2006; Johnston & Everling, 2006; Moore & Armstrong, 2003).

Cognitive control failures may cause behavioral, cognitive, and neural deviations observed in schizophrenia (SZ). Impaired cognitive control in SZ has been studied using a wide variety of tasks and measures. There is evidence of impairment compared to unselected healthy individuals on measures of working memory, attention, processing speed, and executive function in first episode and chronic psychosis (Hutton et al., 2004; Jang et al., 2011; Mcclure et al., 2007; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). SZ also exhibit deficits in early visual processing (Butler, Silverstein, & Dakin, 2008; Matthias M. Müller et al., 2008; Potts, O'Donnell, Hirayasu, & McCarley, 2002) that are attributed to directing, maintaining, and regulating visual selective attention (Fuller et al., 2006; Luck, Chelazzi, Hillyard, & Desimone, 1997). Early-stage visual processing abnormalities, which may limit cognitive performance (Perez et al., 2017; Adcock et al., 2009; Best et al., 2019)(Adcock et al., 2009; L. E. Ethridge et al., 2012; Gómez-Ramírez, Freedman, Mateos, Pérez Velázquez, & Valiante, 2017), are associated with poor long-term outcomes and community functioning in those with severe psychiatric syndromes (Kreither et al., 2017; Lexén, Hofgren, Stenmark, & Bejerholm, 2016). Cognitive performance

is associated with practical evidence of functioning such as job tenure and ability to benefit from rehabilitation, so it is important to understand the relationship between early sensory and higher-order processing in individuals with psychosis (Gold et al., 2002; Green, 1996; Green et al., 2000)(Chen, Seth, Gally, & Edelman, 2003; Constantinidis & Goldman-Rakic, 2002)(Green, 1996; Qreen, Kern, Braff, & Mint, 2000).

Although cognitive control in SZ has been extensively studied, SZ are often compared to healthy individuals with high levels of cognitive function. There is evidence of wide variability in cognitive capacity even among healthy people functioning in the community. Operation span, reading span, and symmetry span tasks index working memory as well as goal maintenance and inhibition (Unsworth & Engle, 2007). Healthy individuals with low cognitive control (LCC) as measured by those span tasks are more easily distracted and have difficulty maintaining goals, especially when those goals involve overriding instinctual responses (Unsworth et al., 2004; Unsworth & Engle, 2007; Kane et al., 2001; Schaeffer et al., 2013)(Schaeffer et al., 2013). LCC healthy persons display similar behavioral deficits and neural dysfunction seen in SZ cases, but without obvious indications of psychosis (Unsworth & Engle, 2007). Considering the similarities in behavioral manifestations of cognitive control abnormalities between LCC and SZ cases, it is unclear the extent to which cognitive deviations can be considered "characteristic features" of SZ-related neuropathology. In order to investigate this issue, two healthy comparison groups were used in this project, one with high (HCC) and one with low (LCC) levels of cognitive control (Unsworth & Engle, 2007).

Numerous mechanisms have been proposed to account for the diverse and often contradictory findings relating cognitive control to attention abilities and behavioral outcomes in SZ, including inhibition failures, deficient attentional resources, poor control or implementation of attention, poor filtering at the level of sensory cortices, insufficient cognitive reserve, and "hyper-focusing" (Kreither et al., 2017; Luck, Leonard, Hahn, & Gold, 2019; Michael et al., 2020; Neuhaus et al., 2011). Most previous studies and theoretical models start with higher order constructs like 'attention', 'inhibition', and 'cognitive capacity,' with only limited reference to more basic mechanisms that can be measured at the

neurophysiological level. Cognitive constructs are useful for facilitating communication, but, by their nature, they are complex and are the product of multiple sensory and perceptual processes that recruit multiple brain circuitries. There are many paths to dysfunction, so deviations can occur for multiple reasons that may or may not be captured by the higher order construct.

A different approach, one that has been successful in the history of neuroscience (e.g., Kandel, 2006), is to start by studying basic functions that underlie more complex constructs. This approach has the strength that more specific questions can be asked and answered, but the limitation that the outcomes may be less generalizable to real world functioning. Aberrant physiological responses are seen in SZ under experimental conditions that parse basic sensory and top-down modulated processes (B A Clementz, Wang, & Keil, 2008; Wang, Clementz, & Keil, 2007), with more basic visual studies indicate SZ cases exhibit deficits in early processing and selective attention tasks (Butler et al., 2007, 2008; Potts et al., 2002; Wang et al, 2009; Wang et al., 2011).

Studies supporting selective attention deficits in schizophrenia often rely on task that rely on target detection as the measure of attentional deployment (e.g., Chen & Faraone, 2000; Green & Nuechterlein, 1999). Procedures that decouple attentional modulation under top-down control and target detection show that these neurophysiological processes may be measured independently while temporally and spatially concurrent (Chen et al., 2003; Wang et al., 2007; Clementz et al., 2008). In addition, (Clementz et al. 2008) showed attentional selection, defined as sustained selective attentional facilitation in visual cortex, was normal in SZ under demanding sensory conditions, but target detection at those same locations was deficient.

Electrophysiological measures of sustained attention-related changes in cortical facilitation are sensitive to electrocortical activity early in processing, can discriminate sensory facilitation to overlapping stimuli (Driver, Davis, Russell, Turatto, & Freeman, 2001), and are capable of illuminating differences in neural background activity before and during stimulus presentation (Pinsk, Doniger, & Kastner, 2004), which may influence sensory and subsequent higher-level processing. A subset of SZ show increased cortical activations (e.g., Callicott et al., 2003; Clementz et al., 2008; Dierks et al., 1999;

Ethridge et al., 2011; Lee et al., 2006; Manoach et al., 2003; Spencer et al., 2004; Wang et al., 2010; Thomas et al, 2019), with Rolls et al. (2008) theorizing that pyramidal cell disinhibition could cause selective attentional dysregulation.

In this study, we replicate and extend Clementz et al. (2008) in two important ways. The steady-state visual evoked potential (ssVEP) was again used as the measure of neural mass activation in cortical regions processing grating-type visual stimuli. These stimuli have the desirable feature that they are optimal for activating simple cells in primary visual cortex (Hubel and Wiesel, 1962), and require little in the way of visual integration for optimal registration. We are testing for sustained selective cortical facilitation, therefore, at a basic visual sensory processing level. Use of ssVEPs again allowed separation of cortical facilitation of sensory processing and target identification at attended (and unattended) locations. The ssVEP is an electrocortical response to flickering stimuli where the frequency of brain activity equals the stimulus flicker rate. The experimenter can select the flicker rate of a stimulus, which facilitates identification of neural activity related to the stimulus by means of "frequency-tagging" (M M Müller, Malinowski, Gruber, & Hillyard, 2003). Steady-state VEPs are characterized by high signal-to-noise ratios (Mast & Victor, 1991), and multiple stimuli flickering at different frequencies can be presented simultaneously so attention to independent elements within the visual field can be tracked (Morgan, Hansen, & Hillyard, 1996; M M Müller et al., 2003; Matthias M Müller & Hübner, 2002).

There were again two features to the task. First, spatial attention was quantified by varying the frequency tagging specific parts of the flickering grating stimuli. The ssVEP entrainment increases for attended stimuli, as opposed to unattended stimuli (Muller, Malinowski, Gruber, & Hillyard, 2003). Thus, changes in spatial attention under top-down control will be reflected in the ssVEP at the driving-frequencies of interest. Second, there were separate events at both attended and unattended spatial locations. These events were quantified both via behavioral recognition of their occurrence and via ERPs locked to target events onset. As previously reported (see Clementz et al., 2008), it was predicted that SZ would show a normal ability to modify sustained cortical facilitation under top-down control but deficient

ability to identify target events even though their neural mass activations indicate proper neural engagement to the target locations of interest. These outcomes will replicate Clementz et al. (2008).

Two extensions of these previous findings are also incorporated into this study design. First, target magnitude was varied from the Clementz et al. (2008) standard (50% change in bar widths) to make targets both theoretically more difficult (25% increases) and easier (75% increases) to detect. Variation of target detection difficulty can be complimentary to aspects of early visual processing features, including, but not limited to, spatial frequency and contrast (Butler et al., 2008). Since psychosis cases show impaired ability to use contextual information to interpret visual stimuli, differentiating these streams within a single visual stimulus type allow for monitoring and manipulation of various contextual features, while maintaining the general structure of the stimulus (Dakin, Carlin, & Hemsley, 2005).

