Altered recovery from inhibitory repetitive transcranial magnetic stimulation (rTMS) in subjects with photosensitive epilepsy

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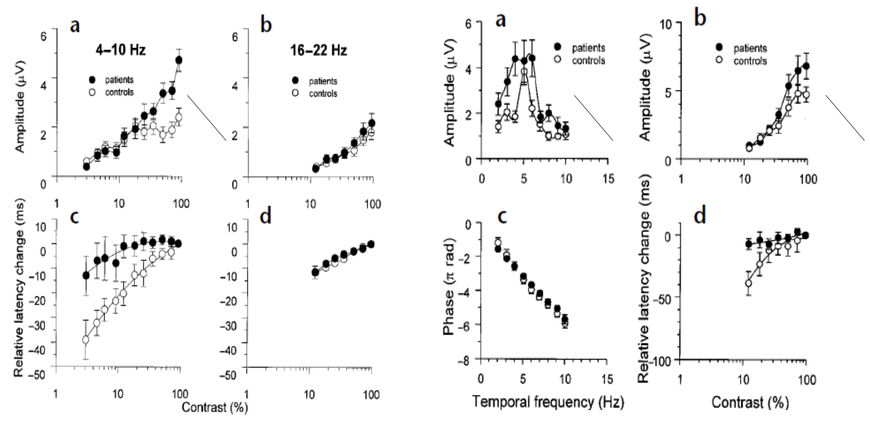
Background

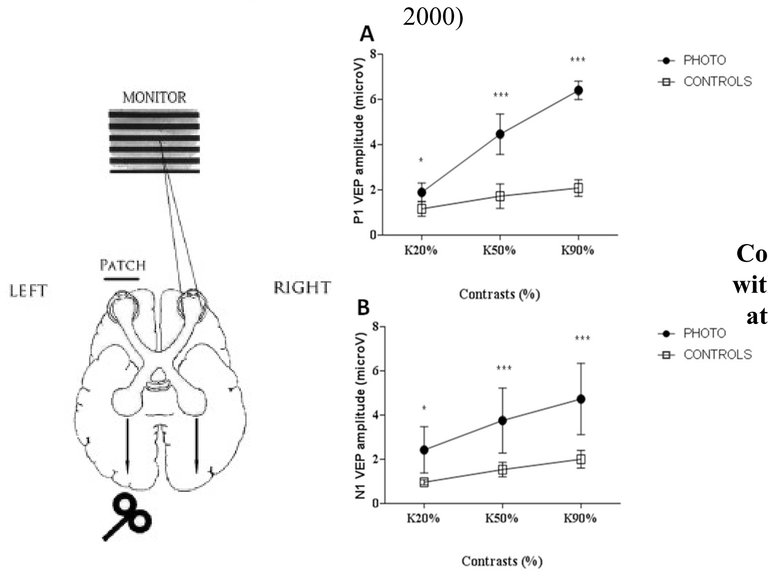
Photosensitive epilepsy (PSE) is the most common reflex epilepsy characterized by seizures induced by intermittent photic stimulation, with a high tendency towards generalization from occipital cortex (Harding et al. , 2005). Only few studies have explored the pathophysiology of PSE; some Authors have suggested a defective visual inhibition as a contributing factor to photoparoxysmal response (Strigaro et al. , 2012), pointing to an overactive visuomotor connectivity thus inducing abnormal motor responses (Strigaro et al. , 2015). Thus, we hypothesized that alterations in transcallosal inhibition may explain the impaired mechanisms of contrast gain control in photosensitive subjects. To address this issue, we enrolled ***twelve drug-free patients with PSE*** and we compared changes in VEP amplitudes induced by off-line low-frequency inhibitory rTMS applied to one occipital lobe.



"…cortical mechanisms of contrast gain control for pattern stimuli of relatively low temporal frequency and high luminance contrast are lacking or severely impaired in photosensitive subjects…" (Porciatti et al., *Nat Neurosci* 2000)

Materials and Methods

Visual evoked potentials (VEPs) triggered by grating stimuli of different contrasts were recorded in both hemispheres before and after transient functional inactivation of the occipital cortex of one side via low-frequency rTMS (0.5 Hz for 20'; Bocci et al., 2011; Bocci et al., 2016). VEPs were bilaterally recorded before (T0), just at the end (T1) and 45' (T2) after rTMS. Two different experimental conditions were tested: 1) grating stimuli were centered on the fixation point and rTMS was applied to V1; 2) grating stimuli were placed in one hemifield and rTMS was applied on ipsilateral V1. The order of these conditions were randomized across subjects. We analyzed 18 blocks of 100 averaged VEP responses (6 blocks at T0, 6 at T1 and 6 at T2), in terms of both mean amplitude (expressed as μV) and latency (ms) for different contrast levels (K90%, 50% and 20%).



