Electrophysiological Markers of Short-term Visual Adaptation: An Examination Across the Schizophrenia Spectrum

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ELECTROPHYSIOLOGICAL MARKERS OF SHORT-TERM VISUAL ADAPTATION:

AN EXAMINATION ACROSS THE SCHIZOPHRENIA SPECTRUM

by

GIZELY N. ANDRADE

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for
the degree of Doctor of Philosophy, The City University of New York

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This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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Abstract

ELECTROPHYSIOLOGICAL MARKERS OF SHORT-TERM VISUAL ADAPTATION:
AN EXAMINATION ACROSS THE SCHIZOPHRENIA SPECTRUM

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Gizely N. Andrade

Adviser: Professor John J. Foxe

The experiments comprising this dissertation sought to contribute to the understanding of basic sensory processing in schizophrenia-spectrum disorders and risk-liability. We leveraged the sensitivity of visual processing deficits along with widely reported sensory-gating deficits (in other modalities) to develop a new paradigm assaying short-term visual adaptation to repetitive stimuli. In the first experiment, adaptation properties of the visual system were characterized in neurotypical adults using a classic "paired adaptation paradigm" and a more taxing "block adaptation paradigm," using high-density EEG. In the second experiment, we deployed our new visual adaptation assay in a clinical population. We replicated classic early VEP amplitude attenuation and uncovered novel visual adaptation deficits in participants diagnosed with a schizophrenia-spectrum disorder. We further tested the specificity of these findings by employing a somatosensory analog to the block adaptation paradigm utilizing vibrotactile stimulation of the median nerve. Differences in basic somatosensory function and adaptation were present in the clinical group although less apparent than in the visual system. In the third experiment, we examined whether altered visual adaptation could serve as a schizophrenia endophenotype. We utilized a shortened version of our visual adaptation paradigm (15mins, 32-channel electrode array) to characterize a larger sample of neurotypical adults who were also assessed using the Schizotypal Personality Questionnaire (SPQ). Multiple regression analysis revealed a significant relationship between high SPQ and less sensitive VEP adaptation. Overall the findings across these studies provide strong support for atypical visual adaptation in schizophrenia and suggest a potential role for altered visual adaptation as an electrophysiological schizophrenia endophenotype. Future studies employing pharmacological manipulations (e.g. administering nicotinic treatment or dopamine/glutamate/GABA agonists) and examining first degree relatives of patients may offer greater mechanistic insight into the processes underlying these observed phenomena.
DEDICATION

This dissertation is dedicated to my parents, Domingos and Simone Andrade. They have sacrificed so much, while giving myself and my siblings everything we could have ever needed. They are the most hard-working, selfless, and brave people I know.

Continuamos seguindo em frente, em pé sem cair, empurrando com a barriga.
ACKNOWLEDGEMENTS

The past five and a half years have been a non-stop whirlwind journey and I've definitely come out of it a changed person. I've thoroughly enjoyed all my classes, have learned so much, and have come to know some truly fascinating people. For all these things I am grateful; here I attempt to humbly acknowledge those that stand out most. Thank you to my adviser, John Foxe, for believing in me and teaching me about the science and business of research. Thank you to John Butler, for never hesitating to get his hands dirty -- he has imparted wisdom, technical expertise, and much needed encouragement and support, with his special hint of comic relief. Thank you to Sophie Molholm for her editorial help and kind words. Thank you to Alice Brandwein and Chris Kelly for such insightful and patient clinical training and supervision. Thank you to Christine Alaimo, Frantzy Acluche, Brenda Malcolm, and Gregory Peters for everything from help collecting and analyzing data, extracting DNA, and clinical assessments, to coffee walks, keeping me company, and reminding me to stay focused. Thank you to the coolest interns ever: Emmett Foxe, Noga Zoborowski, Nessa Foxe, and Lily Kolb. A big thank you is also in order to the whole crew at CNL, past and present, where I was truly surrounded by so much talent, lightheartedness, and vital resources. Lastly, thank you to my committee: Dolores Malaspina, Anil Malhotra, Matthew Hoptman, and Brett Abrahams. You were all incredibly knowledgeable and so supportive. It was truly an honor to get you all together in the same room to sit down and talk about my work. Thank you for all of the questions, feedback, push-back, and insights.

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Thank you to my partner in crime, Dr. Timothy Schmeier, for always being by my side. You always do your best to cheer me up -- whether it's thai boxing, binging on Netflix, or dragging me to D&B's. It's nice to be reminded that there's more to life than work. I am looking forward to a future with you that is full of travels, laughs, and adventures.
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CHAPTER 1

GENERAL INTRODUCTION
1.1. INTRODUCTION

The study of schizophrenia sits at the interface of psychology, neuroscience, epidemiology, neurophysiology, cognitive science, genetics, and pharmacology—among other disciplines. While steady progress has been made in several of these fields individually, the complex nature of this neuropsychiatric disorder has collectively eluded researchers. With its rich genetic makeup (Need & Goldstein, 2014; Schizophrenia Working Group of the Psychiatric Genomics, 2014), strong environmental influences (van Os, Rutten, & Poulton, 2008), heterogeneous presentation (Andreasen, 1995; Bleuler, 1950; Cuthbert & Insel, 2010), and still largely hidden neurodevelopmental timecourse (Insel, 2010; D. A. Lewis & Levitt, 2002; Weinberger, 1987) researchers and clinicians are often left in the dark on three critical issues: causation, prevention, and full rehabilitation.

In the past year, the National Institute of Mental Health (NIMH) put forth an update to their Strategic Plan (http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml) centered around initiatives to bridge gaps, accelerate advancement, and promote true translational research impacting the treatment and understanding of schizophrenia and other serious mental illness. It is clear that progress towards these goals will necessarily rely on two major factors: 1. The study of endophenotypes and neurodevelopmental changes leading up to the clinical state, i.e. observable brain and bio-based changes occurring before disease and symptom manifestation, and 2. Collaboration, i.e. pooling of data within and between many disciplines, such that ‘big data’ cutting across various levels of cognition (from molecules to circuits to symptoms), might provide insight to the ‘big picture.’

In what follows, the clinical presentation, epidemiology, and etiology of schizophrenia is reviewed. The scope of the discussion is then narrowed to basic sensory processing in schizophrenia, with a focus on electrophysiological findings and the concept of altered sensory adaptation. Next a discussion of the schizophrenia-spectrum is introduced, highlighting the contributions of the study of sub-clinical schizotypy to the understanding of schizophrenia pathophysiology and genetics. The main investigations of this dissertation are then introduced: 1. The examination of visual adaptation in neurotypical controls, probing the effectiveness of a paired-presentation paradigm to a block presentation paradigm in modulating visual evoked responses, 2. The examination and specificity of adaptation deficits in schizophrenia, probing
visual and somatosensory adaptation using a block paradigm in patients, and 3. The examination of visual adaptation deficits in sub-clinical schizotypy, probing the role of visual adaptation as a potential endophenotype. The final chapter includes a summary of the main findings, ongoing work, and a discussion of the impact and potential power of collaborative and longitudinal studies -- pooling knowledge, expertise, and samples across disciplines—to advance risk-assessment and treatment.

1.2. CLINICAL PRESENTATION & DIAGNOSIS

Schizophrenia is a complex and often chronic neuropsychiatric disorder. It is characterized on the basis of behavioral observations, thought content, and impairments in social and cognitive functioning. As early as the classic descriptions of Bleuler (Bleuler, 1950), Kraepelin (Kraepelin, 1919), and Schneider (Schneider, 1959), the symptoms of schizophrenia have fallen under three broad categories: positive, negative, and cognitive. Positive symptoms can be conceptualized as traits that are in excess, as compared to the general population. Examples of these are hallucinations – perceptual experiences in the absence of external sensory stimulation – and delusions – strongly held beliefs that persist in light of contradictory evidence often pertaining to persecution, extraordinary powers or abilities, and paranoia.

Negative symptoms can be conceptualized as traits that are in deficit, as compared to the general population. Examples of these are anhedonia (an inability to experience pleasure), social withdrawal, and flat affect. Cognitive symptoms involve altered “executive control”, such as difficulties with attention, working memory, cognitive flexibility. The issue of whether some of these traits are truly absent or even rare in the general population will be revisited in Section 1.6.
An abridged version of the diagnostic criteria for schizophrenia from the Diagnostic and Statistical Manual of Mental Disorders- 4th Edition (DSM-IV-TR, (APA, 2000)) is presented in Table 1, note that only positive and negative symptoms are used for diagnosis. Although this criterion has recently been updated in DSM-V, the DSM-IV criterion is presented as most of the research studies that will be discussed subsequently have used DSM-IV (or earlier) to classify participants. Changes in the DSM-V involve, in brief, the removal of the criterion A note which gives special treatment to “bizarre” delusions and specific types of hallucinations, adds a requirement that at least one of the two criterion A items be hallucinations, delusions or disorganized speech, and eliminates schizophrenia subtypes (see (Moller et al., 2014; Tandon et al., 2013) for an overview and discussion of these changes).

DSM-V also includes the addition of domains, gradients, and dimensions to the schizophrenia-spectrum characterization (see (Heckers et al., 2013) for a discussion). This represents a small step towards a “framework” shift, attempting to better capture the heterogeneity and fluidity of schizophrenia-

<table>
<thead>
<tr>
<th>Table 1. DSM IV-TR Diagnostic Criteria for Schizophrenia (adapted and abridged)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Characteristic Symptoms:</strong> Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):</td>
</tr>
<tr>
<td>1. delusions</td>
</tr>
<tr>
<td>2. hallucinations</td>
</tr>
<tr>
<td>3. disorganized speech (e.g. frequent derailment or incoherence)</td>
</tr>
<tr>
<td>4. grossly disorganized or catatonic behavior</td>
</tr>
<tr>
<td>5. negative symptom (i.e. affective flattening, alogia, or avolition)</td>
</tr>
<tr>
<td><strong>NOTE:</strong> Only one criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping a running commentary or two or more voices conversing</td>
</tr>
<tr>
<td><strong>B. Social/Occupational dysfunction:</strong> significant disruption in work, interpersonal relations or self-care since onset of symptoms</td>
</tr>
<tr>
<td><strong>C. Duration:</strong> disturbance persisting for 6 months, with at least 1-month of symptoms from criterion A</td>
</tr>
<tr>
<td><strong>D. Rule out:</strong> Mood disorders, substance abuse, etc</td>
</tr>
</tbody>
</table>
spectrum disorders. Such updates in the DSM-V seek to take patients “outside the box” by encouraging the use of intensity ratings (gradients) across different dimensions of psychosis and related cognitive/affective domains. This multi-dimensional evaluation provides a clearer quantitative and qualitative descriptor of a patient’s current psychiatric state, and can be a useful aid in tracking disease progression, treatment efficacy, and even conversion-risk.

Fig 1, as published in (Heckers et al., 2013). Original caption: Dimensional assessment of psychosis. The graphs depict three different patients who have been assessed for dimensions of psychosis (blue) and related phenomena in the domains of cognition and affect (red). (A) A patient with schizophrenia displays moderate hallucinations, prominent delusions, equivocal disorganization of speech, but no abnormalities of psychomotor behavior or negative symptoms. In addition, the patient has mild cognitive impairment and equivocal depression. (B) A patient with schizoaffective disorder displays moderate hallucinations, prominent delusions, equivocal disorganization of speech, but no abnormalities of psychomotor behavior or negative symptoms. In addition, the patient has mild cognitive impairment, severe depression, and mild mania. (C) A patient with deficit syndrome schizophrenia displays mild hallucinations, mild delusions, moderate disorganization of speech, no abnormalities of psychomotor behavior, and severe negative symptoms. In addition, the patient has severe cognitive impairment, equivocal depression, but no mania.
1.3. EPIDEMIOLOGY AND BASIC ETIOLOGY

Though often quoted as universally affecting 1 in 100 people, recent studies suggest significant variability around this figure, with differences in prevalence and incidence rates of schizophrenia varying across countries, cultures, socio-economic class, and sex (Goldner, Hsu, Waraich, & Somers, 2002; J. J. McGrath, 2006; J. McGrath, Saha, Chant, & Welham, 2008; J. McGrath et al., 2004; Messias, Chen, & Eaton, 2007; Saha, Chant, Welham, & McGrath, 2005). This sort of variability is in line with trends observed for most diseases in medicine, and, as suggested by McGrath 2005, helps dispel the myth that schizophrenia is egalitarian or biologically unique (J. J. McGrath, 2005).

Several genetic, environmental, and gene x environment factors have been associated with increased schizophrenia risk. These factors span the gamut from having a first degree relative diagnosed with schizophrenia, infections during pregnancy, delivery complications (e.g. hypoxia), and advanced paternal age to migration, cannabis use, exposure to the parasite toxoplasma gondii, and urbanicity (Dalman, Allebeck, Cullberg, Grunewald, & Koster, 1999; Malaspina et al., 2001; Norton, Williams, & Owen, 2006; Torrey, Bartko, & Yolken, 2012; van Os et al., 2002; van Os et al., 2008; Veen et al., 2004). The prevailing philosophy suggests that schizophrenia follows a diathesis-stress model; in which the right combination of inherited predisposition and additional stressors (epigenetic and non-genetic) can lead to the disease state (Kendler, Jaffee, & Romer, 2001; Rosenthal, 1970; Walker, Kestler, Bollini, & Hochman, 2004).

The average onset age for schizophrenia is between 20 and 35 years, with males reliably experiencing a first episode at a younger age than females (Castle, Wessely, Der, & Murray, 1991; Hafner & an der Heiden, 1997). Prospective longitudinal studies report sustained recovery in less than 14% in the first 5 years and perhaps additional 16% at 25 years after an initial episode (G. Harrison et al., 2001; Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004). However, it should be noted that such studies are rare. Nonetheless, the economic burden of schizophrenia, consisting of direct costs from hospitalizations and medication, disability, burden on the family, and indirect cost from unemployment and increased mortality (including due to suicide), is astronomical, both nationally and internationally (Folsom et al., 2005; Goeree et al., 2005; Hor & Taylor, 2010; Rossler, Salize, van Os, & Riecher-Rossler,
One meta-analysis reveals a telling statistic which underscores a 2-3 fold increase in the risk of dying for a person diagnosed with schizophrenia (e.g. standardized mortality rate), coming most as a result of this patient group not sharing in the health improvements experienced across the general population (Saha, Chant, & McGrath, 2007).

Part of what contributes to the continuing of this crisis is the oft-delayed intervention this population receives. Even the notion of an “age of onset” being defined by a first hospitalization (Pemberton, Welham, & McGrath, 1992) -- typically well into the late teens and twenties-- overshadows the developmental nature of this disorder. With mounting evidence for this neurodevelopmental pathophysiology (Feinberg, 1982; Jaaro-Peled et al., 2009; D. A. Lewis & Levitt, 2002; Murray, Jones, & O’Callaghan, 1991; Rapoport, Giedd, & Gogtay, 2012; Thompson & Levitt, 2010; Weinberger, 1987) there has been a shift in focus from understanding the disease-state to understanding the path to schizophrenia, by studying those deemed to be at an increased risk (genetic or psychometric) and identifying objective markers by which development can be tracked.

In a recent editorial, Insel (Insel, 2010) identifies 4 stages of normal cortical developments: 1. Neuronal proliferation, 2. Neuronal migration, 3. Arborization or circuit formation, and 4. Myelination, most of which are poorly understood even in typical development. He also points out that the first two of these processes mostly occur before the person is even born, while the next two move gradually towards completion during the first two decades of life. These premorbid changes, coming in the form of impaired migration, synaptic dysregulation and aberrant pruning, lend support to large longitudinal cohort studies which repeatedly identify factors such as delayed developmental milestones in the first year and reduced IQ in children who go on to develop schizophrenia (Reichenberg et al., 2010; Sorensen et al., 2010; Woodberry, Giuliano, & Seidman, 2008). The effort to understand the disordered circuitry and communication in schizophrenia has lead to specific hypothesis regarding inhibitory/excitatory balance in regulatory pathways in the brain, implicating neurotransmitter systems and basic sensory input dysregulation.
1.4. NEUROTRANSMITTER SYSTEMS

Previous neurochemical models of schizophrenia implicated excessive dopaminergic activity as the likely culprit (Brisch et al., 2014; Davis, Kahn, Ko, & Davidson, 1991; Sayed & Garrison, 1983). This came from observations of methamphetamine-induced psychosis in neurotypical controls and also the effectiveness of anti-dopaminergic drugs at relieving psychotic symptoms in these controls and in patients. A dopaminergic-exclusive hypothesis largely fell out of favor though over the past twenty or so years with the emergence of the PCP/NMDA model of schizophrenia, paving the way for the glutamate hypothesis (Coyle, 2006; Javitt, 1996, 2012; Javitt, Zukin, Heresco-Levy, & Umbricht, 2012). PCP (phencyclidine) and other NMDA (N-methyl D-aspartate) receptor antagonists, such as ketamine, provided a better neurochemical model as these drugs were able to successfully induced negative and
cognitive symptoms in human/animal models associated with schizophrenia in neurotypicals, which were lacking in the dopamine models (Javitt, 1987). Further, as more research developed around brain-based phenotypes for schizophrenia, a widespread expression profile of NMDA receptors was revealed –over basic sensory areas, as well as frontal, and multimodal areas – making it an attractive mechanistic candidate (S. J. Lewis et al., 1987; Nieuwenhuys, 1994).

NMDA/glutamate dysfunction does not preclude dopamine dysfunction, with studies showing glutamatergic regulation of dopamine as well as other interdependencies, particularly in the realm of plasticity (Beninger & Gerdjikov, 2005; Javitt, 2007; Javitt, Hashim, & Sershen, 2005). Lastly, GABAergic (gamma-aminobutyric acid) functioning also appears to be altered in schizophrenia, with impairments noted specifically in inhibitory inter-neurons (Benes & Berretta, 2001; Benes, McSparren, Bird, SanGiovanni, & Vincent, 1991). These changes in the expression and sensitivity of GABA receptors also show a level of interaction with glutamatergic changes, leading some to postulate an excitation/inhibition balance deficit in this disorder (Berretta et al., 2004; Cohen, Tsien, Goff, & Halassa, 2015; Gisabella, Bolshakov, & Benes, 2005; Thompson & Levitt, 2010).

![Fig 3, left as published in (P. J. Harrison & Weinberger, 2005)](image)

Schematic representation of interdependence of NMDA/glutamate, dopamine, and GABA (as well as proposed risk genes); top as published in (Kantrowitz & Javitt, 2010) schematic representation of the role of NMDA dysfunction and sensory processing deficits in the diathesis-stress model.
1.5. SENSORY ADAPTATION DEFICITS

OVERVIEW

The oldest attempts to link descriptive/observational psychology to the neuroscience/biology of schizophrenia are actually contained in the accounts of Kraeplin and Bleuler in which they independently describe altered attentional regulation in their patients (Bleuler, 1950; Kraepelin, 1919). Fast forward a few years to the beginnings of the age of Experimental Psychology, and this notion is further developed, with researchers then attributing such dysregulation to deficits in perception/sensory input (Frith, 1979; McGhie & Chapman, 1961; Venebles, 1971). Based on clinical observation, the theory emerged that those with schizophrenia had a “broken sensory filter”, preventing them from shutting off the processing of irrelevant or distracting sensory information, which in turn lead to “sensory flooding” and the trademark higher-order deficits associated with the disorder, such as hallucinations, delusions, distractibility, and a feeling of being overwhelmed. Or, as McGhie & Chapman wrote, “if [sensory] gating is defective, inhibition and selectivity fail and consciousness is flooded with an undifferentiated and involuntary tide of sensory data sweeping away the stable constructs of reality” (McGhie & Chapman, 1961).

The first formal attempt at operationalizing and testing this claim involved a “sensory overload apparatus” – a geodesic dome in which subjects were locked and bombarded with “suprathreshold” visual and auditory stimuli (Gottschalk, Haer, & Bates, 1972). The authors concluded that under these circumstances, cognitive functioning in neurotypical controls was “driven in a schizophrenic direction,” and that similar cognitive effects were observed under LSD administration (and no sensory bombardment).

Since then, less creepy, albeit at times significantly more boring, ways of quantifying ‘gating’ or sensory adaptation deficits in schizophrenia have emerged. A now classic technique involves presenting participants with pairs of auditory tones while recording the continuous electroencephalography (EEG). Auditory evoked responses to the stimuli are then averaged over trials and the auditory evoked potential (AEP) amplitude to the first stimulus in the pair (S1) is compared to the second stimulus in the pair (S2). The gating ratio is then computed (S2/S1), with small ratios indicating more effective sensory filtering or
adaptation. Altered auditory gating in schizophrenia was first reported by Adler et al (Adler et al., 1982; Adler, Waldo, & Freedman, 1985) and has since been consistently replicated (for a review see Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; Patterson et al., 2008).

Sensory filtering theory has expanded to include other forms of adaptation deficits that go beyond inhibitory processing. Another classic sensory adaptation paradigm using the EEG/ERP technique involves infrequently presenting a deviant auditory stimulus interspersed among a series of frequently presented standard stimuli. The standard and deviant stimuli can vary in pitch, intensity, or duration (or a combination of these). The AEP to the standard tone is averaged across trials, as is the AEP to deviant. When these waveforms are subtracted from each other the resulting difference is termed the mismatch negativity (MMN). The MMN is elicited by the auditory system tuning in to the deviant stimulus (or change) that disrupts the otherwise stable auditory background. Impaired auditory MMN in schizophrenia was first reported in the 90’s (Javitt, Doneshka, Zylberman, Ritter, & Vaughan, 1993; Shelley et al., 1991) and has since been consistently replicated (for a review see Magno et al., 2008; Naatanen & Kahkonen, 2009).

These two forms of adaptation have been dubbed ‘gating out’ – i.e. response suppression – and ‘gating in’ – i.e. response enhancement (Gjini, Arfken, & Boutros, 2010; Hu, Boutros, & Jansen, 2012). Although researchers haven’t quite yet been able to connect this altered sensory modulation to “cognitiveflooding” or “the sweeping away of the constructs of reality,” they have been able to shown that these processes rely on NMDA-dependent mechanisms (Javitt, 2009a; Kantrowitz & Javitt, 2010; Vogels & Abbott, 2007), have used them to characterize those at risk for schizophrenia, as well as to identify and characterize schizophrenia related genes (Freedman et al., 1994; Leonard et al., 1996), and have related these to higher-order processing deficits such as prosodic processing, social cognition, and attention (for a review see Javitt, 2009b)). Although its discussion here will be limited, it should be noted that altered sensory gating out has also been consistently shown at a more basic level in patients with schizophrenia using the pre-pulse inhibition paradigm (PPI). Patients show less inhibition of the startle reflex than what is typical in controls when pre-exposed to a weaker stimulus prior to the presentation of a subsequent
more alarming stimulus, as compared to the response when no pre-exposure is used (D. L. Braff, Grillon, & Geyer, 1992; D. Braff et al., 1978; Nuechterlein & Dawson, 1984).

Although basic sensory processing deficits have been reported across visual (Butler, Silverstein, & Dakin, 2008; Javitt, 2009b), somatosensory (Arnfred, 2012; Chang & Lenzenweger, 2001; Javitt, Liederman, Cienfuegos, & Shelley, 1999), olfactory (Atanasova et al., 2008; Malaspina et al., 2012; Moberg et al., 1999), gustatory (Ansoleaga et al., 2015; Moberg et al., 2012), and vestibular systems (A. M. Jones & Pivik, 1985; Picard, Amado, Mouchet-Mages, Olie, & Krebs, 2008; Warren & Ross, 1998), the investigation of adaptation deficits has relied heavily on the auditory system. The ability of sensory systems to gate information is thought to depend on local cortical, long-range cortical, and subcortical connections (Carlsson & Carlsson, 1990; Grunwald et al., 2003; E. G. Jones, 1997; Swerdlow & Koob, 1987). The generalizability of sensory processing deficits across systems and adaptation deficits across paradigms has lead several researchers to postulate a critical role for the thalamus, as the “sensory gatekeeper,” in schizophrenia (Andreasen, 1997; Woodward, Karbasforoushan, & Heckers, 2012). Further, as evidence mounts for a ‘pandmodal’ theory of early sensory processing deficits (Javitt et al., 1999), one may also expect that adaptation deficits extend across sensory modalities.

**A FOCUS ON THE VISUAL SYSTEM**

In the investigations that comprise this dissertation we focus on visual adaptation to repetitive stimuli in schizophrenia. This route was guided by the overwhelming evidence of this type of adaptation deficit in the auditory system, deficits reported in other forms of visual adaptation in patients, and also the mounting evidence tying visual processing deficits to at-risk populations, genetic markers, and pathophysiological mechanisms. We built these experiments from the premise that careful characterization of the visual system may offer strong, reliable, and sensitive schizophrenia endophenotypes.

Electrophysiological markers of basic visual processing have revealed deficits in chronic schizophrenia (Butler et al., 2007; Butler et al., 2005; Schechter et al., 2005), first-episode patients (Yeap,
Kelly, Thakore, & Foxe, 2008), clinically unaffected first-degree relatives (Yeap et al., 2006), and at-risk groups (Bedwell, Chan, Trachik, & Rassovsky, 2013; Koychev, El-Deredy, Haenschel, & Deakin, 2010), making them excellent candidate endophenotypes for SCZ. These findings, coupled with fact that EEG offers an inexpensive way to rapidly and non-invasively assay visual processing, bring a certain degree of clinical utility to these measures. The notion that such basic processes can be elicited in the absence of a behavioral response and are largely immune to changes in motivation or attention, further hint to the potential translational utility of these measures and provide incentive for additional studies on endophenotypic role of these processes.

An endophenotype in psychiatry is a measurable trait thought to lie on the pathway between specific genetic liability and clinical expression of a disorder, i.e. the phenotype (Bearden & Freimer, 2006; Gottesman & Gould, 2003; Walters & Owen, 2007). The study of endophenotypes in schizophrenia research is useful due to the complex nature of the disorder, both in terms of genetic make-up and clinical presentation. A true endophenotype is associated with the disorder in the clinical population, is state-independent such that it is also present in non-clinical risk carriers, and is heritable, occurring at higher rates in relatives of the proband. Variation at the endophenotype level is thought to depend on fewer genes than variation of the disease phenotype. Endophenotypes can help elucidate disease and resilience mechanisms. Walters & Owen (Walters & Owen, 2007) point out that even if a putative endophenotype is epiphenomenal to the disease state, it can still offer value in simplifying the genetic basis of complex psychiatric disorders.
It is worth noting that visual processing electrophysiological endophenotypes have also been associated with genetic markers implicating altered glutamatergic functioning as a potential deviant mechanism (Donohoe et al., 2008; Javitt et al., 2012; O'Donoghue et al., 2012). Further, visual system assays utilizing FMRI, MRI, and other psychophysical techniques, in a variety of experimental paradigms provide convergent evidence for altered visual processing in schizophrenia and a connection to glutamatergic/GABA-ergic processes (Calkins, Iacono, & Curtis, 2003; Donohoe et al., 2010; Donohoe et al., 2009; Koethe et al., 2009; Lee et al., 2010; Lubow & Gewirtz, 1995; Mechelli et al., 2010; Perez, Shafer, & Cadenhead, 2012; Tan, Lana, & Uhlhaas, 2013). However, it should be noted that much still needs to be done in the area of validating these measures, particularly in terms of reliability and individual level sensitivity (Butler et al., 2012; Calkins et al., 2007; Turetsky et al., 2007).

Deficient visual adaptation to repetitive stimuli would naturally be hypothesized in schizophrenia knowing that the brain's visual pathways are heavily glutamate-dependent (Butler et al., 2008; Javitt, 2009b), that adaptation to repetitive stimuli in general is thought to involve the glutamatergic-system &
NMDA receptors (Callahan, Terry, & Tehim, 2014; Javitt, 2009b; Kantrowitz & Javitt, 2010; Sabbagh, Heaney, Bolton, Murtishaw, & Kinney, 2012; Vogels & Abbott, 2007), and that other forms of adaptation noted in this population—both visual (e.g. (Brenner, Wilt, Lysaker, Koyfman, & O'Donnell, 2003; Y. Chen et al., 1999; Keri, Antal, Szekeres, Benedek, & Janka, 2002; Slaghuis, 1998)), and otherwise (e.g. (Adler et al., 1985; D. L. Braff, Light, & Swerdlow, 2007; Thoma et al., 2007)). Recent EEG studies examining similar forms of visual adaptation are beginning to reveal a consistent pattern of deficits as seen in altered VEP amplitude enhancement following photic tectonic stimulation in schizophrenia (Cavus et al., 2012), attenuated visual MMN (Neuhaus, Brandt, Goldberg, Bates, & Malhotra, 2013), and absent binocular enhancement effect of VEPs following brief monocular deprivation (Foxe, Yeap, & Leavitt, 2013).

1.6. THE SCHIZOPHRENIA SPECTRUM: NON-CLINICAL SCHIZOTYPY

Schizotypy is a psychological construct used to describe the existence and variation of schizophrenia-like traits in the general population (Lenzenweger, 2010; Meehl, 1962, 1990). The schizotypy spectrum consists of elements such as magical thinking, paranoia, social withdrawal, perceptual aberration, odd speech, disorganized thinking and eccentric behavior (J. P. Chapman, Chapman, & Kwapil, 1995; Claridge et al., 1996; Raine, 1991). Schizotypy encompasses all levels of expression, intensity, compensation, and decompensation across these personality traits, such that schizophrenia proper, psychotic disorders more broadly, schizotypal personality disorder, the psychosis prodrome, and subclinical endorsements all fall under this umbrella term.

