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Publication Date

2021-04-01

DOI

10.1016/j.schres.2021.01.028

Peer reviewed



Published in final edited form as:

Schizophr Res. 2021 April ; 230: 26–37. doi:10.1016/j.schres.2021.01.028.

Visual Cortical Plasticity and the Risk for Psychosis: An Interim Analysis of the North American Prodrome Longitudinal Study

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Contributors

Authors Jacob and Roach analyzed the data, drafted the manuscript and contributed equally to the project and final manuscript. Author Mathalon designed the visual plasticity paradigm, devised and oversaw the data analytic plan, and contributed to drafting and editing the manuscript. Authors Loo, Duncan, Niznikiewicz, Carrion, Belger, Cadenhead, Johannesen, and Mathalon oversaw EEG data acquisition at their respective sites. All authors contributed to the manuscript's literature review, results interpretation, and editing of the drafted manuscript. All authors approved.

Conflicts and Financial Disclosures:

No other disclosures were reported.

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Drs Jacob, Hamilton, Duncan, Light, Niznikiewicz, and Mathalon are employees of the US government.

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Abstract

Background: Adolescence/early adulthood coincides with accelerated pruning of cortical synapses and the onset of schizophrenia. Cortical gray matter reduction and dysconnectivity in schizophrenia are hypothesized to result from impaired synaptic plasticity mechanisms, including long-term potentiation (LTP), since deficient LTP may result in too many weak synapses that are then subject to over-pruning. Deficient plasticity has already been observed in schizophrenia. Here, we assessed whether such deficits are present in the psychosis risk syndrome (PRS), particularly those who subsequently convert to full psychosis.

Methods: An interim analysis was performed on a sub-sample from the NAPLS-3 study, including 46 healthy controls (HC) and 246 PRS participants. All participants performed an LTP-like visual cortical plasticity paradigm involving assessment of visual evoked potentials (VEPs) elicited by vertical and horizontal line gratings before and after high frequency (“tetanizing”) visual stimulation with one of the gratings to induce “input-specific” neuroplasticity (i.e., VEP changes specific to the tetanized stimulus). Non-parametric, cluster-based permutation testing was used to identify electrodes and timepoints that demonstrated input-specific plasticity effects.

Results: Input-specific pre-post VEP changes (i.e., increased negative voltage) were found in a single spatio-temporal cluster covering multiple occipital electrodes in a 126–223 ms time window. This plasticity effect was deficient in PRS individuals who subsequently converted to psychosis, relative to PRS non-converters and HC.

Conclusions: Input-specific LTP-like visual plasticity can be measured from VEPs in adolescents and young adults. Interim analyses suggest that deficient visual cortical plasticity is evident in those PRS individuals at greatest risk for transition to psychosis.

Keywords

schizophrenia; psychosis; clinical high risk; visual evoked potentials; plasticity

INTRODUCTION

Deficient neuroplasticity in schizophrenia has been theorized to underlie developmental deficits in sensorimotor systems, cognitive function, learning and memory, and to contribute to the emergence of psychotic symptoms (Forsyth and Lewis, 2017; Haracz, 1984; Stephan et al., 2006). Genetic evidence implicates reduced synaptic strength (Fromer et al., 2014; Kirov et al., 2012; Marshall et al., 2016; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and excess synaptic pruning (Sekar et al., 2016) in schizophrenia. A basic form of neuroplasticity by which synapses are strengthened with experience is long-term potentiation (LTP) (Ho et al., 2011), widely considered the leading candidate mechanism underlying learning and memory (Lamprecht and LeDoux, 2004; Malenka and Nicoll, 1999; Nithianantharajah and Hannan, 2006). LTP critically depends on glutamatergic NMDAR transmission (Ho et al., 2011). Furthermore, multiple lines of evidence implicate NMDAR hypofunction as a core pathophysiological mechanism in schizophrenia (Coyle, 2012; Javitt et al., 2012; Javitt and Zukin, 1991; Krystal et al., 2002; Moghaddam and Krystal, 2012; Uno and Coyle, 2019), including: 1) NMDAR antagonists such as ketamine, when administered in drug challenge studies to healthy participants, transiently induce many of the clinical features and cognitive deficits that characterize schizophrenia (Anticevic et al., 2012; Gunduz-Bruce et al., 2012; Schmidt et al., 2012; Umbricht et al., 2000; van Berckel et al., 1998), 2) schizophrenia risk genes influence NMDAR function (Hall et al., 2015; Harrison and Weinberger, 2005; Kantrowitz and Javitt, 2010), 3) NMDAR abnormalities have been identified in schizophrenia post-mortem tissue (Deakin et al., 1989; Ibrahim et al., 2000; Simpson et al., 1992; Föcking et al., 2015; Funk et al., 2009; Kristiansen et al., 2006; Nascimento and Martins-de-Souza, 2015) 4) NMDAR density measured with Single Photon Emission Tomography is reduced in schizophrenia (Bressan et al., 2005; Pilowsky et al., 2006). Taken together, the dependence of LTP on NMDAR function and the evidence for NMDAR hypofunction in schizophrenia provide a mechanistic basis for hypothesizing dysfunction of LTP and related NMDAR-dependent forms of synaptic plasticity in schizophrenia. The effects of NMDAR hypofunction on neurodevelopmental processes related to synaptic connectivity have also been theorized to contribute to the emergence of psychosis (Eastwood, 2004; Zhang et al., 2013).

1.1 Non-Invasive Recording of LTP-like Neuroplasticity and Schizophrenia

LTP is classically studied in animal tissue slice preparations, wherein electrical high-frequency stimulation (HFS) is utilized to tetanize afferent pathways to induce lasting potentiation of the postsynaptic response (Citri and Malenka, 2008; Cooke and Bliss, 2006; Feldman, 2009). Recently developed non-invasive paradigms can induce LTP-like potentiation of visual cortex in humans via HFS by presenting a visual stimulus at a high “tetanizing” frequency (Clapp et al., 2012; Teyler et al., 2005a) or at a slower frequency for a prolonged period (Elvsåshagen et al., 2012; Normann et al., 2007). The potentiation of visual cortex induced by these paradigms has been documented using visual evoked potentials (VEPs) (Clapp et al., 2006b; Klöppel et al., 2015; McNair et al., 2006; Ross et al., 2008), functional MRI (Clapp et al., 2005b), and behavioral performance (Beste et al., 2011; Clapp et al., 2012).

