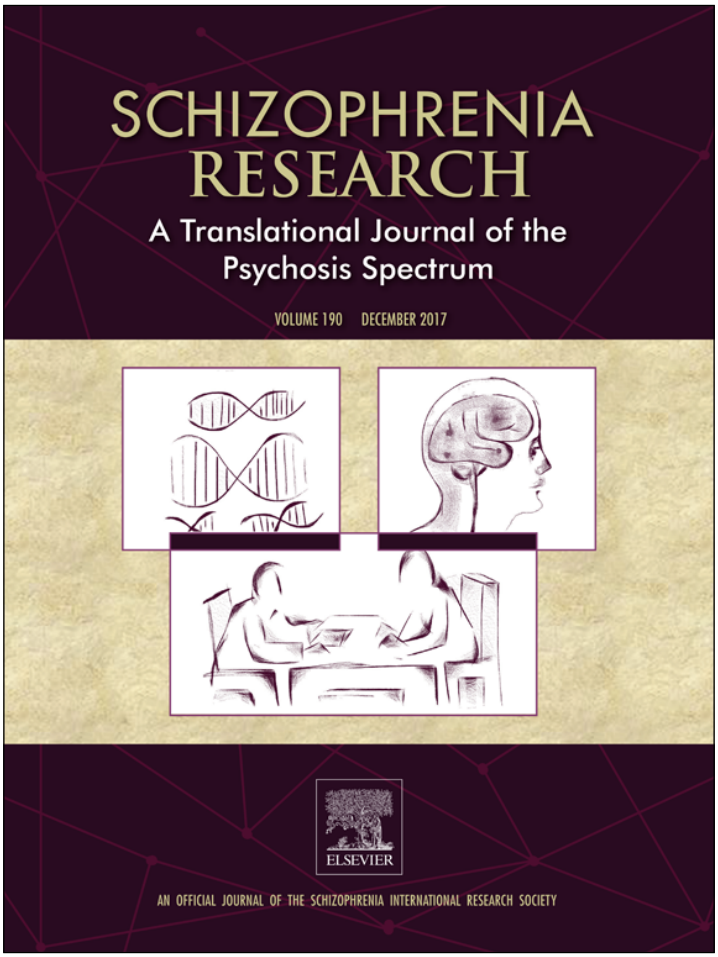

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Cognitive correlates of visual neural plasticity in schizophrenia

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ABSTRACT

Neuroplasticity may be an important treatment target to improve the cognitive deficits in schizophrenia (SZ). Yet, it is poorly understood and difficult to assess. Recently, a visual high-frequency stimulation (HFS) paradigm that potentiates electroencephalography (EEG)-based visual evoked potentials (VEP) has been developed to assess neural plasticity in the visual cortex. Using this paradigm, we examined visual plasticity in SZ patients ($N = 64$) and its correlations with clinical symptoms, neurocognition, functional capacity, and community functioning. VEPs were assessed prior to (baseline), and 2-, 4-, and 20-min after (Post-1, Post-2, and Post-3, respectively) 2 min of visual HFS. Cluster-based permutation tests were conducted to identify time points and electrodes at which VEP amplitudes were significantly different after HFS. Compared to baseline, there was increased negativity between 140 and 227 ms for the early post-HFS block (average of Post-1 and Post-2), and increased positivity between 180 and 281 ms for the late post-HFS block (Post-3), at parieto-occipital and occipital electrodes. The increased negativity in the early post-HFS block did not correlate with any of the measures, whereas increased positivity in the late post-HFS block correlated with better neurocognitive performance. Results suggest that SZ patients exhibit both short- and long-term plasticity. The long-term plasticity effect, which was present 22 min after HFS, was evident relatively late in the VEP, suggesting that neuroplastic changes in higher-order visual association areas, rather than earlier short-term changes in primary and secondary visual cortex, may be particularly important for the maintenance of neurocognitive function in SZ.

