Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Cognitive correlates of visual neural plasticity in schizophrenia

Carol Jahshan [a,b,*], Jonathan K. Wynn [a,b], Daniel H. Mathalon [c,d], Michael F. Green [a,b]

[a] VISN-22 Mental Illness Research, Education and Clinical Center (MIRECC), VA Greater Los Angeles Healthcare System, Los Angeles, CA, United States
[b] Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles, CA, United States
[c] San Francisco Department of Veterans Affairs Medical Center, San Francisco, CA, United States
[d] Department of Psychiatry, University of California, San Francisco, CA, United States

ARTICLE INFO

Article history:
Received 23 December 2016
Received in revised form 3 March 2017
Accepted 5 March 2017
Available online xxxx

Keywords:
Neuroplasticity
Visual plasticity
EEG
VEP
Schizophrenia
Neurocognition

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.

Published by Elsevier B.V.

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

* *Corresponding author at: MIRECC, VA Greater Los Angeles Healthcare System, Bldg. 210, Room 117, 11301 Wilshire Blvd., Los Angeles, CA 90073, United States.
E-mail address: carol.jahshan@ucla.edu (C. Jahshan).

http://dx.doi.org/10.1016/j.schres.2017.03.016
0920-9964/Published by Elsevier B.V.

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)

Please cite this article as: Jahshan, C., et al., Cognitive correlates of visual neural plasticity in schizophrenia, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.03.016