Disinhibition within local cortical circuits compromises pyramidal cell tuning functions (Homayoun & Moghaddam, 2007; Tanaka, Tanaka, Furuta, Yanagawa, & Kaneko, 2008). GABAergic inhibition supports selection and integration of excitatory input to pyramidal cells (Farrant & Nusser, 2005), so compromised functioning in this part of the circuitry among SZ would deleteriously affect information processing within and synchronized firing between cortical columns (Arrington, Carr, Mayer, & Rao, n.d.; Constantinidis & Goldman-Rakic, 2002; Kawaguchi, 2001; Monyer & Markram, 2004). This would limit visual discrimination performance among SZ (Chen et al., 2003; B A Clementz et al., 2008; Wang et al., 2007; Yoon et al., 2009) and has been shown to correlate with GABA levels in visual cortex among SZ (Yoon et al., 2010). In Clementz et al. (2008), SZ may have properly performed the difficult visual attention task because the (1 deg) gratings were supra-threshold but had difficulty with target detection because the bar width increases (0.5 deg) challenged their compromised visual discrimination abilities (secondary to deficient GABA-mediated lateral inhibition). Under this thesis, SZ may show improved target detection to 75% bar width increases in relation to healthy participants, but even worse target detection than healthy persons at 25% bar width increases. This manipulation will help test the physical limits of visual discrimination abilities in SZ.

The second extension of Clementz et al. (2008) involves separation of healthy participants into HCC an LCC. There is evidence LCC have difficulty flexibly allocating attention to specific features in complex visual environments (Bleckley & Durso, 2003). The ability to successfully generate responses as a function of instructional set is dependent on intact cognitive control, with goal maintenance and inhibition being especially relevant in this paradigm. Because problem with the type of later stage (past primary visual cortex) feature integration is required for target detection, SZ will have the worst performance on this aspect of the task, with LCC performing better than SZ but not at the level of HCC.

Methods

Participants: Forty-seven chronic outpatients with a DSM-IV (American Psychiatric Association, 1994) schizophrenia diagnosis (mean age = 40; SD = 10.85; range = 20-55 ; 22 females) and 78 healthy persons (mean age = 32; SD = 11.04; range = 18-58 ; 33 females) were recruited for participation in this study (Table 1). All subjects were interviewed using the SCID Modules A-E (First et al., 1995) in order to confirm the research diagnosis (schizophrenia) or to rule out Axis I disorders (healthy). Participants were absent of neurological hard signs, clinically confounding treatments, history of head trauma, and current psychoactive substance use disorders based on Module E of the SCID. Healthy volunteers were subdivided into two groups based on working memory function as measured by as computer-administered span tasks including operation span, reading span, and symmetry span (Unsworth & Engle, 2007; Unsworth, Heitz, & Engle, 2005). Scores from these tasks were z-transformed and a composite score was created by averaging across the three z-scores. Using established norms (Unsworth, Spillers, & Brewer, 2012), healthy participants with composite scores in the upper quartile (above 75%) were included in the high cognitive control group (HCC; n=37) and participants

with composite scores in the lower quartile (below 25%) were included in the low cognitive control group (LCC; n=41).

Stimuli and Procedure: Visual stimuli consisted of two superimposed images that were used in previous studies (Figure 1A) (Chen et al., 2003; Wang et al., 2007; Clementz et al., 2008) Both the horizontal and vertical images were composed of equally spaced parallel bars of 1° visual angle that were equal in luminance (5.5 cd/m2 against a 0.1 cd/m2 background). These stimuli have the desirable feature that they are optimal for activating simple cells in primary visual cortex (Hubel & Wiesel, 1962) and require little in the way of visual integration for their optimal registration (for review, see Butler et al., 2008). One image was composed of red and black, and the other of green and black, interleaved bars, so the stimuli may have engaged both the magnocellular and parvocellular pathways of the visual system (Butler et al., 2008). Each image was 9° square and consisted of 5 colored bars (one middle bar, two peripheral bars, and two outside bars). A centrally located dim gray dot, on which participants fixated, was visible throughout testing. Stimuli were presented on a 21" high-resolution flat surface color monitor, with a refresh rate of 100Hz, that was 60 cm from the participants' eyes.

Vertical bars were always identified as the to-be-attended image throughout 2 min trial blocks (Clementz et al., 2008). There were two different aspects to the task. First, subjects were instructed to attend to either the middle bar (attend-middle) or the peripheral bars (attend-peripheral). This was the explicit attention component of the task. For the attended image, subjects were instructed to identify width changes (25%, 50%, or 75% increase in bar size) to the middle or peripheral bars, depending on the task instructions (attend-middle bar, attend-peripheral bars). This was the target detection component of the task. During each trial block, bars in any image, attended or unattended, were randomly and independently selected for a width

change. Width changes lasted for ~400 ms before the bar returned to its original size; the interval between width changes was randomly selected from a 1-3 s rectangular distribution. Target events, defined by a change in width, required at least low-level perceptual integration for their detection (Butler et al., 2008), but would not necessarily require involvement of neural architecture outside of visual cortex for their successful detection. Subjects were to respond to target events with a button press.

The attended image had bars flickering at different frequencies. The middle vertical bar flickered at 7.69 Hz, the peripheral vertical bars flickered at 7.14 Hz, and the outside vertical bars flickered at 6.67 Hz. Unattended horizontal bars flickered at 8.33 Hz. Whether and how attention shifted within the attended image depended on attend condition (attend-mid, attend-peripheral). Whether subjects complied with the attentional instruction could be determined by quantifying the strength of response at the flicker rate of the attended versus unattended stimuli within the attended image; no behavioral response was required to determine whether sustained selective attention via top-down control was successfully achieved. The order of trial block presentations was counterbalanced by attentional manipulation (attend-middle, attend-peripheral). We did not randomize either direction of the attended bars or oscillation frequencies of the images because there were no effects associated with these two factors in previous studies (Wang et al., 2007; Clementz et al., 2008). For each condition (attend-middle, attend-peripheral) four 2 min blocks were completed by each participant.

An important requirement when using the "method of multiple stimuli" (Regan and Regan, 2003) is that the tag frequencies be close enough that their differences are undetectable to the observer, differences between them are irrelevant to the sensory system under investigation, and the different frequencies are not harmonically related. In this study, the tag frequencies,

which were created by flashing the figure for one refresh and then varying the number of blank refreshes between flashes, were all within a 1.66 Hz range (6.67– 8.33 Hz). This has the additional advantage of minimizing possible confounds between attention modulation and tagging frequency (cf. Ding et al., 2006).

EEG Recording: EEG data were measured using a 256-channel Geodesic Sensor Net and NetAmps 200 amplifiers (Electrical Geodesics Inc.; EGI). Recordings were referenced to the vertex sensor (Cz). As is standard with high input impedance amplifiers like those from EGI, sensor impedances were<50 kΩ. Data were analog filtered from 0.1–100 Hz, digitized at 500 Hz, stored on disk for later off-line analysis, and recorded continuously throughout the 2 min blocks.

EEG Analysis: Raw data were checked for bad channels (<5% for any participant), which were replaced using a spherical spline interpolation method (as implemented in BESA 5.1). Data were transformed to an average reference and digitally filtered from 2 to 40 Hz (12 db/octave rolloff, zero-phase). To ensure that steady state had been adequately established, we used only the last 100 s of each 120 s trial block. The 100 s window yields 0.01 Hz resolution, which was necessary to quantify neural response magnitudes at the specific oscillation frequencies used in the present study. Eye blink artifact adjustment was achieved by using the ICA toolbox in EEGLAB 4.515 (Delorme and Makeig, 2004) running under Matlab (version 7.0, MathWorks). Before computing FFT power, the mean and linear trends were removed (using Matlab) for each EEG channel. Figure 1B shows the head surface maps and cortical source solutions of FFT power for the SZ, HCC, and LCC groups, collapsing over all frequencies and all conditions. Maximum ssVEP power was localized at midline sensors over visual cortex. There was no other peak of activity associated with the ssVEP at any other spatial location, indicating that the neural response was most likely originating in visual cortex.

FFT power at the frequency of stimulation was averaged over 67 sensors that captured the maximal visual cortex signal was used to quantify strength of sustained visual attention (see also Wang et al., 2007, and Clementz et al., 2008; Figure 1B). To test whether the groups different on level of nonspecific brain activity level (neural activity not at the driving frequencies), we calculated the average power in traditional frequency bands (delta: 1–3.5 Hz; theta: 3.5–8 Hz; low alpha: 8–10 Hz; high alpha: 10–12 Hz), excluding the specific driving frequencies if necessary. We also quantified nonspecific brain activity in the narrow region spanned by the driving frequencies (6.5–8.5 Hz, excluding the driving frequencies themselves). These values were then used in between-group comparisons before testing for selective attention effects on the driving frequencies. To adjust for nonspecific brain activity differences between groups, we subtracted the mean power (± 0.1 Hz) around the unique driving frequencies (6.67, 7.14, 7.69, and 8.33 Hz) from ssVEPs for each subject before making group comparisons on sustained visual selective attention (Srinivasan et al., 1999).

