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Electrophysiological Quantitative Traits and Associations with Cognitive and Functional Outcomes in Typical Development and Early-Onset Psychosis

Author

Owens, Emily M

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Electrophysiological Quantitative Traits and Associations with Cognitive and Functional Outcomes in Typical Development and Early-Onset Psychosis

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

by

Emily Owens

2018

ABSTRACT OF THE DISSERTATION

Electrophysiological Quantitative Traits and
Associations with Cognitive and Functional Outcomes
in Typical Development and Early-Onset Psychosis

by

Emily Owens
Doctor of Philosophy in Psychology
University of California, Los Angeles, 2018
Professor Carrie E. Bearden, Co-Chair
Professor Cindy M. Yee-Bradbury, Co-Chair

Schizophrenia is a biologically complex disorder usually characterized by a decline in cognition and functioning. Current medications do not improve cognition and functioning, thus there is an effort to create a more targeted, objective approach for understanding the relationship between neurobiological and psychological changes in order to facilitate treatment development. I reviewed these methods, termed “quantitative traits”, and discussed their usefulness in neurobiological and genetic research. I then tested whether some measurements of brain activity,

measured using electroencephalography, in response to auditory and visual stimuli were associated with performance on cognitive tests and general functioning in typically developing individuals and in adolescents with schizophrenia. I found that improved processing of auditory stimuli predicted improvements in auditory memory and functioning in healthy individuals. I also found that adolescents with schizophrenia showed impairments in processing auditory and visual stimuli relative to typically developing individuals, and these impairments were related to symptom severity. This research will help us to understand how quantitative measures of brain activity are related to cognition and functioning in schizophrenia, which may lead to a clearer understanding of the biological mechanisms involved in each, and eventual improvements in treatment and outcomes.

The dissertation of Emily Owens is approved.

Robert F. Asarnow

Adriana Galván

Sandra Kan Loo

Carrie E. Bearden, Committee Chair

Cindy M. Yee-Bradbury, Committee Co-Chair

University of California, Los Angeles

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TABLE OF CONTENTS

I. Acknowledgements…….vii

II. Vita……...…….viii

III. General Background…….1

IV. Chapter One: A Review of Electrophysiological Endophenotypes in Schizophrenia…15

V. Chapter Two: Typical Development of Mismatch Negativity and its Association with Cognitive and Functional Outcomes.
…….……...….46

i. Introduction…….…….48

ii. Methods……...….62

iii. Results……..……...….69

iv. Discussion……...….70

VI. Chapter Three: Mismatch Negativity and LTP-like Neural Patterns in Adolescent-Onset Psychosis and Typically Developing Controls.
…….……...….85

i. Introduction……..……...….88

ii. Methods…….....….105

iii. Results……..…….….115

iv. Discussion……..……..…….….118

VII. General Discussion……..……...…..138

VIII. References……...…..145

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I received funding from a UCLA Graduate Division Dissertation Year Fellowship and a NSF Graduate Research Fellowship.

VITA

Education

2012-Present	**University of California, Los Angeles** Ph.D. in Clinical Psychology, Quantitative minor, expected June 2018 Dissertation title: *Electrophysiological biomarkers as correlates and predictors of cognitive and community functioning in adolescent-onset psychosis and typical development.* Dissertation defense: March 8, 2018 Dissertation Chairs: Carrie Bearden, Ph.D., Cindy Yee-Bradbury, Ph.D. GPA: 3.97
2012-2014	**University of California, Los Angeles** M.A. in Clinical Psychology Master's Thesis: *Catechol-O-Methyltransferase and stress as moderators of P50 gating in healthy individuals and patients with schizophrenia.* Advisors: Cindy Yee-Bradbury, Ph.D., Keith Nuechterlein, Ph.D. GPA: 3.97
2008-2012	**University of Kansas** B.S. in Behavioral Neuroscience with Highest Honors Minor: Social and Behavioral Sciences Methodology Honors Thesis: *Difficulties in planning among MS patients: A relative consequence of deficits in information processing speed.* Advisor: Douglas R. Denney, Ph.D. GPA: 4.00

Honors and Awards

2016-2017	*Dissertation Year Fellowship, UCLA*
2016	*Edwin W. Pauley Fellowship, UCLA*
2012-2016	*National Science Foundation Graduate Research Fellow*
2013	*Graduate Summer Research Mentorship Award, UCLA*
2012	Distinguished University Fellowship, UCLA
2012	*Psychology Senior Outstanding Performance Award, KU*
2011-2012	*Undergraduate Research Award, KU*
2011	UCLA Summer Program for Undergraduate Research Fellow; Association for Graduate Excellence and Professoriate
2008 – 2012	Watkins-Berger Scholar, KU
2009; 2011	College of Liberal Arts and Sciences Scholarship, KU

Scholarly Contributions

Publications:

Accepted: Bearden, C.E., Eckfeld, A.S., & **Owens, E.M**. The Psychosis Spectrum in Adolescence. In *Textbook of Mental and Behavioral Disorders in Adolescence*. (pp. 269-291).

Hamilton, H. K., Williams, T. J., Ventura, J., Jasperse, L. J., **Owens, E. M.,** Miller, G. A., Subotnik, K. L., Nuechterlein, K. H., & Yee, C. M. (In Press). Clinical and cognitive significance of auditory sensory processing deficits in schizophrenia. *The American Journal of Psychiatry*.

Herts, K., Loerinc, A., **Owens, E.,** & Keenan-Miller, D. (2017). A Model for Competency-Based Supervision Training. *The California Psychologist, 50*(4)*,* 40-41.

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Denney, D. R., Hughes, A. J., **Owens, E. M.,** & Lynch, S. G. (2012). Deficits in planning time but not performance in patients with multiple sclerosis. *Archives of Clinical Neuropsychology, 27*(2)*,* 148-58.

Research Presentations:

Owens, E.M. (2017). *Borderline personality disorder and co-morbid substance use disorders.* Presentation at the West Los Angeles VA weekly Substance Use Disorders Psychiatry seminar.

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GENERAL BACKGROUND

Schizophrenia is one of the leading causes of disability in the world (Murray & Lopez, 1997). In 2013, the economic burden of schizophrenia in the U.S. was estimated at $155.7 billion (Cloutier et al., 2016). Much of the monetary cost (76%) associated with schizophrenia comes from indirect costs from functional impairment, including unemployment (38%) and productivity loss due to caregiving (34%; Cloutier et al., 2016). One of the most important contributors to functional impairment in schizophrenia is cognitive dysfunction (Evans, 2004; Fett et al., 2011; Green, Kern, Braff, & Mintz, 2000; Nuechterlein et al., 2011). Cognitive dysfunction is a core feature of schizophrenia, as described in early characterizations of the illness by Emil Kraepelin (Kraepelin, 1919; "dementia praecox") and is not addressed by current medications for psychotic illness. Research must focus on understanding contributions to cognitive dysfunction and functional impairment in order to develop more targeted interventions for schizophrenia.

The Research Domain Criteria (RDoC) initiative is an attempt to link symptom constructs of psychiatric problems to pathophysiologic mechanisms using dimensional measures (Cuthbert, 2014; Cuthbert & Insel, 2013; Kozak & Cuthbert, 2016). The RDoC takes a translational approach to further biological understanding of intermediate psychological constructs in order to yield "biopsychological" explanations of clinical symptoms (Kozak & Cutherbert, 2016). The emphasis of the RDoC is on examining smaller, narrower sub-constructs of psychological problems (relative to *DSM* diagnoses) in order to match genetic and neuroscience phenomena to psychological phenomena with the hopes of developing more effective pharmacological or targeted, behavioral

treatments (Yee, Javitt & Miller, 2015). The difficulty with linking genetic liability to clinical symptoms highlights the need to apply the RDoC approach to schizophrenia.

It is now well established that schizophrenia is largely a genetic disorder, with an estimated 80% heritability (Sullivan, Kendler & Neale, 2003). Genome-wide association studies have found multiple genetic variants that are associated with increased risk for schizophrenia (Ripke et al., 2013; Sekar et al., 2016), but the complexity of genetic liability and its interactions with environmental components obscures the links between genes and clinical symptoms. Thus, there is need for additional quantitative measures that can link genetic contributions and symptomatology. Prior to the development of the RDoC framework, the primary conceptual framework for understanding this link was that of endophenotypes. An endophenotype is a variable that lies in the causal pathway between genotype and symptom constellation (Gottesman & Gould, 2003; Gould & Gottesman, 2006). It has been traditionally defined as a quantitative measure that is: (1) heritable; (2) associated with illness; (3) mostly independent of clinical state; (4) impairment in the measure co-segregates with illness within a family; and (5) yields reproducible measurements (Gershon & Goldin, 1986; Gottesman & Gould, 2003; Leboyer et al., 1998; Lenox, Gould, & Manji, 2002). It was initially thought that endophenotypes would be a way to investigate genetic liability using a trait that is genetically more tractable than a clinical syndrome (Gottesman & Gould, 2003; Gould & Gottesman, 2006), however, the results of many studies attempting to identify specific genetic variants for schizophrenia endophenotypes have been largely underwhelming (e.g., Minnesota Twin and Family Studies; Iacono, 2014). Thus, it appears that endophenotypes may not be appreciably less genetically complex than their syndrome

counterparts (Iacono, 2014), but may still be closer to the underlying disease biology (Bearden & Freimer, 2006; Flint, Timpson & Munafò, 2014). The RDoC initiative aligns closely with the principles of endophenotypes, but removes the assumption of a causal chain ending in a *DSM* clinical category and incorporates psychological processes with biological (Yee, Javitt & Miller, 2015). Thus, the RDoC initiative and endophenotype concept share the goal of uncovering a set of more mechanistically-based quantitative traits that will yield new understanding of schizophrenia pathophysiology, thereby leading to novel intervention and prevention strategies (Bearden & Fromer, 2006; Cannon & Keller, 2006).

The RDoC approach is well-positioned to investigate dysfunction in neural connectivity and neuroplasticity (Yee, Javitt & Miller, 2015), both of which have been identified to be key factors in schizophrenia pathophysiology (Goto, Yang, & Otani, 2010; Stephan, Baldeweg, & Friston, 2006). Neuroplasticity refers to the brain's ability to change in response to environmental input, demands, and learning (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). It allows the brain to learn and remember patterns, refine movements, obtain rewards, and recover function after an injury (Feldman, 2009). Synaptic plasticity, one type of neuroplasticity, is the adjustment of synaptic strength in networks of connected neurons, including short-term plasticity, long-term potentiation (LTP) and long-term depression (LTD; Citri & Malenka, 2008). Long-lasting changes in the activity within a neural circuit is the result of LTP, and is considered to be the primary mechanism for storing new information, or learning and memory (Citri & Malenka, 2008; Feldman, 2009). Recently, impaired synaptic plasticity has been proposed as a primary driver of cognitive deficits in schizophrenia (Forsyth & Lewis,

2017). Support for this theory comes from emerging evidence that suggests impaired N-methyl-D-aspartate (NMDA) receptor circuitry is involved in the pathophysiology of schizophrenia (Michie, Malmierca, Harms, & Todd, 2016). This was initially proposed when it was shown that antagonists of NMDA receptors (NMDARs), such as ketamine and phencyclidine, produce transient psychotomimetic effects and neurocognitive deficits in healthy adults similar to those observed in patients with schizophrenia (Adler, Malhotra, Elman, Goldberg, & Egan, 2014; Domino, Mirzoyan, & Tsukada, 2004). Post-mortem studies showing broad and robust reduction in dendritic spine density in individuals with schizophrenia (Glausier & Lewis, 2013) and genetic ablation studies in rodents (Belforte et al., 2010) have added to the evidence for disrupted synaptic plasticity in schizophrenia. Research on the genetic architecture of schizophrenia has also revealed that the disorder is associated with risk variants in genes involved in synaptic plasticity (Kirov et al., 2012; Marshall et al., 2017; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Synaptic plasticity has also been proposed to play a role in the pathophysiology of schizophrenia (Forsyth & Lewis, 2017). Specifically, it is theorized that impaired synaptic plasticity initially disrupts refinement of local sensory and motor circuits, leading to the subtle deficits in sensory and motor function seen in early development of individuals who later develop schizophrenia (Brockhaus-Dumke et al., 2008; Erlenmeyer-Kimling et al., 2000; Schreiber, Stolz-Born, Kornhuber, & Born, 1992). This initial disruption then may induce early deficits in learning and memory (Cannon et al., 2002; Murray et al., 2006; Seidman et al., 2006), which may then compound into robust deficits in higher-level cognitive functions (e.g., verbal memory recall, planning, behavioral inhibition) seen later in development

(Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Heinrichs, 2005; Heinrichs & Zakzanis, 1998; Keefe & Harvey, 2012) and finally the onset of psychotic symptoms. These robust alterations may be the result of disrupted functional integration of populations of neurons, cortical areas, and subareas that is required for adaptive sensorimotor and cognitive processes (Andreasen et al., 1999; Friston, 1998; Hoffman & McGlashan, 2001). Thus, the onset of positive symptoms of schizophrenia in adolescence/young adulthood is increasingly viewed as a 'late stage' of the disorder (McGorry, 2013) that is the result of earlier disrupted neurodevelopmental processes such as impaired synaptic plasticity. Dimensional measures of neurobiological traits that can clarify possible impairments in synaptic plasticity in schizophrenia may help to further establish this pathophysiologic pathway.

An electrophysiological quantitative trait of schizophrenia that appears related to synaptic plasticity as well as cognitive and functional outcomes is the Mismatch Negativity (MMN). Within the RDoC Matrix, the MMN is a physiological measure in the Cognitive Systems domain under the sub-construct of Auditory Perception (www.nimh.nih.gov/research-priorities/rdoc/). The MMN is elicited when a sequence of identical auditory stimuli is interrupted infrequently by a stimulus that is deviant along one or more dimensions, such as pitch, duration, or intensity (Näätänen et al., 2012). It is thought to be an automatic, objective index of auditory sensory memory functioning, often referred to as "echoic memory" (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989) which refers to the ability of the brain to briefly retain representations of the physical features of auditory stimuli (Javitt, Steinschneider, Schroeder, & Arezzo, 1996). In fact, MMN is the first physiologically measurable brain response that differentiates

deviant from standard stimuli (Näätänen et al., 1989). A large body of research has characterized the MMN and shown that it is impaired in schizophrenia (d = ~1.0; Umbricht & Krljes, 2005; Erickson, Ruffle, & Gold, 2015). Reduced MMN amplitude has been associated with reduced social functioning (Kawakubo et al., 2007; Light & Braff, 2005a), social cognition (Wynn, Horan, Kring, Simons, & Green, 2010a), and global functioning (Light & Braff, 2005b) in schizophrenia. In addition to functioning, MMN has also been associated with verbal memory deficits (Baldeweg, Klugman, Gruzelier, & Hirsch, 2002; 2004) and executive functioning (Kiang, Kutas, Light, & Braff, 2007) in patients with schizophrenia. The mechanisms involved in these associations remain unclear; Light, Swerdlow & Braff (2007) hypothesize that:

> "Efficiency at elementary levels of information processing may underlie the successful encoding, retrieval and discrimination of relevant information, which in turn facilitates the iterative and responsive processing necessary for adaptive cognitive and social functioning."

In other words, if there is a disruption in an "upstream", elementary process of auditory sensory functioning, this will eventually cause or contribute to downstream impairments in broader aspects of cognition and community functioning. Given the relationships with functional outcomes in schizophrenia, a large body of research has attempted to understand the specific processes that lead to disrupted MMN. Most notably, the generation of the MMN has been posited to be associated with glutamatergic NMDA receptor hypofunction given that pharmacological antagonists of NMDARs decrease or abolish the MMN (Javitt et al., 1996; Strelnikov, 2007; Umbricht, Schmid, Koller, Vollenweider, Hell, & Javitt, 2000) and agonists may improve the MMN as well as

clinical symptoms of schizophrenia (Kantrowitz et al., 2018). MMN impairments are also associated with other core pathophysiologic dysfunction in schizophrenia, including sensory processing deficits, hypoactivation of the prefrontal cortex (PFC), and disrupted temporal-PFC connectivity (Gaebler et al., 2015). Given its relationship to "upstream" neurobiological components of schizophrenia (NMDAR functioning), as well as "downstream" consequences of schizophrenia (cognitive deficits, global and social functioning), MMN has been hailed as a "breakthrough biomarker" for understanding psychosis (Light & Näätänen, 2013; Näätänen, Shiga, Asano, & Yabe, 2015). In fact, MMN has recently shown success in predicting conversion to psychosis among high-risk individuals (Bodatsch et al., 2011; Shaikh et al., 2012; Perez et al., 2014). While these developments are helpful in understanding the relationships between *disrupted* MMN, cognition, and functional outcomes in psychosis, it remains unclear whether or how MMN is related to cognitive and functional outcome in healthy individuals. In other words, it is unclear whether the associations between MMN and cognition and functioning in psychosis are due to indexing of *disorder-specific* properties (i.e., disrupted NMDAR signaling), or whether MMN can generally predict individual variability in functional outcome. Understanding these relationships in healthy controls is an important step towards clarifying the role of MMN as a dimensional, neurobiological trait that can clarify the pathophysiology of schizophrenia.

One factor that may influence the associations between MMN, cognition and functioning in schizophrenia is the role of neurodevelopmental processes. Given that schizophrenia has typical onset in late adolescence/early adulthood, this question becomes particularly important when considering ability of MMN to predict clinical

outcomes in high-risk individuals (Bodatsch et al., 2011; Shaikh et al., 2012; Perez et al., 2014). Discoveries in developmental neuroscience demonstrate that adolescence and young adulthood involves periods of dramatic neural growth and reorganization (Durston et al., 2006; Paus, 2005). This maturation includes processes such as accelerated pruning of neuronal synapses (Giedd, Blumenthal & Jeffries et al., 1999; Gogtay et al., 2004; Sowell et al., 2003) and increased myelination of axonal connections (Giedd, 2008; Lenroot & Giedd, 2006; Uda et al., 2015), ultimately supporting faster neural transmission and greater efficiency in critical neural pathways (Paus et al., 2008; Stevens, 2009). Accordingly, adolescence is also a time of considerable development in cognitive functions (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Somerville & Casey, 2010; Tamm, Menon, & Reiss, 2002). It is hypothesized that cognitive development during this period is the result of ongoing maturation of neural systems, particularly the prefrontal cortex and its involvement in top-down regulatory control (Goldman-Rakic, 1987; Luna et al., 2001; Somerville & Casey, 2010). Given that the MMN likely changes with development of sensory and cognitive processing abilities (Ponton et al., 2000), it is important to understand the typical developmental trajectory of the MMN; however, existing studies yield conflicting results, and many are characterized by small sample sizes or group comparisons averaging across large age ranges. Thus, the typical developmental trajectory of MMN during adolescence and young adulthood remains unclear.

A relatively recent electrophysiological measure may lead to improved understanding of the role of cortical synaptic plasticity in schizophrenia. While synaptic plasticity in the hippocampus has been studied extensively (Bliss & Collingridge, 1993;

Bliss & Gardner-Medwin, 1973; Bliss & Lomo, 1973), evidence for cortical synaptic plasticity has been found within the PFC in animal models (see Goto et al., 2010 for a review) as well as LTP-like changes in the PFC in human studies (e.g., Nitsche et al., 2009). Additional evidence has been established in visual, auditory, and somatosensory cortices in animal models (Ganguly & Poo, 2013; Kim, Chun, Kim, Mook-Jung, & Jung, 2003; Yin et al., 2009). LTP has traditionally been studied in animals by presenting a high-frequency electrical stimulation to a field of neurons and measuring changes in cellular currents with single-cell of local field recordings. Electroencephalography (EEG) studies now indicate that repetitive presentation of visual or auditory stimuli provides a naturalistic and validated method of inducing LTP in humans and animals (Clapp, Eckert, Teyler, & Abraham, 2006; Cooke & Bear, 2010; Forsyth, Bachman, Mathalon, Roach, & Asarnow, 2015). Using this EEG method, high-frequency repetitive presentation of stimuli (high-frequency stimulation; HFS) modulates sensory evoked potentials that result from postsynaptic potentials in populations of cortical neurons (Forsyth et al., 2015). This modulation of sensory-evoked potentials is interpreted to be the result of LTP (Forsyth et al., 2015; Kirk et al., 2010; Teyler et al., 2005) and further research has shown that this process is disrupted in schizophrenia (Cavus et al., 2012; Mears & Spencer, 2012). Specifically, for healthy controls, sensory-evoked potentials from visual or auditory stimuli are augmented after high frequency presentation of the same stimulus; this augmentation is not seen in either sensory modality in adults with schizophrenia (Cavus et al., 2012; Mears & Spencer, 2012). Additional research has shown that this augmentation is related to NMDAR functioning (Clapp et al., 2006; Forsyth et al., 2015; 2017). However, it is unclear whether neural responses from this paradigm are related to

cognition or functioning in schizophrenia and/or in healthy individuals, and additional replication studies are needed. Continued investigation into this paradigm is a promising path for understanding neurobiological dysfunction in this disorder and may yield another useful dimensional trait for understanding schizophrenia.

Given the aforementioned importance of neurodevelopmental processes for outcomes in schizophrenia, age of onset of illness is a critical consideration. Most of the research on schizophrenia is conducted on individuals whose onset of full psychosis began in early-adulthood; however, approximately 18% of schizophrenia patients experience initial onset of psychosis prior to age 18 (Häfner, Maurer, Löffler, & Riecher-Rössler, 1993; Schimmelmann, Conus, Cotton, McGorry, & Lambert, 2007). Relative to individuals with adult-onset psychotic-spectrum disorders (AOP), individuals with early-onset psychotic-spectrum disorders (EOP; defined here as being diagnosed before age 18), tend to show more severe clinical course (Eggers & Bunk, 1997), greater premorbid abnormalities (Cannon et al., 2002; Vourdas, Pipe, Corrigall, & Frangou, 2003) and greater genetic loading (Asarnow, 1999), potentially due to a larger contribution of neurodevelopmental risk factors (see Kumra et al., 2009 for review). Although individuals with EOP and AOP show generally comparable deficits in the domains of general intelligence, memory, attention, and executive function (for reviews, see Frangou, 2010; Kumra et al., 2009), some studies have demonstrated increased cognitive impairments (relative to AOP) in EOP patients as they move into adulthood, seemingly due to patients' failure to show the expected age-related improvements in these domains (Frangou, 2010; Frangou, Hadjulis, & Vourdas, 2008; Øie, Sundet, & Rund, 2010). These impairments may be, in part, due to disruption of typical adolescent neurodevelopmental

maturation by onset of psychosis, causing cognitive development to plateau (Frangou, 2010; Frangou et al., 2008; Øie et al., 2010), and later contributing to a more severe clinical course and poor functional outcomes (Allott et al., 2011; Bachman et al., 2012; Couture, Penn, & Roberts, 2006; Fett et al., 2011). Given the hypothesis that synaptic plasticity plays a significant role in the pathophysiology of symptoms and functional impairment in schizophrenia, measuring synaptic plasticity throughout the course of psychotic illness in adolescence could lead to a better understanding of the mechanisms involved in this disorder.

Considering the proposed role of synaptic plasticity in typical development of cognitive processes, as well as its possible role in the pathophysiology of schizophrenia, the studies presented here will: 1) review electrophysiological endophenotypes for schizophrenia and establish the role of glutamatergic NMDA receptor signaling in schizophrenia; 2) establish the typical developmental trajectory of the MMN; investigate relationships between MMN, cognition and functioning in a healthy sample of adolescents and young adults; and assess whether MMN can predict outcomes in a healthy control sample; and 3) test whether EOP patients have impairments in proposed EEG measures of synaptic plasticity (the MMN and measures from the LTP-analog paradigm) relative to a typically developing (TD) sample; assess for divergent developmental trajectories in EOP patients relative to TD controls; and assess for associations between EEG measures, cognition, and functioning in EOP and TD individuals.

Specifically, Chapter 1 of this dissertation provides a review of electrophysiological endophenotypes in psychotic disorders. Chapter 1 contains

significant content from a published review of electrophysiological endophenotypes in psychotic disorders published in the *Harvard Review of Psychiatry* (Owens E, Bachman P, Glahn D, Bearden CE, 'Electrophysiological Endophenotypes for Schizophrenia'). This work was co-authored by Peter Bachman, David C. Glahn, and Carrie E. Bearden, all of who have consented to the inclusion of this work in this thesis. In this paper, I wrote some of the introduction, most of the body, and the conclusion. I also edited and compiled the material contributed by my co-authors. David Glahn contributed the introduction and definition of endophenotypes and Peter Bachman contributed the section on gamma abnormalities. Carrie Bearden oversaw the compilation of this work and provided essential editing throughout the writing process.

Chapter 2 utilized data collected from a multi-site longitudinal study (North American Prodrome Longitudinal Study NAPLS2; Addington et al., 2012). These data are used with permission from the Principal Investigator, Ty Cannon, as well as Daniel Mathalon, whose lab processed the MMN data. This study used a subset of the total healthy control sample to establish the typical developmental trajectory of the MMN. Additionally, I explored associations between MMN, cognition and functioning, and whether MMN was capable of predicting one-year outcomes in a healthy control sample. This research will contribute to understanding the MMN and its relationship with these measures of functioning. Given that MMN is an important quantitative measure of auditory perception, a more thorough understanding of MMN in healthy populations may help to clarify aberrant processes in psychosis.

Chapter 3 reports a study that characterizes neural responses to the LTP-analog paradigm and MMN in in EOP relative to TD controls. This study explored the

relationship between these measures and neurocognition, clinical symptomatology, and social and role impairment in EOP. To date, no studies have measured associations between neural responses to the LTP-analog paradigm, neurocognition, and functioning in this clinical population. Additionally, neural responses to the LTP-analog paradigm and MMN have not been measured in the same sample, thus limiting our understanding of whether the two measures contain information from convergent biological processes. This research will contribute to identifying and characterizing the relatively new measurement of LTP-like neural changes in youth with psychotic illness and may provide much needed external validity to this measure. On a broader level, deficits in neural responses to the LTP-analog paradigm may be present in a variety of neuropsychiatric disorders (Goto et al., 2010); therefore the impact of this work may extend well beyond psychosis.

In summary, cognitive and functional impairments in schizophrenia are currently poorly treated. The RDoC initiative aims for improved understanding of the biological and neurodevelopmental processes involved in these deficits, which may lead to new or more targeted treatments. Impaired synaptic plasticity is proposed to be a key pathophysiologic mechanism in the onset and development of cognitive deficits and symptoms of schizophrenia (Forsyth & Lewis, 2017). The MMN, a quantitative measure of schizophrenia that is related to synaptic plasticity processes, has been shown to be related to cognition and functioning in schizophrenia, but it is unclear whether these relationships exist in healthy individuals. A relatively new EEG paradigm that proposes to measure LTP may clarify the role of impaired synaptic plasticity in schizophrenia, but, at this time, there are no studies assessing whether these measures are related to cognition

and functioning. The research presented here will add to growing research on the role of synaptic plasticity functioning in typical neurodevelopment and in the development of psychosis.

CHAPTER ONE: A REVIEW OF ELECTROPHYSIOLOGICAL ENDOPHENOTYPES IN SCHIZOPHRENIA

Abstract:

Endophenotypes are quantitative, heritable traits that may help to elucidate the pathophysiologic mechanisms underlying complex disease syndromes, such as schizophrenia. They can be assessed at numerous levels of analysis; here, we review electrophysiological endophenotypes that have shown promise in helping us understand schizophrenia from a more mechanistic point of view. For each endophenotype, we describe typical experimental procedures, reliability, heritability, and reported gene and neurobiological associations. We discuss recent findings regarding the genetic architecture of specific electrophysiological endophenotypes, as well as converging evidence from EEG studies implicating disrupted balance of glutamatergic signaling and GABA-ergic inhibition in the pathophysiology of schizophrenia. We conclude that refining the measurement of electrophysiological endophenotypes, expanding genetic association studies, and integrating datasets are important next steps for understanding the mechanisms that connect identified genetic risk loci for schizophrenia to the disease phenotype.

Introduction

Despite substantial heritability, the genetic architecture of schizophrenia is incompletely understood (Sullivan, Daly, & O'Donovan, 2012). Using population-based genome-wide association (GWA), susceptibility loci for schizophrenia have been localized (International Schizophrenia Consortium, 2009; O'Donovan et al., 2009; Rietschel et al., 2012; Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011; Shi et al., 2011; Stefansson et al., 2009; Yue et al., 2011). Indeed, the most recent analysis from the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC; 2014) compared 36,989 cases and 113,075 controls to identify 108 conservatively defined loci that meet genome-wide significance, 83 of which had not been previously reported. This work represents an important step forward for genetics of psychoses in understanding the genetic determinants for schizophrenia. However, the identified loci do not directly imply the involvement of specific genes, and identified quantitative trait loci (QTL) explain only a small proportion of the heritable risk (So, Gui, Cherny, & Sham, 2011). Endophenotypes have been proposed as a way to link genetic risk loci to disease phenotype in a mechanistic way. Given the lack of objective laboratory-based diagnostic measures for neuropsychiatric disorders like schizophrenia, as well as the substantial phenotypic heterogeneity, endophenotypes can provide important quantitative metrics that may be closer to the underlying disease biology (Yue et al., 2011).