Plasticity induced by non-invasive sensory stimulation shares much in common with basic synaptic LTP, including frequency dependence (potentiation by HFS and depotentiation by low frequency stimulation (Beste et al., 2011; Clapp et al., 2012; Teyler et al., 2005b), persistence (VEP changes lasting at least 1 hour [Clapp et al., 2012; Teyler et al., 2005b]; behavioral changes lasting up to 1 week [Beste et al., 2011]), input specificity (little or no potentiation of a non-tetanized control stimulus, analogous to synaptic input specificity in LTP [Beste et al., 2011; McNair et al., 2006; Ross et al., 2008; Wynn et al., 2019]), and temporal and spatial specificity (VEP potentiation effects limited to distinct time windows and scalp topographies [Cavu et al., 2012; Clapp et al., 2006b; Clapp et al., 2005a; McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005b]). In one rodent study, potentiation of visual cortex local field potentials by visual HFS was blocked by administration of an NMDAR antagonist (Clapp et al., 2006a), although this failed to replicate in a subsequent study (Eckert et al., 2013). A number of rodent studies support lower frequency prolonged visual stimulation (over multiple days) as effectively inducing visual cortical LTP (Cooke et al., 2015; Cooke and Bear, 2012, 2010).

Evidence for impaired LTP-like plasticity in schizophrenia has emerged using these sensory neuroplasticity paradigms, revealing deficient evoked potential changes induced by sensory HFS in patients relative to controls (Cavu et al., 2012; Jahshan et al., 2017; Mears and Spencer, 2012). To date, most of the visual LTP-like plasticity paradigms showing plasticity deficits in schizophrenia have used a single checkerboard stimulus without a control stimulus, preventing demonstration of input-specific plasticity effects (i.e., greater VEP changes for the “tetanized” visual stimulus than for a non-tetanized control stimulus). There is limited evidence suggesting impaired input-specific plasticity in a small sample of chronic schizophrenia patients compared to controls using an auditory HFS task (Mears and Spencer, 2012), but we recently found evidence for a normal input-specific plasticity effect in chronic patients using the same visual paradigm employed in the present study (Wynn et al., 2019). While deficits in plasticity in schizophrenia may depend on as yet poorly understood variations in plasticity paradigms and sample characteristics, there is additional evidence for deficient LTP-like neuroplasticity in schizophrenia using somewhat more established motor plasticity paradigms such as transcranial magnetic stimulation (Mehta et al., 2019) and direct current stimulation (Hasan et al., 2011). In any case, the impact of deficient LTP may be most evident during the pathogenesis of schizophrenia in late adolescence/early adulthood.

1.2 Deficient Neuroplasticity, Synaptic Over-pruning, and the Pathogenesis of Schizophrenia

Neurodevelopment is characterized by an initial overgrowth of synaptic connections, followed by pruning of weak synapses that have not been strengthened by experience (Marin and Kipnis, 2013; Schafer et al., 2012). Pruning of cortical synapses is accelerated during adolescent brain development (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997; Rakic et al., 1986), an observation that contributed to Feinberg’s seminal hypothesis (Feinberg, 1982) that synaptic over-pruning could account for the typical onset of schizophrenia during late adolescence/early adulthood. While recent genetic evidence implicates a variant of the complement C4 gene in synaptic over-pruning in schizophrenia

(Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Sekar et al., 2016), it is also possible that deficient LTP could result in too many weak synapses that are then subject to over-pruning during late adolescence as part of the pathogenic cascade toward schizophrenia. Thus, deficient synaptic plasticity in schizophrenia could contribute to the reduced cortical neuropil evident in post-mortem studies (Glausier and Lewis, 2013; Selemon et al., 1998; Selemon and Goldman-Rakic, 1999), as well as cortical gray matter volume deficits (Levitt et al., 2010; Shenton et al., 2001) and regional brain dysconnectivity (Fitzsimmons et al., 2013; Giraldo-Chica and Woodward, 2017; Sheffield and Barch, 2016; van den Heuvel and Fornito, 2014) evident *in vivo* in magnetic resonance imaging (MRI) studies (Stephan et al., 2006). Importantly, these *in vivo* structural (Cannon et al., 2015; Chung and Cannon, 2015; Ding et al., 2019) and functional (Anticevic et al., 2015; Chung and Cannon, 2015) brain abnormalities have been observed prior to psychosis onset in young people who meet criteria for the psychosis risk syndrome (PRS) (McGlashan et al., 2010), particularly those who subsequently transition to full psychosis. Thus, deficient neuroplasticity may be present in the PRS before psychosis onset, contributing to the gray matter loss (Cannon et al., 2015) and functional dysconnectivity (Anticevic et al., 2015) evident in PRS individuals who progress to full psychosis.

1.3 Goals of Current Study

To investigate the hypothesis that LTP-like input-specific visual cortical plasticity is deficient in individuals meeting PRS clinical criteria, we conducted an interim analysis in a large sample of healthy control (HC) and PRS participants from the ongoing NAPLS-3 study (Addington et al., 2020). We employed a visual cortical plasticity paradigm consisting of vertical and horizontal square-wave grating stimuli, where only one of these stimuli is presented at a high (tetanizing) frequency to induce neuroplastic changes in VEP amplitude selective to the tetanized stimulus. We used cluster-based permutation testing (Groppe et al., 2011), including all participants, to rigorously identify clusters (electrodes and time windows) showing significant input-specific plasticity effects. Once identified, we tested for group differences between PRS participants who subsequently converted to psychosis, PRS non-converters followed for at least 18 months, and HC. We hypothesized that plasticity deficits would be evident in PRS individuals, particularly those who transitioned to psychosis.

METHODS

2.1. Participants

Participants (N=293) from the third phase of the 9-site North American Prodrome Longitudinal Study (NAPLS-3) (Addington et al., 2020) who had received a baseline electroencephalography (EEG) assessment prior to January 1st, 2016 were considered in this interim analysis. One participant's data were excluded due to intermittent electrode failure during EEG recording. The remaining 292 participants, comprising 246 PRS (139 males, 107 females) and 46 HC (23 males, 23 females) individuals, are included.

PRS participants met the Criteria of Psychosis-Risk Syndromes (COPS) based on the Structured Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan et al., 2010; Miller

et al., 2002) administered by trained interviewers who met high reliability standards (Addington et al., 2012). PRS participants were diagnosed with at least one of three non-mutually exclusive PRS sub-syndromes: Attenuated Positive Symptom Syndrome (n=243), Brief Intermittent Psychotic Syndrome (n=1), and/or Genetic Risk and Deterioration Syndrome (n=13). All participants were between 12 and 30 years old (mean \pm SD: PRS=19.19 \pm 4.02 years, HC=21.66 \pm 4.81 years), and were excluded for any past or current history of a psychotic disorder, significant central nervous system disorder, history of serious head trauma, or impaired intellectual functioning (i.e., Wide Range Achievement Test Reading score \leq 75). HC participants were also excluded if they had a first-degree relative with a past or current psychotic disorder. Detailed recruitment procedures have been previously described (Addington et al., 2020). The study was approved by the Institutional Review Board at each study site. Adult participants provided written informed consent, and minors provided written assent with parents providing written consent. At the time this interim analysis was completed, most enrolled PRS participants had not reached the 18-month follow-up time point, 22 PRS participants had been clinically followed for at least 18 months without evidence of conversion (PRS-NC; age mean \pm SD = 19.46 \pm 4.88 years; 12 males, 10 females), and 20 PRS participants had converted to a psychotic disorder (PRS-C; age mean \pm SD = 19.07 \pm 4.42 years; 12 males, 8 females). At the time of this interim analysis, 7 PRS-C and 9 PRS-NC participants, but none of the HC, were taking psychiatric medication.