Results

Full-field VEPs

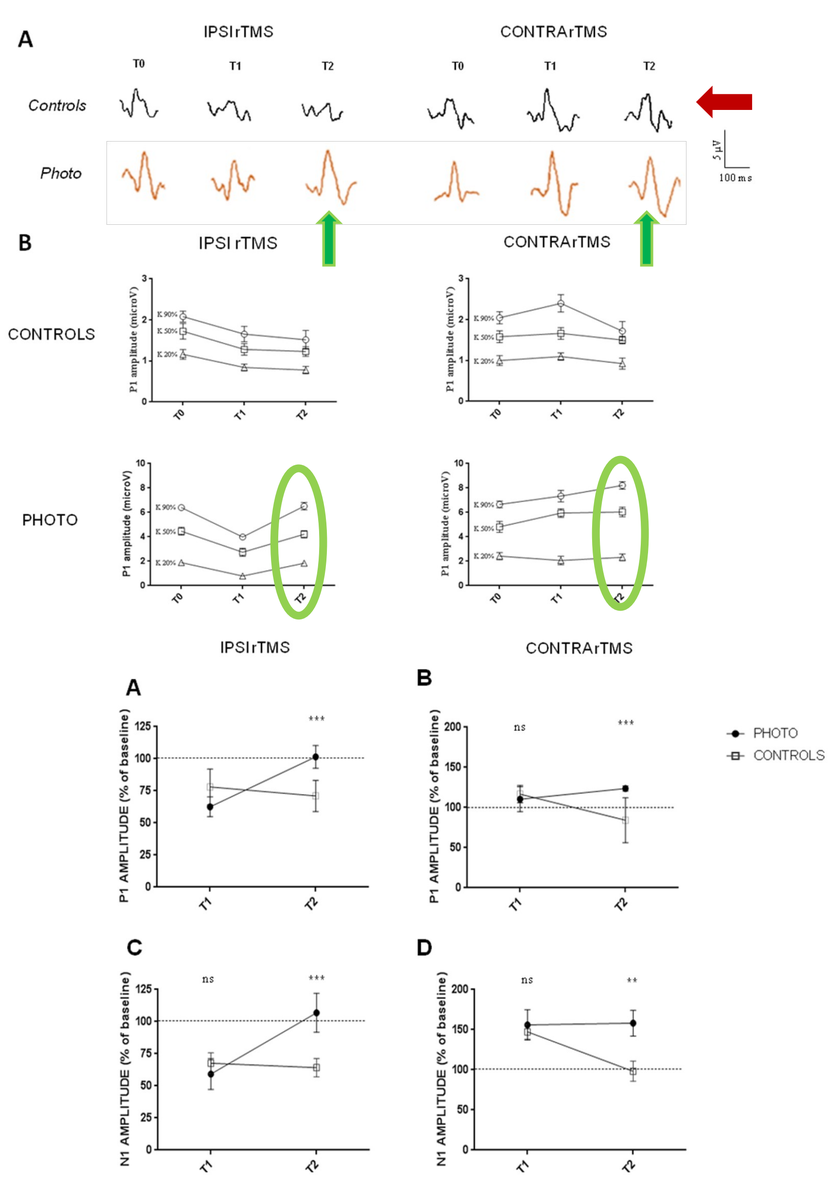


Figure 2 – At the top, representative VEP responses to central stimulation (contrast, 90%) from control and photosensitive patients, in the hemisphere ipsilateral (ipsi rTMS; left) and contralateral (contra rTMS; right) to rTMS intervention. (B) Amplitude of P1 VEP component at different contrasts (K; 20%, 50%, 90%) in the hemisphere ipsilateral (ipsi rTMS; left) and contralateral (contra rTMS; right) to rTMS intervention. Recovery from inhibitory rTMS was remarkably different. VEP amplitudes returned to baseline in the treated side of photosensitive patients (Holm-Sidak test, contrast 90%, T0 vs. T2, p = 0.54) while remaining persistently dampened in controls at T2 (left column; Holm-Sidak test, contrast 90%, T0 vs. T2, p < 0.001)