Furthermore, data are rapidly accumulating that rare variants may have a substantial cumulative effect on disease risk relative to common variants captured in conventional GWA studies (Blangero, 2004; Cirulli & Goldstein, 2010; Gibson, 2011;

Gorlov, Gorlova, Sunyaev, Spitz, & Amos, 2008; Ji et al., 2008; La Vega, Bustamante, & Leal, 2011; Li & Leal, 2008; McClellan & King, 2010). Recently, Lee and colleagues (2012) calculated that only 23% of the variation in schizophrenia can be ascribed to common variants, suggesting that more than 2/3 of the genetic variation may be due to rare variants. Data from the 1000 Genomes Project confirm that rare (<1%) variants constitute the vast majority (73%) of polymorphic sites in humans (Marth et al., 2011). A recent exome sequencing study focused on rare functional variants examined 2,536 schizophrenia cases and 2,543 controls of European ancestry, providing the strongest evidence to date for specific genetic variants that increase risk for psychosis (Fromer et al., 2014; Purcell et al., 2014). Purcell and colleagues (2014) identified numerous primarily rare (<1 in 10,000) mutations across many genes that, when considered in aggregate, are strongly associated with schizophrenia risk. While these genes were distributed throughout the genome, functional characterization identified their involvement in networks that directly influence neuronal function, including the voltage-gated calcium ion channel, the activity-regulated cytoskeleton-associated scaffold protein (ARC), and the N-methyl-D- aspartate receptor (NMDAR) postsynaptic signaling complex, gene sets previously implicated in schizophrenia risk through analyses of copy number variants (CNVs; Kirov et al., 2012). No individual variant or gene-based test achieved statistical significance, which suggests that a complex polygenic burden increases risk for psychotic disorders through multiple targets within each metabolic pathway. Examining exome sequence data from 623 schizophrenia parent proband trios, Fromer and colleagues demonstrated that de novo mutations were over-represented among glutamatergic postsynaptic proteins comprising the ARC and NMDAR

complexes, strikingly consistent with the much larger case-control data presented by Purcell and colleagues (Fromer et al., 2014; Purcell et al., 2014). Although it is possible that with additional samples individual rare variants identified with exome or whole genome sequencing may become significant, the current findings clearly demonstrate the polygenic nature of psychosis risk, and suggest that both common and rare variants confer risk for schizophrenia.

This new understanding regarding the involvement of both common and rare variants in the genetic architecture of schizophrenia is consistent with the notion that multiple rare mutations occurring within common gene pathways appear to contribute to risk for psychotic illness (Walsh et al., 2008). If so, biologically characterizing the impact of identified gene sets on illness risk could be quite difficult using affection status alone. In this context, using a genetically informed quantitative diagnostic proxy could dramatically improve our ability to conceptualize the impact of specific mutations/variants, gene sets, or networks on biological processes predisposing to schizophrenia. At one level, an endophenotype is such a proxy (Glahn et al., 2014). Our manuscript reviews research designed to identify and implement endophenotypes to better understand schizophrenia. We will focus on electrophysiological putative endophenotypes, given the consistent evidence for electrophysiological markers as genetically mediated intermediate traits as well as their potential relevance to underlying disease biology (Braff, Light, & Swerdlow, 2007; Light et al., 2012). Furthermore, electrophysiological endophenotypes have high translational value, as they can also be effectively modeled in animals (Amann et al., 2010; Bickel & Javitt, 2009; Kellendonk, Simpson, & Kandel, 2009; Rosen, Spellman, & Gordon, 2015).

Endophenotype: A Definition

An endophenotype is a trait that is related to the genetic liability for an illness, but is not itself a measure of that illness (John & Lewis, 1966). In other areas of medical genetics, the terms "allied phenotype" or even "risk factor" may be used, though the term "endophenotype" has a close association with psychiatric genetics. Most researchers agree that for a trait to be considered an endophenotype, it must: (1) be heritable; (2) associated with the illness; (3) mostly independent of clinical state; and (4) impairment must co-segregate with the illness within a family; and (5) represent reproducible measurements (Gershon & Goldin, 1986; Gottesman & Gould, 2003; Leboyer et al., 1998; Lenox, Gould, & Manji, 2002). As quantitative endophenotypes may provide a more precise estimate of the underlying liability distribution, they are thought to provide greater power to localize disease-related genes than affection status alone (Bearden & Freimer, 2006; Glahn et al., 2014; Gottesman & Gould, 2003; Puppala et al., 2006). We previously argued that the criteria for an endophenotype can be reduced to evidence for heritability and evidence for a genetic relationship (i.e., pleiotropy) with the illness (Glahn et al., 2014; 2012). This requirement of pleiotropy implies that endophenotypes are directly comparable to allied phenotypes discussed in other areas of complex disease genetics (Almasy & Blangero, 2001). In this context, we conceptualize endophenotypes as quantitative, laboratory-based measures that represent intermediate links between genetic contributions and clinical phenotypes.

While most attempts to define endophenotypes focus on a specific illness (e.g. Glahn et al., 2010; Light et al., 2014) there is growing evidence that endophenotypes often elucidate neurobiological mechanisms that are shared across disorders (Bearden &

Freimer, 2006; Glahn et al., 2014). Given substantial evidence for pleiotropy between schizophrenia and bipolar disorder (Craddock, O'Donovan, & Owen, 2009; Lichtenstein et al., 2009; Purcell et al., 2009), and to a lesser extent major depression (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013), the lack of diagnostic specificity of many endophenotypes is not surprising. Thus, endophenotypes may lack specificity to particular neuropsychiatric disorders, but that may be an accurate reflection of genetic and neurobiological mechanisms shared by the disorders.

Electrophysiological Endophenotypes

Electroencephalography (EEG) is an excellent tool for studying endophenotypes in clinical populations because it is relatively inexpensive, comfortable for subjects, and collects data with high temporal resolution (Niedermeyer & da Silva, 2004). Several candidate neurophysiological endophenotypes in schizophrenia have been proposed, including the P50 event-related potential amplitudes and gating, oculomotor antisaccade, mismatch negativity (MMN), and the P300 event-related potential (Greenwood et al., 2011; Light et al., 2012; Turetsky et al., 2007). The acoustic startle reflex, or prepulse inhibition (PPI), is another commonly investigated EEG marker proposed as a schizophrenia endophenotype, but substantial variability and the presence of PPI deficits across numerous neuropsychiatric disorders has tempered the case for PPI as a specific endophenotype of schizophrenia (Miller & Rockstroh, 2013; Powell, Zhou, & Geyer, 2009). Each measure has demonstrated strong evidence of abnormality in patients with schizophrenia, and all show heritability and have been observed in unaffected first-degree relatives. This review will briefly address how each measure shows: 1) evidence of deficits in schizophrenia; 2) stability over time; 3) relative independence of fluctuations

in clinical symptoms; 4) deficits in unaffected family members; and 5) heritability. Turetsky and colleagues (2007) and Light and colleagues (2012) provide more extensive reviews of empirical data supporting the relationships of each endophenotype to schizophrenia; here we provide an updated review of each potential endophenotype, with discussion of major findings related to neural mechanism and putative genetic links. We also consider potential emerging electrophysiological endophenotypes not discussed in previous reviews. It should serve as a critical evaluation of the current evidence supporting each potential endophenotype as a useful tool in aiding the investigation of schizophrenia genetics. We used the search engines Google Scholar and PubMed to complete the following search: [electrophysiol* OR EEG OR ERP] AND [schizophrenia OR psychosis] AND [endophenotype OR intermediate phenotype OR inherited]. To describe deficits in individuals with schizophrenia relative to healthy controls, we focused on studies that included individuals at clinical high-risk or prodromal states, first episode states, and/or chronic states. Studies on childhood onset schizophrenia were not included in this review. For genetic research, we prioritized studies with very large sample sizes but also included ones with smaller sample sizes to better characterize publications the field and the diversity of results. Titles and abstracts were used to select studies that were associated with the goals of the present review. See **Table 1** for a summary of findings on each endophenotype.

Mismatch Negativity (MMN)

Mismatch negativity (MMN) is an auditory ERP component that is thought to be an objective index of auditory sensory memory functioning and is involved in the assessment of stimulus familiarity/unfamiliarity. Auditory sensory memory refers to the

ability of the brain to retain representations of the physical features (e.g., pitch, intensity) of simple auditory stimuli for up to 30 seconds (Javitt et al., 1996). MMN is elicited when a sequence of repetitive standard sounds is interrupted infrequently (10% of total trials) by deviant "oddball" stimuli, which differ in duration or pitch from the standard sounds. The MMN is present as early as 50 ms after stimulus onset and peaks after an additional 100 to 150 ms. MMN is measured by subtracting the auditory evoked potential to the standard tone from that of the deviant tone, which produces a difference waveform with a prominent negative potential. The response is maximally present at frontocentral scalp recording sites and is thought to be generated within the primary and secondary auditory cortices with contributions from bilateral, dorsolateral prefrontal cortices (Baldeweg et al., 2002).

A meta-analysis has shown a large effect size (d = ~1.0) for group differences in MMN in patients with schizophrenia relative to healthy controls, with patients showing smaller MMN than healthy controls regardless of age, gender, or paradigm type (Erickson et al., 2015; Umbricht & Krljes, 2005). MMN appears to reflect an automatic, memory-based comparison process between sounds and has been shown to have good reliability (Hall et al., 2006; Kujala, Kallio, Tervaniemi, & Näätänen, 2001; Light & Braff, 2005a; Näätänen et al., 1989). Eliciting MMN does not require any response from the participant, making it an excellent tool for studying individuals with varying levels of functioning: as a pre-attentional cognitive measure, researchers can use MMN to characterize the integrity of sensory network function independent of attentional or motivational artifacts (Turetsky et al., 2007). Interestingly, MMN deficits are highly associated with impairments in real-world functioning and psychosocial functioning

(Kawakubo et al., 2007; Light & Braff, 2005a; Wynn et al., 2007). See review by Todd and colleagues (2013) for a more detailed review of the neurobiology of MMN.

MMN deficits in patients with schizophrenia appear to remain stable over time despite antipsychotic use or episodic state (Turetsky et al., 2007). MMN was the highest ranking "longitudinal endophenotype", calculated by summing the effect sizes of state-independence (no significant relationship with positive or negative symptoms), long-term stability (ICC > .80) and magnitude of deficits (d = 0.8) in patients in a 1 year test-retest study (Light et al., 2012). While these studies show that MMN demonstrates stability in a 1-year time frame, cross-sectional studies in patients suggest it may show increasing deficits over longer periods of time (see below). Recently, deficits in MMN have been demonstrated in individuals at clinical or genetic high risk for psychosis (Erickson et al., 2015; Jahshan et al., 2012) and have been shown to predict psychosis onset in clinically high risk individuals (Atkinson, Michie, & Schall, 2012; Bodatsch et al., 2011; Erickson et al., 2015; Light & Näätänen, 2013; Nagai et al., 2013; Perez et al., 2014).

Heritability of MMN has been estimated to be .63 and .68 for peak amplitude and mean amplitude, respectively (Hall et al., 2006). Healthy family members of individuals with schizophrenia, individuals at risk for developing schizophrenia, and recent-onset patients have all been reported to have reduced MMN amplitudes (Brockhaus-Dumke et al., 2005; Jahshan et al., 2012; Jessen et al., 2001; Michie, Innes-Brown, Todd, & Jablensky, 2002; Şevik et al., 2011). One study found normal MMNs in unaffected family members of schizophrenia patients, and two studies have found normal MMN in first-episode patients (Bramon et al., 2004; Salisbury, Shenton, Griggs, Bonner-Jackson, & McCarley, 2002; Umbricht, Bates, Lieberman, Kane, & Javitt, 2006). The first study

may have restricted the variance of MMN amplitudes by using a common average EEG reference, thus reducing power to find effects (Bramon et al., 2004). The latter studies both found reduced MMN in patients who had been diagnosed with a psychotic disorder for at least 18 months, but failed to find an effect in first-episode patients who had very recently undergone their first hospitalization, suggesting that MMN may become more impaired with illness progression (Umbricht et al., 2006). Other evidence exists to suggest that MMN deficits may increase with illness progression: a 1.5 year prospective study of first-hospitalized individuals with schizophrenia found a strong relationship between MMN amplitude reductions and left hemisphere Heschl gyrus gray matter volume reductions (Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007). The patients in this study did not differ from healthy controls or psychotic bipolar disorder individuals at study onset (time of first hospitalization), but did at follow-up (Salisbury et al., 2007). Jahshan and colleagues (2012) additionally found progressively smaller MMN amplitudes across at-risk, recent-onset, and chronic patients.

Collectively, the studies reviewed above suggest that conclusions regarding changes in MMN over time are mixed: the studies that show normal MMN in first episode patients with schizophrenia suggest that MMN indexes a progressive process and is not a marker of vulnerability for the disorder, (Salisbury et al., 2002; 2007; Umbricht et al., 2006) while other studies have found reduced MMN in at risk populations (Atkinson et al., 2012; Bodatsch et al., 2011; Jahshan et al., 2012; Light & Näätänen, 2013; Nagai et al., 2013; Perez et al., 2014). A recent meta-analysis also concludes that, while individuals with chronic schizophrenia have decreased MMN amplitudes relative to first episode individuals, a meta-regression analysis showed no relationship between duration

of illness and MMN effect size (Erickson et al., 2015). Additionally, clinical high-risk individuals who later converted to psychosis had MMN amplitudes indistinguishable from individuals with chronic schizophrenia, but healthy first-degree relatives and high-risk participants who did not convert to psychosis both had nonsignificant reductions in MMN amplitude (Erickson et al., 2015). These findings suggest that: 1) MMN impairment across the illness is a nonlinear process, and 2) reductions in MMN in a high-risk state may be a marker for likely conversion to psychosis rather than a marker of genetic vulnerability (Erickson et al., 2015). Strong studies capable of finding a subtle link between genetic risk for psychosis and MMN have not been done; therefore the latter conclusion is speculative. With regard to the nonlinearity hypothesis, the larger deficits in individuals at clinical high risk and those with chronic schizophrenia relative to those with first episode schizophrenia may also suggest that there exists non-shared variance associated with underlying risk and current clinical state. That is, processes related to being in a clinical high-risk state and processes related to chronic psychosis are independently related to MMN amplitude. Again, large-scale studies capable of parsing these components have not yet been performed.

Attenuated MMN amplitude and prolonged peak latency has been found in a large number of neuropsychiatric, neurological, and neurodevelopmental disorders, as well as in normal aging, suggesting that MMN deficiency may index cognitive decline in general (Näätänen et al., 2012). However, other studies have failed to find MMN deficits in individuals with bipolar disorder (Catts et al., 1995; Salisbury et al., 2007; Umbricht et al., 2003), major depression (Umbricht et al., 2003), and obsessive-compulsive disorder (Oades, Dittmann-Balcar, Zerbin, & Grzella, 1997). Prospective studies are needed to

delineate the specificity of MMN deficits in schizophrenia and whether individuals with schizophrenia have a greater rate of decline relative to other neuropsychiatric populations.

Studies have demonstrated that disruption of NMDA signaling may play a crucial role in MMN generation and contribute to MMN deficits in patients with schizophrenia (Javitt et al., 1996; Umbricht et al., 2000). Research on nonhuman primates has shown that both competitive and noncompetitive NMDA antagonists reduce MMN amplitude without affecting prior ERPs in the primary auditory cortex (Gil-da-Costa, Stoner, Fung, & Albright, 2013; Javitt et al., 1996). The same NMDA antagonists have been shown to elicit some symptoms of schizophrenia when administered to healthy subjects, suggesting that the glutamatergic NMDA receptor system plays a crucial role both in neurocognitive deficits and psychotic symptoms of schizophrenia (Adler et al., 2014; Umbricht et al., 2000). Dopaminergic systems may also play a role in MMN production: two studies have found diminished MMN in adolescents with 22q11.2 deletion syndrome, which includes the catechol-O-methyltransferase *COMT* gene involved in dopamine metabolism (Baker & Skuse, 2005; Cheour et al., 1997). One study found reduced MMN in individuals with the *COMT* Met allele, suggesting differential effects of dopamine on these two ERPs (Baker & Skuse, 2005). To our knowledge, no GWA studies have investigated genetic variants associated with MMN deficits, so it is unclear whether *COMT* or other genes are associated with MMN deficits.

In summary, MMN represents a promising endophenotype for further study in schizophrenia. Its potential ability to predict onset to psychosis is particularly intriguing and should be investigated further. GWA studies on MMN are needed to further elucidate

the genetic and neurobiological contributions to this measure and whether meaningful genetic overlap exists between neuropsychiatric disorders characterized by MMN deficits.

P300

The P300 event-related potential, referred to in some literature as P3, is an index of a variety of cognitive processes, including onset of an unexpected stimulus (Courchesne, Hillyard, & Galambos, 1975), context updating (Donchin, 1981; Verleger, 1988), working memory updating and consolidation (Vogel & Luck, 2002), and the attribution of salience to a deviant stimulus (Soltani & Knight, 2000). The P300 can be identified as a large, positive component with peak latency around 300 ms after stimulus onset when evoked by an auditory stimulus (about 100-200 ms later when evoked by a visual stimulus). The auditory P300 is typically studied using the oddball task in which an infrequent tone is randomly interspersed within an ongoing train of a repeating tone, presented at a rate of about once per second. The P300 is distinct from the MMN in that it requires attention; an MMN will still be elicited even when attention is directed toward a different sensory modality, while a P300 will not (Näätänen & Alho, 1995). Additionally, the stimulus train optimal for eliciting an MMN involves presentations at a rate faster than once per second. Lastly, violations of expectation that occur during the infrequent stimulus can occur on much more abstract properties of the stimulus, consistent with the notion that it represents a more complex level of stimulus evaluation and categorization. MMN appears when a violation is tied to very basic, physical stimulus properties (e.g., duration, pitch, intensity; Näätänen & Alho, 1995).

The P300 has been widely investigated in both healthy and clinical populations. Smaller amplitudes of P300 have been found in studies of chronic (Pfefferbaum, Wenegrat, Ford, Roth, & Kopell, 1984), recent onset (Salisbury et al., 1998), and unmedicated schizophrenia patients (Hirayasu et al., 1998), and has been replicated by numerous independent investigators (Light et al., 2012). Considerable evidence also exists that a significant level of P300 amplitude reduction is a trait abnormality and exists independent of duration of illness, or symptom severity (Turetsky, Colbath, & Gur, 1998). A meta-analysis found an effect size of $d = 0.89$ for auditory P300 amplitude reduction and $d = 0.59$ for delayed peak latency in patients with schizophrenia compared to healthy controls (Jeon & Polich, 2003).

The P300 has a broad, centrally-maximal scalp distribution, and reflects a composite of anatomically and functionally distinct neural generators (Eichele et al., 2005; Linden, 2005; Soltani & Knight, 2000). Accordingly, it is often separated into two discrete subcomponents. The P3a subcomponent is elicited by novel or unexpected stimuli, occurs slightly earlier, has frontocentral scalp topography, and is thought to reflect attentional orienting processes (Polich, 2007; Squires, Squires, & Hillyard, 1975). Source localization studies suggest that the P3a stems from activity in the lateral prefrontal and superior temporal areas (Linden, 2005). The P3b subcomponent is elicited by task relevant stimuli – it is sometimes referred to as the "target P300" – especially when the task relevant stimulus occurs relatively rarely among a series of irrelevant stimuli. It occurs later, has parietal scalp topography, and is thought to reflect cognitive processes associated with stimulus evaluation and response formation (Polich, 2007). Source localization studies suggest that P3b scalp activity arises from the inferior parietal

cortex, particularly the supramarginal gyrus, in addition to sensory modality-specific regions (Linden, 2005). There has been some suggestion that P3a is more strongly associated with dopaminergic neurotransmitter actions, while P3b may be more strongly associated with noradrenergic pathways (Polich, 2007). Both P3a and P3b components are diminished in patients with schizophrenia and also fluctuate with clinical symptoms and state (Mathalon, Ford, & Pfefferbaum, 2000). Diminished P3a and P3b amplitude have also been found in individuals determined prospectively to be at high risk (or determined retrospectively to be in a prodromal state) of developing schizophrenia (Bramon, 2004; Jahshan et al., 2012). Diminished P3b amplitude is additionally present in unaffected biological relatives (Ethridge et al., 2014). There is some evidence that diminished P3a amplitude is apparent across psychotic disorders in general, while reduced P3b amplitude specific to schizophrenia (Ethridge et al., 2015; Perlman et al., 2015; van Beijsterveldt & van Baal, 2002). P3b amplitude reduction was also correlated with a wide range of clinical measures, including severity of symptoms, overall functioning, and clinical traits that had been assessed 15 years earlier (Perlman et al., 2015). Therefore, it was suggested that P3b reduction is a more stable trait-like endophenotype of vulnerability to disease and predictor of outcome rather than a reflection of disease state (Perlman et al., 2015). Alternatively, the P3b has failed to differentiate schizophrenia and bipolar psychosis in other studies (Bestelmeyer, Phillips, Crombie, Benson, & St Clair, 2009; Ethridge et al., 2012).

Disrupted P300, P3a and P3b are not specific to schizophrenia, and in fact have been found in a variety of disorders, including Alzheimer's disease (Polich, Ladish, & Bloom, 1990), substance use (Carlson, Iacono, & McGue, 2004; Hesselbrock, Begleiter,

Porjesz, O'Connor, & Bauer, 2001), disinhibited pathology (Iacono, Carlson, Malone, & McGue, 2002), and bipolar and unipolar depression (Gangadhar, Ancy, Janakiranaiah, & Umapathy, 1993), although there may be some variations that are unique to each disorder (Salisbury, Shenton, & McCarley, 1999). As discussed in the introduction, one can consider whether the usefulness of an endophenotype varies by its specificity to a particular disorder.

Considerable evidence exists for a genetic contribution to P300 amplitude; a heritability estimate of 0.60 to 0.69 has been established among healthy individuals (Hall et al., 2006; O'Connor, Morzorati, Christian, & Li, 1994; van Beijsterveldt & van Baal, 2002). There is also evidence for a genetically-mediated P300 deficit in first degree relatives of patients with schizophrenia (Frangou et al., 1997). More evidence comes from a meta-analysis showed that P300 amplitude was reduced and its latency was delayed in non-psychotic relatives of patients with schizophrenia (Bramon et al., 2005). Of the studies that have deconstructed the heritability of P3a and P3b subcomponents, two have found stronger familial deficits of the P3a, which would suggest stronger heritability for abnormalities of attentional orienting (Kimble et al., 2000; Turetsky, Cannon, & Gur, 2000).

A GWAS study of P300 conducted on a large community sample (N=4026) showed that 65% of the variance in P300 amplitude was due to additive genes, which is consistent with a previous meta-analysis (Malone, Vaidyanathan, et al., 2014b). Estimates of SNP heritability, or phenotypic variance due to the measured genetic variants on the genotyping array, yielded a heritability estimate of .29 for P300 amplitude, which represents about 40% to 50% of the heritable variance of this trait

(Malone, Vaidyanathan, et al., 2014b). This suggests that about half of the additive genetic influence is likely due to common genetic variants as opposed to rare variants or shared environmental influences (Malone & Iacono, 2002). Despite this fact, analyses of individual SNPs did not yield any significant associations. In the same study, a genome-wide analysis of 17,601 autosomal genes did find a novel association with myelin expression factor 2 *MYEF2*, which codes for a major component of the myelin sheath surrounding cells in the central nervous system- an effect that has not been found in prior GWAS studies of P300 (Malone, Vaidyanathan, et al., 2014b). This study demonstrates that even when working with substantial heritability and a relatively large sample, samples may still be underpowered to detect genome-wide significant effects. This issue is discussed further in the section, "Promise of Electrophysiologic Traits as Genetically Tractable Endophenotypes".

Smaller studies of schizophrenia patients and healthy controls have found significant genetic associations with P300, but have yielded different results. For example, a study that selected 21 genetic markers that had prior evidence of association with schizophrenia found that the risk allele of SNP rs1344706 in *ZNF804A* was significantly associated with P300 amplitude (Del Re et al., 2014). Another study also found that having this risk allele yields higher P300 amplitude for both schizophrenia patient and healthy control carriers compared to noncarriers (O'Donoghue et al., 2014). However, this study did not investigate other SNPs (O'Donoghue et al., 2014). *ZNF804A*, a gene implicated in transcriptional regulatory function, has been implicated in risk of schizophrenia by a GWAS and subsequently replicated by several targeted association studies (Del Re et al., 2014). Another study investigated 19 risk SNPs associated with

schizophrenia and did not find an effect for *ZNF804A*, but found that the *TCF4* SNP rs17512836 allele was associated with significant reduction in P300 amplitude and delayed P300 latency (Hall, Levy, & Salisbury, 2014). One large pedigree study of a family with a (1;11)(q42;q14.3) translocation, which is associated with major psychiatric disorders including schizophrenia, found that translocation in the *DISC1* gene was associated with reduced P300 amplitudes, regardless of psychiatric symptomatology (Blackwood et al., 2001), an effect which was not observed in the former two studies.

Difficulties associating P300 amplitude with a specific genetic variant may be due to a variety of state-dependent contributions, which could be addressed by conducting measurements over multiple occasions (Ford, 2014). Differing inclusion criteria for SNPs may also be a problem; for example, in the aforementioned studies by Del Re and colleagues (2014) and Hall and colleagues (2014), both initially selected a limited number of SNPs to investigate based on findings by published GWAS that the selected SNPs confer risk for schizophrenia. Both then go on to include different additional SNPs based on prior findings that these SNPs are associated with other traits related to schizophrenia, such as nicotine dependence or functional neuroimaging measures. SNPs of interest were also then removed if there were too few minor allele carriers in the sample (Del Re et al., 2014). While narrowing the SNPs of interest to those that are likely to be associated with schizophrenia may improve power by reducing the number of comparisons (Newton-Cheh & Hirschhorn, 2005), varying criteria for inclusion of SNPs will undoubtedly cause problems in replication.

In summary, the P300 is altered in schizophrenia, both in terms of reduced amplitude and delayed peak latency (Jeon & Polich, 2003). Diminished P300 amplitude

has been found in several neuropsychiatric disorders, which may reflect shared physiological mechanisms. When individually studying the P300's subcomponents, P3a and P3b, there is evidence to suggest that P3b amplitude reductions may be more specifically related to schizophrenia diagnosis rather than broadly defined psychosis, and may be more stable and therefore better able to predict outcome than P3a (Perlman et al., 2015). If P3b is more specifically related to schizophrenia, this may be an excellent case for breaking down endophenotypes into more specific sub-measures in order to create potentially more genetically tractable traits (discussed below). Lastly, while there is ample evidence that P300 amplitude is heritable, lack of replication remains a problem for discovering specific genetic contributions to this endophenotype (Hall et al., 2006; Malone, Burwell, et al., 2014a; O'Connor et al., 1994; van Beijsterveldt & van Baal, 2002).

Gamma

A potential electrophysiological endophenotype gaining increasing attention is abnormal activity in the gamma range (30-80 Hz) of scalp EEG (Gonzalez-Burgos, Cho, & Lewis, 2015; Mathalon & Sohal, 2015). In the case of EEG activity, as opposed to the time-locked, voltage-averaged ERP measures discussed above, neural time series data are decomposed into constituent oscillating activity across standard frequency bands, producing estimates of signal amplitude (or, when squared, power) and phase.

At the present time, there is little about gamma band activity – from its underlying neural generators, to its functional significance in typical cognition and in schizophrenia – that is *not* controversial (Buzsáki & Schomburg, 2015). For instance, although there is

an emerging consensus that gamma power changes reflect the dynamic balance of excitatory and inhibitory influences on small-scale, localized populations of pyramidal neurons in the cortex (Cardin et al., 2009; Ford, Krystal, & Mathalon, 2007; Gulyás et al., 2010; Sohal, Zhang, Yizhar, & Deisseroth, 2009), disagreement exists regarding the influence of thalamo-cortical circuits on local gamma power (Ray & Maunsell, 2015), as well as regarding the capacity of gamma power or phase to play a significant role in the functional synchronization across populations of pyramidal neurons (Bastos, Vezoli, & Fries, 2015; Fries, Nikolić, & Singer, 2007; Ray & Maunsell, 2015)- the reason for much of the interest in gamma activity in the first place (Engel, Fries, & Singer, 2001; Gandal, Edgar, Klook, & Siegel, 2012).

Regardless of the theoretical motivation, a number of studies have shown that gamma band activity is abnormal in people with schizophrenia (Uhlhaas & Singer, 2010). Kwon and colleagues (1999) were first, reporting that people with schizophrenia are slower to entrain oscillatory brain activity to auditory "steady state" stimulation at 40 Hz and also show lower power in response to the stimulation overall. Since then, these findings have been replicated independently (Light et al., 2006), including among older patients with a chronic course of schizophrenia (Vierling-Claassen, Siekmeier, Stufflebeam, & Kopell, 2008), first-episode schizophrenia patients (Symond, Harris, Gordon, & Williams, 2005), and unmedicated patients (Gallinat, Winterer, Herrmann, & Senkowski, 2004; Krishnan et al., 2009). However, evidence that gamma band abnormalities are present prior to the onset of psychosis, is far from robust (Perez et al., 2013), and if present, may be restricted to the later portion of the auditory steady-state response (Tada et al., 2014). As such, this pattern of findings may cast doubt on its role

as a trait-like vulnerability marker. On the other hand, as discussed below, unaffected relatives of patients with schizophrenia also show gamma effects, which is consistent with an inherited, trait-like deficit.

In addition to passive auditory stimulation, gamma activity has also been examined while patients are at rest and while they perform challenging cognitive tasks. Overall, studies show evidence that resting (Rutter et al., 2009; Venables, Bernat, & Sponheim, 2009) and pre-stimulus baseline gamma activity is elevated (Spencer, 2012; Reinhart, Mathalon, Roach, & Ford, 2011), while task-driven gamma-band responses are reduced in schizophrenia (Cho, Konecky, & Carter, 2006; Gandal et al., 2012; Minzenberg et al., 2010), suggesting deficits in signal-to-noise ratio between neural network states (Rosen et al., 2015).

Also worth considering is the likelihood that the ERP measures discussed earlier and EEG measures like gamma band power and phase are not independent of each other (Makeig et al., 2002). In fact, gamma abnormalities may be an important contributor to these potential endophenotypes. For example, decreased magnitude and delayed latency of gamma synchrony (occurs -150 to 150ms post-stimulus) was demonstrated in patients with schizophrenia relative to healthy controls in a traditional auditory oddball paradigm, which also elicits the P300 (Symond et al., 2005). Another study showed smaller P50 amplitude and weaker gamma response attenuation in patients with schizophrenia with perceptual disturbances relative to patients without perceptual disturbances and healthy controls (Johannesen, Bodkins, O'Donnell, Shekhar, & Hetrick, 2008). With respect to the familial distribution of gamma band abnormalities, studies have detected more subtle abnormalities in unaffected first- degree relatives (Hong et al., 2004). Additionally, both

evoked gamma power and phase-locking of the early auditory gamma-band response were shown to be heritable in a study of twins concordant and discordant for schizophrenia ($h^2 = 0.65$, $h^2 = 0.63$, respectively; Hall et al., 2011; Leicht et al., 2011).