The notion that schizophrenia-like traits could exist in non-clinical populations was first described by Kraeplin and Bleuler in observations of relatives of their patients (Bleuler, 1950; Kraepelin, 1919). The term “schizotype” was first introduced by Rado (Rado, 1953) to describe a schizophrenic phenotype which he placed on a continuum from normal to full blown behavioral and cognitive impairment. Meehl (Meehl, 1962) elaborated on this notion imposing a taxonomic classification onto the schizotypy continuum. Meehl described a schizogene that when combined with other potentiators (e.g. personality and environment) would produce a neurointegrative deficit that was necessary but not sufficient to
develop the schizotype and schizophrenia. He went on to suggest that 10% of the population would exhibit high schizotypy and that 10% of high-schizotypes decompensate into schizophrenia (Kwapil & Barrantes-Vidal, 2014; Meehl, 1990).

Since then, schizotypy has been shown to be elevated in biological relatives of those diagnosed with schizophrenia (Battaglia et al., 1991; Berenbaum & McGrew, 1993; Calkins, Curtis, Grove, & Iacono, 2004; A. Fanous, Gardner, Walsh, & Kendler, 2001; Heston, 1970; Planansky, 1966), including adopted reared-apart relatives (Kety, 1983; Kety et al., 1994). The rates of high-schizotypy posited by Meehl, have also been more-or-less confirmed (Korfine & Lenzenweger, 1995; Linscott, 2013; Rawlings, Williams, Haslam, & Claridge, 2008) and the expression of schizotypy in the general population has been shown to be mediated by several schizophrenia-related genes (A. H. Fanous et al., 2007; Stefanis et al., 2007). The study of non-clinical schizotypy is a valuable research technique, in part due to this shared heritability, as it offers a window into altered neurodevelopmental processes shared with schizophrenia, unconfounded by effects of the disease-state and antipsychotic treatment.

Non-clinical schizotypy is usually assessed via questionnaires or interviews (J. P. Chapman et al., 1995; L. J. Chapman et al., 1984; L. J. Chapman, Chapman, & Raulin, 1976; Eckblad & Chapman, 1983, 1986; Kendler, Lieberman, & Walsh, 1989; Raine, 1991; Raine & Baker, 1992). The factor structure of schizotypy follows the dimensional model of schizophrenia, consisting generally of a positive (e.g. unusual perceptual experiences, suspiciousness, and ideas of reference), negative (e.g. social anxiety, flat affect, and anhedonia), and disorganized (e.g. odd or eccentric behavior and usual speech reflecting disorganized thoughts) domains (Livesley, 2005), although other factor solutions have been proposed (Gross, Mellin, Silvia, Barrantes-Vidal, & Kwapil, 2014; Horton, Barrantes-Vidal, Silvia, & Kwapil, 2014; Vollema & Hoijtink, 2000). The three factor model of schizotypy has been assessed and confirmed in the general population (Claridge et al., 1996; Raine et al., 1994), in college students (Bentall, Claridge, & Slade, 1989; Raine et al., 1994), and across cultures, gender, and religious affiliation (W. J. Chen, Hsiao, & Lin, 1997; Reynolds, Raine, Mellingen, Venables, & Mednick, 2000).

Though the prevalence rate of schizophrenia hovers around 1% (see epidemiology Section 1.3. for a discussion) the worldwide prevalence rate of at least one psychotic symptom ranges from 0.8 to
31.4% (Nuevo et al., 2012), and the combined prevalence of subclinical psychotic symptoms and experiences in help-seeking individuals can total 12% (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Furthermore, several lines of research have also shown that individuals high in psychometrically defined schizotypy convert to schizophrenia at higher rates than low schizotypes (L. J. Chapman, Chapman, Kwapił, Eckblad, & Zinser, 1994; Gooding, Tallent, & Matts, 2005; Kwapił, 1998). It follows that several markers of altered sensory processing in schizophrenia have also been demonstrated in non-clinical schizotypy. Several of these are expressed as deficits in the visual domain, including reduced VEP amplitudes (Bedwell et al., 2013; Koychev et al., 2010), altered latent inhibition (Casa, Hofer, Weiner, & Feldon, 1999; Evans, Gray, & Snowden, 2007a), atypical depth perception (Barbato, Collinson, & Casagrande, 2012; Koethe et al., 2009) and smooth pursuit (Gooding, Miller, & Kwapił, 2000). Deficits in somatosensory processing (Chang & Lenzenweger, 2005), olfaction (Mohr, Rohrenbach, Laska, & Brugger, 2001), and auditory processing (P50 gating, discussed below) have, albeit to a lesser degree, also been characterized in schizotypy.

Altered sensory adaptation and “sensory flooding” have been widely theorized in schizotypy as well, leading to the notion that mechanisms underlying input dysfunction in schizophrenia are also modified by schizotypy status (Freedman et al., 2002). These adaptation deficits have been quantified at the level of PPI (Evans, Gray, & Snowden, 2005; Takahashi et al., 2010), P50 auditory gating (Croft, Dimoska, Gonsalvez, & Clarke, 2004; Evans, Gray, & Snowden, 2007b; Wan, Crawford, & Boutros, 2006), and saccade adaptation (Aichert, Williams, Moller, Kumari, & Ettinger, 2012; Holahan & O'Driscoll, 2005) – for a more comprehensive review of the aforementioned adaptation deficits see (Cadenhead & Braff, 2002).

Visual adaptation paradigms utilizing non-invasive EEG are only now beginning to be leveraged in this population in order to better understand risk-and-resilience mechanisms for schizophrenia. Recently, Koychev and colleagues demonstrated abnormal oscillatory activity in the beta and gamma bands during a visual working memory task in non-clinical schizotypes (Koychev, Deakin, Haenschel, & El-Deredy, 2011). The scalp topographic distribution of this effect pointed to altered connectivity, suggesting deficits in top-down as well as bottom-up regulation of sensory responses. We seek to
contribute to this line of investigation, particularly given the potential strength of visual adaptation electrophysiological endophenotypes discussed above. In Chapter 4 we assess the relationship between visual adaptation, as measured by VEP amplitude modulation in our novel rapid block-presentation paradigm, and psychometrically defined non-clinical schizotypy. We discuss the potential role and utility of this measure as a novel endophenotype.

1.7. SPECIFIC AIMS ADDRESSED IN THIS DISSERTATION

**AIM 1:** Developing a sensitive assay. In Chapter 2, the experiments and analysis serving Aim 1 are described. In brief, we set out to characterize the spatio-temporal properties of visual adaptation in neurotypical adults. To do so we employed a pair of experiments designed to assess: 1. Whether visual adaptation can be assayed employing parameters similar to those used in somatosensory and auditory paired gating studies, 2. Whether further taxation of the visual system in a block-presentation paradigm results in a differing adaptation profile, 3. Whether studying second-order 'dynamic' characteristics of the brain, such as VEP adaptation elicited by different stimulus presentation rates and across various scalp sites would offer additional understanding of sensory processing in the visual system, and 4. Whether visual adaptation effects are robust enough to be statistically identified at the individual participant level. Additionally, we employ inverse source-localization techniques to estimate the major cortical generators of adaptation effects in our novel block-design paradigm.

**AIM 2:** Testing the assay in a clinical population. In Chapter 3, the experiments and analysis serving Aim 2 are described. Electrophysiological studies show reduced VEP amplitude and deficient sensory gating in patients with schizophrenia. Here we examine the adaptation properties of the visual system in a group diagnosed with schizophrenia-spectrum disorders. We further examine the sensitivity and specificity of second-order “dynamic” visual processing (i.e. adaptation) elicited in our “taxing” paradigm, via single subject analysis and logistic regression. Lastly, we ask if adaptation effects observed in the visual domain are modality specific. To do so, we employ a somatosensory analog to our block-adaptation experiment utilizing vibrotactile stimulation of the median nerve in the same sample of patients and controls.
AIM 3: Assessing the role of visual adaptation as a schizophrenia endophenotype. In Chapter 4, the experiments and analysis serving Aim 3 are described. Here we deploy a shorter version of our visual adaptation paradigm (15mins, 32-channel electrode array) in larger sample of neurotypical adults. We use the Schizotypal Personality Questionnaire (SPQ, self-report, (Raine, 1991)) to assess non-clinical schizotypy, and its dimensional components in this sample. We then conduct a multiple regression analysis to determine the relationship between VEP amplitude modulations elicited by the visual adaptation paradigm and global schizotypy as defined by total SPQ score. Lastly, we perform exploratory analysis, using a taxonomic categorization on Disorganization, to characterize a trend effect noted in the main analysis for this schizotypy domain.
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CHAPTER 2

SPATIO-TEMPORAL DYNAMICS OF ADAPTATION IN THE HUMAN VISUAL SYSTEM

ABSTRACT

When sensory inputs are presented serially, response amplitudes to stimulus repetitions generally decrease as a function of presentation rate, diminishing rapidly as inter-stimulus-intervals (ISIs) fall below a second. This "adaptation" is believed to represent mechanisms by which sensory systems reduce responsivity to consistent environmental inputs, freeing resources to respond to potentially more relevant inputs. While auditory adaptation functions have been relatively well-characterized, considerably less is known about visual adaptation in humans. Here, high-density visual evoked potentials (VEPs) were recorded while two paradigms were used to interrogate visual adaptation. The first presented stimulus pairs with varying ISIs, comparing VEP amplitude to the second stimulus to that of the first (paired-presentation). The second involved blocks of stimulation (N=100) at various ISIs and comparison of VEP amplitude between blocks of differing ISIs (block-presentation). Robust VEP modulations were evident as a function of presentation rate in the block-paradigm with strongest modulations in the 130-150ms and 160-180ms visual processing phases. In paired-presentations, with ISIs of just 200-300 ms, an enhancement of VEP was evident when comparing S2 to S1, with no significant effect of presentation rate. Importantly, in block-presentations, adaptation effects were statistically robust at the individual participant level. These data suggest that a more taxing block-presentation paradigm is better suited to engage visual adaptation mechanisms than a paired-presentation design. The increased sensitivity of the visual processing metric obtained in the block-paradigm has implications for the examination of visual processing deficits in clinical populations.

Keywords: Vision, VEP, Visual Gating, inhibition, habituation, EEG, plasticity, ERP
2.1. INTRODUCTION

Adaptation of neural responses to invariant or repetitive environmental inputs is a fundamental property of sensory processing, believed to represent a mechanism by which sensory systems attenuate representational redundancy (Cattan et al., 2014; Muller, Metha, Krauskopf, & Lennie, 1999; Wissig & Kohn, 2012). Adaptation typically manifests as a rapid attenuation of neural responsiveness, providing a good metric of short-term neural plasticity. The hypothesized reduction in representational redundancy likely serves to enhance the brain's ability to detect more relevant novel environmental changes. Visual adaptation can be examined by comparing changes in the amplitude of the visual evoked potential (VEP) to repetition at varying presentation rates. Terminology in the field is not always consistent, with such VEP adaptation effects sometimes referred to as “habituation” or “sensory gating”. Adaptation to presentation rates can be calculated across pairs of consecutive trials by comparing VEP amplitudes between the first and second stimulus of a pair (Adler, Waldo, & Freedman, 1985). Alternatively, comparisons can be made between VEPs elicited by trains of stimuli presented at fixed rates, where rate is varied across blocks of trials (Megela & Teyler, 1979).

In humans, adaptation to repetitive auditory stimulation has been extensively studied and is now quite well characterized (Chang, Arfken, Sangal, & Boutros, 2011; Fruhstorfer, Soveri, & Jarvilehto, 1970; Grzeschik, Bockmann-Barthel, Muhler, Verhey, & Hoffmann, 2013; Lanting, Briley, Sumner, & Krumbholz, 2013; Potter, Summerfelt, Gold, & Buchanan, 2006; Rosburg, Zimmerer, & Huonker, 2010). A main finding in both auditory habituation and gating studies has been that the shorter the period between stimulus presentations, the greater the attenuation observed (Budd, Barry, Gordon, Rennie, & Michie, 1998; Muller-Gass, Marcoux, Jamshidi, & Campbell, 2008; Pereira et al., 2014; Rosburg et al., 2010; Roth et al., 1976). Although the mechanisms behind auditory adaptation are not fully understood, several studies implicate local mechanisms such as neuronal refractoriness and pre-synaptic calcium influx, particularly in paired-presentation designs. Also implicated are top-down mechanisms related to expectancy, sensory memory, and novelty detection, particularly when more than 2 stimuli are used, such as in a block design. These plasticity mechanisms are thought to involve NMDA-mediated glutamate transmission, GABA-ergic inhibition, and changes in the ongoing oscillatory activity of the brain (e.g. in the gamma band frequency) (Brockhaus-Dumke, Mueller, Faigle, & Klosterkoetter, 2008; Carlen et al.,
2012; Chung, Li, & Nelson, 2002; Friston, 2005; Grill-Spector, Henson, & Martin, 2006; Orekhova et al., 2008; Zucker, 1989). In contrast, studies of adaptation to visual stimulation are relatively sparse and have yielded inconsistent and even contradictory findings.

Here, we set out to comprehensively map adaptation functions of the visual system in healthy adults using high-density electrical mapping techniques. Most of the previous literature has been limited to low-density montages and there has been a strong tendency to focus on amplitude changes at discrete VEP components, providing a somewhat static view of what is undoubtedly a dynamic ongoing process. This, along with a bias towards paired-presentation paradigms and a lack of studies examining VEP adaptation to simple presentation rate manipulations has provided an incomplete picture of visual adaptation processes.

In the auditory and somatosensory systems, the amplitude of the neural response dramatically attenuates following repeated rapid paired-stimulation (Arnfred, Eder, Hemmingsen, Glenthoj, & Chen, 2001; Braff, Light, & Swerdlow, 2007; Hetrick et al., 1996; Mclaughlin & Kelly, 1993), although it should be noted that the auditory evoked potential (AEP) can also increase in response to the second stimulus in a pair when very short inter-stimulus-intervals (ISIs) are employed (Loveless, Hari, Hamalainen, & Tiihonen, 1989; Loveless, Levanen, Jousmaki, Sams, & Hari, 1996). In vision, findings are considerably less clear-cut. For example, there are reports of strong adaptation to paired-stimuli using monocular stimulation (D.G. Wastell & Kleinman, 1980b), while others report weakened adaptation to binocularly presented paired-stimuli as compared to other sensory modalities (Davis, Osterhammel, Wier, & Gjerdingen, 1972), and yet others report adaptation effects to paired-stimuli that are specific to right lateral occipital scalp-sites (Gjini, Sundaresan, & Boutros, 2008). On the other hand, there are also reports of adaptation effects over bilateral occipital scalp to non-identical, spatially segregated stimuli (Gawne, Osbourne, & Risner, 2011). Given the differences in the experimental paradigms used to assess visual adaptation to paired-stimuli, it is difficult to form a coherent picture of which effects are consistent, and what variables are driving these effects.

In blocked stimulation designs, the picture is equally confusing. For example, Wastell & Kleinman conducted a pair of studies that highlight the effects of both paradigm and presentation rate on VEP adaptation (D. G. Wastell & Kleinman, 1980a; D.G. Wastell & Kleinman, 1980b). In varying the amount of
time between stimulus presentations within a train of 10 trials, they showed significantly more adaptation (i.e. VEP attenuation) in “fast” conditions (500 & 1000ms ISIs) compared to “slow” conditions (2000 & 3000ms ISIs)(D. G. Wastell & Kleinman, 1980a). In the second of their studies, a paired-presentation design with monocular stimulation was employed and attenuation was observed in ipsilaterally and contralaterally elicited VEPs with an ISI of 1000ms (D.G. Wastell & Kleinman, 1980b). Still other studies failed to show any rapid adaptation effects in the visual domain in healthy controls or in patients with chronic schizophrenia when employing a paired-presentation paradigm(Adler et al., 1985).

Clearly, much remains to be done to adequately characterize the adaptation properties of the human visual system. There is an added imperative to map visual adaptation properties as visual processing and sensory adaptation deficits may serve as strong candidate endophenotypes for various psychiatric disorders. In schizophrenia, for instance, the P1 component of the VEP is attenuated in first-episode drug naive patients, chronic patients, and their first degree unaffected relative (Foxe, Doniger, & Javitt, 2001; Yeap et al., 2006; Yeap, Kelly, Thakore, & Foxe, 2008). Furthermore, patients with schizophrenia consistently display altered auditory adaptation (Adler et al., 1985; Braff et al., 2007; Patterson et al., 2008; Potter et al., 2006) but visual adaptation functions have yet to be closely interrogated in this population. Evidence is also emerging for visual-sensory processing abnormalities in individual with an autism spectrum disorder (Frey, Molholm, Lalor, Russo, & Foxe, 2013). We believe that under adequately taxing conditions, a second-order measure of “dynamic” early visual processing may offer a unique window into specific, observable short-term plasticity and sensory processing, with implications for characterizing psychiatric and neurodevelopmental disorders. However, before addressing deficits in a clinical population, the spatial and temporal profile of visual adaptation in the healthy visual system must be fully elucidated. Questions remain as to how quickly the VEP attenuates, which regions of the visual cortex show the greatest adaptation effects, when during the temporal evolution of the sensory processing period adaptation effects emerge, how different paradigms affect adaptation, how adaptation is affected by presentation rate, and how detectible all these changes are to non-invasive measuring techniques.

We examined these questions here in a pair of related experiments. Experiment 1 involved presenting pairs of stimuli with varying inter stimulus intervals (ISI) and comparing the amplitude of the
VEP to the second stimulus to that of the first (paired-presentation) as a function of ISI. Experiment 2 involved presenting stimuli at a constant ISI in blocks of 100 stimuli, and then comparing the VEP amplitude across blocks for different ISIs (block-presentation). The major goals of this study were the following: 1) To assess whether visual adaptation can be assayed employing parameters similar to those used in somatosensory and auditory studies, as measured by the paired-presentation paradigm (Experiment 1); 2) Whether further taxation of the system in the block-presentation paradigm (Experiment 2) results in a differing adaption profile; 3) Whether studying second-order 'dynamic' characteristics of the brain, such as VEP adaptation changes elicited by different stimulus presentation rates and across various scalp sites would offer additional understanding of sensory processing in the visual system (Experiments 1 & 2); 4) Whether adaptation functions are robust enough to be statistically identified at the individual participant level; and 5) To employ inverse source-localization techniques to estimate the major cortical generators of adaptation effects.
2.2. METHODS

Participants
Eleven healthy adults (4 males, mean age=26, SD=3.6) completed Experiment 1. Fifteen healthy adults completed Experiment 2 (8 males, mean age=26, SD=4.4). Of the 15 participants in Experiment 2, three also completed Experiment 1. All had normal or corrected-to-normal vision. The experimental procedures were approved by the Institutional Review Board at Albert Einstein College of Medicine and conformed to the tenets of the Declaration of Helsinki. All participants provided written informed consent and received a modest fee.

Stimuli
Stimuli were 100% contrast black and white checkerboard annuli (6.5 cm diameter, 1cm width, 4°x4°, white luminance of 120 cd/m², black luminance of 0.2 cd/m²) centered against a grey (luminance = 25 cd/m²) background. A fixation cross was always present on the screen, including during checkerboard presentation. The fixation cross changed color every 20-40s. Checkerboards were presented for 33ms and at different inter-stimulus-intervals (ISIs).

Procedure
Participants sat in a darkened sound-attenuated electrically shielded double-walled booth (Industrial Acoustics Company, Bronx, NY), 90 cm from a 34x55 cm LCD computer screen (ViewSonic VP2655wb, 60Hz refresh rate). They were instructed to minimize head movements and blinking while fixating on a red cross at the center of the screen. They performed a change detection task to ensure fixation in which they were asked to respond to fixation cross color changes (from red to green, lasting 40ms) with a mouse button press using the index finger of their dominant hand. The presentation of checkerboard stimuli was temporally unrelated to this central fixation task.

Paradigms
**Experiment 1 - Paired Presentation**

Participants were presented with the checkerboard stimuli in pairs (first stimulus in pair = S1, second stimulus in pair = S2) with an ISI of either 200ms or 300ms. There was a 2500 ms interval between the paired presentations. A non-paired stimulus (i.e. a “catch” trial) was randomly presented one third of the time during a semi random time point (>2500ms) in the inter-pair interval. Subjects were exposed to approximately 300 presentations of each condition (pair with 200ms ISI, pair with 300ms ISI, and catch). Total run time for this experiment ranged from 45-60mins.

**Experiment 2 - Block Presentation**

Checkerboards were presented in blocks of 100 stimuli. Within each block, the stimuli were centered at an ISI, around which the actual presentations were jittered by +/-50ms. Five different ISIs were used: 200ms, 300ms, 550ms, 1050ms, and 2550ms. For example, the following sequence of ISIs might be typical of a segment of trials in the 300ms ISI condition: 272-267-304-320-336-300-288, etc. Between-block interval was self-paced, with participants allowed to move to the next block by pressing the spacebar on a keyboard 2500-5000ms after the last stimulus of the preceding block. Block presentation was pseudorandom. In total, participants experienced 4 blocks of each of the four shorter ISIs (200ms, 300ms, 550ms, 1050ms) and two blocks of the longest ISI (2550ms). Total run time for the experiment ranged from 35-45 minutes. For a schematic time course representation of Experiment 1 & Experiment 2, the reader is referred to Figure 1.

**Data Acquisition**

Continuous electroencephalographic (EEG) data were recorded in both experiments using a Biosemi ActiveTwo 168-channel electrode array, analog-to-digital converter, and fiber-optic pass-through to a dedicated data acquisition computer. The data were recorded at 512 Hz with a pass-band from DC to 150Hz. The continuous EEG was subsequently low-pass filtered at 45Hz (4th order-zero phase Butterworth filter, 27 dB/octave) and high-pass filtered at 1Hz (4th order-zero phase Butterworth filter, 24 dB/octave). Epochs of 600 ms with 100 ms prestimulus baseline were extracted from the continuous
data. An automatic artifact rejection criterion of ±75 µV was applied across all electrodes in the array. Trials with more than six artifact channels were rejected. In trials with less than six such channels, any remaining bad channels were interpolated using the nearest neighbor spline (Butler et al., 2011; Perrin, Pernier, Bertrand, Giard, & Echallier, 1987). The data were re-referenced to the average of all channels.

Pre-processing

Experiment 1: Catch-trial transformation

For the paired-presentation experiment (Experiment 1) waveforms for the S2 VEP were derived to isolate the responses to the S2 from the continued activity related to the S1, due to the short ISIs used. These waveforms were derived by subtracting the "catch" from the composite S1-S2 VEP and then shifting the isolated S2 response back in time by the appropriate delay. See Supplementary Figure 1 for an illustration of the catch-trial transformation. The subtraction allowed for the examination of the “pure” VEP response to the second stimulus in a pair without any interference from ongoing activity related to the first stimulus. There was an average acceptance rate of 74% of trials per condition for this experiment.

Experiment 2: Adjacent Response Algorithm (ADJAR)

As the timing between the stimuli of the shortest ISI was between 150 to 250ms, we implemented the Adjacent Response (ADJAR) algorithm on our subject-level data to model and remove any response overlap (Fiebelkorn, Foxe, McCourt, Dumas, & Molholm, 2013; Woldorff, 1993). ADJAR correction was only applied to the 200ms ISI condition. See Supplementary Figure 2 for a depiction of data from the 200ms ISI condition before and after the ADJAR procedure. There was an average acceptance rate of 82% of trials per condition for this experiment.

Analysis Strategy

Identifying scalp-sites of interest and time windows for primary analysis
For each experiment, the data from all participants from each electrode were collapsed into a single averaged waveform. These group-averaged waveforms were visually inspected across all scalp sites, and the familiar components of the VEP were identified (Foxe & Simpson, 2002). This allowed for definition of the precise timing of a given component and delineation of the scalp sites at which each component was of maximal amplitude. Evoked responses to these simple visual stimuli showed the typical sequence of VEP components (P1, N1, P2) over occipital sites. Following this procedure, three time-windows were identified for analysis corresponding to peak components over central-occipital (Oz), left occipital (PO7 & O1), and right occipital (O2 & PO8) sites: 90-110ms, 130-150ms, and 160-180ms.

Although the use of broadly defined component peaks is a good means of limiting the number of statistical tests that will be conducted, these components clearly represent the activity of many simultaneously active brain generators at any given moment (Foxe & Simpson, 2002). In order to provide a more complete picture of the mechanisms underlying visual adaptation, we also present the scalp topographic maps for time period in which significant adaptation is observed and conduct a source modeling analysis (discussed below).

Primary Analysis

Statistical analyses were performed using custom MATLAB scripts (Mathworks), the Fieldtrip toolbox for EEG analysis (Oostenveld, Fries, Maris, & Schoffelen, 2011), EEGLAB (Delorme & Makeig, 2004), and the SPSS software package (SPSS). For the paired experiment (Experiment 1), a repeated-measures analysis of variance (ANOVA) with factors of stimulus order (S1, S2), ISI (200ms, 300ms) and scalp-site (PO7, O1, Oz, O2, PO8) was performed for each of the time periods of interest (2x2x5 ANOVA). For the block experiment (Experiment 2), a repeated-measures ANOVA with factors of ISI (200ms, 300ms, 550ms, 1050ms, 2550ms) and scalp-site (occipital/parieto-occipital sites: PO7, O1, Oz, O2, PO8) was performed for each of the time periods of interest (5x5 ANOVA). Significant effects were then examined using protected post-hoc contrasts. The Greenhouse-Geisser correction was used to adjust F values and probabilities when sphericity was violated; the original degrees of freedom are presented for each analysis.
Source Localization

In order to examine the brain generators for representative short and long ISI conditions, the data from experiment 2, which provided greater discrepancy between ISIs, was modeled using the Local Auto Regressive Average inverse solution (LAURA; (Gonzalez Andino et al., 2001; Grave de Peralta Menendez, Gonzalez Andino, Lantz, Michel, & Landis, 2001) as implemented in the Cartool software by Denis Brunet (brainmapping.unige.ch/cartool). The linear distributed inverse solution is based on a realistic head model with 4024 solutions points equally distributed within the grey matter of the Montreal Neurological Institute’s (MNI) average brain. The LAURA method deals with multiple simultaneously active sources of a priori unknown location, and makes no assumptions regarding the number or location of active sources. It selects the source configuration that best mimics the biophysical behavior of the electrical field and produces a unique estimation of the current source density inside the brain. That is, the estimated activity at one point depends on the activity at neighboring points as described by electromagnetic laws (Grave de Peralta-Menendez & Gonzalez-Andino, 1998). Mean scalp topographies of the main periods of interest were down-sampled from the 168-channel montage to a 111-channel montage by means of a 3D-spline interpolation (Lopez, Mercier, Halje, & Blanke, 2011; Perrin et al., 1987).

Source reconstruction was performed at two levels. First, we applied LAURA to VEP maps for the 300ms and 2550ms ISI conditions. Since there were minimal differences in the scalp topography for the 200, 300, 550ms ISIs (Figure 5), the 300ms ISIs served as a representative for the "shorter" ISIs. Additionally, the scalp topographies for the 1050 and 2550ms ISIs were also very similar, and so the 2550ms ISI served as a representative for the "longer" ISIs. With this, we were able to visualize the brain generators for the signals recorded under these two different presentation.

Second, we performed statistical analyses in the source space to test for regions sensitive to adaptation effects (i.e. regions distinguishing between “fast” and “slow” presentation rates). These theoretically play a role in modulating the differences observed in the VEPs across ISIs. To do so, we determined for each participant and each condition (300ms ISI and 2550ms ISI) at the three time periods of interest, the mean corresponding VEP map. The inverse solution was applied to each individual VEP map. The inverse solutions for the representative short and long ISIs were compared statistically (paired
randomization tests), with subjects as a repeated measure. To correct for multiple comparisons we applied a Bonferroni correction (α/number of electrodes, .05/16=.0003125) which decreases the chances of Type I errors (Grave de Peralta Menendez et al., 2001).

Individual Participant Level Analysis

In experiment 2, in order to investigate the robustness of adaptation and the minimum number of sweeps required for statistical significance at the individual participant level we conducted a non-parametric randomization procedure (Maris & Oostenveld, 2007). For each participant we compared the amplitude recorded under the 2500 ISI condition against each of the other ISI conditions (200, 300, 550, 1050ms) at the central occipital and two lateral sites for each of the time periods of interest (90-110, 130-150, 160-180ms). These scalp sites were chosen for analysis as they demonstrated the largest activation and strongest modulation in the group-level statistics.

The observed difference between the 2550ms ISI and the test ISI was compared with a reference distribution of differences that was derived by iteratively randomizing between the two original data sets (i.e. individual-subject VEP amplitudes for the 2550ms and test ISI) 10,000 times. The number of epochs selected for the bootstrapping process was a subset of the total which increased in steps of 10 from 30 epochs until statistical significance or the maximum number of sweeps was reached (Nolan et al., 2012). A one-tailed threshold of p <0.05 was used to define significance. The p value for a randomization test was calculated from the proportion of values in the reference difference distribution that exceeded the observed difference (Fiebelkorn et al., 2011).
2.3. RESULTS

The checkerboard annulus evoked a VEP that exhibited a different morphology based on scalp site. Amplitudes were greatest over central occipital scalp. At the midline site (Oz) the first major VEP component had peak at ~110ms (negative going) and the next major component peaked at ~180ms (positive going). At the most proximal lateral sites (O1 & O2), the first major VEP component had a peak ~150ms (negative going) and the next major component peaked at around 250ms (positive going). At the more distal lateral sites (PO7 & PO8) the first major component had a peak at ~100ms (positive going) and the next major component peaked at ~160ms.