For a measure sensitive to phasic changes in visual target identification at the attended locations, we examined visual event-related potentials (VEPs) elicited by the target events (bar width increases of 25, 50, or 75%). Individual trials of 600 ms duration (beginning 100 ms before target event onset) were averaged separately for target events that occurred in the middle bar, peripheral bars, or unattended image. Data were initially notch-filtered at 7.5 Hz (± 1.5 Hz) to remove activity associated with the driving frequencies that might otherwise complicate VEP scoring. Trials with activity 125V were eliminated from further processing. For the attended image, only target events followed by a correct response were included in VEP averages. Grand averages were baseline corrected using the 100 ms pre-event period.

To maximize signal-to-noise ratios, we collapsed target event VEP averages to three categories: (1) attended objects in the attended image (averaging across middle bar targets in the attend-middle condition and peripheral bar targets in the attend-peripheral condition (Total Trials: SZ M=88.4, SD=7.95; HCC M=95.4, SD=x7.53 LCC M=88.3, SD=7.78); (2) unattended objects in the attended image (middle bar targets in the attend-peripheral condition and peripheral bar targets in the attend-middle condition; Total Trials: SZ M=88.2; SD=7.96; HCC M=94.2, SD=7.19; LCC M=90.3, SD=7.24); and (3) unattended image targets (Total Trials: SZ M=76.4, SD=11.4; HCC M=85.5, SD=8.4; LCC M=80.5, SD=10.9).

Component identification was performed using programs written in Matlab. To identify components above baseline noise level, global field power (GFP) plots were derived for every subject and condition. The only identifiable component in the GFP plots for all subjects in all conditions was the P300 (see Results). Given the 6–9 Hz notch filter, with this frequency range overlapping the frequency range for the P100/N100/P200 (Moratti et al., 2007) it is not surprising that these components were not present; the P300 component, however, occupies a lower frequency range. The magnitude of the P300 was determined based on averaging GFP values around the peak (225-375 ms) from 51 sensors located over posterior parietal/occipital (see Results).

After VEP analyses calculated on voltage data at the sensors, we used standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002) to estimate brain regions involved in determining the (1) ssVEP for SZ, HCC, and LCC and (2) the brain regions accounting for between-groups differences on P300 observed in the sensor space data. sLORETA is a modification of minimum norm least squares (Hamalainen and Ilmoniemi, 1994) that uses the standardization of the minimum norm inverse solution to infer high probability

regions of brain activation given the measured EEG data. sLORETA solutions yield pseudostatistics that are not appropriate for determining strength of activity, but they provide accurate information about the regions of activity that can account for the voltage pattern recorded at the sensors (e.g., Soufflet and Boeijinga, 2005). The sLORETA calculations were performed using Brainstorm (Tadel et al., 2011). An averaged magnetic resonance (MR) image from the Montreal Neurological Institute (Collins et al., 1994) was used to construct a realistic head model (Fuchs et al., 2002) before source localization. The MR images were segmented into skin surface, inside of the skull, and cortex. A three-compartment boundary element method (BEM) model was then constructed. Before source analysis calculations, the fiducial locations from the EEG data collection session were matched to the fiducial locations on the averaged segmented skin surface.

Statistical analyses: To investigate effects involving group and sustained attention effects on background brain activity, neural responses to attended and unattended stimuli, and behavioral and neural responses to target events, we used mixed model ANOVAs and MANOVAs with Greenhouse-Geisser adjusted degrees of freedom where appropriate. Interactions were probed via simple main effects analyses using ANOVA, and post hoc tests were Tukey HSD or Tukey-Kramer where appropriate. To evaluate the bidirectional relationships between behavioral responses and neural responses, we performed canonical correlation analyses (CCAs) across all groups using SPSS software (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). CCA is a data-driven, multivariate approach that identifies the relationship between two sets of variables by maximizing correlations between "predictor" (neural activity in this case) and "criterion" variable sets (behavioral responses to target events in this case; see Lambert, Wildt, & Durand, 1988). CCA is particularly useful when there are high intercorrelations

within variable sets and the relationship between variable sets is nondirectional/biorthogonal (Lambert et al., 1988). Results of a CCA are correlated pairs of latent variates. Each pair is independent and composed of weighted sums of the predictor variables that maximally correlate with the weighted sums of the criterion variables. Interpretation of what the latent variates represent and how they are related to each other can be determined by the weighted sums or loadings of individual measures on the latent structure, much like principal components analysis.

Results

Non-specific Brain Activity

To test for differences in non-specific brain activation, we used a group (HCC, LCC, SZ) by attention condition (attend-middle, attend-peripheral) by frequency band (delta, theta, low-alpha, high-alpha) ANOVA (with Greenhouse-Geisser adjusted degrees of freedom). There was a group by frequency band interaction, $F(6, 119)=2.57$, $p=.050$. This interaction was because, in theta range, SZ ($M=15.7$, $SD=.14$) produced higher power than HCC ($M=15.6$, $SD=.16$) and LCC ($M=15.6$, $SD=.15$), but in the high-alpha range HCC ($M=15.4$, $SD=.15$) produced higher power than that both LCC ($M=15.2$, $SD=.15$) and SZ ($M=15.2$, $SD=.14$) (see Figure 1C). The groups did not differ significantly on delta or low alpha activity.

Adjusted ssVEP Activity

To test for differences in power at each of the four locations (outside bars, peripheral bars, middle bar, background image), we used three different group (HCC, LCC, SZ) by attention condition (attend-middle, attend-peripheral) ANOVAs (with Greenhouse-Geisser adjusted degrees of freedom). The first two ANOVAs interrogated the outside bars and background image separately (the never attended stimuli; see Figure 2). For the outside bars there was a main effect

of condition, F(1,124)=4.77, p=.031, and a group by attend condition interaction, F(2,123)=3.85, p=.024. During the attend middle condition, power was statistically similar across HCC (attend middle M=.282, SD=.059), LCC (attend middle M=.317, SD=.056) and SZ (attend middle M=.302, SD=.052). During the attend peripheral condition, HCC (attend peripheral M=.248, SD=.048) and LCC (attend peripheral M=.331, SD=.046) had power values that were statistically indistinguishable from their attend middle condition values; SZ, however, showed a significant decrease (p=.024) in outside bar power during attend peripheral trials (M=.140, SD=.043) in relation to their attend middle value (Figure 2). For the background image (see Figure 2), there was a main effect for condition F(1,124)=6.92, p<.01, with power being lower during the attend peripheral condition, and there was a main effect of group F(2,123)=3.81, p<.025, with neural activity in relation to the background image being higher for HCC (M=1.75, SD=.148), intermediate for LCC (M=1.48, SD=.141), and lowest for SZ (M=1.21, SD=.132), with only the HCC and SZ significantly differing, p=.019. The third ANOVA interrogated middle and peripheral bar powers in one model because their reciprocal magnitudes were the critical component of testing for control of sustained visual attention (see Figure 3). For middle and peripheral bars, there was an interaction of attend condition and bar location F(1,124)=50.63, p<.001, but no significant effects involving group membership. The interaction of attend condition and bar location showed that there was higher power at the attended bar locations and lower power for the unattended locations for all groups (Figure 3).

Behavioral Responses to Target Events

Correct responses were defined as a button press to target stimuli with latency of response falling within 100-1000ms post stimulus onset (Clementz et al., 2008). A group (HCC, LCC, SZ) by

attend condition (attend-middle, attend-peripheral) by width change percentage (25%, 50%, 75%) repeated measures ANOVA (with Greenhouse-Geisser adjusted degrees of freedom) was performed for d-Prime scores and correct response reaction time. For d-Prime (see Figure 4) there was a main effect of group, $F(2, 123)=23.4$, $p<.001$; a post-hoc Tukey indicated that all three groups significantly differed on d-Prime with HCC>LCC>SZ. There was also a group by bar width change interaction, $F(4, 121)=9.5$, $p<.001$.There were no other significant effects involving group membership. Analysis of simple main effects showed that both HCC and LCC increased their target detection accuracy with increasing bar width change thickness (all P's<.001). SZ, however, did not differ on d-Prime at 25% and 50% bar width increases, but did have better d-Prime at 75% bar width increases compared to both 25% and 50% bar width increases. The effects size differences showed corresponding increases in size between healthy and SZ from 25% (HCC to SZ=0.77; LCC to SZ=0.55) to 50% (HCC to SZ=1.48; LCC to SZ=1.02) to 75% (HCC to SZ=1.63; LCC to SZ=1.33). For reaction times, there were no significant effects involving group membership.

VEPs to Target Events

Target stimuli in the attended image generated clear P300 responses (see Figure 5). Bar width changes in the background image showed no evidence of an ERP response so those events are not considered further (see Supplementary Figure 1). To test for differences in target-related P300 response amplitudes, we used a group (HCC, LCC, and SZ) by location (attended images, unattended images) by bar width change magnitude (25%, 50%, and 75%) ANOVA with Greenhouse-Geisser adjusted degrees of freedom.

