Assessing Visual Experience-Dependent Plasticity in Schizophrenia Using Visual Evoked Potentials

an EEG Study

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Summary

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Author statement: This thesis was written as part of an ongoing research project at The Norwegian Centre for Mental Disorders Research, Oslo University Hospital, Ullevål. The ongoing project aims to explore the roles of synaptic plasticity in the etiology and treatment of schizophrenia and bipolar disorder. As such, the idea for the study and the experimental paradigm was developed beforehand. The author of this thesis has independently generated hypotheses, processed and analyzed data, as well as contributed by enlarging the database used in this project.

Supervisor: Torbjørn Elvsåshagen

Abstract: Synaptic plasticity might be an important neurobiological component in the pathophysiology of schizophrenia. Determining the presence of abnormal synaptic plasticity has nevertheless proven difficult mainly due to a lack of non-invasive assessment of synaptic plasticity. Recently however, advances in electrophysiological research have provided a method for assessing LTP-like plasticity non-invasively in the human brain. By using this method, researchers have demonstrated a lasting enhancement of the visual evoked potential (VEP) following a prolonged period of repetitive visual stimulation, entailing properties corresponding to canonical synaptic processes measured in animal models. This study builds on this experimental procedure and sought to assess whether synaptic plasticity is abnormal in a group of individuals with schizophrenia (n = 22) compared to healthy controls (n = 157). VEPs were evoked by means of repetitive pattern-reversing checkerboard stimulation and assessed in a pre-post design for upwards of one hour following a period of prolonged visual stimulation. The results showed that prolonged visual stimulation produced a lasting enhancement in VEPs for upwards of one hour in healthy controls attesting to validity of this experimental paradigm. There were however, no differences in VEP responses between groups providing evidence suggesting that individuals with schizophrenia do possess capacity for visual plasticity resembling that observed in healthy controls. These results have

implications for future attempts to assay visual plasticity in schizophrenia and nuance the hypothesis of an overall impairment in synaptic plasticity underlying the disorder.

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1 Introduction

Schizophrenia is a devastating neuropsychiatric disorder with an approximate prevalence rate of 1% world-wide (Lieberman, Stroup, & Perkins, 2007). Albeit phenotypically heterogeneous, its symptomatology forms three clusters comprising positive (e.g., hallucinations and delusions) and negative (e.g., apathy and anhedonia) symptoms, and cognitive-impairments (e.g., executive functioning, attention, and memory) that together define the disorder (Association, 2013; Lieberman et al., 2007). Over the past twenty years, neuroimaging studies have shown abnormalities in structure and function both globally and regionally in schizophrenia (Buckley, 2005). These abnormalities in cortical structure and function are thought to give rise to abnormal functional integration across brain regions, i.e., abrupted connectivity, or dysconnectivity in network circuitry (Stephan, Friston, & Frith, 2009). Similarly, evidence from electrophysiological studies have consistently identified abnormal gamma band activity in schizophrenia (Jadi, Behrens, & Sejnowski, 2016), frequency-specific oscillations associated with functional integration of sensory information within neural circuits (Shin, O'Donnell, Youn, & Kwon, 2011). Although the evidence for altered connectivity in schizophrenia is strong (Spencer et al., 2003; Zhou et al., 2018), the underlying pathophysiological mechanisms and significance for clinical symptoms remain unclear (Stephan et al., 2009).

Impaired synaptic plasticity is one of the leading candidate neurobiological processes for dysconnectivity in schizophrenia (Stephan et al., 2009). Synaptic plasticity refers to changes in synaptic transmission within large neural networks in response to endogenous and exogenous information through structural and functional strengthening of connections, thus making the brain malleable to experience (Kaczmarek, 2016). Although different processes and mechanisms acting at different levels make up synaptic plasticity, one of the best understood and widely researched forms of synaptic changes is known as Hebbian plasticity (Lisman, 2017). Within the Hebbian plasticity framework, two opposing complimentary processes work to either increase or decrease synaptic transmission. Long-term potentiation (LTP) refers to an increase in synaptic transmission whereas long-term depression (LTD) refers to a decrease in synaptic transmission (Bliss & Lømo, 1973). Crucial for the induction of both LTP and LTD are a class of ionotropic receptors called N-methyl-D-aspartate receptors (NMDARs) (Lüscher & Malenka, 2012; Zito & Scheuss, 2009). Importantly, the level of functioning of these receptors has been hypothesized to be downregulated in schizophrenia (Coyle, Tsai, & Goff, 2003). In fact, altered NMDAR functioning have been proposed to represent a core deficit in the pathophysiology of schizophrenia (Coyle, 2012; Stephan et al., 2009). Consequently, it is

possible that altered NMDAR signaling is one substrate for synaptic plasticity impairment and dysconnectivity in schizophrenia (Buckley, 2005; Ferri et al., 2018; Liang et al., 2006; Meyer-Lindenberg et al., 2001; Stephan et al., 2009)

Evidence for altered NMDAR signaling in schizophrenia have been demonstrated in large-scale genome studies (Schizophrenia Working Group of the Psychiatric Genomics et al., 2014), and post-mortem studies (Kristiansen, Beneyto, Haroutunian, & Meador-Woodruff, 2006), which collectively converge on disturbances in synaptic pathways arising from NMDA-hypofunction in schizophrenia (Kantrowitz & Javitt, 2010; Sarkar, Marchetto, & Gage, 2017). If abnormal neuroplasticity represents a core feature underlying schizophrenia pathology, then measuring synaptic modifications *in vivo* would further our understanding of the complex etiology of the disorder. Recent advances in electrophysiological theory and method have provided non-invasive indices of synaptic neuroplasticity in the human cerebral cortex (Teyler et al., 2005). These methods have provided *in vivo* evidence for abnormal neuroplasticity in both auditory (Mears & Spencer, 2012) and visual cortices (Çavuş et al., 2012) of individuals with schizophrenia. Targeting these sensory domains are supported by a large body of research showing widespread impairments during perceptual processing in schizophrenia (Butler, Silverstein, & Dakin, 2008). Assessing neuroplasticity in sensory domains is further substantiated by both animal (Sale et al., 2011) and human studies (Spriggs et al., 2018) demonstrating that synaptic modifications likely underlie aspects of perceptual learning (Kirk et al., 2010). Thus, assessing neuroplasticity through non-invasive electrophysiological sensory paradigms represents an intriguing venue for examining the roles of synaptic plasticity in schizophrenia pathophysiology.

1.1 A Brief Description of Long-Term Potentiation and Long-Term Depression

LTP is defined as a "form of experience-dependent synaptic plasticity which results in a persistent enhancement of synaptic transmission" (Bliss & Cooke, 2011, p. 3). Its complement is LTD whereby the efficacy of synaptic transmission is reduced. Because LTP and LTD reflect long-lasting changes in synaptic connections, they are considered primary candidate cellular substrates underlying memory and learning in the human brain (Bliss & Cooke, 2011). At the neuronal level, one form of LTP- and LTD-induction are explicitly associated with NMDARs. NMDARs are ionotropic receptors with high affinity for glutamate, which is the major excitatory neurotransmitter in the central nervous system (Belsham, 2001). NMDARs have high permeability for calcium and, are blocked by magnesium ions at resting membrane potential (Zito & Scheuss, 2009). These biophysical properties form the basis for NMDARs' regulatory

role in synaptic plasticity (Zito & Scheuss, 2009). Induction of LTP requires concurrent activity of both pre- and post-synaptic neurons at the same time. Because the NMDAR is blocked by magnesium ions at rest, it therefore requires simultaneous activation by glutamate and depolarization to relieve the magnesium block, and thus acts as a coincident detector for pre- and post-synaptic activity (Zito & Scheuss, 2009). In other words, these ionotropic receptors receive messages from both the presynaptic terminal and inside its postsynaptic membrane by a mechanism involving both the binding of transmitter and depolarization-induced repulsion of magnesium ions (Bliss & Cooke, 2011). Influx of calcium is then possible, which in turn activates numerous kinases and phosphatases leading to increased insertion and/or conductance of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) – another class of ionotropic receptors – into the postsynaptic membrane (Bliss & Cooke, 2011). This modification of the postsynaptic membrane functionally leads to enhanced synaptic strength, and when strengthened, these synapses will respond more effectively to presynaptic glutamate release. Put differently, when similar temporal activity patterns continue to induce transmission between synapses containing NMDARs, the net result is a strengthening of neighboring neural connections, which in turn increase the probability these synapses will fire upon subsequent presentation of similar input patterns. This form of LTP, called NMDA-dependent LTP, is characterized by rapid development (within the first minutes) and stronger expression during the first hours after induction (Blundon & Zakharenko, 2008). It is best understood at the post-synaptic cell and may be present across all the cerebral cortices (Blundon & Zakharenko, 2008).

LTP is further defined by specific series of properties reviewed in Lüscher and Malenka (2012). The enhancement in synaptic transmission should be *long-lasting* if it is to be a neural correlate of memory and learning. It is *input-specific*, meaning that only the stimulated pathway shows synaptic enhancement while neighboring pathways do not. Stimulation induction parameters matter greatly, and *associativity* is the property asserting that a weak stimulation can produce LTP only if it is associated with a strong stimulation. On the other hand, LTP can be reversed by activation of the set of pathways what were stimulated before when using lower stimulation frequencies, a property called *depotentiation*. Finally, the form of LTP herein described require NMDAR signaling and continued expression is mediated by an increase in glutamatergic transmission and an increase in voltage-gated channel conductance (Bliss & Cooke, 2011; Lüscher & Malenka, 2012).

Crucially, this form of experience-dependent synaptic plasticity may be altered in schizophrenia, possibly affecting abnormal functional connectivity and integration across brain regions (Stephan et al., 2009). A current and prominent theory posits that phenotypical

expressions observed in schizophrenia may in large part be explained by NMDAR hypofunction, whereby abnormal connectivity is a functional consequence (Kantrowitz & Javitt, 2010; Stephan et al., 2009). Indexing experience-dependent processes linked to NMDAR functioning (Clapp, Eckert, Teyler, & Abraham, 2006), and synaptic plasticity (Clapp, Hamm, Kirk, & Teyler, 2012), could represent a viable target of investigation into the underlying pathophysiology of schizophrenia.

1.2 NMDA-Dependent Synaptic Plasticity in Schizophrenia

Although the underlying pathophysiology of schizophrenia is poorly understood, a consistent line of evidence converge on the notion that endogenous excitatory glutamatergic signaling molecules are altered and may represent a key component underlying proposed deficient neuro plasticity in the disorder (Coyle et al., 2003). Kim, Kornhuber, Schmid-Burgk, and Holzmüller (1980) provided one of the earliest demonstrations to implicate hypofunction of NMDARs in schizophrenia by showing reduced concentrations of glutamate in the cerebrospinal fluid of individuals with schizophrenia. This contrasted with the current dominant biological drug-model suggesting largely dopamine neurotransmitter dysfunction in schizophrenia (Belsham, 2001). It also provided a shift in schizophrenia research that had largely focused on specific loci of the cortex, as those favoring the dopaminergic hypothesis construed their hypotheses within a top-down conceptual framework, whereas those favoring deficient amino acid signaling construed their hypotheses within distributed models of schizophrenia, incorporating both bottom-up and top-down aspects of impaired neurocognition (Javitt, 2009).

Then followed a series of studies showing that NMDAR antagonists, such as phencyclidine (PCP), ketamine and MK-801, could induce psychosis-like symptoms in healthy individuals, similar to both negative and positive symptoms of schizophrenia (Javitt & Zukin, 1991). Similarly, when ketamine was administered to individuals with schizophrenia, both positive and negative symptoms were exacerbated (Lahti, Koffel, LaPorte, & Tamminga, 1995). These chemical agents, called dissociative anesthetics, share the neurobiological consequence of blocking NMDARs (i.e., an antagonistic effect), which at that time, pointed to both glutamatergic and gamma-aminobutyric acid, two molecules that fitted better the distributed model of schizophrenia. Building on this reasoning, several studies investigated the effects of ketamine in healthy volunteers using paradigms known to elicit abnormal effects in schizophrenia. For example, Umbricht et al. (2000) demonstrated that ketamine produced aberrant event-related potentials using a mismatch negativity paradigm, while Radant, Bowdle, Cowley, Kharasch, and Roy-Byrne (1998) found ketamine induced oculomotor abnormalities

using eye-tracking. Thus, researchers started working on ideas that went beyond D2 receptor functioning (i.e., dopamine hypothesis) in schizophrenia and sought to gain more insight into NMDAR signaling. Since then, more than 2000 studies on NMDAR signaling have been published in schizophrenia research (Coyle, 2012).

Since these early neurochemical demonstrations, direct evidence of NMDAR hypofunction in schizophrenic patients has been limited. However, one compelling study demonstrated reduction in NMDAR binding in medication-free patients with schizophrenia using single photon emission tomography (PET) (Pilowsky et al., 2006). Similarly, genetic information reliably indicate risk gene variants implicated in NMDAR signaling (Sarkar et al., 2017), adding to the alternative/additional neurochemical model of schizophrenia reflecting glutamatergic signaling rather than the solely dopaminergic model, and prompting further need to investigate NMDAR regulatory pathways in schizophrenia.