Experiment 1: Paired Presentation

Figure 2 shows the group averaged VEP waveforms for the 200ms (red) and 300ms (blue) ISIs, with the three time periods of interested highlighted by the opaque vertical grey boxes. These waveforms contain both the VEP elicited by the first stimulus in a pair (S1) as well as the VEP to the second stimulus (S2) in the pair. The figure also displays the VEP waveform elicited by the "catch" trials (black). This response should be entirely equivalent to the one evoked by the S1 stimulus. Also shown are the "derived" waveforms for the S2 VEP which isolate the responses to the S2 from the continued activity related to the S1. These waveforms were derived by subtracting the "catch" from the composite S1-S2 VEP and then shifting the isolated S2 response back in time by the appropriate delay (red-dashed for the 200ms and blue-dashed for the 300ms ISI). These waveforms are shown for the five scalp sites of interest (PO7, O1, Oz, O2, PO8) over occipital and parieto-occipital scalp regions. The reader is referred to Supplemental Fig 3A for an alternate depiction of these tuning parameters. Contrary to what was expected, S2 response amplitudes appear greater than those to the S1, and this is most prominent over midline and right occipital scalp.

VEP Amplitudes
Results from the 3 main ANOVAs performed to examine the effect of ISI, stimulus order, scalp site, and any interactions at each of time periods of interest are presented in Table 1. In summary, the primary observation is a significant effect of order, with S2 VEP amplitudes larger than S1. This effect is primarily seen at lateral occipital sites for the two later time periods. This analysis captures the major negative going peak in the VEP at these sites, spanning from 130-180ms. At the midline site (Oz), this enhancement effect is seen during the first time window of analysis, which at this site captures the peak of the major negative going component (~100ms). The effect then reverses during the last time window of analysis, with S2 amplitudes attenuated compared to S1. Here the analysis captures the peak of a major positive going component in the VEP at 180ms.

Scalp Topographies
Scalp topographic maps representing interpolated potential distributions of the grand mean are shown for the Catch-trial, the 200ms ISI and the 300ms ISI conditions (columns) and the three periods of interest (rows) in Figure 3. The first row of topographical distributions for the 90-110ms period shows a strong central occipital distribution which is similar for both ISIs. The second row of topographical distributions for the 130-150ms period shows evidence for a somewhat more bilateral occipital distribution, with greater amplitude evident over right occipital scalp, and this activity shows clearly greater negativity for the S2 stimuli. The third row of topographical distributions for the 160-180ms time period of interest shows a positive central occipital distribution with an evident decrease in amplitude to the S2 stimuli. Further, these maps show indistinguishable topographic distributions for the S1 and catch trials, providing further evidence that they are a representation of the same process.

Experiment 2: Block Presentation
Figure 4A shows the group averaged VEP waveforms for the five ISIs at the five targeted scalp-sites over occipital and parieto-occipital areas with the three time periods of interest highlighted by the vertical grey boxes. Figure 5B is a more focused representation of the effects of ISI on VEP at each scalp site during the three time periods of interest. Together, these figures illustrate clear adaptation effects that vary as a function of ISI, scalp site, and time period of analysis. The most prominent effect is seen in the influence
of ISI on the first major negative going response, with a more negative going response for longer ISI conditions. However, the midline occipital site also shows a second phase of adaptation, where a reversal of this effect is seen for the later major going positive component. The reader is referred to Supplemental Fig 3B for an alternate depiction of these tuning parameters, in which tuning functions are derived for each of the five scalp-sites using the group mean and standard error amplitude of the VEP for each ISI for the time periods of interest.

**VEP Amplitudes**

Results from the 3 main ANOVAs performed to examine the effect of ISI, scalp site, and any interactions at the three time periods of interest (90-110ms, 130-150ms and 160-180ms) are presented in Table 2. In summary, significant adaptation effects are noted at all sites examined, with the major finding being that VEP amplitudes decrease with faster ISIs. This robust effect is noted during the later time windows, spanning 130-180ms, for the lateral occipital sites. At these sites (PO7, O1, PO8, O2) this time window captures the major negative going component of the VEP. For the midline site (Oz) the adaptation effect is also noted at the first negative going peak, which at this site occurs earlier and spans 110-140ms. The effect at Oz then reverses during the last time window of analysis, with VEP amplitudes increasing with faster ISIs. This time window captures the major positive-going component at this site, which peaks at ~180ms.

**Scalp Topographies**

Scalp topographic maps representing interpolated potential distributions are shown of the group mean for all ISI conditions (columns) during the three time periods of interest (rows) in Figure 5 right. The first row of topographical distributions for the 90-110ms time period shows a stronger focal midline occipital distribution which is similar for all ISIs in this time window. The second row of topographical distributions for the 130-150ms time period shows a progression of topographies with respect to the ISI, from a positive central occipital distribution for the shortest ISIs of 200ms to a negative bilateral occipital distribution for the longer ISIs of 1050 and 2550ms. The third row of topographical distributions for the 160-180ms time period of interest shows a progression of topographies from a positive central occipital
distribution for the shortest ISI (200ms) to a negative bi-lateral occipital distribution for the longest ISI (2550ms).

Difference topographies were also computed by comparing the interpolated potential distributions for the 2550ms ISI condition against each of the other conditions (200ms, 300ms, 550ms, and 1050ms ISIs) for the later time periods which showed a significant effect of ISI on VEP amplitude (Figure 5 left). The difference scalp topographic maps for the 90-110ms timeframe (top row) show an emerging central negativity focus with the strongest difference signal seen when comparing the 2 most discrepant ISIs (2550 vs 200ms), as can be seen here though differences in this time window are weaker and also highly similar across ISIs. During the 130-150ms timeframe (second row), difference maps reveal a strong central-occipital negativity that is similar across the comparisons between the 2550ms ISI versus the 200ms, 300ms, and 550ms ISI, but weaker between the most similar ISIs (1050 vs 2550ms), confirming a similar activation profile for the 3 shorter ISIs, but a difference between short and long ISIs. The 160-180ms time frame (bottom row) revealed a similar strong central-occipital negativity for each comparison, which again was weakest for the 1050ms versus 2550ms subtraction. In summary, the three shorter ISIs exhibit a response pattern that is different from the two longest ISIs but relatively similar to each other. The 1050ms ISI response is unique as compared to the shorter ISIs and is most similar to the 2550ms condition, but still distinct. More modest differences in frontal activation are also noted in the topographic maps across time and ISI.

Source Localization

A source localization model was applied to better understand the generators of the adaptation effects seen in this experiment for the time period during which there was sufficient signal strength in the waveforms and difference topographies, depicted in Figure 6A. In the 90-110ms interval (top row) the main brain generators were localized bilaterally to regions in and surrounding the occipital pole, pointing to striate and extrastriate generators in this timeframe for both the 300ms and 2550ms conditions. These sources encompassed parts of Brodmann area 17 (primary visual cortex), area 18 (parastriate visual association areas), and area 19 (extrastriate visual association areas). In the 130-150ms interval (middle row) brain activation extended into extrastriate areas (relative to the 90-110ms period) and included both
dorsal and ventral visual regions (Brodmann 18 & 19). Additionally, the 2550ms ISI condition contained
generators located more dorsal/superior in comparison to the 350ms ISI sources for this time period, but
still including strong inferior occipital cortex activation. Additionally, there was minor activation of the
middle temporal gyrus (including association areas in Brodmann 21 involved in object form and motion
processing and temporal recognition) in the 2550ms condition in this time period.

In the 160-180ms time window (bottom row), the main generators for both conditions localized to
more inferior occipital regions as compared with the previous time period. In the 300ms condition,
sources were over Brodmann area 18 along with some activation over Brodmann area 7, which is part of
the parietal cortex and involved in visuo-motor coordination. In the 2550ms condition there was inferior
lateral activation involving the lingual gyrus and Brodmann area 19.

Randomization tests conducted to compare the signal sources identified above revealed
significant differences between the two conditions for all three time periods, as can be seen in Figure 6B.
In the 90-110ms time window, the differences were localized to the occipital lobule, superior parietal
lobule, lingual gyrus, and medial frontal gyrus. Differences in the 130-150ms time window were most
pronounced, spanning the middle temporal gyrus of the temporal lobe, the postcentral gyrus in the
parietal lobe, and the superior frontal gyrus encompassing Brodmann area 8, which is involved in motor
planning and encompasses the frontal eye fields. The 160-180ms time window revealed fewest
significantly different sources across the two conditions. These were localized to frontal areas, including
the middle frontal gyrus (Brodmann area 9) and the superior frontal gyrus.

*Individual Participant Level Analyses*

We sought to establish how robust these measures of adaptation were and to assess whether significant
adaptation functions could be observed consistently at the individual participant level, since a major aim
here is to develop this measure as a potential biomarker of disease. If it is to serve as such, it will be
imperative that it is robust at the individual level. Individual participant randomization analysis was
conducted comparing the longest ISI (2550ms) with each of the other ISIs (200ms, 300ms 550ms,
1050ms) at the three time periods of interest at the central occipital electrode site (Oz) and two lateral
sites (O1 & O2). Table 3 shows the number of participants exhibiting significant adaptation effects along
with the average and standard deviation of the number of sweeps required for this effect, as a function of ISI. Overall, participants showed significant differences in amplitude between the most discrepant ISIs (i.e. 200, 300, and 550 vs 2550ms). For the middle time period of interest (130-150ms), all participants showed significant differences between the shortest (200ms ISI) and the longest (2550ms ISI) at the central occipital site. The 160-180ms time period contained the most stable effects across scalp sites and ISIs. During this period at least 14 of the 15 participants showed significant VEP amplitude differences for all of the ISI comparisons at Oz, all participants showed significant VEP differences for the two shorter ISIs (200 & 300ms) against the 2550ms ISI at Oz & O2, and 13 out of 15 at O1. The individual participant analysis results are in line with the group statistics with the largest difference occurring at the later time periods.

Representative individual waveforms for three participants are depicted in Figure 7. VEPs to a ‘fast’ ISI condition (300ms) and ‘slow’ ISI condition (2550ms) are plotted for the central occipital site and the two lateral sites. Amplitude values along these waveforms were taken for each individual subject to conduct the analysis described above. Here it can be seen that even at the individual level modulations based on presentation rate are evident. The dashed line in this figure represents the difference in amplitude between these two conditions (fast vs. slow) and can be interpreted as an index of adaptation.
2.4. DISCUSSION

High-density VEPs were recorded in a pair of experiments to examine visual adaptation in healthy human adults as a function of presentation rate and of using a blocked versus a paired presentation approach. In Experiment 1, stimuli were presented in pairs with relatively fast ISIs of 200ms or 300ms. In Experiment 2, stimuli were presented in much longer blocks (100 stimuli/block) while ISI was parametrically manipulated across blocks (ISIs of 200ms, 300ms, 550ms, 1050ms, and 2550ms respectively). The data revealed clear evidence for adaptation during blocked presentations, with dramatic and consistent modulation of VEP amplitude as a function of presentation rate. In contrast, the paired stimulation approach resulted in more modest VEP amplitude changes and despite the fact that similarly fast ISIs were employed as in the blocked experiment there was no clear attenuation effect of the major VEP components across scalp sites. In fact, the effects reported for Experiment 1 were opposite to what are classically expected using paired-adaptation paradigms, where the typical finding is a decrease in amplitude of the evoked response to the repeated stimulus during the earliest phases of processing. A second major goal of the current study was to establish whether visual adaptation functions could be reliably observed at the individual participant level. This goal was realized, establishing a potentially powerful biomarker of visual sensory function for deployment in clinical populations. In what follows, we discuss the results of these experiments in further detail and their implications for future work.

Experiment 1- Paired-Presentation Paradigm

While on first consideration a lack of reduced VEP amplitude to the S2 might seem surprising, a close examination of the paired-presentation auditory adaptation literature reveals a more nuanced picture. At ISIs in the range of those used here, response enhancement rather than suppression has sometimes been observed (Budd & Michie, 1994; Loveless et al., 1996; Sable, Low, Maclin, Fabiani, & Gratton, 2004; A.L. Wang, Mouraux, Liang, & Iannetti, 2008). For instance, Loveless and colleagues demonstrated that the classic P50 attenuation effect seen in the AEP can be reversed if ISIs <400ms are
employed (Loveless et al., 1989). This, however, is not always the case with both auditory and visual responses also showing attenuation to even shorter ISIs (<100ms) during both early and late stages of processing (Gawne et al., 2011). Alternatively, it is possible that certain short ISIs (40-90ms) fall within the refractory period of human visual neurons, with observed attenuation occurring as a result of a decrease in the excitability of visual cortex and multiple stimuli being perceived as one (Coch, Skendzel, & Neville, 2005; Musselwhite & Jeffreys, 1983; Skrandies & Raile, 1989).

Another variable that may contribute to apparently contradictory results for the short ISI across paradigms is whether random or blocked presentation of ISIs is employed. Here, the inter-pair interval randomly varied within the same block. Wang and colleagues have argued that S2 attenuation is seen only in blocks containing exclusively pairs of the same ISI (A. L. Wang, Mouraux, Liang, & Iannetti, 2010). Their reasoning is that only when the timing of the second stimulus is constant is it “nonnovel and highly predictable” (p. 2119), thereby eliciting a reduced neural response. Thus if ISI for each pair is variable within a block, S2 suppression may not be seen since timing is somewhat more unpredictable. Such an explanation could account for the lack of attenuation seen in Experiment 1 during the early time windows of analysis. The later change from S2 enhancement to S2 attenuation as a result of processing stage reported here has also been previously observed in other sensory modalities (A.L. Wang et al., 2008). Wang and colleagues in a paired, random ISI design, report enhancement of the N1 wave and attenuation of the P2 wave for auditory and somatosensory stimuli when short ISIs were examined. Clearly, a greater range of ISIs and comparison of random versus blocked ISI rate will be necessary to fully characterize these functions in the visual system.

**Experiment 2- Blocked-Presentation Paradigm**

Comparable to what has been reported in the auditory and somatosensory literatures (Hamalainen, Kekoni, Sams, Reinkainen, & Naatanen, 1990; Pereira et al., 2014), ERP attenuation to repetitive stimulation, which was modulated by presentation rate was observed. In Exp 2 VEP attenuation was modulated by ISI, with faster presentation rates leading to smaller VEP amplitudes. Source analyses pointed to adaptation effects not only in early striate and extrastriate visual cortical areas, but also across a widespread network of higher order dorsal and ventral visual regions that extended into frontal cortex.
Further, the most robust adaptation effects in the visual system occurred some 65 to 100 ms after initial response onset (Foxe & Simpson, 2002), suggesting a more complex neurophysiological profile than previously assumed.

Whereas most ERP characterizations are conducted at the group level, a central aim of the current study was to quantify the individual subject reliability of these effects with the goal of developing a metric of visual processing that might prove useful as a biomarker. In the block-presentation paradigm (Experiment 2) the ISI-specific effects were measurable at both the group and individual level, most reliably seen starting at about 130ms (in 15 out of 15 participants), whereas for the paired-presentation paradigm (Experiment 1) only the group effects were significant.

Very few studies have comprehensively examined the effect of multiple ISIs (presentation rates) on sensory adaptation in the visual system. This is perhaps because the wide variety of presentation paradigms utilized in the study of adaptation has made it difficult to elucidate a clear effect of stimulus repetition on the VEP amplitude. Here we find that a block-paradigm such as used in Experiment 2 is well-suited for investigations of short-term visual adaptation. Our data establish that adaptive filtering of repetitive visual stimulation is reliably characterized by 1) Challenging the visual system with increased repetition and, 2) Thoroughly probing across stages of visual processing and scalp sites. In contrast, the short-term plasticity mechanisms assayed in Experiment 2 are not adequately engaged in the paired-paradigm (Experiment 1).

The analysis approach presented in this paper provides a composite measure of overall adaptation across an entire block (i.e. a period of 100 stimuli) and compares this adaptation between the various ISIs. However, the question as to when during the 100 stimuli in a given block the adaptation function stabilizes is one that our study was not designed to address (i.e. within block adaptation). Taken together, the results from Experiment 1 and Experiment 2, suggest that certainly more than two trials are needed for adaptation to equilibrate. Post-hoc analysis of the data from Experiment 2 indicate that it might be possible to adequately represent adaptation with sequences much shorter than 100 stimuli – likely in the range of 10 stimuli per train (see Supplementary Figure 4). Thus, a shorter version of the experiment run on considerably greater numbers of individuals would allow for a much finer titration of the temporal
course of adaptation in trains of stimuli, while contributing to “normative data” against which clinical populations may be assessed, a matter for future work.

Lastly, source localizations of the effects uncovered during the block experiment provide clues as to the potential mechanisms involved in this form of short-term sensory plasticity. It is noteworthy for instance that the adaptation effects uncovered here were not restricted to early striate and extrastriate regions, as one might initially expect with such a basic sensory assay. Rather, sources well beyond V1/V2 were differentially impacted by the varying presentation rates, including regions in both the dorsal and ventral streams, suggesting that adaptation impacts processing in regions within both superior parietal cortex and the lateral occipital complex. It is perhaps surprising that adaptation should be seen in these higher-order regions for the simple stimuli used, especially since the stimuli were not task-relevant and were essentially ignored by the participants. Studies employing task-relevant stimuli, examining orientation adaptation, have also found response modulation in areas beyond V1 in both human (Brunet et al., 2014; Fang, Murray, Kersten, & He, 2005) and non-human participants (Hudson, Schiff, Victor, & Purpura, 2009; Y. Wang, Iliescu, Ma, Josic, & Dragoi, 2011). In these, changes in neuronal synchronization, both local and between regions, have been implicated in the main findings. Understanding the role and mechanisms underlying the involvement of higher-order regions in the current adaptation paradigm is an important matter for future work.

**Future Directions**

It is clear that the mechanistic and molecular underpinnings of basic adaptation are not yet fully understood. These mechanisms might differ between sensory modalities taking into account inherent differences in disparate neuronal populations such as response, recovery, and sampling rates. Studies employing pharmacologic manipulations and measuring changes under both the paired-presentation and the block-presentation paradigms along with studies using the same paradigms across different sensory modalities may reveal whether the adaptation profile is consistent across paradigms and whether sensory adaptation dynamics are modality-specific.

A more complete understanding of sensory adaptation may follow from pharmacological studies targeting neurotransmitter systems implicated in adaptation. Studies assessing molecular mechanisms of adaptation in the auditory system are sparse and provide varying findings. There are reports of
serotoninergic (Oranje, Wienberg, & Glenthoj, 2011), dopaminergic (Light et al., 1999), and nicotinergic effects (Knott, Fisher, & Millar, 2010) on auditory adaptation. In the visual system, one group conducted an experiment in which light deprivation, which according to the authors down-regulates the gabaergic system, lead to adaptation impairments (Palermo et al., 2011). These impairments were reversed with exposure to high frequency repeated transcranial magnetic stimulation (rTMS), which had previously been shown to reverse light deprivation inhibitory effects.

An additional research question concerns the effects of attention on sensory adaptation. Recent studies have attempted to examine this interaction, and although the findings are still equivocal, there is some evidence for attention-modulated auditory adaptation (Gjini, Burroughs, & Boutros, 2011; Rosburg, Trautner, Elger, & Kurthen, 2009). This is of particular interest for both the characterization of adaptation in the general population, and in clinical groups, particularly those with documented attention deficits (i.e. schizophrenia, autism, etc).

A primary motivation for the current study was to examine whether visual adaptation to varying presentation rates would be used to elicit a robust metric of short-term visual plasticity, one that could ultimately be deployed as a sensitive assay of visual function in clinical populations. Our interest was specifically whetted by the fact that abnormal sensory adaptation functions have been repeatedly demonstrated in patients with schizophrenia, but these have been assayed almost exclusively using auditory stimulation (Olincy et al., 2010; Patterson et al., 2008), although there is emerging evidence for related deficits in the somatosensory system (Thoma et al., 2007). Auditory adaptation deficits represent potentially powerful biomarkers of schizophrenia since they are also seen in a significant proportion of unaffected first-degree biological relatives of patients (Olincy et al., 2010). In a series of experiments, we have shown that visual sensory processing deficits are particularly robust in patients with schizophrenia (Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Foxe et al., 2001; Foxe, Murray, & Javitt, 2005; Lalor, De Sanctis, Krakowski, & Foxe, 2012; Lalor, Yeap, Reilly, Pearlmutter, & Foxe, 2008; Yeap, Kelly, Sehatpour, et al., 2008), a finding that has been observed across multiple labs (Haenschel et al., 2007; Mukundan, 1986; Spencer et al., 2004). Crucially, these deficits are also seen in first-degree relatives (Yeap et al., 2006), first-episode drug naïve patients (Yeap, Kelly, Thakore, et al., 2008) and in young adults with high schizotypy (Bedwell, Chan, Trachik, & Rassovsky, 2013; Koychev, El-Deredy,
Haenschel, & Deakin, 2010), pointing to their potential utility as risk endophenotypes (Foxe et al., 2011; Gottesman & Gould, 2003; Magno et al., 2008).

A drawback of many of these studies, however, is that despite between-group effect sizes that are typically large, intrinsic inter-individual variability in the amplitude and morphology of the VEP response reduces their effectiveness as potential classifiers. We have made the argument that one way to surmount this issue of inter-individual variance is to assay second-order dynamic effects of sensory systems such as short-term plasticity, as with the visual adaptation paradigm at hand. It is of note that dysfunctional sensory plasticity has recently been shown in patients with schizophrenia (Cavus et al., 2012; Foxe, Yeap, & Leavitt, 2013). Of course, if any given metric of sensory processing is ultimately to serve as a diagnostically meaningful biomarker, it must be possible to assay it robustly at the individual patient level, and it is very encouraging that this is precisely what was found here for block-presentation paradigm. Thus, if short-term sensory plasticity is impaired in patients with schizophrenia, mapping visual adaptation functions such as those detailed here may yet prove a very powerful method of assaying said dysfunction.

CONCLUSIONS

Adaptation of brain responses to repetitive stimulation is considered a fundamental property of sensory processing. Here we employed high-density EEG in two variants of an adaptation design, examining the effect of presentation rate on VEP attenuation in a paired-paradigm and a block-paradigm. Robust VEP modulations were evident as a function of presentation rate in the block-paradigm, with strongest modulations seen in the 130-150ms and 160-180ms phases of visual processing. In the paired designed, we observed a more modest enhancement effect, with VEP amplitudes increasing when comparing S2 to S1. In order to better characterize the spatial and temporal properties of visual adaptation we used the full set of information collected from our high-density array to create scalp topographic maps and model the neural generators of adaptation across time. These analyses revealed sources in striate, extrastriate, and higher-order (e.g. superior temporal and lateral occipital) cortex. Importantly, in the block paradigm, adaptation effects were statistically robust at the individual participant level. These results suggest that a taxing paradigm, such as the current block-paradigm, is better suited to engage adaptation mechanisms
in the visual system compared to a paired design. The increased sensitivity of the visual processing metric obtained in the block-paradigm has implications for the examination of visual processing deficits in clinical populations.

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**Conflict of Interest Statement**

All authors of this paper declare no conflicts-of-interest, financial or otherwise, that could have biased their contributions to this work. The senior author, Dr. Foxe, attests that all authors had access to the full dataset and to all stages of the analyses.
2.6. TABLES

Table 1. Experiment 1

A. Main ANOVA results summary for Experiment 1 (paired presentation).

<table>
<thead>
<tr>
<th></th>
<th>90-110ms</th>
<th>130-150ms</th>
<th>160-180ms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ISI</strong></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Order</strong></td>
<td>$F(1, 10)=17.725, p=0.002$ S2 amplitude &gt; S1 amplitude</td>
<td>$F(1, 10)=19.859, p=0.001$</td>
<td>$F(1, 10)=13.609, p=0.004^{†}$</td>
</tr>
<tr>
<td><strong>Scalp site</strong></td>
<td>$F(4, 40)=7.997, p&lt;0.004^{†}$ Midline amplitudes &gt; lateral amplitudes</td>
<td>$F(4, 40)=2.692, p=0.045$</td>
<td>$F(4, 40)=4.554, p=0.015^{†}$</td>
</tr>
<tr>
<td><strong>ISI x Order</strong></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>ISI x Scalp site</strong></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Order x Scalp site</strong></td>
<td>n.s.</td>
<td>$F(4, 40)=4.071, p=0.007$ S2 amplitude &gt; S1 amplitude, greatest differences at midline, lessens more laterally</td>
<td>$F(4, 40)=5.038, p=0.002$ S1 amplitude &gt; S2 amplitude but only at midline, all other lateral sites S2 &gt; S1</td>
</tr>
<tr>
<td><strong>ISI x Order x Scalp site</strong></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

$^{†}$- indicates a Greenhouse-Geisser adjustment was performed
B. Post-hoc comparisons for Experiment 1 (paired paradigm). Italics indicate a significant effect of ISI at that scalp site. Refer to Table 1A for interpreting the directionality of these effects.

<table>
<thead>
<tr>
<th>Time</th>
<th>PO7</th>
<th>O1</th>
<th>Oz</th>
<th>O2</th>
<th>PO8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-110ms</td>
<td>n.s.</td>
<td>t(21)= 3.755, p = .001</td>
<td>t(21)= 4.665, p &lt; .001</td>
<td>n.s.</td>
<td>PO8 - t(21)= 3.879, p = .001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>130-150ms</td>
<td>n.s.</td>
<td>t(21)= 2.957, p = .008</td>
<td>t(21)= 8.525, p &lt; .001</td>
<td>t(21)= 4.479, p &lt; .001</td>
<td>t(21)= 4.004, p = .001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>160-180ms</td>
<td>n.s.</td>
<td>t(21)= 3.828, p = .001</td>
<td>t(21)= 7.294, p &lt; .001</td>
<td>t(21)= 3.862, p = .001</td>
<td>t(21)= 2.959, p = .007</td>
</tr>
</tbody>
</table>
### Table 2. Experiment 2

<table>
<thead>
<tr>
<th></th>
<th>90-110ms</th>
<th>130-150ms</th>
<th>160-180ms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ISI</strong></td>
<td>n.s.</td>
<td>F(4, 56)=15.561, p&lt;0.001†</td>
<td>F(4, 56)=24.573, p&lt;0.0001†</td>
</tr>
<tr>
<td><strong>Scalp site</strong></td>
<td>F(4, 56)=15.956, p&lt;0.001†</td>
<td>F(4, 56)=6.335, p=0.003†</td>
<td>F(4, 56)=12.114, p&lt;0.0001†</td>
</tr>
<tr>
<td><strong>ISI x Scalp site</strong></td>
<td>F(16, 224)= 3.400, p=0.005†</td>
<td>Adaptation strongest at midline, but seen everywhere: faster ISIs = smaller VEPs</td>
<td>F(16, 224)=6.817, p&lt;0.0001†</td>
</tr>
<tr>
<td></td>
<td>Adaptation at midline &amp; O1: faster ISIs = smaller VEPs</td>
<td>Adaptation at midline &amp; O1: faster ISIs = smaller VEPs</td>
<td>Midline: slower ISIs = smaller VEPs</td>
</tr>
</tbody>
</table>

**A.** Main ANOVA results summary for Experiment 2 (block-presentation).

†- Indicated a Greenhouse-Geisser adjustment was performed.
B. Post-hoc comparisons for Experiment 2 (block paradigm). Italics indicate a significant effect of ISI at that scalp site. Refer to Table 2A for interpreting the directionality of these effects.

<table>
<thead>
<tr>
<th>Time</th>
<th>PO7</th>
<th>O1</th>
<th>Oz</th>
<th>O2</th>
<th>PO8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-110ms</td>
<td>n.s.</td>
<td>$F(4,56)=4.209, \ p=.024^\dagger$</td>
<td>$F(4,56)=4.957, \ p=.014^\dagger$</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>130-150ms</td>
<td>$F(4,56)=6.083, \ p=.007^\dagger$</td>
<td>$F(4,56)=15.447, \ p&lt;.001^\dagger$</td>
<td>$F(4,56)=20.017, \ p&lt;.001^\dagger$</td>
<td>$F(4,56)=14.095, \ p&lt;.001^\dagger$</td>
<td>$F(4,56)=4.656, \ p=.017^\dagger$</td>
</tr>
<tr>
<td>160-180ms</td>
<td>$F(4,56)=8.906, \ p=.002^\dagger$</td>
<td>$F(4,56)=21.102, \ p&lt;.001^\dagger$</td>
<td>$F(4,56)=30.012, \ p&lt;.001^\dagger$</td>
<td>$F(4,56)=25.302, \ p&lt;.001^\dagger$</td>
<td>$F(4,56)=10.062, \ p&lt;.001^\dagger$</td>
</tr>
</tbody>
</table>
Table 3. Individual Subject Analysis. Results from randomization tests comparing the VEP at the central occipital site and two lateral sites for the 2550ms condition against all other ISIs, for the three time periods of interest. Individual-level VEP modulation is seen in all participants in the 160-180ms time period when comparing the most disparate ISIs for the central site and one lateral site.