For attended bar width change P300s there was a main effect of group $F(2,123)14.33$, $p<.0001$ and main effect of width change $F(2,123)44.35$, $p<.0001$. There was also a group by width change interaction for attended stimulus changes $F(4,121)3.98$, $p<.005$ (Figure 5). HCC individuals are sensitive to all degrees of width change (25% M=.300, SD=.065; 50% M=.781, SD=.082; 75% M=.850, SD=.090), while LCC have difficulty at small magnitude changes (25% M=.127, SD=.062; 50% M=.371, SD=.079; 75% M=.570, SD=.086), and SZ have difficulty detecting targets at all (25% M=.055, SD=.058; 50% M=.228, SD=.074; 75% M=.250, SD=.081). Bar-width changes at the unattended locations yielded a main effect for group $F(2,123)4.03$, $p<.021$, and a main effect of width change magnitude $F(2,123)6.05$, $p<.003$ (Figure 5).

Canonical Correlation

In order to evaluate the correlational relationship between behavioral responses and neurophysiological measures we performed a canonical correlation analysis. The canonical correlation identifies which variables are most correlated with one another between these two domains, brain and behavior, by maximizing the correlations between "predictors" and "criteria". This type of analysis is of particular use when there are high inter-correlations within variable sets. The outcome of the canonical correlation is correlated pairs of latent variates, each pair being independent and composed of weighted sums of predictor variables that maximally correlate with weighted sums of the criterion variables. Interpretation of what the latent variates represent and their relation to one another are determined by the weighted loadings of individual measures on the latent structure, very similar to that of a PCA.

The 7 neurophysiological (EEG) variables differentiating groups were used to identify canonical variates best capturing group differences. These variables were analyzed, independent of group, for canonical loadings against measures of dPrime. There was one canonical correlation dimension that was found to be significant among these EEG and behavioral measures ($r = .631$, $p<.000$) (Figure 6). Canonical loadings, a type of latent variate, for EEG measures showed high canonical loadings for P300s (25%, 50%, 75%) of -.738, -.681, and -.776, respectively, and never attended stimuli in the attend peripheral condition (outside bars and background image) of -.522 and -.590 (Table 2). Canonical loadings for behavior showed dPrime loadings across width change in targets (25%, 50%, 75%), as -.781, -.981, and -.931, respectively (Table 3).

Discussion

This study investigated visual sustained attention and target detection across dimensions of cognitive control and clinical pathology. By introducing the component of cognitive control proficiency into how groups were defined (HCC, LCC, SZ) the study was afforded the opportunity to determine what neurophysiological markers are specific to pathology and which might be associated with deficient cognitive control, a common feature in individuals with psychosis and often believed to be specific to the pathology. This paradigm required ongoing visuospatial attention, as measured by ssVEPs, within an overlapping grid of oscillatory visual stimuli. Neural entrainment to the oscillating stimuli was measured and interpreted as ability to attend to salient spatial locations amidst adjacent competing stimuli, requiring participants to covertly attend to instructed regions of the stimulus during the more cognitively demanding attend peripheral condition. The findings of this study replicate previous findings (see Clementz, 2008) using a similar set of stimuli and task instruction with regards to ability to properly modulate attention to the instructed spatial location within a static visual field and, in addition,

were found to be intact across the dimension of cognitive control. Procedures, such as this paradigm, decouple attentional modulation, as mediated by top-down control, and target detection. This paradigm in particular is optimal for activating simple cells in visual cortex (Hubel and Wiesel, 1962). The ssVEPs evoke robust sensory registration in V1, and do not demand much cognitively, as they are characterized by high signal-to-noise ratio (Mast and Vistor, 1991).

Next, by employing target events in the form of bar width changes, we were able to measure target detection ability in a manner independent of spatial attention within the same field of view. In this study, however, the magnitude of bar width change was varied across different stimulus types (25%, 50%, and 75% change). Group differences in target detection without perturbance of the ongoing ssVEP indicate two different mechanisms of sustained visual attention and target detection.

In this study it was found that although groups did not differ in ability to direct sustained visual attention to the correct spatial location there were clear group differences on how the stimulus was broadly processed at V1 via top-down mediated biases. The method of frequency tagging never attended aspects of the stimulus allowed for a measure of how narrow the attentional focus was during the task, with these never attended features discerning both cognitive control and pathology. The background image is superimposed over the entirety of the stimulus grid, making it a good measure of whole stimulus processing as it is present in all attended and unattended stimuli. Processing power to this image steadily decreased with cognitive control capability across groups and is reflective a biased competition model of attention (Desimone, 1996)., and therefore may not be indicative of or specific to pathological condition. As stimuli compete for neural resources, both bottom-up and top-down modulation

leads to one stimulus receiving priority over another in the name of task demand. This has also been shown to be a function of cognitive control and one's ability to maintain multiple complex features at any single moment. As task demands increased the window of visual processing decreases as a function of top-down mediated working memory function. This was also evident in the processing of the never attended outside bars, as a decrease in power during the attend peripheral condition, although only as a function of pathology.

The outside bar location is perceptually the most difficult aspect of this stimulus to process as it is laterally located most distant from center, and unlike the background image, not superimposed over the attended central/peripheral bar locations. Power at the outside bar location differentiated groups by pathology only with SZ showing lower processing at V1 during the more difficult attend peripheral task. As task demands increase SZ visuospatial processing is focused in a manner that draws resources away from other aspects of the visual stimulus lending credence to the concept of impaired attentional filtering in individuals with psychosis by hyper-focusing (Luck et al., 2019) on task relevant stimuli and the ability to process features distal to instructed and gaze fixed locations were shown to correlated with target detection behavior. Hyper-focusing has been found to be specific the SZ pathology (Luck et al., 2019) and not necessarily a feature of cognitive control based on these findings.

As was previously shown by Clementz et al., 2008 target detection ability was deficient in SZ. In this study, however, we showed target detection as a function of cognitive control and of magnitude of bar width change. Although early visual processing deficits have been shown in SZ (Butler et al., 2008), top-down mediated control at V1 remains functional in this pathology when processing a complex visual array. Low cognitive control individuals deviate from high cognitive control during processing of basic target detection, and this finding, combined with the

aforementioned findings, suggest these target detection deficits as dysfunction during processes later in the visual stream. Success at modulating visuospatial attention is indicative of initial thalamic input from, likely m/p-pathway processing to primary visual cortex, as normal functioning. As information is processed beyond its basic simple cell features and transitions beyond V1, which is what is required for target detection, it enters the cortical ventral and dorsal visual streams. Adjustments in width change magnitude allowed for a better measure of features beyond that of V1 simple cell processing to where complex cells of the primary visual cortex are required for target detection (Butler et al., 2008). The largest width change of 75% is most easily detected by complex cells of V1 in cortical layers 2 and 3, which are known to project to the ventral steam. The ventral steam, commonly known as the "what" stream of visual processing, are less sensitive to specific spatial locations and more tuned to edges of a particular orientation (Riesenhuber & Poggio, 1999), and SZ have been shown impaired object recognition utilizing the ventral stream (Plomp et al., 2013). Inadequate detection of targets, especially at lower amplitudes of width change, were shown to be a product of cognitive control and were evident in several of the neurophysiological measures that correlated with behavioral target detection.

Measures that correlated with D-Prime scores included the P300, a measure shown to be an indicator of dorsa/ventral processing, and never attended outside/background images. Of these measures all were shown to be a function of cognitive control, except for outside bar processing. Correlating these EEG measures with behavioral performance is instrumental in explaining poor target detection in SZ and how hyper-focusing on attended bar locations might have deleterious effects on the detection task. It also provides a context for why those with low cognitive control capabilities, and have difficulty with goal maintenance and behavioral inhibition, might have

trouble with target detection in a visually demanding task (Unsworth & Engle, 2007; Unsworth, Redick, Heitz, Broadway, & Engle, 2009).

Nonspecific activity in the theta range was shown to be higher in SZ during the more demanding attend peripheral task, replicating previous observations (Clementz et al., 2004, 2008; Winterer et al., 2000; Krishnan et al., 2005), and differentiated pathology from healthy. Increased activity in only SZ is likely a product of glutamatergic disinhibition (Hughes et al., 2004) and is not seen in the healthy HCC and LCC groups. Previous work has shown a subset of SZ exhibit increased cortical activations (Callicott et al., 2003; Brett A. Clementz et al., 2008; Dierks et al., 1999; L. Ethridge, Moratti, Gao, Keil, & Clementz, 2011; Manoach, 2003; Park et al., 2006; Sakoˇ et al., 2010; Spencer et al., 2004), and this lateral disinhibition can be a cause of selective attentional dysregulation. Disinhibition within this circuit would deleteriously affect information processing and synchronized firing between cortical columns and may shed light on why simple cell function remains intact, but complex cell processing of non-static edge features begins to break down in SZ (Goldman-Rakic, 2002; Kawaguchi, 2001; Markram et al., 2004; Rao et al., 2000). High alpha was shown to statistically differentiate groups, but along the dimension of cognitive control. As perceptual requirements increased those with low cognitive control showed high alpha desynchronization, an indicator of top-down integration and task difficulty.