2.2. Visual Cortical Plasticity Paradigm

The visual cortical plasticity paradigm involved EEG-based VEP assessments before and after exposure to tetanizing visual HFS (VHFS, Figure 1). While maintaining focus on a central fixation cross, participants viewed vertical and horizontal square wave line grating stimuli presented centrally against a gray background on a 55 cm ViewSonic VX2252mn liquid crystal display (1920 \times 1080 pixels; 60 Hz refresh rate; 268 mm viewable height; identical at all 9 sites) located 90 cm in front of them. Each line grating stimulus was a square subtending 17 $^\circ$ visual angle and consisted of alternating light and dark 6-pixel bars (\sim 5.3 light-dark cycles per degree) that phase reversed with each presentation to reduce adaptation effects. Each VEP assessment block comprised a pseudorandom oddball sequence of 133 line grating stimuli, including frequent (90%) low-contrast (35% contrast) standard stimuli and infrequent (10%) high-contrast (72% contrast) target stimuli. For both standard and target line grating stimuli, half were horizontal and half were vertical. In order to focus and monitor attention, participants responded to target stimuli with a right index finger button press.

In each VEP block (duration 5:45), stimuli were presented at .833 Hz (1200 ms mean stimulus-onset asynchrony, range 1067–1333 ms). Stimulus duration was jittered (375 ms mean duration, uniformly distributed range 250 – 500 ms) to minimize any offset potentials. A 20 second break was built into the middle of each block to mitigate fatigue. VEP assessment blocks were administered approximately 12 and 6 minutes before VHFS (pre) as well as 30 and 36 minutes after VHFS (post). An unrelated auditory task was performed in the interval between VHFS and the post-VHFS VEP assessments.

The VHFS block designed to induce LTP-like plasticity changes in VEP amplitudes comprised repeated presentation of either a vertical or horizontal line grating (orientation randomly counter-balanced between participants) at 10 Hz (100 ms mean SOA; 33 ms duration). VHFS was delivered in an intermittent (5 s on – 5 s off) temporal pattern, rather than continuously, based on pilot data and evidence from other visual (Beste et al., 2011) and theta burst rTMS motor plasticity studies (Huang et al., 2005). This intermittent VHFS continued for 1067 stimulus presentations (approximately 4 minutes), followed by 2 minutes of blank, gray screen to allow any after effects of VHFS to dissipate. Similar to the pre-VHFS baseline VEP assessment blocks, high-contrast target stimuli were included. Targets (n=11) were presented (100 ms stimulus duration) to keep the frequency of targets per minute similar to their frequency in the baseline VEP blocks (approximately 1 target trial every 20 s). Additional physical parameters of the visual stimuli are described in Supplementary Material. All participants viewed instructions and had practice at the beginning of the experiment, and the experimenter provided feedback and conducted additional practice, if necessary, to ensure the participants understood the task.

2.3. EEG Acquisition and Pre-processing

EEG data were recorded from 64 channels using identical BioSemi ActiveTwo systems (www.biosemi.com) across the 9 NAPLS sites. Electrodes placed at the outer canthi of both eyes, and above and below the right eye, were used to record vertical and horizontal electro-oculogram data. EEG data were continuously digitized at 1024 Hz and referenced offline to averaged mastoid electrodes before applying a 0.1 Hz high-pass filter using ERPLab (Lopez-Calderon and Luck, 2014). Data were next subjected to Fully Automated Statistical Thresholding for EEG artifact Rejection (FASTER) using a freely distributed toolbox (Nolan et al., 2010). Following artifact rejection and baseline correction, VEP average waveforms were calculated separately for each stimulus orientation for standard trials only in pre- and post-VHFS VEP assessment blocks on a per subject basis. Additional details pertaining to data pre-processing have been described previously (Wynn et al., 2019) and are discussed in Supplemental Material. Individual participant pre- and post-VHFS VEP waveforms were low-pass filtered at 50 Hz and re-referenced to the common average reference prior to subsequent statistical analysis.

2.4. EEG Analysis - Non-parametric, Cluster-based Permutation Testing

Initial data-driven testing in the full (N=292) sample focused on identifying time periods (or temporal clusters) that demonstrated input-specific plasticity effects, without making any *a priori* assumptions about specific VEP components or inspection of grand average waveforms to decide which time windows to measure to capture such effects. As noted below, the only assumptions made in our analytic approach was that plasticity effects of interest in the VEP would occur somewhere between 50ms and 250ms post-stimulus onset (based on prior literature), and that these effects would be evident among occipital scalp electrodes.

Given the task design, input-specific effects were defined as pre- versus post-VHFS changes in the VEP for the stimulus orientation that was tetanized during the VHFS block, relative to pre- versus post-VHFS changes in the VEP for the control stimulus orientation that was not

tetanized. These input-specific plasticity effects, if present, should be evident in the VEP double-difference waveforms (i.e., [tetanized orientation post-VHFS VEP – pre-VHFS VEP] – [control orientation post-VHFS VEP – pre-VHFS VEP]). Double-difference waveforms from seven occipital electrodes nearest to Oz (PO3, POz, PO4, O1, Oz, O2, Iz) for each subject were down-sampled to 512Hz and limited to the period of the epoch from 50 ms to 250 ms. One-sample t-tests then tested whether the mean double-difference score was different from zero at each time point in the pre-specified 50–250 ms time window of the VEP double-difference waveforms from each electrode, and these t-tests served as input to a subsequent permutation test procedure. It should be noted that each t-test on the double-difference VEP waveform is equivalent to a test of the Time (Pre- vs. Post-VHFS) X Stimulus Type (Tetanized vs. Non-tetanized Control) interaction effect in an analysis of variance model. Permutation testing of the t-values across time points and electrodes allowed testing for significant spatio-temporal clusters representing input-specific plasticity effects while controlling for the family-wise error (FWE) rate (cluster-corrected FWE $p < .05$, two-tailed). Cluster-based permutation tests of ERP data have been described previously (Maris and Oostenveld, 2007), but the setup along with specific parameters for this analysis are described in greater detail in Supplementary Material.

2.5. Group Comparisons

For any given cluster that showed cluster-corrected statistical significance (cluster $p < .05$), the mean amplitude was calculated from the time points in the double difference VEP waveform and the electrodes associated with the cluster. These mean values were entered into a mixed effects model analysis conducted in SAS v9.4 (PROC MIXED) treating NAPLS Site and Subject, nested within Group, as random factors and Group as the between-subjects factor. We probed two planned contrasts of interest to examine differences between PRS and HC as well as between PRS-C and PRS-NC.

RESULTS

There were no significant differences in target reaction time between HC and PRS participants, or between PRS-C and PRS-NC participants.

