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Evaluating Visual Neuroplasticity with EEG in Schizophrenia Outpatients

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Abstract

Deficient neuroplasticity has been implicated in schizophrenia and can be examined with non-invasive methods in humans. High frequency visual stimulation (HFS) induces neuroplastic changes in visual evoked potential (VEP) components, similar to the tetanizing electrical stimulation that induces synaptic long-term potentiation (LTP). While visual HFS paradigms have been used in schizophrenia, the use of a single visual stimulus has precluded demonstration of whether the plasticity effects are specific to the stimulus presented during HFS (i.e., input specific). Additionally, test-retest reliability of VEP plasticity effects, an important consideration for applications of HFS paradigms in schizophrenia clinical trials, remains unknown. Accordingly, we administered a visual HFS paradigm to 38 schizophrenia patients and 27 healthy controls at baseline and two-weeks later. VEPs were elicited by horizontal and vertical line gratings before and after HFS; only one orientation was tetanized with HFS. Using a mass univariate permutation approach, we identified an input-specific cluster across groups that was a broadly distributed over parietal-occipital areas between 108–183 ms. However, the groups did not differ in terms of the strength of plasticity effect. The test-retest reliability of the input-specific plasticity effect was modest over two weeks, suggesting that this HFS paradigm requires further development before it could be used to track plasticity change in clinical trials. Moreover, while the current HFS paradigm induced significant input-specific neuroplasticity, it did not replicate prior studies showing deficient neuroplasticity in schizophrenia. Accordingly, demonstration of deficient visual LTP-like neuroplasticity in schizophrenia may depend on paradigm parameters that remain to be fully elucidated.

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1. Introduction

Schizophrenia patients exhibit cognitive deficits that impact their daily lives (Green, 1996; Green et al., 2000). A range of cognitive impairments might be explained by a basic underlying deficit in neuroplasticity. Neuroplasticity is the ability of the brain to alter its function or structure as a result of changes in the environment or novel experiences. Long-term potentiation (LTP) is one form of neuroplasticity and reflects long-term (minutes to hours) enhancement of excitatory synaptic transmission and is believed to be the prime cellular mechanism underlying learning and memory (Bliss and Collingridge, 1993; Cooke and Bliss, 2006). LTP is dependent on glutamatergic neurotransmission at *N*-methyl-D-aspartate (NMDA) receptors (Cooke and Bliss, 2006; Malenka and Bear, 2004). NMDA receptor hypofunction is a leading pathophysiological theory of schizophrenia (Javitt et al., 2012; Krystal et al., 1994), and is thought to be responsible for many of its clinical features. Understanding LTP-like neuroplasticity may elucidate the neural processes associated with impaired cognition (Cooke and Bear, 2012; Etienne and Baudry, 1987; Forsyth and Lewis, 2017) and positive symptoms (Hoffman and Cavus, 2002; Port and Seybold, 1995) in schizophrenia.

LTP can be elicited in animals using tetanizing high frequency electrical stimulation (Cooke and Bliss, 2006; Moser et al., 1998) or more recently, repetitive sensory high-frequency stimulation (HFS) (Clapp et al., 2006; Cooke and Bear, 2012; Zhang et al., 2000). While the mechanisms of LTP and neuroplasticity have been studied extensively in animals at the molecular and cellular levels (Cooke and Bliss, 2006; Malenka, 2003; Malenka and Bear, 2004), studies in humans have been largely limited to examination of excised cortical tissue (Chen et al., 1996). Recently, non-invasive methods been developed to assess LTP-like neuroplasticity in humans.

In humans, LTP-like plasticity can be elicited in a similar manner as in animals by presenting tetanizing HFS with visual or auditory stimuli instead of electrical stimulation, with plasticity effects assessed using EEG (Cavus et al., 2012; Clapp et al., 2012; D'Souza et al., 2018; Kompus and Westerhausen, 2018; Mears and Spencer, 2012; Normann et al., 2007; Teyler et al., 2005), fMRI (Clapp et al., 2005b; Lahr et al., 2014; Wijtenburg et al., 2017; Zaehle et al., 2007), and behavior (Beste et al., 2011; Clapp et al., 2012). In visual HFS paradigms designed to induce LTP-like neuroplasticity effects using EEG readouts, visual evoked potentials (VEPs) elicited by simple checkerboards or line gratings are recorded prior to HFS and at varying time intervals (e.g., minutes to hours) afterwards. In prior studies, early VEP components including the C1, N1b, and P2, have shown larger amplitudes post- vs. pre-HFS (Cavus et al., 2012; Clapp et al., 2012; Ross et al., 2008; Teyler et al., 2005). Responses after HFS exhibit LTP-like properties including frequency dependence, input specificity, and persistence for at least 1 hour (Clapp et al., 2012; McNair et al., 2006; Ross et al., 2008; Spriggs et al., 2017; Teyler et al., 2005).