3A. Central occipital site (Oz)

<table>
<thead>
<tr>
<th>No. of subjects out of 15 (Average minimum no. of sweeps required ±Standard Deviation)</th>
<th>200</th>
<th>300</th>
<th>550</th>
<th>1050</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2550 vs.</strong> 200</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>90-110ms</strong></td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>(66±26)</td>
<td>(90±58)</td>
<td>(93±50)</td>
<td>(93.3±31)</td>
</tr>
<tr>
<td><strong>130-150ms</strong></td>
<td>15</td>
<td>13</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>(56±27)</td>
<td>(57±33)</td>
<td>(48±14)</td>
<td>(60±28)</td>
</tr>
<tr>
<td><strong>160-180ms</strong></td>
<td>15</td>
<td>15</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>(57±27)</td>
<td>(58±35)</td>
<td>(49±20)</td>
<td>(69±40)</td>
</tr>
</tbody>
</table>

3B. Right lateral site (O2)

<table>
<thead>
<tr>
<th>No. of subjects out of 15 (Average minimum no. of sweeps required ±Standard Deviation)</th>
<th>200</th>
<th>300</th>
<th>550</th>
<th>1050</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2550 vs.</strong> 200</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>90-110ms</strong></td>
<td>8</td>
<td>10</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>(98±61)</td>
<td>(114±55)</td>
<td>(105±58)</td>
<td>(136±66)</td>
</tr>
<tr>
<td><strong>130-150ms</strong></td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>(50±16)</td>
<td>(50±14)</td>
<td>(62±44)</td>
<td>(76±30)</td>
</tr>
<tr>
<td><strong>160-180ms</strong></td>
<td>15</td>
<td>15</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>(66±34)</td>
<td>(66±24)</td>
<td>(56±17)</td>
<td>(90±42)</td>
</tr>
</tbody>
</table>

3C. Left lateral site (O1)

<table>
<thead>
<tr>
<th>No. of subjects out of 15 (Average minimum no. of sweeps required ±Standard Deviation)</th>
<th>200</th>
<th>300</th>
<th>550</th>
<th>1050</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2550 vs.</strong> 200</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>90-110ms</strong></td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>(72±29)</td>
<td>(79±34)</td>
<td>(95±46)</td>
<td>(127.6±54)</td>
</tr>
<tr>
<td><strong>130-150ms</strong></td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>(65±41)</td>
<td>(69±53)</td>
<td>(53±19)</td>
<td>(75±41)</td>
</tr>
<tr>
<td><strong>160-180ms</strong></td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>(68±34)</td>
<td>(58±19)</td>
<td>(55±14)</td>
<td>(92±54)</td>
</tr>
</tbody>
</table>
2.6. FIGURES

Figure 1 - Schematic diagram illustrating the two paradigms. **A.** Depiction of the paired-presentation paradigm used in Experiment 1. Stimuli were presented in pairs with an inter-stimulus interval of either 200 or 300ms and a long inter-pair interval of 2500ms. Catch trials, consisting of unpaired checkerboards, were presented one third of the time and were used to extract the isolated response to the second stimulus in a pair. **B.** Depiction of the block-presentation paradigm used in Experiment 2. Stimuli were presented in blocks of 100 trials, at an inter-stimulus interval centered around ISIs of 200, 300, 550, 1050, or 2550ms. The stimulus presentation was jittered by +/-50ms to allow for the implementation of an ADJAR procedure which models and removes response overlap (used in the 200ms condition).
**Figure 2**- Waveforms obtained from subtracting the catch trials from the 200 and 300ms trials. The catch serves as the pure response to a single stimulus presentation (S1) and the trial waveform minus the catch represents the 'isolated' response to the second stimulus (S2). At 140ms there is an effect of order, with VEPs to the S2 being greater than to the S1. At 170ms, the effect reverses, with VEPs to the S2 being smaller (less positive) than to the S1. However, neither of these effects depends on ISI.
**Figure 3**- Scalp topographic maps for the paired-paradigm reveal a difference between the first and second stimulus presentations and between the second and the catch for both ISIs. Additionally there is a clear difference in topography when comparing the response at 100 and 140ms (strong negativity) with the response at 170ms (strong positivity).
Figure 4- A. Average waveforms for each of the five ISI conditions (Experiment 2) are displayed for the five occipital and occipito-parietal scalp sites of interest. A clear effect of ISI on VEP amplitude can be seen between 100-200ms, with slower stimulus presentation rates leading to greater absolute VEP amplitude. B. Amplitude by ISI plots. The effect of ISI on VEP amplitude at each scalp site for the three time periods of interest. The greatest adaptation based on ISI is seen in the later time windows (130-150ms & 160-180ms) and is most robust at the central occipital site. Additionally, the directionality of adaptation by ISI at the central site (Oz) is exclusively reversed in the last time period of interest, with the slowest ISI here eliciting the smallest VEP amplitudes.
Figure 5 - Left - Scalp topographic maps reveal similar central-occipital negativity for the early time period across ISIs in the block-presentation. At the later time points the voltage distribution diverges, with the shorter ISIs showing central-occipital positivity and the longer ISIs a bilateral negativity. Right - Scalp topographic maps depicting the difference in electrical activation when comparing the 2550ms condition to each of the other ISIs. The difference topography is most unique when comparing electrical activation across the scalp when comparing the 1050ms ISI to the 2050ms ISI at 140 & 180ms post stimulus presentation.
Figure 6- A. Brain generators estimated using a distributed linear inverse solution on the local auto-regressive average for block-design. Early sources are mainly over occipital cortex, with later sources extending over parietal and temporal cortex. B. Randomization tests reveal significant differences in brain generators between the 300ms and 2550ms conditions. At 90-110ms these differences are mostly occipital. At 130-150ms the differences are most pronounced and expand over occipital, parietal, temporal and frontal areas, including superior parietal cortex and lateral occipital cortex. At 160-180ms, the only significantly different sources are frontal.
Figure 7- Representative individual participant visual evoked potential waveforms. VEP to a ‘fast’ ISI condition (300ms) and ‘slow’ ISI condition (2550ms) is plotted for the central occipital site. The dashed line represents the difference in amplitude between these two conditions and can be interpreted as an index of adaptation.
Supplementary Materials

**Supplement. Fig. 1**- Catch-trial subtraction for paired-presentation. VEP to the single stimulus is subtracted from the convoluted waveform containing both the VEP to the S1 and S2 stimuli (presented as a pair), resulting in the VEP elicited by the S2 alone.

**Supplement. Fig. 2**- Adjacent Response Algorithm (ADJAR) for block-presentation was performed on subject-level data to model and remove any response overlap between short ISI stimuli.
Supplement. Fig. 3- A. Adaptation functions at the occipital and occipito-parietal electrode sites of interest across the three phases of processing in the paired presentation paradigm. This highlights the order effect, with very little influence of ISI on adaptation for the two presentation rates examined. B. Adaptation functions for the occipital and occipito-parietal electrode sites of interest across the three phases of processing in the block presentation paradigm. These were derived by fitting an exponential decay function to the mean VEP amplitude across the 5 ISI, for each site, at the specified time periods. This procedure yields a plot that can be describes the data using 3 parameters - 2 constants (maximum and minimum values for amplitudes) and power (rate decay across ISIs).
A

90-110ms

- +4μV
- -4μV

130-150ms

- +4μV
- -4μV

160-180ms

- +4μV
- -4μV

Stimulus Order

Paired Presentation

B

90-110ms

- +4μV
- -4μV

130-150ms

- +4μV
- -4μV

160-180ms

- +4μV
- -4μV

Inter Stimulus Interval (ms)

Block Presentation
Supplement. Fig. 4- Adaptation across trials. The data matrix was progressively split into ever-finer sequential temporal bins in order to examine adaptation across a block of 100 stimuli. Four of these divisions are illustrated. There are a maximum of 8 trials contributed by each individual per bin when the data is split into 24. It is evident here that adaptation is wholly similar across all bins and that it likely kicks in after just a handful of trials, which we simply do not have the signal-to-noise resolution to address in greater detail.
2.7. REFERENCES


Haenschel, C., Bittner, R. A., Haertling, F., Rotarska-Jagiela, A., Maurer, K., Singer, W., & Linden, D. E. (2007). Contribution of impaired early-stage visual processing to working memory dysfunction in adolescents with schizophrenia: a study with event-related potentials and functional magnetic resonance imaging. [Research Support, Non-U.S. Gov't]. *Arch Gen Psychiatry, 64*(11), 1229-1240. doi: 10.1001/archpsyc.64.11.1229


CHAPTER 3

ATYPICAL SENSORY ADAPTATION IN SCHIZOPHRENIA-SPECTRUM DISORDERS: A COMPARISON OF THE VISUAL AND SOMATOSENSORY SYSTEMS

Gizely N. Andrade, John S. Butler, Gregory A. Peters, Sophie Molholm, and John J. Foxe
3.1. INTRODUCTION

Visual processing deficits are widely reported in schizophrenia and hypothesized to play a role in higher-order cognitive and emotional processing deficits (P. D. Butler et al., 2009; P. D. Butler, Silverstein, & Dakin, 2008; De Sanctis et al., 2013; Foxe, Doniger, & Javitt, 2001; Foxe, Murray, & Javitt, 2005; Javitt, 2009b; D. W. Kim, Shim, Song, Im, & Lee, 2015; Lalor, De Sanctis, Krakowski, & Foxe, 2012; Lalor, Yeap, Reilly, Pearlmutter, & Foxe, 2008). Early sensory processing markers are particularly useful in clinical populations, since they are largely independent of behavioral performance, motivation, and attentional state. Studies consistently report decreased amplitudes of early visual evoked potential (VEP) components in schizophrenia-spectrum disorders, particularly of the so-called P1 component, which occurs 80-120ms post-stimulus (P. D. Butler et al., 2005; Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Haenschel et al., 2007; Roth et al., 1976; Yeap et al., 2008; Yeap et al., 2006). Although effect sizes are often large in these studies, there is nonetheless substantial overlap in the distributions of amplitudes across patients and controls, limiting clinical applicability of these measures. An obvious research prerogative, therefore, is to establish more sensitive measures of visual sensory dysfunction in schizophrenia to provide greater classification sensitivity. In a similar vein, the “Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS)” consortium (Carter & Barch, 2007) has highlighted visual processing (e.g., gain control, perceptual closure) as a domain offering particular promise in novel treatment development (P. D. Butler et al., 2012; Carter et al., 2008; Green et al., 2009).

Here, we set out to exploit second-order “dynamic” visual processing effects on the premise that taxing visual processing capacity could well prove a more effective means of dissociating patients from controls. Consonant with CNTRICS recommendations, we employed an adaptation paradigm whereby stimuli were presented in blocks of varying presentation rates, a VEP assay that yields individual-participant sensitivity in detecting short-term plasticity during visual sensory processing (Andrade, Butler, Mercier, Molholm, & Foxe, 2015). There is good reason to predict that visual adaptation might be impaired in schizophrenia, since patients exhibit other forms of adaptation deficits such as in contrast gain control (Keri, Antal, Szekeres, Benedek, & Janka, 2002; Slaghuis, 1998) and motion processing (Colleen A. Brenner, Wilt, Lysaker, Koyfman, & O'Donnell, 2003; Chen et al., 1999; D. Kim, Wylie, Pasternak,
Butler, & Javitt, 2006; Slaghuis, Holthouse, Hawkes, & Bruno, 2007), and there is a rich literature showing auditory adaptation deficits in schizophrenia (L. E. Adler, M. C. Waldo, & R. Freedman, 1985; Braff, Light, & Swerdlow, 2007; Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; Patterson et al., 2008). Auditory mismatch negativity responses, where adaptation mechanisms are believed to enhance the sensory response to changes in otherwise uniform sensory environments, are also disordered in schizophrenia (Javitt, Doneshka, Zylberman, Ritter, & Vaughan, 1993; Kisley, Noecker, & Guinther, 2004; Leitman et al., 2010; Magno et al., 2008; Naatanen & Kahkonen, 2009).

Uncovering visual adaptation deficits may also speak to the underlying neurobiology of schizophrenia. Dysregulation of N-methyl-D-aspartate receptor (NMDAR) function has been widely implicated in the pathophysiology schizophrenia (Coyle, 2006; Javitt, 2010; Javitt, Zukin, Heresco-Levy, & Umbricht, 2012) and visual pathways are thought to be heavily dependent on NMDA-mediated activity (Fox, Sato, & Daw, 1989; Miller, Chapman, & Stryker, 1989; Rivadulla, Sharma, & Sur, 2001; Sillito, Murphy, Salt, & Moody, 1990). In turn, adaptation to repetitive stimuli is thought to rely on NMDA-mediated mechanisms (Barkus et al., 2014; Callahan, Terry, & Tehim, 2014; Cavus et al., 2012; Javitt, 2009b; Sabbagh, Heaney, Bolton, Murtishaw, & Kinney, 2012), suggesting it as a potentially powerful tool in this population. Lastly, as studies of somatosensory adaptation in schizophrenia are sparse and have produced inconsistent findings (Arnfred & Chen, 2004; Arnfred, Hemmingsen, & Parnas, 2006; Bak, Rostrup, Larsson, Glenthoj, & Oranje, 2014; Huang et al., 2010; Thoma et al., 2007), we also employed a somatosensory analog of our visual paradigm, with an eye to assessing potential sensory-specificity of the these short-term plasticity mechanisms.
3.2. METHODS

Participants

15 adults diagnosed with a schizophrenia-spectrum disorder (SCZ, 4 female) and 15 neurotypical adults (NT, 5 female) completed the visual adaptation experiment. 12 of the 15 NT and 12 of the 15 SCZ also participated in the somatosensory adaptation experiment. All SCZ participants met DSM-IV criteria for schizophrenia or schizoaffective disorder, using the Structured Clinical Interview for DSM-IV Disorders-Research Version (SCID-R). NT participants had no self-reported history of Axis I or Axis II disorders; Axis I disorders were ruled-out using the SCID-R-NP. Thirteen participants in the SCZ group were currently receiving antipsychotic treatment (see Table 1 for details). The SCZ group was also interviewed using the Positive and Negative Syndrome Scale (PANSS) to quantify current symptom severity. All clinical interviews were conducted by a certified trained rater, with established reliability in the administration of these scales. All participants had normal or corrected vision. All procedures were in accordance with the Albert Einstein College of Medicine institutional review board policies and in accordance with the Declaration of Helsinki. Participants were provided a modest compensation fee for participating in these studies ($12/hr).

Experiment 1. Visual Adaptation

Stimuli

Stimuli were 100% contrast black and white checkerboard annuli (6.5 cm diameter, 1 cm width, $4\times4^\circ$, white luminance of 120 cd/m$^2$, black luminance of 0.2 cd/m$^2$) centered against a grey (luminance = 25 cd/m$^2$) background. A fixation cross was always present on the screen, including during checkerboard presentation. The fixation cross changed color every 20-40s. Checkerboards were presented for 33ms and at different inter-stimulus-intervals (ISIs). See Figure 1 for a schematic time course representation of the experiment.

Procedure

Participants sat in a darkened sound-attenuated electrically shielded double-walled booth (Industrial Acoustics Company, Bronx, NY), 90 cm from a 34x55 cm LCD computer screen (ViewSonic VP2655wb, 60Hz refresh rate). They were instructed to minimize head movements and blinking while fixating on a red
cross at the center of the screen. They performed a change detection task to ensure fixation in which they were asked to respond to fixation cross color changes (from red to green, lasting 40ms) with a mouse button press using the index finger of their dominant hand. The presentation of checkerboard stimuli was temporally unrelated to this central fixation task.

Paradigm
Checkerboards were presented in blocks of 100 stimuli. Within each block, the stimuli were centered at an ISI, around which the actual presentations were jittered by +/-50ms. Five different ISIs were used: 200ms, 300ms, 550ms, 1050ms, and 2550ms. Between-block interval was self-paced, with participants allowed to move to the next block by pressing the spacebar on a keyboard 2500-5000ms after the last stimulus of the preceding block. Block presentation was pseudorandom. In total, participants experienced 4 blocks of each of the four shorter ISIs (200ms, 300ms, 550ms, 1050ms) and two blocks of the longest ISI (2550ms). Total run time for the experiment ranged from 35-45 minutes.

Experiment 2. Somatosensory Adaptation
Stimuli
Tactile mechanical stimuli were generated using an in-house custom-built vibrotactile stimulator. The vibrotactile device was worn as a bracelet on the right wrist, with the stimulator placed over the median nerve (Tsuji & Murai, 1986; Tsuji, Murai, & Hashimoto, 1988). The vibrotactile device uses a small (4 x 8mm, 1.1g) powerful (1.2G-force, 200Hz) vibration motor and is powered by a custom-built 1.5V amplifier. The device was operated using Neurobehavioral Systems Presentation Software, ensuring precision timing in stimulus delivery.

Procedure
Participants were seated in the same sound-attenuated electrically shielded double-walled booth described above as they watched a movie of their choosing on a laptop (Dell Latitude E640). The laptop was placed 80cm from the participant. The volume on the movie was adjusted to each participant's personal preference level at the beginning of the experiment.
Paradigm

Stimuli were presented in blocks of 400 stimuli. Within each block, stimuli were presented at a constant ISI of 150, 200, 300, 550, 1050, or 2550ms. ISI block presentation was pseudo-randomized. Participants were exposed to two blocks of each of the faster ISIs (150, 200, 300) and one block of the slower ISIs (550, 1050, 2550).

Data Acquisition

Continuous electroencephalographic (EEG) data were recorded in both experiments using a Biosemi ActiveTwo 168-channel electrode array, analog-to-digital converter, and fiber-optic pass-through to a dedicated data acquisition computer. The data were recorded at 512 Hz with a pass-band from DC to 150Hz. The continuous EEG was subsequently low-pass filtered at 45Hz (4th order-zero phase Butterworth filter, 27 dB/octave) and high-pass filtered at 1Hz (4th order-zero phase Butterworth filter, 24 dB/octave). Epochs of 600 ms with 100 ms prestimulus baseline were extracted from the continuous data. An automatic artifact rejection criterion of ±75 µV was applied across all electrodes in the array. Trials with more than eight artifact channels were rejected. In trials with less than eight such channels, bad channels were interpolated using the nearest neighbor spline (J. S. Butler et al., 2011; Perrin, Pernier, Bertrand, Giard, & Echallier, 1987). The data were re-referenced to the average of all channels. For Exp 1. the Adjacent Response (ADJAR) algorithm was implemented on the subject-level data to model and remove any response overlap in fastest ISI condition (150-250ms) (Fiebelkorn, Foxe, McCourt, Dumas, & Molholm, 2013; Woldorff, 1993).

Analysis Strategy

Group-Level Analysis

Statistical analyses were performed using custom MATLAB scripts (Mathworks), the Fieldtrip toolbox for EEG analysis (Oostenveld, Fries, Maris, & Schoffelen, 2011), EEGLAB (Delorme & Makeig, 2004), and IBM SPSS software package (Version 20). Scalp sites and time periods of interest were selected for
analysis based on maximal activation in the group waveforms and the methods described in the literature (Andrade et al., 2015; Foxe & Simpson, 2002; Thoma et al., 2007; Tsuji & Murai, 1986). In brief, group-averaged waveforms were visually inspected across all scalp sites, and the familiar components of the ERP were identified. This allowed for definition of the precise timing of a given component and delineation of the scalp sites at which each component was of maximal amplitude. For Exp 1 we restrict our analysis to 3 occipital sites over midline and lateral scalp (highlighted in the electrode array depicted in Figure 1A) at four time periods of interest: 100-120ms & 190-210ms for the midline occipital site and 145-165ms & 235-255ms for the lateral occipital sites. A mixed repeated measures analysis of variance, with group as the independent factor (SCZ and NT) and ISI as repeated measures (2x5 ANOVA) was performed for each scalp site of interest at the appropriate time periods. For Exp 2 electrode clusters surrounding the midline frontal site and the left central parietal area (highlighted in Figure 1B) were identified as regions of interest and analyses were performed at a single time period, 70-100ms, surrounding the major prominent ERP peak. A mixed repeated measures analysis of variance, with group as the independent factor (SCZ and NT) and ISI as repeated measures (2x6 ANOVA) was performed for each scalp site of interest at the appropriate time period.

Although the use of broadly defined component peaks is a good means of limiting the number of statistical tests that will be conducted, these components clearly represent the activity of many simultaneously active brain generators at any given moment (Foxe & Simpson, 2002). In order to provide a more complete picture of the mechanisms underlying visual and somatosensory adaptation, we also generated scalp topographic maps for the time periods of interest.

Individual-Level Analysis

In order to investigate the robustness of adaptation at the individual participant-level, a non-parametric randomization procedure was conducted (Maris & Oostenveld, 2007). For each participant we compared the amplitude recorded under the 2550 ISI condition against each of the other ISI conditions at the scalp sites of interest for the time periods during which adaptation effects differed between the groups (e.g.
significant Group x ISI effect in the group analysis). The observed difference between the 2550ms ISI and the test ISI was compared with a reference distribution of differences that was derived by iteratively randomizing between the two original data sets (i.e. individual-subject VEP amplitudes for the 2550ms and test ISI) 10,000 times. The number of epochs selected for the bootstrapping process was a subset of the total which increased in steps of 20 from 30 epochs until statistical significance or the maximum number of sweeps was reached (Nolan et al., 2012). A one-tailed threshold of p <0.05 was used to define significance. The p value for a randomization test was calculated from the proportion of values in the reference difference distribution that exceeded the observed difference (Fiebelkorn et al., 2011). Lastly, a Chi-Square analysis was conducted to assess whether the proportion of participants exhibiting individual level effects differed across the two groups.
3.3. RESULTS

Experiment 1

*Group-Level Analysis*

**VEP**

The midline occipital site of interest exhibited a unique VEP morphology and timecourse as compared to the lateral sites of interest. Figure 1 depicts the group VEPs for sites of interest for the NT group (top) and the SCZ group (bottom). At the midline site the first major deflection for both groups is negative-going and peaks at ~110ms, followed by a second major positive-going deflection peaking at ~210ms. For the lateral sites, the first major negative deflection for both groups peaks at ~150ms, followed by a major positive deflection at ~250ms. A minor positive-going deflection peaking at ~100ms is also noted for the right lateral site. Although not included in the main analysis, a mixed repeated measures ANOVA at the right lateral site for this time period did not reveal any effect of ISI, Group, or Group x ISI (all p’s >.5).

*Main Findings*

Results from the main ANOVA and post-hoc comparisons for significant Group x ISI interactions are presented in Table 1 and Table 2, respectively. The main findings are summarized below.

The earliest between group effect occurred at ~110ms over midline occipital scalp. Posthoc comparisons, showed significantly reduced VEP amplitudes at all ISIs for the SCZ group as compared to the NT group (mean differences ranging from 2.5 to 3.6uV, all p’s<.05). At 150ms a significant adaptation effect between the groups was observed over bilateral occipital sites (*Right partial η²=.21, Left partial η²=.12*). Posthoc ANOVAs and contrasts, Bonferroni corrected, revealed a significant difference between the two slower ISIs against all other ISIs and each other for the NT group, with smaller VEP amplitudes observed for faster ISIs. For the SCZ group there effects were less ubiquitous and less clear. Slower ISI VEP modulations failed to reach significance when compared to each other. Additionally, increased variability at the shorter ISIs (200 & 300) interfered with clear VEP separation even when comparing some of the most discrepant ISIs (e.g. p>.05 for 2550 vs 300 but p<.05 for 2550 vs 550 at the right occipital site). Overall, unlike the NT group, adaptation in the SCZ group necessarily relied on high frequency
stimulation and was less titrated. For both groups there were no significant differences in the VEP amplitudes evoked by the three faster ISIs (200, 300, 550ms) compared against each other.

A significant adaptation effect between groups was also observed at ~200ms over midline occipital scalp (partial $\eta^2=.15$). Posthoc ANOVAs and contrasts, Bonferroni corrected, were used to examine the effect of ISI within each group at this site. At this time the adaptation effect is generally "reversed," with faster ISIs eliciting greater VEP amplitudes. For the NT group the VEP elicited by the 2550 ISI was significantly reduced as compared to all other ISIs and the 1050 ISI was reduced as compared to the 200 ISI. For the SCZ group, the VEP elicited by the 2550 ISI was significantly reduced as compared to most other ISIs (300, 550, 1050 but not 200) comparisons against the shortest ISI once again failed to reach statistical significance. Here the 1050 ISI was not significantly different than the other faster ISIs. This again reflected a pattern of less titrated VEP adaptation based on presentation rate; one not especially sensitive to lower frequency stimulation.

During the last time period of analysis, ~250ms, a significant main effect of Group was observed over bilateral occipital scalp. This once again reflected significantly reduced VEP amplitudes in the SCZ group as compared to the NT group. A significant main effect of ISI, was also observed over bilateral occipital scalp at this time. Posthoc comparisons, Bonferonni corrected, reveal an inconsistent effect, with the 300, 550, and 1050ISI amplitude being significantly larger than the 200ISI on the left and the 550ISI significantly larger than the 200, 300, and 2550ISI on the right.

**Individual Analysis**

Individual level comparisons were conducted at time periods during which a significant Group x ISI effect was observed. Testing at 145-165ms for the two lateral occipital sites revealed significant differences for on average 14 of the 15 participants in the NT group when comparing the amplitude to 2550ms ISI against all other ISIs (200, 300, 550, 1050ms). For the SCZ group on average 10 of the 15 participants showed significant differences when comparing the 2550ms ISI against the 200, 300, and 550 ISI with this number dropping 7 when comparing against the 1050ms ISI at right occipital scalp. As in the group level analysis, the single subject SCZ VEP amplitudes appeared to be less sensitive to modulation
elicited by the lower frequency ISI. A chi-square test indicated a significantly greater frequency of adapters in the 2550 vs 1050 ISI for NT, as compared to the SCZ group for both lateral occipital sites. There was also a significant difference in the proportion of adapters in NT when comparing the 2550 vs the fastest ISI for the left occipital site and a trend towards significance for the right occipital site (2550 vs 300, p=.067).

Sensitivity of Visual Adaptation Deficits

To further examine the robustness and clinical usefulness of second order 'dynamic' properties of the visual system, we subjected the titrated VEPs measures recorded under a representative 'fast' ISI (300ms), the 1050 ISI, and the 2550 ISI over lateral occipital sites (at ~150ms) to a binary logistic regression. In using these combined adaptation measures to predict group membership (threshold= .5), we were able to correctly classify 80% of our sample (13/15 SCZ, 11/15 NTs, p<.01). This model performs significantly better than chance and is not improved by the addition of predictors reflecting baseline amplitude deficit between the groups (VEP at Oz under the 2550 ISI at ~110ms).

Experiment 2

Group-Level Analysis

SEP

Both scalp sites of interest exhibited a similar morphology and timecourse. For the central parietal site this was a positive-going potential and for the frontal midline site this was a negative-going potential. Both sites showed a singular prominent peak, with maximal amplitude occurring at ~85ms. Figure 6 depicts the group SEPs for sites of interest for the NT group (top) and the SCZ group (bottom).

Main Findings

Results from the main ANOVA and post-hoc comparisons for significant Group x ISI interactions are presented in Table 3 and Table 4, respectively. The main findings are summarized below.
No significant group or ISI x Group effects were observed at the central parietal scalp site. However, a significant ISI effect was observed. Post-hoc comparisons, Bonferroni corrected, reveal a robust effect with overall faster ISIs resulting in reduced SEP amplitudes.

A significant adaptation effect between groups was observed at the midline frontal site at this time period (partial $\eta^2 = .12$). Again, faster ISIs resulted in reduced (less negative) SEP amplitudes. Post-hoc comparisons, Bonferroni corrected, reveal a pattern similar to what was observed in the visual adaptation experiment, with less effective SEP modulation elicited by the slower ISIs in the SCZ group. In the NT group there were significant differences in the SEP amplitude evoked by the 2550ms ISI as compared to all other ISIs and the 1050 as compared to most other ISIs (excluding 550). For the SCZ group significant differences were noted in the 2550 ISI SEPs as compared to the 150, 250, 350, 550 but not the 1050 ISI. Additionally the SEP elicited by 1050 ISI was significantly different than that elicited by fastest ISI, as was the 350 ISI SEP. In summary, somatosensory adaptation at this site mirrors what was seen in the visual domain, will less sensitive SEP modulation at slower stimulus presentation rates and overall less titrated modulations.