By varying magnitude of bar width change we were able to discern groups across cognition and pathology. Activation of the circuitry needed to properly modulate spatial attention showed no group differences and suggests that the early visual processes required to successfully attend to appointed spatial locations are no different than that of healthy individuals. This finding could be due to the experimental design's confinement to an optimal field of view for highest

signal-to-noise ratio. SNR is often discussed within the psychosis literature and inadequacies in gaining enough SNR for reliable, replicable, findings are commonly discussed. Due to this study's success in replicating previous findings and capturing clear robust visual signals at the cortex, a reasonable next step would be to test the limits of visual spatial attention in the early visual processing stream in hopes of finding the point at which pathology deviates from healthy.

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		High CC	Low CC	SZ	Total
N		37	41	47	125
SPAN composite		0.85 (0.22)	-0.65 (0.63)	-1.98 (1.3)	_
Age (years)		29.5 (11.6)	34.8 (10.0)	40.4 (10.8)	--
Gender	Male	25	19	25	69
	Female	12	22	22	56
Race/Ethnicity	White	31	23	16	70
	Black	5	16	31	52
	Hispanic	1	2	0	3
Handedness	Right	33	34	37	104
	Left	4	7	7	18
	Ambidextrous	0	0	3	3

Table 5.1 Demographic and SPAN scores for participants

EEG MEAURES	CANONICAL LOADINGS
P300 25% WIDTH CHANGE	-.738
P300 50% WIDTH CHANGE	-.681
P300 75% WIDTH CHANGE	-.776
ATTEND PERIPHERAL THETA ACTIVITY	.303
ATTEND PERIPHERAL HIGH ALPHA ACTIVITY	.085
ATTEND PERIPHERAL OUTSIDE BAR POWER	-.522
ATTEND PERIPHERAL BACKGROUND IMAGE POWER	-.590

Table 5.2 Canonical loadings for EEG measures

BEHAVIORAL VARIABLES	CANONICAL LOADINGS
D-PRIME 25% WIDTH CHANGE	-.781
D-PRIME 50% WIDTH CHANGE	-.981
D-PRIME 75% WIDTH CHANGE	-.931

Table 5.3 Canonical loadings for behavioral measure d-Prime

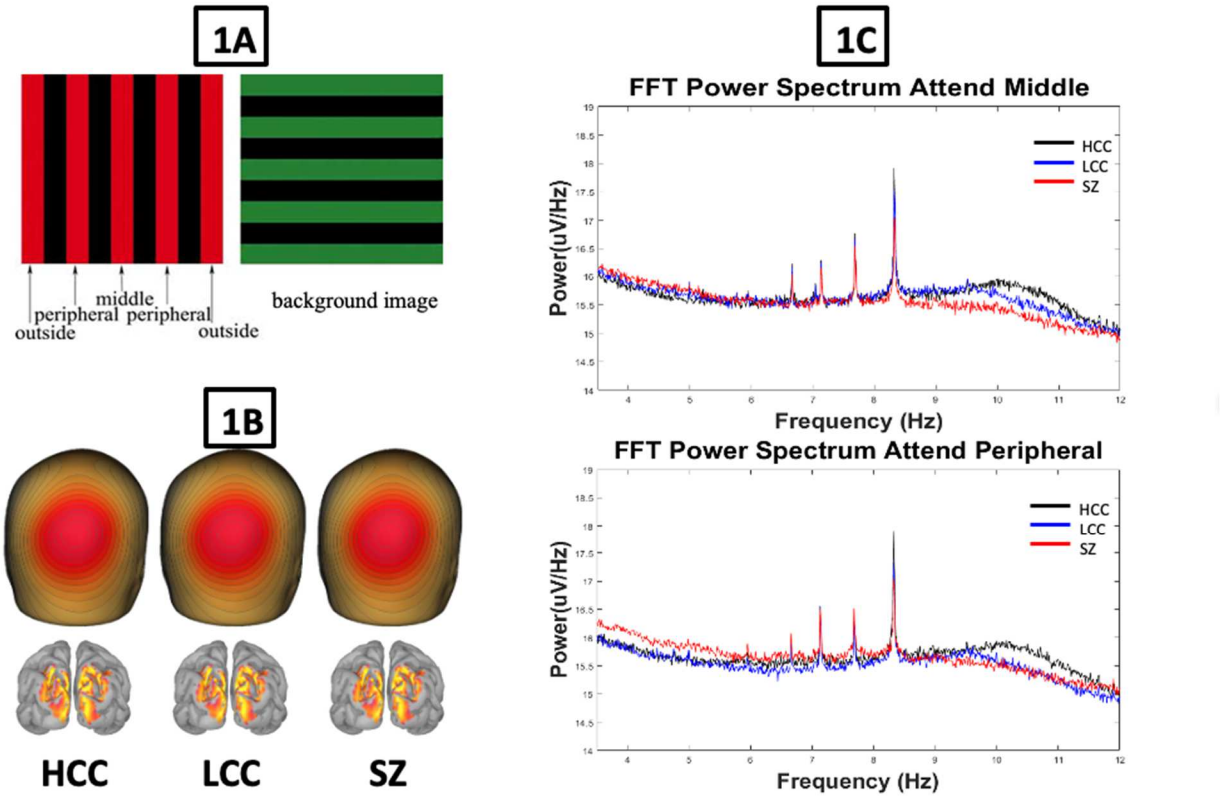

Figure 5.1A Shows the images that were superimposed over one another and presented to participants. **B.** FFT power at the frequency of stimulation for each group (HCC, LCC, and SZ) and their respective sLORETA source estimates on the second row. **C.** FFT power spectrum for each group (HCC, LCC, and SZ) for attend middle condition on top and attend peripheral condition on the bottom.

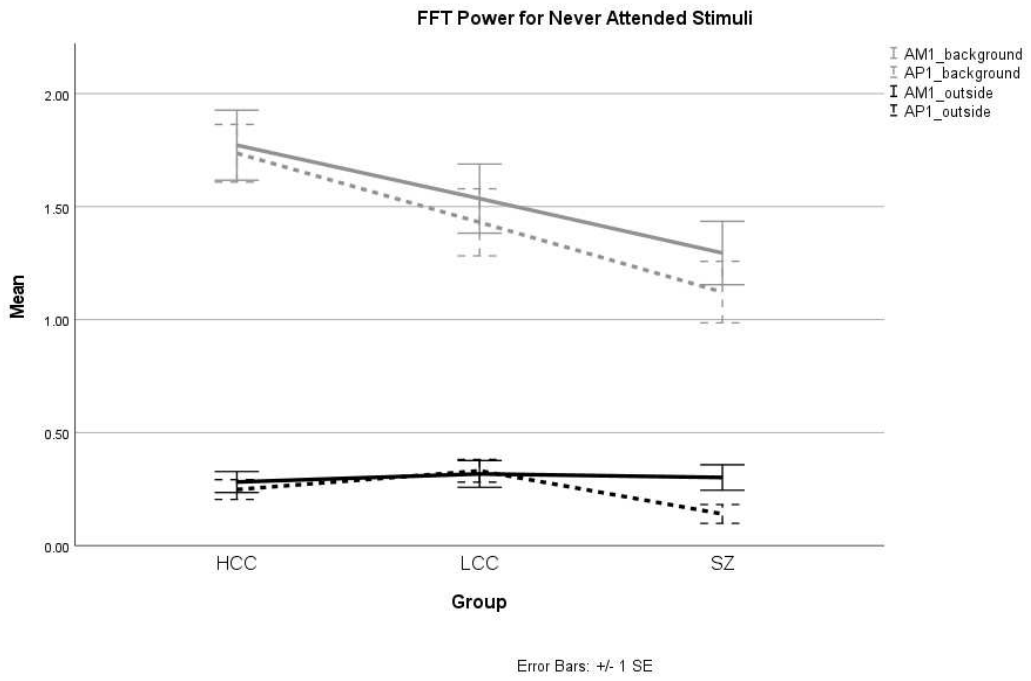

Figure 5.2 Never attended bar power for each group (HCC, LCC and SZ) for both never attended stimulus features (outside bars in black, background image in grey) for each attend condition (attend middle solid line and attend peripheral dotted line).