1.3 A Genetic Link Between Schizophrenia Risk Genes and Synaptic Plasticity

A recent twin study comprising the largest sample size to date ($N > 30.000$) provided heritability estimates for schizophrenia to be roughly 80% (Hilker et al., 2017), suggesting a clear genetic component in schizophrenia. In addition, large genome wide association studies and exome studies consistently show both rare and common gene variants implicated in the pathology of schizophrenia (Pocklington et al., 2015; Schizophrenia Working Group of the Psychiatric Genomics et al., 2014). Many of these gene variants are associated with NMDAR functioning (Devor et al., 2017; Funk, Rumbaugh, Harotunian, McCullumsmith, & Meador-Woodruff, 2009; Ripke et al., 2014; Sebat, Levy, & McCarthy, 2009; Weickert et al., 2013). For example, Weickert et al. (2013) demonstrated altered expression in five genetic polymorphisms associated with NMDAR functioning, whereas a large genome-wide association study (GWAS) carried out by the schizophrenia working group (2014) found both common and rare genetic variations in schizophrenic patients believed to be involved in encoding synaptic proteins and regulating synaptic transmission. These studies emphasize that NMDAR functioning might represent a key etiological component in the neurobiology of schizophrenia. Moreover, a recent meta-analysis on NMDAR expression in post-mortem brain tissue found decreases in the expression of mRNA of NMDAR subunits (Catts, Lai, Weickert, Weickert, & Catts, 2016). These glutamatergic signaling deficits might initiate compensatory mechanisms that increase level of excitability in pyramidal neurons, that could lead to altered regulation of synaptic structure and function (Krystal et al., 2017). For example, when one such subunit, called GluN1, was eliminated from cortical pyramidal neurons in mice, these pyramidal neurons adapted by

increasing net excitability (Tatard-Leitman et al., 2015). Aberrant compensatory mechanisms would within this framework, represent a deviation from optimal signaling dynamics, and therefore altered connectivity (Krystal et al., 2017). Given the role of synaptic plasticity, not only in memory and learning across the lifespan, but also as a factor during development critically involved in organizing neurons into finely-tuned circuits, an imbalance in excitation/inhibition during brain maturation suggests synaptic plasticity may be a crucial pathogenic process in schizophrenia that go awry during brain development (Forsyth & Lewis, 2017).

Although researchers working to uncover the genomic background of schizophrenia disagree whether the disorder reflects a developmental or degenerative disease progression, they commonly agree its pathophysiology involve a complex neurodevelopmental polygenic component reflecting interacting environmental influences and risk genes (Sarkar et al., 2017). From a neurodevelopmental viewpoint, abnormal experience-dependent synaptic plasticity during brain maturation due to NMDA-hypofunction would be consistent with observations suggesting that schizophrenia cannot be explained by genetics alone (Stephan, Baldeweg, & Friston, 2006). Determining the influence of predispositions and environmental disturbances that may lead to an imbalance in the timing of critical synaptic processes during development could offer invaluable information into the underlying pathophysiology of schizophrenia. More studies indexing electroencephalogram (EEG) based indices of experience-dependent synaptic plasticity in the context of specific gene variants are needed. Such studies would further our understanding of the functional correlates that genes regulating synaptic plasticity might have on connectivity changes arising from altered NMDAR signaling in schizophrenia. At present, the preponderance of genetic information accumulated indicate a primary deficit in glutamatergic synaptic pathways (Sarkar et al., 2017), pointing to the relevance for indexing LTP-like plasticity in schizophrenia.

1.4 Is it Possible to Measure Long-Term Potentiation *in vivo* in Humans?

If schizophrenia is associated with abnormal NMDA-dependent LTP, then indexing LTP in the human brain *in vivo* may substantiate current theory regarding this form of synaptic transmission in individuals with schizophrenia. In animal models, where it is possible to invasively manipulate one pathway and not another, the cellular and molecular mechanisms underlying LTP have been extensively researched (Bliss & Lømo, 1973; Clapp et al., 2012). Inducing LTP in animals is commonly done by high-frequency electrical stimulation (HFS or tetanus) of afferent pathways, usually in hippocampal areas, while simultaneously recording

the changes in the response of downstream hippocampal neurons. If stimulating one neuron trigger surrounding neurons to increase their responses, then the signaling between them has become more efficient (i.e., potentiated). This immediate and enduring increase in postsynaptic response has been observed at glutamatergic synapses (Clapp et al., 2012). This increase in excitability will activate both NMDAR and voltage-dependent calcium channels to briefly increase postsynaptic calcium ion levels, leading to more depolarization (Clapp et al., 2012). As the postsynaptic cell become more excitable, intracellular cascades result in insertion of more ionotropic receptors into the postsynaptic membrane as well as increasing conductance of already existing receptors, thus producing a net result of a larger postsynaptic excitatory response (Clapp et al., 2012).

A decade ago, Frenkel et al. (2006) reasoned that changing the stimulus to a more realistic and naturally occurring visual stimulus could produce similar lasting synaptic changes corresponding to canonical LTP as induction protocols using invasive electrical stimulation. They recorded electrophysiological visual evoked potentials (VEPs) from layer 4 of binocular V1 in awake mice which were visually stimulated by a screen showing phase-reversing sinusoidal grating stimuli. VEPs are transiently evoked potentials to a visual stimulus recorded using EEG as measurement device (see detailed description of VEPs later in the introduction). When the same protocol was performed over several days, the VEP response increased in amplitude, specific to the stimulus-properties. This stimulus-specific response potentiation was demonstrated to last for days or weeks and changing the stimuli as little as 5 degrees reset the VEP amplitudes to baseline levels. The same was true when contrast and spatial frequency was altered. Input specificity was further exemplified by showing that when only one eye was stimulated, the potentiated stimulus-selective response did not transfer to the inexperienced eye. Lastly, this response potentiation was shown to be NMDAR-dependent by demonstrating that pharmacologically interfering ionotropic receptor signaling prevented potentiation of this response. By demonstrating that the response was input-specific, long-lasting and NMDAR-dependent, Frenkel et al. (2006) argued that stimulus-specific response potentiation shared many of the same mechanisms as canonical LTP synaptic plasticity, and provided a novel way to assess this form of plasticity in the visual cortex of awake rodents using repetitive high-frequency visual stimulation. However, because this protocol does not include the same level of control over stimulated pathways as traditional invasive electrical stimulation, they referred to the effects seen as “LTP-like”.

Translating repetitive visual stimulation to induce LTP-like (because it mimics canonical LTP) potentiation from animal models to human models was the next step. Teyler et

al. (2005) provided the first demonstration that repetitive presentation of a visual checkerboard stimulus (a visual tetanus) leads to persistent enhancement of one of the earliest components of the VEP signal in normal humans, the N1b. To infer that LTP-like effects was in fact what produced the amplitude increase in the VEP signal following HFS (i.e., 9Hz), they carried out the same stimulation protocol, but omitted the modulation/high-frequency stimulation. When no visual tetanus was delivered, the VEP response did not change significantly. Interestingly, there was also a significant decline in the VEP response over time when a lower stimulation rate was used, suggesting that receiving lower frequency rates of visual stimulation in itself depotentiated the response consistent with results from animal studies (Clapp et al., 2012). Importantly, the potentiated response lasted for upwards of one hour, suggesting that what they observed converged with a known property of LTP being long-lasting (Teyler et al., 2005). According to Teyler et al. (2006, p. 2048) LTP was "…the most parsimonious explanation" for the VEP amplitude increase observed in their study.

Because LTP is defined by several properties, manipulating characteristics of the induction stimulus should substantiate the inference that it really was LTP they observed in the VEP amplitude change following induction with high-frequency visual stimulation. In addition to longevity (Teyler et al., 2005), another such property is *input-specificity* (Clapp et al., 2012). Input-specificity has been demonstrated in two studies by varying stimulus properties (McNair et al., 2006; Ross et al., 2008). The researchers reasoned that VEP potentiation should be specific to one stimulus and not another when repetitively presented across several blocks like in Teyler et al. (2005) study. McNair and colleagues (2006) tetanized one group of participants with a one cycle-per-degree sine grating, while a second group was tetanized using a five cycles-per-degree sine grating. They found an increase in amplitude following high-frequency stimulation in an early component specific to stimulus properties. The N1b was specifically potentiated to the sine gratings of the same spatial-frequency as the tetanus, no effects were observed in the N1b for sine gratings of a different spatial frequency. As only visual neurons which received stimulation showed the response, the authors suggested that the potentiation effect induced by the sensory tetanus was isolated to a discrete neural population in the human visual cortex (McNair et al., 2006). Ross and colleagues (2008) extended McNair's result by showing that in addition to spatial-frequency, VEP potentiation was also specific to orientation of the stimulus. Collectively, these results support the notion that visually induced LTP-like changes in human visual cortex do entail cardinal features of LTP demonstrated in animal studies (Bliss & Cooke, 2011).

LTP is also defined by being *associative* which means that synapses that are weakly

stimulated but paired with synapses that receive strong LTP-inducing stimulation of other synapses on the same cell, also undergo potentiation (Bliss & Cooke, 2011). Although this feature of LTP has not been demonstrated in the human visual cortex using similar protocols as Teyler et al. (2005), it has been found in the human motor cortex using paired associative stimulation (PAS) (Stefan, Kunesch, Benecke, Cohen, & Classen, 2002). This method involves pairing somatosensory and transcranial magnetic stimulation inputs in a temporally specific manner (Stefan et al., 2002). It is unclear whether sensory plasticity differ between sensory cortices and using high-frequency trains of transcranial stimulation to induce LTP-like plasticity may involve different mechanisms compared to using repetitive checkerboard visual stimulation. However, a study assessing both PAS-Transcranial- magnetic-stimulation in the motor cortex and VEPs induced by checkerboard reversals in the visual cortex, showed that both LTP-like plasticity measures correlate among those participants who displayed potentiation effects (Klöppel et al., 2015). These results suggest that both induction protocols may share a common neuronal substrate across sensory cortices.

Lastly, LTP-like plasticity induced by rapid visual presentation in healthy humans has been found to be augmented by an NMDAR agonist called D-cycloserine (DCS) (Forsyth, Bachman, Mathalon, Roach, & Asarnow, 2015). Participants in the treatment group showed enhanced potentiation of early components in their VEPs compared to participants in the placebo group, suggesting that NMDA-dependent synaptic plasticity underlie potentiation of VEPs following high-frequency visual stimulation. Besides chemically augmenting potentiation, a multi-modal neuroimaging study using a similar high-frequency checkerboard stimulation protocol found experience-dependent visual plasticity in humans to be correlated with higher levels of glutamine (i.e., a potential index of glutamate) using proton magnetic resonance spectroscopy (Wijtenburg et al., 2017).

Numerous studies have now demonstrated LTP-like effects in the sensory cortex of humans using EEG as measurement tool. These LTP-like effects have been induced in different sensory cortices using repetitive visual (Teyler et al., 2005) and auditory stimulus (Clapp, Kirk, Hamm, Shepherd, & Teyler, 2005), as well as in motor cortex using transcranial stimulation (Stefan et al., 2002). Consequently, studies using visual or auditory stimulus rely on the assumption that the high-frequency sensory stimulus will reflect high-frequency electrical stimulation used in animal models, and importantly that this sensory stimulation will initiate LTP-like effects comprising the characteristics as those found in animal models. Indeed, by showing that LTP-like effects in humans using non-invasive stimulation protocols inhibit defining characteristics of LTP such as longevity (Teyler et al., 2005), input-specificity

(McNair et al., 2006; Ross et al., 2008), pathway specificity (Clapp, Zaehle, et al., 2005), and augmented by a NMDAR agonist (Forsyth et al., 2015), the abovementioned series of experiment have demonstrated the potential use of rapidly presented sensory stimulation to study neuroplasticity non-invasively in humans.

1.5 The Visual Evoked Potential

A transient VEP is produced when a participant is exposed to a pattern-reversing checkerboard stimulus. The signal commonly comprise an initial negative peak with latency of around 75 ms known as C1, followed by a positive peak around 100 ms called the P1, and a second negative peak at around 145ms called the N1 (Di Russo et al., 2005). Source localization procedures have suggested that the C1 component primarily arise in the primary visual cortex (V1) with a neural generator near the calcarine fissure (Di Russo et al., 2005). Further implicating that early visual areas are the neural source of the C1 component are findings demonstrating that the component is not modulated by attention (Baumgartner, Graulty, Hillyard, & Pitts, 2017). C1 is stimulus position-dependent and will change in polarity if stimuli are presented to the upper or lower visual field, further attesting to a neural source located near the calcarine fissure (Di Russo et al., 2005). In other words, an electrode placed directly above the calcarine fissure will record either positive or negative activity dependent on whether the lower or upper bank of the primary visual cortex is stimulated respectively. Thus, the C1 component is considered dipolar in nature and is therefore named C1, rather than commonly P for positive or N for negative scalp potentials.

Source localization results into the neural generators of P1 have produce more variable results. Some studies have localized a P1 generator in V1 (Tabuchi et al., 2002; Whittingstall, Stroink, & Schmidt, 2007), while others provide evidence for a generator in extra-striate cortices, more specifically V5 (Di Russo et al., 2005). Neural generators of N1 have been localized to ventral occipital areas, but like the P1, have shown to be difficult to localize. In fact, Di Russo et al. (2005) suggested modeling the source of N1 required at least four dipoles. In contrast to C1, both P1 and N1 have been shown to be modulated by visuo-spatial attention (Di Russo, Martínez, & Hillyard, 2003).

Locating the underlying components in the VEP signal becomes important when considering that one feature of LTP-like plasticity is that only the stimulated neurons should be potentiated. Results from functional imaging studies utilizing repetitive checkerboard stimulation in a pre-post design have shown both increased and decreased blood-oxygen-level-dependent responses following high-frequency visual stimulation in healthy controls (Clapp,

Zaehle, et al., 2005; Lahr et al., 2014). High inter-subject variability in the anatomy of the visual cortices might be one reason why localizing VEP potentiation has proven difficult. Taken together, these preliminary results suggest that C1 has mainly neuronal generators in primary visual cortex, while the neural generators of P1 and N1 may involve extra-striate cortical areas.

