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Markers of TMS-evoked visual conscious experience in a patient with altitudinal hemianopia

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ABSTRACT

Transcranial magnetic stimulation (TMS) of the occipital and parietal cortices can induce phosphenes, i.e. visual sensations of light without light entering the eyes. In this paper, we adopted a TMS-EEG interactive co-registration approach with a patient (AM) showing altitudinal hemianopia. Occipital and parietal cortices in both hemispheres were stimulated while concurrently recording EEG signal.

Results showed that, for all sites, neural activity differentially encoding for the presence vs. absence of a conscious experience could be found in a cluster of electrodes close to the stimulation site at an early (70 ms) time-period after TMS.

The present data indicate that both occipital and parietal sites are independent early gatekeepers of perceptual awareness, thus, in line with evidence in favor of early correlates of perceptual awareness. Moreover, these data support the valuable contribution of the TMS-EEG approach in patients with visual field defects to investigate the neural processes responsible for perceptual awareness.

1. Introduction

A central goal for modern cognitive neuroscience is to uncover the neural processes that are both necessary and sufficient for perceptual awareness (Crick & Koch, 2003). During the last decades, several approaches have been proposed to disentangle the temporal and spatial dynamics correlating with visual awareness from those correlating with the absence of it. Brain imaging techniques have been useful to detect nodes and networks while event-related potential (ERP) studies gave high contribution to the temporal aspects of the emergence of perceptual awareness (Koch, Massimini, Boly, & Tononi, 2016). A recent approach (Ilmoniemi et al., 1997), which is gaining high attention in the field of consciousness studies, is the combination of electroencephalography (EEG) with transcranial magnetic stimulation (TMS). TMS is a non-invasive direct brain stimulation technique that can interfere with neural activity in a safe and reversible manner. Importantly, TMS of occipital cortex can elicit the sensation of phosphenes (e.g. Marg & Rudiak, 1994), i.e. the conscious experience of light without light entering the eyes. These forms of artificial conscious vision have been repeatedly reported both in healthy participants (e.g. Kammer, Puls, Erb, & Grodd, 2005; Mazzi, Mancini, & Savazzi, 2014; Tapia, Mazzi, Savazzi, & Beck, 2014) and in patients with visual field defects (e.g. Bagattini, Mazzi, & Savazzi, 2015; Cowey & Walsh, 2000; Mazzi et al., 2014; Silvanto, Cowey, Lavie, & Walsh, 2007). Interestingly, phosphene generation and processing seems to resemble that of real external stimuli. Indeed,

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like external stimuli, phosphenes are reacted to faster as their luminance (Knight, Mazzi, & Savazzi, 2015b) or brightness (Knight, Mazzi, & Savazzi, 2015a) increases and they show an inter-hemispheric transfer time (Marzi, Mancini, & Savazzi, 2009) in line with that of healthy subjects in response to external visual stimuli. Phosphenes are thus an ideal tool to study conscious vision and its neural correlates in a direct manner, both in the healthy and damaged brain.

Moreover, TMS-EEG co-registration methods have the advantage to record TMS-evoked potentials (TEPs), i.e. highly reproducible EEG oscillations induced by the TMS pulse (Ilmoniemi et al., 1997). TEPs can thus provide important information on the cortical reactivity and connectivity of different cortical areas (Miniussi & Thut, 2010; Taylor, Walsh, & Eimer, 2008), thus being useful for gaining access to both the temporal and spatial dynamics of neural activity during conscious experience. Importantly, TEPs provide information on the causal relationship in the connections across the network of activated areas subserving a specific task or a cognitive process with a very high temporal resolution. Thanks to the properties of the spreading of activity induced by TMS, TMS-EEG approach can thus be informative on the network of interconnected areas and, more importantly, the order of activation of these areas. The reasoning underlying this approach is that (1) if an area A results to be active prior to area B it can be assumed that the activity in area A causes a change in the activity of area B through effective connections between the two areas and (2) that the earliest differential effect found between two conditions in the experimental set-up can be assumed to be the ignition of the subsequent processing.

In the field of perceptual awareness this approach can be strongly effective in understanding whether conscious experience correlates with early or late neural processing. Two main components have, indeed, been described (Koivisto & Revonsuo, 2010) in event-related potentials (ERPs) studies: an early component, called Visual Awareness Negativity (VAN) peaking at about 200 ms after stimulus presentation and a late component, called Late Positivity (LP), peaking at about 300–400 ms after stimulus presentation. A debate exists among scientists in attributing conscious perception to early or very early processes (Aru & Bachmann, 2009; Koivisto & Revonsuo, 2010; Pins & Ffytche, 2003; Pitts, Padwal, Fennelly, Martínez, & Hillyard, 2014; Tagliabue, Mazzi, Bagattini, & Savazzi, 2016), to late processes (Del Cul, Baillet, & Dehaene, 2007; Sergent, Baillet, & Dehaene, 2005) or to a multistage process involving both early and late neural correlates (Rutiku, Martin, Bachmann, & Aru, 2015).