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1. Introduction

Altered neuroplasticity has been implicated in the pathophysiology of schizophrenia and is thought to contribute to the cognitive deficits associated with the illness (Stephan et al. 2009). Neuroplasticity is the brain's capacity to alter its structure and function in response to new experiences or changes in the environment. Synaptic plasticity, one type of neuroplasticity, refers to the adjustment of synaptic strength in networks of connected neurons and includes both short-term plasticity and long-term potentiation (LTP) (Bliss and Collingridge 1993). Short-term plasticity is achieved through the temporary enhancement of a synaptic connection, which quickly returns to its initial state after tens of milliseconds to a few minutes (Ohno et al. 2011). LTP involves a more durable increase in the strength of excitatory synaptic transmission, lasting minutes to hours, and is considered to be the leading candidate cellular mechanism underlying learning and memory (Bliss and Collingridge 1993; Cooke and Bliss 2006). Although some cognitive training studies have demonstrated improvements in neurocognitive functioning in schizophrenia patients on average (McGurk et al. 2007; Twamley et al. 2003), responses to training are quite variable (Corbera et al. 2016; Wykes et al. 2011). The degree to which neurocognition improves following a cognitive remediation intervention in patients with schizophrenia may depend on the integrity of their synaptic plasticity mechanisms. Accordingly, understanding the nature of neuroplasticity dysfunction in schizophrenia may shed light on the neural processes underlying impaired cognition.

To date, it has been difficult to study basic mechanisms of neuroplasticity in vivo in humans, although it has been studied extensively at the cellular and molecular level in animals (Clapp et al. 2012; Cooke and Bear 2012; Fox 2002; Heynen and Bear 2001; Kandel et al. 2013; Komatsu et al. 1981). Investigation of neuroplasticity in humans was therefore limited to examining post-mortem cortical tissue (e.g., Duric et al. 2013; Knable et al. 2002) and intracranial electroencephalographic (EEG) recordings (e.g., Matsuzaki et al., 2012). Recently, novel repetitive sensory stimulation paradigms using scalp-recorded EEG readouts have been developed to noninvasively assess neural plasticity

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in humans. Similar to electrical stimulation in animals (Heynen and Bear 2001), tetanizing visual or auditory high frequency stimulation (HFS) can induce repetitive synchronous afferent activity resulting in LTP-like effects (Çavuş et al. 2012; Clapp et al. 2005a, 2005b, 2012; McNair et al. 2006; Mears and Spencer 2012; Ross et al. 2008; Teyler et al. 2005). LTP from rapid sensory stimulation has similar characteristics to synaptic LTP in animal models, including persistence, input specificity, and frequency dependence (Clapp et al. 2012), as well as dependence on glutamatergic neurotransmission at NMDA receptors (Forsyth et al. 2015). Aside from a critical role of NMDA receptors in the induction of LTP, there is extensive evidence for deficient NMDA receptor functioning in schizophrenia (e.g., Olney and Farber 1995; Paz et al. 2008; Pilowsky et al. 2006). For example, NMDA antagonists can induce schizophrenia-like symptoms and neurocognitive deficits in healthy individuals (Krystal et al. 2003). Hence, plasticity impairments are predicted in patients.

In schizophrenia, there has been a single published report utilizing rapid sensory stimulation to examine neural plasticity of the visual cortex (Çavuş et al. 2012). Visual plasticity was assessed by examining amplitude changes in the visual evoked potential (VEP) elicited by a checkerboard stimulus after it was presented at a high frequency. Using this paradigm and other similar paradigms, healthy controls exhibited an enhancement of early VEP components, including the C1 component that peaked at about 100 ms and the N1b component evident between 140 and 180 ms post-stimulus onset (Çavuş et al. 2012; McNair et al. 2006; Ross et al. 2008; Teyler et al. 2005) that persisted up to 22 min after HFS. Çavuş et al. (2012) found that relative to the more enduring potentiation induced in healthy controls, visual HFS induced only short-term potentiation of the N1b (i.e., up to 6 min after HFS) and no potentiation of the C1 in patients, consistent with deficient visual plasticity in schizophrenia. However, their sample size was relatively modest ($n = 19$) and correlates with important external variables (e.g., cognition, functional outcomes) were not explored.

In the current study, we examined visual neural plasticity in a relatively large sample of schizophrenia patients using the same paradigm as Çavuş et al. (2012). We used a different analytic approach based on difference waves that was intended to better capture plasticity effects with fewer assumptions about the neural changes reflecting potentiation or depotentiation of specific VEP components (Luck 2014). Although there is a distinction between LTP and long-term depression (LTD), we believe it is best to refer to these changes more generally as "plasticity" effects until the field develops more precise criteria for ERP-determined potentiation or depotentiation. The data presented are from a baseline assessment of people with schizophrenia who were participating in an ongoing randomized controlled trial of cognitive training. We investigated the neurocognitive, functional, and clinical correlates of visual neuroplasticity. We hypothesized that larger amplitude changes in the VEP after HFS, reflecting more intact neuroplasticity mechanisms, would be associated with better neurocognitive performance and community functioning. Exploratory analyses of the potential correlations with clinical variables were also conducted.