To date there have been only four studies of neuroplasticity in schizophrenia using a visual HFS paradigm designed to elicit LTP-like changes (Cavus et al., 2012; D'Souza et al., 2018; Forsyth et al., 2017; Jahshan et al., 2017). Two of these studies directly compared schizophrenia patients to controls; one found no enhancement of VEPs in patients after HFS (Cavus et al., 2012), while the other did show enhancement of VEPs (i.e., an LTP effect) in patients only when administered a 40 mg dose of a glycine transport inhibitor (PF-03463275) (D'Souza et al., 2018). None of the studies in patients examined input specificity, a valuable feature that provides evidence that plasticity effects are tapping into LTP-like processes.

Given the increased interest in neuroplasticity in schizophrenia, the crucial role of neuroplasticity (especially LTP) in the processes of learning and memory, the possibility that these indices may be malleable, and the link of LTP to the NMDA receptor, EEG measures of neuroplasticity are potentially promising biomarkers and endpoints for clinical trials in schizophrenia targeting deficient neuroplasticity. However, before being applied to clinical trials, some basic information is required. First, we need to know whether the paradigm implemented is sensitive to plasticity deficits in people with schizophrenia, since there must be a deficit to improve (or normalize) with intervention. Second, we need to know whether the EEG-based plasticity readouts are reliable enough to track treatment-induced plasticity changes in clinical trials.

In the current study, we evaluated a recently-developed version of a visual neuroplasticity paradigm that includes two types of visual stimuli to assess input specificity. Only one of the visual stimuli is tetanized (i.e., presented at high frequency) to determine whether any plastic changes are specific to that stimulus. This paradigm was developed and implemented in a study of psychosis-risk syndrome participants that is still underway, although an interim data-driven analytic approach showed input-specific plasticity deficits to predict transition to psychosis (Mathalon, 2017). Given the relative novelty of the paradigm, we made no assumptions about which VEP components or time windows would show plasticity effects. Instead, we used a statistically rigorous unbiased data-driven mass univariate analysis approach (Groppe et al., 2011) to discover where and when plasticity effects were evident in the VEPs. First, we used this approach to identify significant spatio-temporal clusters with input specific plasticity effects; resulting clusters were then compared between groups. Next, we used the same approach to identify clusters that showed non-input specific plasticity effects (i.e., present for both the tetanized and non-tetanized stimulus, referred from here on as non-specific plasticity); again, resulting clusters were then compared between groups. Last, we assessed the test-retest reliability of the EEG-based plasticity effects over a two-week interval. These analyses address critical questions regarding the validity and reliability of the visual plasticity paradigm implemented, its sensitivity to neuroplasticity deficits in schizophrenia, and its suitability for use in clinical trials targeting deficient neuroplasticity in schizophrenia.

2. Methods

2.1 Participants

Participants with schizophrenia (n = 44) and healthy controls (n = 30) were recruited from the VA Greater Los Angeles Healthcare System (VAGLAHS), residences in the greater Los Angeles area, and through online ads (e.g., Craigslist). Selection criteria for all participants included: a) age 18 – 60 years; b) understand spoken English sufficiently to comprehend testing procedures; c) no clinically significant neurological disease determined by medical history (e.g., epilepsy); d) no history of serious head injury (i.e., no loss of consciousness > 1 hour, no neuropsychological sequelae, no cognitive rehabilitation post head injury); e) no sedatives or benzodiazepines within 12 hours of testing, and no anticholinergic medications within 48 hours of testing; f) no anticonvulsant medication; g) no alcohol or substance use disorder in past 3 months; and h) corrected vision of at least 20/30. Additional selection criteria for patients included: a) DSM-IV diagnosis of schizophrenia based on structured clinical interview and review of medical records; b) ≥ 3 months since any psychiatric hospitalization; and, c) currently prescribed an antipsychotic medication with no changes in the past 2 months and none anticipated for 1 month. Additional selection criteria for healthy participants included no psychiatric history of: a) a schizophrenia spectrum disorder (including avoidant, paranoid, schizotypal, and schizoid personality disorders); b) borderline personality disorder; and c) other psychotic or recurrent mood disorder.

All participants were required to have a clean urine toxicology test on each day of testing. All participants had the capacity to give informed consent and provided written informed consent in accordance with procedures approved by the Institutional Review Boards at VAGLAHS and the University of California, Los Angeles.