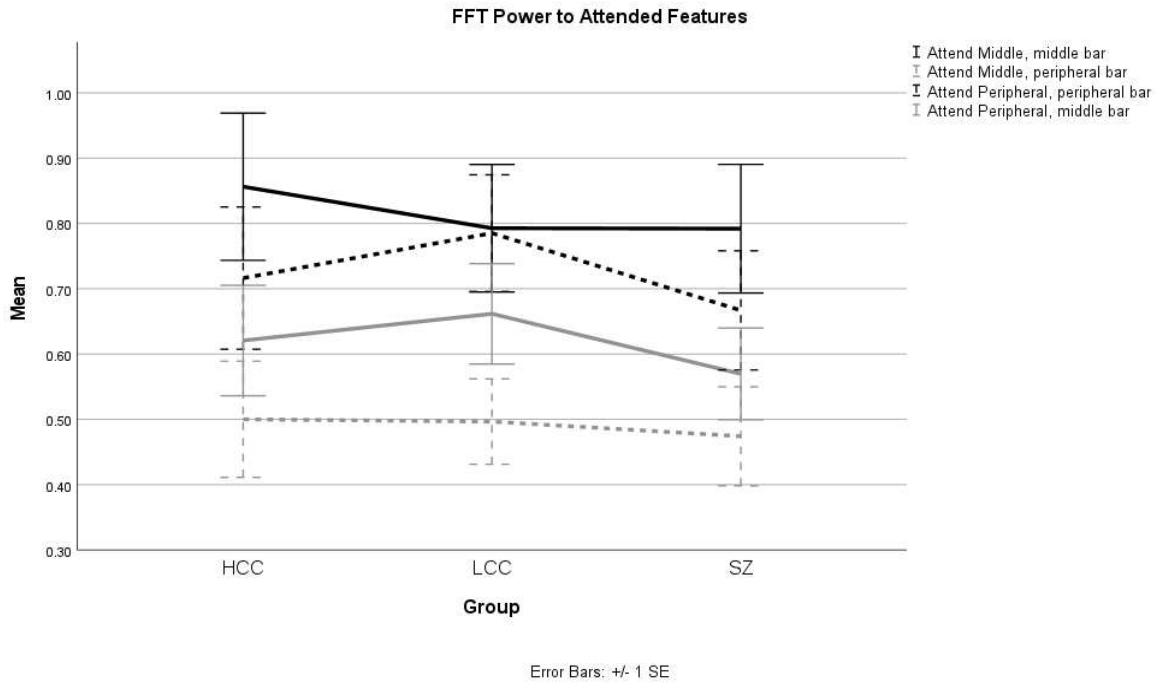

Figure 5.3 Attended bar power for each group (HCC, LCC and SZ) for attended stimulus features (black lines and unattended grey lines) for each attended location (middle bar solid lines and peripheral bar dotted lines).

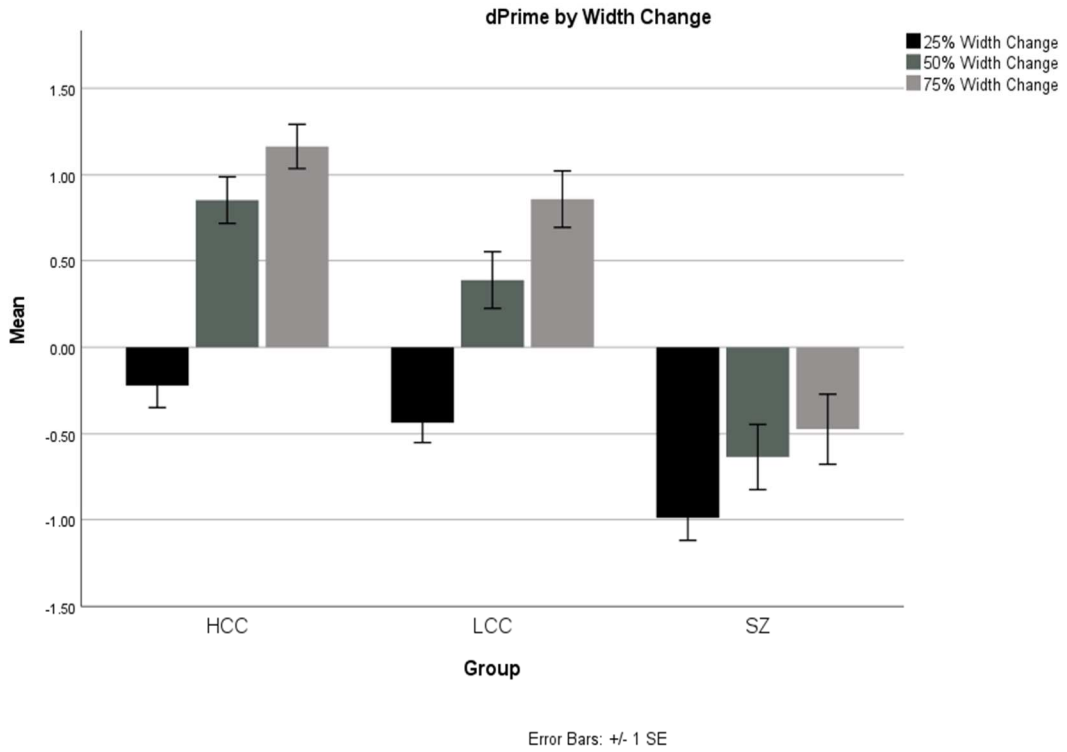

Figure 5.4 d-Prime values for target detection behavioral responses for each group (HCC, LCC, and SZ) by width change magnitude (25% black, 50% dark grey, and 75% light grey).

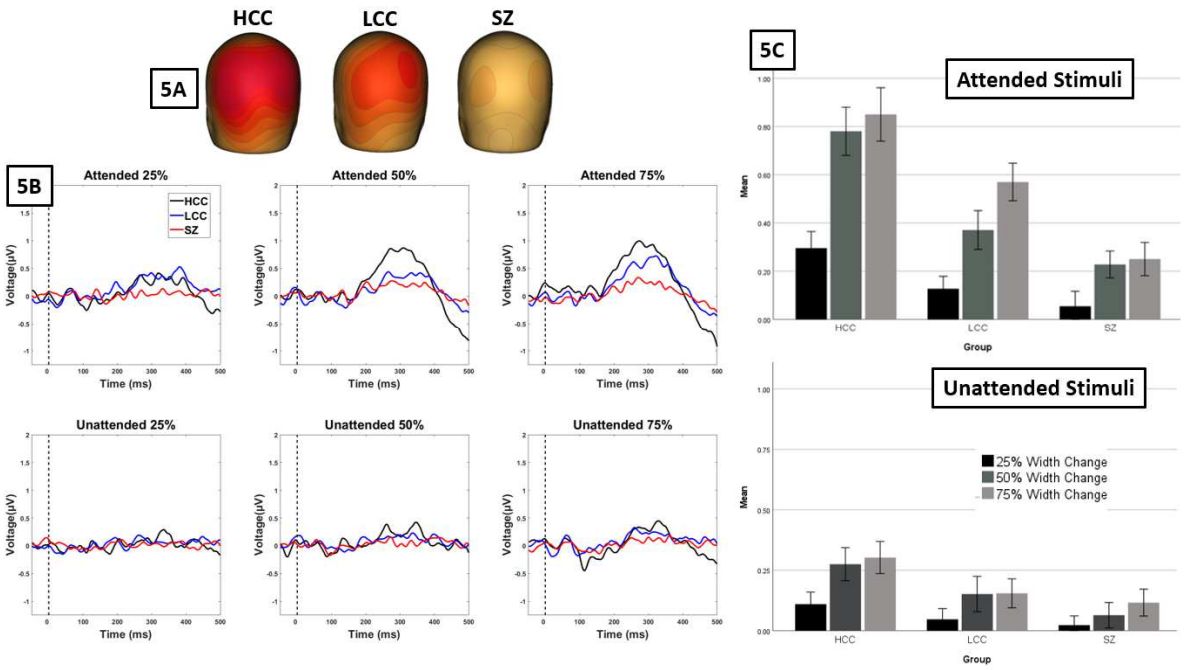

Figure 5.5A. P300 topographies over parietal cortex for each group (HCC, LCC, and SZ) **B.** ERP responses for each group (HCC in black, LCC in blue, and SZ in red) for each bar width change magnitude (25%, 50%, 75%) for both attended stimuli (top row) and unattended stimuli (bottom row). **C.** P300 quantified values for time window (225-375ms) for each group (HCC, LCC, and SZ) and each width change magnitude.