Future studies are needed to compare various measures within the same subjects to better understand the associations between gamma oscillations during resting-state, sensory-driven and cognitively-driven tasks. Along these same lines, innovative methods are needed to establish with certainty that the gamma band findings derived from animal models actually reflect the "same" gamma as is measured in non-invasive human studies. Factors like developmental stage must also be taken into account, as sensory-evoked gamma activity has been shown to have a distinct non-linear developmental trajectory over the course of adolescence and young adulthood (Cho et al., 2015), a key epoch in schizophrenia pathophysiology. Furthermore, whether gamma alterations are specific to schizophrenia (Gandal et al., 2012), are general across psychosis, or are present across a range of diverse pathologies (Hamm et al., 2012), must be established. Although seemingly contradictory results have been published (e.g., Ethridge et al., 2012; Hall et al., 2011), the most recent study -consisting of a large sample of schizophrenia and bipolar patients and their relatives - showed that gamma abnormalities are a feature of psychosis, regardless of diagnosis, and are heritable (Ethridge et al., 2015).

LTP-Analog Paradigm

In the long list of neurobiological mechanisms that contribute to endophenotypes in schizophrenia, NMDA-receptor hypofunction and disrupted glutamatergic signaling are increasingly highlighted as key targets (Cohen, Tsien, Goff, & Halassa, 2015;

Heckers & Konradi, 2015; Howes, McCutcheon, & Stone, 2015; Iwata et al., 2015; Jadi, Margarita Behrens, & Sejnowski, 2015). A relatively new EEG paradigm may extend our understanding of NMDAR-mediated signaling and, more specifically, its importance in learning and memory. Long-term potentiation (LTP) refers to the process whereby the efficacy of communication between neurons can be rapidly increased, and is the principal candidate mechanism underlying learning and memory formation (Citri & Malenka, 2008). NMDARs play a central role in LTP (and in plasticity more generally) at glutamatergic synapses (Stephan et al., 2006). LTP can be induced in a number of ways, but most conveniently by delivering a tetanus (stimulus presented at a high rate of frequency, typically 100 Hz or more). Changes in presynaptic and postsynaptic responses can then be measured in a variety of ways, but historically has been accomplished using electrodes surgically implanted in the hippocampus. Decades of animal research have helped us understand some of the complex interactions that modulate LTP at NMDAR sites: for example, metabotropic glutamate receptor agonists can reverse the effects of NMDAR antagonists (Moghaddam, 2003), D1 agonists and D2 antagonists increase NMDAR-dependent LTP (Centonze et al., 2004), and cholinergic mechanisms modulate NMDA-dependent LTP and LTD in the visual cortex (Kirkwood, Rozas, Kirkwood, Perez, & Bear, 1999). Until recently, inquiry of the functional significance of LTP has been hindered by the absence of a human model. There is now evidence that the rapid repetitive presentation of a photic tetanus leads to persistent enhancement of an early visual evoked potential in humans, the N1b (Teyler et al., 2005). This paradigm has recently been used to show impaired cortical plasticity in patients with schizophrenia relative to healthy controls (Cavus et al., 2012). The paradigm consists of two types of

stimulus presentation: at baseline, participants view a checkerboard flashing at a rate slightly below 1 Hz, then during the photic tetanus period ("high frequency stimulation"), the checkerboard flashes at a rate of almost 9 Hz (Cavus et al., 2012). The slower rate is then presented again in several post-high frequency stimulation blocks (Cavus et al., 2012). Initial studies show enhanced negativity for the C1 and N1b components that appears in blocks after the presentation of the high frequency stimulation (Kirk et al., 2010; Teyler et al., 2005). Enhanced negativity has been shown to be significant for healthy controls but not individuals with schizophrenia, and in individuals with schizophrenia is the enhanced negativity is associated with improved reaction time to oddball targets (Cavus et al., 2012). Given the aforementioned relationships between brain plasticity, glutamate, NMDA-receptor functioning and schizophrenia, future studies using this paradigm may have broad implications for predicting the onset of schizophrenia and understanding and possibly improving positive symptoms and cognitive deficits in schizophrenia.

Promise of Electrophysiologic Traits as Genetically Tractable Endophenotypes

A recent series of studies published by Iacono and colleagues from the Minnesota Center for Twin and Family Research (MCTFR) attempted to uncover the genetics involved in 17 psychophysiological endophenotypes using a wide range of genetic approaches: biometric heritability analyses, molecular- genetic heritability analyses, GWAS, candidate gene studies, rare variant analyses of nonsynonymous SNPs in the exome, and analyses using variants identified through whole-genome sequencing (Iacono, Malone, Vaidyanathan, & Vrieze, 2014a). The endophenotypes studied by the MCTFR group are broadly implicated in psychopathology (i.e., substance use disorders,

mood disorders, and schizophrenia; Iacono, Malone, Vaidyanathan, & Vrieze, 2014a). While these studies represent unprecedented work in terms of effort, sample size and cutting-edge statistical methods, they did not reveal specific genetic effects on endophenotypes: a 153-cell summary table of the statistically significant effects of SNP- and gene-based tests for all 17 endophenotypes investigated was mostly (89%) empty (Iacono, Vaidyanathan, Vrieze, & Malone, 2014b). If endophenotypes are indeed genetically less complex than psychiatric disorders, why are we still having so much difficulty finding genes that are implicated in psychopathology? One possibility is that electrophysiology is not optimal for measuring endophenotypes. However, as discussed in Munafó & Flint's (2014) response to the MCTFR studies, the effect sizes found are consistent with findings from GWAS of other potential endophenotypes, including brain structural variation and cognitive performance. Thus, power to detect genome-wide significant effects may have been limited due to sample size: as pointed out in another response, the sample size of the MCTFR studies is actually small compared to other disorder-based studies (~4,200 vs. ~149,000; Cuthbert, 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Additionally, because the studies relied on a community sample, the data may be too centrally distributed and lacking in extreme values at the tails to garner much power (Braff, 2014). Iacono and colleagues replied they had ample power to detect small effects (d = .014) and that, statistically speaking, at least 20% of their sample were affected by disorders like depression and substance abuse, but admittedly more "extreme" pathology like schizophrenia or autism were not represented (Iacono, Vaidyanathan, Vrieze, & Malone, 2014b).

It is also possible that the assumption that endophenotypes are genetically less

complex than other traits is wrong (Flint, Timpson, & Munafò, 2014). While other disorders have had success linking electrophysiological endophenotypes to susceptibility genes (see COGA study; Dick et al., 2006; Porjesz et al., 1998; Rice & Saccone, 2005), the field of schizophrenia research has not enjoyed consistent success. As discussed in Flint and colleagues' (2014) review, the premise that endophenotypes are genetically less complex than other traits assumes that the endophenotype is part of the causal pathway from genetic variant to disease and inflicts the naïve notion that "biology causes psychology" (Miller, 2010). Focusing only on the effect size of endophenotypes may lead to: 1) ignoring potentially important information from an endophenotype because it is genetically "too complex", or 2) increasing statistical efficiency at the cost of meaningfully translated outcomes (Flint et al., 2014). If we assume that endophenotypes are no more genetically tractable than other complex traits, then the results from the MCTFR studies are in fact expected, and instead can be used to ask new questions. One important consequence of studies such as MCTFR is the realization of the need for larger datasets and data sharing, such as the development of RDoC's "information commons" based on the National Database for Autism Research (ndar.nih.gov). In order to achieve the desired sample sizes, it is essential that researchers share experimental protocols and paradigms. If we accept that we are working with small effect sizes, we must focus on gaining power wherever we can, and this should begin with reducing measurement error. Shared data inherently has larger measurement error than data collected within a single lab due to logistical differences that are difficult to reconcile (e.g., EEG system type, number of channels collected, monitor type and size, room size and lighting). While there are recommendations for many EEG measurements, uniform protocols and paradigms

would drastically improve variation in measurement and, therefore, improve power when combining datasets. Another method involves developing a single, multivariate psychophysiological endophenotype that combines several indices into one summary score. The rationale for doing so is that the combination of features may provide extra group differentiation, making the positive predictive power substantially higher (Iacono, 1998). This has been done using MMN, P50 suppression, P300 auditory oddball, and antisaccadic error rate; the resulting multivariate endophenotype was shown to be more closely related to diagnosis than to any individual feature (Price et al., 2006). Similarly, the Consortium on the Genetics of Schizophrenia (COGS) study combined results from three neurophysiological measures (P50 gating, PPI and antisaccade) along with 12 neurocognitive tasks using factor analysis to yield 5 distinct factors (Seidman et al., 2015). These 5 factors were then evaluated for heritability and differences across probands, siblings and healthy controls. A similar concept was proposed for structural neuranatomic traits and termed "extended endophenotype", created by combining brain morphometric measures in individuals with schizophrenia (Prasad & Keshavan, 2008). Techniques such as these can help identify the utility of individual measures while improving statistical power by both increasing the reliability of individual measures (removing measurement error) and limiting the number of statistical comparisons. An alternative approach is to break down endophenotypes into even more distinct measurements, thereby providing "endophenotypes for endophenotypes" (Miller & Rockstroh, 2013). For example, one can break the P300 down into its separate components, which may prove to be genetically more tractable (Ford, 2014). Both methods are viable approaches for increasing the signal to noise ratio in these

endophenotypes.

Another take-away from the lack of significant genetic findings could be the need to expand genetic studies beyond individuals of European ancestry, which may improve the likelihood of finding rare variants of at least moderate effect size (Iacono, Malone, Vaidyanathan, & Vrieze, 2014a; Iacono, Vaidyanathan, Vrieze, & Malone, 2014b). Future studies should also augment GWA studies with studies that link structural genomics with functional genomics (e.g, gene expression or eQTL studies) and epigenetic effects, e.g. DNA methylation. While currently such studies are inherently more difficult, such effects are likely to be an extremely important source of variance in human health and behavior. For example, the psychoneuroimmunology field has recently focused on a pattern of up-regulated proinflammatory immune response gene activity and down-regulated antiviral immune response gene activity called a "conserved transcriptional response to adversity" (CTRA), which can be activated by social adversity (Slavich & Cole, 2013). Defining and characterizing these shifts in gene expression has helped explain chemical, cellular, and behavioral changes, some of which last for years (Slavich & Cole, 2013). Identifying such changes in the brain and their effects on neurophysiology and clinical phenomena could be a crucial next step in our understanding of schizophrenia.

Conclusion

Research on the etiology, course, and treatment of schizophrenia is complicated by the diversity of clinical presentation and risk factors. Objectively measureable endophenotypes are therefore needed in order to causally link genetic liability to clinical

symptoms and clinical disorder (Miller & Rockstroh, 2013). Electrophysiological endophenotypes may be particularly useful, as most of them have been studied extensively in both human and animal models and are relatively inexpensive and therefore able to be used in large studies. We reviewed some of the most researched and most promising electrophysiological endophenotypes for schizophrenia: MMN, P300, and gamma power and phase measures. With the exception of gamma measures, which are relatively recently-studied phenomena in schizophrenia, these measures show evidence that they are disrupted both in patients with schizophrenia and their clinically unaffected first degree relatives, heritable, and have genetic associations (see Table 1). Other than P300, which appears to be driven by dopaminergic and noradrenergic signaling pathways (Polich, 2007), each of these putative endophenotypes has demonstrated evidence for a role in glutamate signaling and/or NMDA-receptor dependent signaling. Several lines of evidence converge to suggest a prominent role of glutamatergic and NMDA-receptor dependent signaling in schizophrenia, including: cellular processes, which show changes in dendrite growth with LTP (Stephan et al., 2006); pharmacologic induction of psychotic symptoms (Krystal et al., 1994), reduced MMN (Javitt, Steinschneider, Schroeder, Vaughan, & Arezzo, 1994) and impaired sensory gating (Bickel, Lipp, & Umbricht, 2008) with NMDA antagonists; and GWA studies that have found candidate genes for schizophrenia involved in glutamatergic and NMDAR- dependent signaling (Ehrlichman et al., 2009; Greenwood et al., 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Vaidyanathan et al., 2014). Continued investigations into the mechanisms that link these genetic and biological alterations to deficits in endophenotypes may be a promising next

step for schizophrenia research (Coyle, 1996). While the present review did not specifically address the clinical utility of these endophenotypes, this is also an important avenue for future research. The ability to use endophenotypes in a clinical context may improve efforts to take into account individual variability in the prevention and treatment of disorders, in line with the National Institute of Health's initiative, "precision medicine" (http://www.nih.gov/precisionmedicine/). However efforts to use endophenotypes as diagnostic tools may be muddled by evidence that endophenotypes lack specificity to particular neuropsychiatric disorders (see **Introduction**). For schizophrenia in particular, variability in treatment makes it considerably more difficult to understand changes in endophenotypes over time. Usefulness of endophenotypes in a clinical context may be improved by more research on the longitudinal course of these endophenotypes prior to disease onset, i.e., in genetically high risk or prodromal populations. Lastly, while these endophenotypes may not be genetically less complex than psychiatric disorders, a substantial amount of variance in each has been shown to be due to genetic factors, making them important trans-diagnostic tools (Iacono, Vaidyanathan, Vrieze, & Malone, 2014b). By improving our measurement of endophenotypes and advancing our genetic association studies with the techniques described above, we can look forward to continued improvement in our understanding of the genetic, biological and psychological mechanisms in schizophrenia.

Table 1. Summarized Evidence for Electrophysiological Endophenotypes for Schizophrenia

EEG/ERP measure	Dependent Variable	Neurocognitive Function	Effect size	Heritability (h^2)	Impairment in unaffected relatives	GWAS and linkage results	Candida-te genes
MMN	Peak or mean amplitude of difference waveform (deviant tone response - standard tone response)	Index of auditory sensory memory functioning; measure of stimulus feature analysis[1]	d = 1.0[2]	0.63 (mean amp) 0.68 (peak amp)[3]	d = 0.81[4]	NA	*NRG1*[5]
P300	Peak amplitude and latency	Updating and consolidation of perceptual information into mental representation[6]	d = 0.89 (amp) d = 0.59 (latency)[7]	0.65[8] – 0.69[3]	PSES = 0.61 (amp) PSES= 0.50 (latency)[9]	No individ-ual SNPs[8]	*TCF4*[10] *MYEF2*[8] *DISC1*[11]
Gamma	Event-related gamma power and gamma phase-locking (>30Hz)	Associated with perceptual activity, including object detection and basic analysis[12]	d = 0.43 (G1 amp) d = 0.63 (G2 amp)[13] d = 0.80 (evoked gamma amp)[14]	0.65 (gamma power) 0.63 (phase locking)[15]	d = 1.13[14]	NA	NA

MMN = Mismatch Negativity; Amp = amplitude; PSES = Pooled standardized effect size; SNP = single nucleotide polymorphism; G1 = gamma 1; G2 = gamma 2

1. Naatanen, (1978); 2. Umbricht et al., (2005); 3. Hall et al., (2006); 4. Jessen et al., (2001); 5. Ehrlichman et al., (2009); 6. Turetsky, (1998); 7. Jeon et al., (2003); 8. Malone et al., (2014); 9. Bramon et al., (2005); 10. Hall et al., (2014); 11. Blackwood et al., (2001); 12. Gandal, (2012); 13. Lee et al., (2003); 14. Leicht et al., (2011); 15. Hall et al., (2011).

CHAPTER TWO: TYPICAL DEVELOPMENT OF MISMATCH NEGATIVITY AND ITS ASSOCIATION WITH COGNITIVE AND FUNCTIONAL OUTCOMES

Abstract:

Adolescence and young adulthood are characterized by critical changes in neural growth and organization, as well as development of important cognitive functions. Electroencephalography is an important tool used to understand the relationship between neuronal and cognitive development, as it is capable of providing temporally sensitive measures of synchronized activity in large-scale neural circuits. The mismatch negativity (MMN) is an auditory event-related potential (ERP) component and a pre-attentional indicator of early perceptual processing. It is calculated as the difference between the neural response to a repetitive standard tone and a rare deviant tone, yielding the first physiologically measurable brain response that differentiates acoustic sounds. Given that the MMN likely changes with development of sensory and cognitive processing abilities, it is important to understand the typical developmental trajectory of the MMN. However, existing studies on the typical development of the MMN have yielded mixed results, and many have methodological flaws such as using group averages across a large age range. The amplitude of MMN has also been shown to index cognition and functioning in individuals with psychotic disorders and is capable of predicting outcomes in individuals at clinical high risk for psychosis, but few studies exist on these relationships in healthy individuals. Thus, the present study used a large sample (N = 157) of healthy adolescents and young adults (ages 12-35) to: 1) assess the developmental trajectory of the MMN; 2)

test whether MMN is associated with cognition and functioning; and 3) test whether MMN can predict changes in cognition and functioning over one year. We found that, with increasing age, there was reduced latency and amplitude of the MMN. We also found that MMN was not associated with cognition and functioning measured at the same time point, but larger amplitude of MMN at baseline predicted improvements in verbal learning and memory over one year. These results indicate that automatic processing of auditory deviance continues to develop in a linear fashion throughout adolescence and young adulthood, and that MMN appears to be able to specifically index verbal learning and memory ability, as well as general functioning. We suggest the need for more longitudinal studies of healthy individuals to further develop comprehensive models on the association between MMN, cognition and functioning.

Introduction

Discoveries in developmental neuroscience demonstrate that adolescence and young adulthood involves periods of dramatic neural growth and reorganization (Durston et al., 2006; Paus, 2005). This maturation involves processes such as accelerated pruning of neuronal synapses (Paus et al., 2008) and increased myelination of bundles of long axonal connections (Giedd, 2008; Lenroot & Giedd, 2006; Uda et al., 2015). Ultimately, these changes support faster neural transmission and greater efficiency in critical neural pathways (Paus et al., 2008; Stevens, 2009), especially in tracts linking prefrontal areas of the cortex with more posterior sensory and motor areas (Olesen, Nagy, Westerberg, & Klingberg, 2003; Stevens, Skudlarski, Pearlson, & Calhoun, 2009). Accordingly, adolescence is also a time of considerable development in cognitive functions, e.g., cognitive control (Somerville & Casey, 2010); task switching (Crone et al., 2006); holding items in memory (Crone et al., 2006); and speed of processing (Tamm et al., 2002). It is hypothesized that cognitive development during this period is the result of ongoing maturation of neural systems, particularly the prefrontal cortex and its involvement in top-down regulatory control (Goldman-Rakic, 1987; Luna et al., 2001; Somerville & Casey, 2010).

Electrophysiological studies of development

Various imaging methodologies have been used to understand the relationship between neuronal and cognitive development. Electroencephalography (EEG) is particularly well suited for this task, as it is capable of providing temporally sensitive

measures of synchronized activity in large-scale neural circuits. The high temporal resolution of EEG makes it particularly well-suited for studying sensory perception and related cognitive functions (Woodman, 2010). Previous electrophysiological studies have demonstrated that developmental changes in neural oscillation amplitude and neural synchronization are associated with improved cognitive abilities across a number of domains, including visual perception (Uhlhaas et al., 2009; Werkle-Bergner, Shing, Müller, Li, & Lindenberger, 2009); auditory perception (Müller, Gruber, Klimesch, & Lindenberger, 2009); attention and working memory (Chorlian et al., 2015); and memory maintenance (Kardos, Tóth, Boha, File, & Molnár, 2014). Some propose a causal relationship between the increased optimization of neural assemblies and the emergence of cognitive abilities (Barriga-Paulino, Rodríguez-Martínez, Arjona, Morales, & Gómez, 2017; Uhlhaas & Singer, 2010).

Event-related potentials (ERPs) are also used in the study of cognitive development. ERPs are the result of averaged, time-locked EEG waveforms representing discharges from large populations of neurons, and are linked to specific aspects of sensory and cognitive processing (Taylor & Baldeweg, 2002). In general, ERP amplitudes (in absolute value) grow with age from infancy through adolescence (Taylor & Baldeweg, 2002), followed by a decrease in amplitude with age throughout adulthood, with some exceptions (Barriga-Paulino et al., 2017). This general pattern is thought to reflect the synaptic pruning process, which produces a decrease in ERP amplitude beginning in adolescence due to a reduction in the number of active synapses available to produce local field potentials (Ponton et al., 2000a; Whitford et al., 2007). Faster developmental maturation of posterior ERP components also corresponds to the posterior-anterior

gradient of brain maturation that has been established by neuroanatomical research (Giedd et al., 2009). Thus, developmental trajectories of ERPs appear to mirror established neuroanatomical changes. Because ERPs are capable of indexing specific aspects of cognitive processing, they are particularly useful in understanding the functional implications of anatomical and physiological changes in development. For example, an early auditory ERP component (the N1c) matures earlier in development over the left hemisphere than over the right hemisphere, and also matures earlier to speech stimuli relative to tone stimuli, suggesting earlier development of the left hemisphere and generators contributing to speech processing (Pang & Taylor, 2000).

Mismatch Negativity and Development

An early auditory ERP component that is particularly important to the study of cognition is the auditory mismatch negativity (MMN), which is a pre-attentional indicator of early perceptual processing. It is elicited when a sequence of identical auditory stimuli is interrupted infrequently by a stimulus that is deviant along one or more dimensions, such as pitch, duration, or intensity (Näätänen et al., 2012). The MMN, which is present as early as 50 ms after stimulus onset, is the first physiologically measurable brain response that differentiates acoustic sounds (Alho, Sainio, Sajaniemi, Reinikainen, & Näätänen, 1990; Näätänen et al., 1989). It is calculated as the difference between the neural response to a repetitive standard tone and a rare deviant tone, yielding a negative component distributed over fronto-central scalp locations.

Given that the MMN likely changes with development of sensory and cognitive processing abilities (Ponton et al., 2000b), it is important to understand the typical

developmental trajectory of the MMN. Many studies have attempted to map the normative development of MMN (all measured cross-sectionally) with mixed results, summarized in **Table 1.** Notably, studies differ in MMN paradigm, MMN measurement, and age of the sample; many studies have also utilized relatively small group sample sizes (group N < 20). Some studies found that MMN amplitude decreases with age (e.g., Cooper, Todd, McGill, & Michie, 2006; Kiang, Braff, Sprock, & Light, 2009; Kisley, Davalos, Engleman, Guinther, & Davis, 2005; Todd et al., 2008), while others found the opposite effect (Bishop, Hardiman, & Barry, 2011; Oades et al., 1997), and still others found no effect of age on MMN amplitude (e.g., Cooray, Garrido, Brismar, & Hyllienmark, 2016; Morr, Shafer, Kreuzer, & Kurtzberg, 2002). Studies of the normative development of MMN latency report either reduced latency with age (e.g., Cooper et al., 2006; Gomot, Giard, Roux, Barthélémy, & Bruneau, 2000) or no effect of age on latency (e.g., Kisley et al., 2005; Kraus et al., 1993; Kraus, McGee, Sharma, Carrell, & Nicol, 1992). Of the four studies that assessed the development of MMN in adolescent samples, three found that MMN amplitude increased and latency decreased with age (Bishop et al., 2011; Oades et al., 1997; Wild-Wall, Oades, & Juran, 2005) and one found no effect of age on MMN amplitude (but did not report on MMN latency; Cooray et al., 2016). All the studies using adolescent samples, and in fact most studies of the normative development of MMN, utilize a group comparison approach by averaging across relatively wide age ranges to test effects between different age groups. This practice is problematic in that it may average out subtle age effects: Taylor & Baldeweg (2002) suggest age group ERP averages "should be made over no more than one or two years in childhood [and] 2-3 years in adolescence". Furthermore, utilizing group comparisons

does not allow tests for non-linear effects of age. Only one study of adults (ages 18-65) tested for a quadratic effect of age and found that it was not significant (Kiang et al., 2009). A non-linear effect of age on auditory MMN is feasible given that it has been found in visual MMN for individuals ages 2-27; specifically, visual MMN latency decreased with increasing age up until age 16, then stabilized (Tomio, Fuchigami, Fujita, Okubo, & Mugishima, 2012). Additionally, established neurodevelopmental changes often follow a non-linear function with age, such as changes in gray matter volume (Giedd, 2008; Lenroot & Giedd, 2006; Tanaka, Matsui, Uematsu, Noguchi, & Miyawaki, 2012). To our knowledge, a non-linear function of auditory MMN and age has not been tested in sample that included adolescents.

Neurodevelopmental changes may impact more than just MMN amplitude and latency; scalp distribution of MMN is also likely to change with typical development. As discussed in more detail below, the MMN is thought to be generated with contributions from the auditory cortices (Giard, Perrin, Pernier, & Bouchet, 1990; Javitt et al., 1994) and frontal cortex (Alho, 1995; Näätänen & Michie, 1979). Although changes in scalp distribution of MMN are not synonymous with changes in neural generators (Luck, 2014; Luck & Kappenman, 2011), evidence from source localization studies (MacLean, Blundon, & Ward, 2015; also see Näätänen, Paavilainen, Rinne, & Alho, 2007 for a review) and functional magnetic resonance imaging (fMRI) studies (Deouell, Heller, Malach, D'Esposito, & Knight, 2007; Molholm, 2004; Opitz, Rinne, Mecklinger, Cramon, & Schröger, 2002; Tse, Rinne, Ng, & Penney, 2013) suggest that the topographic pattern of MMN arises from neural sources located in bilateral superior temporal cortices and regions in and near the inferior frontal cortices (MacLean et al.,

2015; Tse et al., 2013). Thus, it is likely that ongoing neural development of these regions during adolescence (Giedd et al., 2009) will influence MMN scalp topography. Two developmental studies of MMN scalp topography have shown broader and more central MMN scalp distribution in school-age children compared to adults (Cheour, Leppänen, & Kraus, 2000) and increased fronto-temporal connectivity in adults compared to adolescents (Cooray et al., 2016). The latter study found no significant correlations with age within either the adolescent or adult sample (Cooray et al., 2016), thus the timeline of these developmental changes remains unclear. Additional work is clearly needed to fully understand the normative development of auditory MMN through adolescence.

Relevance to Developmental Neuropsychiatric Disorders

In addition to an improved understanding of the development of auditory perceptual processing, understanding this trajectory also has clinical relevance: schizophrenia is a developmental neuropsychiatric disorder with typical onset in late adolescence/early adulthood, characterized by lasting deficits in neurocognition (Nuechterlein et al., 2012). Impaired MMN is common in individuals with schizophrenia (see Erickson et al., 2015; Umbricht & Krljes, 2005 for meta-analyses; Michie et al., 2016 for a review) and it is thought that understanding this impairment may shed light on the etiology of cognitive dysfunction in this disorder (Light & Näätänen, 2013). Therefore, a thorough understanding of the typical developmental trajectory of MMN is critical for understanding how it may go awry in developmental neuropsychiatric disorders like schizophrenia.

Neuronal mechanisms of MMN

The MMN is considered to be an objective marker for auditory sensory memory accuracy (Näätänen, 2000), and has been used in research to better understand mechanisms of perceptual learning and cognition. The neuronal mechanisms that contribute to the MMN and the theoretical interpretations of the MMN response have been extensively investigated, and various hypotheses have been put forth to explain the phenomenon.

The *model adjustment hypothesis,* put forth largely by Näätänen and colleagues, states that a temporo-prefrontal network compares the current sensory input with a memory trace of previous stimuli (Näätänen & Michie, 1979; Näätänen, Gaillard, & Mäntysalo, 1978). When a deviant response occurs within the time frame of the memory trace (10s in normal subjects; Böttcher-Gandor & Ullsperger, 1992), an automatic change-detection response results in the MMN (Javitt et al., 1996; Näätänen & Winkler, 1999; Näätänen, Teder, Alho, & Lavikainen, 1992; Sussman & Winkler, 2001; Winkler, Karmos, & Näätänen, 1996). Thus, the MMN is thought to be an automatic, objective index of auditory sensory memory functioning, often referred to as "echoic memory" (Näätänen et al., 1989). Two distinct neural generators create the MMN in this model: a sensory memory mechanism from temporal sources creating "bottom-up" inputs, and an automatic attention-switching process from frontal sources providing "top-down" modulation of the deviance detection system (Escera, Yago, Corral, Corbera, & Nuñez, 2003; Giard et al., 1990; Maess, Jacobsen, Schröger, & Friederici, 2007). This model has received support from source localization studies, showing that MMN generators are

located bilaterally in the temporal cortex (Giard et al., 1990; Hari et al., 1984) and in the prefrontal cortex (Pulvermüller, 2001; Tervaniemi et al., 2000). A combined EEG/MEG (magnetoencephalography) study showed that prefrontal generators are activated after auditory cortex generators, which supports the notion that the deviance detection system in the prefrontal cortex is triggered by inputs from the temporal cortex (Garrido, Kilner, Stephan, & Friston, 2009; Rinne et al., 2000).

The *neuronal adaptation hypothesis* proposes that the MMN results from local neuronal adaptation (i.e., synaptic plasticity) in the auditory cortex, causing changes to the N1 response. The N1 is a negative component that peaks 100 ms after stimulus onset and is associated with early auditory processing at the level of A1 (Garrido et al., 2009). This hypothesis, put forth largely by Jääskeläinen and colleagues (2004), suggests that the N1 is suppressed and delayed as a function of the repeating standard stimulus, i.e., a habituation effect (Jacobsen & Schröger, 2001). The N1 to the novel, deviant stimulus then creates a relatively larger N1, and the MMN is the result of the difference wave between the two components (deviant – standard; Jääskeläinen et al., 2004). Consistent with this hypothesis is research showing that when the deviant and standard tones are more similar in frequency, the MMN amplitude is attenuated (May et al., 1999). However, the neuronal adaptation hypothesis cannot account for the fact that the MMN does not match the N1 in terms of duration and latency (Winkler, Tervaniemi, & Näätänen, 1997), scalp distribution (Giard et al., 1990) or neural generators (Grau, Fuentemilla, & Marco-Pallarés, 2007; Molholm, Martinez, Ritter, Javitt, & Foxe, 2005; Opitz et al., 2002). Moreover, given the tonotopic structure of the auditory cortex, this hypothesis also cannot account for the fact that the MMN can be elicited when the

deviant is a decrease in tone intensity, omission of stimulus (Näätänen et al., 1989), or a violation of abstract rules (e.g., an ascending tone pair in the midst of a sequence of descending tone pairs; Saarinen, Paavilainen, Schöger, Tervaniemi, & Näätänen, 1992).