*Individual Analysis*

Individual level comparisons were conducted for the midline frontal site where a significant Group x ISI effect was observed. Testing at the 70-100ms time-period revealed significant differences for 11 of the 12 participants in the NT group when comparing the amplitude to 2550ms ISI against the fastest ISI, with this number dropping to 8 for comparisons against 550, and 5 for comparisons against 1050. For the SCZ group 10 of the 12 participants showed significant differences when comparing the 2550ms ISI against the 200ISI, with this number dropping to 4 when comparing against the 550ms ISI and 3 when comparing against 1050. As in the group level analysis, there was a drop off in the sensitivity of SEP amplitude modulation for comparisons between the lower frequency ISIs. However, this drop off is seen for both groups. A more interesting comparison might be made when examining the number of single subject adapters in the 2550 vs 550 condition where (NT = 8, SCZ= 4). A chi-square test failed to show a significantly greater frequency of adapters in the NT, as compared to the SCZ group for any of the ISI comparisons.
3.4. DISCUSSION

The current investigation compared adaptation properties in two sensory systems in participants diagnosed with a schizophrenia-spectrum disorder. In the visual adaptation experiment, robust VEP amplitude differences and differences in VEP adaptation were noted between groups across all scalp sites examined. Interestingly, patients with SCZ exhibited adequate VEP amplitude modulation to fast ISIs. Over lateral occipital sites this was reflected in a decrease in VEP amplitude under fast presentation rates (200, 300, 500ms ISIs) as compared to slow presentation rates (1050, 2550ms ISIs). It was only in comparing *between* the slow ISIs that adaptation differences between NTs and SCZ were reliably observed. In the NT group, the VEP evoked under the 1050 ISI was significantly reduced as compared to the VEP evoked under the 2550 ISI. In the SCZ group, however, these two conditions were indistinguishable from each other. The same pattern emerged when comparing the “reverse” adaptation observed later (~210ms) over midline occipital scalp. At this period over midline occipital scalp faster ISIs results in increased VEP amplitude. Once again for the NT group, VEP amplitudes elicited under the ‘fast’ ISIs, the 1050 ISI, and the 2550 ISI were all significantly different from each other. In the SCZ group, the VEP amplitude elicited under the 2550 ISI was significantly reduced as compared to the fast ISIs, whereas the VEP elicited by the 1050 ISI was not.

A similar, albeit less clear, pattern was observed in the somatosensory adaptation experiment. In this modality, differences in SEP amplitude and SEP adaptation were seen over central-parietal and midline frontal sites, with statistically significant differences between groups noted at frontal sites. As in the visual adaptation experiment, these differences highlighted the notion that in SCZ the basic somatosensory response is adequately modulated by ‘fast’ ISIs, but fails to distinguish between slower ISIs. This is evidenced by a significant decrease in SEP amplitude under ‘fast’ presentation rates (e.g. 150, 350ms ISI) as compared to ‘slow’ (1050, 2550ms ISI). However, when comparing *between* slow ISIs, no significant differences in SEP modulation are noted in the SCZ group. The NT group, on the other hand, exhibited a finely tuned SEP adaptation across the the various ISIs, with significant amplitude differences also noted between slow ISIs. Much like what was observed in the visual domain, the somatosensory system in NTs seems more sensitive to low frequency modulation than in SCZ.
These findings are in line with a 'panmodal' theory of sensory processing deficits. Although this notion is not unique (Javitt, 2009a; Javitt, Liederman, Cienfuegos, & Shelley, 1999), investigations aimed at characterizing these deficits are largely skewed to the auditory domain. Auditory plasticity, particularly in the form of assessing adaptation and 'gating' of the auditory evoked potential in SCZ, for instance, is very well characterized (Patterson et al., 2008; Wilde, Bour, Dingemans, Koelman, & Linszen, 2007), whereas the examination of visual plasticity in this population is much more rare, does not benefit from any unified paradigms, and has yielded inconsistent findings (L.E. Adler, M.C. Waldo, & R. Freedman, 1985; Cavus et al., 2012; Foxe, Yeap, & Leavitt, 2013; Schwarzkopf et al., 1990). What's more, the study of somatosensory plasticity in SCZ is largely "uncharted territory." Three studies pave the way: a 2010 (Huang et al., 2010) MEG study showing altered somatosensory plasticity in an MMN task in schizophrenia, a 2008 MEG study (Thoma et al., 2007) showing altered secondary somatosensory gating in schizophrenia, and a 2006 EEG study (Arnfred et al., 2006) showing no gating deficits. For the most part, the study of somatosensation in schizophrenia has been focused on graphesthesia and two-point discrimination (Chang & Lenzenweger, 2001, 2004, 2005; Lenzenweger, 2000; Lenzenweger & Maher, 2002; Martin, Tewesmeier, Albers, Schmid, & Scharfetter, 1995). Although some of these studies have shown somatosensory deficits to be endophenotypic e.g. (Chang & Lenzenweger, 2005), a characterization of the basic neurophysiology underlying these phenomena is lacking.

An obvious question that arises is why adaptation in SCZ would be altered specifically at 'slower' ISIs. An argument could be made for separate mechanisms underlying adaptation to very fast vs slower sensory stimulation. The failure of both visual and somatosensory modalities, regardless of psychiatric diagnosis, to differentiate between the fastest ISIs suggest might suggest an adaptive mechanism in which inconsequential stimulation in rapid succession is simply "shut off" to conserve resources. This form of adaptation could come as a result of an active gating mechanism (e.g. inhibition) or a passive one, suggestive of a refractory period (e.g. depletion). The mechanism underlying adaptation to the slower ISIs seems to represent an additional filter. Under these conditions, in NTs, we observe evoked responses that are still dampened by a faster ISI, but that is also specific to the presentation rate— that is to say that the 1050 ISI is significantly greater than the 'fast' ISIs and also significantly smaller than the
next ‘slowest’ ISI. In SCZ however, in both modalities examined, the 1050 ISI is not different than the 2550 ISI.

In this sense, the slow ISI modulation more closely resembles a ‘tuning in’ to the presentation rate rather than a ‘shutting off’ to repetitive stimulation. A recent paper, examining response modulations in the auditory system argues for dissociable effects of so-called ‘repetition suppression’ (e.g. fast ISI) and ‘expectation suppression’ (e.g. slow ISI) (Todorovic & de Lange, 2012). Also in the auditory domain, separate mechanisms have been recently proposed to explain P50 & N200 adaptation (dubbed ‘gating out’) and MMN & P3 adaptation (dubbed ‘gating in’) (Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004; Gjini, Arfken, & Boutros, 2010), with one study relating SCZ AEP deficits to rare, but salient audio stimuli specifically to power at the beta band frequency (C. A. Brenner et al., 2009). It is unclear however exactly how our measures relate to those obtained in the auditory adaptation experiments discussed above.

Another possible explanation could relate to increased unreliability of the neural signal in SCZ when the sensory system isn’t being driven to depletion. Some have shown that increased unreliability (i.e. reduced inter-trial coherence) could account for auditory P50 gating deficits described in SCZ (Patterson et al., 2000). An unreliable signal could also come as a result of abnormal neural synchrony, in local cortical sensory circuits, cortical sensory-frontal circuits, and cortical sensory-thalamic-frontal circuits, and aberrant neurotransmitter functioning (Benes, 2000; Cohen, Tsien, Goff, & Halassa, 2015; Friston & Frith, 1995; Kantrowitz & Javitt, 2010). Further, these findings are in line with a neurodevelopmental and altered connectivity conceptualization of schizophrenia (Jaaro-Peled et al., 2009; Lewis & Levitt, 2002; Rapoport, Giedd, & Gogtay, 2012; Stephan, Baldeweg, & Friston, 2006). Of course none of these explanations are mutually exclusive and further research is necessary to disentangle the mechanisms underlying the short-term sensory plasticity observed in the current study.

It will also be important to determine whether these adaptation deficits can be useful as endophenotypes of schizophrenia (Gottesman & Erlenmeyer-Kimling, 2001), a promising proposition given that early visual sensory processing deficits have already been found in healthy first-degree biological relatives of schizophrenia probands (Yeap et al., 2006). As an endophenotype, adaptation would lie closer to the “shared genetic risk” contributing to the clinical state while being genetically less
complex than higher-order symptoms and easier to objectively measure. It will also be informative to assess whether adaptation deficits are related to risk variants on Schizophrenia-related risk genes associated with NMDA-mediated processing, since as introduced above, it seems likely that adaptation processes rely heavily on NMDA-mediated mechanisms. Again, it is instructive that basic visual sensory processing differences have already been associated with two NMDA-related genes, DTNBP1, both implicated in schizophrenia risk NOS1 (Donohoe et al., 2008; O'Donoghue et al., 2012). Emerging evidence also implicates NMDA dysfunction in altered somatosensory responses in animal models of schizophrenia (Balu, Basu, Corradi, Cacace, & Coyle, 2012; Barz, Bessaih, Abel, Feldmeyer, & Contreras, 2014). This convergence of evidence leads us to hypothesize that variation in genes implicated in glutamatergic function may very well influence both visual and somatosensory adaptation.

LIMITATIONS

As with most studies in this population, it is unclear how antipsychotic and other psychotropic medications affect the measures at hand. Perhaps a more interesting question though concerns the effects of nicotine on these plasticity measures, particularly given its role in auditory 'sensory gating' (Freedman et al., 1997; Heishman, Kleykamp, & Singleton, 2010; Stevens & Wear, 1997) and the high prevalence of smoking among individuals with SCZ (Grant, Hasin, Chou, Stinson, & Dawson, 2004; Lasser et al., 2000; Poirier et al., 2002). A 2007 study (Wan, Helen, & Boutros, 2006) reports a P50 gating deficit in non-clinical, unmedicated high-schizotypes who are not smokers, but a 'rescued' phenotype in high-schizotypes who smoke yet no effect of smoking on P50 gating in low-schizotypes. In the current investigation, smoking was not an exclusionary criteria for either group and we did not control for how soon before the experiment a participant smoked.

Lastly, our smaller sample in the somatosensory experiment, coupled with the site specific group x ISI effect certainly warrant further study. However, it should be noted that the size of this effect was nonetheless large (partial $\eta^2=.12$). To the best of our knowledge, this study is among only a handful employing EEG to investigate spatio-temporal dynamics of somatosensory processing in schizophrenia-spectrum disorder.
CONCLUSION

This study employed high density EEG to characterize visual and somatosensory adaptation properties in schizophrenia-spectrum disorder. In the visual system, robust adaptation deficits, detectable at the individual-subject level, were observed over lateral occipital sites but only when comparing VEP adaptation between slower presentation rates. At very fast rates VEP attenuation, or 'shut down', was observed in both SCZ and NT groups. These electrophysiological markers of visual adaptation were used to correctly classify group membership in 13/15 SCZ and 11/15 NT (80% correct classification rate). To test the specificity of these findings, a somatosensory adaptation experiment was also conducted in the same sample. A similar adaptation deficit, in which SEP modulation was not sensitive to changes between slower presentation rates, was observed over midline frontal scalp-sites. Further study is needed to uncover the mechanisms underlying these effects, with altered neuronal synchronization and aberrant glutamatergic (as well as nicotinic) signaling arising as potential candidates.
### 3.5. TABLES

**Table 1. Participant Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Gender</th>
<th>Medication</th>
<th>PANSS Positive Scale</th>
<th>PANSS Negative Scale</th>
<th>PANSS General Scale</th>
</tr>
</thead>
</table>
| **SCZ** | 37 (13) | 11 M, 4 F | 3 typical  
3 atypical  
7 atypical + mood  
2 none | M=19.3, SD=6.6  
Range: 8-30 | M=17.3, SD=5.8  
Range: 9-25 | M=35.7, SD=7.9  
Range: 21-49 |
| **NT**  | 31(7)  | 10 M, 5 F | none              |                      |                      |                     |

*ages are not significantly different; typical/atypical refer to first and second generation antipsychotics, respectively*
Table 2. Visual Adaptation - Main ANOVA

<table>
<thead>
<tr>
<th>Time</th>
<th>ISI</th>
<th>Midline Occipital</th>
<th>Right Occipital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F(4,112)=31.5, p&lt;.001</td>
<td>ns</td>
<td>F(4,112)=34, p&lt;.001</td>
</tr>
<tr>
<td></td>
<td>F(1,28)=7.4, p&lt;.02</td>
<td>F(1,28)=7.4, p&lt;.02</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>F(4,112)=7.6, p&lt;.003</td>
<td>ns</td>
<td>F(4,112)=3.8, p&lt;.03</td>
</tr>
</tbody>
</table>

*Midline: Time 1= 100-120ms, Time 2=190-210ms, Lateral: Time 1= 145-165ms, Time 2= 235-255ms

Table 3. Visual Adaptation posthoc for significant interactions

<table>
<thead>
<tr>
<th>Group</th>
<th>Left Occipital</th>
<th>Midline Occipital</th>
<th>Right Occipital</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEUROTYPICAL</td>
<td>F(4,56)=25, p&lt;.001</td>
<td>F(4,56)=15, p&lt;.001</td>
<td>F(4,56)=29, p&lt;.001</td>
</tr>
<tr>
<td></td>
<td>2550 vs all, p&lt;.001</td>
<td>2550 vs all, p&lt;.008</td>
<td>2550 vs all, p&lt;.001</td>
</tr>
<tr>
<td></td>
<td>1050 vs all, p&lt;.008</td>
<td>1050 vs 250, 2550, p&lt;.03</td>
<td>1050 vs all, p&lt;.02</td>
</tr>
<tr>
<td></td>
<td>200, 300, 500 ns*</td>
<td>200, 300, 500 ns*</td>
<td>200, 300, 500 ns*</td>
</tr>
<tr>
<td>SCHIZOPHRENIA</td>
<td>F(4,56)=8, p&lt;.001</td>
<td>F(4,56)=9, p&lt;.002</td>
<td>F(4,56)=8, p&lt;.002</td>
</tr>
<tr>
<td></td>
<td>2550 vs 300 &amp; 550, p&lt;.05</td>
<td>2550 vs 300, 550, 1050, p&lt;.003</td>
<td>2550 vs 200 &amp; 550, p&lt;.05</td>
</tr>
<tr>
<td></td>
<td>1050 vs 200, 300 &amp; 550, p&lt;.04</td>
<td>200, 300, 500, 1050 ns*</td>
<td>1050 vs 200, 300, 550, p&lt;.05</td>
</tr>
<tr>
<td></td>
<td>200, 300, 500 ns*</td>
<td></td>
<td>200, 300, 500 ns*</td>
</tr>
</tbody>
</table>

* ns = not significantly different from each other, bold italics= p<.06
Table 4. Visual Adaptation Single Subject Analysis

<table>
<thead>
<tr>
<th></th>
<th>Left Occipital 2550 vs</th>
<th>200</th>
<th>300</th>
<th>550</th>
<th>1050</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotypical</td>
<td>15 (60+/-31)*</td>
<td>14 (60+/-33)^</td>
<td>14 (64+/-36)^</td>
<td>12 (75+/-26)*</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>9 (63+/-31)</td>
<td>10 (78+/-48)</td>
<td>10 (77+/-38)</td>
<td>9 (113+/-42)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Right Occipital 2550 vs</th>
<th>200</th>
<th>300</th>
<th>550</th>
<th>1050</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotypical</td>
<td>13 (62+/-29)</td>
<td>14 (57+/-30)^</td>
<td>13 (51+/-14)</td>
<td>14 (83+/-39)**</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>11 (76+/-37)</td>
<td>10 (86+/-42)</td>
<td>12 (89+/-40)</td>
<td>7 (91+/-31)</td>
<td></td>
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<table>
<thead>
<tr>
<th></th>
<th>Midline Occipital 2550 vs</th>
<th>200</th>
<th>300</th>
<th>550</th>
<th>1050</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotypical</td>
<td>7 (74+/-46)</td>
<td>10 (83+/-47)</td>
<td>10 (81+/-30)</td>
<td>9 (104+/-51)</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>6 (67+/-29)</td>
<td>10 (90+/-50)</td>
<td>11 (95+/-44)</td>
<td>6 (116+/-32)</td>
<td></td>
</tr>
</tbody>
</table>

**=p<.01, * = p<.05, ^= trend (Left p=.067) in the Chi-Square analysis, indicating a significant difference in frequency of adapters between groups**
Table 5. Somatosensory Adaptation – Main ANOVA

<table>
<thead>
<tr>
<th>Time</th>
<th>Central Parietal</th>
<th>Frontal Midline</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-100ms</td>
<td>ISI (F(5,110)=24, p&lt;.001)</td>
<td>(F(5, 110)=50, p&lt;.001)</td>
</tr>
<tr>
<td>Group</td>
<td>ns</td>
<td>(F(1,22)=4.5, p=.046)</td>
</tr>
<tr>
<td>ISI x Group</td>
<td>ns</td>
<td>(F(5,110)=3, p&lt;.03)</td>
</tr>
</tbody>
</table>

Table 6. Somatosensory Adaptation – Posthoc comparisons

<table>
<thead>
<tr>
<th>ISI</th>
<th>Central Parietal</th>
<th>Group x ISI</th>
<th>Frontal Midline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main effect across groups</td>
<td>2550 vs all</td>
<td>NEUROTYPICAL</td>
<td>(F(5, 55)=37, p&lt;.001)</td>
</tr>
<tr>
<td></td>
<td>550 vs 150, 2550</td>
<td></td>
<td>2550 vs all</td>
</tr>
<tr>
<td></td>
<td>350 vs 150, 1050, 2550</td>
<td></td>
<td>1050 vs 150, 250, 2550</td>
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<td></td>
<td>250 vs 1050, 2550</td>
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<td>550 vs 150, 250, 2550</td>
</tr>
<tr>
<td></td>
<td>150 vs 350, 550, 1050, 2550</td>
<td></td>
<td>350 vs 150, 1050, 2550</td>
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<td></td>
<td>SCHIZOPHRENIA</td>
<td></td>
<td>SCZ-(F(5,55)=17, p&lt;.001)</td>
</tr>
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<td></td>
<td>2550 vs 150, 250, 350, 550</td>
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<td>150 vs 350, 1050</td>
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** all comparisons listed \(p<.05\)

Table 7. Somatosensory Adaptation – Single Subject Analysis

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<tr>
<th>Midline Frontal</th>
<th>2550 vs</th>
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<th>200</th>
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<td>10</td>
<td>10</td>
<td>8</td>
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<tr>
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<td>8</td>
<td>9</td>
<td>4</td>
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3.6. FIGURES

Figure 1. Schematic representation of the visual (top) and somatosensory (bottom) adaptation experiments

**Experiment 1 - Visual Adaptation**
- 200, 300, 550, 1050, 2550 ms ISI
- Stimuli are jittered by +/- 50ms
- Self-paced 2500-5000ms inter-block interval
- Consistent within block ISI (100 trials)

**Experiment 2 - Somatosensory Adaptation**
- 150, 200, 300, 550, 1050, 2550 ms ISI
- 2500-5000ms inter-block interval
- Consistent within block ISI (400 trials)
- Passive; participant watches movie of own choosing
Figure 2. Group VEPs- A. Visual evoked responses at the 3 scalp sites of interest for the neurotypical group (top) and schizophrenia-spectrum group (bottom). Highlighted in gray are the time periods used for statistical analysis. A significant amplitude effect is observed over midline occipital scalp at an early time period. A significant adaptation effect is observed more laterally at 150ms and at 200ms over the midline.

B. Tuning curves- representing the significant visual adaptation effects between groups
* = significant main effect, **= significant interaction effect
Figure 3. **Visual scalp topographic maps** - The activity across the entire electrode array is depicted for the 5 ISI conditions across the time periods used for statistical analysis for both groups. Overall topography is generally similar, with marked reduction in amplitude throughout (note difference in scale). Additionally, there appears to be a differential engagement of more frontal areas in the later time periods for the slower ISIs between groups.

A. **NEUROTYPICAL**

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<th>Time Period</th>
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B.

SCHIZOPHRENIA

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Figure 4. Visual processing difference topographies – Scalp topographic maps representing the difference between the slowest ISI condition and all other ISI conditions for the time periods in which an adaptation effect between groups (sig Group x ISI) was observed. The difference topographies suggest the local and distal sources might be contributing to the VEP modulation and the differences observed between groups.
Figure 5. Group SEPs - A. Somatosensory evoked responses at the 2 scalp sites of interest for the neurotypical group (top) and schizophrenia-spectrum group (bottom). Highlighted in gray is the time period used for statistical analysis. A significant ISI effect but no group differences is observed over central-parietal scalp contralateral to stimulation side. A significant adaptation effect is observed over midline frontal scalp. B. Tuning curves- representing somatosensory adaptation effects in both groups.
**Figure 6. Somatosensory Scalp topographic maps** - The activity across the entire electrode array is depicted for the 6 ISI conditions across the time period used for statistical analysis for both groups. Overall topography is nearly identical with slight amplitude reductions noted for the shortest ISIs (note both groups are presented on the same scale).
Figure 7. Somatosensory processing difference topographies – Scalp topographic maps representing the difference between the slowest ISI condition and all other ISI conditions are presented for the time period of interest. The difference topographies suggest a similar pattern of adaptation between groups for the slow vs fast comparisons, with more nuanced differences perhaps emerging in the comparisons between 2550 and some of the slower ISIs (e.g. 550 & 1050).
3.7. REFERENCES


Haenschel, C., Bittner, R. A., Haertling, F., Rotarska-Jagiela, A., Maurer, K., Singer, W., & Linden, D. E. (2007). Contribution of impaired early-stage visual processing to working memory dysfunction in adolescents with schizophrenia: a study with event-related potentials and functional magnetic resonance imaging. [Research Support, Non-U.S. Gov't]. Arch Gen Psychiatry, 64(11), 1229-1240. doi: 10.1001/archpsyc.64.11.1229


Naatanen, R., & Kahkonen, S. (2009). Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review. [Research Support, Non-U.S. Gov't Review]. *Int J Neuropsychopharmacol, 12*(1), 125-135. doi: 10.1017/S1461145708009322


CHAPTER 4

ATYPICAL VISUAL ADAPTATION IN NON-CLINICAL SCHIZOTYPY: AN ELECTROPHYSIOLOGICAL ENDOPHENOTYPE FOR SCHIZOPHRENIA?

Gizely N. Andrade, John S. Butler, and John J. Foxe
4.1. INTRODUCTION

An endophenotype is an intermediate phenotype lying between the genetic underpinnings and the clinical expression of a disorder. As such, endophenotypes are thought be state-independent and present whether or not a specific disorder has manifested itself. Because endophenotypes can be used to identify those at-risk and as well as molecular mechanisms implicated in the pathophysiology of a disorder, they are of critical scientific and clinical interest.

Schizotypy is a psychological construct, which posits that schizophrenia-like traits are also distributed within the non-clinical population (e.g. (Lenzenweger, 2010; Meehl, 1962, 1990)). Schizotypy exists on a continuum and encompasses elements such as magical ideation, paranoia, social anhedonia, disorganized thinking, and impulsive behaviors (J. P. Chapman, Chapman, & Kwapiil, 1995; Claridge et al., 1996). Studies have shown that the expression of schizotypy is modulated by several schizophrenia risk genes (A. H. Fanous et al., 2007; Stefanis et al., 2007) suggesting shared heritability. Several lines of research have also shown that individuals high in schizotypy convert to schizophrenia at higher rates than those low in schizotypy (L. J. Chapman, Chapman, Kwapiil, Eckblad, & Zinsier, 1994; Gooding, Tallent, & Matts, 2005; Kwapiil, 1998) and that schizotypy is elevated in non-clinical first-degree relatives of patients with schizophrenia (Calkins, Curtis, Grove, & Iacono, 2004; A. Fanous, Gardner, Walsh, & Kendler, 2001). For example, Kwapiil (Kwapiil, 1998) showed that 24% of high schizotypes had been diagnosed with a SCZ-spectrum disorder as compared with 1% of low schizotypes after a 10-year longitudinal follow-up and Gooding et al (Gooding et al., 2005) showed that ~16% of high SZT converted to a SCZ-spectrum diagnosis after a 5-year follow-up, compared to none in the control group.

The study of SZT may offer an exceptional window into neurodevelopmental processes associated with SCZ, unconfounded by changes in the brain that come as a result of the disease-state or antipsychotic treatment. This population is also more easily accessible and likely to endorse higher compliance rates than patients. Furthermore, several brain-based phenotypes identified in SCZ have also been noted to vary with SZT, with several of these involving visual processes, including P1 amplitude (Bedwell, Chan, Trachik, & Rassovsky, 2013), depth perception (Barbato, Collinson, & Casagrande, 2012; Koehe et al., 2009), smooth pursuit (Gooding, Miller, & Kwapiil, 2000), latent inhibition (Casa, Hofer, Weiner, & Feldon, 1999), visual working memory (Koychev, El-Deredy, Haenschel, & Deakin, 2010), as
well as altered sensory adaptation (Croft, Dimoska, Gonsalvez, & Clarke, 2004; Wan, Crawford, & Boutros, 2006). These factors combined make the study of schizotypy an ideal aid in the pursuit of schizophrenia sensory processing endophenotypes, with the potential for identification of both risk and resilience factors.

The current study seeks to examine whether visual adaptation deficits, identified by our group in a sample of patients with schizophrenia spectrum disorders (Andrade, Butler, Peters, & Foxe, in prep), can also be seen along the schizotypy-spectrum. Our group has developed a quick, non-invasive, and uniquely sensitive paradigm, in which we elicit VEP amplitude changes by modulating the presentation rate of a simple visual stimulus over a short period of time while recording continuous EEG (Andrade, Butler, Mercier, Molholm, & Foxe, 2015). It is hypothesized that atypical VEP amplitudes and modulation will be seen with increasing levels of schizotypy, as assessed by the Schizotypal Personality Questionnaire (SPQ, (Raine, 1991)).
4.2. METHODS

Participants

62 neurotypical adults completed the visual adaptation experiment and the SPQ. Demographic characteristics of the sample are given in Table 1. All procedures were in accordance with the institutional review board policies and all participants had normal or corrected vision.

Schizotypal Personality Questionnaire

The SPQ is a 74 item (yes/no) self-report. The items are used to assess nine schizotypal features: ideas of reference, excessive social anxiety, odd beliefs or magical thinking, unusual perceptual experiences, odd or eccentric behavior, social anhedonia, odd speech, constricted affect & suspiciousness. The SPQ has high reliability and validity against DSM Schizotypal Personality Disorder (Raine, 1991; Salokangas et al., 2013). Several studies suggest the SPQ conforms to a three-factor structure including Cognitive-Perceptual, Interpersonal, Disorganization factors (Chen, Hsiao, & Lin, 1997; Fossati, Raine, Carretta, Leonardi, & Maffei, 2003; Raine, 1991; Reynolds, Raine, Mellingen, Venables, & Mednick, 2000; Rossi & Daneluzzo, 2002; Suhr & Spitznagel, 2001). These Cognitive-Perceptual and Interpersonal factors are at times referred to as Positive and Negative factors, respectively. Further, the existence of these factor constructs in the general population is supported by neurocognitive (Daneluzzo, Bustini, Stratta, Casacchia, & Rossi, 1998), genetics (Raine & Baker, 1992) and clinical (Axelrod, Grilo, Sanislow, & McGlashan, 2001).

Visual Adaptation

Stimuli

Stimuli were 100% contrast black and white checkerboard annuli (6.5 cm diameter, 1cm width, 4°x4°, white luminance of 120 cd/m², black luminance of 0.2 cd/m²) centered against a grey (luminance = 25 cd/m²) background. A fixation cross was always present on the screen, including during checkerboard presentation. The fixation cross changed color every 20-40s. Checkerboards were presented for 33ms and at different inter-stimulus-intervals (ISIs).
Procedure
Participants sat in a darkened sound-attenuated electrically shielded double-walled booth (Industrial Acoustics Company, Bronx, NY), 90 cm from a 34x55 cm LCD computer screen (ViewSonic VP2655wb, 60Hz refresh rate) while wearing the EEG cap (described below). They were instructed to minimize head movements and blinking while fixating on a red cross at the center of the screen. They performed a change detection task to ensure fixation in which they were asked to respond to fixation cross color changes (from red to green, lasting 40ms) with a mouse button press using the index finger of their dominant hand. The presentation of checkerboard stimuli was temporally unrelated to this central fixation task.

Paradigm
Checkerboards were presented in blocks of 100 stimuli. Within each block, the stimuli were centered at an ISI, around which the actual presentations were jittered by +/-50ms. Five different ISIs were used: 200ms, 300ms, 550ms, 1050ms, and 2550ms. Between-block interval was self-paced, with participants allowed to move to the next block by pressing the spacebar on a keyboard 2500-5000ms after the last stimulus of the preceding block. Block presentation was pseudorandom. In total, participants experienced 2 blocks of each ISIs. Total run time for the experiment ranged from 15-20 minutes.

Data Acquisition
Continuous electroencephalographic (EEG) data were recorded in using a Biosemi ActiveTwo 32-channel electrode array, analog-to-digital converter, and fiber-optic pass-through to a dedicated data acquisition computer. The data were recorded at 512 Hz with a pass-band from DC to 150Hz. The continuous EEG was subsequently low-pass filtered at 45Hz (4th order-zero phase Butterworth filter, 27 dB/octave) and high-pass filtered at 1Hz (4th order-zero phase Butterworth filter, 24 dB/octave). Epochs of 600 ms with 100 ms prestimulus baseline were extracted from the continuous data. An automatic artifact rejection criterion of ±75 µV was applied across all electrodes in the array. Trials with more than 3 artifact channels were rejected. In trials with less than three such channels, any remaining bad channels were interpolated using the nearest neighbor spline (Gonzalez Andino et al., 2001; Perrin, Pernier, Bertrand, Giard, &
The data were re-referenced to the average of the frontal midline electrode (Fz). As the timing between the stimuli of the shortest ISI was between 150 to 250ms, we implemented the Adjacent Response (ADJAR) algorithm on our subject-level data to model and remove any response overlap (Fiebelkorn, Foxe, McCourt, Dumas, & Molholm, 2012; Woldorff, 1993).