2. Method

2.1. Participants

The sample consisted of 64 patients diagnosed with schizophrenia ($n = 57$) or schizoaffective disorder ($n = 7$) recruited from VA outpatient clinics and board-and-care residences in the community. They were considered to be clinically stable based on: no medication changes in the past six weeks, no psychiatric hospitalization in the past three months, and no changes in housing in the past two months. Exclusion criteria included having an estimated premorbid IQ below 70 based on reading ability, having an identifiable neurological disorder, seizures, or history of serious head injury, meeting criteria for substance dependence in the past 6 months or abuse in the past month, or being insufficiently fluent in English as determined by the participant's ability to understand the consent form.

All subjects received a diagnostic interview with the Structured Clinical Interview for DSM-IV (SCID-I; First et al. 1997) to confirm diagnosis and eligibility. The SCID-I was conducted by interviewers trained to reliability through the Treatment Unit of the Department of Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center (MIRECC) based on established procedures (Ventura et al. 1998). Positive and negative symptoms were evaluated using the expanded 24-item UCLA version of the Brief Psychiatric Rating Scale (BPRS; Ventura et al. 1993) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984), respectively. Demographics, medication information, and symptom ratings are shown in Table 1.

2.2. Measures

2.2.1. Visual HFS paradigm

Subjects viewed visual stimuli presented centrally against a white background on a 15-in. computer screen located 1 m in front of them. Each 2-min VEP assessment block consisted of a pseudorandom oddball sequence of 90% standard (black and white circular checkerboard) and 10% target (blue and white square checkerboard) stimuli (duration 33 ms) presented at 0.83 Hz (1216 ms mean stimulus-onset asynchrony, range 1075–1340 ms). The infrequent target stimuli, to which subjects were required to respond with a right-handed button press on a keypad, were included to ensure that subjects remained attentive throughout each VEP assessment block. VEPs elicited by the standard circular checkerboard were compared before and after HFS with the same checkerboard stimulus. Two VEP assessment blocks were administered before HFS and averaged to derive the Baseline VEP. Three VEP assessment blocks were administered 2 min (Post-1), 4 min (Post-2), and 20 min (Post-3) after HFS. Post-1 and Post-2 blocks were combined to form an early post-HFS block, while the single Post-3 assessment constituted a late post-HFS block. The 2-min HFS block involved repeated presentation of the standard circular checkerboard at 8.87 Hz, which is below the perceptual flicker-fusion threshold. An unrelated auditory task, a mismatch negativity (MMN) paradigm, was administered in the 20-min interval between the early and late post-HFS VEP blocks. During the MMN paradigm, subjects watched a silent movie (Fig. 1).

2.2.2. EEG recording and analysis

EEG recordings were acquired with a BioSemi ActiveTwo amplifier and a 64-channel electrode cap spatially distributed according to the international 10–20 system (Biosemi B. V., Amsterdam, Netherlands). Additional electrodes were placed above and below the left eye and at

Table 1
Demographics, clinical characteristics and behavioral performance.

	Mean (SD) $N = 64$
Age	51.53 (9.10)
Education	12.69 (1.87)
Parental education	12.42 (2.86)
Male	90.6%
African Americans	49.2%
Duration of illness	22.32 (6.51)
Total hospitalizations	7.81 (9.03)
BPRS total	40.56 (9.03)
SANS total	31.90 (15.31)
Atypical antipsychotics	71.9%
Typical antipsychotics	17.2%
Both types	4.7%
No antipsychotics	4.7%
Missing	1.5%
MCCB composite	40.20 (7.69)
UPSA total	74.36 (12.77)
RFS total	17.56 (4.24)