1.6 Clinical Studies Using Repetitive Sensory Stimulation to Study LTP-Like Effects

Recently, electrophysiological paradigms comprising repetitive visual stimulation induction protocols have been used to assess LTP-like neuroplasticity in patients with bipolar disorder (Elvsåshagen et al., 2012), major depression (Normann, Schmitz, Fürmaier, Döing, & Bach, 2007), and schizophrenia (Çavuş et al., 2012; Forsyth et al., 2017; Jahshan, Wynn, Mathalon, & Green, 2017). These studies have in common that they used paradigms involving visual checkerboard stimuli presented repetitively for a prolonged time-period as induction of LTP-like plasticity in a pre-post design to probe cortical synaptic plasticity in the visual cortex. For example, Normann et al. (2007) presented pattern-reversal checkerboard stimulus to patients with major depression disorder and compared their responses to that of healthy controls. First, they demonstrated that VEP amplitudes changed following a period of prolonged repetitive visual stimulation relative to baseline visual stimulation, and second, that the degree of change was different between groups in that patients had an altered VEP response compared to healthy controls. Early components of the VEP signal were potentiated following modulation (e.g. prolonged repetitive stimulation) in healthy controls, whereas both the extent and polarity of change in the VEP response was significantly different in patients with major depression. Specifically, the C1 (i.e., earliest component of the VEP) was reduced in healthy controls whereas it was increased in negativity in patients. Likewise, the N1 was increased in healthy controls, while it was decreased in patients. The component potentiation was evident for upwards of 20 minutes after the modulation phase. However, although they initially included a large sample size into the study, only ten patients were included in the parametric model pertaining to effect of modulation. This might offer a possible explanation as to why the polarity of C1 peaks changed compared to healthy controls. Because the C1 is thought to be generated near the calcarine fissure, and because the surface of the visual cortex varies greatly between individuals, VEP morphology could be affected by larger variation due to smaller sample size in the patient group relative to the control group. Because this sample size was small and because Normann et al., (2007) specified only sphericity corrections during statistical modeling, these results should be taken as preliminary indicative of LTP-like differences between patients with major depression and healthy controls.

Using the same paradigm as in Normann et al. (2007) study, Elvsåshagen et al. (2012) demonstrated altered neuroplasticity in a large sample comprising individuals with bipolar disorder relative to healthy controls. Individuals with bipolar disorder did not display an effect of modulation in any components of their VEP response, while P1, N1 and P1-N1 peak-to-peak was significantly potentiated in healthy controls. Group comparisons revealed that only the P1-N1 peak-to-peak was significantly different between groups and might possibly represent the most robust dependent variable when investigating effect of modulation both within- and between-groups using this paradigm. These findings thus collaborated results from Normann et al. (2007) study by showing that a period of prolonged repetitive pattern-reversing checkerboard stimulation do produce an enhancement in VEP components, and further add to the hypothesis that neuroplasticity is altered in individuals with bipolar disorder (Elvsåshagen et al., 2012). Importantly, the degree of potentiation of P1-N1 in the controls was significant upwards of an hour post modulation indicative of LTP-like plasticity by being long-lasting.

There are only three reports using repetitive high-frequency visual stimulation paradigms to measure LTP-like plasticity in individuals with schizophrenia. Çavuş et al. (2012) rapidly presented a circular checkerboard stimulus to both patients with schizophrenia and healthy controls and extracted factor loading by means of temporal principal component decomposition. They readily identified two components that described the most variance to be the C1 and N1 of the VEP response. The effect of modulation was evident by an increased negativity in both components in healthy controls. This effect differed between groups in that individuals with schizophrenia had a non-significant change in the C1 component, whereas both groups displayed a change in N1b, however, this change was smaller for schizophrenic patients. Further differentiating the groups were the finding that potentiation lasted for upwards of 20 minutes in healthy controls, but only up to 6 minutes in patients. In addition to component change following visual high-frequency stimulation, these researchers correlated visual steady-state-response in both groups with degree of potentiation and found that although similar and entrained to the modulation frequency in both groups, the response was only associated with potentiation in healthy controls, not in patients. Because the visual steady-state response is related to levels of attention (Brenner et al., 2009), similar peak power entrained to the frequency and phase of the visual stimulus suggests that both patients and controls did not differ in allocation of attentional resources. Furthermore, because it only correlated with N1b and not C1, these results suggest that each component arise from different neural networks and could be modulated by different mechanisms. The authors argue this is evidence of impaired neuroplasticity in schizophrenic patients, a finding converging with the hypothesis of NMDAR

hypofunction in schizophrenia. A drawback from this study is that they did not control for medication status and only assessed VEP change up until 20 minutes following high-frequency modulation.

The second report using high-frequency visual stimulation to probe neuroplasticity in schizophrenic patients sought primarily to associate levels of LTP-like plasticity with cognitive ability measure, clinical symptoms and community functioning, and consequently did not include a healthy control group (Jahshan et al., 2017). However, the results are interesting because they demonstrated that the VEP response was significantly potentiated in this patient group following inducing visual stimulation. It basically extended the findings from (Çavuş et al., 2012) paradigm, but differed in methodology by using mass-univariate permutation testing instead of decomposition procedures. An increased negativity relative to baseline corresponding to possibly the N1 component was found to last upwards of 6 minutes following high-frequency visual stimulation, whereas an increased positivity possibly corresponding to P2 was found to last upwards of 22 minutes, both effects were apparent at parieto-occipital and occipital electrodes. This late potentiation effect contrasted with Çavuş et al. (2012) findings who only showed potentiation effects in the schizophrenic sample lasting roughly 6 minutes. These results suggest that schizophrenic patients exhibit LTP-like plasticity effects resembling those seen in previous studies using healthy controls. Late VEP potentiation also correlated with better neurocognitive performance. The authors speculate that this lasting potentiation effect may reflect compensatory processes working to overcome plasticity deficits in earlier visual processing stages, which therefore should correlate with better neurocognitive function in patients (Jahshan et al., 2017). Intriguingly, both studies have demonstrated that LTP-like plasticity are present following high-frequency visual stimulation in schizophrenic patients. However, without a control group in Jahshan et al. (2017) study, any group-difference between individuals with schizophrenia and healthy controls could not be tested.

The last study using a similar paradigm as the two abovementioned, was conducted by Forsyth et al. (2017). This was a follow-up study to Forsyth et al. (2015) article and sought to explore whether enhancing NMDAR signaling would produce differences in VEP potentiation in a schizophrenic sample. One group of schizophrenic participants received DCS whereas another group of schizophrenic participants did not. Results showed no group effect of enhancing NMDAR signaling, however, when they compared this patient dataset to the dataset from the previous study comprising healthy controls who received placebo, one of the early components of the VEP was significantly different in the schizophrenic placebo group compared to the healthy control placebo group. Specifically, the C1 component potentiation

was impaired in patients who did not receive DCS, whereas the C1 amplitude were similar between patients who received DCS and healthy controls (Forsyth et al., 2017). These findings add to the possibility that experience-dependent synaptic plasticity indexed by VEPs was altered due to differing levels of NMDAR signaling in individuals with schizophrenia relative to healthy controls. What is interesting from viewing their results, is the fact that the DCS treated schizophrenic sample had overall higher VEP amplitudes, from baseline assessment to post-modulation assessment, compared to non-treated schizophrenic. In fact, these VEP amplitudes are comparable to healthy controls, however, the degree of change from baseline to post-modulation is similar between patient samples. This suggests that NMDAR mediated transmission may be involved in the generation of C1 and furthermore, that increasing NMDAR signaling might increase the early VEP response in schizophrenia. Again, like in Çavuş et al. (2012) study, LTP-like potentiation was only apparent up until 6 minute.

The variable findings from the few reports using repetitive checkerboard stimulation to induce LTP-like effects in the visual cortex in individuals with schizophrenia might reflect differences in methodology, stimulus-induction parameters, or confounding heterogeneity among patients. None of these studies assessed LTP-like effects for more than 22 minutes, and only one study compared LTP-like effects between individuals with schizophrenia to that of healthy controls. Since a cardinal feature of LTP entail longevity, and further that LTP-like effects have been shown to last for upwards of one hour in the visual cortex (Teyler et al., 2005), it is important to assess LTP-like effects over a longer interval to ensure these effects converge with cardinal LTP of being long-lasting. Because previous reports vary greatly in how they quantify and test VEP potentiation, it is also a need for a less sample-specific methodological procedure that allow for easier generalization and implementation across studies.

1.7 Aim of the current study

The main objective of this thesis is to investigate whether schizophrenic patients will differ in visual LTP-like plasticity compared to healthy controls. Currently, one study have assessed visual plasticity in schizophrenic patients relative to healthy controls (Çavuş et al., 2012), however, these researchers used statistical decomposition procedures to quantify an effect of modulation and only assessed longevity of these effects for up to 22 minutes. By applying traditional ERP averaging-procedures the results from the current study are easier generalizable and reproducible to future patient samples for other researchers interested in exploring similar paradigm protocols in schizophrenia. In collecting VEP data for upwards of one hour, these results will further add to current conceptualization of visual LTP-like neuroplasticity

possessing characteristics indicative of canonical LTP. Unfortunately, due to issues pertaining to a hold up in diagnostic inclusion and important patient characteristics, possible interacting effects of medication status as well disease progression could not be assessed.

A second objective of this paper is to further substantiate current attempts to establish the possible use of rapid reversing binocular checkerboard stimulation to induced visual LTP-like plasticity *in vivo* in a large sample of healthy controls. Because these paradigms remain exploratory this far, determining direction of change in early VEP components represents a valuable methodological property for future studies using similar protocols.

Finally, this study will add to current investigations using similar paradigms exploring which if any of the early VEP components most consistently produce largest effect sizes in terms of LTP-like differences reflected in amplitude change from pre to post conditions.

Hypotheses Explicitly Stated

H1: There will be an effect of modulation in healthy controls evident by a change in early VEP component amplitudes from pre-modulation assessment to post-modulation assessment. In line with previous studies using similar protocols (Elvsåshagen et al., 2012; Normann et al., 2007) the C1 component should decrease in amplitude whereas the P1 and N1 should both increase in amplitude.

H2: Effect of modulation will differ between healthy controls and schizophrenic patients in terms of longevity and amplitude change in VEP components. Neither which components nor direction is hypothesized given the variation in previous reports into visual LTP-like neuroplasticity (Çavuş et al., 2012; Forsyth et al., 2017; Jahshan et al., 2017).

H3: In line with Elvsåshagen et al. (2012) the P1-N1 complex would should the most consistent change following modulation compared to the other components in healthy controls in terms of effect sizes.

2 Methods and Materials

2.1 Participants

All participants were recruited as part of an ongoing study of psychotic disorders (Thematically Organized Psychosis Research) at the Norwegian Centre for Mental Disorders Research (NORMENT) at Oslo University Hospital. All participants gave informed consent to participation, and the study has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. Inpatients and outpatients were referred from clinicians in psychiatric units from four major hospitals in the greater Oslo area. Patients were included regardless of level of involvement in their respective treatment programs. The controls were randomly selected from statistical records from the same catchment area as the patient groups. Exclusion criteria for all participants were a history of moderate or severe head injury, neurological disorder, IQ < 65, and age outside the range 18–65 years. The healthy control sample was screened with the Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer, Williams, Kroenke, & et al., 1994). Control participants were excluded if they had used cannabis within the last 3 months or had a dependency on the drug, if they or any of their first-degree relatives had a lifetime history of severe psychiatric disorder, or if they had a history of medical problems thought to interfere with brain function.

The schizophrenia sample comprised 25 participants and the healthy control sample comprised 160 participants. Because of technical issues during recording of EEG in which more than 75% of their data were missing, three schizophrenia participants and three healthy control participants were excluded from further analysis. The total sample thus comprised 22 schizophrenia participants and 157 healthy control participants. Mean age of the healthy control participants was 35.5 (SD = 9.84) and in participants with schizophrenia 31.5 (SD = 10.34). A total of 80 men and 77 females comprised the healthy control sample. A total of 11 men and 11 females comprised the schizophrenic patient sample. See table 1 for detailed information about demographics and clinical variables.

Table 1.

Demographics and Clinical Characteristics

	Schizophrenia Patients (n = 22) Mean (SD)	Healthy Controls (n = 157) Mean (SD)	p Values
Age (Years)	31.5 (10.01)	36.1 (10.01)	.048
Sex			
Male	11	80	.993
Female	11	77	
Education (Years)	13.73 (2.48)	13.73 (2.48)	.046
Illness Duration (Years)	8.94 (10.32) *		
PANSS Score[1]			
Total	57.76 (12.52)		
Negative	13.90 (4.90)		
Positive	13.29 (4.35)		
MADRS[2]	15.43 (8.23) *		
YMRS[3]	2.00 (2.53) *		
IQ	106.42 (10.47)		

[1] Positive and Negative Syndrome Scale
[2] Montgomery-Åsberg Depression Rating Scale
[3] Young Mania Rating Scale
*Note: * estimate from a total of 8 participants*

2.2 Experimental Paradigm

Participants completed the same experimental procedure in one session. Before each EEG acquisition, clinical variables and demographical data was collected and visual acuity were assessed. The complete EEG paradigm was adopted from Elvsåshagen et al. (2012) study and modified for this experiment. As outlined in figure 1, the complete EEG paradigm comprised four parts; one visual evoked potential part; one mismatch negativity part; one pre-pulse inhibition (PPI) part; and a resting state part which collectively lasted roughly ~80min in total. Only the visual evoked potential part is analyzed in this study.