3.1 Cluster-Based Permutation Testing

One-sample t-statistics performed on the VEP double difference waveforms ($[(\text{tetanized post-VHFS} - \text{pre-VHFS}) - (\text{control post-VHFS} - \text{pre-VHFS})]$) isolated input-specific plasticity effects of VHFS tetanization in the full participant sample (Figure 2A). Applying an initial height threshold to the t-statistic raster plots ($-1.96 < t < 1.96$) and subsequent permutation testing of the t-sum statistics yielded one significant negative cluster (FWE cluster-corrected $p = 0.012$), spanning a 126–223 ms time window, as well as a single positive cluster that did not achieve FWE-corrected cluster-level significance (FWE $p = 0.624$) (Figure 2A). For the significant negative cluster, electrode O2 yielded the largest t-sum statistic and was therefore the strongest contributor, with all of the remaining electrodes except for O1 also contributing. Cluster means for the paradigm conditions shows the input-specific interaction effect captured by the cluster (Figure 2B). Inspection of the mean VEP double-difference waveform from electrode O2 shows that the input-specific plasticity effect

involved a ~ 0.25 μV increased negativity (or, equivalently, decreased positivity) (Figure 3A). Separate VEP difference waveforms (post-VHFS – pre-VHFS) from electrode O2 for both the tetanized and the non-tetanized control stimuli are presented in Figure 3B. Both tetanized and control stimuli showed increased negativity (or reduced positivity) in the post-pre difference waveforms within the cluster's time window, but this effect was more prominent for the tetanized stimulus (Figure 3B). The simple grand average VEP waveforms from electrode O2 for the pre-VHFS and post-VHFS VEP assessments, separately presented for the tetanized and control stimuli, show classic pattern-onset VEP morphology, with an N1 peaking at ~ 90 ms, a P2 peaking at ~ 140 ms, and an N2 peaking at ~ 195 ms (Figure 3C and 3D). The overlay of the significant cluster's time window on these simple pattern onset VEPs indicate that the VHFS-induced plasticity effect was reflected by superimposed enhanced negativity beginning during the transition from N1 to P2, continuing past the P2 peak, and resolving just after the N2.

3.2 Converters and Non-converters

We conducted two planned follow-up tests of group differences in mean amplitude within the negative spatiotemporal cluster. There was no difference in mean cluster amplitude between HC and all PRS participants ($F(1,85)=0.01$, $p=0.9204$). The mean cluster amplitude was reduced (more positive) in PRS-C relative to PRS-NC (Figure 4A, $F(1,85)=5.32$, $p=0.0235$), reflecting a deficient input-specific plasticity effect in the PRS-C. The Group x Time x Stimulus Type interaction effect captured by the group difference in the cluster mean is presented in Figure 4A (right panel). This reflects a Time x Stimulus interaction effect that is present for the PRS-NC participants (Figure 4B) but not the PRS-C participants (Figure 4C).

DISCUSSION

In a large sample of PRS and HC adolescents and young adults, we found that 4 minutes of 10 Hz VHFS (5 s off/on) induced a significant LTP-like input-specific visual cortical plasticity effect that was evident in the VEP waveforms as an increase in negativity over posterior occipital electrodes between 126 and 223 ms post-stimulus onset and endured for at least 40 minutes. We did not observe a significant difference in this neuroplasticity effect between the HC and PRS groups, contrary to our hypothesis. However, a preliminary comparison of PRS-C and PRS-NC followed for at least 18 months did support our hypothesis that PRS individuals who progress to full-blown psychosis have deficient LTP-like visual cortical plasticity relative to PRS individuals who do not progress.

4.1 Comparison with Previous Literature

Previous VHFS plasticity paradigms using checkerboard stimuli have reported impaired plasticity in schizophrenia (Cavu et al., 2012), and greater impairments at 20 minutes post-VHFS correlated with worse overall cognitive performance (Jahshan et al., 2017). Deficient LTP in schizophrenia may be one consequence of genetically-mediated NMDAR hypofunction (Hall et al., 2015; Harrison and Weinberger, 2005; Kantrowitz and Javitt, 2010). Consistent with this, a glycine transporter inhibitor was shown to enhance LTP-like visual cortical plasticity in schizophrenia, presumably through enhanced co-agonism of

glycine at the NMDAR (D'Souza et al., 2018). In contrast, D-cycloserine, which also modulates NMDAR function at the glycine site, was shown to enhance LTP-like visual plasticity in healthy participants (Forsyth et al., 2015) but not in schizophrenia patients (Forsyth et al., 2017). While it remains unclear whether this plasticity deficit in schizophrenia can be rescued with pharmacological augmentation of NMDAR neurotransmission, both of these studies can be viewed as broadly consistent with NMDAR-dependent plasticity deficits in schizophrenia. NMDAR involvement in this visual cortical plasticity effect is also supported by a magnetic resonance spectroscopy study in healthy volunteers. This study showed concentrations of glutamine (and less strongly, glutamate and GABA) in occipital cortex to predict the magnitude of the increases in visual cortical activation induced by VHFS when fMRI is used to read out the plasticity effect (Wijtenburg et al., 2017). While the above studies are suggestive of NMDAR-mediated LTP-like visual cortical plasticity impairments in schizophrenia, the paradigms employed did not include a non-tetanzing control stimulus.

Several previous VHFS studies have demonstrated input-specific LTP-like visual cortical plasticity effects in healthy participants by assessing VEPs to two visual stimuli with different spatial frequencies (McNair et al., 2006) or line-grating orientations (Ross et al., 2008; Spriggs et al., 2019), but tetanzing with only one of them, with the other serving as a “control” stimulus. Although a few prior human visual stimulation studies (McNair et al., 2006; Ross et al., 2008; Sumner et al., 2019) have shown input-specific plasticity effects on the measured VEPs, tetanzation effects were not tested directly using a difference wave approach nor reported as stimulus-by-tetanzation interaction effects. Moreover, none of these studies included patients with schizophrenia or participants with the PRS.

We note that impairment in visual plasticity has been demonstrated in major depressive disorder (Normann et al., 2007) and bipolar disorder (Elvsåshagen et al., 2012; Zak et al., 2018) using a low frequency (2Hz) visual stimulation paradigm that has been shown to induce LTP-like VEP amplitude changes, although input-specificity has not been assessed in these studies. While the plasticity effects elicited using such single-stimulus paradigms appear to be replicable (Elvsåshagen et al., 2012; Normann et al., 2007; Zak et al., 2018) the lack of a control stimulus leaves open the possibility that effects are not specifically related to the features of the tetanzing stimulus, reflecting either a global change in visual cortical excitability, or simply changes in the subject’s state (e.g., arousal level) over the course of the paradigm due to the passage of time. Because synaptic input-specificity is a characteristic feature of LTP (Beste et al., 2011; McNair et al., 2006; Ross et al., 2008; Wynn et al., 2019), the ties between visual sensory stimulation-induced plasticity and LTP are strengthened by demonstration of plasticity effects specific to the tetanzing stimulus, relative to a control stimulus.