**Analysis Strategy**

**Identifying ERP predictors**

EEG processing and statistical analysis were performed using custom MATLAB scripts (Mathworks), Fieldtrip toolbox for EEG analysis (Oostenveld, Fries, Maris, & Schoffelen, 2011), EEGLAB (Delorme & Makeig, 2004), and SPSS software package (SPSS). Group-averaged waveforms were visually inspected across all scalp sites, and the familiar components of the VEP were identified (Foxe & Simpson, 2002). This allowed for definition of the precise timing of a given component and delineation of the scalp sites at which each component was of maximal amplitude. Electrodes over midline and lateral occipital scalp were selected for analysis based on the group averaged waveforms. The VEP over midline occipital scalp (Oz) consisted of a negative going potential, peaking at ~110ms, followed by a positive going potential peaking at ~200ms. At lateral sites (PO3, PO4) the VEP was characterized by a major negative going potential peaking at 155ms, followed by a major positive going potential peaking at about 250ms. A robust ISI effect was observed over lateral occipital sites at ~155ms, PO3 F(4, 61)=52, p <.001, PO4 F(4,61)= 45, p<.001. Post-hoc comparisons, revealed that faster stimulus presentation rates lead to reduced VEP amplitudes (less negative) but no significant differences in amplitude were noted between the three fastest ISIs as compared to each other. These findings replicate results from two previous investigations (discussed in detail in Andrade et al 2014).

Selection of VEP components to be entered into the regression were guided by reports of atypical visual adaptation in a sample of participants diagnosed with schizophrenia-spectrum disorders (SCZ) collected under this same paradigm using a 160-channel electrode array. In that study (Andrade et al in prep) VEP amplitude modulation in SCZ was found to be less sensitive to low frequency stimulation (1050 ISI) and more variable the fastest ISIs (300ms) at lateral occipital sites in the 140-160ms time window. Additionally, significantly reduced VEP amplitudes in the SCZ group was recorded at the midline occipital
site in the 100-120ms time window, with the most striking differences seen when comparing the “baseline VEP amplitudes” (2550 ISI) between groups. In sum, considering the findings in the clinical group, in order to see if altered visual adaptation may serve as a schizophrenia endophenotype, the follow ERP measures were selected as predictors for schizotypy intensity (total SPQ score): VEP amplitude elicited by the 2550, 1050 & 300ms ISI at PO3 & PO4 at 150ms, as well as VEP amplitude recorded in the 2550ms ISI condition at Oz, for a total of 7 electrophysiological predictors.

*Predicting Schizotypy*

A hierarchical multiple linear regression analysis was performed to assess the extent to which the neurophysiological measures (ERPs) obtained under the abbreviated visual adaptation paradigm described here could predict global schizotypy. As some studies have shown a relationship between schizotypy and age (Badcock & Dragovic, 2006; Bora & Baysan Arabaci, 2009; Mason & Claridge, 2006; Paino-Pineiro, Fonseca-Pedrero, Lemos-Giraldez, & Muniz, 2008), age was controlled for in this analysis by being included in 'Step 1' of the regression. In 'Step 2' the ERP measures are added to the regression. In order to further characterize the role of visual adaptation ERPs as schizophrenia endophenotypes, a second set of multiple linear regressions were also conducted using each of the SPQ sub-factors as outcome measures. Age was also entered as a 'Step 1' predictor in these analyses. The follow-up regressions were intended to examine if a particular sub-facet of schizotypy is most closely associated with the neurophysiological-risk profile. The $R^2$ resulting from regressions was used to evaluate the extent to which these experimental indices are associated SZT variability.
4.3. RESULTS

Age alone did not predict SPQ scores, $F(1,61)= .04$, $p= .85$. The linear combination of the seven ERP measures and age was significantly related to total SPQ scores, $F(8, 61) =2.5$, $p= .02$. Approximately 28% ($R^2 = .277$) of the variance of in schizotypal traits in this non-clinical sample, as measured by the SPQ, could be accounted for by the electrophysiological measured elicited by our brief visual adaptation paradigm (Figure 1).

In order to better visualize the results of the main regression, the total sample was divided into a “high-SPQ” and a “low SPQ” group and group-level waveforms were generated for each sample (Figure 2). A median split was used to assign group membership. Thirty-one participants were assigned to the low SZT group (mean SPQ= 7.8, SD=4.8) and 31 participants were assigned to the low SZT group (mean SPQ= 24.3, SD=7.4). Unlike the low SZT group in which a fine gradation of VEP amplitude by ISI can be seen, in the high SZT group visual adaptation effects appear to be less sensitive, with less separation between the VEP amplitudes elicited by the faster ISIs over lateral occipital sites at 150ms. Additionally, a basic VEP amplitude deficit is noted in the high SZT over the midline occipital scalp site, which is most striking at ~110ms. These findings mirror the atypical visual adaptation described in patients with schizophrenia, using a longer version of the paradigm here and a high-density electrode array.

Next we subjected the same set of predictors three follow-up regressions to see if a specific domain of SZT was more closely related to the electrophysiology than the other. In the first follow-up we tested the relationship between our predictors and the Cognitive-Perceptual domain of the SPQ (Ideas of Reference, Magical Ideation, Perceptual Aberration, Paranoia) and found no significant effect, $F(8,61)= 1.8$, $p= .08$. Second we tested the Interpersonal domain of the SPQ (Social Anxiety, Close Friends, Affect, Paranoia) and found a trend, $F(8,61)= 2$, $p= .06$. Lastly, we found a significant effect when testing the relationship between our visual adaptation ERP predictors and the Disorganization domain of the SPQ (Odd Behavior, Odd Speech) $F(8,61)= 2.4$, $p = .025$. After adjusting for multiple comparisons ($\alpha= .05/3 = .017$), none of the follow-up regressions meet criterion for statistical significance. However, the trend noted in the Disorganization domain may underlying the effects noted in the main regression, we elected to undertake a set of follow-up exploratory analysis in order to better understand the relationship between visual adaptation and this domain of schizotypy.
Post-hoc Analyses

Here we set out to understand the driving contribution of SPQ-D to altered visual adaptation. In doing so we seek to quantify potential differences in true “high” and “low” schizotypes and preliminarily assess the potential individual level-sensitivity of this measure. The following comparisons employ a taxonomic categorization of schizotypy (Kwapil & Barrantes-Vidal, 2014; Meehl, 1990; Rawlings, Williams, Haslam, & Claridge, 2008) which argues that the extremes of the schizotypy continuum constitutes a unique taxa or class of individuals. It is in the top extreme, typically defined as the highest ~10% of the schizotypy distribution, that elevated conversion rates to the full-blown clinical phenotype resides. The low extreme (lowest ~10% of the distribution) is associated with very low schizophrenia-risk. Such divisions are common place in schizotypy research and have been successfully used to identify individuals at risk for schizophrenia-spectrum disorders in prospective, longitudinal studies (L. J. Chapman et al., 1994; Gooding et al., 2005; Meyer & Keller, 2001; Mishlove & Chapman, 1985; Raine, 1991).

Statistical Cluster Plots

To further investigate the adaptation differences driving our effect, we selected participants from the ‘tails’ of the SPQ-Disorganization distribution (i.e. >1 SD and <1SD from the mean), as this was the only factor significantly predicted by our combination of ERP measures. Fourteen participants were assigned to the low disorganization group (Mean SPQ-D =0.1, SD=0.4) and fifteen participants were assigned to the high disorganization group (Mean SPQ-D=10.6, SD=1.4) and group level VEPs were generated (Figure 3). Post-hoc analysis testing the entire EEG data matrix for possible effects was then conducted as a means of fully investigating our data set and as a hypothesis-generating tool for future research. To do so, statistical cluster plots (SCPs) were derived by calculating point-wise, paired, 2-tailed t-tests between the VEP generated at each time period for the different stimulation rates across all scalp sites. This allows for the visualization of any and all significant between-conditions comparisons.

In brief, the VEP at each scalp site was compared for the ISI pairings of interest (e.g. 2550 vs 300 & 2550 vs. 1050.) for all time periods. In order for these VEP comparisons to be considered statistically significant using the present clustering approach, the alpha criterion for significance (p < .05) must be attained for 11 consecutive data points (> 20ms). The rationale for this method is that type I errors are
very unlikely to occur simultaneously at adjacent electrodes and equally unlikely to endure for several consecutive time points (i.e. in clusters), even accounting for auto-correlation (Guthrie & Buchwald, 1991). The results of the running t-tests for the entire electrode array for each VEP comparison are displayed as intensity plots with 3 major axes to efficiently summarize and facilitate the comparison of the multiple data sets comprising this study. The x-axis represents time (post-stimulus onset), the y-axis represents electrode, and z-axis represents the t-test result (indicated by a color value from red to blue) at each data point. Areas represented in grey do not meet criteria for statistical significance.

Figure 4 shows the SCP for the 2550 vs 300ISI & 2550 vs 1050ISI within each group for both the Low SPQ-D participants (top) and High SPQ-D participants (bottom). The plots indicate less sensitive VEP modulation in the high SPQ-D group, which is most striking when comparing against the ‘slower’ ISIs—VEP amplitude to the 2550 vs. the 1050 condition. In other words, the VEP does not adequately ‘tune in’ to differences between the slower ISIs to the same degree in the High SPQ-D participants as in the Low SPQ-D participants; an effect similar to what our group found in an earlier study on participants diagnosed with a schizophrenia-spectrum disorder (Andrade et al, in prep). Further the SCPs suggest a lag in the peak VEP modulations between the slow ISIs when comparing across groups.

**Exploratory investigation individual-subject level sensitivity**

In order to investigate the robustness of adaptation at the individual participant-level, a non-parametric randomization procedure was conducted (Maris & Oostenveld, 2007). For each participant we compared the amplitude recorded under the 2550 ISI condition against each of the ISIs of interest at a lateral occipital scalp site (PO3) for the time periods during which adaptation effects differed between the high and low SPQ-D groups (~155ms). The observed difference between the 2550ms ISI and the test ISI was compared with a reference distribution of differences that was derived by iteratively randomizing between the two original data sets (i.e. individual-subject VEP amplitudes for the 2550ms and test ISI) 10,000 times. The number of epochs selected for the bootstrapping process was a subset of the total which increased in steps of 20 from 30 epochs until statistical significance or the maximum number of sweeps was reached (Nolan et al., 2012). A one-tailed threshold of p <0.05 was used to define significance. The p value for a randomization test was calculated from the proportion of values in the reference difference
distribution that exceeded the observed difference (Fiebelkorn et al., 2011). Using this procedure individual subject level differences appear more robust in comparing between the slow ISIs, with nearly 80% of Low SPQ-D participant showing significant VEP amplitude modulation when comparing 2550 & 1050 ISI, as compared to 47% in the high SPQ-D group (Table 3). These descriptive individual-level findings are in line with the group-level results.
4.4. DISCUSSION
The current study demonstrated a relationship between non-clinical schizotypy and electrophysiological measures of visual adaptation to repetitive stimuli. Bilateral VEP amplitudes were modulated by a checkerboard stimulus presented at different rates (ISIs) and served as predictors for global schizotypy, as measured by the SPQ. Follow-up comparisons suggest that the visual adaptation measures most significantly predicted the Disorganization factor of the SPQ.

Sensory adaptation deficits and visual processing deficits have been repeatedly demonstrated in schizophrenia, however it is the identification of these deficits in a non-clinical population that will propel further understanding of the molecular mechanism underlying the effects observed in patients and the relationship of these deficits to a risk-syndrome. Research in sensory adaptation in non-clinical schizotypy is still a budding field. Nonetheless, a small number of studies have shown a relationship between schizotypal traits and latent inhibition, which is a form of visual adaptation (e.g. (Casa et al., 1999; Evans, Gray, & Snowden, 2007a)). The latent inhibition effect, usually investigated through psychometric techniques, states that a previously familiar and unimportant stimulus is more difficult to learn under new contexts in which it is actually relevant due to the initial dampening of its processing. In only one of these studies (Evans et al., 2007a) was a paradigm used which allowed for the identification of individual subject-level effects, a common problem in the study of endophenotypes (Walters & Owen, 2007). Although the findings were compelling, the use of a behavioral task alone precludes precise information about the timing or localization of the observed effect; thus limiting a true understanding of the sensory deficits underlying the behavioral phenomena. Such an approach is still too many steps removed from mechanism and could be highly confounded by other factors (i.e. motivation, attention, fatigue).

Studies of auditory adaptation, using the scalp-recorded evoked potentials in a paired-click auditory paradigm, present a more objective and direct measure of altered sensory modulation in schizophrenia (Patterson et al., 2008; Wilde, Bour, Dingemans, Koelman, & Linszen, 2007). The so-called P50 deficit presents as failure of the AEP to sufficiently attenuate the second stimulus in a pair of inconsequential, identical auditory tones. Studies in non-clinical schizotypy show P50 deficits comparable to those observed in schizophrenia (Croft et al., 2004; Evans, Gray, & Snowden, 2007b; Wan, Crawford, & Boutros, 2007). Interestingly, Evans et al 2007b also report a relationship between atypical P50 gating
and the Disorganizaiton factor of the SPQ. In a related set of studies, measuring prepulse-inhibition (PPI) of the startle response, adaptation deficits were also related to disorganization features of schizotypy in a non-clinical sample (Evans, Gray, & Snowden, 2005; Takahashi et al., 2010). In the PPI adaptation paradigm, a milder conditioning stimulus serves to dampen the response to a subsequent startling stimulus.

There is some evidence supporting a special role for disorganization in schizophrenia-proper as well, with patients ranking high on cognitive disorganization measures presenting with significantly less P50 suppression (e.g. greater deficit) than those high on paranoia/positive traits (Boutros, Zouridakis, & Overall, 1991; Erwin, Turetsky, Moberg, Gur, & Gur, 1998; Ringel et al., 2004). A caveat to these findings however exists in that some elements of the Disorganization domain of schizotypy appear to overlap with Cognitive-Perceptual elements, particularly as they relate to suspiciousness/paranoia (Vollema & Hoijtink, 2000). This has recently lead some to suggest that Cognitive-Perceptual and Disorganization are not distinct SPQ factors (Gross, Mellin, Silvia, Barrantes-Vidal, & Kwapił, 2014), while others argue that self-report questionnaires simply lack the sensitivity to tap into disorganization traits, as compared to interview methods (Tarbox & Pogue-Geile, 2011). Additionally disorganization traits can contribute to poor social functioning, thus also being rated in the Interpersonal items (Vollema & Hoijtink, 2000). Lastly, although this domain is widely characterized, reported, and followed in clinical, non-clinical, and biological relative samples, it has been described as being “less stable” than the other schizotypy domains (Bergman et al., 1996; Bergman, Silverman, Harvey, Smith, & Siever, 2000; Rosa et al., 2000).

Lastly, in comparing the current findings to the 'gold standards' of sensory adaptation in schizophrenia research, an important open question remains: if these measures are to be clinically relevant, they should exhibit strong reliability over time (e.g. high test-retest reliability). Surprisingly this issue has not been much explored and has seemingly become more of an interest as of late (Bearden & Freimer, 2006; Calkins et al., 2007; Turetsky et al., 2007). Studies examining the reliability of the P50 gating ratio, for instance, have shown weak or non-significant intra-subject associations coefficients of this measure over time; suggesting that a P50 amplitude difference index is a more stable measure (e.g. Dalecki, Croft, & Johnstone, 2011; Fuerst, Gallinat, & Boutros, 2007; Smith, Boutros, & Schwarzkopf, 1994). Nonetheless, the P50 gating ratio persists. The reliability of visual evoked responses, has shown
some promise, with inter class correlation coefficients (ICC) upwards of .7 (Cassidy, Robertson, & O’Connell, 2012; Huffmeijer, Bakermans-Kranenburg, Alink, & van Ijzendoorn, 2014; Sarnthein, Andersson, Zimmermann, & Zumsteg, 2009), as compared to P50 adaptation (both gating and difference) ICC’s ranging anywhere from .00-.62 (e.g. (Cardenas, Gerson, & Fein, 1993; Clementz, Geyer, & Braff, 1997; Fuerst et al., 2007; Smith et al., 1994)).

It should be noted that the reliability of the auditory mismatch-negativity (MMN), a form of sensory adaptation which involves inhibition of the neural response to repetitive inconsequential stimuli and a ‘re-tuning in’ to a change in the auditory stream, has been much more widely investigated, replicated across various labs, including in large samples, and demonstrates excellent reliability (e.g. (Escera, Yago, Polo, & Grau, 2000; Light et al., 2012; Tervaniemi et al., 1999)). With that said, at the time of writing there was no evidence to suggest altered MMN processes in non-clinical schizotypy. Future research should examine the reliability of visual adaptation measures, which may also represent a dynamic ‘tuning-in’ form of adaptation, including a comparison of the stability of these measures across clinical populations (see (Franks, Adler, Waldo, Alpert, & Freedman, 1983).

LIMITATIONS

It has been shown that nicotine influences auditory sensory adaptation, having an enhancement effect on P50 gating in patients and controls (Adler, Hoffer, Griffith, Waldo, & Freedman, 1992; Crawford, McClain-Furmanski, Castagnoli, & Castagnoli, 2002; Freedman et al., 1997). Further, two recent studies have highlight ‘smoking-status’ as a significant moderator in the relationship between auditory adaptation and schizotypy (Wan et al., 2006, 2007). In these studies smoking had a normalizing effect on an otherwise less adapted P50 ratio for high schizotypes. Although it is yet unknown if similar mechanisms may govern the type of sensory adaptation in the current study, knowledge of participants smoking status may contribute to a further understanding of the reported effect. Future studies applying this paradigm should assess smoking status in clinical and non-clinical populations.

Recent studies also suggest that differences in the inter-trial variability of ERPs in schizophrenia may be contributing to effects observed in both across conditions and groups (Jin et al., 1997; Patterson et al., 2000). It has also been argued that differences in ERP amplitudes are in part driven by modulations
of the underlying, ongoing oscillations in brain activity (Bieniek, Pernet, & Rousselet, 2012; Brockhaus-Dumke, Mueller, Faigle, & Klosterkoetter, 2008; Sauseng et al., 2007). Thus our current analysis approach may be limited and a characterization of potential changes in dynamic brain networks implicated in sensory adaptation is ripe for future investigation. It is of note that one recent study (Koychev, Deakin, Haenschel, & El-Deredy, 2011) demonstrated reduced reliability (e.g. inter-trial coherence of phase-locking factor) in the beta/gamma band in non-clinical high schizotypes in a visual processing task. In light of the discussion above, there is also some evidence to suggest that measures of EEG oscillations may be more reliable over time and more closely linked to the underlying neuropathophysiology, \( r = .96 \), (Fingelkurts, Fingelkurts, Ermolaev, & Kaplan, 2006; Monastra, Lubar, & Linden, 2001). These findings in the time-frequency domain have recently contributed to a major FDA decision to allow an EEG metric, assessing the ratio of theta to beta power, to be used in the diagnosis of another neurodevelopmental disorder, ADHD, and may offer additional insight into schizophrenia-risk.

CONCLUSION

The current investigation demonstrates a relationship between non-clinical schizotypy, and visual adaptation. The results are in line with findings from a study using a similar paradigm to characterize schizophrenia-spectrum disorders. Follow-up comparisons suggest the combination of ERP measures obtained in the visual adaptation task most strongly predicted the Disorganization factor of the SPQ. Questions remain regarding the mechanism and the role smoking may have on the observed phenomena. The sensitivity of the current measure is highlighted showing individual-level subject effect in 47% of high schizotypes (>1SD from mean) as compared to 80% low schizotypes (<1SD from mean).
### 4.5. TABLES

**Table 1. Participant Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>SPQ</th>
<th>Gender</th>
<th>Age</th>
<th>Race/Ethnicity</th>
<th>Education</th>
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<tr>
<td>N= 62</td>
<td></td>
<td>Range= 0-46</td>
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<td>Median=15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median=15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>Age M=29 , SD=9</td>
<td>Education</td>
</tr>
<tr>
<td>33 Female</td>
<td>29 Male</td>
<td></td>
<td></td>
<td>47 White (9 Hispanic)</td>
<td>3 High School Diploma</td>
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<tr>
<td>5 African American</td>
<td></td>
<td></td>
<td></td>
<td>1 Unknown</td>
<td>2 Professional Certificate</td>
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<tr>
<td>3 Asian</td>
<td></td>
<td></td>
<td></td>
<td>8 Bachelor's Degree</td>
<td>16 Some college</td>
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<tr>
<td>4 Multiple Races</td>
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<td></td>
<td></td>
<td>17 Some grad school</td>
<td>12 Master's Degree</td>
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<tr>
<td>1 Unknown</td>
<td></td>
<td></td>
<td></td>
<td>3 Doctoral</td>
<td>1 Unknown</td>
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**Table 2. Regression Coefficients**

<table>
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<th>Standardized Beta</th>
<th>Zero-order Correlation</th>
<th>Partial Correlation</th>
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<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>.04</td>
<td>.026</td>
<td>.026</td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Oz Amplitude (VEP at 100ms, 2550 ISI)</td>
<td>.001</td>
<td>.243</td>
<td>.001</td>
</tr>
<tr>
<td>Fast ISI Left (VEP at PO3, 300 ISI)</td>
<td>.9*</td>
<td>-.053</td>
<td>.339</td>
</tr>
<tr>
<td>Fast ISI Right (VEP at PO4, 300 ISI)</td>
<td>-1.4*</td>
<td>-.267</td>
<td>-.467</td>
</tr>
<tr>
<td>Slow ISI Left (VEP at PO3, 1050 ISI)</td>
<td>-.733</td>
<td>.029</td>
<td>-.15</td>
</tr>
<tr>
<td>Slow ISI Right (VEP at PO4, 1050 ISI)</td>
<td>1.14*</td>
<td>-.037</td>
<td>.230</td>
</tr>
<tr>
<td>Slowest ISI Left (VEP at PO3, 2550 ISI)</td>
<td>.155</td>
<td>.1</td>
<td>.037</td>
</tr>
<tr>
<td>Slowest ISI Right (VEP at PO4, 2550 ISI)</td>
<td>-.319</td>
<td>.038</td>
<td>-.037</td>
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Table 3. Posthoc single subject analysis on High SPQ-D vs Low SPQ-D

<table>
<thead>
<tr>
<th>Group</th>
<th>2550 vs 300</th>
<th>2550 vs 1050</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Disorganization</td>
<td>13/14</td>
<td>11/14</td>
</tr>
<tr>
<td>High Disorganization</td>
<td>11/15</td>
<td>7/15</td>
</tr>
</tbody>
</table>
4.6. FIGURES

Figure 1. Main Regression – Scatter plot representing the relationship between the 7 ERP measures and schizotypy, as measured by total SPQ score, $R^2 = .28$, $p<.05$. 
Figure 2. Visualization of the adaptation effect - A median split on SPQ was employed to visualize the differential VEP adaptation based on schizotypy level. The effect of schizotypy can be seen in reduced amplitudes in the sample half containing the higher SPQ total scores and also the less sensitive ISI modulation (e.g. tighter VEP spread across the ISIs).
Figure 3. Exploratory analysis of visual adaptation in high Disorganization- Group waveforms were generated for individuals with frank "high" and "low" disorganization. A taxonomic approach was used to define high and low disorganization, thus VEPs represent the 'tails' of the SPQ-D distribution (high = more than 1SD above the mean for the entire sample, Low = more than 1 SD below the mean for the entire sample). VEPs in the high SPQ-D group show smaller amplitudes and less titrated ISI modulation.
Figure 4. SCP illustrating visual adaptation in high SPQ-D- Exploratory statistical cluster plots were generated to help quantify potential differences in adaptation between individual exhibiting frank high Disorganization (bottom) as compared to low disorganization (top). Both groups show successful VEP amplitude modulation, however the degree of adaptation varies based on SPQ-D, particularly when comparing between slow ISIs (right column) – a pattern similar to what has been observed by this group in schizophrenia patients.


CHAPTER 5

DISCUSSION
5.1. SUMMARY OF FINDINGS

The investigations comprising this dissertation examined the sensitivity and utility of visual adaptation measures obtained during a block-presentation paradigm while recording non-invasive scalp EEG.

AIM 1: In the first set of experiments (Chapter 2) we defined the spatio-temporal characteristics VEP adaptation to repetitive stimuli under different presentation rates in a sample of neurotypical adults. We also compared the VEP response profile in this paradigm to VEP modulation using a paired-presentation design. Robust VEP adaptation at the individual subject level was only obtained in the more taxing block-design. Further source localization analysis suggested a role for both local and long range visual adaptation ‘generators.’

AIM 2: In the second set of experiments (Chapter 3) we deployed the visual adaptation paradigm in a sample of participants diagnosed with schizophrenia-spectrum disorders and an additional set of neurotypicals. Here we noted classic early VEP amplitude attenuation in our patient sample and novel visual adaptation deficits were reveal. In the patient group lateral VEP modulation was less sensitive to ISI change than controls, particularly at lateral occipital sites at ~150ms and over central occipital scalp at 200ms. Curiously, Group x ISI effects were mostly driven by faulty VEP differentiation when comparing between slower ISIs (e.g. 2550 vs 1050ms ISIs). We also tested the specificity of this adaptation effect by examining somatosensory modulation in the same samples, using an almost identical block-design paradigm and vibrotactile stimulation of the median nerve over the right wrist. Differences in basic somatosensory function and adaptation between groups were noted, albeit less apparent than in the visual system. In this experiment altered somatosensory adaptation and reduced SEP amplitudes in the SCZ group reached statistical significance over frontal midline scalp (and not over central parietal scalp). Additionally, robust individual level effects were observed in the visual adaptation paradigm but not in the somatosensory experiment. Nonetheless, we conclude that adaptation deficits appear to be non-specific and call for further study of these processes in larger samples.

AIM 3: In the third experiment (Chapter 4) we examined whether altered visual adaptation could serve as a schizophrenia endophenotype. Here we utilized a shortened version of our visual adaptation paradigm
(15mins, 32-channel electrode array) to characterize a larger sample of neurotypical adults. All participants were rated on total, Cognitive-Perceptual, Interpersonal, and Disorganization domains of schizotypy using the Schizotypal Personality Questionnaire (self-report, (Raine, 1991)). Multiple regression analysis revealed a significant relationship between high SPQ and less sensitive VEP adaptation. The Disorganization domain of the SPQ appeared most associated with altered VEP adaptation, although this effect did not survive a correction for multiple comparisons. Nonetheless, we conducted an exploratory taxonomic investigation of VEP adaptation in high SPQ-D. When comparing a group scoring in the highest 15% of SPQ-D in our sample to the lowest 15% visual adaptation deficits which mirror the effects noted in the schizophrenia patients emerge (albeit much less extreme). Furthermore individual subject analyses on these participants follow the group level effects and suggest the potential sensitivity of this measure.

Overall the data provides strong support for atypical visual adaptation in schizophrenia and suggest a potential role for altered visual adaptation as an electrophysiological schizophrenia endophenotype. Ongoing work in the lab is focused on characterizing the relationship between specific glutamatergic schizophrenia-risk genes and visual adaptation. This line of research has the potential to strengthen the findings discussed above, offering mechanistic insights and an additional layer of shared heritability. Further study is needed to better characterize somatosensory adaptation in schizophrenia (e.g. larger samples) and to eliminate pharmacological confounds (e.g. smoking, antipsychotic treatment). Studies employing pharmacological manipulations (e.g. administering nicotinic treatment or dopamine/glu/gaba agonists) and examining first degree relatives of patients offer powerful tools capable of addressing aforementioned concerns.

5.2. A BROADER DISCUSSION

The study of endophenotypes can offer a window into neurodevelopmental mechanisms contributing to disease state. The characterization of sensory processing deficits can help corroborate
these mechanisms and offer potential treatment targets. It has also been suggested that a multivariate endophenotype approach, combing high sensitivity and high selectivity measures at different levels of characterization (e.g. electrophysiology, cognitive tests, environmental risk, etc), along with large sample sizes, would offer the greatest experimental insight towards understanding the course of schizophrenia (Braff, Freedman, Schork, & Gottesman, 2007; Cornblatt & Malhotra, 2001; Gur, Calkins, et al., 2007; Gur, Nimgaonkar, et al., 2007; Weiser, van Os, & Davidson, 2005).

However, with the low success rate in treatment of currently diagnosed individuals with schizophrenia – particularly in the realm of negative and cognitive symptoms (Erhart, Marder, & Carpenter, 2006; Leucht, Pitschel-Walz, Abraham, & Kissling, 1999; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009) – poor functional outcome even after recovery from acute symptoms (Green, 1996; Green, Kern, Braff, & Mintz, 2000; Meltzer, Thompson, Lee, & Ranjan, 1996), low quality of life (Malla & Payne, 2005; Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004), and stigma (Rossler, Salize, van Os, & Riecher-Rossler, 2005; Stuart & Arboleda-Florez, 2001) that arises from the disease state, certainly the ‘big picture’ goal lies in applying research knowledge gained towards an effort to identify risk and prevent initial conversion to schizophrenia. This raises two important questions: If identified, can we actually help individuals at risk? and Do people even want to know they are at risk? Available evidence is discussed that may help address each of these concerns.