A unifying theory, the *predictive coding hypothesis,* states that the brain constantly strives to minimize prediction error using interactions between levels of a cortical hierarchy in order to estimate the most likely cause of an input (Friston, 2005; Friston, Harrison, & Penny, 2003; Garrido et al., 2009; Mumford, 1992; Rao & Ballard, 1999). The MMN is the result of a failure to predict bottom-up input (i.e., a "mismatch" between the predicted and actual sensory input), resulting in a "prediction error signal" (Friston, 2005; Garrido et al., 2009; Garrido, Kilner, Kiebel, & Friston, 2007; Lieder, Daunizeau, Garrido, Friston, & Stephan, 2013; Wacongne, 2016). The prediction error signal is then used to make online modifications to the model for predicting auditory inputs (Näätänen & Winkler, 1999; Winkler et al., 1996). In other words, the repetitive standards lead to the prediction that the next sound is likely to be a continuation of this regularity. When a deviant sound violates this prediction, a prediction error leads to the updating of the predictive model, reflecting the principles of experience-dependent plasticity (Michie et al., 2016). The MMN, then, is not *just* a response to novelty, but to how unlikely a particular sound transition is given a preceding sequence (Todd, Harms, Schall, & Michie, 2013). This model predicts the adjustment of a fronto-temporal stimulus comparison model (cf. *model-adjustment hypothesis*) via plastic changes in synaptic connections within the primary auditory cortices (cf. *neuronal adaptation hypothesis*; Garrido et al., 2009; 2008). Indeed, a number of studies convincingly demonstrate that MMN, at least in part, reflects genuine memory-based deviance

detection rather than a habituation effect or refractoriness of neurons (Jacobsen & Schröger, 2001; Ruhnau, Herrmann, & Schröger, 2012). Recent computational modeling has also shown that the generation of the MMN can be explained by local adaptation within the primary auditory cortex and interactions within a fronto-temporal network (Cooray et al., 2016).

Corroborating the predictive coding hypothesis and particularly the dependence of prediction error on synaptic plasticity, a number of studies have also shown that MMN relies at least partially on N-methyl-D-aspartate receptor (NMDAR) functioning (Mitchie et al., 2016; Friston, 2005; Garrido et al., 2009). Research on nonhuman primates has shown that both competitive and noncompetitive NMDA antagonists reduce MMN amplitude without affecting prior ERPs in the primary auditory cortex (Gil-da-Costa et al., 2013; Javitt et al., 1996). Additionally, the administration of other agonists and antagonists at various non-NMDA receptors does not reduce the MMN, again suggesting a pivotal role of NMDARs (for reviews, see Todd et al., 2013; Umbricht & Krljes, 2005). These findings also have particular clinical relevance in that attenuated MMN amplitude is typically found in individuals with schizophrenia (Erickson et al., 2015; Umbricht & Krljes, 2005); a disorder which is thought to at least partially reflect impairment in NMDAR-glutamatergic system functioning (Todd et al., 2013). This theory arose from observations that, in healthy individuals, antagonists of NMDARs such as ketamine or phencyclidine create both transient psychotomimetic effects and attenuations in the MMN (Todd et al., 2013; Umbricht, Schmid, Koller, Vollenweider, Hell, & Javitt, 2000b; Wacongne, 2016). A recent double-blind study demonstrated that treatment with D-serine, a naturally occurring NMDAR glycine-site agonist, led to improvement in MMN

amplitude and clinical symptoms in individuals with schizophrenia, providing further support for the role of NMDARs in MMN generation (Kantrowitz et al., 2018).

MMN, cognition, and functioning

As a measure of auditory deviance detection, MMN is often used to investigate or index behavioral performance on auditory or linguistic tasks. For example, MMN amplitude is capable of predicting behavioral performance on auditory and linguistic discrimination tasks in healthy individuals (Cheour, Shestakova, Alku, Ceponiene, & Näätänen, 2002; Winkler et al., 1999). In children receiving auditory training for cochlear implants or perceptual learning deficits, increases in MMN amplitude precede behavioral measures of learning and improvements in performance on auditory tasks (Tremblay, Kraus, & McGee, 1998).

MMN has also been used to investigate relationships with other domains of cognition and community functioning. The rationale for investigating these relationships is put forth by Light and colleagues (2007):

> "Efficiency at elementary levels of information processing may underlie the successful encoding, retrieval and discrimination of relevant information, which in turn facilitates the iterative and responsive processing necessary for adaptive cognitive and social functioning."

In essence, Light and colleagues suggest a computational modeling, "garbage in, garbage out" effect of disrupted MMN on cognition and functioning. If there is a disruption in an upstream, elementary process of auditory sensory functioning, this will eventually cause or contribute to downstream impairments in broader aspects of cognition and community

functioning. Indeed, in individuals with schizophrenia, attenuated MMN amplitude is associated with: lower clinician ratings of global daily functioning (Light & Braff, 2005a), lower ratings of functional status (Light & Braff, 2005b), reduced social skills acquisition following 3-month social training program (Kawakubo et al., 2007; Light & Braff, 2005a), poorer social cognition (Wynn et al., 2010a), deficits in verbal memory (Baldeweg et al., 2004; Kawakubo et al., 2006), and reduced executive functioning (Kiang et al., 2007).

Much less is known about how MMN relates to cognition across typical development. In a small sample of healthy adults (N = 20) Light and colleagues (2007) found that MMN was associated with community functioning but not neurocognitive test performance (reading ability, verbal memory, executive functioning, working memory; Light, Swerdlow, & Braff, 2007). A study of older adults (N = 25, ages 55-85) found that greater MMN amplitude was significantly associated with better verbal learning and memory and executive functioning speed (Tower of London completion time), but not processing speed or behavioral performance on executive functioning tasks (Kisley et al., 2005). Another study found that children with high IQ had larger MMN compared to children with average IQ (Liu, Shi, Zhang, Zhao, & Yang, 2007). **To our knowledge, no studies of typically developing adolescents and young adults have investigated the association between MMN, cognition, and community functioning.** This knowledge is critical for advancing understanding of how a complex neurodevelopmental disorder like schizophrenia can affect these relationships.

MMN as a predictor of outcomes

There has been increasing interest in using MMN to predict outcomes in clinical populations, particularly in schizophrenia. Many studies have noted MMN impairments in individuals at clinical high-risk for schizophrenia (Bodatsch et al., 2011; Jahshan et al., 2012; Perez et al., 2014; Shaikh et al., 2012) and three have found that the degree of baseline MMN impairment predicts conversion to psychosis in clinical high-risk individuals (Bodatsch et al., 2011; Shaikh et al., 2012; Perez et al., 2014). This suggests that neural MMN generators associated with processing auditory deviance may be compromised even in early stages of schizophrenia (Perez et al., 2014). However, given the paucity of studies in healthy control populations, **it is unclear whether the ability of MMN to predict outcome in clinical high-risk psychosis is due to its indexing of *disorder-specific* properties (i.e., disrupted NMDAR signaling), or whether MMN is broadly predictive of individual variability in functional outcome, regardless of disorder status**. This question is of particular importance given that many clinical high-risk individuals are adolescents, and that MMN may continue to evolve throughout adolescence (Cooray et al., 2016) and perhaps index future cognitive and community functioning (Light et al., 2007).

Specific Aims

Aim 1 of this study is to assess the typical developmental trajectory of MMN in a large sample of healthy adolescents and young adults. We will test non-linear and linear effects of MMN amplitude and latency with increasing age. Given prior research on normative development of MMN (see **Table 1**), we hypothesize that MMN amplitude and latency will decrease with increasing age. Evidence for a non-linear trajectory of

MMN could be a reflection of other non-linear neurodevelopmental changes during adolescence, such as reduction of cortical gray matter (Lenroot & Giedd, 2006; Tanaka et al., 2012). Linear changes in MMN amplitude and latency may be a reflection of established linear developmental changes in EEG frequency oscillations (Marshall, Bar-Haim, & Fox, 2002; Matousek, 1973), or, in the case of decreased MMN latency, a reflection of linear increases in white matter over this age range (Giedd, 2008; Lenroot & Giedd, 2006; Uda et al., 2015). Lastly, given prior research suggesting that frontal and temporal generators of MMN may mature at different rates (Alho, 1995; Olesen et al., 2003; Stevens et al., 2009), we predict differences in MMN scalp distribution across adolescent development.

Aim 2 of this study is to examine cross-sectional relationships between MMN, cognition, and functioning in a large sample of typically developing adolescents and young adults. We will investigate three measures of cognition: 1) verbal learning and memory; 2) processing speed; and 3) general intelligence. Verbal learning and memory will be used as previous research has found associations between MMN and verbal learning and memory performance (Baldeweg et al., 2004; Kawakubo et al., 2006; Kisley et al., 2005) as well as more general associations between MMN and auditory sensory memory ability (Näätänen, 2000). While some findings suggest working memory reaches adult levels in childhood, several recent studies have found that working memory capacity continues to improve throughout adolescence (Brockmole & Logie, 2013; Isbell, Fukuda, Neville, & Vogel, 2015; Spronk & Jonkman, 2012). Processing speed will be investigated, as it continues to improve throughout adolescence (Kail, 1991; Kail & Ferrer, 2007) and may be associated with MMN via increased myelination in fronto-

temporal white matter tracts (Uda et al., 2015; Wozniak & Lim, 2006). General intelligence will be assessed as an overall measure of cognitive ability, thus parsing out whether MMN is associated with specific neurocognitive domains, or cognition more generally. Given relationships between MMN and auditory sensory memory (Cheour et al., 2002; Näätänen, 2000; Winkler et al., 1999), we hypothesize that MMN will be associated with measures of verbal learning and memory, but not general intelligence or processing speed. Based on prior literature in smaller adult samples (Light et al., 2007)) and in clinical populations (Light & Braff, 2005a), we also hypothesize that MMN will be associated with community functioning.

Aim 3 of this study is to examine whether MMN measured at baseline can predict functional and cognitive outcomes in typically developing adolescents and young adults one year later. Given previous research in clinical populations (Kawakubo et al., 2007; Light & Braff, 2005a), we also hypothesize that MMN will be predictive of functioning one year later.

Methods

Participants

Data were collected from a consortium of eight programs focusing on the psychosis prodrome (North American Prodrome Longitudinal Study NAPLS2; see Addington and colleagues (2012) for additional recruitment information). Only healthy control participants are included in the present study. As described in prior publications, individuals were excluded if they: had a first-degree relative with a psychotic disorder or

any disorder involving psychotic symptoms; met criteria for any prodromal syndrome on the Structured Interview for Prodromal Syndromes (SIPS; McGlashan, Miller, Woods, Hoffman, & Davidson, 2001; Miller et al., 2002; Rosen, Woods, Miller, & McGlashan, 2002); met criteria for any current or past psychotic disorder or a Cluster A personality disorder diagnosis; were currently using psychotropic medication; had a history of a central nervous system disorder or significant head injury; had IQ < 70. The present study represents a subset of the total healthy control sample, consisting of individuals who completed neurocognition, social and role functioning and EEG assessments at baseline, then completed 12-month follow-up neurocognition and functioning assessments. After removing six subjects for poor quality MMN data (described below), the final sample consisted of N = 157 individuals. The average length of follow-up was 55.26 weeks (range 47-75, SD = 6.27). See **Table 2** for additional demographic information.

Neurocognitive measures

Neurocognitive measures were administered at baseline and at 12-month follow-up (see **Table 2**).

- General Intelligence: Wechsler Abbreviated Scale of Intelligence (WASI, (Wechsler, 1999). Age-corrected T-scores from the Vocabulary and Matrix Reasoning subtests of the WASI are combined to form an estimate of IQ.
- Verbal learning and memory: Three learning trials of the Hopkins Verbal Learning Test - Revised (HVLT-R; Brandt, 1991) are administered to assess verbal learning. The HVLT-R includes 12 words that contain three sets of categorically related words that are read by the assessor at a rate of one per two

seconds. After each trial, the subject is asked to recall the words. The dependent variable is the total number of correct responses over all three trials.

- Processing speed: Brief Assessment of Cognition in Schizophrenia: Symbol-Digit Coding (BACS; Keefe et al., 2004). The subject uses a key to match numerals 1-9 with symbols on a response sheet for 90 seconds. The dependent variable is number of correct numerals (range: 0-110).

Assessment of functioning

Functioning was measured at baseline and at 12-month follow-up (see **Table 2**).

- Global Assessment of Functioning (Hall, 1995). The GAF scores symptom severity and functioning on a 1-100 scale in 10-point intervals, with the 81-100 interval signifying absent or minimal symptoms or problems and the 0-10 interval signifying an individual in persistent danger of severely hurting self or others (Hall, 1995). The GAF scale shows adequate to excellent reliability and acceptable concurrent validity (Hall, 1995).

MMN Paradigm

The present study used MMN data from administration at baseline only. Auditory stimuli were presented to participants at 78 dB sound pressure level via Etymotic ER3-A insert earphones (Etymotic Research, Inc., Elk Grove Village, Illinois). Each subject completed three runs of stimuli, with each run comprising a fixed pseudorandom sequence of 875 tones, consisting of 90% standards (50ms, 633 Hz) and 10% deviants: frequency deviant 50 ms 1000 Hz; duration deviant 100ms, 633 Hz; double-deviant 100

ms, 1000 Hz. Because frequency-MMN is the most widely used MMN paradigm (Jacobsen & Schröger, 2001), only frequency-MMN was used for all analyses. All tones had 5ms rise/fall times and were presented with a 510-ms SOA. Participants were instructed to attend to an unrelated visual task.

Data Acquisition and Preprocessing

EEG was recorded from a 64-channel (standard 10-20 scalp locations) BioSemi Active Two recording system (Biosemi, Amsterdam, Netherlands). Continuous EEG data were digitized at a rate of 1024 Hz, referenced offline to averaged earlobe electrodes, high-passed filtered at 1 Hz, and separated into 600-ms epochs (-100 to 500ms) relative to onsets of auditory stimuli. Electro-oculogram (EOG) data were recorded from electrodes placed above and below the right eye and at the outer canthi of both eyes to capture vertical and horizontal eye movements. These electrodes were then used to correct for blink and eye movement artifacts using the method by Gratton & Coles (1983). Epochs were baseline corrected (-50 to 0 ms). Then, following methods from (Hay et al., 2015), electrodes containing epochs with outlier values ($|z| > 3$) were replaced by interpolated values based on a routine implemented in an automated EEG data cleaning algorithm (Nolan, Whelan, & Reilly, 2010). This method is similar to using independent component analysis (ICA) to detect and delete artifacts from EEG data, but is improved for application to high-density EEG data and reduces variance in ERP baseline (a measure of noise; Nolan et al., 2010). Epochs were then rejected if they contained amplitudes greater than ±100μV in fronto-central electrodes used in the analyses: F3, Fz, F4, C3, Cz, C4.

Next, ERP averages for standards and deviants were determined using a sorted averaging method previously shown to reduce noise in the MMN waveform by averaging over the subset of trials that optimizes the estimated signal to noise ratio (eSNR; Hay et al., 2015; Perez et al., 2014; Rahne, Specht, & Mühler, 2008). Briefly, single-epoch root mean squared (RMS) amplitude values for each trial were calculated and sorted in ascending order for each standard and deviant stimuli. The subset of sorted trials selected for ERP averaging were associated with the largest eSNR, which is the ratio of the number of trials to the variance of the amplitude values across trials (Hay et al., 2015). This method is thought to improve the MMN signal, which, due to the 90% standard to 10% deviant paradigm, results in fewer numbers of epochs and thus worse SNR (Rahne et al., 2008). Additionally this method can reduce any superposition of preceding responses onto the consecutive epoch, again yielding a cleaner MMN waveform (Rahne et al., 2008). Following sorted averaging, ERPs for standards and deviants were low-pass filtered at 30 Hz, then the standard tone ERP waves were subtracted from frequency-deviant tone ERP waves to create difference waves. The MMN was identified in each subject's difference wave as the most negative peak between 90 and 170ms. MMN peak amplitudes and latencies were quantified. Data from six individuals were excluded who retained fewer than 40 frequency-deviant epochs, resulting in a total sample of N = 157.

Statistical Analyses

An average MMN peak amplitude from six frontal and central electrodes (F3, Fz, F4, C3, Cz, C4) was used in order to reduce multiple comparisons and test robust effects (Hay et al., 2015). The effect of site was controlled for according to methods from Perez

and colleagues (2014; 2011; 2012). Specifically, averaged MMN amplitude (from F3, Fz, F4, C3, Cz, C4) was regressed on site. Resulting values were used to derive predicted normal MMN amplitudes for each participant based on his/her site. Differences between observed and site-specific predicted MMN amplitudes were then divided by the standard error of regression (from the original regression model), yielding site-adjusted MMN *Z* scores. This *Z* score expresses, in standard units, the degree to which a participant's MMN amplitude deviates from the expected value for his/her site (Perez et al., 2014). The same adjustment was done separately for averaged MMN latency and average MMN amplitude by site (F3, Fz, F4 and C3, Cz, C4). Thus, all statistical models used site-adjusted MMN scores. For each dependent measure of MMN, data were examined for outliers (operationalized as ±2* interquartile range; Tukey, 1977); significant outliers were removed and the analysis was repeated excluding outliers to ensure that outliers were not driving any significant effects observed. All statistical analyses were performed using SPSS software v. 24 (Chicago, Illinois). Regression equations were used to assess the effect of average MMN amplitude and latency (referred to simply as MMN amplitude and latency) on all outcomes. Effect sizes for regression analyses are reported as Cohen's f^2. Age was treated as a continuous variable in all regression analyses. All significance tests were two-tailed with alpha set at $p = .05$.

Aim 1: To test the trajectory of MMN amplitude and latency with age, hierarchical regression was conducted to test non-linear effects of age. Specifically, we applied a quadratic regression and tested whether this significantly improved r^2 compared to linear regression (Zar, 2010). If there was significant improvement, we applied the next higher-order (cubic) regression and tested for significant improvement in r^2, and so on, until no

significant additional improvement was found. This was done separately for MMN amplitude and latency.

Next, we assessed whether the scalp topography of MMN amplitude changed over development, which would theoretically indicate accompanying changes in the neural generators of the MMN components (Cooray et al., 2016; MacLean et al., 2015; Tse et al., 2013). We tested the interaction between Frontal MMN amplitude (from F3, F4, Fz) and Central MMN amplitude (from C3, C4, Cz) on Age using hierarchical linear regression. A significant interaction would indicate divergent trajectories of MMN from Frontal vs. Central electrode sites with increasing age.

Aim 2: Separate linear regression models were used to test associations between variables measured at the baseline time point. Functioning (GAF), verbal learning and memory (HVLT), processing speed (BACS), and estimated intelligence (WASI-IQ) were entered as dependent variables. MMN amplitude and latency were entered as independent variables. An Age X MMN interaction was tested first. If the interaction was not significant, then it was removed from the model, and Age remained as a covariate.

Aim 3: Separate linear regression models were used to test whether baseline MMN can predict 12mo outcomes. Twelve-month scores for functioning (GAF), verbal learning and memory (HVLT), processing speed (BACS), and estimated intelligence (WASI-IQ) were entered as dependent variables. MMN amplitude and latency were entered in each model as independent variables. For each model, the baseline value of the dependent variable (e.g., baseline GAF) was entered first to control for individual difference effects. The reported MMN *B* value, therefore, indicates the extent that MMN can predict an outcome *over and above* the association at baseline. For each model, an Age X MMN

interaction was tested first. If the interaction was not significant, then it was removed from the model, and Age remained as a covariate.

Results

See **Table 2** for baseline demographic information and neurocognitive and functioning scores. The mean number of frequency-deviant MMN epochs was 80.16 (SD = 8.6). The mean weeks between baseline and 12mo assessment was 55.26 (SD = 6.27, range 47 – 75). Time in weeks between assessments was added as a covariate in separate models and did not affect outcomes; therefore, it was left out of the reported analyses. There were no significant effects of gender on MMN amplitude ($p > .50$) or latency ($p > .40$).

Aim 1: There was a significant linear (but not quadratic; R^2-change < .01, $p > .80$) association between Age and MMN amplitude ($B = .046$, $p = .004$, $f^2 = .054$). Similarly, there was a significant linear (but not quadratic; R^2-change < .01, $p > .50$) association between Age and MMN latency ($B = -.032$, $p = .046$, $f^2 = .026$), indicating shorter latency with increasing age. See **Figures 2** and **3**.

After removing a significant outlier in Central MMN amplitude (> 2* interquartile range) the interaction between Frontal X Central electrode MMN amplitude and Age was not significant ($B = -0.468$, $t(155) = -1.57$, $p = .12$), indicating a similar trajectory of Frontal vs. Central MMN amplitude with increasing age across the sample.

Aim 2: As there were no significant Age X MMN interactions for any dependent variables, Age remained in all regression equations as a covariate. There were no significant associations between baseline MMN amplitude and baseline functioning (GAF; $p = .12$), or between baseline MMN amplitude and any neurocognitive variables at

baseline (all *p*s > .20). All associations for MMN latency were also not significant (all *p*s > .20).

Aim 3: As there were no significant Age X MMN interactions for any dependent variables, Age remained in all regression equations as a covariate. All regressions were modeled by controlling for baseline (BL) levels of the dependent variable. For example, 12mo GAF = BL GAF + Age + BL MMN. Baseline MMN amplitude significantly predicted 12mo HVLT Total score (MMN amplitude B = -0.577, p = .030; full model adj-R^2 = 0.396, R^2-change for MMN = 0.019). Full regression model: 12mo HVLT Total = 10.53 + 0.554(BL HVLT Total) + 0.121(Age) – 0.577(MMN amplitude). Baseline MMN amplitude also predicted 12mo GAF score with marginal significance (MMN amplitude B = -1.053, p = .056; full model adj-R^2 = 0.451, R^2-change for MMN only = 0.011). Full regression model: 12mo GAF Total = 37.42 + 0.557(BL GAF) + 0.037(Age) – 0.957(MMN amplitude). Baseline MMN amplitude did not significantly predict 12mo BACS (p = .183) or 12mo WASI-IQ (p = .807). There were no significant outcomes for MMN latency models (all *p*s > .20).

Discussion

The present study investigated the normative development of MMN from adolescence through adulthood, and its association with cognition and community functioning. There were significant linear relationships between age and MMN amplitude and latency, showing diminishing MMN amplitude and latency with increasing age, consistent with some prior, smaller studies of adolescents (Oades et al., 1997), studies comparing younger to older adults (Cooper et al., 2006; Kisley et al., 2005; Wild-Wall et

al., 2005), and a study comparing children to adults (Gomot et al., 2000). This indicates that automatic processing of auditory deviance continues to develop throughout adolescence. A strength of the present study is that we examined age as a continuous variable rather than utilizing an age group comparison approach. This avoided the possibility of averaging out age effects (Taylor & Baldeweg, 2002) and allowed us to test for nonlinear associations between MMN and age. Consistent with the findings of Kiang and colleagues' (2009) study of healthy adults (age range 18-65), we did not find a significant quadratic effect of age on MMN amplitude or latency. However, prior research suggests such a relationship occurs in the development of visual MMN (Tomio et al., 2012). Specifically, in a sample of 107 youth (age range 2-27), Tomio and colleagues (2012) found a quadratic association between visual MMN latency and age, characterized by decreased latency with increasing age that plateaued at age 16. Given the differences between auditory and visual MMN (Cammann, 1990) it is unclear whether we should expect a similar quadratic relationship in the auditory domain. It is possible that our sample size – although the largest to date – was not sufficient to detect a significant nonlinear effect. Kiang and colleagues (2009) estimated an effect size R^2 = 0.26 for the non-significant quadratic relationship between MMN amplitude and age with a slightly smaller sample size. Given the much lower observed effect size for the quadratic effect of age in the present study (R^2 = 0.040), our study is slightly under-powered to find this effect (B = 0.73). Notably, while Tomio and colleagues (2012) also utilized a smaller sample size, effect sizes for visual MMN were also larger compared to the present study (R^2 = 0.33). Therefore, it is possible that our narrower age range yielded a smaller effect size. Future studies should assess for nonlinear changes in auditory MMN

in childhood through adulthood to better understand the full typical development of auditory sensory memory ability. Longitudinal designs are also needed, as almost all existing research is cross-sectional.

The finding that MMN amplitude and latency both decrease with age is consistent with some previous studies (Cooper et al., 2006; Kiang et al., 2009; Todd et al., 2008; Wild-Wall et al., 2005) but not all (Bishop et al., 2011; Oades et al., 1997). The amplitude of later component, the P3a, has also shown to decline as a function of age in healthy adults (Kiang et al., 2009); as such, our results are consistent with the majority of research on neural responses to an auditory oddball paradigm. Decreased MMN latency with age is consistent with established linear changes white matter myelination during this age range (Giedd, 2008; Lenroot & Giedd, 2006; Uda et al., 2015). Declining MMN amplitude with age may be related to several processes. First, as MMN is a difference waveform, declining MMN may be due to a) smaller amplitude response to the deviant tone; b) larger amplitude response to the standard tone; or c) a combination of both. The data presented here are not capable of parsing out the separate trajectories of the standard vs. deviant response; however, future analyses will examine this factor, as this question has not been examined in the existing literature. Structural brain changes may contribute to a declining MMN signal with age: gray matter thickness in auditory cortical areas decrease linearly from childhood into early adulthood, likely due to synaptic pruning processes (Gogtay et al., 2004). Such changes could contribute to a smaller response to the deviant MMN tone and, thus, smaller MMN. In adults with schizophrenia, left hemisphere Heschl gyrus reduction has been shown to be highly correlated with MMN reduction over one year (Salisbury et al., 2007), but similar studies in typically

developing populations are lacking. Developmental changes that contribute to alterations in EEG frequency oscillations may also contribute to the decline seen in MMN amplitude. A recent study showed that neural responses to deviant tones occur primarily in the theta (4-7 Hz) frequency band, consistent with cortico-cortical processes, whereas responses to standard tones occurred primarily in alpha (8-12 Hz) frequency band, consistent with thalamo-cortical activation (Lee et al., 2017). Developmental research has shown that during childhood and adolescence, there is a relative reduction in activity of lower frequency oscillations (e.g., theta) and an increase in activity in oscillations in the alpha and beta-range (see Uhlhaas & Singer, 2010 for a review). These changes would be consistent with a developmental decrease in MMN amplitude. Lastly, the role of intra-individual neural variability on MMN amplitude is unclear. A longitudinal study recently demonstrated that decreased trial-to-trial variability in amplitude of brain state signals during a working memory task occurs in adolescence and young adulthood (Montez, Calabro, & Luna, 2017). Thus, developmental stabilization of neural signals could also contribute to the reduction in MMN amplitude seen here.

In order to better understand the development of MMN, we examined changes in scalp distribution with age. After removing an outlier, we did not find evidence for a significant Electrode Site X Age, suggesting that MMN generators yield similar changes in Frontal and Central scalp topographic locations with age. While here we did not find a significant topographical shift in MMN with age, ample neurodevelopmental evidence suggests that neural generators of MMN develop at different rates in adolescence and young adulthood. Specifically, MMN neural generators have been found primarily in temporal (Giard et al., 1990; Javitt et al., 1994) and frontal cortices (Deouell et al., 2007;

Molholm, 2004; Opitz et al., 2002; Tse et al., 2013) which is reflected in scalp measurements: MacLean and colleagues (2015) demonstrated that right inferior frontal gyrus and right superior temporal gyrus generators accounted for 27.8% and 10.4% of scalp MMN variance, respectively, in a young adult sample. Divergent trajectories of gray matter maturation in these cortical areas (Giedd et al., 1999) and/or increased myelination in white matter tracts linking prefrontal areas of the cortex with more posterior sensory and motor areas (Olesen et al., 2003; Stevens et al., 2009) could alter MMN amplitude, therefore the site of MMN measurement may be important when considering developmental changes. Additionally, established regional differences in neuronal development (Giedd et al., 2009) have found that primary sensory areas show earlier maturation than areas that mediate higher-order cognitive functions (Rubia, Hyde, Halari, Giampietro, & Smith, 2010; Shaw et al., 2008), making it likely that changes in MMN in adolescence and young adulthood are reflective of development of frontal cortices. This pattern has been demonstrated in the generation of the auditory ERP component N100, which shifts from temporal to frontal areas of processing between childhood and adolescence (Bender, Oelkers-Ax, Resch, & Weisbrod, 2006; Ponton, Eggermont, Khosla, Kwong, & Don, 2002). Additional source localization studies and longitudinal studies combining EEG and MRI methods will lead to a better understanding of how brain development impacts MMN neural generators and scalp topography.

The second aim of this study was to examine cross-sectional relationships between MMN, cognition and functioning in typical development. There were no significant associations between MMN amplitude and general functioning, verbal learning and memory, processing speed, or general intelligence. There were also no significant

relationships between MMN latency and functioning or cognition. These results are similar to one prior study that assessed a small sample of healthy adults (Light et al., 2007). Significant relationships between MMN, cognition, and functioning have typically been demonstrated in studies of individuals with schizophrenia (e.g., Kawakubo et al., 2007, Light & Braff, 2005a; 2005b; Wynn et al., 2010a). A lack of association in a typically developing sample could be the result of restricted range or ceiling effect of functioning and cognitive ability. One could also posit that disrupted glutamatergic NMDAR signaling in schizophrenia (Mitchie et al., 2016; Friston, 2005; Garrido et al., 2009) could partially contribute to impairment in MMN, cognition, and functioning, yielding greater shared variance and significant associations. Additional research is needed to clarify the mechanisms by which MMN and functioning are related in schizophrenia, and whether these translate to healthy individuals.

