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HOT TOPICS

Probing long-term potentiation-like visual cortical plasticity in humans using repeated visual stimulation: effects on visual evoked potentials

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Long-term potentiation (LTP) is a mechanism of experience-dependent synaptic plasticity that depends on glutamatergic transmission at NMDARs and is the leading candidate mechanism of learning and memory. While basic neuroscience research has yielded an understanding of the molecular substrates and functional significance of LTP, our ability to translate these findings to human neuroplasticity has been limited by the lack of valid, non-invasive methods.

Recently, however, human sensory stimulation paradigms have been developed that demonstrate LTP-like plasticity, with EEG-based evoked potentials (EPs) as readouts of plasticity effects. Visual variants of these paradigms are analogous to animal LTP paradigms involving electrical stimulation and provide translational bridges to rodent studies demonstrating LTP in visual cortex following repeated visual stimulus presentations [1], a plasticity mechanism thought to subserve visual perceptual learning. Plasticity induced by such paradigms conforms to characteristics of synaptic LTP, including induction by repeated "Hebbian" stimulation, persistence (≥1 h), stimulus-specific potentiation, and temporal/spatial specificity.

Because of their translational links to animal models, human LTP-like plasticity paradigms are poised to facilitate development of interventions targeting plasticity deficits implicated in neuropsychiatric disorders, including depression, bipolar disorder, and schizophrenia e.g., [2–4]. Indeed, such paradigms may index individual differences in plasticity, indicating who is likely to benefit from interventions that depend on intact plasticity (e.g., cognitive training, neuromodulatory brain stimulation). Furthermore, these paradigms may provide measures of target engagement for novel drugs aimed at restoring plasticity, enabling more patients to benefit from plasticity-dependent treatments, and for examining effects of drugs hypothesized to improve plasticity, such as psychedelics and ketamine [5].

Despite promising advances, paradigm parameters vary across studies, underscoring the need for systematic investigation of the parameter space. Variation in stimulus features, presentation frequency and patterns, and measurement electrodes can influence the magnitude/timing of successive positive- and negative-going waves in visual EP (VEP) waveforms, resulting in ambiguity concerning which VEP components exhibit plasticity-related effects across studies. Indeed, plasticity-related voltage changes may be superimposed on well-characterized VEP components, rather than reflecting potentiation/depotentiation of each specific component. Accordingly, it is misleading to assume that plasticity-related voltage increases over a specific post-stimulus time window reflect "potentiation" of positive-going, and "depotentiation" of negative-going, components. Therefore, plasticity effects are likely best determined from post-visual stimulation minus baseline VEP "difference waves," considering changes to reflect plasticity irrespective of the polarity of the superimposed voltage change or underlying VEP components. Resulting plasticity effects may be more consistent across studies when considering latency windows in which difference waves show effects, typically an increased negativity 140–230 ms post-stimulus.

Research is also needed to examine plasticity effects on stimulus-evoked neuro-oscillations, as EP analysis obscures frequency-specific power and/or phase synchrony changes in the EEG that may underlie observed VEP changes. Indeed, one study has shown stimulus-related increases in theta power and synchrony following repetitive visual stimulation, consistent with animal studies implicating theta oscillations in synaptic plasticity [6]. Studies examining behavioral correlates of VEP changes are also needed to further validate this paradigm with respect to human learning. Ultimately, identification of an optimal plasticity paradigm will support advances in clinical studies of disease mechanisms and intervention development.

REFERENCES

1. Cooke SF, Bear MF. Stimulus-selective response plasticity in the visual cortex: an assay for the assessment of pathophysiology and treatment of cognitive impairment associated with psychiatric disorders. Biol Psychiatry. 2012;71:487–95.
2. Normann C, Schmitz D, Furmaier A, Doing C, Bach M. Long-term plasticity of visually evoked potentials in humans is altered in major depression. Biol Psychiatry. 2007;62:373–80.
3. Zak N, Moberget T, Boen E, Boye B, Waage TR, Dietrichs E, et al. Longitudinal and cross-sectional investigations of long-term potentiation-like cortical plasticity in bipolar disorder type II and healthy individuals. Transl Psychiatry. 2018;8:103.
4. Cavus I, Reinhart RM, Roach BJ, Gueorguieva R, Teyler TJ, Clapp WC, et al. Impaired visual cortical plasticity in schizophrenia. Biol Psychiatry. 2012;71:512–20.
5. Sumner RL, McMillan R, Spriggs MJ, Campbell D, Malpas G, Maxwell E. et al. Ketamine enhances visual sensory evoked potential long-term potentiation in

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patients with major depressive disorder.Biol Psychiatry Cogn Neurosci Neuroimaging. 2020;5:45–55.
6. Hamilton HK, Roach BJ, Cavus I, Teyler TJ, Clapp WC, Ford JM, et al. Impaired potentiation of theta oscillations during a visual cortical plasticity paradigm in individuals with schizophrenia. Front Psychiatry. 2020;11:590567.

AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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