In the visual cortical plasticity paradigm implemented in the current study, and in our prior report using this same paradigm (Wynn et al., 2019), we collected pattern onset VEPs from two square wave line gratings with orthogonal orientations, but used only one of them as a visual tetanus. This two stimulus approach, which has been used by others as well (McNair et al., 2006; Ross et al., 2008), capitalizes on the orientation-specific columnar organization of the visual cortex (Gilbert and Wiesel, 1983; Mountcastle, 1997) in order to minimize the

overlap between the tetanized and control neuronal populations. While input-specific (McNair et al., 2006; Mears and Spencer, 2012; Ross et al., 2008; Sumner et al., 2019) and non-specific effects (Cavu et al., 2012; Clapp et al., 2006b; Clapp et al., 2005a; Klöppel et al., 2015; Lei et al., 2017) have been reported using such paradigms, the purpose of incorporation of a control stimuli is to demonstrate input-specific plasticity effects. Our analysis focused exclusively on testing for such effects, reflecting our view that they are the only effects we can confidently attribute to the visual tetanus.

Our focus on input-specificity motivated our analysis of double difference waveforms, which effectively isolated the Time (Pre- vs. Post-VHFS) X Stimulus Type (Tetanized vs. Non-tetanized) interaction effect. In adopting this approach, we deliberately depart from prior approaches that measure and assess amplitude changes in specific VEP components (e.g., C1, N1, N1b, P2), instead adopting a more conservative view that any changes in VEP voltages induced by VHFS are simply superimposed on the VEP components without assuming that they reflect specific “potentiation” or “depotentiation” of these components (Jahshan et al., 2017). Our results demonstrated a significant spatio-temporal VEP cluster showing an increased negativity over occipital electrodes that was specific to the tetanizing stimulus, persistent over time (evident 30–42 minutes post-tetanus), and identified by a statistically rigorous clustering approach, similar to what we previously found using this paradigm (Wynn et al., 2019). These findings parallel stimulus-specific response potentiation effects in animal models that rely on feedforward, excitatory connections and the NMDA receptor (Cooke and Bear, 2012, 2010).

Of note, in our first application of the current version of the LTP-like visual cortical plasticity paradigm (Wynn et al., 2019), while we observed a similar significant spatio-temporal input-specific cluster, we did not observe a deficit in this effect in patients with chronic schizophrenia. This contrasts with several prior studies showing plasticity deficits in schizophrenia patients using single-checkerboard visual paradigms (Cavu et al., 2012; Forsyth et al., 2017). It is unclear at this point whether our failure to demonstrate a deficit in chronic schizophrenia patients is somehow related to poorer sensitivity of our paradigm in an older age range or during chronic stages of schizophrenia (Wynn et al., 2019), unique features of our paradigm, or idiosyncrasies of the patient and HC samples. More research is needed to map the task conditions and parameters that capture sparing and loss of plasticity function across the illness course of schizophrenia.

4.2 Plasticity in the Psychosis Risk Syndrome

As predicted, we observed deficient input-specific LTP-like visual cortical plasticity in PRS participants who later converted to psychosis relative to PRS participants who did not convert to psychosis after at least 18 months of follow-up. This plasticity deficit in PRS-C participants is consistent with a pathogenic model of schizophrenia onset involving NMDA-glutamate hypofunction and an impairment in the ability to strengthen synapses with experience.

We theorize that the cortical gray matter decline (Cannon et al., 2015) and functional dysconnectivity (Anticevic et al., 2015) previously observed in PRS individuals who transition to psychosis results from the failure to strengthen synapses (Citri and Malenka,

2008; Cooke and Bliss, 2006; Feldman, 2009), leading to an overabundance of weak synapses that are then subject to over-pruning (Feinberg, 1982). This could contribute to gray matter loss during the transition from the PRS to full-blown psychosis (Cannon et al., 2015; Chung and Cannon, 2015; Ding et al., 2019), gray matter reduction in chronic schizophrenia (Levitt et al., 2010; Shenton et al., 2001), and the reduced neuropil evident in post-mortem studies (Glausier and Lewis, 2013; Selemon et al., 1998; Selemon and Goldman-Rakic, 1999). Among promising cellular mediators is dysregulated activation of microglia, resident immune cells in the brain that influence synaptic plasticity in health (Schafer et al., 2013; Zhang et al., 2014) and impair plasticity in disease (Takano et al., 2014). In the developing brain there is an excess of synaptic connections, sculpted by dynamic iterations of formation and elimination on the basis of experience dependent patterns of neural activity (Hua and Smith, 2004), an NMDA receptor-dependent process (Zhang et al., 2013) supported by LTP (Durand et al., 1996). In late-childhood and adolescence, synaptic density decreases (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997; Rakic et al., 1986) mediated by microglial pruning of weak/inactive synapses (Chechik et al., 1998; Hua and Smith, 2004; Paolicelli et al., 2011; Schafer et al., 2013, 2012). Thus, deficient LTP may result in over-pruning of an excessive number of weak synapses by microglia, thereby contributing to gray matter decline and functional dysconnectivity (Zhan et al., 2014) during the transition to psychosis. Prenatal neuroinflammatory processes (Meyer, 2013) or genetic risk background (Fromer et al., 2014; Sekar et al., 2016) could “program” for vulnerability. However, subsequent exposure to stress, infection, autoimmune processes and/or synaptic pruning during adolescent brain development may represent influences more proximal to psychosis onset.

4.3 Limitations, Future Directions

The present investigation has several important limitations. First and foremost, this is an interim analysis of NAPLS-3. As this study remains ongoing, group differences reported here await confirmation in the final sample. In addition, examination of correlations with clinical, behavioral and cognitive measures also awaits completion of the study. Second, although attempts were made to standardize VEP methods across sites, and site was included in statistical models, subtle differences in the recording environment across sites may have introduced additional variance, a price that is often paid in cross-site EEG studies in order to benefit from the larger sample sizes afforded by such studies. Third, VEP recordings in this study reflect a single assessment in time and future studies might employ serial recordings to observe how LTP-like visual cortical plasticity changes over time and correlates with changes in clinical and cognitive measures. In our prior work, we found limited test-retest reliability of the input-specific visual cortical plasticity effect in older HC and patients with chronic schizophrenia (Wynn et al., 2019), the test-retest reliability of the plasticity effects observed here remains to be determined. Finally, while current efforts to develop and validate paradigms to assess LTP-like cortical plasticity *in vivo* in humans have great potential to identify plasticity deficits as a pathophysiological mechanism in psychiatric disorders including schizophrenia and its prodrome, more research is needed to determine to how to best optimize these paradigms for induction of input-specific plasticity effects and for detection of abnormal plasticity in patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We gratefully acknowledge the contributions of Dr. Lawrence Seidman, who died on September 7th, 2017. Dr. Seidman contributed substantially to the conception, design and acquisition of the data presented in this manuscript. This work was supported by grants from National Institute of Mental Health (U01MH081902 to TDC, P50 MH066286 to CEB, U01MH081988 to EFW, U01MH076989 to DHM, U01MH081944 to KSC, U01MH081984 to JA, U01MH082004 to DOP, U01MH081857 to BAC, U01MH081928 to LJS, U01MH082022 to SW).