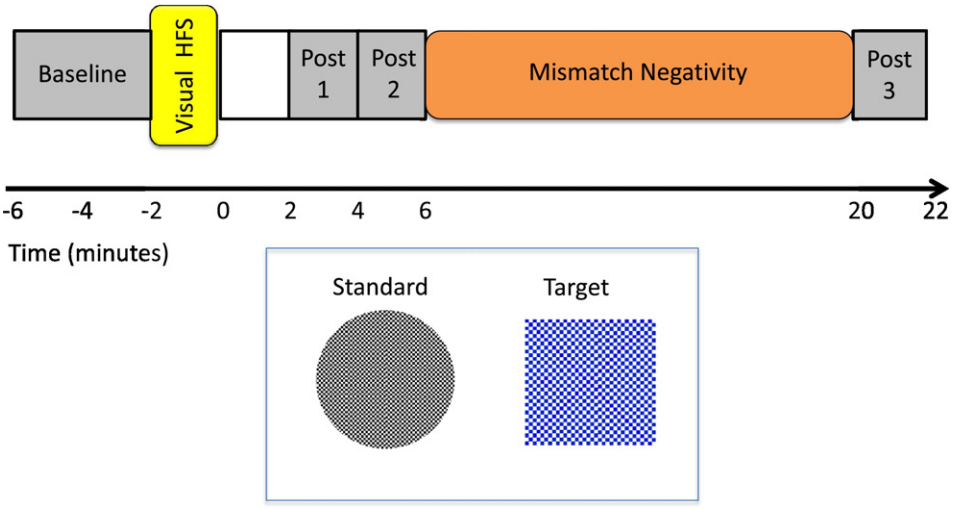

Fig. 1. Stimuli and timeline of the visual high-frequency stimulation (HFS) paradigm: A standard circular black and white checkerboard stimulus (8 cm diameter, subtending 8° of visual angle, each check subtending 0.3°) was presented during baseline, visual HFS, and post-HFS blocks. A target square blue and white checkerboard stimulus (9 × 9 cm, subtending 9° of visual angle, each check subtended 0.5°) was presented infrequently during baseline and post-HFS blocks. A passive auditory oddball task, the mismatch negativity, was administered between Post-2 and Post-3. Post-1 = 2 to 4 min after HFS; Post-2 = 4 to 6 min after HFS; Post-3 = 20 to 22 min after HFS.

the outer canthi of both eyes to record the vertical and horizontal electro-oculogram (VEOG, HEOG) used to monitor blinks and eye movements. Each active electrode was measured online with respect to a common mode sense electrode during data collection, forming a monopolar channel. Data were sampled at 1024 Hz and re-referenced offline to Fz. ERP data processing was performed using BrainVision Analyzer 2 (Brain Products, Gilching, Germany). A high-pass filter at 0.1 Hz (zero phase shift, 24 dB/octave rolloff) was applied to the raw continuous EEG data. Bad electrodes were removed from the recording and a spherical spline interpolation was used to recreate the electrode (Perrin et al. 1989; Picton et al. 2000). VEOG and HEOG eye movement and blink activity were removed from the EEG data using a regression-based algorithm (Gratton et al., 1983). Data were low-pass filtered at 20 Hz (24 dB/octave) and 600 ms (−100 to 500 ms) epochs were extracted, time-locked to the standard checkerboard onsets. Data were then baseline corrected to the average of the prestimulus interval and epochs that contained activity exceeding ±75 μV at any electrode were automatically rejected. Trials were then averaged separately for each of the VEP assessment blocks, generating VEP waveforms. The grand average VEP waveforms and topographical maps elicited by the standard checkerboard at baseline, early post-HFS (average of Post-1 and Post-2), and late post-HFS (Post-3) are shown in Figs. 2 and 3, respectively.

In order to identify plasticity effects, we focused on examining difference waves, comparing VEPs before and after HFS. Use of difference waves is recommended to identify time windows of interest when there are no a priori expectations for effects on specific evoked potential components, and when changes in amplitude during particular time windows might be *superimposed* on well-defined VEP components (Vogel et al. 1998; Luck 2014). Difference waves were generated for each participant by subtracting the baseline VEP from each of the post-HFS VEPs and t-scores were computed for the difference at every