2.2 Clinical Assessments

All clinical interviewers were trained at the Treatment Unit of the VISN 22 Mental Illness Research, Education and Clinical Center (MIRECC) to a minimum kappa of 0.75 for key psychotic and mood items. Patients and controls received a diagnostic interview with the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1997); controls received an additional interview with the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-PD) (First et al., 1996).

To characterize the sample, patients' symptoms were assessed with the UCLA expanded 24-item Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993) and the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013). We examined the total BPRS score as well as the positive symptom subscale of the BPRS (Kopelowicz et al., 2008). We examined the CAINS total expressive and experiential subscale scores (Horan et al., 2011).

2.3 Visual HFS Paradigm

All participants were assessed using the EEG-based visual plasticity paradigm at baseline and at two-week retest. This paradigm involved measurement of VEPs evoked by visual

stimuli before and after tetanizing visual HFS. All stimuli were presented on a 23-inch LCD monitor (1920 × 1080 pixels, 60 Hz refresh rate) located 1 m in front of participants.

The current study implemented a visual HFS paradigm to assess input-specific LTP-like visual cortical plasticity (Mathalon, 2017). Examples of the stimuli and the sequence of VEP assessments are shown in Figure 1. VEPs were assessed in four 6-minute runs: 12 and 6 minutes before HFS (pre-HFS) and 30 and 36 minutes after HFS (post-HFS). Each run included 266 trials in which participants were shown vertical and horizontal line gratings (133 of each). The dark and light stripes were reversed on every other presentation to minimize adaptation effects. Stimuli were presented at an ITI of 1067–1333 ms (1200 ms average) for variable durations (ranging from 250–500 ms, with an average duration of 375 ms) to minimize the influence of offset potentials on the VEPs. On 90.2% of the trials, the line gratings were presented with 35% contrast; on the remaining trials, contrast was set to 72%. To ensure that participants were paying attention during the task, they were instructed to push a button on a game controller whenever they saw the infrequent higher contrast gratings.

After the two pre-HFS VEP runs, HFS was administered. In HFS, stimuli were rapidly presented at 10 Hz for 5 s, followed by a 5 s blank screen, and this sequence was repeated for 4 minutes. To assess input specificity of any HFS-induced plasticity effects, participants were randomly assigned to receive HFS with only one of the two line grating orientations (i.e., vertical or horizontal). This participant-specific orientation was used for both the baseline and two-week follow-up assessments. As with the VEP runs, participants were instructed to push a button on a game controller when they saw the infrequent higher contrast stimulus. After HFS, participants were instructed to sit quietly with their eyes closed for 2 minutes before starting an unrelated 30-minute somatosensory oddball task with concurrent passive auditory tone presentations.

For analysis, to assess for input-specific effects, VEPs were averaged separately for pre- and post-HFS VEP runs (collapsing across the two runs for each) and for tetanized (i.e., line orientation used in HFS) and non-tetanized (i.e., line orientation not used in HFS) stimuli. We also examined for general plasticity effects (i.e., examining for plasticity effects that generalized to both tetanized and non-tetanized stimuli) by averaging over tetanized and non-tetanized stimuli.

2.4 EEG Acquisition and Processing

Continuous EEG was recorded using a custom electrode cap (Cortech Solutions, Wilmington, North Carolina, USA) and an ActiveTwo BioSemi amplifier (BioSemi, Amsterdam, Netherlands). EEG data were processed in BrainVision Analyzer 2 (Brain Products, Munich, Germany) and with custom-written Matlab scripts (Mathworks, Natick, MA) similar to prior ERP studies (Kort et al., 2017) using the Fully Automated Statistical Thresholding for EEG artifact Rejection (FASTER) Matlab toolbox (Nolan et al., 2010) and EEGLab (Delorme and Makeig, 2004). The median number of rejected trials from each condition (pre-HFS, post-HFS; tetanized, non-tetanized) was seven. See Supplemental Methods for further details on data acquisition, cleaning and processing.

After data cleaning, epochs were extracted from −100 to 500 ms, time-locked to the onset of the visual stimulus, and baseline corrected using the −100 to 0 ms baseline. VEP average waveforms were produced using trimmed means which excluded the top and bottom 10% of single trial values at every data sample in each epoch before averaging (Leonowicz et al., 2005). VEP waveforms were then low-pass filtered at 50 Hz and re-referenced to an average reference.