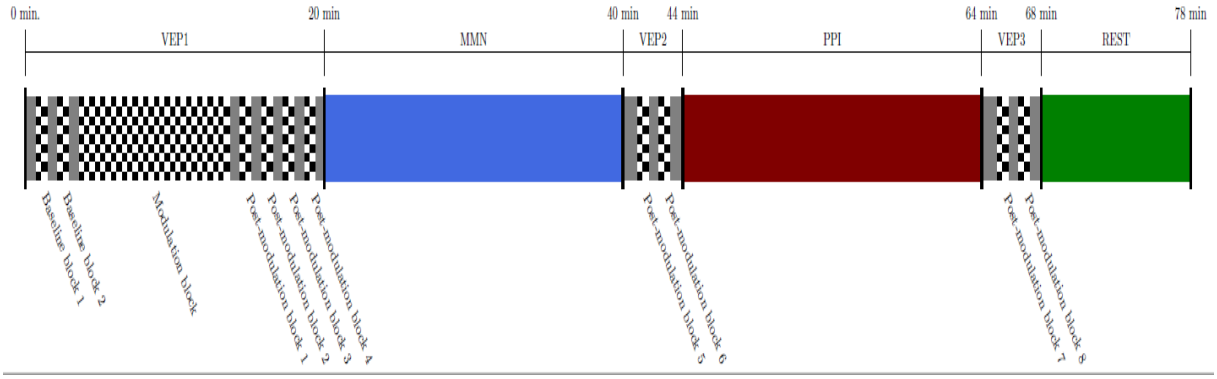

Figure 1. VEP assessment blocks comprised a visual pattern-reversing checkerboard stimulus. Visual checkerboard stimuli were presented at varied inter-stimulus interval (i.e., 2 reversals per second (rps) – 0.6 rps) in every baseline and post-modulation VEP assessment block, whereas the VEP modulation block lasted 10 min and comprised a constant inter-stimulus interval of 2rps (2Hz). Time points for presentation of the post-modulation blocks following the modulation block were; 2min, 3 min 40 sec, 6 min 20 sec, 8 min, 30 min 50 sec, 33 min 30 sec, 53 min 30 sec, 55 min 30 sec.

2.3 Visual Evoked Potential Paradigm

2.3.1 ***Stimulus characteristics and visual acuity.*** Full screen (i.e., full visual field) visual stimulation through black and white pattern-reversing checkerboard stimuli with a check size of 0.5˚were used to evoke VEPs. Participants were seated centered to and at 60 cm distance from the screen. Visual acuity was assessed using Snellen's chart at a distance of ~4meters. Participants used their regular glasses or lenses if they usually had any. Contrast was kept constant at 100%.

2.3.2 ***VEP stimulus presentation.*** A total of eleven blocks comprised the VEP assessment protocol; two baseline blocks, one modulation block, and eight post-modulation blocks. Each baseline block and post-modulation block lasted ~2 minutes, while the modulation block lasted 10 minutes. Only the modulation block had a fixed inter-stimulus interval (ISI) of 500ms (2Hz, 2 reversals per second), the other blocks had a jittered ISI ranging from 500ms – 1500ms (0.66Hz - 2 Hz). The varied ISI in the VEP assessment blocks except modulation was used to minimize overlap in the resulting averaged data (Woodman, 2010). The constant reversal rate in the modulation block was chosen to ensure maximum potentiation of the VEP components in the subsequent post-modulation blocks. Time points for presentation of the post-

modulation blocks following the modulation block were; 2min, 3 min 40 sec, 6 min 20 sec, 8 min, 30 min 50 sec, 33 min 30 sec, 53 min 30 sec, 55 min 30 sec.

2.3.3 ***VEP procedure.*** Participants were first presented the two baseline blocks and these two blocks constituted the pre-modulation condition. Following the pre-modulation condition, participants viewed the LTP-inducing modulation phase in which the same checkerboard stimuli were presented at a higher reversal rate for a longer time interval thereby constituting the "visual tetanus". After the modulation phase, the same baseline stimulation parameters were shown to the participants in eight blocks, and each of these blocks reflect one post-modulation block respectively. Immediately following each stimulation block, was a short break with no visual stimulus (a grey screen) displayed allowing for retinal afterimages to dissipate. In total, roughly 1200 trials were collected from the modulation block, and roughly 40 trials were collected from each of the other blocks.

2.4 Behavioral measure of Attention

Reaction times and error rates were collected throughout each VEP assessment block to ensure that all participants maintained similar levels of attention during the experiment. All were instructed to focus on a filled red circle (0.1˚) located in the center of the screen and respond with a button press when the dot changed color.

2.5 Clinical assessments

Current psychotic symptoms were rated using the Positive And Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opfer, 1987), depressive symptoms with the Inventory of Depressive Symptomatology (IDS-C) —Clinician Rated (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996), and current manic symptoms with the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978). Psychosocial functioning in patients was assessed with the Global Assessment of Functioning (GAF) scale, split version (Pedersen, Hagtvet, & Karterud, 2007). The patients were assessed for current alcohol and drug use by the use of Alcohol Use Disorder Identification Test (AUDIT) (Saunders, Aasland, Babor, De la Fuente, & Grant, 1993) and Drug Use Disorder Identification Test (DUDIT) (Berman, Bergman, Palmstierna, & Schlyter, 2005).

2.6 Equipment

An AOC G2460PQU 24-inch LCD monitor with screen dimensions 53.3cm x 30,4cm (1920 x 1080 pixels; 144Hz refresh rate) were used to display stimuli. The whole experiment was programmed in Psychtoolbox-3 (site) running on Matlab R2015a (Mathworks Inc., Natick, MA) and button-press responses were collected using DS3 Tool version 0.6.0.3 (MotionJoy), an application that connects a Playstation 3 controller to Windows software.

2.7 EEG Acquisition

Continuous EEG data were recorded from 72 Ag/AGCI electrodes, comprising 64 active scalp channels positioned according to the international 10/20 system (see supplementary materials for example layout of scalp electrodes), using a Biosemi Active-Two amplifier system (BioSemi, Amsterdam, The Netherlands). Vertical and horizontal electrooculography activity (VEOG and HEOG) was recorded using 6 electrodes placed at sub- and supraorbital regions as well as at the lateral chanti of each eye. In addition, two electromyography (EMG) electrodes were placed adjacent to each other below the pupil of the right eye for recording m. orbicularis oculi activity (for the PPI). Electrocardiography (ECG) electrodes were placed on the left pelvic bone and the right clavicle. All channel recordings were referenced to a common mode sense using an active electrode (common mode sense) and a passive electrode (driven right leg) that forms a constant feedback loop, reducing the potential of the participant and increase the common mode rejection (Biosemi, 2013). EEG data were sampled at 2048Hz and online bandpass-filtered between 0.05 – 417Hz. Impedance were kept below 5kOhm for all electrodes. All electrode offsets were below +/- 30 µV.

Offline pre-processing was conducted in Matlab 2016a (Mathworks Inc., Natick, MA) using EEGLAB (Delorme & Makeig, 2004), and a semi-automated preprocessing plugin called pre-processing pipeline (Bigdely-Shamlo, Mullen, Kothe, Su, & Robbins, 2015). Continuous data were down-sampled to 516Hz, high-pass filtered at 0.01Hz and low-pass filtered at 40Hz. Bad channels were identified and interpolated before ICA using the spherical option of the EEGLAB function. On average, 7 electrodes were interpolated in the HC sample and 5 channels were interpolated in the patient sample. All channels were re-referenced to the averaged reference. This choice of reference is argued to retain the biophysical characteristics of ERP components (i.e., being bipolar in nature) and more suitable for later univariate parametric testing of components of different orientations (Dien, 2017). To compute ERPs, data were segmented into epochs starting -200ms and ending 500ms after stimulus onset defined by a

checkerboard reversal. To detect and remove artifacts, independent-component decomposition was run on all electrodes first before principle component decomposition reduced these components to 35 from 64. Stereotypical eye blink components were removed from the data. On average one component stereotypical of ocular activity were removed across participants. After identification and removal of eye blink components, all epochs containing VEOG or HEOG activity or EEG artifacts exceeding amplitudes of +/- 100 microvolts were rejected. Participants in both groups had on average ~35 trials in each VEP assessment block after artifact rejection, none included in the finale analysis had less than 25 trials in each block. Finally, the ECG, EMG, VEOG, and HEOG channels were removed, and the data were baseline corrected using -200 ms baseline period.

2.8 Data Analysis

2.8.1 ***Quantification of VEPs.*** VEP amplitudes were quantified using local peak maxima/minima implemented corresponding to Luck (2014) suggestions defined as the local peak value relative to surrounding lower voltages. The posterior midline Oz electrode was selected as the electrode of interest since previous studies have shown the effects of high-frequency visual stimulation to be captured at that location (Çavuş et al., 2012), and because temporal effects were of primary interest. VEP peak latencies were also calculated as the temporal point at which each peak was identified. Visual inspection of individual participants ERPs did confirm that the function indeed selected the local peaks in the time windows selected. Of interest were the three commonly studied early pattern-reversing checkerboard VEP components, C1, P1 and N1, with time windows for each defined based on prior research (Elvsåshagen et al., 2012). Time widow for C1 ranged from 50ms – 110ms, for P1 ranged from 90 – 135 ms, and for N1 the time window ranged from 110 – 200ms. These three components were extracted from each of the baseline and post-modulation blocks separately, along with each individual peak value's latency. P1-to-N1 peak-to-peak was calculated by subtracting P1 peak values from N1 peak values. Peak latencies were calculated to ensure the peak amplitudes did correspond to previously defined time-windows (Elvsåshagen et al., 2012). Butterfly plots in the appendix show individual VEP signal variation as well inter-block variation in grand average VEP signals for each group separately.

2.8.2 ***Model specification.*** A two-way mixed ANOVA model was specified for each dependent variable (i.e., component) to test whether there was a significant two-way Group by Time interaction. The two baseline blocks were averaged to form one pre-condition, while the

remaining post-modulation blocks each constituted a level in the within-factor Time. One-way repeated measures ANOVAs were run for each component within each group separately to follow up any significant main effects of time. A priori planned simple contrasts were specified for the one-way ANOVA models to test which post-block was significantly different from baseline, thus limiting the number of comparisons being tested (i.e., not testing difference between post-blocks). Each simple linear contrast was specified such that the post-block mean would be subtracted from the baseline mean. Bonferroni correction for multiple comparisons was calculated for each of the one-way ANOVAs yielding adjusted p values for each simple linear contrast and simultaneous confidence intervals. Alpha level for mixed model analyses was set to 0.05 while corrected/adjusted for the number of contrasts in one-way repeated ANOVAs (i.e., alpha/number of levels – 1).

Levene's test of equality of error variances was used to assess homogeneity of variance. Box's test of equality was used to assess homogeneity of covariances, Mauchly's test of sphericity was used to assess the assumption of sphericity, and dependent on Epsilon, either Greenhouse-Geisser or Huyhn-Feldt correction was used. As there is no current convention as to how to deal with mean/peak value outliers in ERP analysis, they were kept such that all statistical models were based on raw data (i.e., not transformed data). As ANOVA has been shown to be robust to violations of a Gaussian distribution (Glass, Peckham, & Sanders, 1972; Harwell, Rubinstein, Hayes, & Olds, 1992; Lix, Keselman, & Keselman, 1996), and because ERP data, even when treated univariate by *a priori* choices (i.e., peak amplitudes in specified temporal windows), often fail to meet this assumption (Groppe, Urbach, & Kutas, 2011; Maris, 2012), this assumption was assessed by confirming their underlying distributions had less than moderate as well as unidirectional skewness. This step was suggested by two separate statisticians.

Age and education duration was covaried into each two-way mixed Anova model to explore whether there was a significant interaction with time. Independent sample t-tests were run to test whether there was significant difference in mean age or education duration between groups. A chi-square test was run to see if there were statistical independence between groups in gender. All statistical analysis was carried out on IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

2.9 Reaction time measure

The data from the reaction time measures included both response latencies (in milliseconds) and error rates. Following Greenwald, McGhee, and Schwartz (1998) suggestions, responses

faster than 300ms was recoded into exactly 300ms. Responses slower than 1200ms were excluded from this analysis. To stabilize latency variances which are commonly right-skewed, all response times were log-transformed. After recoding and transforming, separate distributions from all assessment time points revealed normal tendency. Averaged data across time points were then submitted to an Independent-sample t-tests to compare the two groups mean reaction times.

3 Results

3.1 Demographic results

Independent sample t-tests were run to see if there were a significant difference in mean age or education duration between groups. There was a significant difference in mean age between healthy controls (M = 36.06, SD = 10.01) and individuals with schizophrenia (M = 31.50, SD = 10.35), $t(177) = 1.99$, $p = .048$, mean difference 95% CI [0.45, 9.07]. There was also a significant difference in mean education duration between healthy controls (M = 14.83, SD = 2.07) and individuals with schizophrenia (M = 13.73, SD = 2.48), $t(146) = 2.01$, $p = .046$, mean difference 95% CI [0.02, 2.17]. A chi-square test indicated that there was no statistical difference between groups in gender distribution, ($\chi^2(1, N = 179) = 0.01$, $p = .993$).

3.2 Behavioral results

An independent-sample t-test showed that reaction times in healthy controls (M = 0.459, SD = 0.06) did not significantly differ from reaction times in individuals with schizophrenia (M = 0.436, SD = 0.03) throughout the VEP assessment blocks, $t(164) = 1.488$, $p = 0.139$ (95% CI, -0.007 to 0.053). This finding indicates that both groups allocated similar levels of attention throughout the experimental paradigm.

3.3 Differences at Baseline between Groups

As can be seen in figure 2. below, the paradigm successfully evoked VEP responses in both groups. Mean peak amplitudes for each component and each VEP assessment block can be seen in table 2. In terms of differences at baseline, independent-sample t-tests were used to investigate whether groups had a different baseline mean. No difference were found for C1 $t(177) = 0.19$, $p = .843$, nor for P1 $t(176) = 0.21$, $p = .829$, N1 $t(177) = 0.44$, $p = .654$, or the P1-N1 peak to peak $t(176) = 0.337$, $p = .736$. This constitute a necessary preliminary step in

pre-post designs as differences at baseline can influence inferences made when later comparing group effects (Dimitrov & Rumrill Jr, 2003).