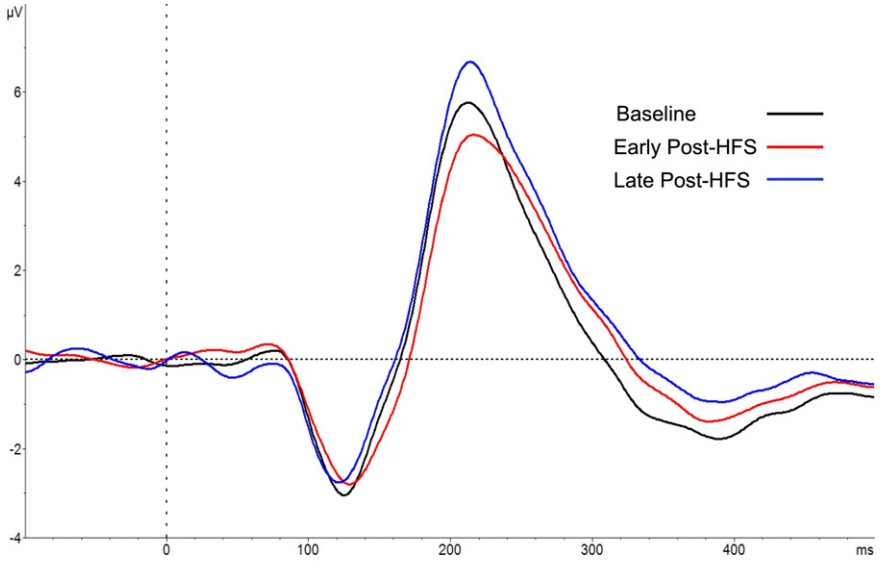

Fig. 2. Grand average VEP waveforms (at pooled parietal, parieto-occipital, and occipital electrodes) elicited by the standard circle at baseline, early post-HFS (2 to 6 min) and late post-HFS (20 to 22 min) following high-frequency stimulation.

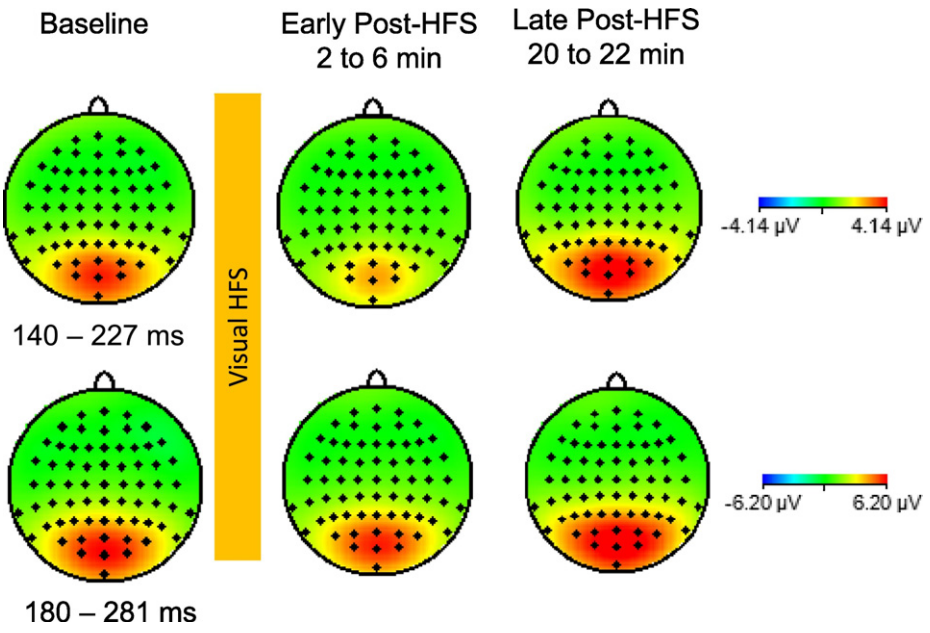

Fig. 3. Topographical maps of the baseline, early post-HFS, and late post-HFS VEP blocks in the early (140–227 ms) and late (180–281 ms) time windows.

time point and electrode. In order to detect significant differences between the pre- and post-HFS blocks, we performed mass univariate analyses utilizing a cluster-based permutation test (Groppe et al. 2011; Woolrich et al. 2009). This approach corrects for multiple comparisons and yields temporal-spatial clusters for analysis.

Based on recommendations by Luck (2014), data were down-sampled to 128 Hz (for the mass univariate analysis only), and analyses were restricted to parietal, parieto-occipital and occipital electrodes between a time window of 50–400 ms. By using these constraints, we were able to increase our power to detect real significant differences in time windows and electrodes where we would reasonably expect to see effects. A cluster-based permutation ($n = 5000$ permutations) was then performed on *t*-tests exceeding an uncorrected threshold of $p < 0.05$. A cluster was formed based on either two electrodes showing a significant effect at a particular time point or two or more consecutive time points showing a significant effect at a single electrode. We imposed a further constraint on identifying the beginning of a time window by stating that at least two electrodes with significant effects were necessary. The analysis provides a figure in the form of a raster diagram highlighting in colour time points and electrodes belonging to a significant cluster. The time window and electrodes identified as a significant cluster were then applied to the VEPs to calculate mean activity for use in correlations.

2.2.3. Neurocognitive and functional measures

We assessed neurocognition with the MATRICS Consensus Cognitive Battery (MCCB; Kern et al. 2008; Nuechterlein et al. 2008). The MCCB includes 10 tests measuring 6 cognitive domains (speed of processing, attention/vigilance, working memory, verbal memory, visual memory, reasoning and problem solving) and a social cognitive domain. Standardized T-scores for each domain were computed as well as a composite score based on the average of the T-scores from the 6 cognitive domains.