2.5 Data Analyses

First, we conducted cluster-based permutation analyses (Groppe et al., 2011; Luck, 2014) of VEP difference waves (Luck, 2014; Vogel et al., 1998) from the baseline session to determine whether there were input-specific plasticity effects (i.e., plasticity to tetanized vs. non-tetanized stimuli). We also examined for general effects of HFS (i.e., plasticity effect averaged over tetanized and non-tetanized stimuli) only if the resulting cluster did not substantially overlap with the input-specific interaction cluster. For input-specific effects, we calculated primary difference waves (i.e., post-HFS minus pre-HFS VEP, referred to as ΔVEP) and then secondary difference waves between tetanized and non-tetanized primary differences waves (ΔVEP-tetanized minus ΔVEP-non-tetanized). This corresponds to a HFS (post vs. pre) x Tetanization (tetanized vs. non-tetanized) interaction effect. For general effects, we examined the ΔVEP difference waves averaged over tetanized and non-tetanized conditions. This corresponds to a main effect of HFS (post vs. pre). By using primary difference waves, or secondary difference waves, these main effects and interactions are reformulated as simple one-sample t-test, which are calculated at each time point and electrode.

For the cluster-based permutation tests, we used a cluster mass statistic (Bullmore et al., 1999) with a family-wise alpha level of 0.05, based on the one-sample t-tests conducted on the difference waves. As recommended (Groppe et al., 2011; Luck, 2014) and done previously (Jahshan et al., 2017), data were down-sampled to 128 Hz, and all time points between 50 and 252 ms (26 time points) at 20 parieto-occipital scalp electrodes (P1, P2, P3, P4, P5, P6, P7, P8, P9, P10, PO3, PO4, PO7, PO8, O1, O2, Pz, POz, Oz, Iz) were included (i.e., 520 total comparisons). The results are depicted as a raster diagram highlighting in color the time points and electrodes belonging to a significant cluster.

For any significant input-specific effects or general effects spatio-temporal clusters identified from the permutation testing, mean microvolt values from all time points and electrodes in the cluster were extracted separately from the VEP waveforms for post-HFS and pre-HFS assessments, and for input-specific plasticity effects tetanized and non-tetanized stimuli. Subsequently, these mean cluster values were entered into mixed model ANOVAs with fixed effects of Group (SZ, HC), HFS (post-HFS, pre-HFS), and Tetanization (tetanized, non-tetanized) only for input-specific effects, with Subject specified as a random effect. In these models, we were only interested in significant interactions with Group, indicating patient-control differences in plasticity, as tests of plasticity effects across groups were redundant with the permutation tests used to identify the clusters.

In addition to testing for Group differences, for any significant clusters showing input-specific effects or general effects in baseline data we also extracted mean VEP data from

Time 2 data (based on the baseline data cluster analyses). We then examined two-week test-retest reliability by examining intraclass correlation coefficients (ICCs) and their 95% confidence intervals (CIs) using two-way (person × time), mixed-effects models with the measure type being consistency on the relevant difference scores for the input-specific and general effects.

3. Results

3.1 Demographic and Clinical Characteristics

Six SZ and 3 HC participants were excluded due to excessive (> 25%) bad electrodes or not returning for the follow-up assessment. Thus, a total of 38 SZ and 27 HC were ultimately included in the analyses. The demographic and clinical characteristics of the final sample can be seen in Table 1. There were no significant between-group differences in age, gender, or parental education; however, SZ had significantly lower personal education compared to HC. The patients had mild to moderate levels of symptoms as assessed by the BPRS and CAINS. Most patients were on clinically-determined doses of antipsychotic medications (35 atypical, 1 typical, 1 no medication, 1 missing).

3.2 Cluster-Based Permutation Results

Regarding input-specific plasticity effects, a significant cluster emerged showing greater negativity post- vs. pre-HFS for tetanized vs. non-tetanized stimuli between 108–183 ms at all analyzed electrodes except P9 and PO4 (cluster $p < 0.05$). The difference waveforms, topographic map, and raster diagram for this cluster are shown in Figure 2a and 2b. Constituent VEP waveforms are shown in Supplemental Figure 1. As can be seen by the plot of the means (Figure 2c), there was significantly more negativity to the tetanized stimuli after HFS ($t_{64} = 2.73$, $p = 0.008$), and a non-significant increase in positivity for the non-tetanized stimulus ($t_{64} = -1.84$, $p = 0.070$) across the two groups. However, the Group × Post-Pre HFS × Tetanization interaction was not significant, $F_{1,63} = 0.80$, $p > 0.37$, indicating comparable input-specific plasticity effects across the groups. We also found an unexpected significant difference in amplitude between tetanized and non-tetanized stimuli pre-HFS ($t_{64} = -3.22$, $p = 0.002$) in both SZ and HC.