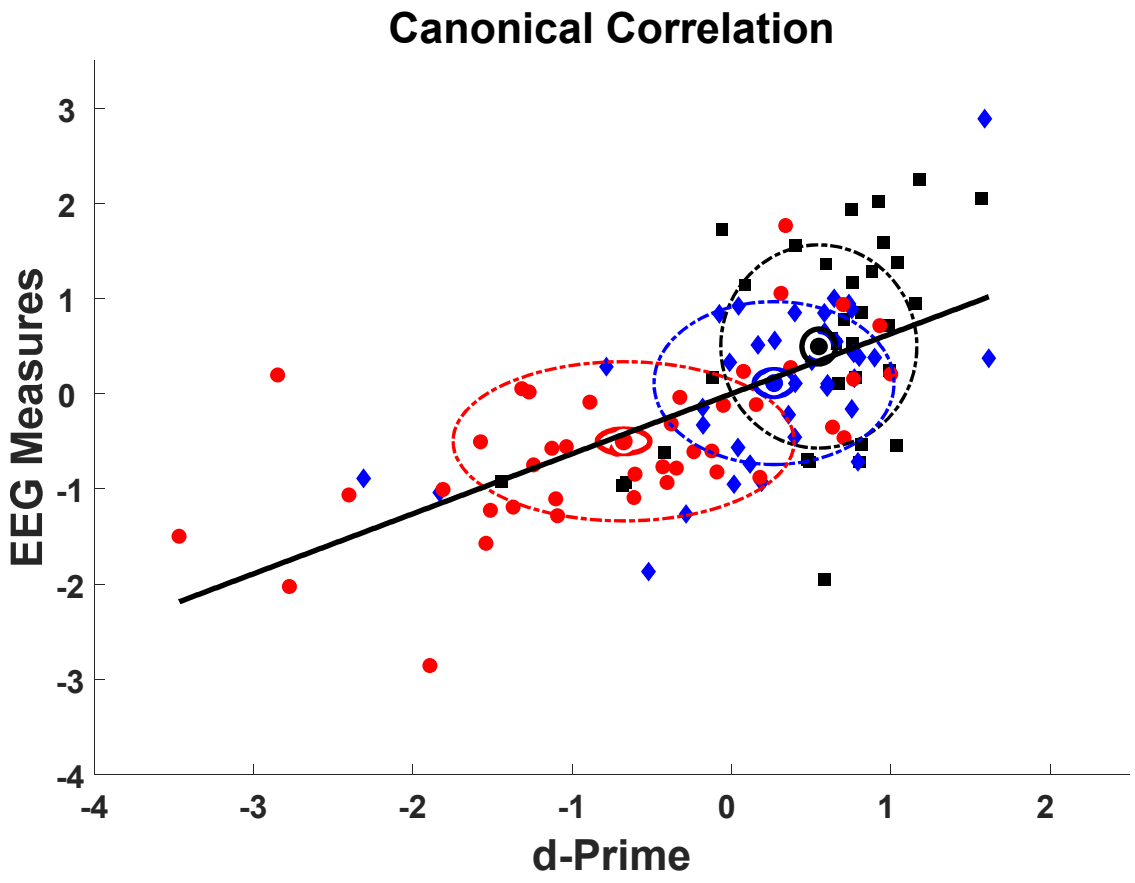

Figure 5.6 Canonical Correlation including 7 EEG measures (P300 width change 25%, 50%, 75%; attend peripheral Theta activity; attend peripheral High Alpha activity; attend peripheral outside bar power; attend peripheral background image power) and 3 behavioral variables (d-Prime for 25%, 50%, and 75% width change).

Conclusions

Disassociating top-down processing from lower-level sensory processing are central to learning where is the sensory processing stream features and context of a stimulus are managed. Careful consideration of the context within which stimuli are presented is required to accurately assess intricate and reciprocal brain functions and can be of assistance in determining the outcome a study. Understanding what top-down biases are imposed on primary sensory processing units as a function of contextual alterations can inform the experimenter on auditory and visual stream deviations across a multitude of human characteristics, symptomologies, pathologies, and inherent properties. These studies have shown that simple sensory stimuli can be presented in a manner that draws out variance across the dimension of cognitive control by utilizing contextual changes.

Study 1 addressed the contextual nature of the classic paired-stimulus auditory paradigm and if this configuration is indeed necessary to elicit the S1-S2 response typically seen in psychosis cases and healthy individuals. Creating a simple inter-stimulus interval procedure, using only two possible intervals of 'long' and 'short' ISIs allows for several top-down biases to be implemented during the testing procedure. Two of the three procedures presented stimuli in a manner that creates an expectation within participants due to the repetitive format of the paired-stimulus and blocked conditions, thus imposing subtle top-down biased signal into the early auditory processing stream. The third randomly interleaved stimulus presentation is removed from the 'paired' and 'blocked' conditions by no longer allowing for stimulus expectation due to its random nature of stimulus intervals. Altering context in this manner revealed several notable features of auditory processing in psychosis cases. First, when categorizing stimuli as 'long' and 'short' ISI clear deviations in healthy vs psychosis cases were identified. Second, the findings replicate previous findings of

three neural response features, enhanced pre-stimulus activity, reduced amplitude in the M100/N100 to S1 stimuli, and the recovery period after sensory registration and before the next stimulus when there is no obvious evoked response. Third, altering context using only two ISIs under these three contextual designs did not have a significant influence on how the two stimuli types were processed, indicating the neural response associated with the traditional paired-stimulus paradigm may be independent of the contextual expectation and more a function fundamental auditory sensory processing. In this study it appears that the expectation created by traditional paired-stimulus procedure is not required for indexing early auditory processing deviations in psychosis cases, and that it is a consequence of inter-stimulus interval. Assessing the expectation of the traditional paired-stimulus paradigm and showing that it is not a necessary context may offer future research more flexibility in experimental procedure and design, while still extracting replicable results and group variance in psychosis. These results are also informative with respect to capturing acceptable signal-to-noise ratios while using less time during paradigm runs. This can afford the experimenter more trials, time for further paradigm testing, and cost savings due to less run time at the scanner, thus optimizing experimental protocol and efficiency.

Study 2 addressed the what role visual spatial attention plays during a target detection task when viewing a complex grid-style array. The task required participants to shift spatial attention across instructed conditions while locking gaze to a central fixation point throughout the task. This aspect of central fixation allowed for evaluation of contextual modulation through task instruction. The attend peripheral condition required participants to covertly attend to peripherally located stimulus features, thus altering the context of the static retinal image. Across contextual conditions, attend middle and attend peripheral, both young and older groups showed clear top-down biasing over visual cortex, a sign that they were able to properly modulate spatial attention in a selective

manner. This selective focusing of attention also showed some perceptual narrowing in the older group, but only during the more cognitively demanding attend peripheral condition. Analysis of ongoing non-specific activity within the range driving frequencies, but excluding those specific frequencies, showed no differences across young and older participants indicating that group differences to stimulus features are independent of ongoing intrinsic brain activation. The inclusion of retinal measures of macular pigment optical density provided a valuable aid to the interpretation and delineation of bottom-up and top-down processing features as a function of context and retinal health. Contextually, both groups were able to successfully modulate spatial attention, suggesting intact task performance, albeit at the cost of non-relevant stimulus features. Perhaps, not all stimulus features processing, however, is completely top-down modulated. Macular pigment optical density was shown to be correlated with the parafoveally located peripheral bar power, suggesting that there may be mechanisms critical to visual spatial attention that influence ongoing spatial attention prior to top-down biases, or that retinal health is predictive of neural processing efficiency. This finding leaves the door open for determining where in the visual stream top-down biasing is imposed during spatial attention allocation and whether or not parafoveal m-pathway processing is influenced at the level of the retina or beyond, but indexed by retinal measures such as macular pigment optical density. Modulation of context using this sustained visual attention paradigm proved useful in indexing top-down influence over visual cortical processing, as well as potential bottom-up mechanisms, although future work will be needed to further disentangle these physiological features.

Study 3 assessed near identical stimulus features to that of study 2 with a greater focus on aspects of target detection and the impact cognitive control capacity has on visual spatial attention and target detection. This study used a stimulus and task procedure almost identical to that of the

previous study, with a critical difference being the degree to which target stimuli were varied. Stimuli were strongly related to previously published works in structure and task design, with bar width change magnitude being the defining difference in this procedure (Brett A. Clementz et al., 2008; Wang et al., 2007). This study also introduced the component of cognitive control into group selection. Contextually, paradigms used in studies 2 and 3 were identical, both requiring participants to maintain central fixation, thereby locking stimulus transduction at the level of the retina and only altering context directing spatial attention through task instruction. Study 3, like study 1, included healthy persons and psychosis cases, but by introducing the dimension of cognitive control, divided the healthy group into high cognitive control and low cognitive control. Poor cognitive control is a hallmark symptom of psychosis cases, but not exclusive to the pathology. A subset of non-pathological persons show similar cognitive control deficiencies and have trouble with goal maintenance and behavioral inhibition, functions critical to successfully completing the tasks used in studies 2 and 3 (Unsworth et al., 2005, 2009; Unsworth & Engle, 2007). Using identical contextual changes in the task to study 2, this study was able to induce top-down biasing of visual cortical processing showing that all groups are able to properly modulate spatial attention at attended locations within the task demands. Attention at never attended locations, outside bars and background image, were reliant on context and varied across both cognitive control and pathology. Results from this study also showed group differences in detection of targets and how target detection varied over magnitudes of width change. This finding, however, was independent of contextual changes as introduced through attend condition instruction. Finally, there was a correlation between behavioral target detection and several EEG measures including, P300 and never attended stimuli, that was also independent of contextual changes.