Financial Disclosures: Dr. Bearden reported grants from the NIMH during the conduct of the study. Dr. Cornblatt reported grants from NIMH during the conduct of the study. Dr. Duncan has received research support for work unrelated to this project from Auspex Pharmaceuticals, Inc. and Teva Pharmaceuticals, Inc. Dr. Johannesen reported grants from the NIMH during the conduct of the study and was employed by Sage Therapeutics at time of manuscript preparation. Dr. Perkins reported grants from the NIMH during the conduct of the study; personal fees from Sunovion and personal fees from Alkermes outside the submitted work. Dr. Woods reported grants from the NIMH during the conduct of the study; grants and personal fees from Boehringer Ingelheim, personal fees from New England Research Institute, personal fees from Takeda, grants from Amarex, grants from Teva, grants from One Mind Institute, and grants from Substance Abuse and Mental Health Services Administration outside the submitted work; in addition, Dr. Woods had a patent to Glycine agonists for prodromal schizophrenia issued and a patent to Method of predicting psychosis risk using blood biomarker analysis pending. Dr. Cannon reported grants from NIMH during the conduct of the study. Dr. Mathalon reported grants from NIMH during the conduct of the study; consulting fees from Boehringer Ingelheim, consulting fees from Aptinyx, consulting fees from Takeda, consulting fees from Upsher-Smith, and consulting fees from Alkermes, outside the submitted work.

Role of Funding Source:

This work was supported by grants from National Institute of Mental Health. The study design and rationale was approved by the funder, but the funder had no involvement in the collection, analysis, interpretation, decision to submit, or the writing of this manuscript.

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Stimulus Specific Visual Plasticity Paradigm

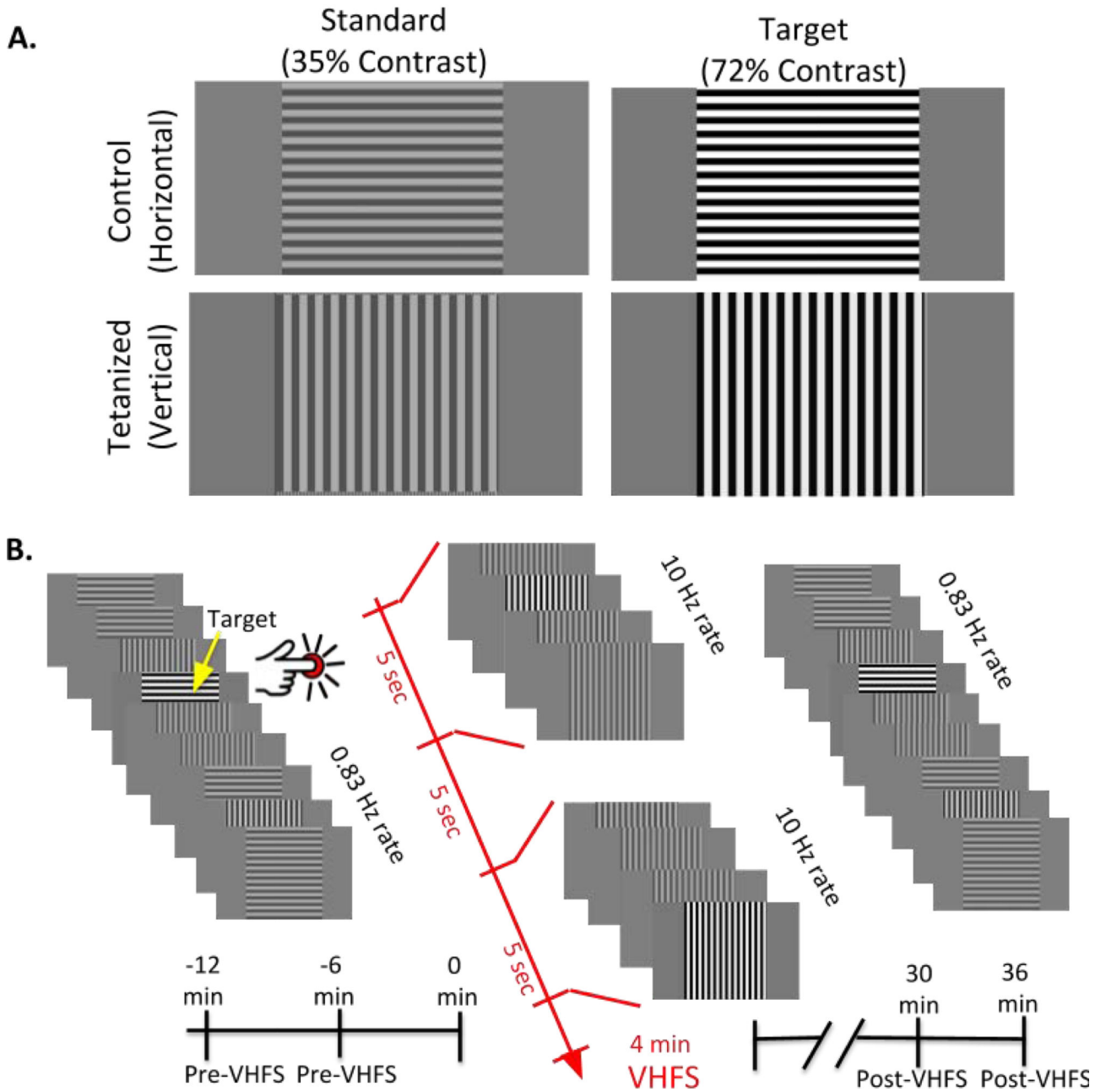
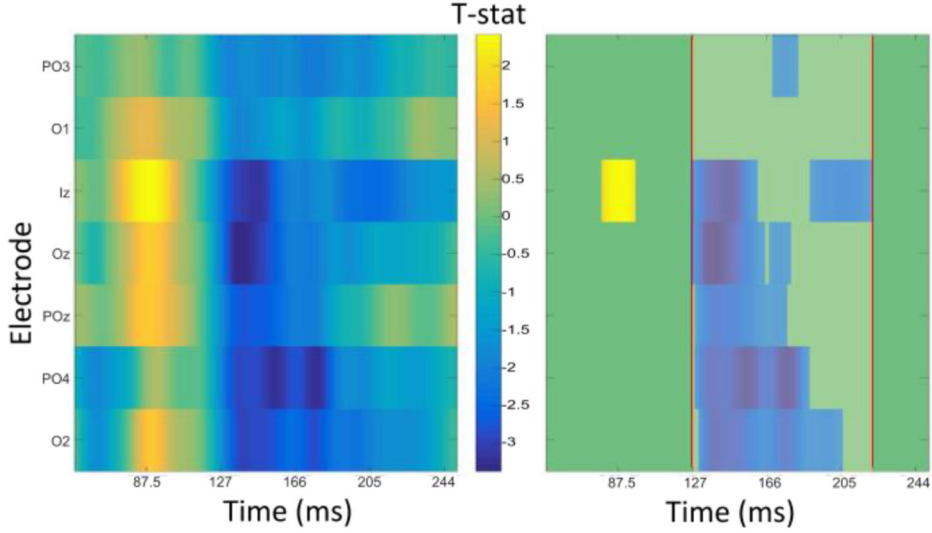


