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Visual Cortex Hyperexcitability Contributes to The Pathophysiology of Photoparoxysmal Response

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Over recent years, a number of authors have increasingly explored the possible physiological basis of the photoparoxysmal response (PPR) in humans. A PPR consists of specific electroencephalographic (EEG) signature such as spikes, spike-waves and intermittent slow waves recorded from occipito-frontal regions in response to intermittent photic stimulation (IPS) (Fisher et al. , 2005). Although PPR may be present in asymptomatic healthy subjects as an isolated EEG response, more commonly the PPR elicits focal or generalized myoclonus leading to isolated or recurrent seizures in specific epileptic syndromes (Rubboli et al. , 1999 and Koepp et al. , 2016). There is a robust amount of experimental evidence in animal models (Fischer-Williams et al. , 1968 and Ostrach et al. , 1984) and in humans (Naquet et al. , 1960 and Guerrini et al. , 1998) indicating that an abnormal primary visual cortex (V1) excitability plays a crucial role in the pathophysiology of PPR. Specifically, it has been suggested that a breakdown of inhibitory γ-aminobutyric acid (GABA)-ergic neurotransmission in V1 might contribute to the PPR (Porciatti et al. , 2000 and Parra et al. , 2003).

The present issue of *Clinical Neurophysiology* includes a recent study of Bocci et al. (2016) who investigated the excitability of V1 with transcranial magnetic stimulation (TMS), in a cohort of patients with PPR. Following the hypothesis that PPR reflects decreased contrast gain control in visual cortical areas (Porciatti et al. , 2000), the authors investigated whether an inhibitory form of low-frequency repetitive TMS (rTMS), applied over the occipital pole, is able to restore contrast gain control of high-contrast stimuli, in patients with PPR (Bocci et al. , 2016). In a previous study, Bocci et al. (2011) showed that the same protocol of low-frequency rTMS (600 pulses at supra-threshold intensity, at 0.5 Hz, 20 minutes of stimulation) is able to dampen V1 excitability through mechanisms of long-term depression (LTD)-like phenomena. Given that in PPR, visual cortex hyperexcitability may arise from impaired transcallosal inhibition, in this study the authors also investigated the excitability of the V1 contralateral to that targeted by rTMS. The authors found increased-amplitude early components of visual evoked potential (VEP) in patients compared to controls. Following rTMS, VEPs decreased in amplitude in the target V1 in both patients and

controls. However, the amount of VEP inhibition differed in the two study groups being greater in controls than in patients. In addition, after rTMS, VEP amplitude recovery occurred earlier in patients with PPR than in controls. The authors interpreted these findings as a result of decreased rTMS-induced LTD-like phenomena in V1 in PPR. In the contralateral V1, VEPs increased in amplitude in patients as well as in controls possibly due to rTMS-induced inhibition of transcallosal inhibitory connections. However, in the contralateral V1, the facilitation of VEPs lasted longer in patients compared to controls pointing to decreased transcallosal inhibition in PPR. The authors concluded that impaired LTD-like phenomena in V1 and decreased transcallosal inhibition both contribute to the pathophysiology of PPR.

The study of Bocci et al. (2016) is interesting and provides new insights into the pathophysiology of PPR. A positive methodological aspect of the study is that patients were all drug-naive at the time of the experiments. It is known that a number of anti-epileptic drugs (AEDs) including valproate, levetiracetam, lamotrigine and carbamazepine may affect cortical excitability (Ziemann et al. , 2015). When interpreting the results however, several points should be taken into account. The study cohort is not homogeneous in terms of clinical features since some of the patients studied are affected by Juvenile Myoclonic Epilepsy and others by a rare epileptic syndrome, called Familial Cortical Myoclonic Tremor with Epilepsy (FCMTE) (Suppa et al. , 2009). The authors did not report the reversal of VEP components, achieved by hemifield stimulation, across the two hemispheres, a factor possibly reflecting the specific electrode montage used (Suppa et al. , 2015a). When considering the neural pathway responsible for the observed findings, it should be noted that pathways other than the corpus callosum may have contributed to the present results including the thalamo-cortical pathways. Finally, as stated by the authors, the lack of a control group with patients with idiopathic generalized epilepsy without PPR does not allow to clarify whether the present findings are specific or not for the photosensitive trait. Notwithstanding several methodological limitations, the study of Bocci and coworkers (2016) provides important information into the role of LTD-like plasticity in V1 and interhemispheric

interaction in visual cortical areas in PPR. In conclusion, it is important to state that in addition to V1 hyperexcitability and reduced transcallosal inhibition, recent studies have demonstrated mechanisms of abnormal early visuo-motor integration in PPR (Suppa et al. , 2015a and Suppa et al. , 2015b). Experimental evidence supports the pathophysiological role of abnormal activation in frontal cortical areas, including the primary motor cortex (M1) in patients with PPR (Varotto et al. , 2012, Suppa et al. , 2015b and Strigaro et al. , 2015). Hence, the pathophysiology of PPR should be investigated further taking into account recent advances in this research field. The PPR should be framed into the concept of "System Epilepsy", which refers to functionally coupled networks characterized by large scale neuronal populations with enduring propensity to generate seizures (Laufs, 2012 and Suppa et al. , 2015b).

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"None of the authors have potential conflicts of interest to be disclosed"

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