The purpose of these studies was to determine how context changes neural processing of simple auditory and visual stimuli. All three managed to test what role context played on top-down control of lower-level sensory function during their respective paradigms. These studies also replicated previous works using very similar or identical sensory stimuli formats lending credence to the idea that we are indeed measuring what, if any, influences context has on the simple sensory procedures (Brett A. Clementz et al., 2008; Wang et al., 2007).

Perhaps the most passive of contextual manipulation used in these studies were that of imposing an expectation of stimuli by introducing repetitive stimuli configurations, including the widely used pair-stimulus procedure, and put those against a randomly interleaved design that removes the expectative context. There was no set of instructions regulating this change in context, as was the case in the subsequent studies, and it relied solely on the participants to form the cognitive construct of context on their own. Statistically, this study found no differences across contextual presentation, suggesting that simple auditory stimuli configured in this manner are really just a product of inter-stimulus interval, and that as long as these intervals exist within the paradigm, context does not really matter. It also implies that these long and short intervals are processed in a manner that is minimally influenced by top-down processing, at least as far as the expectative context imposed here. This contextual procedure has shown that the traditional paired-stimulus configuration is not a required context and that future studies may be well served to think about presentation of simple auditory stimuli in a different ‘context’, and that there may be some creative room, more than previously thought, to explore long and short inter-stimulus intervals.

For the field of psychosis, it shows that the widely replicated findings of the paired-stimulus paradigm is independent of the expectative context and more a function of fundamental auditory sensory processing. In the case of Study 1, however, it fails to take into account the recent

findings in larger studies that were centered around the concept of data-driven grouping within the psychosis symptomologies (Brett A Clementz et al., 2016; Hamm et al., 2014; Parker et al., 2020). Although this study didn't have the group numbers to support such an analysis approach and statistical grouping method, the findings of that work can be extrapolated to the findings of this study. It may be the case that when psychosis cases are 'Biotyped' based on behavior and neurophysiology that group variance can be extracted based on the expectative context and different Biotypes respond differently, physiologically, under the contexts used here.

For the visual systems under the paradigm used here context was shown to be an excellent tool of experimental design and procedure that can be used to draw out top-down biased signals in the visual stream. This specific procedure was used across a multitude of groups, including dimensions of cognition, age, pathology, and retinal condition, and successfully showed group variance across each of these dimensions as a function of context and independent of contextual change. Alterations in context were implemented by altering the participant's visual spatial attention to different features of the stimulus requiring direct and covert attentional deployment, with the covert attention condition being the more demanding of the two tasks. In this case by altering the context of the visual stimulus array through instructed direction of attention we were able to create a more cognitively demanding task in the attend peripheral condition, and by including features other than those attended we were able to measure visuospatial attention span, in the physical sense, in a broader stimulus array using never attended features. This aspect of the stimulus design allows for testing of basic models selective attention, including attentional filtering and hyperfocusing in psychosis (Luck et al., 2019; Müller et al., 2008).

Contextual changes in the visual stimulus and task demand of this paradigm proved useful in determining differences in visual spatial processing in young vs older persons, and in finding

biological markers associated with features of the stimulus. Both groups showed the ability to modulate spatial attention according to the contextual changes based on task instruction, but increasing task demands through context was able to determine young from older individuals. Older persons showed an increase in power to the attended stimuli compared to the younger group, indicating a compensatory mechanism in the processing of visual stimuli as age increases and perhaps as cognition declines. Alterations in context also revealed a correlation across all participants between power at the peripheral bar location, a parafoveally location at the level of the retina, with retinal health, as measured by macular pigment optical density. Although this may be a function of contextual change, it is not clear where in the visual stream macular pigment might be altering processing of this specific stimulus, and this determination may be made by using procedures known to alter macular pigment ocular density and performance on cognitive performance and neural activations in top-down mediating regions of prefrontal cortex (Mewborn et al., 2018; Renzi et al., 2014)

This strategy of contextual manipulation proved useful in providing informative results to the psychosis literature by showing where in the visual stream top-down biasing may occur and in what ways it can alter visual processing of a stimulus. No differences were found in ability to properly modulate spatial attention to the appropriate locations in either the psychosis group or as a function of cognitive control, replicating previous findings (B A Clementz et al., 2008; Wang et al., 2007). This is an indicator that psychosis cases have intact and normal functioning spatial orientation under experimental conditions to optimally facilitate visual cortex, with high signal-to-noise oscillatory stimuli, and that it is not a function of deficient cognitive control. The inclusion of a never attended stimulus at a superimposed background image was able to show group separation along the dimension of cognitive control, with power at this driving frequency

diminishing as a function of task difficulty (lower power during the attend peripheral condition) for all groups, and decreasing in lower cognitive control groups. At the laterally located never attended stimulus of the outside bars only psychosis cases showed aberrant processing during the more demanding attend peripheral condition. This specific feature is located most distant from central fixation and is likely indicative of abnormal function in m-pathway due to the parafoveal retinal image as previously reported in psychosis cases (Butler et al., 2005, 2007, 2008). Much of these findings were a result of contextual differences across attend conditions, with the cognitive control dimension showing the least group variance based on context. Cognitive control was more a function of never attended background stimulus image and the ability of participants to detect targets based on magnitude of deviant target width.

Target detection, interestingly, showed no differences as a function of context during this visual sustained attention paradigm. Although the P300 associated with target presentation showed robust correlation with D-prime measures of behavior, it was not a function of context. This may be due to modulations in edge features of the stimulus and how simple and complex cells in visual cortex process different aspects of the visual stimulus (Butler et al., 2008). Bar width change would likely be features detected by complex cells in visual cortex. Complex cells are known to project to the ventral stream of visual processing and are less sensitive to specific spatial location and more tuned to edge features of a particular orientation (Riesenhuber & Poggio, 1999), and SZ have shown impaired object recognition in ventral stream processing (Plomp et al., 2013). That is, visual spatial attention may be a function of context, but the finer aspects of an image may do not show similar top-down biasing may not be affected by the same biasing signals. The transient nature of the bar width change, although also flickering at the proper rate for its spatial location, may not

evoke a signal as robust as the ssVEP, and therefore, would fail to show contextual modulation under these conditions.

It is worth noting the optimal method used here to evoke neural entrainment to the oscillating visual stimulus. This stimulus was designed to be highly evocative in terms of driving visual cortex in a way that best defined the driving frequencies (and spatial locations) of each stimulus feature with oscillatory neural activity (Hubel & Wiesel, 1962, 1968). The stimulus may have saturated the m-pathway signals and while it was able to show that all groups can properly modulate attention based on contextual instruction, it could have been overbearing in its generation of the ssVEP. The stimulus may not have the sensitivities to capture group differences to attended stimuli as a function of context due to the overall gain of the evocative stimulus being too high. This could be accounted for at least two different ways, by varying the square wave (on/off) type oscillation into something more sinusoidal or by varying the luminance of the 'off' frame of flicker somewhere between relative zero luminance and full 'on' luminance during each cycle. A truly sinusoidal design would be next to impossible for this particular stimulus due to the limitations of modern CRT/LCD monitor design, and the fact that these stimuli must be locked to the refresh rate of these monitor types, or a multiple of that refresh rate. A better way to account for potential saturation of early visual pathways might be to modulate optical density of the stimulus. This stimulus was optimally designed for one degree visual angle bar width due to how simple cells in visual cortex optimally respond to this particular shape and stimulus size. By varying bar width as a function of visual angle, essentially just changing the size of the current stimulus, making it smaller or larger, it would essentially increase or decrease the load simple cells would be under to process the stimulus, potentially drawing out previously unseen group variance or consequences of stimulus context.

These studies have shown the use in careful consideration of context surrounding visual and auditory experimental designs. In these studies, context was employed in designs that held basic features of simple auditory/visual stimuli in a semi-static fashion, allowing for optimal observation of contextual outcome. Experimental alterations of context allowed for disclosure of top-down and bottom-up mediated processing pathways across a multitude of groups, behavioral characteristics, and biological measures as early in the processing stream as the retina. In short, context is key to well-designed non-invasive electromagnetic studies in humans.