Regarding general effects of plasticity, a significant cluster emerged showing greater positivity post-HFS, relative to pre-HFS, that extended from approximately 173–252 ms over several parieto-occipital electrodes mainly over the right hemisphere (P1, P3, PO3, Oz, POz, P2, P4, P6, P8, P10, PO8, PO4, O2). This showed little overlap with the input specific cluster; as it didn't particularly overlap, we view this as a legitimate effect that was not further modified by an interaction with tetanization. The difference waveform and its constituent VEP waveforms, topographic map, and raster diagram for this cluster are shown in Figure 3a and 3b. When the extracted mean VEP amplitudes for this cluster for post-HFS and pre-HFS assessments (Figure 3c) were analyzed in a mixed model ANOVA, the Group × Post-Pre HFS interaction was not significant ($p > 0.85$), again indicating that this non-specific plasticity effect was comparable across the groups.

Descriptive statistics for all constituent VEPs (i.e., non-difference waves) averaged over the relevant time windows and electrodes contributing to the significant input-specific and non-specific clusters are presented in Supplemental Tables 1 and 2.

3.3 Test-Retest Reliability

For test-retest reliability of the input specificity effects (Table 2), the ICCs for ΔVEP – Tetanized-Non-tetanized were modest when examined across groups (ICC = 0.39), modest within SZ (ICC = 0.33), and fair within HC (ICC = 0.43). It should be noted that the pre-HFS and post-HFS VEP amplitude values were highly correlated (see Supplemental Table 3), and this positive covariance can substantially reduce variability in the difference scores, likely contributing to the modest test-retest reliability of these difference scores (Furr and Bacharach, 2013). Consistent with this notion, ICCs to the constituent VEPs pre- and post-HFS were good to excellent in SZ (0.79–0.91) and HC (0.79–0.87).

For test-retest reliability of the general effect of plasticity (Table 2), the ICCs for ΔVEP were modest when examined across groups (ICC = 0.40), fair within SZ (ICC = 0.405), and low within HC (ICC = 0.29). As with above, ICCs to constituent VEPs pre- and post-HFS were good to excellent in SZ (0.85–0.88) and moderate in HC (0.57–0.63).

4. Discussion

In the current study, we demonstrated an input-specific neuroplasticity effect assessed with a visual HFS paradigm using an EEG-based VEP readout in a combined sample of SZ patients and HC. The groups, however, did not differ from each other. Additionally, we identified a more spatially circumscribed cluster in a later time window that showed a non-specific plasticity effect (i.e., evident in VEPs averaged over tetanized and non-tetanized stimuli), and this effect was also comparable across groups. Reliability was modest to fair in both groups for input-specific and non-specific plasticity effects. These results demonstrate that input-specific LTP-like plasticity can be assessed *in vivo* in both SZ and HC, but we failed to find a plasticity deficit in the SZ patients relative to the HC with the particular version of the visual HFS paradigm tested here.

Demonstration of an input-specific visual cortical plasticity effect following visual HFS strengthens the argument that the plasticity assessed is related to LTP (Clapp et al., 2012). The input-specific changes to the stimulus-locked VEPs occurred between 108–183 ms at scalp regions overlying primary visual and visual association cortices and they remained up to 36 minutes after stimulation. It is also important to note that the plasticity effects did not carry over to the pre-HFS stimuli at the two-week follow-up in that there were no significant differences between tetanized pre-HFS stimuli at baseline vs. follow-up ($F_{1,63} = 2.25$, $p = 0.139$). This lack of carry-over effect suggests that the paradigm would have use in clinical trials as the plasticity effects at baseline do not persist over a two-week span. An input-specific plasticity effect around 150 ms across a wide range of parietal-occipital electrodes is consistent with the latency, topography, and direction of multiple previous reports of LTP-like plasticity in VEPs following HFS in healthy individuals (Cavus et al., 2012; Clapp et al., 2005a; McNair et al., 2006; Ross et al., 2008). Interestingly, a similar input-specific spatio-temporal cluster emerged using the same visual HFS paradigm as used in the current study

in an interim analysis of individuals with the psychosis risk syndrome (PRS) and healthy controls, and deficits in this input-specific plasticity effect were found to predict future transition to psychosis among the PRS participants (Mathalon, 2017). In contrast, using the current visual HFS paradigm, we did not replicate LTP-like visual cortical plasticity deficits in schizophrenia (Cavus et al., 2012). Indeed, our results represent the first demonstration of intact input-specific LTP-like plasticity effects in schizophrenia patients.