Most “at-risk” studies – intervention and natural history – currently employ specific criteria for inclusion requiring (in some form) one or more of the following: 1. Attenuated distressing positive symptoms, 2. Genetic risk in the form of a first-degree relative with schizophrenia or a shared heritability disorder, and 3. Brief/intermittent presence of frank psychotic symptoms (Cornblatt et al., 2003; Miller et al., 1999; Yung & McGorry, 1996; Yung et al., 1998). Since participants are already manifesting overt cognitive or behavioral traits related to the disease state, are help-seeking and experiencing distress, coupled with the fact that most of these studies enroll teenagers and young adults, in some sense, they do not tap-in to true premorbid state. As such, it is possible that changes in the neurodevelopmental course leading up to a full-blown break are already well underway. Nonetheless, efforts have been made at testing interventions aimed at preventing conversion to schizophrenia in this population.
Pharmacological intervention studies using low dose antipsychotics have yielded difficult-to-interpret results. One study comparing risperidone plus cognitive-behavioral therapy (treatment group) to a more generic psychosocial support intervention (control group) showed significant differences in conversion rates during the 6 month period in which treatment was administered, with 3/31 (9.7%) in the drug treatment group and 10/28 (35.7%) in the control group going on to develop a psychotic disorder (McGorry et al., 2002). However, at a 12 month follow-up, 6 months after treatment cessation, 3 additional participants from the treatment group converted. A 3-4 year follow-up showed no significant differences in the groups in the probability of developing psychosis, current symptoms, or overall functioning (Phillips et al., 2007). It is important to note that even non-converters continued to experience distressing symptoms and either sought or received treatment during this time period.

The next of these studies employed a randomized double-blind placebo-controlled approach in testing the preventative power of olanzapine in high-risk participants over a 12 month period (McGlashan et al., 2006). At the end of the 12 month period during which active treatment was administered there were no significant differences in conversion between the groups, with rates of 5/31 (16.1%) in the treatment group and 11/29 (37.9%) in the control. In a small subset of participants (17 of the original 60) who took place in a 2 year follow-up during which no treatment was administered, no significant differences in conversion rates were noted, with 33% conversion rate in those originally in the treatment group.

### Table 1: Criteria for ultra-high risk syndromes of schizophrenic psychoses

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attenuated positive symptom syndrome</strong></td>
<td>Within the past year, attenuated (subclinical positive) but not frankly psychotic symptoms occurred.</td>
</tr>
<tr>
<td></td>
<td>Symptoms occurred at least once a week in the past month.</td>
</tr>
<tr>
<td><strong>Brief intermittent psychotic syndrome</strong></td>
<td>Brief, time-limited, frankly psychotic experiences occurred within the past 3 months.</td>
</tr>
<tr>
<td></td>
<td>The experiences do not meet DSM-IV criteria for psychotic disorders.</td>
</tr>
<tr>
<td></td>
<td>Symptoms occur for at least several (but not more than 60) minutes per day, up to 4 days per week.</td>
</tr>
<tr>
<td></td>
<td>Symptoms are not seriously disorganizing or dangerous.</td>
</tr>
<tr>
<td><strong>Genetic risk and recent deterioration syndrome</strong></td>
<td>Individual has either a schizotypal personality disorder or a first-degree relative with psychosis.</td>
</tr>
<tr>
<td></td>
<td>In the past year, function has been reduced by 30 points or more on the GAF scale for at least a month.</td>
</tr>
</tbody>
</table>

**DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; **GAF** = Global Assessment of Functioning.

Table 1. Originally published in (Addington, 2003) – provides guiding criteria for identifying individuals at risk for schizophrenia or conversion to psychosis.
group and 25% for the control. Strikingly, the treatment group also experienced a weight gain of nearly 20 lbs during the one year active phase of the study.

A randomized parallel-group study compared amisulpride plus a “needs-based” psychosocial treatment to the psychosocial treatment alone over the course of 12 weeks (Ruhrmann et al., 2007) and reported on symptom severity. They found the treatment group experienced significant reductions in prodromal and depressive symptoms, as well as improved global functioning. Side effects were also noted, with 81.8% of the treatment group experiencing increased prolactin levels (e.g. galactorrhoea) and overall slight but significant weight gain. An additional study assessing symptom severity found similar results when examining open-label aripiprazole for 8 weeks in significant symptom reduction as well as functional improvement (Woods et al., 2007). Side effects here included akathisia and slight weight gain.

Investigations are also underway examining the treatment efficacy of antidepressants in prodromal patients (Cornblatt et al., 2007; Fusar-Poli, Valmaggia, & McGuire, 2007; Walker et al., 2009). These open-label, more naturalistic studies report increased efficacy and compliance for antidepressants as compared to antipsychotics, as well as fewer side effects. These findings however are presented in the context of uncontrolled experiments with added caveats such as non-compliance contributing to increased conversion in participants treated with antipsychotics and more severe baseline symptoms in antipsychotic-treated converters as well. Nonetheless, increased functional improvement as well as symptomatic relief was noted with antidepressant treatment.

A handful studies have looked of non-pharmacological interventions. A randomized 6 month trial of cognitive therapy vs. standard treatment significantly reduced conversion rates at a 12 month follow-up (Morrison et al., 2004). This type of intervention was also associated with higher compliance rate/low dropout rates and significantly improved attenuated psychotic symptoms. About 50% of the original sample completed a follow-up at 3 years in which conversion rates were no longer significantly different between treatment groups, however those originally assigned to cognitive treatment showed a decreased likelihood of being treated with antipsychotics (Morrison et al., 2007). A separate randomized controlled trial compared cognitive-behavioral therapy to a counseling service over a 12 month period in improving symptom severity in 67 prodromal patients (Bechdolf et al., 2007). No significant differences were noted
between groups, yet both treatments were associated with improvements in global and social functioning. The authors do note a high-rate of participants lost to follow-up.

A final intervention of note concerns the use of omega 3 fish oils in symptom reduction and conversion prevention. A 12 weeks double-blind, randomized, placebo-controlled treatment study found a significantly smaller conversion rate at completion of active administration for an omega-3 fatty acid treatment group vs. placebo, 1/38 (2.6%) vs. 8/38 (21.1%) (Amminger et al., 2007). Significantly higher global assessment of functioning scores were associated with the treatment group and no serious side effects were noted. At a 12 month follow-up differences between the groups persisted, with 2 participants in the treatment group (5%) and 11 in the placebo group (29%) converting to a full clinical diagnosis (Amminger et al., 2010). Surprisingly, unlike in any of the antipsychotic studies, symptom improvements persisted and remained significantly better for the treatment as compared to the placebo group even at follow-up. Further, no side effects were reported in addition to high consent rates, as well as low dropout rates.

So can we help those currently being identified as being at risk? The answer depends on how help is being defined. A brief conclusion across the studies reviewed would suggest that antipsychotic treatment may be effective at reducing symptoms during active administration, but not successful at reducing conversion rates in the long run. Further, benefits experienced seem to dissipate with treatment cessation. One must also keep in mind the considerable side effects associated with these interventions and the notion that the drugs being tested in these samples have been not been FDA-approved for use in those under the age of 18 (Zito et al., 2003). On the other hand, emerging evidence suggests the potential for longer relief provided by antidepressants, psycho-social, even fish oils, with fewer side-effects. High treatment compliance and lower long-term dropout rates provide an additional layer of “real world” hope for these interventions.

Another important issue to be highlighted in these studies concerns the fact of simply being labeled “at risk” (Corcoran, Malaspina, & Hercher, 2005). Study enrollment and psychiatric treatment, whether successful or not, can affect how participants are perceived and treated by the community at large. Families may seek to shelter their perceived vulnerable child and limit opportunities for growth.
Practitioners may be quick to attribute oddities or quirks to latent disease traits. Self-perception, self-confidence, motivation, and aspirations may forever be changed in the putatively at risk individual. Additionally, the notion that conversion rates even among “ultra high risk” untreated samples ranges from 20-40% over 2 years introduces another layer of complication: falsely identifying true risk (Cadenhead, 2002; Cannon et al., 2008; Miller et al., 2003). And, as they say, you can’t un-ring the bell.

At this point it is worth reiterating that several of these concerns may be addressed by a better understanding of the disease mechanisms (Insel & Scolnick, 2006). If we can map the trajectory of schizophrenia – identifying critical wrong turns and when they occur – then we might be able to better identify risk and develop more successful biologically-based interventions. The identification of endophenotypes may prove pivotal in this regard. This should be viewed with somewhat cautious optimism though as clinically identified risk does provide the best predictive power for risk to conversion, 3-4 fold higher than the next best thing – familial history of the disorder (Cannon, 2008). Retrospective analysis using combined predictor models have been able to identify converters at higher rates using clinical plus cognitive traits (Yung, Phillips, Yuen, & McGorry, 2004); and other multivariate characterizations of the transition to psychosis are underway (Wood et al., 2004). Furthermore, given relatively low conversion rates, high dropout rates, and the inherently heterogeneous makeup of the population of interest, large scale collaborative studies will be needed to power investigations aimed at thoroughly tracking development and assessing treatment (Cannon, 2008).

But even if the field does get better at predicting risk, do individuals actually want to know whether or not they personally are at-risk? At its core the answer to this question is likely to be confounded by the existence of and access to adequate interventions. That said, two recent studies attempted to empirically address this question. Linscott and colleagues (Linscott & Cross, 2009) asked participants, who on a separate occasion also completed schizotypy assessments, to rate the anticipated impact of discovering their risk status for schizophrenia and six other diseases. They completed surveys rating anticipated felt distress, ability to cope, optimism, helplessness, affect on future lifestyle choices, and expected survival. Risk for schizophrenia was judged more negatively than risk for heart disease, arthritis, depression, and diabetes, but not worse than cancer or Alzheimer's disease. Additionally, fear of
stigma was significantly associated with perceived negative impact of risk-status awareness and higher schizotypy was related to an overall perception that risk-status awareness (regardless of disease) would be distressing.

As a recent follow-up, Alder and colleagues (Alder, Young, Russell, McHardy, & Linscott, 2013) sought to replicate these findings and also quantify the value of such anticipated reaction assessments in predicting actual reactive behavior. When asked to rate the potential impact of discovering at-risk status for schizophrenia, this sample rated schizophrenia-risk as being just as bad as cancer-risk. This negative outlook related to a strong stigma associated with schizophrenia, as well as a (false) confidence in the ability of a screen to confidently prevent future conversion. Furthermore, actual increased knowledge about schizophrenia or personal experience with psychiatric problems did not predict perceived burden of risk. This time investigators also asked whether participants, regardless of imagined perceived negative impact, would want to know their own personal risk status. Eighty-one percent of the sample indicated a preference for knowing. However, when presented with the option of undergoing risk-screening, asked “Taking part in this study may have prompted you to think about whether you are at risk for schizophrenia… Screening would be offered as a free confidential service and held at a time that is convenient to you… Information collected will not be disclosed … Would you like to arrange an appointment?”, only 11% agreed.

In the second phase of this study, participants provided a saliva sample and for a sham enzyme test, rigged to give positive results, and for which they were deceived into believing conferred a 10% risk of developing schizophrenia (or one of the other disorders being tested). This news created visible distress in several participants. Interestingly though, degree of distress in this study was most strongly predicted by the participant’s mental-health state (POMS- Profile of Mood States) prior to undergoing the sham test and their perceived locus of control over health (MHLC- Multidimensional Health Locus of Control). These findings suggested that the most vulnerable individuals were the most likely to react negatively to knowledge about being at-risk. They also underscore an important point—that most individuals, regardless of anticipated burden or indicated preference for wanting to know their risk-status, did not show a desire to follow through with risk assessment.
What can be concluded from these studies about the desire to identify self-risk? Perhaps not much as participants in these samples were only deceived into believing themselves to be at risk for a total of 20 minutes. Nonetheless the discrepancy between endorsing a preference for knowing risk (81%) and actually following through with testing (11%) is telling. A real-life analog to this finding relates to the development of genetic testing for Huntington’s disease. Whereas initial surveys of at-risk individuals indicated that 60-80% were interested in genetic testing, upon actual availability of the test in three centers across the Northeast only 13 of an estimated 1500 at-risk in the catchment area actually underwent complete testing (Corcoran et al., 2005; Wexler, 1995). To add to the comparison, large scale assessments of individuals electing to undergo genetic testing for Huntington’s have shown extreme negative reactions to receiving an at-risk diagnosis, with suicide being among these (Almqvist, Bloch, Brinkman, Craufurd, & Hayden, 1999). Certainly the motivations behind testing for risk will impact reactions, as well as current quality of life or distress, and again, so will available treatment options. It is hard to compare between college students asking to imagine reactions, those receiving an at-risk label for 20 minutes as part of testing that was prompted by a research study, reactions upon detection for a fatal neurodegenerative disease for which even those testing positive will likely not be under any current distress and the factors surrounding someone interested in schizophrenia testing. The early “true onset” (i.e. premorbid difficulties), the slow transition to the clinical phenotype, the likely access to personal knowledge of the difficulties associated with recovering from a psychotic break, and the low guarantee of conversion (i.e. 50% even in monozygotic twins) may help weigh a decision towards greater education about one’s own risk. These might also all make an individual better equipped to handle news of being at-risk, because at each of these features also lies a potential opportunity for rescue. And therein lies the imperative to continue research aimed at understanding the neurodevelopment and the pathophysiological mechanisms of schizophrenia.
5.3. FINAL THOUGHT

In the grand scheme, the experiments making up this dissertation do not even equate to a drop in the bucket. However, the bucket is certainly worth filling. My close contact with and first-hand knowledge of the debilitating and seemingly hopeless nature of this disorder for the individual affected as well as their families - acquired through interactions with my own family and study volunteers - continues to fuel my desire to contribute to the field. I wish I could do more.
5.4. REFERENCES


CHAPTER 6
APPENDIX

ATYPICAL MULTISENSORY INTEGRATION IN NIEMANN-PICK TYPE C DISEASE -- TOWARDS POTENTIAL BIOMARKERS

Reprinted from Andrade GN, Molholm S, Butler JS, Brandwein AB, Walkley SU, Foxe JJ. Atypical multisensory integration in Niemann-Pick Type C disease -- towards potential biomarkers, Orphanet Journal of Rare Diseases, 2015, 9 (149).
ABSTRACT

Background: Niemann-Pick type-C (NPC) is an autosomal recessive disease in which cholesterol and glycosphingolipids accumulate in lysosomes due to aberrant cell-transport mechanisms. It is characterized by progressive and ultimately terminal neurological disease, but both pre-clinical studies and direct human trials are underway to test the safety and efficacy of cholesterol clearing compounds, with good success already observed in animal models. Key to assessing the effectiveness of interventions in patients, however, is the development of objective neurobiological outcome measures. Multisensory integration mechanisms present as an excellent candidate since they necessarily rely on the fidelity of long-range neural connections between the respective sensory cortices (e.g. the auditory and visual systems).

Methods: A simple way to test integrity of the multisensory system is to ask whether individuals respond faster to the occurrence of a bisensory event than they do to the occurrence of either of the unisensory constituents alone. Here, we presented simple auditory, visual, and audio-visual stimuli in random sequence. Participants responded as fast as possible with a button push. One 11-year-old and two 14-year-old boys with NPC participated in the experiment and their results were compared to those of 35 age-matched neurotypical boys.

Results: Reaction times (RTs) to the stimuli when presented simultaneously were significantly faster than when they were presented alone in the neurotypical children, a facilitation that could not be accounted for by probability summation, as evidenced by violation of the so-called 'race' model. In stark contrast, the NPC boys showed no such speeding, despite the fact that their unisensory RTs fell within the distribution of RTs observed in the neurotypicals.

Conclusions: These results uncover a previously undescribed deficit in multisensory integrative abilities in NPC, with implications for ongoing treatment of the clinical symptoms of these children. They also suggest that multisensory processes may represent a good candidate biomarker against which to test the efficacy of therapeutic interventions.

Keywords: Race model, neurodegeneration, NPC1, NPC2, lysosomal disease, Cross-modal, rare disease, Sensory Processing, Audio-visual, Sensory Integration.
6.1. INTRODUCTION

Niemann-Pick type C (NPC) disease is a rare progressive lysosomal storage disorder caused by mutations in either the \( \text{NPC1} \) or \( \text{NPC2} \) gene, with about 95% of cases attributable to the former (Vanier, Duthel, Rodriguez-Lafrasse, Pentchev, & Carstea, 1996; Vanier & Suzuki, 1998). Individuals with NPC cannot properly metabolize cholesterol and other lipids which accumulate in the brain and in visceral organs (e.g. liver and spleen), ultimately causing cell dysfunction and organ system failure. Although NPC1 and NPC2 proteins are expressed ubiquitously, brain tissue is the most severely affected, resulting in widespread intraneuronal storage of cholesterol and glycosphingolipids that ultimately results in massive neurodegeneration (Mengel et al., 2013; Vanier, 1983, 1999; Zervas, Dobrenis, & Walkley, 2001). While appearing relatively typical during the early stages of the disease, over time NPC children develop vertical gaze palsy, motor system impairment, learning difficulties and clumsiness, as well as seizures (Garver et al., 2007; Patterson et al., 2012; Wraith et al., 2009). Documented changes in brain include ectopic dendrite growth, altered synaptic connectivity affecting cortical pyramidal neurons, axonal degeneration, myelin loss, gliosis and the formation of neurofibrillary tangles similar to Alzheimer's disease (Liu et al., 2009; Walkley & Suzuki, 2004). Neuronal death is prominent in some brain regions such as the cerebellum where Purkinje cells selectively die, undoubtedly contributing to the clinically-evident motor system dysfunction (Sarna et al., 2003; Walkley & Suzuki, 2004; Zervas et al., 2001). Effective treatments are limited, although promising clinical trials are underway based on results in animal models of NPC (Aql et al., 2011; Davidson et al., 2009; Liu et al., 2009).

Key to advancing new treatments for this and related lysosomal diseases with neural involvement is the development of objective biomarkers of neurological function against which the efficacy of new drugs can be tested in human patients. Our work and that of others has demonstrated the essential role that multisensory integration (MSI) plays in typical perception and cognition (Bair, Kiemel, Jeka, & Clark, 2007; Foxe, 2009; Foxe et al., 2013; Foxe & Schroeder, 2005; Molholm, Martinez, Shpaner, & Foxe, 2007; Molholm, Ritter, Javitt, & Foxe, 2004; Molholm et al., 2002; Ross et al., 2011; Ross, Saint-Amour, Leavitt, Javitt, & Foxe, 2007; Stein & Meredith, 1990). Because inputs from the various senses (e.g., the auditory, visual and somatosensory systems) initially arrive into widely separated regions of the neocortex, MSI must involve ongoing communication between relatively far-flung cortical regions,
although it may well be initiated even earlier in the hierarchy within nuclei of the thalamus (Cappe, Rouiller, & Barone, 2012). In this sense, probing multisensory functioning provides an excellent assay of inter-regional communication, and the fidelity of the multisensory system must at least in part be a function of the integrity of long-range neural connectivity. For this reason we expected measures of MSI to provide a sensitive metric of neural dysfunction in NPC disease. What's more, MSI processes show a prolonged period of neuroplasticity, with continued development of these abilities seen into the late teenage years (Brandwein et al., 2011; Ross et al., 2011). As such, measures of MSI may provide useful biomarkers against which to test the impact of treatment on brain function.

A straightforward way to measure multisensory integration is to compare reaction times (RT) to unisensory and multisensory events during a simple speeded response task. It has been firmly established that adults react more quickly to multisensory than unisensory inputs (Harrington & Peck, 1998; Hughes, Reuter-Lorenz, Nozawa, & Fendrich, 1994; Maravita, Bolognini, Bricolo, Marzi, & Savazzi, 2008; Molholm et al., 2002; Murray et al., 2005). For such behavioral facilitation to be unequivocally attributed to multisensory integration, this speeding up must exceed what is predicted due to the mere presence of a redundant signal (i.e. two inputs). That is, when two stimulus copies are presented simultaneously, even if both were to be processed entirely independently in the brain, one would still expect to see a speeding up of responses since there is increased likelihood that either of the two stimuli will yield a fast reaction-time relative to just one input. This is often referred to as the Redundant Signals Effect (RSE), and its presence does not, of itself, necessarily point to integration effects. The so-called "race model" is applied to test for the presence of true multisensory effects, by assessing whether responses to multisensory inputs are faster than the fastest possible responses produced by the unisensory conditions (Miller, 1982, 1986; Ulrich, Miller, & Schroter, 2007). This is achieved by comparing the probabilities of making fast responses during multisensory events to those during unisensory events. The race model is said to be violated whenever the cumulative probability (CP) of a response at a given latency for the multisensory condition is greater than the sum of the CPs from each of the unisensory conditions. When the race model is violated, it is taken to be a strong indication that the inputs from the two different senses are interacting (in a non-additive way) to produce the speeding of the responses. Work from our laboratory suggests that this metric of MSI RT-speeding follows a developmental
trajectory, with little evidence for behavioral enhancement before age 9, but that near full maturity is reached by age 16 (Brandwein et al., 2013; Brandwein et al., 2011). Moreover, in these developmental studies, behavioral performance was shown to benefit from MSI at the single participant level for 95% of neurotypical participants aged 11-16, and 100% of participants aged 13-16. This relatively protracted developmental trajectory of MSI behavioral facilitation is consistently seen across laboratories (Gori, Del Viva, Sandini, & Burr, 2008; Nardini, Jones, Bedford, & Braddick, 2008). Here we used this behavioral approach to assay multisensory function in three boys with NPC -- two adolescents (14 years, 7 months & 14 years, 5 months old) and one younger boy (11 years, 1 month) -- comparing their performance to that of 16 neurotypical adolescent boys aged 13-15, and 19 neurotypical boys aged 10-13, respectively.
6.2. METHODS

Participants

Two adolescent boys with NPC (14 years, 7 months & 14 years, 5 months of age respectively) and one 11 year old boy with NPC (11 years, 1 month) participated in the study. NPC was clinically diagnosed by metabolic specialists and confirmed via genetic testing. Participants were administered the Wechsler Abbreviated Scales of Intelligence (WASI-II) and Full Scale IQ (FSIQ). Verbal Comprehension Index (VCI), and Perceptual Reasoning Index (PRI) scores were also obtained. The three NPC patients were within the mild to moderately impaired range and moderately to severely impaired range (Patient 1: FSIQ= 76, VCI= 82, PRI= 74; Patient 2: FSIQ= 62, VCI= 69, PRI= 58; Patient 3: FSIQ= 63, VCI= 72, PRI= 56). Scores on each subtest of the WASI-II are detailed in Table 1. The two older patients exhibited mild high-frequency hearing loss and one of the older patients as well as the younger one had lower than average visual acuity. It is important to emphasize that both auditory and visual stimuli used in the experiment were well above their detectability thresholds. The reader is referred to Box 1 entitled “Clinical Impressions” for more comprehensive phenotypic descriptions of each of the three NPC participants.

Thirty-five neurotypical boys also participated in this study. Sixteen adolescent boys aged 13-15 served as an age-matched control group for the two older patients. Nineteen boys aged 10-12 served as an age-matched control group for the younger patient. Participants were screened for neurological and psychiatric disorders, as well as other major medical conditions. These data were partially reported in a pair of previous studies (Brandwein et al., 2013; Brandwein et al., 2011). Participants were also administered the WASI-II and Full Scale IQ (FSIQ), Verbal Comprehension Index (VCI), and Perceptual Reasoning Index (PRI) scores were obtained, which for these groups were in the average or high average range (Older group mean (standard deviation - SD): FSIQ= 113 (12), VCI= 104 (14), PRI= 110 (12); Younger group: FSIQ= 113 (14), VCI= 108 (12), PRI= 113 (13)). Audiometric evaluation confirmed that all participants had within-normal-limits hearing thresholds. All participants had normal or corrected-to-normal vision.

Before entering into the study, informed written consent was obtained from the children’s parents, and verbal or written assent was obtained from children. All procedures were approved by the Institutional
Review Board at The Albert Einstein College of Medicine and were in accordance with the tenets for the responsible conduct of human research laid out in the Declaration of Helsinki.

Paradigm & Task

Stimuli

Auditory Alone

A 1000-Hz tone (duration 60 ms; 75 dB SPL; rise/fall time 5 ms) was presented from a single Hartman Multimedia JBL Duet speaker located centrally atop the computer monitor from which the visual stimulus was presented.

Visual Alone

A red disc with a diameter of 3.2 cm (subtending 1.5° in diameter at a viewing distance of 122 cm) appearing on a black background was presented on a Liquid Crystal Display (LCD) monitor (Dell Ultrasharp 1704FTP, 60Hz refresh rate) for 60 ms. The disc was located 0.4 cm superior to central fixation along the vertical meridian (0.9° at a viewing distance of 122 cm). A small cross marked the point of central fixation on the monitor.

Auditory and Visual Simultaneous

The “auditory-alone” and “visual-alone” conditions described above were presented simultaneously. The auditory and visual stimuli were presented in close spatial proximity, with the speaker placed atop the monitor in vertical alignment with the visual stimulus.

Procedures

Participants were seated in a dimly lit, sound-attenuated electrically shielded room (Industrial Acoustics Company, Bronx, New York) 122 cm from the monitor. They were given a response pad (Logitech Wingman Precision) and instructed to press a button with their right thumb as quickly as possible when they saw the red circle, heard the tone, or saw the circle and heard the tone together. The same response
key was used for all 3 stimulus types. Presentation software (Neurobehavioral Systems, Inc., Albany CA) was used for stimulus delivery. This software ensures precise timing of stimulus presentation and is commonly used in neuroscience, psychophysics, and psychological experiments. It takes into account the refresh rate of the computer monitor when presenting visual stimuli. In this experiment, stimulus delivery in the multisensory condition was triggered by the onset of the visual stimulus. All 3 stimulus types were presented with equal probability and in random order in blocks of 100 trials. Inter-stimulus-interval (ISI) varied randomly between 1000 and 3000 (ms) according to a uniform (square wave) distribution. Participants completed a minimum of 8 blocks, with most completing 10. Breaks were encouraged between blocks to help maintain concentration and reduce restlessness or fatigue (these methods are also presented in detail in Brandwein et al (Brandwein et al., 2013; Brandwein et al., 2011) and Molholm et al (Molholm et al., 2002)).

Interrogating the Race Model

To test the race model, we first calculated the cumulative probability of reaction times across the three stimulus types (audio-alone, visual-alone, and audio-visual) for each of the participants. The range of RTs accepted was determined at the individual participant level with the slowest and fastest 2.5% of trials excluded. Using a 95% cutoff to define the time window for acceptable trials rather than an absolute cutoff value allowed us to more accurately capture the range of RTs for each participant, an important factor in calculating the race model (described below). The RT distribution was then divided into quantiles from the 5th to the 100th percentile in increments of 5%. For any RT latency, t, the race model holds when this CP value is less than or equal to the sum of the CP from each of the unisensory conditions. Conversely, the race-model is said to be violated if the CP for any audiovisual RT latency is larger than that predicted by the race model (the sum of the unisensory CPs) at any quantile. Violations were expected to occur in the first third of the distribution (i.e. the quantiles containing the fastest RTs at the lower end of the RT range) because this is when interactions between visual and auditory inputs would result in the fulfillment of a response criterion before either input alone could satisfy the same criterion (Miller, 1982). At the individual level, a participant was said to have shown race model violation if the CP of his RT to the audiovisual
stimulus was larger than that predicted by the race model at any quantile within the first third of the distribution. In order to more easily interpret results from the race model test, a Miller inequality value can be computed, both at the individual and group levels, by subtracting the CP predicted by the race model from the CP of the multisensory condition. Any positive "Miller values" indicate race model violation and RT speeding that cannot be accounted for by probability summation or by the ‘redundant signals effect’. 
6.3. RESULTS

Behavioral Performance - Reaction Times & Hit Rates

The neurotypical group had a higher percentage of hits (correctly pressing the button to stimulus presentations) than the NPC participants. Hit rates are presented in Table 2. The current report was primarily concerned with the speed of responding. Overall, neurotypical participants were faster than the NPC patients (Table 3 and Figure 1). In order to examine RT variability independent of mean RT differences between the groups and between experimental conditions, the coefficient of variation (CV) was calculated for auditory, visual, and audiovisual conditions for each individual participant. The CV for the older patients fell within the neurotypical distribution or overlapped with individual neurotypical outliers. The CV for the younger patient fell outside (but close) to the neurotypical distribution; however there were also younger neurotypical controls that were more variable than this younger patient (see supplemental materials for details). What's more, in both neurotypical age-groups, variability was greatest for the auditory condition and did not differ significantly between the two other conditions. Observationally, the CV for individual NPC patients did not appear to differ substantially across experimental conditions. Nonparametric tests revealed no significant differences in RT variability based on stimulus type. Thus, increased variability in the multisensory condition should not affect the race model analysis presented below (for a discussion see (Otto & Mamassian, 2012) ). Detailed analyses and figures related to CV are provided in supplementary materials.

A repeated measures ANOVA revealed a significant effect of stimulus type on RTs for both the older F (2, 30) = 12.1, \( p < .001 \) and younger F(2, 36) = 91.4, \( p < .001 \) neurotypical groups. Follow-up protected t-tests confirm a speeding up of RTs for the multisensory condition for the older neurotypical group \( (\text{Audio vs. AV} - t(15)= 3.4, \ p < .01; \ \text{Visual vs. AV} - t(15)= 5.0, \ p < .01; \ \text{Audio vs. Visual} - t(15)= -.31, \ p = .76) \) and for the younger neurotypical group \( (\text{Audio vs. AV} - t(18)= 10.4, \ p < .01, \ \text{Visual vs. AV} - t(18)=12.4, \ p < .01) \). Additionally, the younger group had significantly faster RTs to the auditory condition as compared to the visual condition, \( t(18)= -3.1, \ p < .01 \).