Similarly to ERPs, with TEPs it is possible to reveal the earliest components correlating with perceptual awareness, that is the earliest temporal interval in which neural processing for conscious experience diverges from that of unconscious processing. In addition to what can be gathered with ERPs, with TEPs it is also possible to obtain information on the causal role of neural activity in the stimulated area and the network of functionally connected areas (i.e. effective connectivity) which are responsible for awareness to emerge.

In this respect, a recent paper (Bagattini et al., 2015) investigated the neural correlates of phosphenes induced by occipital and parietal TMS while recording EEG signal. The authors found, in healthy participants, a significant difference in TEPs amplitude for phosphene-present vs. phosphene-absent trials (the so-called phosphene present/absent effect) in an early time window, around 70–100 ms after stimulation, in temporal sites for occipital TMS and in centro-parietal sites for parietal TMS. This early activity was followed by late activity, around 300 ms after stimulation, in circumscribed functionally connected sites, which has been interpreted as the consequences of the ignition induced by the earlier neural activity. Importantly, the authors also tested a patient (SL) with left hemianopia caused by a complete lesion of the left primary visual cortex. The patient was stimulated in her ipsilesional parietal cortex and she could perceive phosphenes in her damaged hemifield indicating that the integrity of V1 was not necessary to experience conscious percepts in her blind field. Moreover, the early activity found at time window around 70 ms after stimulation, was not followed by a later activity, thus indicating that late activity is not necessary for conscious perception.

In the present paper, we extended the investigation of the neural correlates of phosphenes in a patient showing altitudinal hemianopia in his upper visual field due to a bilateral damage to the lower banks of his primary visual cortex. Differently from the patient previously described whom V1 was completely damaged and thus no phosphenes could be elicited by stimulating her occipital cortex, patient AM's lesion offered the unique possibility to try and induce phosphenes by stimulating both the occipital and parietal cortices in both hemispheres. This investigation could thus offer more insight on the possibly different neural correlates of conscious vision induced by occipital and parietal stimulation and the opportunity to investigate whether hemispheric differences exist in the generation of perceptual awareness.

2. Method

2.1. Patient

Patient AM. A right handed male patient, 65-years old, suffered a bilateral altitudinal hemianopia on the upper part of his visual field resulting from an ischemic stroke. MRI evidenced a bilateral lesion of the lingual gyrus which extended to the lower bank of the primary visual cortex in the right hemisphere (Fig. 1A). The lesion location was reconstructed from the high resolution (1 mm isovoxel) T1-weighted 3D MPRAGE images by means of the MRIcro software (http://www.mccauslandcenter.sc.edu/mricro/mricro/mricro.html). Visual field defect (Fig. 1B) was assessed by means of a computerized perimetry (Humphrey system). The patient was tested in 2016, 41 months after his neurological event. The patient gave his written informed consent prior to participate in the study and he was free to withdraw at any time. The study was approved by the local Ethics Committee and conducted in accordance with the 2013 Declaration of Helsinki.