A non-specific visual cortical plasticity effect was also evident in response to both tetanized and non-tetanized stimuli in a 173–252 ms temporal window of the VEP waveforms in parieto-occipital electrodes mainly over the right hemisphere. This effect was present in both controls and patients, again failing to support the hypothesis that SZ patients would have plasticity deficits relative to HC. Interestingly, the increased positivity following HFS in this spatio-temporal cluster occurred in a similar time window to the post-HFS increase in positivity for the VEP P2 component observed in a prior visual cortical plasticity study using a checkerboard stimulus in healthy subjects (Forsyth et al, 2015), and in schizophrenia patients (Forsyth et al, 2017). The fact that an effect in a similar temporal window occurred in response to both the tetanized and non-tetanized stimulus raises the possibility that this relatively late VEP amplitude increase might reflect the latter, rather than the former. This non-specific plasticity effect may reflect the fact that the tetanized and non-tetanized stimuli shared some visual features (e.g., spatial frequency, gray/white color alternation) that are likely processed by the same visual cortical neurons, creating some potential for neurons tetanized by one of the stimuli to show a potentiated response to both stimuli. Since this effect was evident for both the tetanized and non-tetanized stimulus, we cannot rule out the possibility that the increased positivity arose from the repetition of the VEP assessments themselves, or even from the passage of time alone.

The lack of patient-control differences is inconsistent with the only other study to find LTP deficits in schizophrenia compared to controls, in which a different LTP paradigm was used (Cavus et al., 2012). A couple of differences in the paradigms may account for this inconsistency. First, the current study used two line-grating stimuli presented at less than 100% contrast, whereas the prior studies presented a single checkerboard stimulus at 100% contrast. Second, the prior studies used a 2-minute HFS block with stimuli continuously presented at ~9 Hz, whereas we utilized a 4-minute HFS block with stimuli presented at 10 Hz in alternating 5s on/5 s off intervals.

The input-specific visual plasticity effect exhibited modest test-retest reliability, likely due to both limited person variance in the VEP Pre-Post HFS Tetanized vs. Non-tetanized double difference scores, as well as strong correlations between the constituent VEPs from which these difference scores are derived. Similarly, the non-specific reliability effects exhibited modest test-retest reliability. The modest reliability, the paradigm’s lack of sensitivity to presumed plasticity deficits in schizophrenia, and both input and non-input specific plasticity effects suggest that this particular visual HFS paradigm would not serve as a useful outcome measure in clinical trials aiming to ameliorate neuroplasticity impairments in schizophrenia. However, it could be argued that for clinical trials any positive change in LTP in people with schizophrenia, even in the absence of a baseline “deficit” (as seen in the current study), would indicate clinical utility. While our finding of an input specific plasticity effect with the

current paradigm is encouraging, there is still a considerably large parameter space that needs to be systematically investigated (e.g., type of visual stimuli used, contrast levels, rate, pattern, and duration of high frequency stimulation) before an optimum visual LTP-like plasticity paradigm is ready for widespread use in clinical research, including clinical trials.

There are several limitations to the study. First, in contrast to the prior studies in schizophrenia, we did not include an early post-HFS VEP assessment block due to the possibility that the lower-frequency stimulation used to assess VEPs could result in long-term depotentiation (LTD) (Barr et al., 1995; Huang et al., 2001; Teyler et al., 2005). Instead, we assessed VEPs a minimum of 30 minutes after HFS, avoiding potential depotentiation induced by the VEP assessments themselves but foregoing the opportunity to assess early post-HFS plasticity effects. Similarly, we did not examine long-term plasticity at blocks extending out to an hour after HFS, leaving open the possibility that the input specific plasticity effects we detected would not have persisted. Second, we only assessed visual neuroplasticity, and did not assess neuroplasticity of other cortical processes (e.g., auditory processing, motor, etc.). Third, we utilized tetanization based on presenting visual stimuli at high frequency. However, visual stimulation at a lower frequency but longer duration (e.g., 2 Hz for 10 minutes; e.g., (Normann et al., 2007) have also been used to induce LTP-like neuroplastic changes in VEP studies. Finally, as our patients were all medicated, it is difficult to determine if the plasticity deficits were influenced by antipsychotic medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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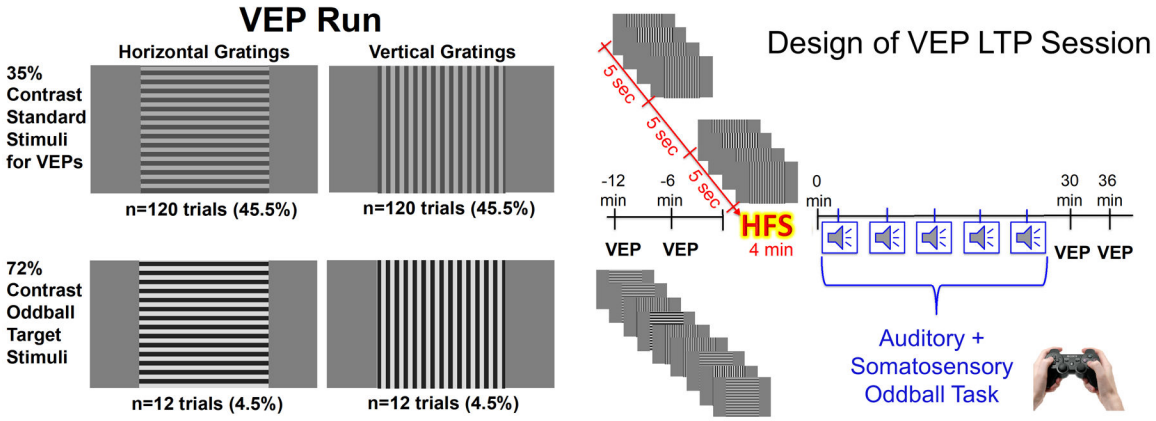