As our NPC sample contained only 3 participants, we performed a nonparametric bootstrapping procedure at the level of the individual participant data to compare RTs across the three sensory
conditions (Figure 2). For each NPC patient, we compared the RTs in each of the unisensory conditions against the multisensory RTs, as well as against each other. The observed differences in mean RT between Audio vs. AV, Visual vs. AV, and Audio vs. Visual were compared with reference distributions of differences that were derived by iteratively randomizing (10,000 times) between the two original RT distributions - i.e. individual-subject single trial RTs for 1) Audio and AV, 2) Visual and AV, and 3) Audio and Visual. A two-tailed threshold of \( p < 0.05 \) was used to define significance. The \( p \) value for a randomization test was calculated from the proportion of values in the reference difference distribution that exceeded the actual observed difference. In other words, we created a randomized sample distribution of possible reaction time differences, and sought to determine the likelihood that the actually observed differences (either speeding up or slowing down) were due to chance. There was no significant difference between auditory and visual RTs for the older NPC participants. The younger participant (Participant 3) showed significantly faster RTs in the visual condition compared to the auditory (\( p = 0.015 \)). A significant speeding up was noted in the multisensory condition relative to the visual condition (\( p < 0.01 \)), but not the auditory condition, for Participant 1. This was likely driven by the response to the auditory stimulus as the speeding up is only significant in the AV vs. V comparison. A significant speeding up was noted in the multisensory condition relative to the auditory condition (\( p < 0.05 \)), but not the visual condition, for Participant 3. Again, this was likely driven by the response to the visual stimulus as the speeding up is only significant in the AV vs. A comparison. A significant speeding up in the multisensory condition compared to both unisensory conditions (\( p \)'s < .01) was noted for Participant 2, indicating the presence of a Redundant Signals Effect. These tests, however, do not take into account facilitation due to multisensory interactions, which will be tested below using the race model calculation.

If motor difficulties alone were to account for the larger variance in RTs and lower hit rates in the NPC participants, one would expect these to occur at the same probability across all three experimental conditions, which is not the case in this sample. Deficits in motor response do not account for the differential effect noted in 2 of the patients across the unisensory and multisensory conditions. The two NPC adolescents had faster RTs and a higher percentage of hits in the multisensory conditions compared to the unisensory. To probe the nature of this speeding up and assess whether the patients may be benefitting from an integrative process, we applied a test for multisensory integration effects (i.e. testing
the race model). In this test a within-individual analysis is employed, thus accommodating the between group differences already noted.

**Multisensory Integration Effects - Race Model**

None of the three NPC participants showed any evidence of race model violation. Although in some cases, they showed faster RTs in the audiovisual condition (see above), this was not greater than could be accounted for by simple probability summation. In stark contrast, all of the neurotypical adolescents in our older sample of 13-15 year olds showed individual-level race model violation, suggesting that in this age group, multisensory integration reliably improves behavioral performance under these conditions. For the 11 year old NPC patient, an additional cutoff criterion was applied to his RT data before computing the race model. Unlike the rest of our sample, even after excluding the fastest 2.5% of RTs, this participant still had several anticipatory RTs that would be physiologically impossible (i.e. response latencies in the 40-100 ms range). These anticipatory responses were evenly distributed across all stimulus conditions (12% of the Audio trials, 13.5% Visual trials, and 10% of the AV trials). In order to eliminate any button presses that weren't directly in response to the stimulus, a hard cutoff criteria of 150ms was employed in his case, as it is generally agreed upon that shorter response latencies indicate actions that were initiated before the stimulus onset (Brebner & Welford, 1980; Fieandt, Huhtala, Kullberg, & Saarl, 1956; Galton, 1899; Jevas & Yan, 2001; Welford, 1977, 1980, 1988). In the younger sample of 10-12 year olds, 16 of the 19 participants showed individual-level race model violation. Figure 3 depicts the CP distributions of reaction times for each of the experimental conditions -- audio-alone (blue), visual-alone (green), audiovisual (red), and the race model prediction (using the sum of the CPs of the unisensory responses (teal). Data for the three NPC boys are depicted across the top row. Across the middle row, data from three neurotypical individuals whose RT variability closely matched that of the NPC children are plotted for comparison. Despite similar RT variance, each of these neurotypicals shows race model violation. The bottom row shows data from an additional three neurotypical boys, where RT mean has been matched to each of the NPC boys. Again, all 3 neurotypicals show clear race model violation.
Figure 4A & 4C depict plots of "Miller inequality" values which were obtained by subtracting the CP predicted by the race model from the CP for the multisensory condition. Positive values represent race model violation. Here it can be seen that the traces representing the two older NPC participants (4A - red) are never positive, whereas the trace representing the older neurotypical controls (blue) is positive for the quantiles representing the fastest ~30% of RTs. The shape of this Miller inequality function for neurotypical controls is highly similar to those reported in similar studies examining audio-visual integration (Brandwein et al., 2013; Brandwein et al., 2011). The Miller inequality plot for the younger neurotypical controls (Figure 4C - blue) closely approximates the pattern seen in the older children, albeit more immature. In the younger NPC participant, no race model violation is noted and the shape of his Miller inequality plot has the same atypical pattern noted in the two older NPC participants. Figure 4B & 4D depict box and whisker plots, which offer an additional representation of these data. Here the box and whiskers (blue rectangles with black bars) represent the Miller inequality values for all of the participants in the neurotypical group for the first six quantiles, which is the section of the RT distribution containing the fastest responses and also where race model violations are expected and seen in the neurotypical group (shaded area in Figure 4A & 4C). The small red shapes (squares and circles) represent the Miller inequality values for each NPC participant at these quantiles. This plot clearly shows that all three NPC boys fall completely outside the normal distribution between the second and sixth quantiles (10th, 15th, 20th, 25th, and 30th percentiles). Although race model violation is seen from the first quantile onward for the neurotypical participants, it is not necessarily seen for all participants at the exact same quantiles. That is to say that some participants will show race violation sooner than others and some will continue to show race model violation for several quantiles while the effect for others will dissipate more quickly. These effects, however, are generally seen in first third of the CP distribution as interactions between auditory and visual stimuli are likely to occur during these shorter latencies and so here we focus on the first 5 quantiles of this distribution. Further, we note that multisensory facilitation, as evidenced by race model violation (i.e. Miller inequality value greater than 0) was noted at the individual participants level for all 16 of the 13-15 year old neurotypical controls. For the 10-12 year olds, an age in which multisensory integration is still emerging and somewhat immature (Barutchu, Crewther, & Crewther, 2009; Nardini, Begus, & Mareschal, 2013), individual-level race model violation was seen for 16 out of 19 (84%)
neurotypical controls. The NPC participants, on the other hand, failed to violate the race model at any point along the CP distribution. This lack of race model violation is especially striking for the older NPC participants as mean RT values for these NPC participants fall well within the neurotypical distribution in the case of one of the NPC patients, and overlaps with neurotypical outliers for the other patient (Figure 1A). This suggests a true multisensory deficit in that AV gains are accounted for by probability summation and there are no clear overall unisensory deficits contributing to this finding. For the younger participant, this is harder to say as his mean RTs for the auditory and the AV conditions fall slightly outside the neurotypical distribution. Nonetheless, the gains noted in his case can be adequately explained without evoking multisensory interactions as they are no greater than that predicted by probability summation.
6.4. DISCUSSION

To our knowledge, this is the first study to examine multisensory processes in NPC. The observed lack of race model violation in NPC suggests compromised connectivity between auditory and visual areas of the brain, possibly at both sub-cortical and cortical levels. It is likely that these inter-sensory connections develop very early in life, strengthen across childhood, and stabilize during adolescence (Brandwein et al., 2013; Brandwein et al., 2011; Wallace, Carriere, Perrault, Vaughan, & Stein, 2006; Wallace & Stein, 2007). Understanding when exactly during the progression of NPC that MSI becomes compromised will require further investigation and will be crucial to maximizing the clinical usefulness of this measure in the NPC population. Two possible scenarios are that; 1) MSI-induced behavioral facilitation never quite reaches "healthy" levels in these individuals or 2) that like many of the other symptoms exhibited in this population, NPC patients experience a degradation of MSI function with progression of the disease state. In either case, this metric of MSI presents a behavioral marker against which to measure improved neurocognitive function due to experimental treatment interventions.

In terms of everyday functioning, an obvious question is what impact deficits in multisensory processing will have on the abilities of NPC children to effectively navigate their environment. For example, effective MSI leads to improved speech perception when a listener has the benefit of watching the facial articulations of a speaker, especially if the fidelity of the auditory input is affected by noisy background environmental conditions (Foxe et al., 2013; Ma, Zhou, Ross, Foxe, & Parra, 2009; Ross et al., 2011; Ross et al., 2007; Saint-Amour, De Sanctis, Molholm, Ritter, & Foxe, 2007). Thus, one implication is that these children may find communication more difficult in challenging multi-speaker scenarios, not uncommon in classrooms or other social settings. MSI is also vital to more basic functions, such as maintaining balance through visuo-vestibular and visual-somatosensory integration (Bair et al., 2007) and in speeded orienting to reliable multisensory events, whether it be for object identification or cueing initiation of approach/avoidance behaviors (Foxe, 2009; Foxe & Schroeder, 2005; Molholm et al., 2007; Molholm et al., 2004; Molholm et al., 2002; Stein & Meredith, 1990). A more comprehensive understanding of the multisensory integration abilities of these children is clearly called for, and it will be
of significant interest to assess the underlying neurophysiology in turn (Foxe et al., 2000; Foxe et al., 2002).

Another obvious outcome of the current study is that the NPC children show basic motor deficits. While it is true that there are neurotypical participants who are as slow to respond to unisensory inputs, and others who show similarly high variance in RTs, no neurotypical children show the poor response rates we see in the NPC children. Simply put, the NPC children are slow, variable and inaccurate and this triumvirate of issues clearly points to fundamental sensory-motor issues. That said, we do not believe that the MSI deficits observed here are primarily due to these issues, since these issues apply equally to all the experimental conditions (both unisensory and multisensory; also see supplementary materials). As the race model analysis is conducted at the individual participant level, where the cumulative probability distributions are calculated for each participant and within-subject RTs are compared to determine the multisensory benefit, general motor delays are accounted for. It could reasonably be asked, though, whether simple tests of motor speed, variance and accuracy might not prove equally useful biomarkers for NPC. However, it bears re-emphasizing that while the NPC children do show these issues, their performance levels do not fall completely outside the normal distribution for these measures, whereas for the measures of multisensory integration, they clearly do.

It is worth pointing out that these children with NPC are, at some basic level, benefitting from multisensory stimulation, even if not in an integrative manner. The fact that mean RTs and hits are improved in some cases, even in the absence of significant multisensory integration, when patients are exposed to stimulation in two sensory streams is promising, especially in terms of sensory training. This may have implications for the development of assistive technologies used for communication, particularly during the more progressed phases of the disease.

A natural question that arises is whether the multisensory deficit we observe in NPC can be meaningfully impacted through intervention. The landscape is actually quite promising in this regard since several studies now point to multisensory and unisensory gain with repeated training. These studies show that training can lead to improvement in MSI-dependent tasks such as speech-perception (Bernstein, Auer,
Eberhardt, & Jiang, 2013), that training can narrow the time window during which two sensory inputs are seen as "synchronous" and thus integrated (Powers, Hevey, & Wallace, 2012), and that MSI networks can be engaged and enhanced in training activities where abstract stimuli are paired, such as specific sounds with abstract shapes, or musical tones with symbols (Butler & James, 2013; Paraskevopoulos, Kuchenbuch, Herholz, & Pantev, 2014). Work in animal models also supports the notion that sensory integration abilities can be impacted through practice with training-induced multisensory enhancement noted in both behavior and activity patterns at the single cell level in the superior colliculus, in both juvenile (Stein & Rowland, 2011) and adult cats (Yu, Rowland, Xu, & Stein, 2013).

An obvious limitation of the current work is the relatively small cohort of three patients with NPC that we were able to test. Ideally, one would like to have greater numbers. However, the disease prevalence rate for NPC is estimated at 1-in-120,000 (Mengel et al., 2013; Patterson et al., 2012; Vanier, 2010), so recruitment of larger populations is extremely challenging. It is worth emphasizing that the atypical multisensory integration pattern noted here is highly consistent across the 3 NPC patients in our sample and the findings are strengthened by comparison of these 3 patients to large existing datasets of neurotypical age-matched children. In all 3 cases, the performance metrics of the NPC patients fall completely outside the "normative" curve for MSI development.

CONCLUSIONS

This study uncovered clear multisensory deficits in three patients with NPC. The simple-to-acquire measures of multisensory response speed described here may prove to be useful endpoints against which to track disease progression and to assess the efficacy of therapeutic interventions. Specific environmental accommodations should be considered to address the potential impact of deteriorating multisensory mechanisms in these children.

Acknowledgements

We extend our deep appreciation to the families involved in this research for their time, patience, and care. The Human Clinical Phenotyping Core, where the children in this study were clinically evaluated, is
a facility of the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center (IDDRC) which is funded through a center grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD P30 HD071593). Ongoing support of the Cognitive Neurophysiology Laboratory is provided through a grant from the Sheryl and Daniel R. Tishman Charitable Foundation. Support for this work was provided in part by the Support of Accelerated Research of NPC Disease foundation (SOAR-NPC). We thank Greg Peters and Emmett Foxe for assistance with data collection and Drs. Juliana Bates and Zonya Mitchell for help with clinical testing.

**Author Contributions**

GA, SM, SUW and JJJF conceived the study. GA and ABB coordinated data collection. JSB and GA conducted the primary data analyses. GA wrote the initial draft of the paper and all authors provided multiple rounds of input during the editorial process. The senior author, JJJF, attests that all authors had full access to the data and that each author saw and approved the final submitted version of this manuscript. All authors declare no conflicts of interest, financial or otherwise, that could have impacted the work reported herein.
6.5. CLINICAL IMPRESSIONS

Box 1. Clinical Impressions

The Wechsler Abbreviated Scale of Intelligence (WASI-II) is a short and reliable measure of intelligence that assesses general intellectual functioning. All four subtests were used: Vocabulary, Block Design, Similarities, and Matrix Reasoning. Vocabulary measures the individual’s expressive vocabulary, verbal knowledge, and fund of information. Block Design measures spatial visualization, visual-motor coordination, and abstract conceptualization. The Similarities subtest measures verbal concept formation, abstract verbal reasoning ability, and general intellectual ability. Matrix Reasoning measures non-verbal fluid reasoning and general intellectual ability. Scores are reported as a Verbal Comprehension Index (VCI), a Perceptual Reasoning Index (PRI), and a Full Scale Intelligence Quotient (FSIQ), which represents performance on all 4 subtests.

NPC - PARTICIPANT 1

Participant 1 is a 14 year 8 month old adolescent boy, who was evaluated 3 months after his participation in our behavioral study. He was diagnosed with NPC in 2005 and is currently on the following medications: Zavesca (miglustat), Depakote (divalproex sodium), Keppra (levetiracetam), and Coumadin (warfarin). He has a history of seizures onsetting at age 14. Parental reports indicate clumsiness and unclear speech, which were also observed in the lab. The participant currently receives occupational and speech therapy. He is home-schooled due to the frequency of his seizures. A routine hearing screen performed at the lab revealed mild high frequency hearing loss (i.e. 4,000 Hz tones were not detected at <60 dB & 2,000 Hz tones were not detected at <45 dB). A routine vision screen (Snellen chart) revealed 20/20 and 20/30 visual acuity, in the right and left eyes respectively.

Overall intellectual functioning, as measured by the Full Scale IQ on the WASI-II, was estimated in the mild to moderately impaired range (FSIQ= 76). His Verbal Comprehension Index score fell in the mildly impaired range (VCI=82) and was somewhat higher than his Perceptual Reasoning Index score which fell in the mild to moderately impaired range (PRI=74); however this difference was not statistically significant. The examiner noted that on several trials of the Block Design subtests of the PRI, the participant was able to reproduce the modeled design, however with a 90° rotation. The examiner noted that the participant performed much better when verbal items called for short succinct answers. This likely contributed to his higher Similarities score, as several of the relationships probed by the subtest can be addressed with one word explanations, as compared to the Vocabulary subtest which requires a more lengthy, developed explanation. Further, the examiner notes that speech was effortful and may have affected performance, with the current scores underestimating the participant’s true abilities. The examiner also noted that the participant appeared fatigued and yawned frequently towards the end of the testing session.
**Box 1. Cont. Clinical Impressions**

**NPC -PARTICIPANT 2**

Participant 2 is a 14 year 10 month old adolescent boy, who was evaluated 3 months after his participation in our behavioral study. He was diagnosed with NPC in 2005; this patient has a I1061T and M1142T mutation on exons 21 and 22. He is currently on the following medications: Trileptal (oxcarbazepine) and Zavesca (miglustat). He has a history of seizures with the last seizure occurring 10 months prior to testing. The participant currently receives occupational therapy, speech therapy, and has a 1:1 aide at school. A routine hearing screen performed at the lab revealed mild high frequency hearing loss (i.e. 4,000 Hz tones were not detected at <60 dB). A routine vision screen (Snellen chart) revealed 20/60 visual acuity in both eyes.

Overall intellectual functioning, as measured by the Full Scale IQ on the WASI-II, was estimated in the *moderately impaired* range (FSIQ= 62). His Verbal Comprehension Index score was in the *mild to moderately impaired* range (VCI=69) and somewhat higher than his Perceptual Reasoning Index score which fell in the *moderately to severely impaired* range (PRI=58); however, this difference was not statistically significant. The examiner observed that the participant had motor difficulties when manipulating the blocks used in one of the PRI subtests (*Block Design*). Poor articulation was noted at times, but this was not believed to have interfered with testing.

**NPC -PARTICIPANT 3**

Participant 3 is an 11 year 1 month old boy, who was evaluated on the same day as his participation in our behavioral study. He was diagnosed with NPC in 2013. He is currently on the following medications: Keppra (levetiracetam) and Zavesca (miglustat). He has a history of seizures, including a 4 day hospitalization due to seizure-like activity. He has suffered a concussion that did not render him unconscious. The participant currently receives occupational therapy and academic help with reading and math in a specialized classroom setting at school. Normal hearing was confirmed through a routine hearing screen performed at the lab. A routine vision screen (Snellen chart) revealed 20/50 and 20/30 visual acuity, in the right and left eyes respectively.

Overall intellectual functioning, as measured by the Full Scale IQ on the WASI-II, was estimated in the *moderately impaired* range (FSIQ= 63). His Verbal Comprehension Index score fell in the *mild to moderately impaired* range (VCI=72) and was significantly higher than his Perceptual Reasoning Index score which fell in the *moderately to severely impaired* range (PRI=56). The examiner noted that the participant had much difficulty with *Block Design* subtest of the PRI, often asking whether the designs presented to him were ‘even possible’. On the *Matrix Reasoning* subtest of the PRI, the participant could not correctly answer any of items at or beyond the starting point for his age and testing here was quickly discontinued. The examiner notes that the participant was pleasant, friendly, and cooperative testing session.
6.6. TABLES

Table 1. Wechsler Abbreviated Scale of Intelligence scores

<table>
<thead>
<tr>
<th>Wechsler Abbreviated Scale of Intelligence (WASI-II)</th>
<th>NPC Participant 1</th>
<th>NPC Participant 2</th>
<th>NPC Participant 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FULL SCALE IQ (FSIQ)</strong></td>
<td>76 (5%)</td>
<td>62 (1%)</td>
<td>63 (1%)</td>
</tr>
<tr>
<td><strong>Verbal Comprehension Index (VCI)</strong></td>
<td>82 (12%)</td>
<td>69 (2%)</td>
<td>72 (3%)</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>29</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>Similarities</td>
<td>49</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td><strong>Perceptual Reasoning Index (PRI)</strong></td>
<td>74 (4%)</td>
<td>58 (0.3%)</td>
<td>56 (0.2%)</td>
</tr>
<tr>
<td>Block Design</td>
<td>32</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Matrix Reasoning</td>
<td>36</td>
<td>25</td>
<td>21</td>
</tr>
</tbody>
</table>

IQs are standard scores, with a range of 50-160, mean = 100, SD = 15. Corresponding percentile ranks are in parenthesis. Subtests scores (Block Design, Vocabulary, Matrix Reasoning, and Similarities) are T-scores, with a range of 20-80, mean = 50, and SD = 10.

Table 2. Hit Rates

<table>
<thead>
<tr>
<th></th>
<th>Auditory</th>
<th>Visual</th>
<th>Audio-visual</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPC Participant 1</td>
<td>59%</td>
<td>60%</td>
<td>62%</td>
</tr>
<tr>
<td>NPC Participant 2</td>
<td>78%</td>
<td>73%</td>
<td>83%</td>
</tr>
<tr>
<td>NPC Participant 3</td>
<td>57%</td>
<td>63%</td>
<td>68%</td>
</tr>
<tr>
<td><strong>Older Neurotypicals</strong> (13-15 years old; N=16)</td>
<td>92% (3)</td>
<td>91% (4)*</td>
<td>93% (2)*</td>
</tr>
<tr>
<td><strong>Younger Neurotypicals</strong> (10-12 years old; N=19)</td>
<td>91% (4)*</td>
<td>88% (6)*</td>
<td>91% (4)*</td>
</tr>
</tbody>
</table>

*Hit rates are depicted as a percentage reflecting correct responses divided by total number of stimuli presented, with the standard deviations in parenthesis for the neurotypical group data. For the NPC participants hit rates is a within subject value and therefore has no SD.
Table 3. Reaction Times

<table>
<thead>
<tr>
<th></th>
<th>Auditory</th>
<th>Visual</th>
<th>Audio-visual</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPC Participant 1</td>
<td>416 (218)</td>
<td>426 (156)</td>
<td>387 (168)</td>
</tr>
<tr>
<td>NPC Participant 2</td>
<td>555 (282)</td>
<td>545 (277)</td>
<td>472 (225)</td>
</tr>
<tr>
<td>NPC Participant 3</td>
<td>749 (440)</td>
<td>680 (374)</td>
<td>643 (397)</td>
</tr>
<tr>
<td>Older Neurotypicals (13-15 years old; N=16)</td>
<td>379 (95)*</td>
<td>381 (93)*</td>
<td>348 (79)*</td>
</tr>
<tr>
<td>Younger Neurotypicals (10-12 years old; N=19)</td>
<td>390 (109)*</td>
<td>404 (109)*</td>
<td>341 (102)*</td>
</tr>
</tbody>
</table>

*Reaction times are given in milliseconds with the standard deviations in parenthesis. For the NPC participants the SD reflect a within subject value. For the neurotypicals the SD is computed on the group mean.
6.7. FIGURES

Figure 1. Box and whisker plots show the distributions of mean RT values for 13-15 year olds (Panel A) and for 10-12 year olds (Panel B), for the two unisensory (Audio and Visual) and the multisensory (Audiovisual) conditions. The red symbols represent the mean RT values for each of the Niemann-Pick Type C participants and the black crosses represent mean RT values for individual outliers from the neurotypical groups.
Figure 2. Nonparametric randomization plots are depicted for the individual-participant reaction time data for each of the Niemann-Pick Type C patients. RTs in each of the unisensory conditions were compared against the multisensory RTs (middle and right columns), and against each other (left column). The observed differences in mean RT between Audio vs. AV, Visual vs. AV, and Audio vs. Visual (red line) were compared with reference distributions of differences that were derived by iteratively randomizing (10,000 times) between the two original data sets (i.e. individual-subject single trial RTs for 1) Audio and AV, 2) Visual and AV, and 3) Audio and Visual). Significant differences (p < .05) are indicated by an asterisk. The findings are mixed. In two of the three patients, any apparent multisensory speeding is not significantly faster than the faster of the two unisensory responses. However, in one of the patients (Participant 2), RTs to the AV condition are significantly faster compared to both unisensory inputs. This particular patient is showing strong evidence for the so-called redundant sensory effect, but this speeding does not violate the race model.
Figure 3. Cumulative reaction time (RT) probability distributions are shown for the three Niemann-Pick Type C patients (top row). These are compared to those of six neurotypical boys. The three age-matched comparison subjects depicted along the middle are chosen for their highly similar RT variance. The bottom row depicts three age-matched controls chosen for their highly similar mean RTs to those of the NPC boys. In the case of all six neurotypical controls, the observed cumulative RT distribution to the multisensory audio-visual condition (red curve) is faster than the prediction of the race model (cyan curve), indicating race model violation (i.e. multisensory integration). In none of the three NPC cases is this pattern observed.
Figure 4. A & C). Race model plots depict the Miller value for the neurotypical groups (blue curves) and the Niemann-Pick Type C patients (red curves). Values above zero indicate race model violation, which are evident in both the older neurotypicals (N=16; Panel A) and the younger neurotypicals (N=19; Panel B), but not in the NPC patients. The shape of the Miller inequality plot observed in the NPC patients is highly atypical and consistent across all three patients. B & D). Box and Whisker plots depict the spread of Miller values for the first 6 RT quantiles for the neurotypical group and the single subject Miller values for each of the NPC adolescents (red circles and red squares). This plot depicts the spread of Miller values for approximately 99% of both neurotypical groups, with the box representing 50% of the data, the whiskers representing the top 25 and bottom 25 percent, and the horizontal bisecting line representing the median Miller value for each neurotypical group at that quantile. It can be seen that all three NPC patients (red shapes) fall outside of the distribution of Miller values for their age-matched neurotypical group. Multisensory facilitation at the individual participant level was noted in all 16 of the 13-15 year olds and in 16 of 19 of the 11-12 year old neurotypicals.
6.8. REFERENCES


study. [Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. J Neurophysiol, 88(1), 540-543.

Galton, F. (1899). On instruments for (1) testing perception of differences of tint and for (2) determining reaction time. Journal of the Anthropological Institute, 19, 27-29.


6.9. SUPPLEMENTARY MATERIALS

Variability Analysis

We calculated the coefficient of variation (CV) for RTs for each individual in each of the three sensory conditions. Mean and standard deviation of the CV are presented for both neurotypical groups below, along with the individual values for the three NPC patients. We also provide a boxplot figure depicting the spread of the CV for the neurotypical groups along with the CV values for the individual NPC patients. We see that the CV for the older patients either falls within the neurotypical distribution or overlaps with individual neurotypical outliers. The CV for the younger patient falls outside (but close) to the neurotypical distribution; however there were also younger neurotypical controls that were more variable than this patient.

Interestingly, the plots also suggest that, RT variability was smallest in the multisensory condition. For the neurotypical groups we formally tested this using a repeated measures ANOVA which revealed a significant effect of stimulus type on CV for the older (F (2, 30) = 9.71, p = .001) and younger (F(2, 36) = 19.58, p < .001) neurotypical groups. Follow-up protected t-tests show significantly higher variability, as measured by the coefficient of variation, for the auditory condition only for the older neurotypical group (Audio vs. Visual - t(15)= 3.7, p = .002; Audio vs. AV - t(15)= 3.46, p = .004; Visual vs. AV - t(15)= 1.2, p = .24) and as well as the younger neurotypical group (Audio vs. Visual - t(18)= 4.41, p < .001, Audio vs. AV - t(18)=5.28, p < .001, Visual vs. AV - t(18)= .74, p= .47). To reiterate, we didn't observe any evidence of "increased noise" in the multisensory RTs.

As our NPC sample contained only 3 participants, we are unable to conduct the same set of analyses for the patients. However, visual inspection of the coefficient of variation spread plots show that the older NPC boys seem to follow the same pattern observed in the neurotypical controls. Both of the older boys show the highest variation in RTs in the auditory condition, as with no obvious increase in CV in the multisensory condition. The younger NPC participant does not appear to follow this trend. To better understand CV across the three sensory conditions in this small sample we employed a nonparametric test. A Related-Samples Friedman ANOVA by ranks test on the NPC patient data (treating them as a
single group, N=3) showed no significant difference in the coefficient of variation between the three experimental conditions (p .44). This is a reassuring finding and seemingly in line with the individual patient data, however this is an N of 3 sample and clearly more work needs to be done before the relationship between 'noise,' variability, and multisensory facilitation is understood in this population. For a discussion on the role of noise in MSI see (Barutchu, Crewther, & Crewther, 2009; Otto & Mamassian, 2012; Senkowski, Saint-Amour, Hofle, & Foxe, 2011).

**Supplementary Table 1.** Coefficient of Variation

<table>
<thead>
<tr>
<th></th>
<th>Auditory</th>
<th>Visual</th>
<th>Audio-visual</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPC Participant 1</td>
<td>.53</td>
<td>.37</td>
<td>.43</td>
</tr>
<tr>
<td>NPC Participant 2</td>
<td>.51</td>
<td>.51</td>
<td>.48</td>
</tr>
<tr>
<td>NPC Participant 3</td>
<td>.59</td>
<td>.55</td>
<td>.62</td>
</tr>
<tr>
<td>Older Neurotypicals</td>
<td>.29 (.14)</td>
<td>.24 (.12)</td>
<td>.23 (.15)</td>
</tr>
<tr>
<td>(13-15 years old;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger Neurotypicals</td>
<td>.36 (.15)</td>
<td>.29 (.19)</td>
<td>.28 (.14)</td>
</tr>
<tr>
<td>(10-12 years old;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=19)</td>
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</tbody>
</table>
Supplementary Figure 1. Coefficient of Variation Spread. Box and whisker plots show the distributions of the coefficient of variation values for 13-15 year olds (Panel A) and for 10-12 year olds (Panel B), for the two unisensory (Audio and Visual) and the multisensory (Audiovisual) conditions. The red symbols represent the CV values for each of the Niemann-Pick Type C participants and the blue crosses represent mean RT values for individual outliers from the neurotypical groups.

REFERENCES