Figure 1. The visual stimuli and behavioral paradigm used in these studies. A. Example tetanized, control, standard and target stimuli. Note: targets are always 72% contrast, but tetanized and target stimuli can be either vertical or horizontal gratings. B. Left: The VEP pre-VHFS stimulus stream consists of two 5 minute and 45 second blocks with randomly interleaved horizontal and vertical square wave gratings (35% contrast) at a rate of 0.83 Hz. Target stimuli occur approximately every 20 sec, at 72% contrast, for either stimulus orientation and require a button press. Center: The 4 minute VHFS session consists of 10 Hz

presentation of one of the orientations in 5 second blocks. Target stimuli are the same as for the VEP trials. Right: The VEP post-VHFS stimulus stream is the same as the pre-HFS blocks and occurs ~30 minutes after HFS.

A. Permutation Testing Results



B. Pre-VHFS x Post-VHFS Interaction Effect

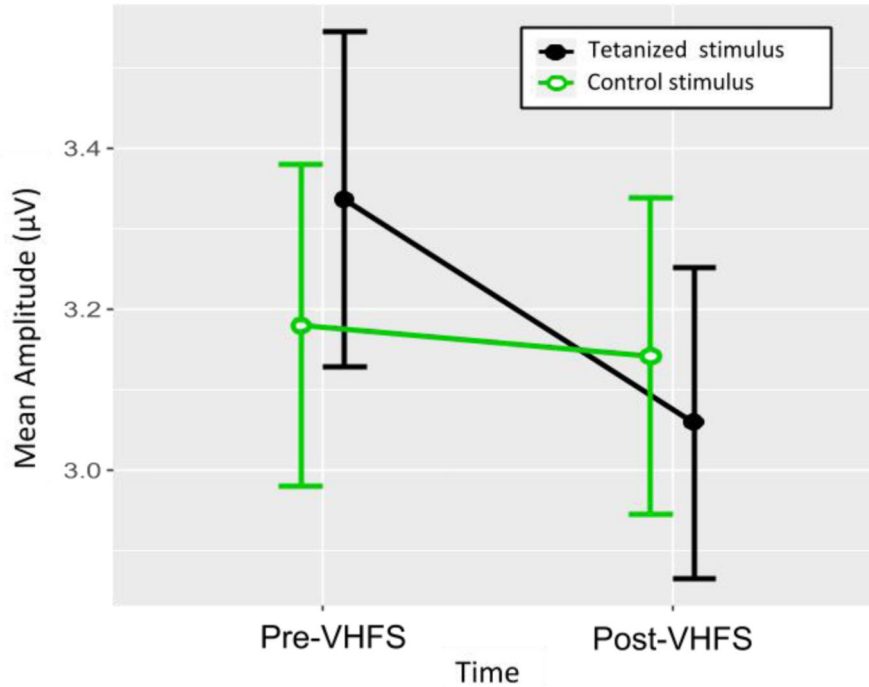


Figure 2.

A. Double difference waves [tetanized (post-VHFS minus pre-VHFS) minus control (post-VHFS minus pre-VHFS)] (all participants, n=292) from seven occipital electrodes nearest to Oz (PO3, POz, PO4, O1, Oz, O2, Iz) limited to the epoch 50 to 250 milliseconds (ms) served as input for permutation testing. *Left:* One-sample t-test statistics are calculated for every time sample and electrode on the double difference wave. This tests the null hypothesis that the double difference value is equal to zero. *Right:* Test statistics that survived an initial height-threshold (right, $-1.96 < t < 1.96$) reveal two clusters, one positive

cluster that was not significant (yellow, FWE $p = 0.6243$) and one negative cluster that was significant (blue, FWE $p = 0.0116$). Red lines define the temporal boundaries of the cluster. B. Double difference waves are equivalent to a Time (pre-VHFS/post-VHFS) x Stimulus Type (control/tetanized) interaction effect.

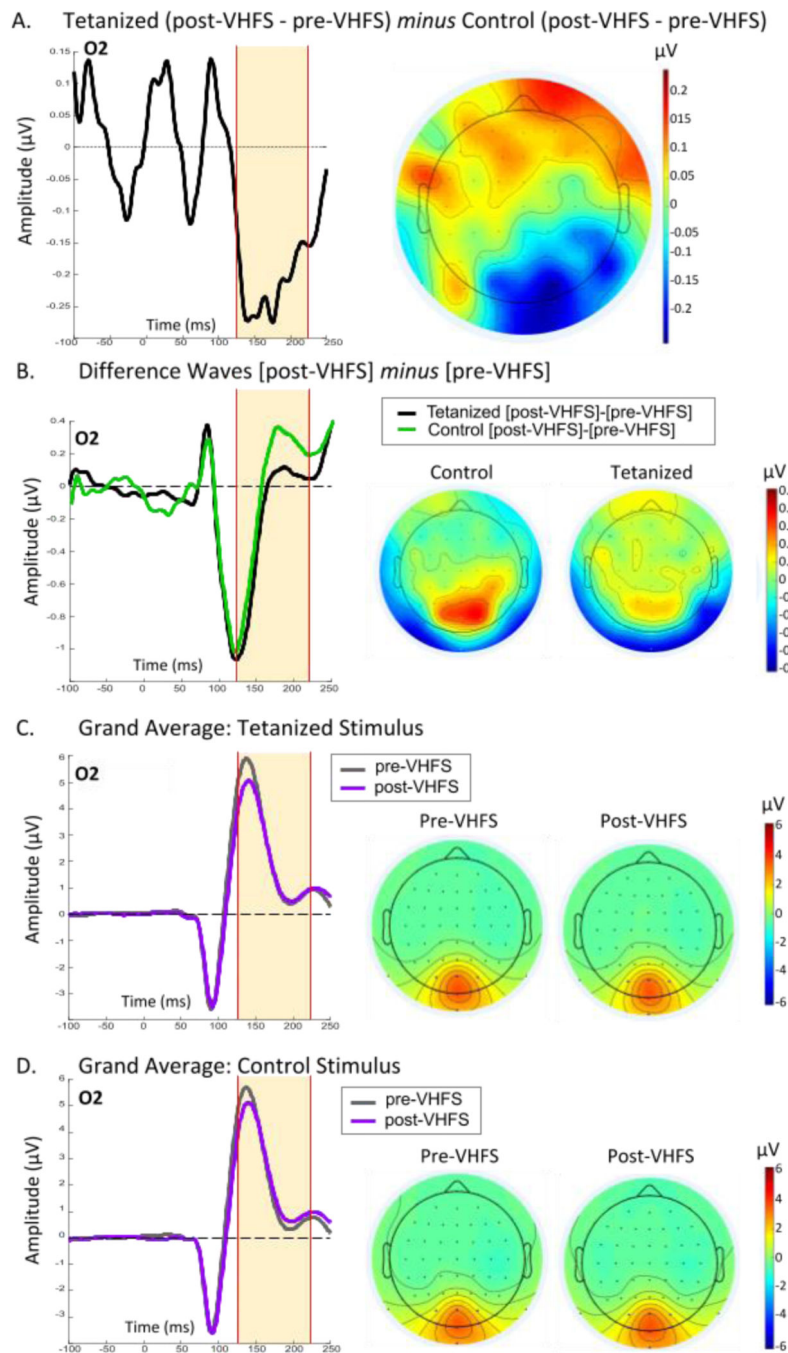


Figure 3.