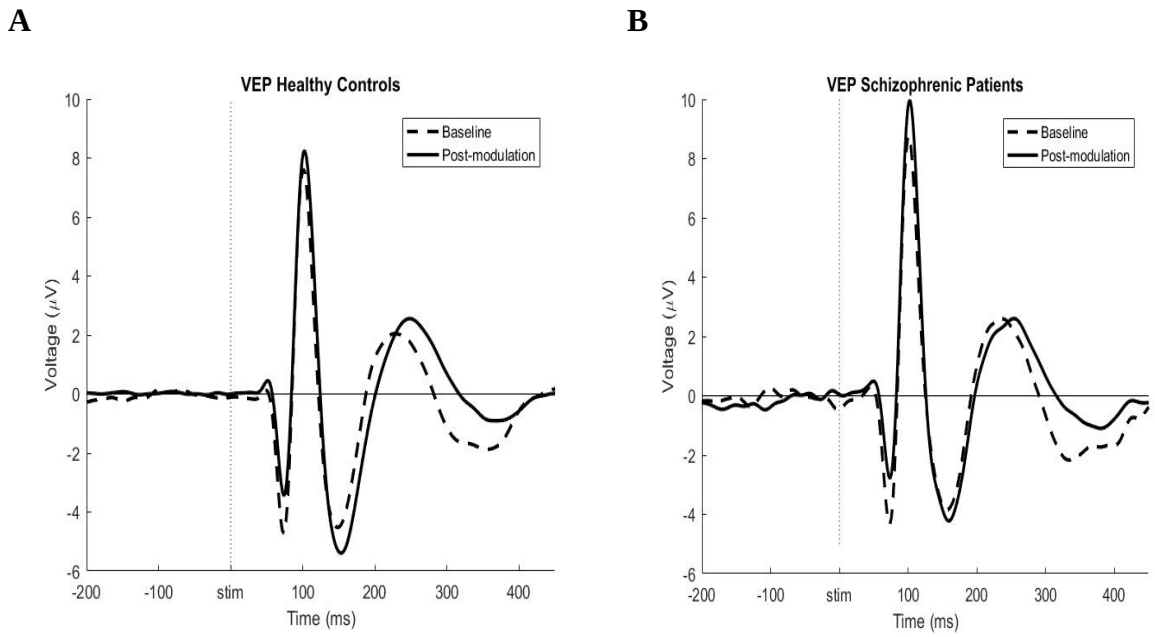

Figure 2. A) Grand Average visual evoked potentials for healthy controls where the baseline blocks have been averaged and all the post-modulation blocks have been averaged, *B)* show the same Grand averaging procedure of baseline and post-blocks in Schizophrenic patients.

Table 2.

Visual evoked Peak amplitudes across assessment blocks

		Baseline	Post1	Post2	Post3	Post4	Post5	Post6	Post7	Post8	
Group	Component	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	N
Schizophrenic	C1	-5.85 (4.55)	-3.54 (3.17)	-3.19 (2.77)	-3.67 (3.43)	-4.43 (3.52)	-5.88 (4.19)	-4.19 (3.74)	-4.56 (3.97)	-4.19 (4.10)	20
Patients	P1	9.76 (7.15)	12.11 (7.17)	12.99 (8.07)	11.52 (5.51)	12.51 (6.55)	7.96 (5.89)	10.77 (6.75)	9.21 (5.43)	10.77 (7.39)	21
	N1	-5.61 (5.97)	-5.43 (5.85)	-6.49 (7.05)	-6.30 (5.86)	-6.50 (6.16)	-7.17 (6.28)	-6.35 (6.30)	-5.39 (5.24)	-6.53 (5.47)	22
	P1-N1	15.43 (9.33)	17.43 (8.88)	19.51 (11.90)	17.95 (9.26)	19.05 (11.03)	15.28 (8.91)	17.15 (9.80)	14.53 (8.03)	17.28 (10.09)	21
Healthy	C1	-5.97 (5.37)	-3.88 (4.31)	-3.47 (3.80)	-3.98 (3.95)	-3.71 (3.64)	-5.50 (4.84)	-5.17 (4.72)	-6.09 (5.30)	-5.26 (4.73)	140
Controls	P1	8.73 (6.01)	10.71 (6.34)	11.21 (6.33)	10.53 (6.88)	11.21 (6.76)	8.23 (6.65)	9.02 (6.35)	7.48 (6.63)	9.17 (6.35)	136
	N1	-6.18 (4.56)	-6.90 (4.66)	-6.75 (4.78)	-6.93 (4.99)	-7.08 (4.42)	-6.23 (4.93)	-7.30 (5.11)	-6.78 (5.15)	-7.05 (5.13)	153
	P1-N1	15.08 (8.15)	17.86 (8.33)	18.22 (8.90)	17.60 (9.10)	18.44 (9.05)	14.64 (8.57)	16.58 (8.51)	14.33 (8.37)	16.50 (9.14)	135

Note. VEP mean peak amplitudes and standard deviations for each VEP component in both groups across time.

3.4 C1 component

A two-way mixed repeated measure ANOVA with group and time as fixed factors sought determine if there were a statistically significant group by time interaction, or main effect of time in patients and controls. There was homogeneity of variances, as assessed by Levene's test of homogeneity of variance ($p > .05$). Similar underlying distribution was assured for each fixed factor by visual inspection of box plots and variance. There was homogeneity of covariances, as assessed by Box's test of equality of covariance matrices ($p = .259$). Mauchly's test of sphericity indicated that the assumption of sphericity was not met for the two-way interaction, $\chi^2(35) = 118.59$, $p < .001$. Epsilon was larger than 0.75, so Greenhouse-Geisser was used to correct degrees of freedom (Maxwell & Delaney, 2004). There were no significant interaction between group and time on C1 potentiation, $F(10.64, 1045) = 1.42$, $p = .197$. partial $\eta 2 = .009$. However, there was a significant main effect of time, $F(6.62, 1045) = 9.49$, $p < .001$, partial $\eta 2 = .057$ indicating that C1 mean amplitudes changed significantly at different time points. No significant main effect of Group was found, $F(1, 158) = 0.19$, $p = .665$, partial $\eta 2 = .001$. All findings remained significant after covarying for age and education duration (all $p < .05$).

A repeated one-way ANOVA was run to follow-up analysis of the C1 component in patients and yielded a significant main effect of time $F(8, 152) = 2.86$, $p = .005$, partial $\eta 2 = .132$. Mauchly's test was nonsignificant, $p < .05$. After Bonferroni correction, only the second post-modulation block (3.19 ± 2.77) was significantly different relative to baseline (-5.85 ± 4.55), a mean difference of -2.66, 95% CI [-5.1, -0.16], adjusted $p = .032$, partial $\eta 2 = .360$. These findings suggest that C1 potentiation lasted for upwards of 4 minutes relative to the modulation block evident through a decrease in amplitude in the patient sample.

The same procedure was run to follow up main effect of time in healthy controls. Mauchly's test was significant $\chi 2(35) = 116.742$, $p < .0005$. Epsilon was larger than 0.75, so Greenhouse-Geisser was used to correct degrees of freedom. The main effect of time was significant, $F(6.44, 894.42) = 23.44$, $p < .001$, partial $\eta 2 = .144$. A significant change from baseline (-5.96 ± 5.37) was observed; for the first post-block with a mean difference of -2.08, 95% CI [-2.88, -1.28], partial $\eta 2 = .274$; for the second post-block with a mean difference of -2.491, 95% CI [-3.37, -1.61], partial $\eta 2 = .307$; the third post-block with a mean difference of -1.98, 95% CI [-2.83, -1.14], partial $\eta 2 = .235$; the fourth post-block with a mean difference of -2.254, 95% CI, [-3.16, -1.35], partial $\eta 2 = .256$, all adjusted $p < .001$. There was also a significant difference in means in post-block 6 with a mean difference of -0.80, 95% CI [-1.45, -0.10] with adjusted $p = .016$, partial $\eta 2 = .067$. This indicates that potentiation lasted upwards

of 27 minutes in healthy controls for the C1 component following the modulation block. There was an overall reduction in amplitude for both groups relative to the baseline assessment block.

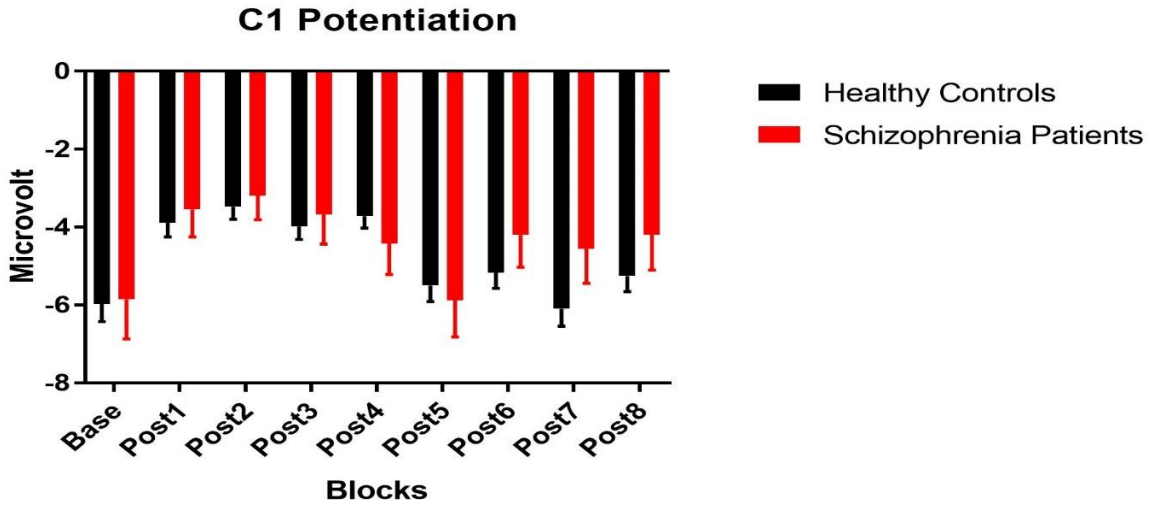

Figure 3. Mean values and SEM error bars reflect peak amplitudes for each block respectively. There is a clear similarity in the C1 component VEP response between groups.

3.5 P1 component

A two-way mixed repeated measure ANOVA with group and time as fixed factors sought determine if there were a statistically significant group by time interaction, or main effect of time in patients and controls. There was not homogeneity of covariances as assessed by Box's test of equality ($p < .001$), which in turn might influence estimated probabilities concerning the interaction term. Similar underlying distributions were assured through similar variance and visual inspection of box plots. Mauchly's test of sphericity was violated $\chi^2(35) = 126.26$, $p < .001$, epsilon > 0.75, so Greenhouse-Geisser correction was used. Time by Group interaction was non-significant, $F(6.38, 989.41) = 1.07$, $p = .381$, partial $\eta 2 = .007$. This finding indicates that there were no group differences in P1 potentiation across any time points. Again, irrespective of group, there was a significant main effect of Time, $F(6.38, 989.41) = 22.44$, $p < .001$, partial $\eta 2 = .126$. No main effect of group. All findings remained significant after covarying for age and education duration (all $p < .05$).

The main effect of time was assessed using repeated measure one-way ANOVAs, one for each group. In patients, corrected using Greenhouse-Geisser, results showed a significant main effect of time $F(4.72, 94.44) = 6.69$, $p < .001$, partial $\eta 2 = .251$ There was significant change relative to baseline (9.76 ± 7.15) in post-block 1 with a mean difference of -2.34, 95%

CI [-4.45, -0.23], adjusted p = .024, partial η2 = .366; in post-block 2 with a mean difference of -3.23, 95% CI [-6.25, -0.21], adjusted p = .032, partial η2 = .348; and in post-block 4 with a mean difference of -2.74, 95% CI [-5.35, -0.13], adjusted p = .032, partial η2 = .340. Thus, P1 modulation was evident in early post-modulation blocks in patients lasting upwards of 8 minutes after modulation. There was an overall increase in amplitude from pre- to post-modulation in P1 component peak amplitudes.

The results from one-way repeated ANOVA in healthy controls showed a significant main effect of time, F(6.26, 845.96) = 36.96, p < .001, partial η2 = .215, corrected using Greenhouse-Geisser. Results from the planned linear contrasts showed significant difference relative to baseline 8.73 ± 6.01, in the first post-modulation block with a mean difference of -1.980, 95% CI [-2.79, -1.17], partial η2 = .274; the second post-block with a mean difference of -2.45, 95% CI [-3.40, -1.58], partial η2 = .307; the third post-block with a mean difference of -1.80, 95% CI [-2.67, -0.94], partial η2 = .235; the fourth post-block with a mean difference of -2.48, 95% CI [-3.39, -1.57], partial η2 = .256, and as late as the seventh post-block with a mean difference of 1.24, 95% CI [0.48, 2.00], partial η2 = .067, all adjusted p < .001. Interestingly, while there was an increase in amplitude across the first four post-blocks, there was a decrease in P1 amplitudes at later post-blocks relative to baseline in both groups suggesting active depotentiation at lower baseline stimulation. P1 modulation in healthy controls lasted for upwards of 48 minutes after the modulation block.