The third aim of this study demonstrated that baseline MMN amplitude significantly predicts 12-month outcomes in a typically developing sample. Specifically, baseline MMN amplitude significantly predicted 12mo verbal learning and memory (HVLT) performance *over and above* baseline performance and age. Baseline MMN amplitude also predicted 12-month global functioning *over and above* baseline functioning and age with marginal significance. MMN amplitude did not significantly predict other cognitive measures of processing speed (BACS) or general intelligence (WASI-IQ). No significant relationships were found between baseline MMN latency with subsequent cognitive and functional outcome.

The ability to predict 12-month outcomes in a typically developing sample using MMN amplitude has significant implications for psychosis risk research. Three studies of

individuals at clinical high-risk for psychosis have found that the degree of baseline MMN impairment can predict conversion to psychosis (Bodatsch et al., 2011; Perez et al., 2014; Shaikh et al., 2012). All interpreted this relationship to be the result of disrupted glutamate/NMDAR functioning impacting MMN and leading to progression of prodromal symptoms (Bodatsch et al., 2011; Perez et al., 2014; Shaikh et al., 2012). While the present study does not negate the possibility that MMN could add to the predictive validity of the clinical high-risk paradigm (Perez et al., 2014), researchers should be wary of attributing these effects solely to disease-specific processes and disrupted signaling. Rather, the present study adds to evidence that MMN may impact cognition and functioning via iterative effects of efficiency at elementary levels of information processing (Light et al., 2007). In other words, improved detection of auditory deviance and predictive coding could impact encoding, retrieval and discrimination of relevant information, eventually influencing auditory/verbal memory and community functioning (Light et al., 2007). These processes are likely to utilize glutamatergic NMDAR functioning across the normal range of functioning as well; we are simply noting that impaired NMDAR signaling is not necessary (or likely sufficient) to predict outcomes from MMN amplitude. It is also noteworthy that the present study, and most studies of the psychosis prodrome, utilized an adolescent and young adult sample. While we did not find an interaction between age, MMN, and outcomes, the ongoing neural, social, and cognitive development in adolescence and young adulthood could contribute to the ability of MMN to predict outcomes.

The finding that the prediction of cognitive outcomes by MMN was specific to the domain of verbal/auditory learning and memory also supports the theory that iterative

effects of elementary levels of auditory processing can influence outcomes; if MMN is considered to be an objective index of auditory sensory memory functioning (Näätänen et al., 1978), then it stands to reason that these iterative effects would be greatest in the auditory memory domain. This result is also similar to a study of older adults that found greater MMN amplitude was associated with improved verbal learning and memory, but not processing speed or executive functioning (Kisley et al., 2005). It should be noted that we are not assuming that auditory sensory memory functioning, verbal learning and memory, and community functioning only interact in a linear, unidirectional or "downstream" fashion (Miller & Rockstroh, 2013), only that iterative interactions occur. Given that the present study showed that greater MMN amplitude predicted improvements in cognition and functioning one year later, a longitudinal meditational model could establish a temporal pattern to these effects and possibly lead to causal models, which could have significant pharmacological implications (Light & Näätänen, 2013; Näätänen et al., 2015).

There are several limitations of this study that should be explicitly noted. Namely, given that we did not use source localization techniques, we cannot definitively know what changes in the brain contributed to changes in MMN with age. Also, widening the age range to include school-age children could increase the effect size of non-linear effects of age on MMN, as was found in a prior study of visual MMN (Tomio et al., 2012). Lastly, the design and sample size of the present study did not allow us to test longitudinal models of changes in MMN in relation to changes in cognition and functioning.

Summary

Mismatch negativity is a useful objective measure of pre-attentive auditory sensory memory functioning (Näätänen et al., 2012). Given research that has established major MMN neural generators in the temporal and prefrontal cortices (Deouell et al., 2007; Giard et al., 1990; Javitt et al., 1994; Molholm, 2004; Opitz et al., 2002; Tse et al., 2013), it follows that adolescent neuronal development in and between these regions (Durston et al., 2006; Paus, 2005; Uda et al., 2015) would contribute to changes in MMN throughout adolescence. However, existing research has yielded mixed outcomes (Bishop et al., 2011; Wild-Wall et al., 2005) and most did not test for non-linear associations between MMN and age. In addition to neuronal changes, changes in neurocognitive functions occur during adolescence (Crone et al., 2006), many of which have been linked to changes in the brain (Goldman-Rakic, 1987; Luna et al., 2001; Somerville & Casey, 2010). Mismatch negativity has been shown to be cross-sectionally correlated with cognition (Baldeweg et al., 2004; Kawakubo et al., 2006) and functioning in individuals with schizophrenia (Light & Braff, 2005b), but few studies have examined these associations in healthy individuals (Kisley et al., 2005; Light et al., 2007) and none have examined these associations in typically developing adolescents. New research has shown that MMN impairment predicts conversion to psychosis in clinical high-risk individuals (Bodatsch et al., 2011; Shaikh et al., 2012; Perez et al., 2014); however, no research has tested whether MMN can predict outcomes in a healthy population. The present study thus addressed these gaps by utilizing, to our knowledge, the largest sample of healthy adolescent and young adults in MMN literature. This sample is also unique in that they completed cognition and functioning measures at baseline and one year later.

With this design, we showed: 1) significant linear (but not quadratic) reductions in MMN amplitude and latency with age; 2) no cross-sectional associations between MMN and cognition or functioning; and 3) Baseline MMN amplitude significantly predicted verbal learning and memory performance (over and above baseline performance) and community functioning, one year later (over and above baseline functioning), but did not significantly predict processing speed or general intelligence at 12 month follow-up. These results demonstrate that MMN continues to develop throughout adolescence and young adulthood, which may be a reflection of other neuronal changes occurring at that time. The results of Aim 3 also show that MMN amplitude can predict outcomes in a typically developing population. We suggested that MMN could impact these outcomes via iterative processes beginning in auditory sensory memory functioning: better processing in early stages of perceptual memory and predictive coding may yield better encoding, retrieval, and discrimination of information, which then may eventually yield improved performance in auditory memory and functioning, in agreement with the theory put forth by Light and colleagues (2007). Our findings suggest that these findings in populations can be extended to typical development; i.e., MMN amplitude can predict outcomes in both samples. Future research can build on these findings to develop more comprehensive models on the association between MMN, cognition and functioning.

Table 1. Summary of research on normative development of MMN.

Article	Sample	MMN stimuli	Electrodes	Amplitude findings	Latency findings
Kraus et al., 1992	7-11yo (N=10); 16-29yo (N=10)	Speech sounds	Fz	No significant age effects	No significant age effects
Kraus et al., 1993	7-11yo (N=16); 17-29yo (N=10)	Speech sounds	Fz	Trend toward larger amplitude in children (NS)	No significant age effects
Korpilahti & Lang, 1994	7-13yo (N=12)	Tones	F8 F4 Fz F3 F7 C6 C4 Cz C3 C5	Not reported	Significant decrease with increasing age
Oades et al., 1997	Four groups with N=11 per group; Group mean ages 10, 14, 17, 21, respectively	Tones	Fz T5 Fz Pz F8 T6 F7 F8 T3 T4 T5 T6	Significant Age X Site interaction: bigger amp at frontocentral sites in 17-21yos vs. 10-14yos	Across all subjects: significant correlation (decrease with increasing age) at frontal and posterior sites
Cheour et al., 1998	Full-term neonates (N=12); 3mo infants (N=6)	Speech sounds	F4	No significant age effects	No significant age effects
Pang et al., 1998	8mo infants (N=15); 26-44yo (N=10)	Speech consonants	Fz Cz C3 C4 T3 T4 Pz P3 P4 T5 T6	Significant group X electrode interaction: greater adult MMN at Cz and C3; greater infant MMN at T3.	No significant age effects
Gomot et al., 2000	5-10yo (N=25); 20-30yo (N=8)	Tones	Fz	Trend toward larger amplitude in children vs. adults (NS)	Significant decrease in adults vs. children
Shafer et al., 2000	4-10yo (N=66); 22-38yo (N=12)	Tones	Fz	No significant age effects	Significant decrease in adults vs. children; and significant negative correlation in child group

Morr et al., 2002	Infants 2-47mo (N=63)	Tones	Fz	No significant age effects	Significant reduction with age
Maurer et al., 2003	6-7yo (N=29); Mean age 26.6 (N=24)	Tones and phonemes	Fz	Positive mismatch response in children and negative mismatch response in adults.	Not reported
Wild-Wall et al., 2005	Mean age 17.6 (N=22); Mean age 30.4 (N=18)	Tones	F3 Fz F4 FC3 FCz FC4 Cz mastoids	Significant decrease in adults vs. adolescents at FCz and Cz	Trend toward decrease in adolescents vs. adults at FCz (NS)
Kisley et al., 2005	18-23yo (N=18); 55-85yo (N=18)	Tones	Fz Cz mastoids	Significant decrease in older adults vs. younger adults	No significant age effects
Cooper et al., 2006	18-39yo (N=27); 51-79yo (N=21)	Tones	Fz	Significant decrease in older adults vs. younger adults	Significant decrease in older adults vs. younger adults
Todd et al., 2008	16-70yo (N = 42)	Tones	Fz	Significant linear reduction with age for duration and intensity MMN but not frequency	Not reported
Kiang et al., 2009	18-65yo; N=147	Tones	Fz	Significant linear reduction with age; NS quadratic relationship	Not reported
Bishop et al., 2011	7-12yo (N=30); 13-17yo (N=23); 35-56yo (N=32)	Tones and syllabi	Fz	Significant between-group increase with age	Significant between-group reduction with age
Cooray et al., 2016	10-18yo (N=52); 20-35yo (N=26)	Tones	Fz	No significant age effects	Not reported

Table 2. Demographics N = 157

Mean age, years (± SD)	**20.26 (4.89)**
Age range, years	**12.09 – 34.50**
Number male (%)	**84 (53.5)**
Number left-hand dominant (%)	**8 (5.1)**
Mean participant education, years (± SD)	**12.7 (3.6)**
Race/Ethnicity (%)	
Asian	**16 (10.1)**
Black	**30 (19.1)**
Latin American/Middle East/White	**94 (59.8)**
Native American or Pacific Islander	**1 (.6)**
Interracial	**14 (8.9)**
Hispanic or Latino (%)	
Yes	**29 (18.5)**
No	**128 (81.5)**
Mean WASI IQ (± SD)	**111.5 (14.2)**
Mean HVLT Total (± SD)	**27.8 (4.4)**
Mean BACS score (± SD)	**64.5 (12.9)**
Mean GAF score (± SD)	**83.8 (10.3)**

Table 3. MMN by Site Number

Site Number	MMN Peak Amp	MMN Peak Latency	Age
1 (N=18)	-5.1 (1.8)	133.8 (26.2)	19.5 (3.6)
2 (N = 18)	-3.1 (2.1)	142.3 (16.3)	22.1 (5.2)
3 (N = 23)	-4.7 (2.0)	131.3 (18.3)	18.8 (4.4)
4 (N = 20)	-4.6 (2.4)	154.0 (29.0)	17.2 (2.5)
5 (N = 24)	-5.3 (1.6)	133.9 (22.7)	20.6 (2.1)
6 (N = 16)	-4.8 (2.8)	143.8 (28.2)	20.4 (6.9)
7 (N = 21)	-5.5 (2.3)	133.4 (24.0)	21.2 (6.1)
8 (N = 17)	-5.6 (2.1)	129.6 (21.1)	22.9 (5.6)
Total (N = 157)	-4.8 (2.2)	137.5 (24.2)	20.3 (4.9)

Amp = amplitude

Figure 1. Grand Average MMN Waveform.

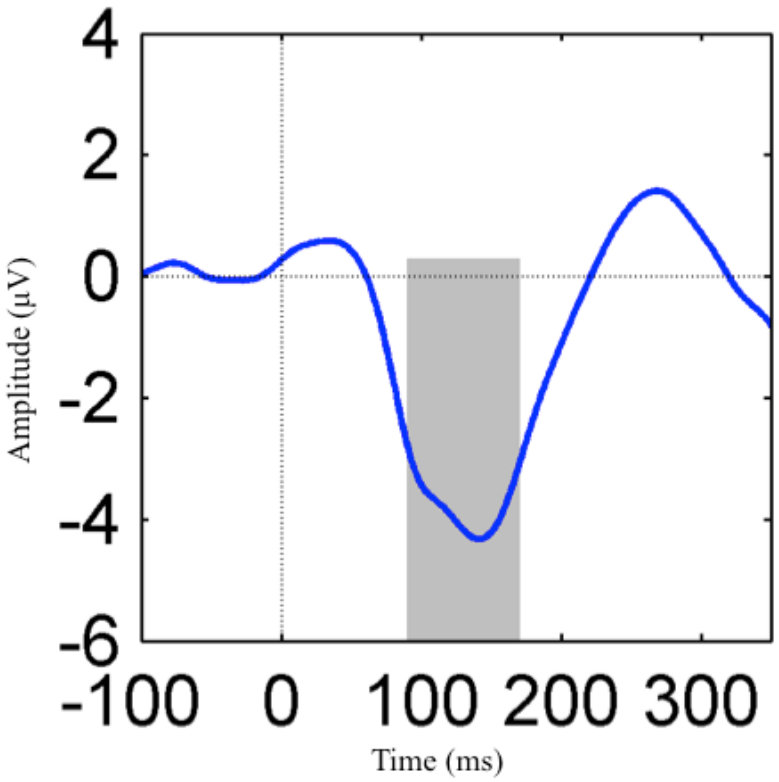
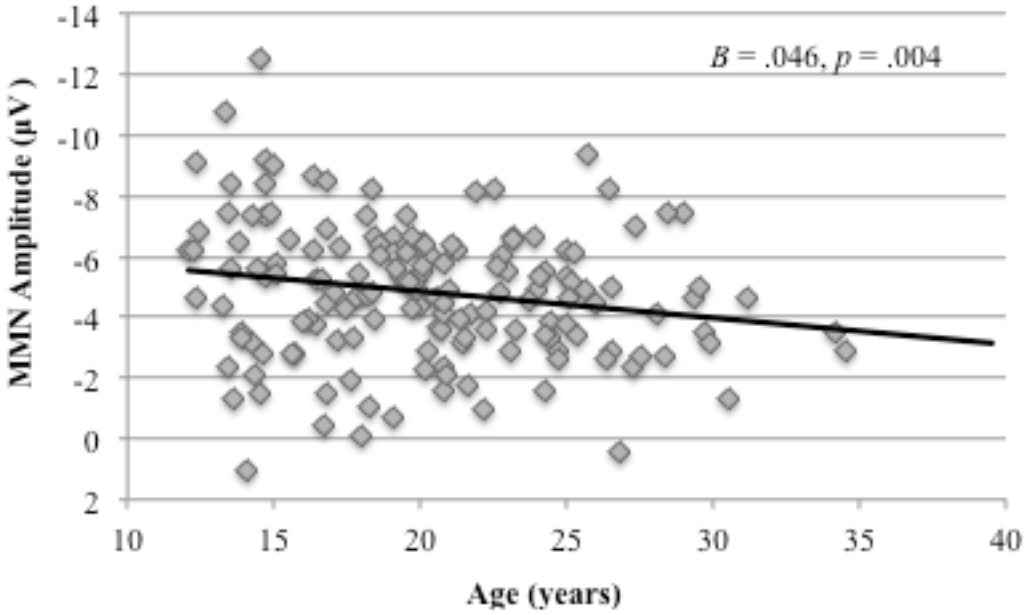
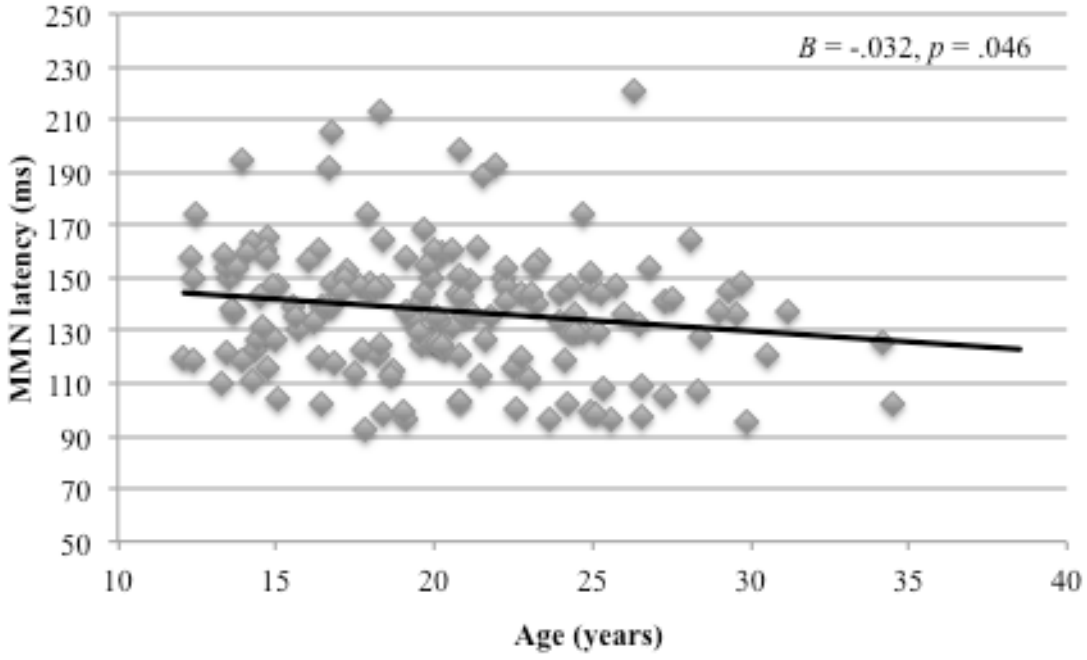


Figure 2. Average MMN amplitude and age.



MMN amplitude averaged across Fz, F3, F4, Cz, C3, C4 electrode sites.

Figure 3. Average MMN latency and age.



MMN latency averaged across Fz, F3, F4, Cz, C3, C4 electrode sites.

CHAPTER THREE: MISMATCH NEGATIVITY AND LTP-LIKE NEURAL PATTERNS IN ADOLESCENT-ONSET PSYCHOSIS AND TYPICALLY DEVELOPING CONTROLS

Abstract:

Impaired neuroplasticity may be a core feature of the development of schizophrenia and, more specifically, a primary driver of its characteristic cognitive deficits. Advances in understanding the role of synaptic plasticity in the typical trajectory of neural and cognitive development have led to a theoretical model specifying how impaired synaptic plasticity may interact with neurodevelopmental processes, leading to the development of the altered sensory and cognitive functions seen in individuals with schizophrenia. This model may be particularly relevant for individuals with early-onset psychotic-spectrum disorders (EOP; defined here as onset prior to age 18), as the development of the illness coincides with typical maturational changes in neural and cognitive functioning. A better understanding of the association between synaptic plasticity, symptoms, and cognitive and community functioning in typical and atypical (EOP) adolescent development is needed to better understand the application of the impaired synaptic plasticity model to EOP. Until relatively recently, the Mismatch Negativity (MMN) event-related potential (ERP) component was the primary ERP measure seen as indirectly related to synaptic plasticity in auditory processing, as models of MMN generation posit that it is produced by perceptual learning mechanisms that are dependent on synaptic plasticity, which is also consistent with pharmacological evidence showing that MMN generation relies at least partially on N-methyl-D-aspartate (NMDA) receptor signaling. The amplitude of MMN has also been shown to index cognition and

functioning in individuals with psychotic disorders and healthy individuals, both cross-sectionally and longitudinally, making it a measure that may link early perceptual deficits and impaired synaptic plasticity to general functional decline in psychosis. A relatively new ERP paradigm is posited to measure synaptic plasticity by comparing the amplitude of visual-evoked potentials (VEPs) pre- and post-high-frequency visual stimulation (HFvS). While it has gained some validation as an indirect measure of synaptic plasticity, it is unclear how or if it relates to cognition or functioning. Therefore, the goals of the present study were to 1) compare putative electrophysiological measures of synaptic plasticity, the MMN and potentiated VEPs from the HFvS paradigm, in EOP and typically developing (TD) adolescents; 2) assess the cross-sectional effect of age on these ERP measures in EOP vs. TD adolescents; and 3) cross-sectionally examine associations between the ERP measures, cognitive and community functioning in EOP vs. TD adolescents; and associations with symptoms in EOP adolescents. We gathered data from N = 20 TD adolescents and N = 24 EOP adolescents (ages 12-19). We found that: 1) relative to TD controls, youth with EOP showed reduced potentiation of VEPs in the HFvS paradigm; 2) this deficit in potentiation of VEPs in youth with EOP was consistent across the adolescent age range (ages 12-19); and 3) potentiation of VEPs in the HFvS paradigm was associated with MMN amplitude in TD controls, and positive and general symptoms in EOP patients. These results are consistent with previous research in adults with schizophrenia compared to healthy controls, showing impaired potentiation of VEPs in the HFvS paradigm. The results also suggest that this impairment is stable across adolescent development and that the HFvS paradigm is generally associated with other indicators of synaptic functioning (i.e., cognitive function), lending some external

validation to this measure. We suggest the need for more longitudinal studies to examine synaptic plasticity across phases of psychotic illness, and the need for continued validation of this measure, including prospective studies.

Introduction

Neuroplasticity is a fundamental property of the brain. In cortical regions, it is essential for sensory, motor, and cognitive tasks, all of which are influenced by prior experience and learning (Feldman, 2009). Long-term potentiation and depression (LTP and LTD) of synaptic strength have been demonstrated to be fundamental mechanisms of cortical plasticity; in particular, LTP has been proposed to underlie use-dependent strengthening of sensory responses (Feldman, 2009; Feldman & Brecht, 2005). This study will examine evidence for impaired neuroplasticity in psychotic-spectrum disorders and the theoretical basis for using electroencephalography (EEG) probes to assess plasticity in typically developing adolescents and adolescents with a psychotic disorder.

Neuroplasticity and N-methyl-D-aspartate receptors (NMDARs)

Long-term potentiation and depression of cortical neural circuitry is usually dependent on NMDA-receptor activity (Feldman, 2009). The NMDAR is a primary glutamate receptor that has unique biophysical properties which allow it to have a functional impact on neural firing output (Hunt & Castillo, 2012). First, NMDARs conduct current only when glutamate is bound and the postsynaptic neuron is depolarized, meaning both the pre- and postsynaptic neurons must be active to open NMDARs (Lüscher & Malenka, 2012). The cascading consequences of this coincident depolarization eventually lead to structural changes in the synapse; in the case of LTP, this includes enlarged and new dendritic spines and insertion of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptors (AMPARs; Lüscher & Malenka, 2012). These changes result in altered synaptic efficacy, lasting changes in neural circuitry, and ultimately are responsible for learning and memory. For example, studies of mice show

that blocking NMDARs impairs LTP-related neural changes and performance on behavioral tests of learning and memory, while enhancing NMDAR activity enhances LTP as well as retention of information (Lee & Silva, 2009). Synaptic plasticity and NMDAR circuitry appear to be particularly important for encoding declarative and spatial learning in medial temporal lobe areas (Citri & Malenka, 2008), motor sequence learning in motor cortex areas (Fu, Yu, Lu, & Zuo, 2012; Yu & Zuo, 2011), and perceptual learning in sensory cortex areas (Feldman, 2009). Long-term potentiation, NMDARs, and learning and memory are therefore intrinsically linked.

Synaptic plasticity in typical adolescent development

Principles of synaptic plasticity are also a critical component of general neural circuitry development. The over-proliferation of neurons in early development (Tau & Peterson, 2010) is followed in childhood and adolescence with mass elimination of weak synapses (i.e., synaptic pruning) and strengthening of intact synapses (Zhang, Peterson, & Liu, 2013). These processes depend on the same mechanisms responsible for plasticity in the adult brain, especially the aforementioned NMDAR-dependent changes of AMPAR insertion in potentiated synapses, LTP, and LTD (Ehrlich & Malinow, 2004; Takahashi, Svoboda, & Malinow, 2003; Zhang et al., 2013). Development and refinement of cortical functions coincide with the process of synaptic pruning and synaptic strengthening. In childhood, these functions are more basic, such as sensory and motor functioning, whereas adolescence sees the development of higher-order cognitive functioning, such as planning and behavioral inhibition (Best & Miller, 2010; Johnson, 2001). Neuroimaging studies have demonstrated that the development of these cognitive processes is dependent upon these changes in neural circuitry. Specifically, regional changes in neuronal cell

bodies, dendrites, axons, and synaptic processes can be indirectly measured by structural MRI as an index of regional gray matter density (Menon, 2013). Developmental thinning of gray matter (a marker of regional maturation) progresses in a manner that mirrors the development of cortical functions; specifically, it begins in primary sensory areas, then moves into multisensory association areas, and ends in higher-order association areas involved in executive functions (Gogtay et al., 2004; Shaw et al., 2008). Recent neuroimaging studies have shown that typical developmental changes (from childhood to adulthood) in parietal and prefrontal gray matter volume predict improvement in information processing, working memory, and executive function (Breukelaar et al., 2017; Tamnes et al., 2013). Functional MRI (fMRI) studies have also found that increased neural activation and functional integration within prefrontal and superior temporal cortices predicts developmental improvements in higher-order cognitive functions (Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010; Luna, Padmanabhan, & O'Hearn, 2010; Menon, 2013). Notably, other neural changes such as increased myelination of long-range axonal connections also support the increasing integration of spatially distributed neural structures (Lenroot & Giedd, 2006). Taken together, these findings suggest that maturational changes in synaptic connections are a critical component of neural and cognitive development.

Schizophrenia as a disorder of impaired cognition and neuroplasticity

Individuals with schizophrenia demonstrate global cognitive impairment (~1 standard deviation (SD) below population norms, on average) and significant impairments in long-term memory, working memory, attention, processing speed, verbal fluency (Fioravanti et al., 2005; Heinrichs, 2005; Heinrichs & Zakzanis, 1998; Keefe &

Harvey, 2012) and social cognition (Penn, Sanna, & Roberts, 2007). These deficits are robust, enduring, and resistant to pharmacological treatment (Keefe & Harvey, 2012). Notably, impaired cognitive functioning in schizophrenia is predictive of later deficits in community functioning (Green, Kern, & Heaton, 2004). Given the relevance of cognitive impairments for outcomes in schizophrenia and its enduring nature, present even prior to overt illness onset, it has been suggested that schizophrenia is primarily a disorder of cognition (Kahn & Keefe, 2013; Kraepelin, 1899). Recently, impaired synaptic plasticity has been proposed as a primary driver of cognitive deficits in schizophrenia (Forsyth & Lewis, 2017).

Support for this theory comes from emerging evidence that suggests impaired NMDAR-related circuitry is involved in the pathophysiology of schizophrenia (Michie et al., 2016). The initial impetus for this link was the observation that antagonists of NMDARs, such as ketamine and phencyclidine, produce transient psychotomimetic effects, neurocognitive deficits, and positive symptoms in healthy adults similar to those observed in patients with schizophrenia (Adler et al., 2014; Domino et al., 2004). Post-mortem studies showing broad and robust reduction in dendritic spine density have added to the evidence for disrupted synaptic plasticity in schizophrenia (Glausier & Lewis, 2013). More specifically, a recent meta-analysis of post-mortem studies of individuals with schizophrenia revealed a significant reduction in mRNA expression and protein levels of NR1, a subunit of the NMDAR, compared to healthy controls in the prefrontal cortex (Catts, Lai, Weickert, Weickert, & Catts, 2015). Genetic evidence has also implicated disrupted synaptic plasticity in schizophrenia. Genetic alterations of NMDARs in rodents have shown associations with schizophrenia-relevant phenotypes: in one study,

selective ablation of NR1 resulted in deficits in mating and nest-building, social memory, spatial working memory and sensory gating, as well as anhedonia and anxiety-like behaviors (Belforte et al., 2010). Interestingly, these deficits only appeared when NR1 was deleted pre-adolescence, which corresponds to the typical development of schizophrenia in late-adolescence to early-adulthood in humans (Belforte et al., 2010). Research on the genetic architecture of schizophrenia has also revealed that the disorder is associated with risk variants in genes involved in glutamatergic function and synaptic plasticity (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Copy-number variant and *de novo* genetic mutations associated with schizophrenia disproportionately affect genes involved in synaptic function, including genes and proteins involved in creating the structural changes in neurons that leads to LTP (Kirov et al., 2012; Marshall et al., 2017; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Although the evidence for impaired synaptic plasticity in schizophrenia is compelling, it is not enough to explain the robust and diverse consequences of the disorder, which includes impairments in cognitive, sensory, and motor domains. Of note, while many of the cardinal features of schizophrenia appear at or after the first break of positive symptoms, more subtle impairments in cognitive, motor, language and socio-emotional function are often apparent prior to the onset of full psychosis, and some are even present in early childhood (Bearden et al., 2000; Cannon et al., 2003; Gogtay, Vyas, Testa, Wood, & Pantelis, 2011; Niendam et al., 2003). Research on individuals at genetic and clinical high-risk for schizophrenia have demonstrated subtle impairments in sensory and motor functions early in development (Brockhaus-Dumke et al., 2008; Erlenmeyer-

Kimling et al., 2000; Johnstone, Ebmeier, Miller, Owens, & Lawrie, 2005; Schreiber et al., 1992), and impairments in cognition beginning in childhood and worsening over the course of development (Cannon et al., 2002; Murray et al., 2006; Seidman et al., 2006), corroborating epidemiologic studies of people who later develop psychosis in adulthood (Cannon et al., 2002; Isohanni et al., 2001; Jones, Rodgers, Murray, & Marmot, 1994; Walker, Savoie, & Davis, 1994). The emergence and worsening of these deficits seems to parallel the timing of regional synaptic maturation and gray matter thinning (discussed above; (Gogtay et al., 2004; Shaw et al., 2008). Given these relationships, Forsyth & Lewis (2017) recently used the framework of impaired synaptic plasticity to propose a heuristic model for the development of the symptoms of schizophrenia. They suggest that impaired synaptic plasticity initially disrupts refinement of local sensory and motor circuits, leading to subtle deficits in sensory and motor function early in development, which in turn induces deficits in learning and memory early in development, and finally contributes to robust deficits in higher-level cognitive functions (e.g., verbal memory recall, planning, behavioral inhibition) seen later in development. The final step, they argue, occurs when disrupted synaptic plasticity impairs functional integration of information between cortical regions. This hypothesis of impairment in functional integration in schizophrenia has previously been termed the 'disconnection hypothesis' (Friston, 1998). Functional integration refers to the interconnection of populations of neurons, cortical areas, and subareas that is required for adaptive sensorimotor and cognitive processes (Friston, 1998). Evidence for impaired functional neural integration in schizophrenia is wide-ranging (Andreasen et al., 1999; Hoffman and McGlashan 2001; Friston 2005). For example, reduced and abnormal connectivity has been demonstrated in

regions within and between the cortico-cerebellar-striatal-thalamic loop in individuals with schizophrenia relative to healthy controls (see Sheffield & Barch, 2016 for a review). Reduced neural synchrony in the gamma range of frequency (30-80 Hz) during sensory processing, which is reflective of impaired functional integration, has also been observed in individuals with schizophrenia compared to healthy controls (Johannesen et al., 2008; Kwon et al., 1999; Light et al., 2006). Functional MRI studies have demonstrated altered connectivity within large-scale brain networks in individuals with schizophrenia relative to healthy controls, and in particular, larger alterations in connectivity between association cortices relative to sensory regions (Barch & Ceaser, 2012; Yang et al., 2016). Although beyond the scope of this chapter, there is also compelling evidence that synaptic plasticity may be a major contributor to aberrant synaptic pruning (Ripke et al., 2013; Sekar et al., 2016), imbalanced glutamatergic excitation/GABAergic inhibition, and excessive striatal dopamine function in schizophrenia (Howes et al., 2011; Weinstein et al., 2017), all of which are hypothesized to contribute to the broad spectrum of symptoms seen in this disorder.