Figure 1.

Example of stimuli and sequence of events of the visual high-frequency stimulation (HFS) paradigm. Low and high-contrast horizontal or vertical line gratings are presented 6 and 12 minutes prior and 30 and 36 minutes after HFS in visual evoked potential (VEP) runs. During HFS, only one orientation line grating (i.e., only vertical or horizontal) is presented at 10 Hz for 5 seconds, followed by a blank screen for 5 s. This HFS pattern is presented for a total of 4 minutes. During all VEP assessments and HFS participants are instructed to push a button on a game controller whenever they see a high-contrast stimulus. After the HFS block, an unrelated auditory and somatosensory oddball task is presented for 30 minutes.

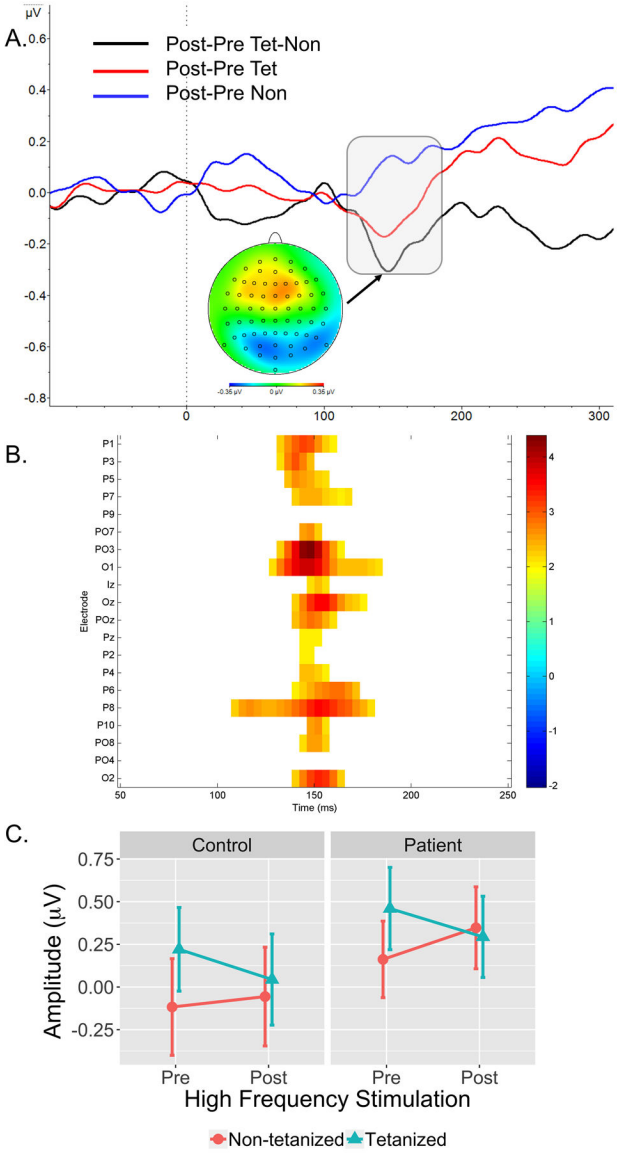

Figure 2.

Input specificity effects for Time 1. (A) Grand average post – pre HFS ΔVEP waveforms (at pooled parietal, parieto-occipital, and occipital electrodes) to tetanized (red) and non-tetanized (blue) stimuli, and the post – pre tetanized – non-tetanized HFS difference wave (black). (B) Raster plot of significant post – pre tetanized – non-tetanized HFS differences. Color bar represents t-values that survive correction; non-significant values are shown in white. (C) Mean (+/− 1 standard error) amplitudes for controls (left panel) and patients (right panel) for tetanized (blue) and non-tetanized (red) stimuli pre and post high frequency stimulation.