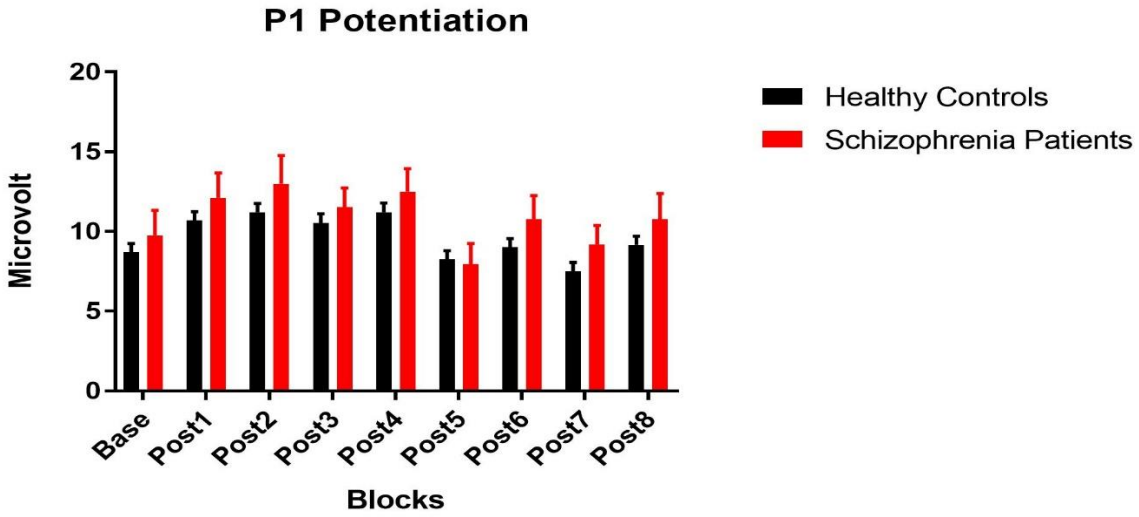

Figure 4. Mean values and SEM error bars reflect peak amplitudes for each block respectively. Both groups VEP inhibit strikingly similar VEP potentiation pattern over time. Notice the subtle different outset at baseline keeps throughout most post-assessment blocks.

3.6 N1 component

A two-way mixed repeated ANOVA were run with N1 as dependent variable to see whether the VEP signals changed significantly between groups. Box's test of equality was non-significant (p = .070). Variance and skewness was similar for each term. Mauchly's test of sphericity was significant, $\chi^2(35) = 109.83$, $p < .001$, epsilon > 0.75, so Greenhouse-Geisser correction was used. The Time by Group interaction was not significant for the N1 component, $F(6.87, 1190) = 1.23$, $p = .286$, partial η2 = .007. No significant main effect of time was found, $F(6.87, 1190) = 1.22$, $p = .291$, partial η2 = .007, indicating that the N1 component did not change significantly over time. This contrasts with previous findings that showed a subcomponent of the N1 to represent a possible target for potentiation using a similar paradigm (Çavuş et al., 2012; Teyler et al., 2005). No main effect or interaction was found after covarying for age and education duration (all $p < .05$).

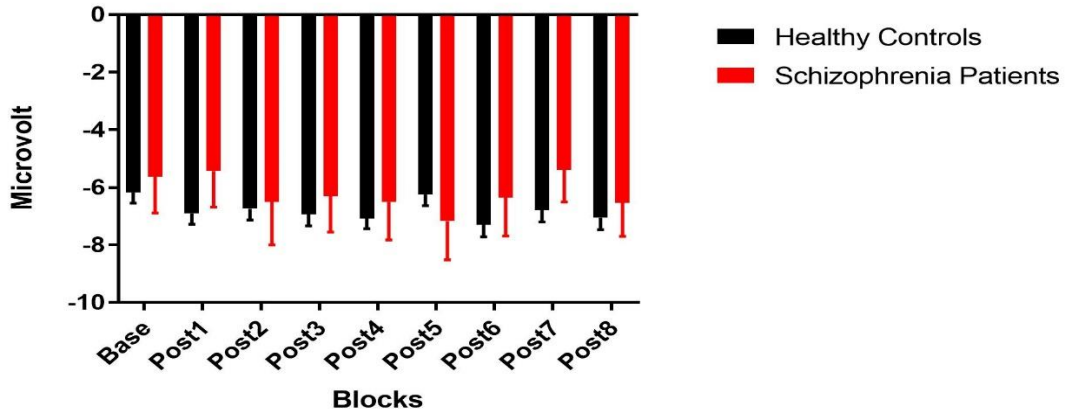

Figure 5. Mean values and SEM error bars represent peak amplitudes for each VEP assessment block. As can be seen when inspecting the y-axis range small differences in amplitude change are present across time in both groups, however no time point was significantly different from baseline assessed by two-way repeated ANOVA.

3.7 P1-N1 peak-to-peak

A two-way mixed repeated ANOVA were run with P1-N1 as dependent variable. Homogeneity of covariances was assured, p = .378. Similar variance and distributions was visually inspected and assured. Mauchly's test was significant, $\chi^2(35) = 147.93$, $p < .001$, epsilon > 0.75, so Greenhouse-Geisser correction was used. The time by group interaction was non-significant, $F(6.20, 955.73) = 0.38$, p = .900, partial η2 = .002, indicating at no two time points did the means differ between groups. The main effect of Time was significant, $F(6.21, 955.74) = 18.26$, $p < .001$, partial η2 = .106. Neither age nor education duration had any significant effect on P1-N1 peak to peak modulation when these were covaried into the model (all $p > .05$).

To follow up the main effect of time, a one-way repeated measure ANOVA of the main effect of time in patients, yielded a significant main effect of time, $F(8, 160) = 5.52$, $p < .001$, partial η2 = .216. There was a significant change relative to baseline (15.43 ± 9.33) in post-block 2 with a mean difference of -4.08, 95% CI [-7.78, -0.38], adjusted p = .024, partial η2 = .362; and in post-block 4 with a mean difference of -3.62, 95% CI [-7.23, -0.01], adjusted p = .048, partial η2 = .319. Like the P1, potentiation was observed upwards of 8 minutes post modulation in patients.

The same follow-up analysis for healthy controls yielded a significant effect of time, $F(6.29, 842.81) = 32.24$, $p < .001$, partial η2 = .194. Relative to baseline (15.08 ± 8.15) there was a significant change in means across all post-modulation blocks except the fifth and the seventh, $p > .00625$. As can be seen in figure 6, the P1-N1 was significantly increased in amplitude during the first four post-modulation blocks, before it decreased during the last post-modulation blocks. Mean difference for the first post-block is -2.78, 95% CI [-3.98, -1.58], partial η2 = .242; the second post-block with a mean difference of -3.14, 95% CI [-4.24, -2.04], partial η2 = .362; the third post-block with a mean difference of -2.52, 95% CI [-3.50, -1.55], partial η2 = .208; the fourth with a mean difference of -3.36, 95% CI [-4.43, -2.29], partial η2 = .319; the sixth with a mean difference of -1.51, 95% CI [-2.45, -0.58], partial η2 = .179; and the last post-modulation block with a mean difference of -1.41, 95% CI [-2.31, -0.52], partial η2 = .219, all adjusted $p < .001$. An overall increase in the P1-N1 component peak amplitude across post-modulation blocks relative to baseline was observed for both groups. This effect lasted upwards of 60 minutes in healthy controls.

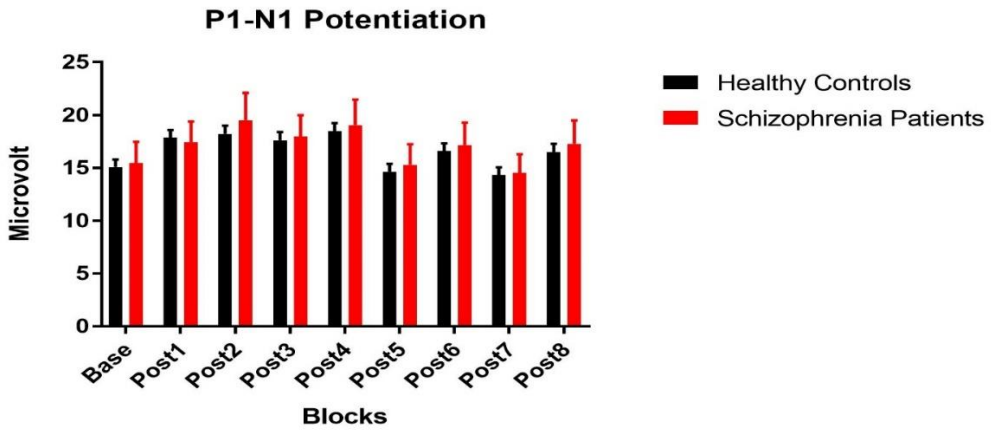

Figure 6. Mean values and SEM error bars represent peak amplitudes for each VEP assessment block. Both groups VEP potentiation pattern over time follow each other almost perfectly suggesting that both groups displayed a similar effect of modulation across post-assessment blocks.

4 Discussion

The current study successfully demonstrated potentiation of early VEP components following a prolonged period of repetitive reversing checkerboard stimulation thereby furthering the notion that sensory experience-dependent neuroplasticity can be indexed *in vivo* in the human brain. The main interest was whether VEP potentiation would be different in a group of individuals with schizophrenia when compared to healthy controls. Contrary to expectations, the pattern of VEP potentiation was strikingly similar in the patients and the controls. Potentiation effects in both groups were apparent through a significant decreased negativity in C1 peak amplitude, and an increased positivity in P1 peak amplitude following the visual tetanus. Potentiation was also observed in an increased absolute amplitude in the P1-N1 complex whereas the N1 component did not change significantly from baseline to post-modulation assessment blocks. These findings are line with previously demonstrated VEP component change using a similar pattern-reversing checkerboard paradigm in healthy controls (Elvsåshagen et al., 2012; Normann et al., 2007). However, these findings seem to contradict previous observations obtained from comparing visual plasticity in schizophrenia to healthy controls (Çavuş et al., 2012).

In the Çavuş et al. (2012) study, the C1 component was shown to be potentiated in healthy controls only, whereas the N1b component was potentiated in both groups. The authors interpreted this as evidence for impaired visual cortical plasticity in schizophrenia. One possible explanation for why the current study did not show the same pattern of results as those in Çavuş et al. (2012) could be a difference in methodology relating to how VEP component values were extracted from the VEP signals. The current study is the first study to use traditional peak amplitude procedures in comparing VEP plasticity between individuals with schizophrenia and healthy controls. Çavuş et al. (2012) took a different approach in using statistical decomposition procedures in the form of a temporal principle component analysis to extract factor loadings from the grand averaged VEP signal (Dien, 2012). The former procedure makes generalization across studies and samples easier but may yield estimates that suffer from higher inter-individual variability. The latter might be a better procedure when attempting to distinguish between underlying VEP components yielding oblique temporal factor likely better suited for pattern-reversal visual neural signals that have been shown to possess great inter-individual variation (Lahr et al., 2014). As such and given the inherent dipolar nature of the C1 component, it is possible that inter-individual variation was less influencing VEP component values tested in Çavuş and colleagues study than in the current study. The reasoning for this is that they

decomposed the grand averaged VEP signal, rather than each individual's erp. Indeed, neither of the later components in either the current study nor in Çavuş et al. (2012) study differed between groups, suggesting that averaging before extracting rather than vice versa, might yield better estimates effectively reducing inter-individual variance. On the other hand, findings from the current study corroborate other reports demonstrating preserved VEP plasticity in individuals with schizophrenia (Forsyth et al., 2017; Jahshan et al., 2017). This conflicting picture suggests that visual experience-dependent plasticity is complex when induced and assessed over time in human visual areas using a visual tetanus solely. In fact, Jahshan et al. (2017) adopted the very same paradigm used in Çavuş et al. (2012) study, but identified only partially overlapping time-windows for VEP potentiation effects to that of Çavuş and colleagues, attesting to the variation possibly inherent in capturing visual neocortical plasticity using VEP paradigms.

Results from current methods used in this study showed that there were no group differences in modulation effects in any of the early VEP components investigated. There was neither any difference in behavioral measure of attention between the two groups suggesting that participants in both groups allocated similar levels of attention during VEP assessment. However, there were differences in how long VEP potentiation lasted with potentiation lasting for upwards of one hour in healthy controls and a maximum of 8 minutes in the patients with schizophrenia. A difference in longevity have to be viewed in the context of sample size variation between groups tested in this study given the variable anatomy of the visual cortex by which early VEP components are thought to originate (Di Russo et al., 2005; Lahr et al., 2014). Given large within-subject variation in VEP morphology alongside the fact that this complex study design imposed many statistical comparisons/corrections, it is possible that differences in longevity were driven by the larger sample size in healthy controls. In fact, the pattern of VEP mean peak amplitudes across time points in both groups indicates a highly similar VEP response development, and furthermore, effect sizes were highly similar for both groups. Additionally, exploratory preliminary analyses found that when no statistical corrections were made (not reported), statistical testing of pre vs. post VEP assessment block within-subject contrasts indicated that both groups possessed almost identical VEP potentiation over time.

Taken together, the results of the current study suggest that individuals with schizophrenia display similar levels of experience-dependent neuroplasticity in visual pathways when compared to healthy controls. They add to previous reports assessing visual neuroplasticity in schizophrenia (Çavuş et al., 2012; Forsyth et al., 2017; Jahshan et al., 2017)

suggesting that the capacity for visual neuroplasticity is not impaired but rather spared in schizophrenia. Whether these differences are driven by methodological variation remain an interesting future inquiry into assessing VEP potentiation in schizophrenia. In addition, these results have implications for current attempts to assess experience-dependent neuroplasticity in schizophrenia using either auditory or visual paradigms. Importantly, these implications might offer a possible explanation as to why visual plasticity in schizophrenia was found to be comparable to that of healthy controls.