Research on early-onset schizophrenia

Much of the above research on the developmental trajectory of schizophrenia assumes the onset of full psychosis occurs in late adolescence or early-adulthood; however, approximately 18% of schizophrenia patients experience initial onset of psychosis prior to age 18 (Häfner et al., 1993; Schimmelmann et al., 2007). Relative to individuals with adult-onset schizophrenia (AOP), individuals with early-onset psychotic-spectrum disorders (EOP; defined here as being diagnosed before age 18), tend to show more severe clinical course (Eggers & Bunk, 1997; Werry, McClellan, & Chard, 1991),

greater premorbid abnormalities (Cannon et al., 2002; Vourdas et al., 2003) and greater genetic loading (Asarnow, 1999). The general research consensus on the etiology of EOP vs. AOP is that they both share the same pathophysiology, but EOP may be a more severe variant due to a larger component of neurodevelopmental risk factors (see Kumra et al., 2009 for review). Although individuals with EOP and AOP show generally comparable deficits in the domains of general intelligence, memory, attention, and executive function (for reviews, see Frangou, 2010; Kumra et al., 2009), increased impairments in the domains of attention, memory and executive function have been demonstrated in EOP patients as they move into adulthood, seemingly due to patients' failure to show the expected age-related improvements in these domains (Bachman et al., 2012b; Frangou, 2010; Frangou et al., 2008; Øie et al., 2010). The degree of cognitive impairment has also been found to be predictive of poor functional outcome (Allott et al., 2011; Bachman et al., 2012a; Couture et al., 2006; Fett et al., 2011). To explain the increased levels of impairment in EOP, we can look again to adolescent neural and cognitive development. Higher-order cognitive processes such as verbal memory recall mature later in adolescence (Waber et al., 2007), with peak performance requiring mature white matter tracts linking prefrontal-parietal (Karlsgodt et al., 2008) or prefrontal-temporal cortices (Nestor et al., 2008) and efficient cognitive processing speed (Fry & Hale, 2000). Notably, these later-developing cognitive processes are among the most severely and reliably compromised in adult-onset schizophrenia (Rajji et al., 2009). Thus, it could be that disruption of adolescent neurodevelopmental maturation by onset of psychosis causes these cognitive processes to plateau (Frangou, 2010; Frangou et al., 2008; Øie et al., 2010), contributing to a more severe clinical course. If we hypothesize that synaptic

plasticity is a critical feature of typical neurodevelopment, and that impairment in synaptic plasticity plays a significant role in the pathophysiology of the symptoms and functional impairment in schizophrenia, then measuring synaptic plasticity throughout the course of psychotic illness in adolescence could lead to a better understanding of the mechanisms involved in this disorder. Recently, electrophysiological research has proposed a way to measure synaptic plasticity and assess synaptic plasticity deficits in schizophrenia.

EEG as a neuroplasticity probe

Long-term potentiation of synapses in the human cortex can be observed as changes in the amplitude of scalp-recorded event-related potentials (Kirk et al., 2010). This has been demonstrated via several experimental designs and manipulations. First, baseline visual-evoked potentials (VEPs) to a stimulus potentiate (increase in amplitude) following viewing a photic 'tetanus' (i.e., high frequency visual stimulation; HFvS) of the same stimulus (Teyler et al., 2005). Specifically, VEP components in response to a stimulus show significantly increased amplitude following high-frequency stimulation of that same stimulus (Teyler et al., 2005). The HFvS used to induce VEP potentiation in humans is similar to the visual stimulation used to drive visual steady state responses (VSSR; Vilette et al., 2010; Regan et al., 1989). In the VSSR paradigm, a visual tetanus is used to enhance EEG power and phase synchrony in the same frequency of the stimulation, and several studies have demonstrated impairments in VSSR in schizophrenia (Brenner et al, 2009; Jin et al., 1995; Butler et al., 2001). In contrast, the present paradigm uses HFvS as a tetanus to induce potentiation in VEPs, which are measured before and after viewing the HFvS. Potentiation of sensory component

amplitude has also been demonstrated in the auditory domain (Mears & Spencer, 2012).

Several studies have provided additional evidence that potentiation is due to cortical LTP processes. First, low-resolution source estimation (LORETA) of the VEPs and replication using fMRI showed that the neural activation associated with the potentiation was located in bilateral extrastriate areas and striate cortex, and that hemodynamic response in area V2 of the associative visual cortex significantly increased after viewing the HFvS (Clapp et al., 2005; Pascual-Marqui, Michel, & Lehmann, 1994). This provides evidence that the VEPs are localized within the secondary visual cortex. It was also demonstrated that, analogous to reports from animal studies, the potentiated response can be de-potentiated by low-frequency stimulation (Teyler et al., 2005). Next, these LTP-like processes were shown to demonstrate *input specificity*, or the notion that LTP involves selective potentiation of a subset of synapses, rather than general changes in the excitability of cells (Kirk et al., 2010). An analogue of input specificity was demonstrated by recording baseline responses of two closely related stimuli and only tetanizing one of them; results showed that potentiation was specific to only the tetanized stimulus (McNair et al., 2006; Ross et al., 2008). Lastly, studies have shown that this process demonstrates NMDAR dependence: the VEP method induced lasting cortical LTP in rodents, which was then blocked by a competitive NMDAR antagonist (CPP) (Clapp et al., 2006). Human subjects who received the NMDAR antagonist ketamine similarly failed to demonstrate potentiation after HFvS (Kirk et al., 2010), while human subjects who received the NMDAR signaling enhancer D-cycloserine showed enhanced potentiation as well as improved performance on a learning task (Forsyth et al., 2015). Collectively, the above evidence shows that: 1) HFvS can induce potentiated VEPs in

humans and animals; 2) this potentiation is localized in the visual cortex, rather than the ascending visual system; 3) potentiation demonstrates input specificity; and 4) potentiation is NMDAR-dependent. Therefore, the potentiation of the VEPs in response to HFvS is indicative of an LTP-like neural pattern. Recent findings indicate that adult schizophrenia patients fail to show significant potentiation of event-related potentials after high frequency stimulation (Cavus et al., 2012; Mears & Spencer, 2012). Specifically, while healthy controls showed significant potentiation of VEPs after high-frequency stimulation, adult patients with schizophrenia did not (Cavus et al., 2012; Mears & Spencer, 2012). Interestingly, the non-significant potentiation seen in patients with schizophrenia was significantly correlated with improvement in response accuracy to an oddball stimulus (Cavus et al., 2012), suggesting that this measure may be associated with other neuropsychological outcomes in schizophrenia.

Mismatch negativity in schizophrenia

Another electrophysiological measure, the Mismatch Negativity (MMN), has also been proposed to be related to synaptic plasticity (Ehrlichman et al., 2009; Michie et al., 2016; Stephan et al., 2006; Strelnikov, 2007). The MMN is considered to be an objective index of auditory sensory memory functioning and is involved in the assessment of stimulus familiarity. It is elicited when a rare "oddball" stimulus, which differs in duration or pitch, is heard amidst a string of "standard" stimuli. The MMN is measured by subtracting the auditory evoked potential produced by the standard tone from that of the deviant tone, which yields a difference waveform with a prominent negative potential. Because MMN is elicited without any response or even attention from the participant, it is an excellent way to characterize the integrity of sensory network function independent

of artifacts due to attention or motivation (Turetsky et al., 2007). While the MMN is typically found to be impaired in schizophrenia, more recent research on its trajectory has found that MMN may have a non-linear course with the progression of the illness, such that it is impaired in individuals in the prodromal phase of psychosis and individuals with chronic schizophrenia (>5 years illness duration), but often is found to be unimpaired in individuals with first-episode schizophrenia (1-2 years illness duration; Erickson et al., 2015; Owens et al., 2016). Notably, large-scale longitudinal studies capable of understanding this non-linear course are lacking. The MMN has maximum amplitude at fronto-central scalp recording sites and is generated within the primary and secondary auditory cortices with contributions from bilateral, dorsolateral prefrontal cortices (Baldeweg et al., 2002; Lee et al., 2017).

This *predictive coding hypothesis* of MMN generation hypothesizes that the MMN signifies a failure to predict bottom-up input, resulting in a prediction error signal (Friston, 2005; Garrido et al., 2007; 2009; Lieder et al., 2013; Wacongne, 2016). Neuroimaging and computational modeling research suggests that this error signal arises via a fronto-temporal stimulus comparison network, utilizing neuroplastic changes in synaptic connections within the primary auditory cortices (Cooray et al., 2016; Garrido et al., 2008; 2009). Synaptic plasticity has long been hypothesized to play a role in MMN generation, as healthy individuals who receive NMDAR antagonists show patterns of impaired MMN similar to the impairment seen in schizophrenia (Umbricht, Schmid, Koller, Vollenweider, Hell, & Javitt, 2000a). Nonhuman primates have also demonstrated reduced MMN amplitude after receiving competitive or noncompetitive NMDAR antagonists, which did not affect earlier ERPs in the primary auditory cortex (Gil-da-

Costa et al., 2013; Javitt et al., 1996), suggesting that the effects of the NMDAR antagonists are specific to the MMN component. Recently, the NMDAR agonist $_{D}$-serine improved MMN generation and clinical symptoms in individuals with schizophrenia in a double-blind crossover treatment study (Kantrowitz et al., 2018). Additional research has shown that the administration of other agonists and antagonists at various receptors does not reduce the MMN, again suggesting a pivotal role of NMDARs in MMN generation (for review, see Umbricht et al., 2005). Similar to the above discussion of cascading consequences of impaired synaptic plasticity in schizophrenia, there is ample evidence that impaired auditory sensory memory functioning as measured by the MMN contributes to "downstream" consequences of impaired cognition and community functioning (Light & Braff, 2005b). Specifically, in individuals with schizophrenia, MMN deficits are associated with poorer social functioning (Kawakubo et al., 2007; Light & Braff, 2005a), social cognition (Wynn et al., 2010a), negative symptoms (Javitt, Shelley & Ritter, 2000), cognitive functioning (Baldeweg et al., 2002), and global functioning (Light & Braff, 2005b). Given its implications for both neurobiological and clinical aspects of schizophrenia, MMN has received much attention for its potential to contribute understanding to psychosis (Light & Näätänen, 2013).

Specific aims

Collectively, the above evidence suggests that 1) synaptic plasticity is a critical component of typical development; 2) aberrant synaptic plasticity likely plays a role in the pathophysiology of cognitive deficits and symptoms of schizophrenia; 3) early-onset psychosis may provide a unique window into the consequences of disrupted adolescent neurocognitive development; and 4) EEG-measured neural responses to the HFvS

paradigm and MMN may provide a way to assess NMDAR-mediated neuroplasticity (Cavus et al., 2012; Forsyth & Lewis, 2017; Michie et al., 2016; Stephan et al., 2006). To our knowledge, no studies to date have examined both ERP measures in the same sample. Additionally, while MMN deficits in adult schizophrenia patients have been shown to be related to several domains of real-world functioning (e.g., Light & Braff, 2005a; Wynn, Sugar, Horan, Kern, & Green, 2010b), no published studies to date have established similar measures of external validity for the HFvS paradigm. The MMN has also been well-characterized in individuals at high-risk for psychosis and in adults with first episode and chronic schizophrenia (Erickson et al., 2015), but only one study to date has investigated MMN deficits specifically in a sample of adolescents and young adults with EOP (N = 25, mean age = 17.6), finding modest reduction of MMN amplitude compared to age-matched controls (Oknina et al., 2005). Given that EOP is associated with a more severe clinical course (Eggers & Bunk, 1997) and greater genetic loading (Asarnow, 1999), it is particularly important to determine the integrity of MMN and neural responses to the HFvS paradigm in adolescents with psychosis and typically developing adolescents who are still undergoing a critical period of brain maturation. In addition to cross-sectionally examining the association between these ERP measures and community functioning, we will also examine associations with neurocognitive performance as measured by verbal learning and memory, processing speed, and general intelligence. We selected these domains in particular, as all three show robust evidence for marked impairment in patients with schizophrenia relative to healthy controls (Holmén, Juuhl-Langseth, Thormodsen, Melle, & Rund, 2010) and are predictive of community functioning in adults with schizophrenia (Fett et al., 2011; Green et al., 2004;

Nuechterlein et al., 2011). They are distinct in that, relative to other specific cognitive domains, verbal learning and memory deficits in schizophrenia seem to be more closely related to functional outcomes (Green, 1996; Green et al., 2000). Additionally, verbal learning and memory deficits in schizophrenia appear to be linked to specific functional and structural brain alterations in schizophrenia. In relation to neural functioning, these deficits are associated with abnormal brain activation in and connectivity between the medial temporal and frontal lobes (Francis et al., 2015; Guimond, Chakravarty, Bergeron-Gagnon, Patel, & Lepage, 2016; Haut et al., 2015; Hutcheson et al., 2015). Structurally, individuals with schizophrenia with more severe verbal memory deficits (measured using a list learning task) have been shown to have thinner cortex in the parahippocampal gyrus and left frontal cortex relative to patients with mild verbal memory deficits (Guimond et al., 2016). Processing speed deficits in schizophrenia, on the other hand, are likely more broadly related to abnormal coordination or inefficiency of neural assemblies serving a wide range of cognitive tasks (Roach & Mathalon, 2008), and appear to be more closely related to white matter integrity than learning and memory (Karbasforoushan, Duffy, Blackford, & Woodward, 2014; Kochunov et al., 2017). Verbal learning and memory is also more closely linked to auditory processing, whereas processing speed can be measured across the range of sensory and motor domains. Thus, we used verbal learning and memory to index a specific sensory domain and the frontal-medial temporal network, processing speed as a general measure of neural assembly coordination and efficiency, and general intelligence as an estimate of global cognitive functioning across multiple domains.

The purpose of the present study is to:

1) **Assess for differences in synaptic plasticity in EOP patients compared to typically developing (TD) adolescent controls using ERP measures from the HFvS and MMN paradigms.** Based on previous research on MMN (Erickson et al. 2015) and neural responses to the HFvS paradigm (Cavus et al., 2012; Erickson et al., 2015) in adults with schizophrenia, I predict that EOP patients will show impairments in both ERP measures relative to TD controls. Specifically, I predict that EOP patients will demonstrate reduced MMN relative to TD controls. I also predict that TD controls will show significant VEP potentiation in response to the HFvS tetanus, indicating synaptic plasticity, while EOP patients will not.

2) **Examine the effects of age on ERP measures from the HFvS and MMN paradigms in EOP vs. TD individuals.** A significant Group X Age interaction would indicate a divergent trajectory of maturation. Given the literature suggesting that schizophrenia is a consequence of cascading effects of impaired synaptic plasticity with development, I predict greater impairments on ERP measures from the MMN and HFvS paradigms in EOP relative to TD with increasing age.

3) **Cross-sectional associations: Examine associations between cognitive performance or measure of community functioning and ERP measures from the HFvS and MMN paradigms on EOP vs. TD individuals.** Of the two studies to date that have measured neural responses to the HFvS paradigm in individuals with schizophrenia, only one investigated relationships between component potentiation and a behavioral measure: specifically, Cavus and colleagues (2012) found that non-significant potentiation from pre- to post-HFvS

was significantly correlated with improved target reaction time in individuals with schizophrenia. Therefore, I predict neural responses to the HFvS paradigm (as measured by C1 and P2 potentiation) will be associated with faster processing speed. Given the association between neuroplasticity and learning and memory (Feldman, 2009; Feldman & Brecht, 2005), I also predict neural responses to the HFvS paradigm will be associated with better performance on measures of learning and memory. Given the rich literature on MMN deficits and their functional consequences in adults with schizophrenia (Light & Braff, 2005a), I predict MMN will be associated with community functioning and verbal memory performance in EOP, and will explore whether similar patterns are observed in TD youth. **Lastly, given the novelty of the HFvS paradigm and the exploratory nature of these analyses, I will also assess whether neural responses to the HFvS paradigm are related to positive and negative symptom severity in EOP patients.** I predict that greater potentiation will be associated with less severe positive and negative symptoms in EOP patients. **I will also assess whether neural responses to the HFvS paradigm are associated with MMN amplitude in EOP patients and TD controls.** I predict that degree of MMN amplitude will be positively correlated with degree of potentiation across all participants.

If these hypotheses are confirmed, they would provide: 1) essential external validity data on the HFvS paradigm; 2) a better understanding of the role of synaptic plasticity (as measured by EEG components) in neurocognitive and functional neurodevelopment; and 3) given the unique sample of EOP individuals in this study, the

results will also help characterize neural and cognitive deficits that occur when psychosis onsets during an important developmental phase.

Methods.

Participants.

Data were collected from the UCLA Center for Assessment and Prevention of Prodromal States (CAPPS). Twenty-four patients with schizophrenia spectrum disorders and 20 typically developing controls enrolled and completed all assessments. All patients with early-onset psychotic-spectrum disorders were recruited from CAPPS and part of a larger study assessing adolescent-onset psychosis (Adolescent Brain and Behavior Research Clinic). Schizophrenia-spectrum patients (EOP patients) were assessed in a clinically stable state and met criteria for schizophrenia, schizoaffective disorder, depressed type, schizoaffective disorder, bipolar type, or psychotic disorder not otherwise specified (NOS), using the Structured Clinical Interview for DSM-IV Disorders (First, Spitzer, Gibbon, & Williams, 1994). All EOP patients were diagnosed with a psychotic disorder prior to age 18 with less than 5 years illness duration. EOP patients were excluded if they had a known neurological disorder, active significant alcohol/substance abuse, or IQ < 70. Typically developing controls were recruited from UCLA undergraduate psychology classes and from posting flyers around the UCLA campus. TD controls were excluded if they had a known neurological disorder, were taking psychotropic medication at the time of the assessments, reported a first-degree relative with a disorder involving psychotic symptoms, had active significant alcohol/substance abuse, or IQ < 70. All EOP patients and healthy controls completed neuropsychological assessments, EEG assessments, and functioning scales (see below). Unless otherwise

noted, the experimental paradigms for schizophrenia-spectrum patients and healthy controls were equivalent. See **Table 1** for demographic information.

Clinical Assessment Measures

Clinical measures characterized participants' symptoms and behavior over the past month. In addition to symptom assessments, data on drug and alcohol use, psychosocial therapy, hospitalizations, and medication were also obtained via individual and/or parent report. All assessments were administered by masters-level clinicians who had been trained to a standard reliability criterion (Ventura, Liberman, Green, Shaner, & Mintz, 1998). See **Table 2** for summary of symptom severity and functioning measures.

Structured Interview for Prodromal Syndromes (SIPS; McGlashan et al., 2001; Miller et al., 2002; Rosen et al., 2002). The SIPS is a structured diagnostic interview used to assess dimensional symptoms of psychosis and includes the Scale of Prodromal Symptoms (SOPS; McGlashan et al., 2001; Miller et al., 1999), the Schizotypal Personality Disorder Checklist (APA 1994), a questionnaire regarding family history of mental disorders (Andreasen, Endicott, Spitzer, & Winokur, 1977), and a measure of Global Assessment of Functioning (GAF; Hall, 1995). While typically used to diagnose prodromal symptoms of schizophrenia, the SOPS also identifies fully psychotic symptoms, measured on a dimensional scale (McGlashan et al., 2001). Rather than being used diagnostically, the SOPS was used in this study to measure symptom severity. The SOPS measures symptoms in four domains: positive symptoms (unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/hallucinations,

disorganized communication); negative symptoms (social anhedonia, avolition, expression of emotion, experience of emotions and self, ideational richness, occupational functioning); disorganization symptoms (odd behavior and appearance, bizarre thinking, trouble with focus and attention, personal hygiene); and general symptoms (sleep disturbance, dysphoric mood, motor disturbances, impaired tolerance to normal stress) (McGlashan et al., 2001). The four domains of symptoms are rated on a scale of severity from 0 (absent) to 6 (fully psychotic). With training, interrater reliability on the SOPS is excellent (Miller et al., 2003). The modified GAF scale used in the SIPS increases the number of criteria and includes additional scoring directions compared to the original GAF (Hall, 1995). It retains the same 1-90 scale with the same 10-point intervals as the original GAF, with the 81-90 interval signifying a patient with absent or minimal symptoms and problems and the 0-10 interval signifying a patient in persistent danger of severely hurting self or others (Hall, 1995). The modified GAF scale shows adequate to excellent reliability and acceptable concurrent validity (Hall, 1995).

Only positive symptoms were assessed in the TD control sample to screen out any individuals with prodromal-level psychotic symptoms (i.e., all controls must have ratings < 3 on all five positive symptom domains). Healthy controls also were assessed for current or past depression and mania, current significant anxiety symptoms, and obsessive-compulsive disorder symptoms using selected sections from the SCID-IV. One control participant was screened out due to prodromal-level symptoms and was referred to a nearby counseling center.

Neuropsychological Assessment Measures

General Intelligence: Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999). Age-corrected T-scores from the Vocabulary and Matrix Reasoning subtests of the WASI were combined to form an estimate of IQ.

Processing Speed: Brief Assessment of Cognition in Schizophrenia: Symbol-Digit Coding (BACS; Keefe et al., 2004) was administered to assess processing speed. The subject used a key to match numerals 1-9 with symbols on a response sheet for 90 seconds. The dependent variable was number of correct numerals (range: 0-110).

Verbal list learning: Three learning trials of the Hopkins Verbal Learning Test - Revised (HVLT-R; Brandt, 1991) was administered to assess verbal learning. The HVLT-R includes 12 words that contain three sets of categorically related words that were read by the assessor at a rate of one per two seconds. After each trial, the subject was asked to recall the words. The dependent variable was the total number of correct responses over all three trials.

High-Frequency Visual Stimulation (HFvS) Paradigm

The HFvS paradigm was adapted from Cavus and colleagues (2012). Visual evoked potentials (VEPs) were assessed in 2-minute blocks before and after exposure to the high-frequency visual stimulation (HFvS). VEP assessment blocks consisted of a

pseudorandom oddball sequence of 90% standard and 10% target stimuli presented for 33 ms (jittered 1-1.33s stimulus onset asynchrony). The standard stimulus was a circle with a black and white checkerboard pattern, presented at 0.83 Hz. To maintain attention, participants pressed a button whenever they saw a target square containing a blue and white checkerboard pattern, equally emphasizing speed and accuracy. No feedback was given regarding performance. The HFvS was a 2-minute block of repeated presentation of the standard circle at ~8.87 Hz (113 ms mean stimulus onset asynchrony). No response was required during the HFvS; participants were asked to simply attend to the center of the display. VEP assessment blocks were administered 4 (Pre-1) and 2 (Pre-2) minutes before HFvS and 2 (Post-1), 4 (Post-2), 20 (Post-3) and 60 (Post-4) minutes after HFvS (see **Figure 1**). Unrelated auditory and resting tasks were performed between the post-HFvS VEP blocks (between Post-2 and Post-3). The MMN task occurred between Post-3 and Post-4 blocks. Two EOP patients were unable to complete the final block of the HFvS paradigm (Post-4) due to fatigue, thus, they were not included in the Aim 1 full ANOVA analysis. When testing for group differences from the HFvS paradigm, analyses were repeated excluding these individuals, which did not affect the significance of outcomes. Therefore, they were retained in all analyses that did not include the Post-HFvS 4 block.

MMN Task

Auditory stimuli were presented at 78 dB sound pressure level using Etymotic ER3-A insert earphones (Etymotic Research, Inc., Elk Grove Village, Illinois). All participants completed two blocks of stimuli, each block consisting of a fixed

pseudorandom sequence of 875 tones, comprised of 90% standard (50 ms 633 Hz) and 10% deviants (duration deviants: 100 ms, 633 Hz; frequency deviants: 50 ms, 1000 Hz; double-deviant: 100 ms, 1000 Hz), with 510 ms stimulus onset asynchrony. All tones had 10 ms rise/fall times. For the present analyses, only frequency deviant tones were analyzed. Participants were instructed to attend and respond to an unrelated visual stimulus.

Psychophysiological Recording Methods and Apparatus.

All participants' EEG was recorded at the Center for Cognitive Neuroscience using either a 128-channel or 64-channel Biosemi Active-Two EEG system (Biosemi, Amsterdam). The first seven EOP patients in the study underwent EEG recording from 128 electrodes arranged according to the extended 10-20 EEG system. The remaining EOP patients and all healthy controls had EEG recorded from 64 electrodes arranged according to the extended 10-20 EEG system. This change was made for both technical and practical reasons, as the 64-channel system was newer, had a shorter set-up time, and was generally more available than the 128-channel system. Importantly, the 64-channel system is nested within the 128-channel system, both are arranged according to the extended 10-20 system. Within the EOP patient group, there were no significant differences between the 128-channel and the 64-channel arrays on any measure of amplitude or latency (all *p*'s > .08). Analyses with significant results were repeated with montage included as a covariate, and it did not affect the significance of outcomes. All EEG data were recorded and processed using the same techniques. Horizontal and vertical eye movements were recorded using two electrodes 1 cm lateral to the outer

canthi of each eye and 1 cm above and below the orbit of the right eye, respectively. All impedances were maintained below 5 kΩ.

For the HFvS paradigm, EEG data were processed in MATLAB (Mathworks) using the open-source toolbox EEGLAB (Delorme & Makeig, 2004) and custom MATLAB scripts. Continuous EEG data were re-referenced offline to nose and bandpass filtered 0.5-50Hz (48 dB/octave roll off; Forsyth et al., 2017; 2015). All data were visually inspected in order to remove noisy channels or noisy data segments. Noisy channels were spherically interpolated in EEGLAB. Eye movement and blink artifacts were removed using independent components analysis (ICA) implemented in EEGLAB. Epochs were time-locked to the standard stimulus onsets and extracted from 100ms prestimulus to 500ms poststimulus, with baseline correction from 100ms prestimulus onset. Epochs with voltage exceeding ±100 μV between 0 and 250 ms after stimulus onset at parietal or occipital sites were excluded. VEP blocks following artifact rejection contain a minimum of 80 epochs (EOP M = 87.2, SD = 4.8; HC M = 89.1, SD = 2.2). Epochs were averaged generating VEPs for the two pre-HFvS and four post-HFvS blocks. A custom MATLAB script identified the C1 negative peak with the greatest amplitude between 80-120ms and the P2 positive peak with greatest amplitude between 150-250ms for each participant. Consistent with previous research, maximal amplitude of VEPs were seen at Oz, thus all analyses were completed with regard to measurements at this site (Cavus et al., 2012; Forsyth et al., 2017; 2015). As no significant differences or Group effects between the two baseline assessments were observed for either component (all *p*s > .20), the two pre-HFvS blocks were averaged together to create one baseline VEP measure (Cavus et al., 2012; Forsyth et al., 2017; 2015).

For the MMN paradigm, EEG data were processed in MATLAB (Mathworks) using the open-source toolbox EEGLAB (Delorme & Makeig, 2004). Continuous EEG data were re-referenced offline to averaged mastoids and high-pass filtered at 1 Hz (Perez et al., 2014). All data were visually inspected in order to remove noisy channels or noisy data segments. Noisy channels were spherically interpolated in EEGLAB. Eye movement and blink artifacts were removed using ICA implemented in EEGLAB. Epochs were time-locked to the standard stimulus onsets and extracted from 100 prestimulus to 500ms poststimulus, with baseline correction from 50ms prestimulus onset. Epochs with voltage exceeding ±100 μV between 0 and 250 ms after stimulus onset at frontal or central sites are excluded. Epochs were averaged separately for the standard and frequency deviant tones and then low-pass filtered at 30Hz (Luck et al., 2011). One EOP patient retained less than 40 frequency deviant epochs and was removed from all MMN analyses (but retained for all non-MMN analyses); all other participants retained a minimum of 50 frequency deviant epochs (EOP Standard M = 978.8, SD = 30.2 Deviant M = 57.7, SD = 1.7; HC Standard M = 976.0, SD = 54.8 Deviant M = 57.7, SD = 3.3). Mismatch negativity was calculated by subtracting standard from deviant waveforms for each participant. The amplitude and latency of MMN was measured using peak amplitude in the 90-290ms latency range at Fz, Cz, F3, F4, C3, and C4 (Perez et al., 2014). The amplitude and latency measures from the six sites were then averaged together.