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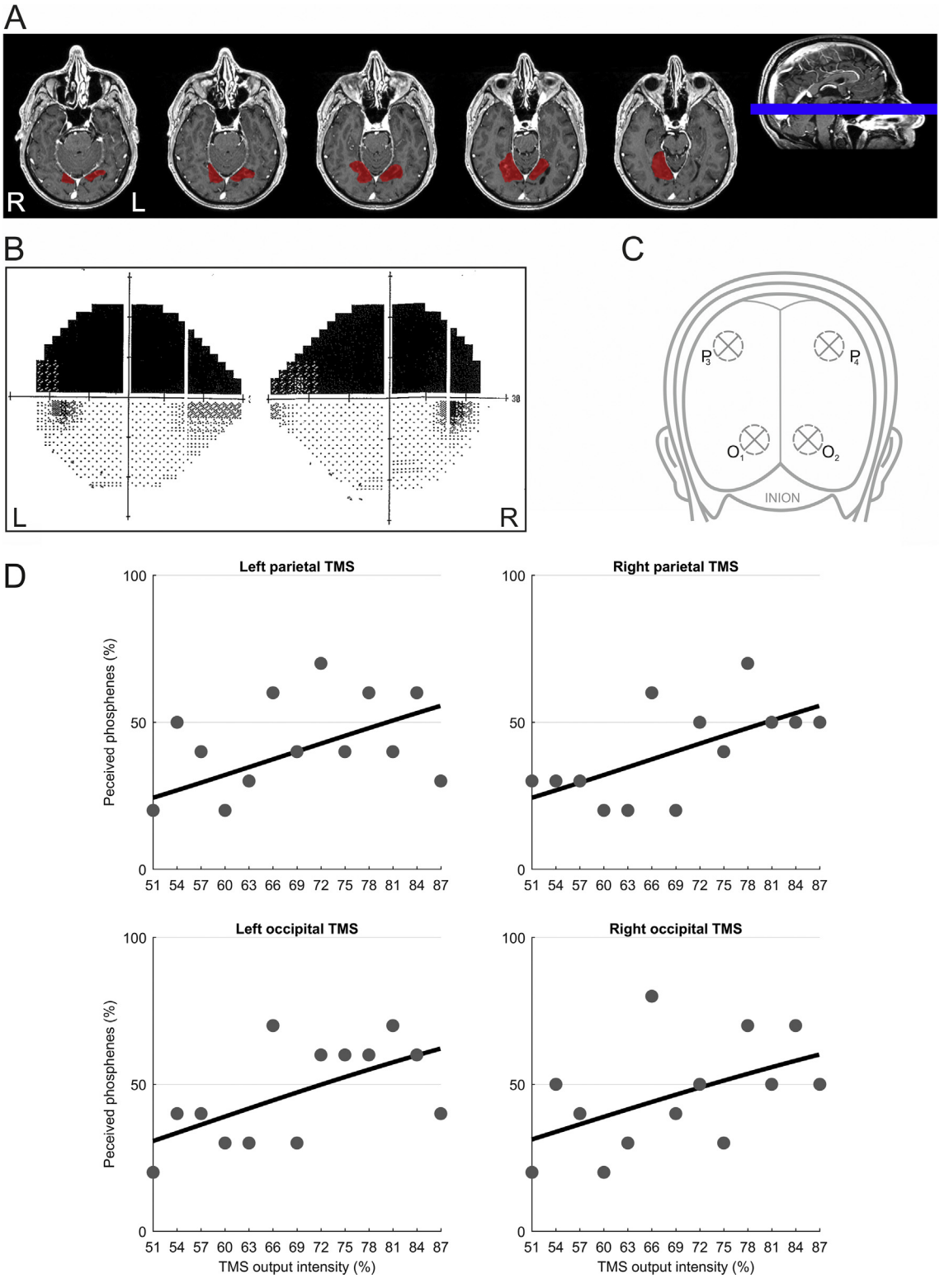

Fig. 1. Patient AM. (A) Brain lesion reconstruction on axial slices of a T1-weighted image. (B) Monocular visual field perimetry showing bilateral altitudinal hemianopia. Black areas depict the portion of the visual field interested by the visual deficit. (C) The four stimulation sites identified as the best location within a circle of 2 cm in diameter (dashed line) centered on each of the four selected electrodes, resulting in reliable phosphenes. (D) Psychometric functions of the four stimulation sites. Each dot represents the percentage of perceived phosphenes at each TMS output intensity. The black line represents the threshold function obtained. The value corresponding to the 50% was used in the experimental session while recording EEG.

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As assessed by a safety screening questionnaire (adapted from Keel, Smith, & Wassermann, 2000), patient AM was negative for the risk factors associated with TMS: he did not report cardiac pacemaker, nor any implanted metallic devices. Moreover, he had no prior history of seizure or epilepsy.

2.2. Experimental procedure

Patient AM was tested in a dimly illuminated room. He sat in front of a 17-in. CRT monitor placed at a viewing distance of 57 cm with his head secured in a chin and forehead rest. At the beginning of each of the four sessions, the cap with electrodes for EEG recording was placed on the head of the patient and then phosphene threshold (PT) was assessed for occipital or parietal sites, by means of an automatic, non-adaptive, psychophysical method ("Method of constant stimuli") implemented with Matlab (Abrahamyan et al., 2011). Thirteen randomly intermixed different intensities were employed (ranging from 51% to 87% of maximum stimulator output (MSO), with changes in steps of 3%) and ten pulses were given for each stimulator output intensity (total number of pulses per each stimulated site = 130). The data obtained were then fitted with a cumulative Weibull psychometric function via a maximum likelihood criterion using the Palamedes toolbox (http://www.palamedestoolbox.org) for Matlab. The stimulation intensity at which the patient could perceive a phosphene on 50% of trials was taken as the threshold value and used in the subsequent experimental session, in which EEG signal was recorded.

Each experimental session comprised 10 blocks of 36 trials each, for a total number of 360 stimulations per site. After each TMS pulse, the patient was requested to report the presence or absence of a phosphene with a "yes/no" response by pressing respectively the left button or the right button on the mouse. After the response was given, and after a waiting time ranging from 3000 to 3300 ms, the subsequent pulse was automatically delivered. The inter-pulse interval was never shorter than 4 s, well above the criterion assessed by safety (Anand & Hotson, 2002; Wassermann, 1998).