4.1 NMDA-Dependent Plasticity in Auditory and Visual Cortices

Until recently, both brain imaging and electrophysiological evidence for sensory experience-dependent neuroplasticity in the human brain have been collaborated by studies using auditory (e.g. auditory evoked potentials) and visual (e.g. visual evoked potential) paradigms suggesting that these paradigms index a type of neuroplasticity that rely on similar neural correlates of NMDAR signaling across cortices (Clapp et al., 2012; Kompus & Westerhausen, 2018; Zaehle, Clapp, Hamm, Meyer, & Kirk, 2007). However, given consistent findings of reduced mismatch-negativity (MMN; evoked response in auditory paradigm) in schizophrenia (Friedman, Sehatpour, Dias, Perrin, & Javitt, 2012; Javitt, Lee, Kantrowitz, & Martinez, 2018), it is likely that visual neuroplasticity may rely on different mechanisms and/or be modulated by different pathways than neuroplasticity in auditory domains. A recent study employing dynamical causal modeling to assess the similarity, in terms of effective connectivity, between both paradigms suggests VEP neuroplasticity rely only on forward connections whereas auditory neuroplasticity rely on both forward and backward projecting connections (Spriggs et al., 2017). Thus, it is possible that experience-dependent *visual* neuroplasticity is preserved while experience-dependent *auditory* neuroplasticity is reduced in schizophrenia, and that these sensory processes rely on different mechanisms effecting synaptic modifications during perceptual learning. Hebbian synaptic mechanisms may still underlie LTP-induced visual plasticity reflected in a strengthening of forward projecting visual pathways, however, it may not entail the same mechanisms as auditory neuroplasticity, reflecting reciprocal projections from both forward and backward pathways. As such, the capacity of visual pathways to undergo LTP may be preserved in individuals with schizophrenia, whereas mechanisms governing backward projections might be compromised. Further substantiating the difference was the finding that only top-down pathways were modulated by a single-nucleotide polymorphism on the gene controlling the secretion of brain-derived neurotropic factor (BDNF) known to impact

NMDAR efficacy (Lamb et al., 2015) whereas forward pathways were not (Spriggs et al., 2017). Interestingly, the same BDNF single-nucleotide polymorphism have been implicated in schizophrenia and not in bipolar patients (Neves-Pereira et al., 2005). Viewing these results in light of the Elvsåshagen et al. (2012) article demonstrating impaired visual neuroplasticity in bipolar patients, it is possible that neuroplasticity assessed through VEPs do rely on different mechanisms compared to neuroplasticity assessed in the auditory domain. Indeed, the results obtained in this study suggests that visual neuroplasticity is not abnormal in schizophrenia, a finding consistent with previous reports using similar paradigms to index visual neuroplasticity in this patient group (Forsyth et al., 2017; Jahshan et al., 2017; McCleery et al., 2017). Consequently, different task demands may elicit different forms of neuroplasticity, suggesting that visual plasticity can be preserved in individuals with schizophrenia whereas auditory plasticity can be reduced (Spriggs et al., 2017). In other words, the propensity for plasticity might not be homogeneous across the brain, and sensory LTP paradigms likely differ in their underlying mechanisms facilitating the amplitude shift in ERPs from pre- to post-assessments (Spriggs et al., 2017). It is also interesting that neither of the VEP plasticity studies have succeeded in finding a link between visual plasticity and measures of cognitive impairments (Forsyth et al., 2017; Jahshan et al., 2017), whereas reduced MMN have been found to be strongly correlated with degree of cognitive functioning (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004). These findings further substantiate the possibility that the capacity for visual plasticity remains normal in schizophrenia.

While this study did not attempt to investigate the relationship between auditory and visual paradigms, it is interesting to speculate whether the results from the current investigation coupled with previous findings (Elvsåshagen et al., 2012; Spriggs et al., 2017) nevertheless suggest a nuanced picture of a uniform deficits across cortices driven by altered NMDAR signaling in schizophrenia. Whereas Çavuş et al. (2012) conclusion of a deficient cortical plasticity in schizophrenia fitted the NMDA-dependent plasticity framework, the results from the current study suggests that deducing one neurobiological component may not suffice to explain potentiation effects following a visual tetanus. Indeed, both evidence from similar studies (Jahshan et al., 2017) and reasoning from computational models (Fox & Stryker, 2017) suggest the presence of additional neuromodulatory agents and processes likely effecting the net result of increased or decreased synaptic transmission. Whether visual neuroplasticity rely on both feed-forward and -backward connections remains a future inquiry in attempts to establish the mechanical underpinnings of visual neuroplasticity assessed *in vivo* in the human

brain. At present, research indicate different forms of experience-dependent neuroplasticity rely on different mechanisms relative to whether visual or auditory encoding takes place (Baldeweg & Hirsch, 2015; Spriggs et al., 2017). Future studies investigating clinical populations would thus benefit from employing more than one electrophysiological index of experience-dependent sensory plasticity to ensure critical differences between such mechanisms may not be mistakenly unreported. Findings from the current investigation, which is the second investigation to compare visual plasticity in schizophrenia to that of healthy controls, further suggest that abnormal neocortical plasticity measured using EEG may be more readily observable in auditory rather than visual processing areas in schizophrenia.

4.2 Patient Characteristics

Neither this study nor the Çavuş et al. (2012) study did investigate possible confounding effects of medication or illness progression in individuals with schizophrenia. Meanwhile, an article reviewing imaging-based neurochemistry studies suggests different abnormalities in the glutamatergic system depending on stage of disease progression (Salavati et al., 2014). It is not yet known how an imbalance in neurochemistry might translate to mechanisms governing neural network dynamics in schizophrenia. However, it is likely, given evidence of duration specific patterns of neurochemical alterations (Salavati et al., 2014), that some heterogeneity in visual plasticity at group level might be dependent on both stage of illness progression and medication interventions. Studies have demonstrated evidence supporting differential effects of atypical compared to typical antipsychotic medication at the molecular level (Konradi & Heckers, 2001), differences which might translate into differential regulation of visual plasticity by targeting distinct postsynaptic proteins known to interact with synaptic plasticity (Critchlow, Maycox, Skepper, & Krylova, 2006; Keshavan, Mehta, Padmanabhan, & Shah, 2015). Controlling for both illness duration and medication status was initial hypotheses of the current study but could unfortunately not be explored because the complete patient database was not ready before this thesis was due to be submitted. Future attempts to assay visual plasticity in schizophrenia using EEG should include analysis of both illness duration and medication to map the possible effects these factors might have.

4.3 Methodological Strengths and Limitations

Statistically, parametrically modeling this design is not an easy feat. It reflects a tradeoff between increasing signal to noise ratio by collapsing blocks and thereby loose temporal information or keeping enough trials during averaging in each block separately and thereby retaining temporal information. Temporal information is critical when making the inference that the effects of modulation indeed share features with canonical LTP. In this study, all post-modulation blocks were kept separate with the result of increasing the number of statistical comparisons (decreasing power) but also leaving the possibility to express how long potentiation effects were observed. This statistical procedure resemble previous attempts to model VEP LTP-like plasticity in humans (Normann et al., 2007), and will likely demand a higher number of participants to enter into each group during statistical comparisons.

How many blocks are needed and which component(s) in which electrode(s) to statistically test remain largely in its exploratory phase. Presently, there is no consensus as to how to capture LTP-like potentiation in the pattern-reversing checkerboard elicited VEP response. Several studies using similar paradigms extract univariate peak amplitudes (Elvsåshagen et al., 2012; Normann et al., 2007), whereas other studies have used either statistical decomposition procedures (Çavuş et al., 2012; Teyler et al., 2005) or utilized non-parametric mass univariate approaches (Jahshan et al., 2017). This variation in methods attests to the difficulty of how to best capture visual LTP-like neuroplasticity in the human brain. It furthermore leaves comparisons between studies harder (comparing studies gets even more complicated by the fact that numerous studies fail to report necessary details in their results section). Indeed, several studies report firstly no group difference before reporting a trending pattern of significance from exploratory analyses, and rather commonly, no measure of effect is reported (Forsyth et al., 2017; McCleery et al., 2017).

Results from the current study found relatively large effect sizes when considering the effect of modulation across time (sample specific within-subject repeated ANOVA effect sizes) (Baguley, 2009; Lakens, 2013). Among the components tested, both the P1 component and the P1-N1 peak to peak component were found to produce the strongest effect of modulation in healthy controls. It is interesting to note that the neurogenesis of both the P1 and the initial segment of the N1 has been found to be determined solely by excitatory post-synaptic activity in rodents, whereas the temporal distribution of the N1 increase as post-synaptic inhibition increases (Bruyns-Haylett et al., 2017). As such, it is possible that future studies using pattern-reversing checkerboard stimulus as plasticity inducing stimulus would benefit from

investigating the temporal profile of the P1 and the initial trough of the N1 component as this may possibly represent afferent thalamocortical projections. However, whether these results transfer to human VEP responses remain an open question. Since both the P1 and P1N1 components was shown to produce the largest and lasting effect of modulation in this study, future studies using full visual field pattern-reversing checkerboard stimulus as plasticity inducing stimulus could benefit from investigating these components as a measure of plasticity.

Rather consistently, the effect of modulation was larger in early post-modulation blocks (i.e., 1-4) compared to later post-modulation blocks (i.e., 5-8). This pattern of VEP potentiation over time suggests the presence of two opposing processes, one responsible for increasing (i.e., LTP) and one for decreasing (i.e., LTD) the VEP block averages relative to the pre-modulation block. As such, point estimates used in traditional waveform averaging procedures would be susceptible to a regression towards a zero point (i.e., baseline) as a function of these processes. Therefore, it is possible that the threshold between LTP and LTD induction may impose subtle differences not necessarily captured in waveform averaging when relatively low-frequency visual stimulation (e.g. ~2Hz) is applied as the inducing tetanus of visual neuroplasticity (Abraham, 2008; Clapp et al., 2012). Indeed, combined transcranial stimulation and VEP protocols have demonstrated the presence of a mechanism in the visual cortex likely working to tune networks towards a homeostatic range (Bocci et al., 2014). Consequently, if the block averages consistently progress towards this threshold during baseline-stimulation, disentangling one process over the other might prove difficult, and quite possibly, these effects might get washed out if all post-modulation blocks were averaged together into one. An optimal LTP-inducing visual stimulation frequency is needed, so are a better understanding of the time interval at which the visual response starts to decay/depotentiate.

To date, it is safe to say that assessing VEP LTP-like plasticity *in vivo* in human visual cortex remain in its exploratory phase suggesting that more research is needed to establish standards for how to measure visual neuroplasticity using specific stimulus parameters. Because these designs are complex and possess multiple assessment blocks over time and, and because it is hard to model interaction effects in non-parametric factorial analyses (Pesarin, 2001), standardizing how many assessment blocks are needed for particular stimulus parameters and a particular induction frequency remain a necessary future step in establishing VEP plasticity paradigms. These concerns should guide future attempts to assess visual neuroplasticity using pattern reversing checkerboard stimuli.

In addition to concerns regarding the configuration of the experimental design, there is

great inter-individual variability in VEP amplitudes, even when close consideration of factors influencing signal/noise ratio is taken (Klistorner & Graham, 2001; You, Thie, Klistorner, Gupta, & Graham, 2012). A proposed solution to this problem is to normalize amplitudes by a frequency decomposition of VEP signals (Klistorner & Graham, 2001). Future studies would likely benefit from implementing these procedures as they have been shown to alleviate effects of gender and might have similar effect for other possible confounding factors (Klistorner & Graham, 2001). This procedure would also have beneficial consequences for assumptions underlying later parametric modeling of this complex study design as well.

The study design and paradigm used in this study builds on previous research showing that the change observed from baseline to post-modulation condition reflect an effect of the modulation block (Normann et al., 2007; Teyler et al., 2005). As such, potentiation effects observed in this study are likely to be produced by the modulation block, however, future studies should include a control group receiving no modulating stimulation to ensure this inference. In addition, future studies could investigate whether paradigms comprising both periods of auditory- as well as visual-stimulation protocols might influence the underlying stimulated neural networks. If auditory stimulation in the form of pre-pulse inhibition or MMN bias visual network dynamics towards some set tuning, then these represent confounds in determining effects of visual stimulation alone.

An important drawback from this study was the small patient sample size and the cross-sectional design. Because the power to detect a significant interaction is reflected in the smallest sample during statistical testing, it is possible that the parametric model used in the current study was underpowered. In addition, association between clinical variables and VEP LTP-like plasticity is better researched in a longitudinal design. This would offer insight into whether VEP plasticity change in relation to illness duration or are related to changes in other clinical outcomes.

5 Conclusion

The results from the current study contribute to previous findings by demonstrating that it is possible to assess neocortical plasticity *in vivo* using pattern-reversing checkerboard stimuli in the human visual cortex. However, the field has yet to reach consensus in how to best probe and capture VEP potentiation, with highly variable paradigm and VEP stimulus configurations as well as variable VEP signal quantification methodology. Whether the change from baseline to post-assessment blocks reflect cardinal features of NMDAR-dependent LTP remains an

additional important future inquiry. Assessing effects of NMDA antagonists on VEP potentiation in humans seems a fruitful exploratory step. Although it is impossible to speak to the role of NMDARs from the results herein obtained, it is nevertheless likely, given the NMDAR hypofunction hypothesis of schizophrenia, that potentiation following a visual tetanus reflect the interplay of various mechanisms and biochemical factors acting at distinct cortical levels and timescales to effectuate changes in synaptic transmission. Thus, a close consideration of the time course and network level at which VEP potentiation is facilitated would contribute to our understanding of the biological underpinnings of experience-dependent plasticity. It is so far interesting to view the current results in light of previous studies assessing visual plasticity in schizophrenia with all but one study demonstrating evidence of preserved capacity for visual plasticity among individuals with schizophrenia. The findings from the current study add to the notion that the capacity for visual plasticity in schizophrenia is not abnormal relative to healthy controls, a finding important for future investigations into sensory synaptic plasticity among individuals with schizophrenia.