Data analysis.

All statistical analyses were performed using SPSS software v. 20 (Chicago, Illinois). All significance tests were two-tailed with alpha set at $p = .05$. We first examined effects

of gender on all EEG measures of amplitude and latency and found no significant effects (all *p*s > .20); therefore, gender was not included as a covariate in any subsequent analyses.

To address Aim 1, independent-samples *t*-tests tested for group (EOP vs. TD) differences between average MMN amplitude and latency and between pre-HFvS (Baseline) C1 and P2 amplitude and latency. We then created difference scores for each component (C1 and P2) at each Post-HFvS block relative to Baseline (e.g., Post-HFvS Block 3 minus Baseline amplitude). Each difference score was created such that a larger positive number reflected component potentiation (larger amplitude at the Post-HFvS block relative to Baseline). We then conducted a repeated-measures ANOVA of the Post-HFvS Block differences scores (abbreviated as Post-HFvS diff) to assess for a Group (EOP, TD) X Block (Post-HFvS 1 diff, Post-HFvS 2 diff, Post-HFvS 3 diff, Post-HFvS 4 diff) interaction with a Greenhouse-Geisser corrections for degrees of freedom. This analysis was repeated for C1 and P2 amplitude. Bonferroni-corrected $p = .0125$ (.05 / 4 Post-HFvS blocks = .0125) was used to control for multiple comparisons. A significant interaction was followed up by tests of simple main effects to assess for Group differences in each Post-HFvS Block difference score. For C1 and P2 amplitude, we also assessed for significant potentiation using confidence intervals of the Post-HFvS difference scores within each group and interpreted any confidence interval that did not include zero as evidence for significant potentiation (positive values) or *de*-potentiation (negative values). See **Table 3** for amplitude and latency raw scores. Effect sizes for paired sample *t*-tests are reported as Hedge's *g*; effect sizes for ANOVAs are reported as partial-η^2.

To address Aim 2, linear regression analyses were used to examine a Group (EOP, TD) X Age (as a continuous variable) interaction on MMN and HFvS amplitude and latency measures. Difference scores (Baseline relative to Post-HFvS block) were used as outcome variables in all HFvS analyses. A significant Group X Age interaction, coupled with a post-hoc comparison showing greater group differences at higher age values, would be evidence for a divergent trajectory of maturation in the EOP group. For all HFvS analyses, Bonferroni-corrected $p = .0125$ was used to control for multiple comparisons. Effect sizes for regression analyses are reported as Cohen's f^2.

To address Aim 3, we first assessed for Group (EOS, TD) x Age (continuous) associations for all cognitive variables (HVLT Total, BACS total, and WASI IQ) and for general functioning (GAF). Given no significant interactions (all ps > .20), Age was included in all other models as a covariate. Linear regression analyses were then used to test whether there was an effect of Group on the association between amplitude/latency measures and cognitive performance or functioning. The measure of cognition/functioning was entered as the outcome variable, with Group (EOP, TD), Amplitude or Latency variable, and the Group X Amplitude or Latency interaction as predictors.

To address the exploratory analyses for the HFvS paradigm, linear regression analyses were used to test whether there was an effect of Group on the association between amplitude measures from the MMN and HFvS paradigms (Group (EOP, TD) X Amplitude (continuous) interaction). Within EOP patients only, correlations between HFvS amplitude and symptom severity were also assessed. For all HFvS correlations,

Bonferroni-corrected $p = .0125$ was used to control for multiple comparisons. Effect sizes for regression analyses are reported as Cohen's f^2.

Results

See **Table 1** for demographic information and **Table 2** for clinical and functioning scores and neurocognitive scores. Groups were well matched in terms of age, gender, education, and parental education. The TD control group was more racially/ethnically diverse than the EOP group ($p < .02$). As expected, the EOP group demonstrated significant impairments in Social, Role, and General Functioning relative to the TD group (all ps $< .001$). The EOP group also showed significant cognitive impairment in all domains tested, with the exception of the Matrix Reasoning subtest of the WASI (all other ps $< .05$).

Aim 1:

MMN. There were no significant group differences between average MMN amplitude or latency (all ps $> .20$; see **Table 3** and **Figure 2** for Grand Average waveforms).

HFvS. There were no significant group differences for C1 or P2 amplitude or latency in Baseline blocks (combined Pre-1 & Pre-2; all ps $> .40$). This suggests that all Pre vs. Post-HFvS effects are due to differences in component potentiation and not a result of Baseline Group differences. See **Table 3** and **Figure 3.**

C1. The interaction between Group and Block was not significant for C1 amplitude (F (2.1, 85.5) = 2.59, $p = .078$). There was a significant main effect of Block (F (2.1,

85.5) = 2.59, $p < .001$, partial-η^2= .22) driven by significantly larger amplitude in Post-HFvS 4 potentiation relative to potentiation in all other blocks (all *p*s < .005). We then examined 95% confidence intervals of the mean difference scores for each Post-HFvS block to test for significant potentiation (i.e., does the confidence interval include zero). For TD controls, there was significant potentiation (increased amplitude) at the Post-HFvS 4 Block (M = 3.4, SD = 5.9, 95% CI [0.78, 5.97]). In contrast, for EOP patients, there was significant *de*-potentiation (decreased amplitude) at the Post-HFvS 2 Block (M = -2.3, SD = 3.6; 95% CI [-3.75, -0.86]) and at the Post-HFvS 3 Block (M = -1.6, SD = 3.6; 95% CI [-3.0, -0.15]).

P2. There was a significant Group X Block interaction for P2 amplitude (F (2.1, 83.5) = 4.55, $p = .012$, partial-$\eta^2 = .103$). Post-hoc tests examined simple main effects for Group and found no significant Group differences for Post-HFvS 1 diff ($p = .79$) or Post-HFvS 2 diff ($p = .16$), but significant Group differences for Post-HFvS 3 diff (F (1,40) = 6.09, $p = .018$) and Post-HFvS 4 diff (F (1,40) = 12.87, $p = .001$). When examining confidence intervals of Post-HFvS difference scores within each group, EOP patients failed to show significant potentiation at Post-HFvS 3 (M = 1.18 SD – 3.84, 95% CI [-0.30, 2.66]) and at Post-HFvS 4 (M = -0.73 SD = 3.89, 95% CI [-2.17, 0.71]), while TD controls showed significant potentiation at Post-HFvS 3 (M = 3.79 SD = 2.90, 95% CI [2.52, 5.06]) and Post-HFvS 4 (M = 2.98 SD = 2.62, 95% CI [1.83, 4.13])

Aim 2:

MMN. There was a trend towards a Group (EOP, TD) X Age (continuous variable) interaction for MMN amplitude ($t(41) = -1.818$, $p = .07$, Cohen's $f^2 = 0.10$) reflecting a

non-significant negative linear relationship between age and average MMN amplitude for EOP patients and a non-significant positive linear relationship between age and average MMN amplitude for TD controls. The Group X Age interaction for MMN latency was not significant ($p > .50$).

HFvS. There were no significant Group (EOP, TD) X Age (continuous) interactions for any Post-HFvS block difference score measure of amplitude or latency (all ps > .10). Given the lack of Group effects in the C1 component, we conducted a post-hoc exploratory analysis to assess whether there was a significant effect of Age on C1 potentiation, controlling for the effect of Group. Using Bonferroni-corrected $p = .0125$, we found a marginally significant association between Age and Post-HFvS 2 diff ($B = -0.66$, $p = .03$).

Aim 3.

MMN. There were no Group X MMN amplitude or latency interactions on any measure of cognitive performance or functioning.

HFvS. There were no Group X HFvS amplitude or latency interactions on any measure of cognitive performance or functioning.

Additional HFvS analyses. There was a significant Group (EOP, TD) X MMN amplitude interaction on Post-HFvS 4 C1 amplitude difference score ($B = -2.42$, $p = .001$, Cohen's $f^2 = 0.58$). Pearson's correlations were used to examine the association between MMN and Post-HFvS 4 C1 amplitude difference score in each group separately. In TD controls, there was a significant correlation between Post-HFvS 4 C1 amplitude difference score and MMN amplitude ($r = -.60$, $p = .006$). In EOP patients, this association was not significant ($r = .16$, $p > .40$); see **Figure 5**. The interaction analyses

for all other measures were not significant (all *p*s > .20). Within EOP patients only, there were marginally significant correlations (using Bonferroni-corrected $p = .01$) between Post-HFvS 4 P2 amplitude difference score and positive symptoms ($r = .447$, $p = .037$). Within EOP patients only, there was also a marginally significant correlation between Post-HFvS 4 P2 amplitude difference score and general symptoms ($r = .449$, $p = .036$). See **Figure 6**.

Discussion

The overall goal of the present study was to assess putative electrophysiological measures of synaptic plasticity in adolescents with early-onset psychosis and typically-developing controls. Specifically, we measured Mismatch Negativity (MMN), a measure that has been associated with synaptic plasticity due to properties suggesting it serves as a signal of perceptual learning (Friston, 2005; Garrido et al., 2007; 2009; Lieder et al., 2013; Wacongne, 2016), and because of pharmacological evidence linking its generation to NMDA receptor signaling (Gil-da-Costa et al., 2013; Javitt et al., 1996; Kantrowitz et al., 2018). We also measured changes in VEPs following repetitive HFvS (Cavus et al., 2012), which has been shown to induce lasting potentiation of neural responses in a way that is consistent with principles of synaptic LTP (Clapp et al., 2005; 2006; Forsyth et al., 2015; Kirk et al., 2010; McNair et al., 2006; Pascual-Marqui et al., 1994; Ross et al., 2008; Teyler et al., 2005). We hypothesized that both ERP measures would be impaired in EOP patients relative to TD controls, and that a cross-sectional analysis of the effect of age would show a divergent developmental trajectory for EOP patients. Given that both ERP measures are theorized to be generated by synaptic plasticity processes, we

hypothesized that they would be correlated, and that each would be associated with cognitive performance and general functioning. Lastly, we assessed whether VEP potentiation in the HFvS paradigm were related to symptom severity in EOP patients. To our knowledge, this is the third study to measure such potentiation using a high-frequency stimulation paradigm in a sample of patients with psychotic disorders and healthy controls (Clapp et al., 2006; Mears & Spencer, 2012), and the first to use this paradigm in a sample of adolescent patients with early-onset psychosis. To our knowledge, this is also the first study to measure MMN and ERP potentiation by high-frequency stimulation in the same sample.

The results of Aim 1 demonstrated a significant Group by Block interaction for P2 component potentiation following HFvS. Specifically, TD controls showed significant P2 component potentiation (increase in amplitude) after viewing high frequency stimulation in the Post-HFvS 3 and Post-HFvS 4 Blocks (20 and 60-minutes after viewing HFvS, respectively), while EOP patients did not show significant potentiation in either block. This is consistent with previous research showing that adults with adult-onset psychotic disorders failed to show potentiation in sensory ERPs after high frequency stimulation (Cavus et al., 2012; Mears & Spencer, 2012) and extends these findings to adolescents with EOP. If one assumes the observed component potentiation is driven by synaptic plasticity (LTP; Kirk et al., 2010) then the present findings add to existing research suggesting that schizophrenia is associated with deficits in synaptic plasticity. The present study was also the first to demonstrate potentiation of VEPs following HFvS in healthy adolescents, suggesting that such processes can be measured in this age range. Again, assuming that potentiation is reflective of synaptic plasticity processes, this

paradigm can be used to examine typical and atypical developmental changes in synaptic plasticity and related neurodevelopmental processes.

We did not find a similar significant Group by Block interaction for the C1 component. When examining the confidence intervals surrounding the Post-HFvS difference scores within each group, we found that EOP patients did not show significant potentiation at any block, however they showed significant *de*-potentiation (decreased amplitude relative to baseline) at the Post-HFvS 2 Block and the Post-HFvS 3 Block (4 and 20 minutes post-HFvS, respectively). TD controls also showed a similar pattern of non-significant *de*-potentiation at the Post-HFvS 2 Block, followed by significant potentiation at the Post-HFvS 4 block. The pattern of initial *de*-potentiation followed by potentiation is consistent with the pattern seen in healthy adults (Forsyth et al., 2015) and adults with schizophrenia (Forsyth et al., 2017) receiving D-cycloserine using the same HFvS paradigm. These non-linear changes in C1 amplitude following HFvS may be reflective of interactive effects of homosynaptic LTP and heterosynaptic LTD (long-term depression) across visual cortex synapses, where homosynaptic LTP is the result of direct electrical stimulation at tetanized synapses, and heterosynaptic LTD is the opposite effect at non-tetanized synapses (Chistiakova, Bannon, Bazhenov, & Volgushev, 2014; Royer & Paré, 2003). This "balancing" LTD effect may represent a homeostatic mechanism to provide stability at the neural system level (for review, see Chistiakova et al., 2014). While the present study is not capable of separating the relative contribution of LTP and LTD to changes in VEP amplitude, this homeostatic mechanism may explain the variable effects of the HFvS on C1 amplitude over time (Forsyth et al., 2015). This homeostatic mechanism may also help to explain the finding that P2 potentiation began 20 minutes

post-viewing the high frequency stimulation in TD controls, which is consistent with the results of previous studies of healthy adults using a similar paradigm (Cavus et al., 2012; Forsyth et al., 2015). While the effects of NMDAR activation at the level of the synapse begin immediately following coincident detection of pre- and postsynaptic activity, the time frame for the maximum effect of subsequent signaling cascades leading to structural changes such as AMPA receptor upregulation and enlarged dendritic spines (Lüscher & Malenka, 2012) is unclear. One study of the rat neocortex found that heterosynaptic depression of somatosensory neurons following high-frequency stimulation was more transient (<10 minutes) than the induced homosynaptic LTP (Castro-Alamancos, Donoghue, & Connors, 1995), which is consistent with the findings here. The delayed potentiation, or initial *de*-potentiation, following HFvS may thus be partially due to the initial effect of homeostatic mechanisms, which is then overcome by LTP processes leading to potentiation 20-60 minutes following the visual tetanus. Further research at the level of neural signaling is needed to better understand this pattern; additional research should also examine changes in VEPs occurring at more regular intervals following the HFvS to establish when potentiation is at its maximum.

In the present study, we found no evidence for pre-HFvS group differences in either C1 or P2 component, contrary to some prior reports on patients with schizophrenia (Butler et al., 2007; Schechter et al., 2005; Wynn et al., 2015). C1 is the first major visual ERP and is generated by neurons in the primary visual cortex (Jeffreys & Axford, 1972; Woodman, 2010). Impairments in C1 generation in schizophrenia have been demonstrated to be due to specific impairment in the magnocellular (vs. parvocellular) visual pathway, which is associated with “transient” neural circuits involved in contrast

sensitivity (Schechter et al., 2005). Thus, it is possible that intact contributions from the "sustained" parvocellular pathway led to similar baseline C1 amplitude in EOP vs. TD. Much less is known about the nature of the visual P2 component or its role in schizophrenia (Wynn et al., 2015). Visual P2 has been shown to be generated in parieto-occipital regions and is associated with phase-locking in the theta range (4-6 Hz) (Freunberger, Klimesch, Doppelmayr, & Höller, 2007). It is proposed to be involved in a variety of cognitive processes including attention, working memory, and memory performance (McDonough, Warren, & Don, 1992; Wolach & Pratt, 2001). In general, P2 is thought to be part of a cognitive matching system that compares sensory inputs with stored memory (Luck et al., 2011). Thus, one way to differentiate the two components is to view C1 as a reflection of very early perceptual processing tied to stimulus-bound features, whereas the P2 is affected by additional top-down cognitive control mechanisms. The differential findings for the two components may thus be due to such differences in component generation. Another factor influencing component generation are brain oscillations (Freunberger et al., 2007). The present study did not examine the effects of VSSR power or phase synchrony from the HFvS on component potentiation. To our knowledge, only one study has examined the effects of VSSR power on component potentiation in healthy adults relative to adults with schizophrenia and found that VSSR power from the HFvS did not differ between groups, but greater VSSR power predicted greater component potentiation in only in the healthy control sample (Cavus et al., 2012). Several studies have demonstrated impairments in VSSR in schizophrenia (Brenner et al., 2009; Butler et al., 2001; Jin, Sandman, Wu, Bernat, & Potkin, 1995), thus it possible that impaired VSSR power or phase synchrony contributed to the lack of

potentiation in EOP patients. Additional research will test this hypothesis in the present sample; other research is needed to parse out the factors that contribute to C1 vs. P2 component potentiation in schizophrenia and in healthy controls.

One additional factor may influence the group differences in component potentiation after HFvS. Given that the HFvS is posited to be the tetanus inducing LTP-driven potentiation of VEPs, it would follow that a lower "dose" of the tetanus would lead to less potentiation. Given the attentional deficits seen in schizophrenia and that increased sensory stimulation is generally reported to be aversive by these patients, it could be that patients with schizophrenia simply are not looking at the HFvS as much as healthy controls are, which would lead to a lower "dose" of the visual tetanus and thus, less potentiation. Therefore, we believe that an eye-tracking version of this paradigm is needed to control for this potential confound and further validate that the impairments seen in patients with schizophrenia are due to impairments in processes related to synaptic plasticity.

The finding of intact MMN in EOP patients relative to TD controls is consistent with some studies of adult first-episode psychosis (Erickson et al., 2015; Umbricht & Krljes, 2005) but inconsistent with others (e.g., Atkinson et al., 2012; Hay et al., 2015; Hermens et al., 2010). Given that meta-analyses have consistently found an effect size of $d = \sim 1.0$ for MMN amplitude impairment in schizophrenia patients relative to healthy controls, the present sample size was adequate to detect an effect (Erickson et al., 2015; Umbricht & Krljes, 2005). While the sample here was not exclusive to first-episode psychosis, the mean duration of illness was two years, and only two patients endorsed greater than three years duration of illness. Given consistent reports of impaired MMN amplitude in

individuals at clinical high risk and in chronic phases of psychotic illness (Erickson et al., 2015), the present study supports the hypothesis that MMN impairment does not follow a linear trajectory with psychotic illness onset. It is unclear what may contribute to the relative improvement in MMN in first-episode psychosis; one possible explanation is that MMN improves with initial stabilization of psychotic symptoms, but then becomes impaired again as the illness progresses. This apparent discrepancy may also be due to sampling bias and variable outcomes of individuals in first episode psychosis: individuals in a first episode group with intact MMN may go on to have relatively good outcomes, whereas individuals with impaired MMN may go on to have poor outcomes and would later comprise a chronic patient group (Erickson et al., 2015). In other words, a first episode group may be relatively heterogeneous compared to a chronic patient group. Additional longitudinal research across stages of illness is needed to understand what may contribute to relative improvements in MMN in first-episode psychosis and the progression of MMN over illness course.

In Aim 2 of the present study, we did not find evidence of significant Group X Age X ERP component interactions, suggesting that EOP patients do not show large deviations from the typical pattern of developmental changes in the ERP components measured here. In a post-hoc exploratory analysis, we found a trend-level negative correlation between age and C1 potentiation at the Post-HFvS 2 block after controlling for the effect of group. Specifically, increasing age was associated with greater *de*-potentiation 4-6 minutes following HFvS for all participants, which was the overall trend seen for C1 in this block (see **Figure 4**). Given the aforementioned explanation that processes related to heterosynaptic LTD may lead to this observed initial *de*-potentiation (Chistiakova et al.,

2014; Royer & Paré, 2003), it may be that developmental processes somehow strengthen this homeostatic mechanism. One possibility may be related to the fine-tuning of microcircuits utilizing GABAergic interneurons (Jadi et al., 2015), a process which has been shown to develop in adolescence and young adulthood (Cho et al., 2015). However, given the exploratory nature of this analysis, this conclusion remains highly speculative. Prospective within-subjects studies are needed to clarify this result. The data also suggested a trend toward divergent trajectories of MMN amplitude in EOP patients vs. TD controls; however, given the trend-level significance, this result should be interpreted with caution.

A significant interaction showed that C1 amplitude potentiation at Post-HFvS 4 was significantly associated with MMN amplitude in TD controls only, such that greater potentiation was associated with a larger MMN response. This association indicates that the processes involved in VEP potentiation overlap with the processes involved in signaling the detection of a deviant tone. One source of this association may be that both signals are dependent upon NMDAR functioning and synaptic cortical plasticity (Kirk et al., 2010; Umbricht & Krljes, 2005; Wacongne, 2016). Given that the responses are occurring in different sensory modalities, this association seems to be a reflection of general sensory cortical plasticity rather than within one sensory modality. It is also notable that the visual C1 component, similar to the auditory MMN component, is pre-attentional and is influenced by simple stimulus features (e.g., orientation, visual hemisphere), thus the association may also be related to generation of early sensory ERPs. There was no association between VEP potentiation and MMN in EOP patients, which may be a reflection of impaired NMDAR functioning, or a statistical lack of power

and restricted range given the lack of potentiation in this group. Future research with larger sample sizes should be done to confirm this finding. Given the aforementioned intact MMN signal found in the present patient sample, the association between component potentiation and MMN across phases of illness may also elucidate potential the development of synaptic plasticity impairments in schizophrenia.

Within the EOP group, there were marginally significant correlations between Post-HFvS 4 P2 potentiation and positive symptoms, and between Post-HFvS 4 P2 potentiation and general symptoms, with both correlations indicating that greater potentiation was associated with more severe symptoms. While greater potentiation would theoretically be associated with improvements in synaptic plasticity, it is important to note that the EOP group as a whole did not show significant potentiation of the Post-HFvS 4 P2 component and, on average, showed *de*-potentiation at this block (see **Figures 4** and **6**). Thus, as discussed above, the *de*-potentiation of the P2 component for the EOP patients may be more reflective of processes related to heterosynaptic LTD rather than homosynaptic LTP. Less symptom severity in EOP patients, then, may be associated with enhanced heterosynaptic LTD, whereas heightened symptom severity may reflect balanced homosynaptic LTP/heterosynaptic LTD processes, or a lack of either process. The latter interpretation would suggest largely absent synaptic plasticity processes. Notably, hypotheses regarding the role of NMDARs in schizophrenia suggest a specific role in the generation of positive symptoms (Krystal et al., 2003; Stephan et al., 2006), which aligns with the findings here. Further research is needed to confirm and clarify this finding.

We did not find evidence for an association between MMN or VEP potentiation from the HFvS paradigm and cognition or functioning. Previous reports have found associations between MMN and cognition and functioning in adults with adult-onset schizophrenia (Baldeweg et al., 2002; Kawakubo et al., 2007; Light & Braff, 2005a; Light & Näätänen, 2013; Wynn et al., 2010a). To our knowledge, this is the first study to examine these associations in an early-onset sample, thus further research using larger sample sizes is needed to confirm this finding. Again, examining the longitudinal associations between MMN, cognition and functioning across phases of illness is an important next step in clarifying the course of these associations. Using a similar HFvS paradigm in adults with adult-onset schizophrenia, Cavus and colleagues (2012) found that faster reaction time to the oddball target was associated with larger VEP potentiation; however Forsyth and colleagues (2017) failed to find a significant association between VEP potentiation and cognitive performance. Thus, additional research is needed to clarify the relationship between potentiation from the HFvS task and cognition and functioning.

There were several limitations to the present study. Although the present study utilized a sample size similar to (Cavus et al., 2012) or greater than (Mears & Spencer, 2012) other studies using the HFvS paradigm in patients with schizophrenia and healthy controls, a larger sample may yield greater power to find group effects. A larger age range that extends into early-mid adulthood could also be needed to find evidence for divergent developmental trajectories of the ERP components measured here. Because the EOP patients in our study were medicated, it is possible that lack of potentiation is due to medication effects; future studies will need to disentangle this medication confound in

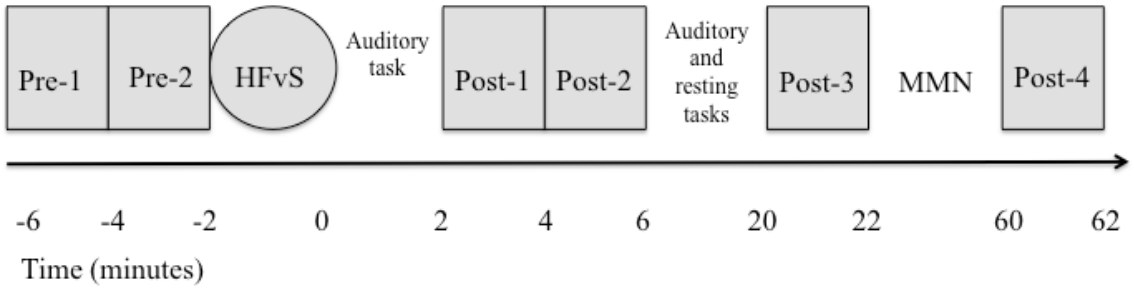
patients with psychotic disorders. In general, future studies should utilize longitudinal studies across phases of illness (e.g., clinical high-risk, first episode, chronic schizophrenia) to examine factors that contribute to impairment in MMN or VEP potentiation in the HFvS paradigm.

Summary

Mounting evidence supports impaired synaptic plasticity in the pathophysiology and symptom severity of schizophrenia and other psychotic disorders. In a minority of cases, the onset of psychosis occurs in early- to mid-adolescence, a time of dramatic neural circuit development and reorganization. Perhaps because of this disruption in typical neural development, individuals with EOP tend to show more severe clinical course relative to individuals with adult-onset psychosis (Eggers & Bunk, 1997). The goals of the present study were to assess the integrity of cortical synaptic plasticity in individuals with EOP relative to TD controls, as well as the contribution of impaired synaptic plasticity to functional and cognitive deficits and symptom severity in this population. To do so, we used a relatively well-established measure, the MMN, which is believed to be produced by perceptual learning mechanisms within the primary auditory cortices (Cooray et al., 2016; Garrido et al., 2008; 2009) that are dependent on synaptic plasticity and NMDAR signaling (Friston, 2005; Lieder et al., 2013; Wacongne, 2016). We also used a relatively new ERP paradigm that examines potentiation of VEPs by high-frequency visual stimulation (Kirk et al., 2010; McNair et al., 2006; Ross et al., 2008). This paradigm has been used to demonstrate impaired cortical synaptic plasticity in adults with adult-onset chronic schizophrenia in two prior studies (Cavus et al., 2012; Mears & Spencer, 2012) and is also proposed to be reliant on NMDAR functioning

(Clapp et al., 2006; Forsyth et al., 2017; 2015). We found that TD controls showed significant potentiation of VEPs 20-60 minutes following HFvS, whereas EOP patients showed initial *de*-potentiation of the C1 component 4-6 minutes following HFvS, but otherwise failed to show potentiation. Across the adolescent age range, there was no cross-sectional evidence that EOP patients showed a divergent developmental trajectory of VEP potentiation or MMN response. We also found that VEP potentiation was positively correlated with MMN amplitude in TD controls only, suggesting that intact NMDAR-driven synaptic plasticity processes may contribute to both signals. In EOP patients, we also found evidence for an association between VEP potentiation and symptom severity. We did not find evidence for an association with cognition or functioning for either measure, however, given the small sample size, we suggest additional studies in larger samples are warranted. We propose that eye tracking research is needed to further validate that the lack of potentiation in patients with schizophrenia is due to impaired synaptic plasticity processes and not attentional deficits, and that additional manipulations of the HFvS paradigm are needed to parse out the divergent potentiation or *de*-potentiation of early vs. late perceptual components. In general, we find that the results here support evidence that schizophrenia is related to impairments in NMDAR-driven synaptic plasticity, and extends this evidence to an early-onset adolescent patient sample.

Figure 1. Timeline of the EEG paradigm



HFvS = High-frequency visual stimulation; MMN = mismatch negativity
Pre-1, Pre-2, Post-1, Post-2, Post-3 and Post-4 refer to visual evoked potential (VEP) assessment blocks.