A. Visual evoked potential double difference waveforms [tetanized (post-VHFS minus pre-VHFS) minus control (post-VHFS minus pre-VHFS)] reveal a negative deflection peaking between 125–175 ms (right, all participants, $n=292$). Red lines with yellow shaded background indicate the time window of the significant input-specific cluster. The voltage scalp map (right) for this waveform displays prominent occipital/posterior activity in the 126–223 ms time window. B. Difference waves post-VHFS minus pre-VHFS, for the tetanized (black) and control (green) stimuli show a negative deflection peaking between

100–150 ms. Voltage scalp maps (right panels) display prominent occipital/posterior activity in the 126–223 ms ms time window. Grand averaged VEPs for the tetanized stimulus (C) and control stimulus (D) during pre-VHFS (gray) and post-VHFS (purple) conditions show a similar C1-P1 waveform (all participants, $n=292$). Voltage scalp maps (right panels) display prominent occipital/posterior activity in the 126–223 ms time window for both stimuli and conditions. T-tests of pre-VHFS vs post-VHFS (in the time window of the significant cluster, see main text) yields a significant difference for the tetanized stimulus only: tetanized $t(291) = -3.543$, $p = 0.0005$; non-tetanized: $t(291) = -.507$, $p = .613$.

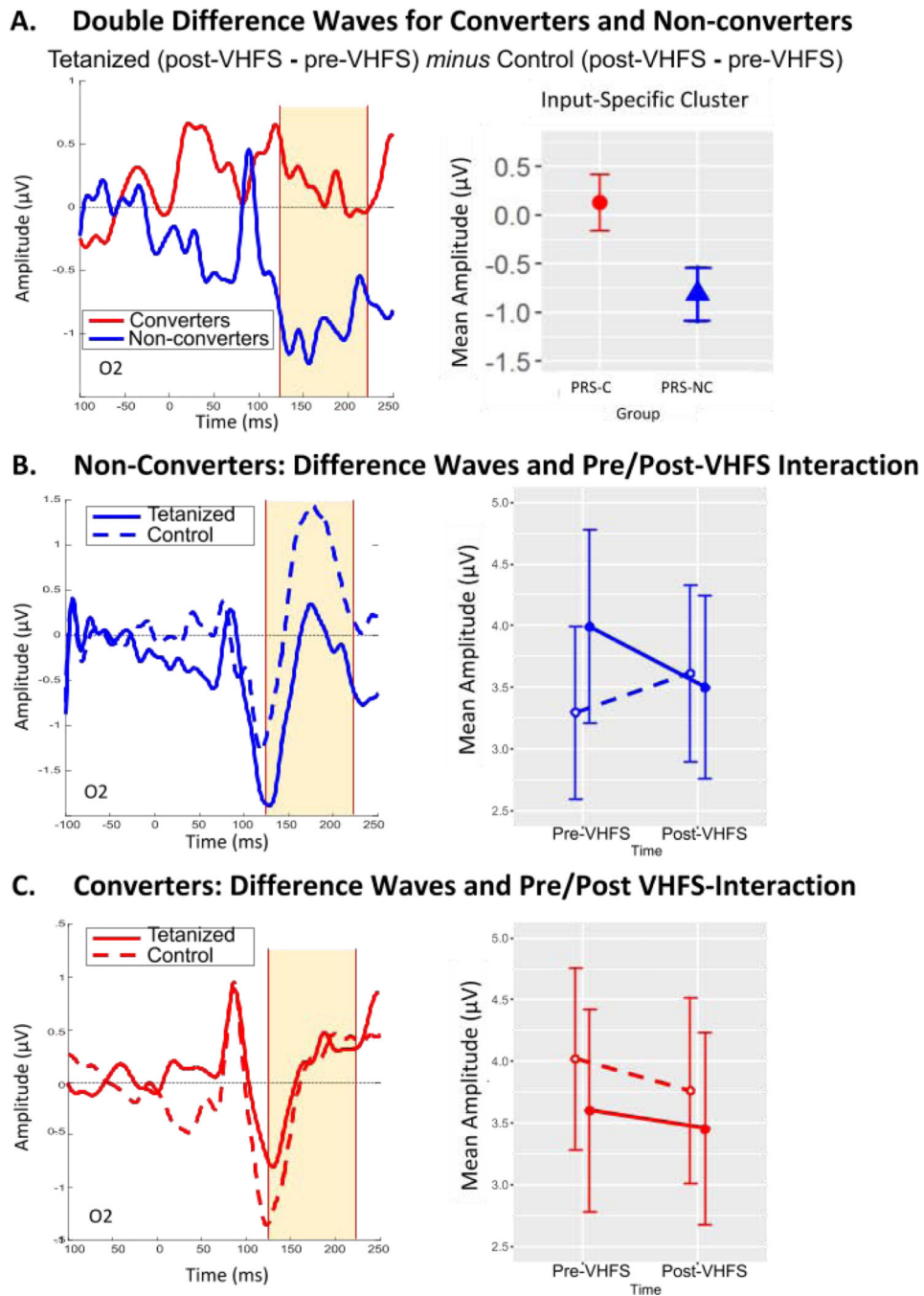


Figure 4. A. Double difference waves [tetanized (post-VHFS minus pre-VHFS) minus control (post-VHFS minus pre-VHFS)] reveal a loss of a negative deflection 125–200 ms in PRS-C (red) relative to PRS-NC (blue; $F(1,85)=5.32$, $p=0.0235$). Mean amplitude is plotted in the right panel. B. Difference waves (post-VHFS minus pre-VHFS), for the tetanized (solid) and control (dashed) stimuli for PRS-NC participants (blue, $n=22$). *Right panel:* A Time (pre-VHFS/post-VHFS) x Stimulus Type (control/tetanized) interaction effect is present for PRS-NC participants. C. Difference waves (post-VHFS minus pre-VHFS), for the tetanized

(solid) and control (dashed) stimuli for PRS-C (red, n=20) participants. *Right panel:* There is no time (pre-VHFS/post-VHFS) x Stimulus Type (control/tetanized) interaction effect for PRS-C participants.

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