The UCSD Performance-based Skills Assessment (UPSA; Patterson et al. 2001) was administered to evaluate 5 skill areas that are considered essential to functioning in the community (general organization, finance, social/communications, transportation, household chores). The UPSA involves role-play tasks with props that are performed in the laboratory as simulations of situations that the person is likely to encounter in the community.

The Role Functioning Scale (RFS; Goodman et al. 1993) was also used to assess patients' functioning in the past month. It includes 4 domains of functioning (working productivity, independent living, social and family relationships). Ratings are based on a semi-structured interview with standardized probe questions. Higher MCCB, UPSA, and RFS scores indicate better functioning. Mean (SD) performance on each of these measures can be seen in Table 1.

2.3. Statistical analyses

Means and standard deviations of the VEP amplitudes for each post-HFS assessment vs. baseline in the time windows and at the pooled electrodes identified with the mass univariate analyses were calculated. Next, relationships between the post-HFS – baseline difference wave measurements were correlated with performance on the neurocognitive (MCCB composite score), functional (UPSA and RFS total scores), and clinical (BPRS and SANS total scores) measures using Spearman's correlations. Alpha was set to $p < 0.05$, two-tailed, for all statistical tests.

3. Results

3.1. Neuroplasticity effects

Results of the cluster-based permutation tests comparing each of the two post-HFS blocks to the pre-HFS block are shown in Fig. 4 and the two post-HFS VEP difference waveforms are shown in Fig. 5. Relative to baseline, there was a significant negative cluster between 140 and 227 ms for the early post-HFS block (average of Post-1 and Post-2), and a significant positive cluster between 180 and 281 ms for the late post-HFS block (Post-3). Both effects were present at a similar set of electrodes: P1, P5, P7, P9, PO7, PO3, POz, Pz, P2, P4, P6, P8, P10, PO8, PO4, O2 for both post-HFS blocks, in addition to P3, O1, Oz, Iz for early post-HFS.

The significant amplitude difference between baseline ($M = 2.41$; $SD = 3.56$) and the early post-HFS assessment ($M = 1.74$; $SD = 3.10$), reflecting short-term plasticity, was therefore evident in the