Table 1. Demographic information

	EOP Patients (N=24)	TD Controls (N = 20)
Mean age, years (± SD)	**15.6 (2.2)**	**16.9 (2.3)**
Mean illness duration, years (± SD)	**2.0 (1.3)**	**--**
Number female (%)	**10 (42)**	**12 (60)**
Number left-hand dominant (%)	**2 (8)**	**1 (5)**
Mean participant education, years (± SD)	**10.0 (2.4)**	**12.0 (2.4)**
Mean parental education, years (± SD)	**14.6 (2.9)**	**16.2 (2.0)**
Race/Ethnicity (%)*		
Caucasian	**17 (71)**	**9 (45)**
Hispanic	**5 (21)**	**1 (5)**
African American	**1 (4)**	**3 (15)**
Asian/Other/Mixed	**1 (4)**	**6 (30)**
DSM-IV-TR Diagnoses (%)		**--**
Schizophrenia	**12 (50)**	**--**
Schizoaffective, Bipolar Type	**1 (4)**	**--**
Schizoaffective, Depressive Type	**5 (21)**	**--**
Psychosis, Not Otherwise Specified	**6 (25)**	**--**
Comorbid Diagnoses[+]	**22 (92)**	**--**
Medications (%)		
Atypical Antipsychotic	**15 (63)**	**--**
Typical Antipsychotic	**1 (4)**	**--**
Anticonvulsant/Mood stabilizer	**6 (25)**	**--**
SSRI/SNRI/MAOi/other anxiolytics	**7 (29)**	**--**
Anticholinergic	**2 (8)**	**--**

[+]Autism Spectrum Disorder N = 3; ADHD N = 3; Cannabis Abuse N = 2; Alcohol Abuse N = 2; Panic Disorder N = 3; Anxiety Disorder NOS N = 5; Dysthymic Disorder N = 1; Specific phobia N = 3; Social anxiety disorder N = 1

SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Serotonin and Norepinephrine Reuptake Inhibitor; MAOi = Monoamine Oxidase Inhibitor

*Pearson Chi-Square $p < .05$

Table 2. Functioning, cognition and symptom severity in EOP patients vs. TD controls

	EOP Patients (N=24)	TD Controls (N = 20)	Significance test
Mean GAF current (± SD)	**45.2 (14.4)**	**86.2 (6.1)**	***t* = 12.6, *p* < .001**
Mean SIPS P symptoms (± SD)	**2.8 (1.6)**	**0.33 (0.3)**	***t* = 7.0, *p* < .001**
Mean SIPS N symptoms (± SD)	**1.8 (1.1)**	**--**	
Mean SIPS D symptoms (± SD)	**1.3 (0.9)**	**--**	
Mean SIPS G symptoms (± SD)	**1.5 (1.2)**	**--**	
Mean WASI IQ (± SD)	**104.3 (12.7)**	**116.6 (9.7)**	***t* = 3.5, *p* = .001**
Mean BACS Symbol-Digit Coding (± SD)	**53.6 (13.7)**	**62.4 (10.0)**	***t* = 2.4, *p* < .022**
Mean HVLT-R Total (± SD)	**23.3 (5.6)**	**28.1 (3.9)**	***t* = 3.2, *p* = .003**
HVLT-R Trial 1 (± SD)	**6.1 (1.8)**	**7.2 (1.2)**	***t* = 2.4, *p* = .022**
HVLT-R Trial 2 (± SD)	**8.1 (2.5)**	**10.1 (2.2)**	***t* = 2.8, *p* = .008**
HVLT-R Trial 3 (± SD)	**9.1 (2.0)**	**10.8 (1.3)**	***t* = 3.3, *p* = .002**

GAF = Global assessment of functioning; SIPS = Structured Interview for Prodromal Symptoms; P = Positive; N = Negative; D = Disorganized; G = General; WASI = Wechsler Abbreviated Scale of Intelligence, measured by Vocabulary and Matrix Reasoning subtests; HVLT-R = Hopkins Verbal Learning Test – Revised, measured by total recall; BACS = Brief Assessment of Cognition.
GAF is on a scale of 1-100 scale, with the 91-100 interval signifying absent or minimal symptoms and problems and the 0-10 interval signifying an individual who is in persistent danger of severely hurting self or others.
All SIPS scales are on a 0-6 scale, where scores of 3-5 are considered subthreshold/prodromal psychotic symptoms and 6 indicates severe and psychotic symptoms.

Table 3. Component amplitude and latency.

		TD controls		EOP patients	
		Mean	SD	Mean	SD
C1	Baseline VEP amp	-10.95	8.56	-7.37	9.65
	Latency (ms)	99.34	10.17	97.68	11.08
	Post-HFvS 1 amp	-9.20	8.38	-6.68	8.86
	Latency (ms)	99.66	10.50	97.17	10.02
	Post-HFvS 2 amp	-8.94	7.07	-5.06	8.07
	Latency (ms)	97.61	12.13	95.62	10.79
	Post-HFvS 3 amp	-10.59	9.00	-5.79	8.01
	Latency (ms)	100.83	10.88	96.80	10.70
	Post-HFvS 4 amp	-14.33	9.90	-8.62	9.38
	Latency (ms)	99.80	11.55	96.55	10.72
P2	Baseline VEP amp	10.03	5.75	10.81	5.76
	Latency (ms)	200.05	36.58	193.97	43.49
	Post-HFvS 1 amp	8.78	4.73	10.32	6.10
	Latency (ms)	211.67	38.00	193.89	42.72
	Post-HFvS 2 amp	10.12	5.24	9.69	6.01
	Latency (ms)	203.47	38.86	191.12	40.09
	Post-HFvS 3 amp	13.82	5.66	12.08	5.45
	Latency (ms)	198.53	31.45	198.33	41.99
	Post-HFvS 4 amp	13.01	6.28	10.35	6.77
	Latency (ms)	194.67	33.76	198.95	46.18
MMN	Average Fz, F3, F4, Cz, C3, C4	-4.35	1.46	-4.10	2.01
	Latency (ms)	125.46	20.06	128.28	19.42

Amp = amplitude, in microvolts; VEP = visual-evoked potential; HFvS = High-frequency visual stimulation; MMN = mismatch negativity.

Figure 2. Mismatch Negativity Amplitude by Group.

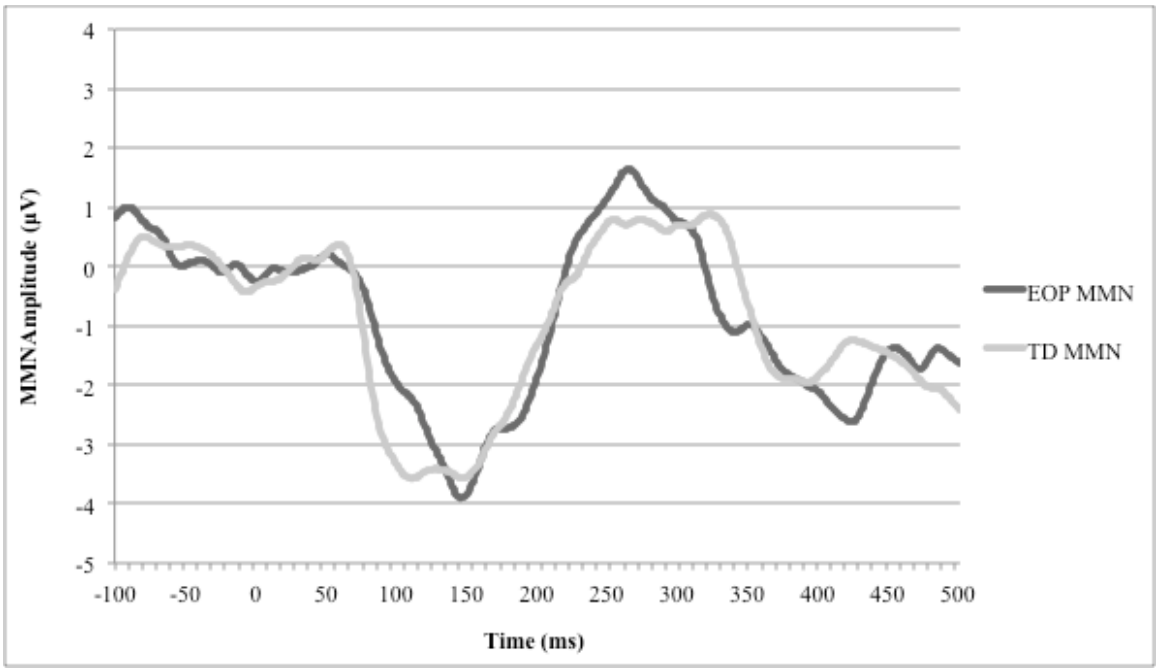
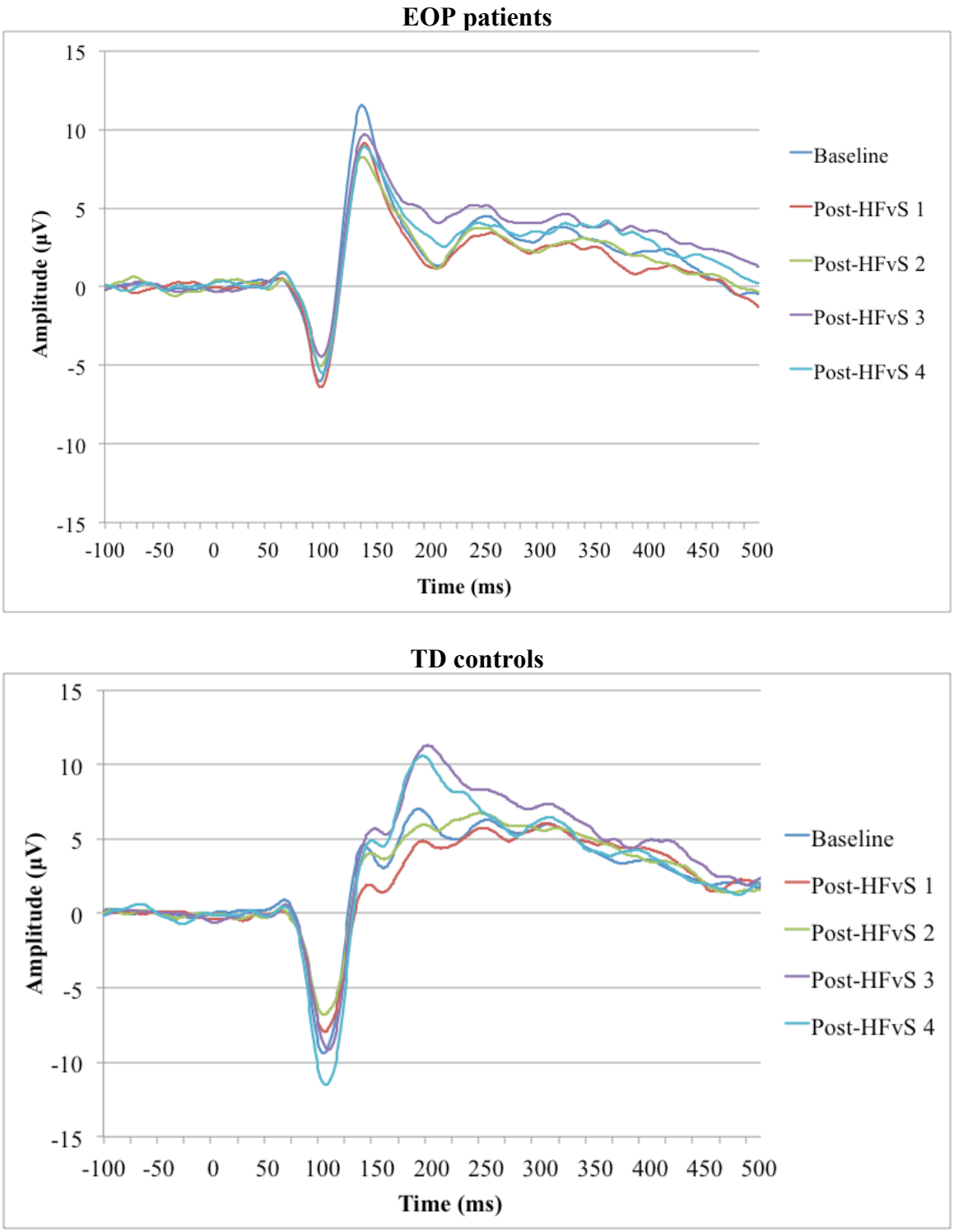
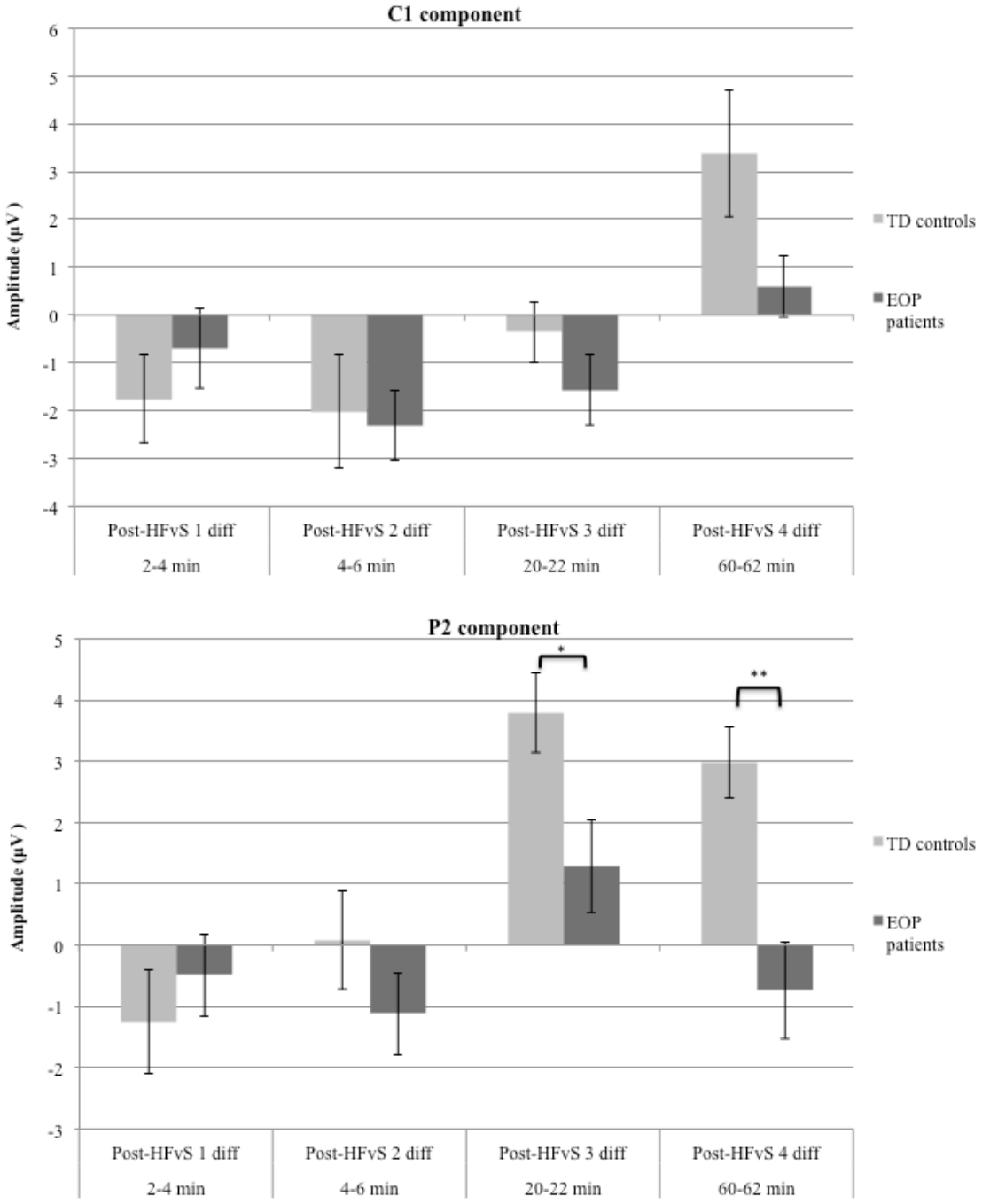


Figure 3. Visual-evoked potential amplitude from the HFvS paradigm.



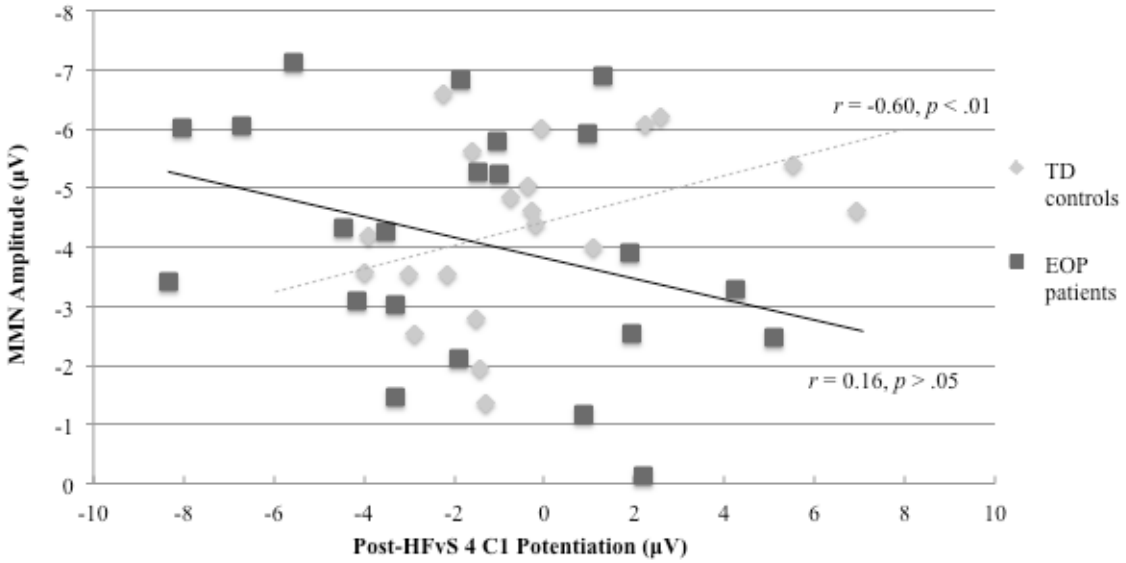
HFvS = High-frequency visual stimulation
Post-HFvS 1 = 2-4 min after viewing HFvS; Post-HFvS 2 = 4-6 min after viewing HFvS; Post-HFvS 3 = 20-22 min after viewing HFvS; Post-HFvS 4 = 60-62 min after viewing HFvS.

Figure 4. C1 and P2 Potentiation in the High-Frequency Visual Stimulation paradigm.



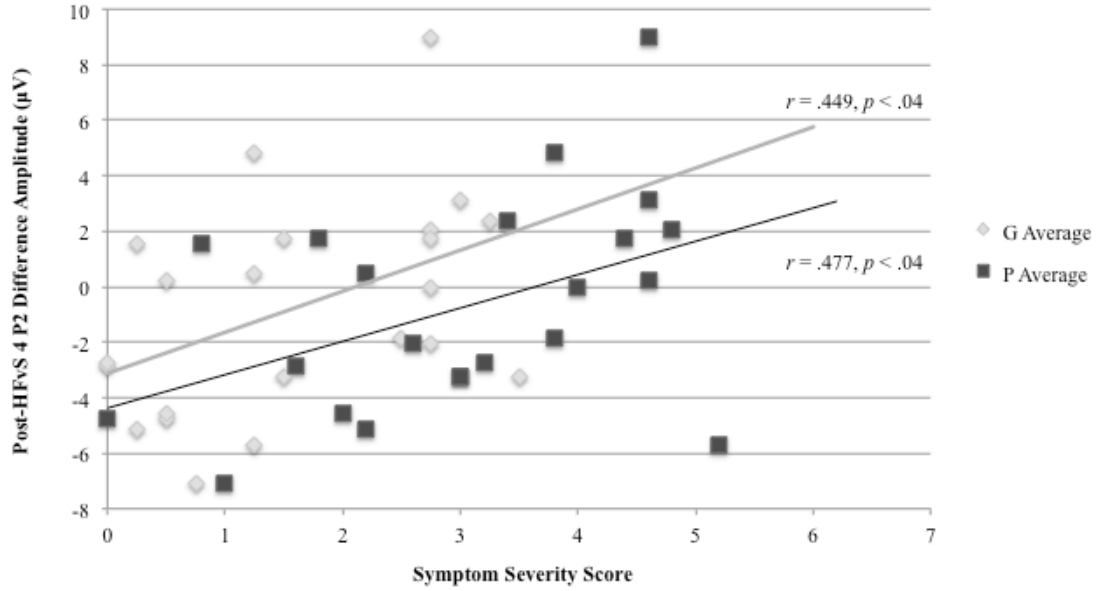
Diff = Amplitude difference score relative to Baseline; HFvS = High-frequency visual stimulation.
* $p < .01$; ** $p = .001$

Figure 5. Association between MMN amplitude and Post-HFvS 4 C1 potentiation.



MMN = Mismatch Negativity; HFvS = High-frequency visual stimulation

Figure 6. Association between P2 Potentiation and Symptom Severity in EOP patients.



G = General symptoms; P = Positive symptoms; HFvS = High-frequency visual stimulation.

GENERAL DISCUSSION

Much of the economic burden associated with schizophrenia comes from indirect costs from functional impairment, including unemployment and productivity loss due to caregiving (Cloutier et al., 2016). A key contributor to functional impairment in schizophrenia is cognitive dysfunction (Evans, 2004; Fett et al., 2011; Green, Kern, Braff, & Mintz, 2000; Nuechterlein et al., 2011), which is not addressed with current pharmacological treatments. Thus, there is great need for new, mechanistically distinct therapies to target these symptoms of schizophrenia. The RDoC initiative creates a novel framework for investigating the neurobiological and behavioral constructs that contribute to cognitive dysfunction and other symptoms of schizophrenia (Cuthbert, 2014; Cuthbert & Insel, 2013; Kozak & Cuthbert, 2016). It aims to use quantitative, dimensional measures to establish biological understanding of intermediate psychological constructs, hopefully leading to the development of effective pharmacological and/or behavioral treatments for schizophrenia and other disorders (Kozak & Cuthbert, 2016; Yee, Javitt & Miller, 2015). The RDoC approach closely aligns with the endophenotype concept, which attempts to establish variables that lie in the pathway between genotype and symptom constellation (Gottesman & Gould, 2003; Gould & Gottesman, 2006; Lenzenweger, 2010). Given significant research on endophenotypes of schizophrenia, Chapter One of this dissertation reviewed several proposed electrophysiological endophenotypes of schizophrenia and how each shows: 1) evidence of deficits in schizophrenia; 2) stability over time; 3) relative independence of fluctuations in clinical symptoms; 4) deficits in unaffected family members; and 5) heritability (Gottesman & Gould, 2003; Gould &

Gottesman, 2006; Lenzenweger, 2010). I also addressed quantitative electrophysiological traits implicated in schizophrenia, including neural activity in the gamma range (30-80 Hz; Gonzalez-Burgos, Cho, & Lewis, 2015; Mathalon & Sohal, 2015) and augmented sensory-evoked potentials from an LTP-analog paradigm (Cavus et al., 2012; Kirk et al., 2010; Teyler et al., 2005). Lastly, I discussed the results from a recent set of publications from the Minnesota Center for Twin and Family Research (MCTFR), which attempted to uncover the genetic architecture of 17 psychophysiological endophenotypes using data from approximately 4,900 twins and parents and largely failed to find significant effects of genetic variants (Iacono, Vaidyanathan, Vrieze, & Malone, 2014). I concluded that these endophenotypes might not be appreciably less genetically complex than clinical symptoms, and thus there is great need for very large sample sizes and comparable methodology across studies to facilitate combined datasets across sites.

An important area of investigation for the RDoC initiative is dysfunction in neural connectivity and synaptic plasticity (Yee, Javitt & Miller, 2015). The role of disrupted synaptic plasticity has been gaining much traction as a core feature of the development of symptoms (Forsyth & Lewis, 2017). Specifically, impaired synaptic plasticity may initially disrupt refinement of local sensory and motor circuits, leading to subtle deficits in sensory and motor function early in development and well before the onset of clinical symptoms (Brockhaus-Dumke et al., 2008). This early disruption may eventually compound into robust deficits in higher-level cognitive functions (e.g., verbal memory recall, planning, behavioral inhibition) seen later in development but still prior to the onset of full psychosis (Seidman, 2010). Finally, disrupted synaptic plasticity may impair functional integration of information between cortical regions (Andreasen et al., 1999;

Friston 2005; Hoffman & McGlashan 2001), and eventually contribute to the onset of full psychosis. Establishing quantitative, dimensional measures capable of indexing synaptic plasticity functioning and examining their relationship to psychological constructs aligns with the RDoC initiative and may be critical in establishing therapeutic targets for schizophrenia.

The Mismatch Negativity (MMN) shows great promise as a translatable quantitative trait of schizophrenia (Näätänen, Shiga, Asano, & Yabe, 2015). Within the RDoC Matrix, the MMN is a physiological measure in the Cognitive Systems domain under the sub-construct of Auditory Perception (www.nimh.nih.gov/research-priorities/rdoc/). It is found to be consistently and markedly impaired in individuals with chronic schizophrenia (Erickson, Ruffle, & Gold, 2015; Umbricht & Krljes, 2005) and MMN deficits have been shown to predict psychosis onset in clinically high-risk individuals (Atkinson, Michie, & Schall, 2012; Bodatsch et al., 2011; Perez et al., 2014). Additionally, MMN deficits in schizophrenia are highly associated with impairments in real-world functioning and psychosocial functioning (Kawakubo et al., 2007; Light & Braff, 2005; Wynn et al., 2007). Many studies have also demonstrated that disruption of N-methyl-D-aspartate (NMDA) signaling plays a crucial role in MMN generation and contributes to MMN deficits in patients with schizophrenia (Javitt et al., 1996; Michie et al., 2016; Umbricht et al., 2000). Thus, MMN appears to be associated with important clinical, functional, and neurobiological aspects of psychosis. However, there is much that remains to be understood about MMN and how it may index the development of symptoms of schizophrenia. One factor that is poorly understood is how MMN changes with typical development: given well-established patterns of neural growth and

reorganization in adolescence and young adulthood (Durston et al., 2006; Paus, 2005), which is when psychosis onset typically occurs, one must first understand the typical developmental trajectory of MMN before clarifying the development of aberrant trajectories. Many studies have attempted to map the normative development of MMN with mixed results and methodologies (e.g., Cooray et al., 2016; Kisley et al., 2005; Kraus et al., 1993; 1992). Thus, the first goal of the study presented in Chapter Two was to measure and establish the typical developmental trajectory of the MMN. Using the largest typically developing sample to date (N = 157), we found that MMN amplitude and latency decreased in a linear fashion with age, in individuals ages 12-35. This MMN latency reduction corresponds to linear increases in white matter over this age range (Giedd, 2008; Lenroot & Giedd, 2006; Uda et al., 2015). The biological basis for reduction in MMN amplitude with increasing age warrant further exploration; I hypothesized that a decrease in deviance signal could be due to structural changes in cortical gray matter thickness (Gogtay et al., 2004) and/or to developmental changes in EEG frequency oscillations (Lee et al., 2017). Future studies could address this question by assessing the developmental trajectories of responses to the deviant and standard tones separately.

In addition to incomplete understanding of the typical development of MMN, little is known about the relationship of MMN to cognition and functioning in healthy individuals. Given that MMN has been shown to predict clinical outcomes in individuals at high risk for psychosis (Atkinson et al., 2012; Bodatsch et al., 2011; Perez et al., 2014), I also wondered whether MMN could predict outcomes in healthy individuals. Thus, I assessed these questions using the same healthy control dataset. I found that MMN was

not related to cognition or functioning measured at the same time point, but that MMN predicted changes in verbal learning and memory as well as general functioning one year later, controlling for baseline performance. Specifically, greater MMN amplitude at baseline was associated with improvements in verbal memory and functioning over one year. I suggest that the specific predictive relationship with verbal memory and not other domains of cognition supports the theory that iterative effects of elementary levels of auditory processing can influence cognitive outcomes in the auditory domain, which may influence functioning more generally (Light et al., 2007). I suggest the need for within-subjects studies mapping longitudinal MMN changes to longitudinal changes in cognition and functioning (i.e., longitudinal meditational models) to establish a temporal pattern to these effects. Such studies could possibly lead to causal models, which could have significant pharmacological implications for schizophrenia (Light & Näätänen, 2013; Näätänen et al., 2015).

A relatively new electrophysiological paradigm has been developed in an attempt to noninvasively measure synaptic plasticity (Kirk et al., 2010). While many studies have established that neural changes measured during this paradigm are due to the effects of NMDA-mediated long-term plasticity (LTP; Clapp et al., 2005; Kirk et al., 2010; McNair et al., 2006; Teyler et al., 2005; Forsyth et al., 2017; 2015) only two have examined whether individuals with schizophrenia show impairments relative to healthy controls (Cavus et al., 2012; Mears & Spencer, 2012). Both studies found that adults with schizophrenia (relative to healthy controls) showed impairments in potentiation of sensory-evoked potentials after exposure to a high-frequency stimulation (i.e., a sensory "tetanus") designed to induce cortical LTP (Cavus et al., 2012; Mears & Spencer, 2012).

Notably, both studies utilized adult-onset schizophrenia samples, largely comprising individuals with chronic schizophrenia. I sought to use an adolescent sample with early-onset psychosis (EOP; onset prior to age 18) to test whether similar deficits could be seen earlier in development, as well as at an earlier, largely first-episode stage of illness. I also tested whether measures from this paradigm were related to cognition and functioning in EOP (N = 24) relative to typically developing controls (TD; N = 20), as well as symptom severity in EOP. Lastly, given that both the LTP-analog task and the MMN are posited to index NMDA-receptor functioning (Kirk et al., 2010; Michie et al., 2016), I tested their association with each other and the developmental trajectories of each in EOP relative to TD.

The study presented in Chapter Three found that EOP patients failed to potentiate visual sensory-evoked components after viewing the high frequency stimulation (HFvS), while TD controls showed significant potentiation of components beginning 20-60 minutes after viewing HFvS. I suggest that this supports accumulating evidence for impaired synaptic plasticity processes in schizophrenia. Across the adolescent age range, there was no cross-sectional evidence that EOP patients showed a divergent developmental trajectory of component potentiation or MMN response. Additionally, consistent with other studies of first-episode schizophrenia, I found no group differences in MMN, and highlighted the need for longitudinal, within-subjects designs to parse apart the factors leading to the non-linear course of MMN impairment with illness progression (Erickson et al., 2015) as well as to establish the developmental trajectory of synaptic plasticity (as measured by the LTP-analog paradigm). In TD controls only, I found that VEP potentiation was positively correlated with MMN amplitude, bolstering other

evidence that intact NMDA-receptor signaling may contribute to both signals. In EOP patients, I also found evidence for an association between VEP potentiation and symptom severity. I did not find evidence for an association with cognition or functioning for either measure; however, given the small sample size, additional studies in larger samples are warranted. Further, additional validation studies (e.g., eye-tracking studies) are needed to confirm that the impairments seen in schizophrenia patients in the LTP-analog paradigm are not due to general deficits in attention during the task.

In conclusion, I reviewed literature that has attempted to use electrophysiological measures as intermediaries between genetic variants and clinical symptoms of schizophrenia. I then examined two quantitative electrophysiological measures that are posited to index synaptic plasticity. I showed that one measure, the MMN, develops in a linear fashion and is capable of predicting verbal memory and functional improvements in healthy adolescents and young adults, which may have important implications understanding its ability to predict clinical outcomes in psychosis. I also added to evidence that a relatively new electrophysiological measure, augmented sensory-evoked potentials in the LTP-analog paradigm, can index impairments in adolescents with schizophrenia. I suggest the need for additional longitudinal research to further clarify the role of disrupted synaptic plasticity in the development and clinical course of schizophrenia, with the hope of developing new therapeutic targets for prevention and early intervention of psychosis.

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