Hemifield VEPs

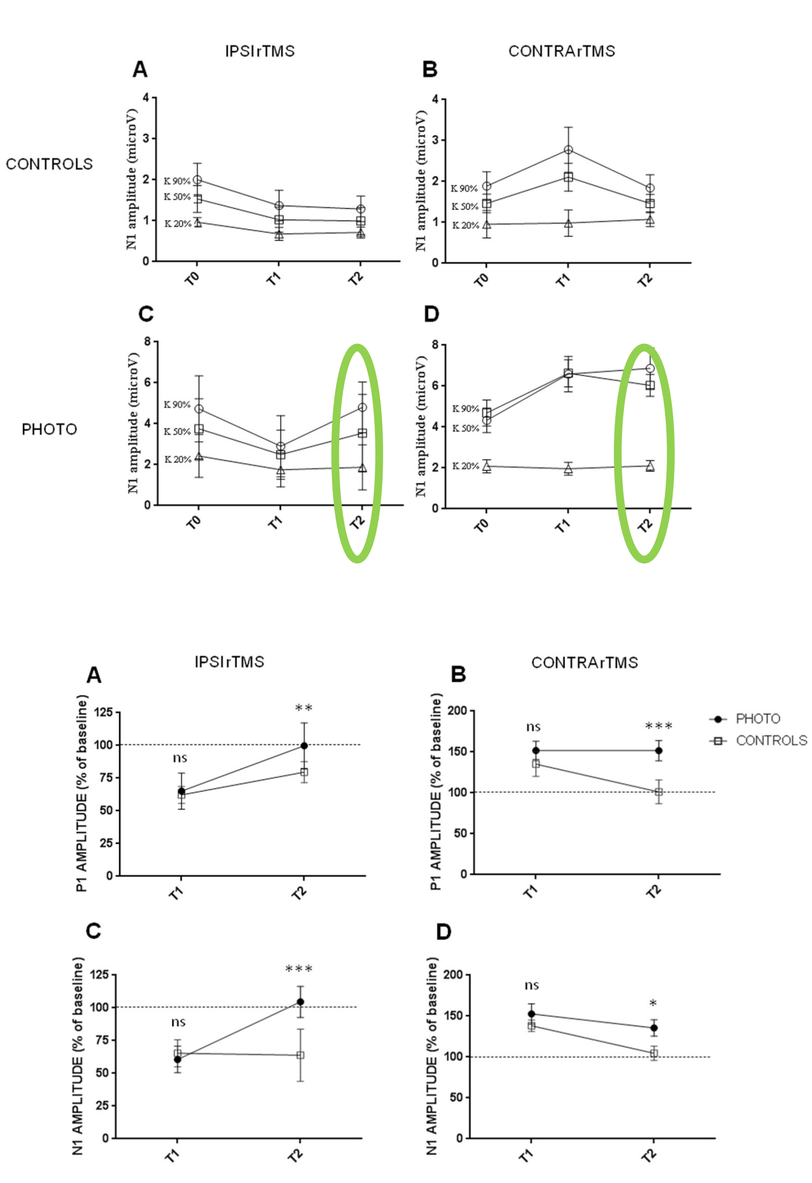


Figure 3 – N1 VEP amplitude following rTMS (hemifield stimulation): note the reduction of N1 amplitudes in the hemisphere ipsilateral to rTMS at T1 and the corresponding increase in VEP amplitudes in the contralateral side. In PSE patients, the recovery in the ipsilateral hemisphere was complete at T2 , while it was negligible in controls (Holm-Sidak test, contrast 90%, T0 vs. T2, p < 0.001; panels A,C). The contralateral hemisphere of photosensitive patients displays a persistent facilitation of visual responses at T2 (Holm-Sidak test, contrast 90%, T0 vs. T2, p < 0.001) which was absent in naïve subjects (Holm-Sidak test, contrast 90%, T0 vs. T2, p = 0.23; panels B, D).

Discussion and Conclusions

1. **Visual responses recovered more quickly in the stimulated hemisphere, and disinhibition persisted in the contralateral side of photosensitive subjects.**
2. **The rapid recovery of excitability and the persistent transcallosal disinhibition following perturbation of cortical activity may play a role in the pathophysiology of photosensitive epilepsy.**
3. **This hypothesis of an overactive visuomotor connectivity and our findings are not mutually exclusive. Beyond the stereotyped dichotomy between generalized and focal epilepsies, both sets of data seem to indicate PSE as a "system disease", possibly contributing also to a better knowledge of non-photosensitive generalized epilepsies.**