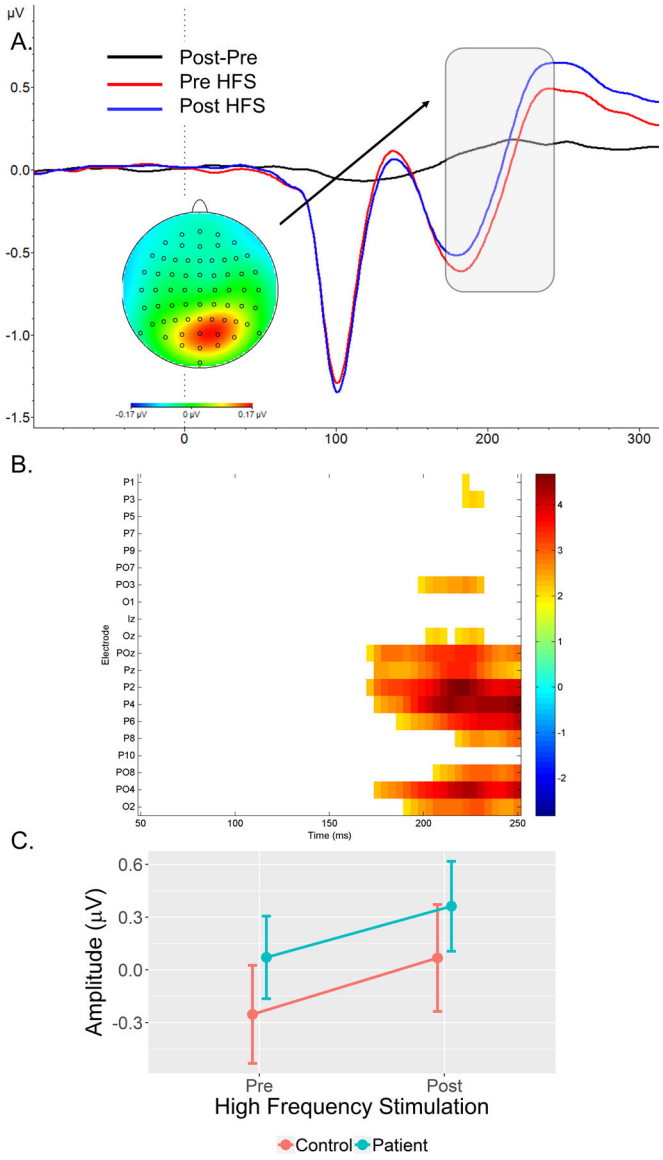

Figure 3.

Non-specific plasticity effects for Time 1. (A) Grand average post – pre ΔVEP waveforms for pre-HFS (red) and post-HFS (blue), and the post-pre HFS difference wave (black). (B) Raster plot of significant HFS differences. Color bar represents t-values that survive correction; non-significant values are shown in white. (C) Mean (+/− 1 standard error) VEP amplitudes for pre-HFS and post-HFS for patients (blue) and controls (red).

Table 1:

Demographics and clinical characteristics.

	Patients (n = 38)	Controls (n = 27)
Age	47.6 (9.9)	45.4 (8.3)
Gender (F:M)	13:25	10:17
Personal Education *	12.4 (2.0)	14.9 (1.5)
Parental Education	13.1 (4.4)	14.9 (2.8)
BPRS		
Total	41.7 (10.4)	
Positive	2.1 (1.0)	
Negative	2.1 (1.1)	
Agitation/Mania	1.3 (0.4)	
Depression	1.7 (0.6)	
CAINS		
Motivation/Pleasure	14.9 (5.5)	
Expressiveness	4.6 (4.1)	

* $p < 0.05$

Table 2:

Intraclass correlation coefficients (95% confidence interval) of ΔVEPs (post minus pre HFS) for input specific and non-input specific effects between baseline and 2-week follow-up separately for schizophrenia patients and healthy controls.

	Schizophrenia Patients	Healthy Controls
Input Specific		
ΔVEP – Tetanized	0.262 (−0.06 – 0.53)	−0.039 (−0.41 – 0.34)
ΔVEP – Non-tetanized	0.390 (0.09 – 0.63)	0.344 (−0.03 – 0.64)
ΔVEP – Tet-Non	0.333 (0.02 – 0.59)	0.429 (0.07 – 0.69)
Non-Input Specific		
ΔVEP	0.452 (0.16 – 0.67)	0.289 (−0.10 – 0.60)