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Appendix

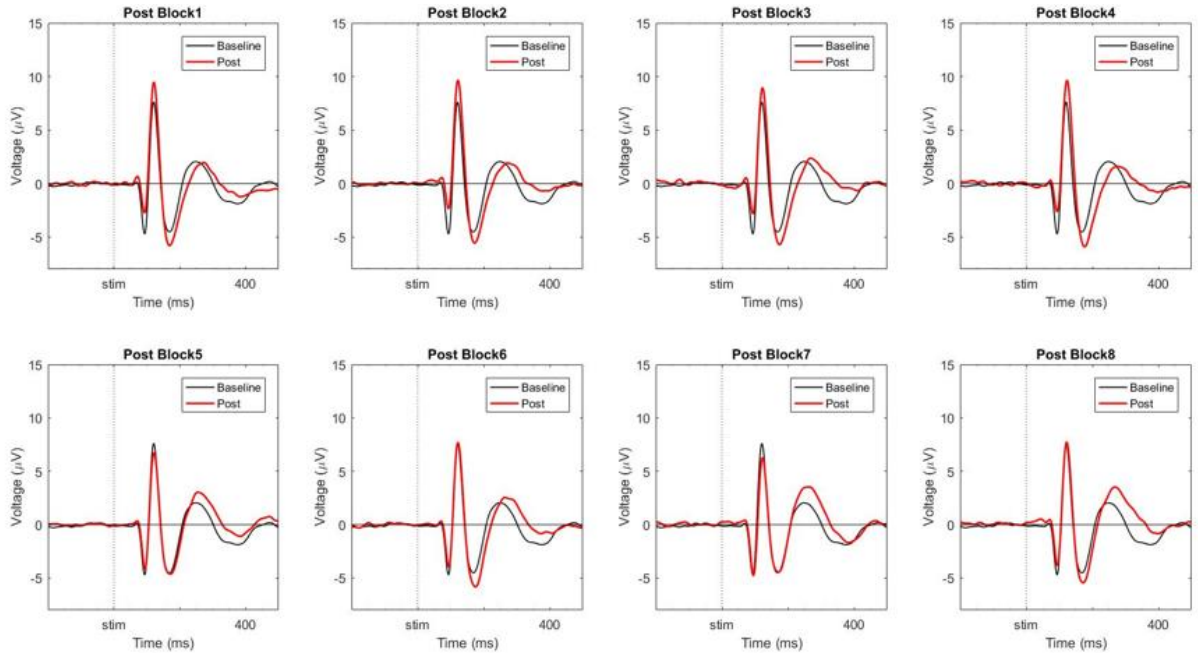

Figure A1. Grand average visual evoked potentials at Oz from (*n* = 157) healthy controls where the blue line represents baseline condition and the red line represent each post-block condition respectively.

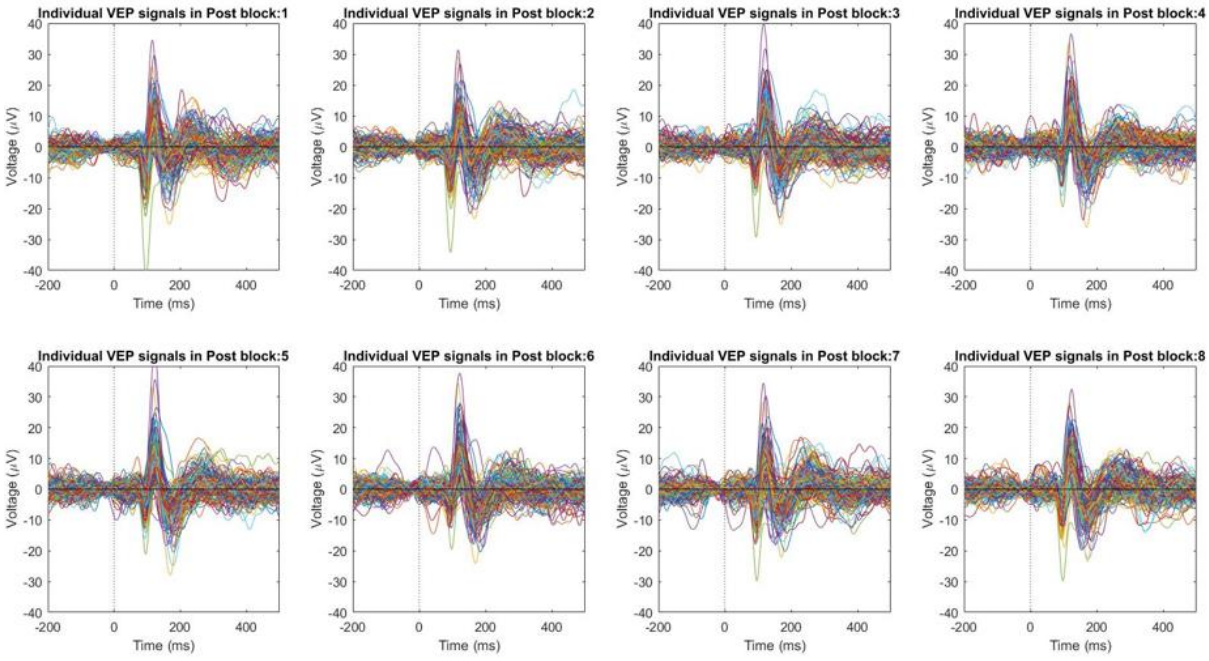

Figure A2. Butterfly plot showing individual variation in VEP signals at Oz from (n = 157) healthy controls for each post-modulation block respectively.

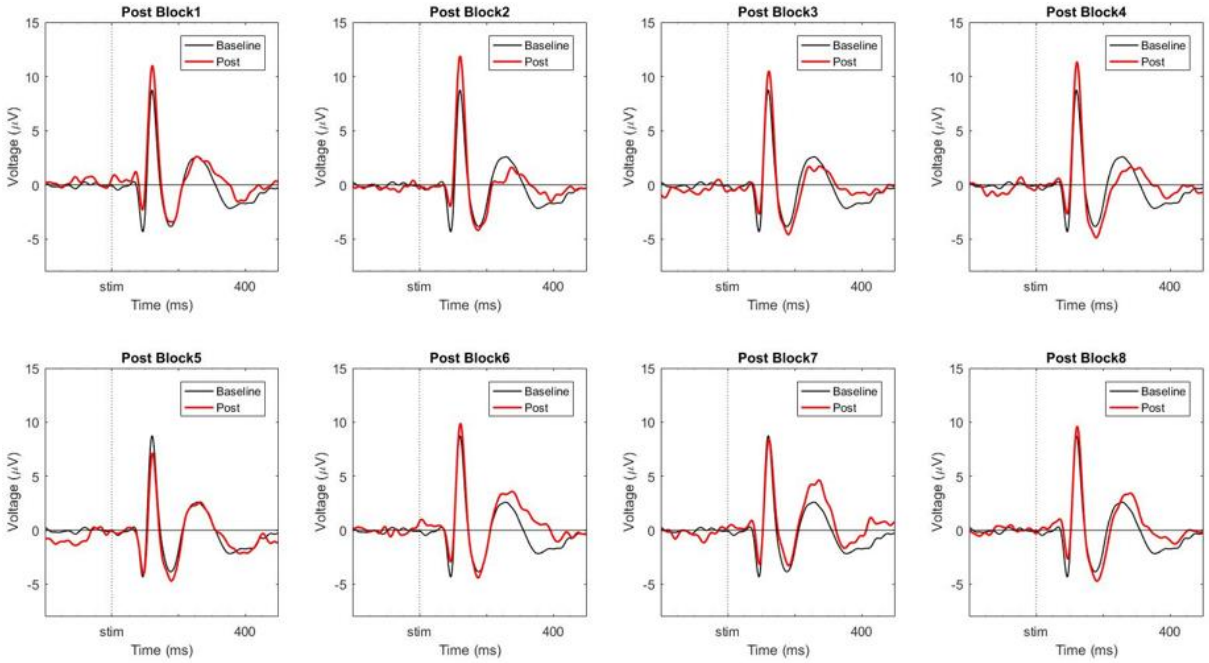

Figure A3. Grand average visual evoked potentials at Oz from (*n* = 22) schizophrenic patients where the blue line represents baseline condition and the red line represent each post-block condition respectively.

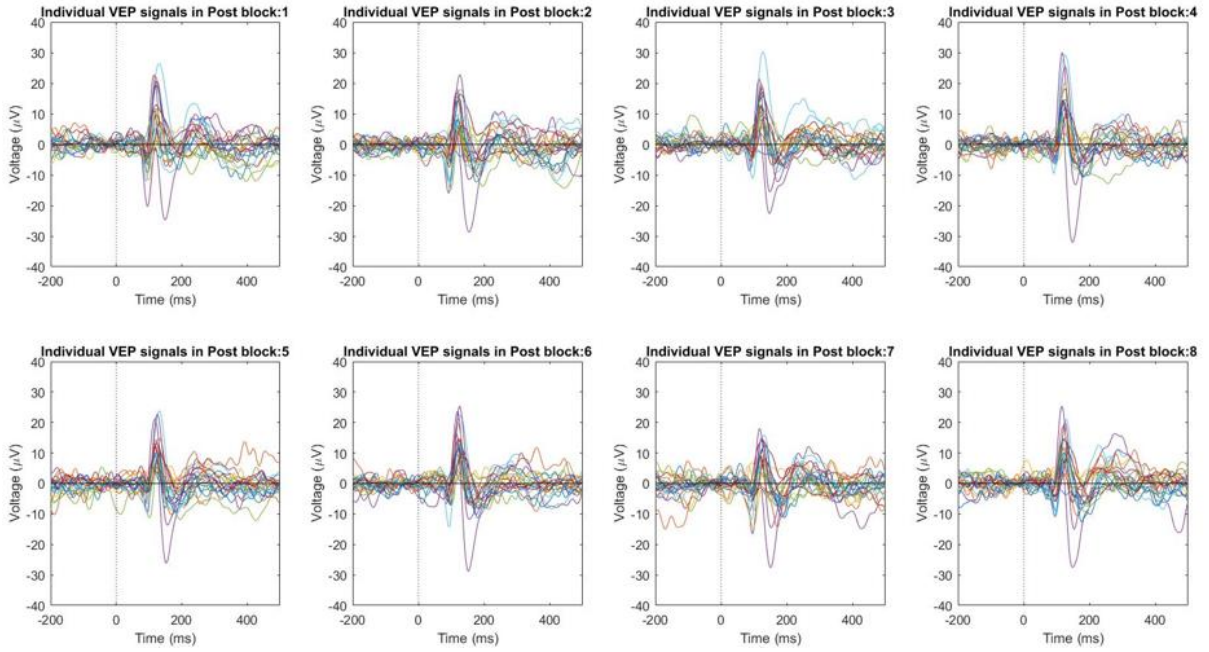

Figure A4. Butterfly plot showing individual variation in VEP signals at Oz from (n = 22) schizophrenic patients for each post-modulation block respectively.

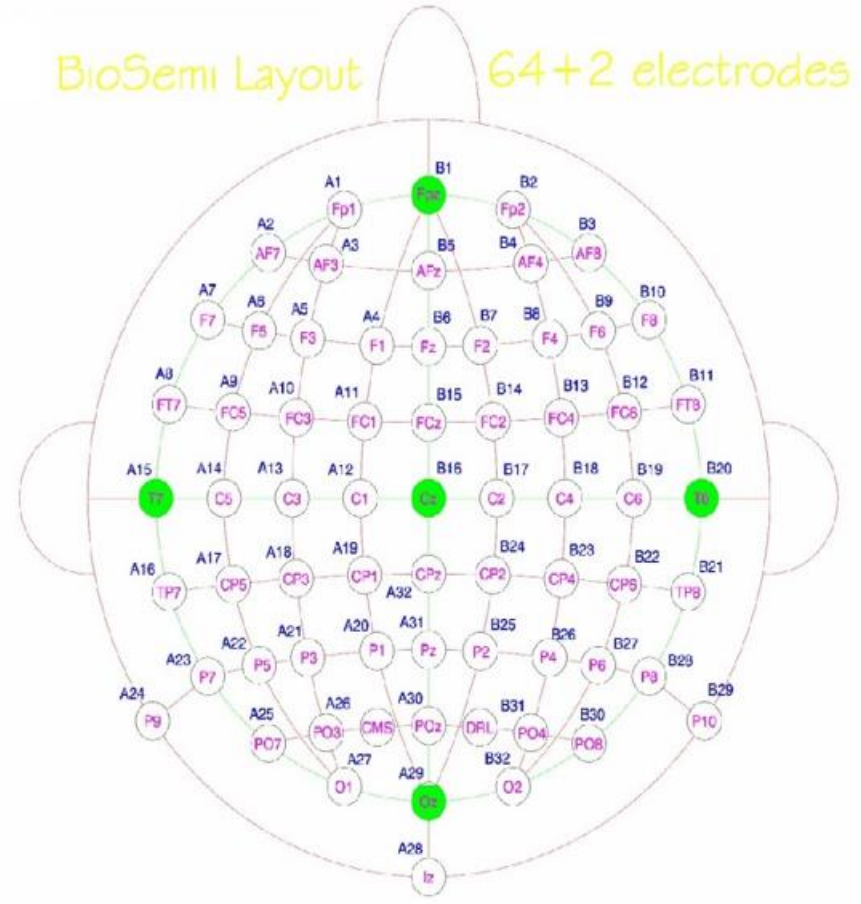

Figure A5. 10-20 electrode layout with 64 active electrodes used during EEG recordings. (Cortech Solutions Inc, 2018). https://cortechsolutions.com/product-category/eeg-ecg-emg-systems/eeg-ecg-emg-systems-activetwo/eeg-ecg-emg-systems-activetwo-head-caps/ (accessed 25 April 2018).