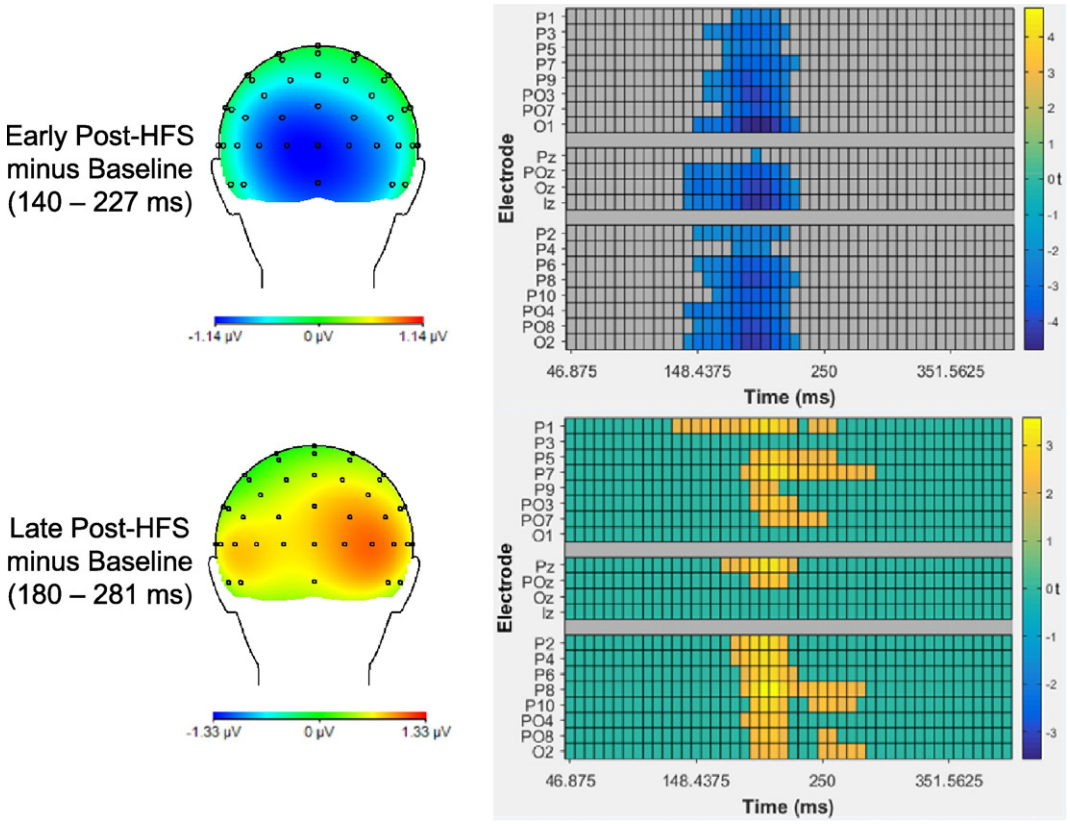

Fig. 4. Topographical maps of the difference waves and raster diagrams illustrating significant differences between the baseline and post-HFS blocks according to a cluster-based permutation test. One significant negative cluster was found (in blue) between 140 and 227 ms for the early post-HFS block and one significant positive cluster (in yellow) between 180 and 281 ms for the late post-HFS block.

form of increased negativity in the 140–227 ms range. The significant amplitude difference between baseline (M = 3.83; SD = 3.23) and the late post-HFS assessment (M = 4.62; SD = 3.91), reflecting long-term plasticity, was evident in the form of increased positivity in the 180–281 ms range.

3.2. Correlations with neurocognitive, functional, and clinical measures

The short-term plasticity evident in the early post-HFS block (increased negativity) was not correlated with any measure. However, the long-term plasticity in the late post-HFS block (increased positivity)

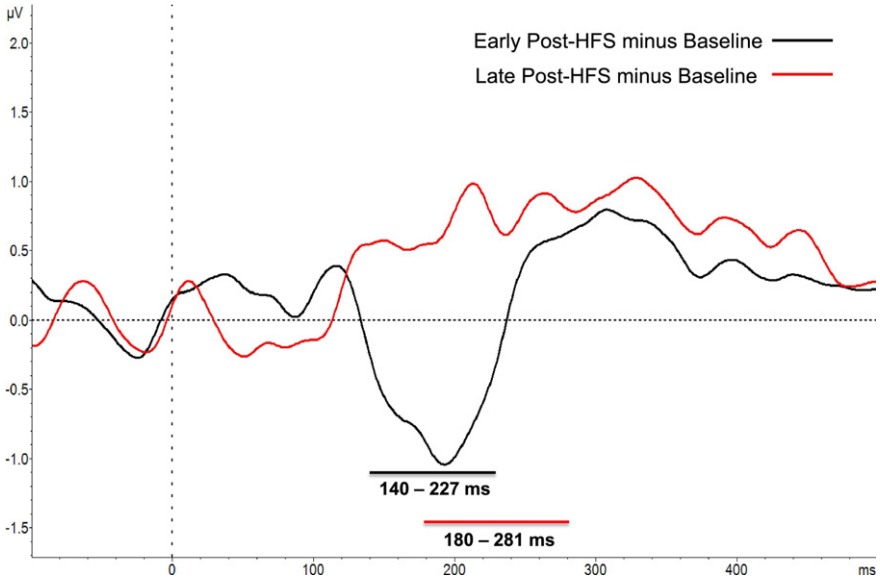

Fig. 5. Difference waveforms at pooled parietal, parieto-occipital, and occipital electrodes. The baseline waveform was subtracted from the early and late post-HFS waveforms. Two time windows were identified (based on the cluster-based permutation test) reflecting an early negativity in the 140–227 ms latency range for the early post-HFS block (black bar), and a later positivity in the 180–281 ms range for the late post-HFS block (red bar).

was significantly correlated with better total MCCB performance (rho = 0.26, $p = 0.04$).

4. Discussion

Our findings demonstrate that after exposure to repetitive visual HFS, patients with schizophrenia showed evidence of visual plasticity. More specifically, compared to the pre-HFS baseline, we observed changes in VEP amplitudes post-HFS, with differing effects depending on how much time elapsed after HFS. For the early post-HFS block, we identified a plasticity effect resulting in increased *negativity* between 140 and 227 ms, and for the late post-HFS block a plasticity effect resulting in increased *positivity* between 180 and 281 ms. Thus, the early post-HFS block likely reflects short-term plasticity, with effects only evident up to 6 min after HFS, whereas the late post-HFS block likely reflects long-term plasticity evident 20–22 min after HFS. This enduring plasticity effect is more likely to be subserved by the basic mechanism of synaptic plasticity known as LTP (Clapp et al. 2012; Çavuş et al. 2012). Plasticity in the early post-HFS block did not correlate with any external measure, whereas long-term plasticity in the late post-HFS block correlated with better MCCB performance.

We used the same paradigm as the only other published study in schizophrenia (Çavuş et al. 2012), though our study differed in a couple of important ways. First, Çavuş et al. used a component-based approach to measure the effects of visual HFS, whereas our study identified time windows based on mass univariate analyses of difference waves (Groppe et al. 2011). The approach of Çavuş et al. was based on prior work by Teyler et al. (2005) and assumes that the plasticity effect is exerted on specific components of the VEP (Elvsåshagen et al. 2012; Normann et al. 2007). However, there is little basis for assuming that "potentiation" (or LTP) or "depotentiation" (or LTD) are reflected in a change in voltage during discrete temporal components of the VEP. Hence, our analytical approach focused on difference waves and cluster-based permutation tests to identify time windows of significant differences in neural activity post- vs. pre-HFS. We found plasticity effects in the early post-HFS block (i.e., 2–6 min after HFS) in a time window (140–227 ms) that partially overlapped with the N1b component (120–180 ms) previously examined by Çavuş et al. and others (McNair et al. 2006; Ross et al. 2008; Teyler et al. 2005). The results from Çavuş et al. and the current study provide support for a short-term plasticity effect present in schizophrenia patients. This transient early plasticity effect likely corresponds to activity in the secondary (extra-striate) visual cortex (Di Russo et al. 2001; Tobimatsu and Celesia 2006).

Schizophrenia patients also showed enduring plasticity effects (not identified in Çavuş et al.) in the form of increased positivity 20–22 min after HFS at a later time window (180–281 ms) than the early post-HFS block. This finding suggests that the plasticity effects are evident relatively late in the visual processing stream, extending beyond striate and extra-striate cortex. The plasticity effect in this window likely reflects multi-synaptic higher-order visual association cortex activity (Di Russo et al. 2001; Tobimatsu and Celesia 2006) that integrates feed forward information from primary and secondary visual cortex (Foxe and Simpson 2002), local inhibitory feedback loops (Clapp et al. 2012), and top-down modulatory signals from prefrontal cortex (Barcelo et al. 2000). This later effect may provide multiple pathways for compensatory processes that could overcome plasticity deficits in earlier visual processing stages (i.e., that process basic sensory information rather than more integrative perceptual aspects of visual stimuli). This interpretation may explain why a greater long-term plasticity effect in this later time window is associated with better neurocognitive function in patients. Future longitudinal development studies can explore whether plasticity effects show trait-like stability over time in patients, and whether plasticity deficits earlier in life predict cognitive impairments later in life or are related to disease progression.

The second way our study differed from that of Çavuş et al. was that our study included only people with schizophrenia, whereas Çavuş et al. included a healthy comparison group. Thus, we were not able to say whether the plasticity effects we observed in our patient sample were "deficient" compared to a healthy sample. However, we did examine the clinical, neurocognitive, and functional correlates of plasticity. Like Çavuş et al., visual plasticity effects did not correlate with clinical symptom severity. They also did not correlate with functional capacity or role functioning.

While the paradigm we used in the current study focused on visual neural plasticity, other paradigms have documented deficient plasticity in schizophrenia in motor (Daskalakis et al. 2008; Frantseva et al. 2008; Hasan et al. 2011; Strube et al. 2016) and auditory cortex (Mears and Spencer 2012). Further, one study has shown correlations between motor and visual plasticity in healthy individuals (Klöppel et al. 2015). It remains unclear whether individual differences in plasticity are correlated across cortical regions and systems, whether plasticity abnormalities induced by an illness such as schizophrenia converge across cortical regions and systems, or whether they reflect relatively independent domains of plasticity impairment subserved by distinct pathophysiological processes.

The relationship between neuroplasticity and cognition remains an important area to investigate, especially in the context of neuroplasticity-based cognitive training interventions that depend on intact neuroplasticity to produce cognitive gains (Vinogradov et al. 2012). Measuring sensory-induced potentiation with EEG might provide a useful indicator of an individual's ability to benefit from cognitive remediation or perform well on cognitive tasks that require new learning and the formation of new memories.

Conflict of interest

All authors declare that they have no conflicts of interest arising from this manuscript.

Contributors

Drs. Jahshan and Green designed the study. Dr. Mathalon provided the visual neural plasticity paradigm and contributed to the data analytic approach. Drs. Jahshan and Wynn conducted the data analyses. Dr. Jahshan wrote the first draft of the manuscript. Drs. Wynn, Mathalon, and Green edited the manuscript and helped with the interpretation of the findings. All authors contributed to and have approved the final manuscript.

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