The four sessions were performed on two separate days; in the first day, the two occipital sites were stimulated while, one month later we stimulated the two parietal sites. The patient took a long break between the two stimulated sites (left | right hemisphere) within the same day. In total, each experimental session lasted about three and a half hours, including the setup of the EEG cap and neuro-navigation system.

2.3. TMS protocol

For all stimulated sites, single-pulse magnetic stimulation (inter-pulse interval >4 s) was delivered through a 70-mm figure-of-eight coil connected to a biphasic Magstim Rapid^2 system (maximum output 3.5 T) (Magstim Company Limited, Whitland, UK). The TMS pulse trigger and response acquisition were controlled with Matlab (The MathWorks, Natick, MA) for the phosphene threshold assessment, and with E-Prime2 software (Psychology Software Tools, Pittsburgh, PA) for the experimental session.

Neuronavigation software (SofTaxic, E.M.S., Bologna, Italy) combined with a 3D optical digitizer (Polaris Vicra, NDI, Waterloo, Canada) was used throughout the experiment to maintain the coil position over the patient's head within a 2-mm accuracy threshold. The TMS coil was placed tangentially on the surface of the scalp, parallel to the patient's sagittal midline, with the handle pointing upwards to avoid unspecific activation of neck and shoulder muscles.

The best location found for eliciting circumscribed contralateral phosphenes, the "hot spot", was then acquired by the neuro-navigation system and the coil was kept in the targeted position by means of a mechanical arm (Manfrotto magic arm, Italy, www.manfrotto.com). Further details of the procedure can be found in Mazzi et al. (2014) and in Bagattini et al. (2015).

Hot spots were located using the functional method of inducing phosphenes by stimulating with supra-threshold intensities in a region within an area of 2 cm in diameter centered on four different scalp positions (see Fig. 1C): the occipital lobes in correspondence to the O1 and O2 electrode positions and the parietal lobes in correspondence to the P3 and P4 electrode positions of the 10–20 International EEG system. These sites are most likely to correspond, respectively, to visual cortical areas V1/V2 (Salminen-Vaparanta, Noreika, Revonsuo, Koivisto, & Vanni, 2012; Thielscher, Reichenbach, Uğurbil, & Uludağ, 2010) and intraparietal sulcus in all participants (Mazzi et al., 2014).

2.4. EEG recording and TMS-evoked potentials (TEPs) analysis

TMS-compatible EEG equipment (BrainAmp, Brain Products GmbH, Munich, Germany) was used to record EEG signals (BrainVision Recorder). EEG activity was continuously recorded from a Fast'n Easy cap with 59 TMS-compatible Ag/AgCl pellet pin electrodes (EasyCap GmbH, Herrsching, Germany) placed according to the extended 10–20 International System (O1, Oz, O2, PO7, PO3, POz, PO4, PO8, P7, P5, P3, P1, Pz, P2, P4, P6, P8, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, T7, C5, C3, C1, Cz, C2, C4, C6, T8, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FT8, F7, F5, F3, F1, Fz, F2, F4, F6, F8, AF7, AF3, AF4, AF8, FP1, FP2). Additional electrodes were used as reference and ground and for the electro-oculogram. The ground electrode was placed in AFz, i.e. at the maximal distance from the stimulating TMS coil. All scalp channels were online referenced to the right mastoid (RM) and then re-referenced offline to the average of all scalp electrodes. Horizontal and vertical eye movements were detected with electrodes placed at the left and right canthi and up and below the right eye, respectively. The impedance of all electrodes was constantly kept below 5 KΩ. The EEG was recorded at 5000 Hz sampling rate with a time constant

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of 10 s as low cut-off and a high cut-off of 1000 Hz. The EEG signal was processed off-line using BrainVision Analyzer 2, MATLAB 2016b (Mathworks, USA) with the EEGLAB toolbox (version 13.6.5b, Swartz Center for Computational Neuroscience, University of California at San Diego, see Delorme & Makeig, 2004) and the TMS–EEG signal analyser (TESA) extension implemented in EEGLAB (Rogasch et al., 2016).

To reduce TMS artifacts and to record the EEG signals from the electrodes placed right beneath the TMS coil, we devised a custom-made polystyrene C-shaped annulus. The annulus was positioned over the stimulated electrodes (O1, O2, P3, P4), making it possible to place the coil over the target electrode without the need to physically remove it.

EEG preprocessing followed the pipeline suggested by Rogasch et al. (2016) in a recent paper specifically dealing with TMS-EEG data analysis. First, continuous raw signal was re-referenced offline to the average of all electrodes and segmented 500 ms before and 800 ms after the TMS pulse. Epoched data were then demeaned using the whole epoch and the TMS pulse artifact was removed from −2 ms to 10 ms and replaced with cubic interpolation with the aim of preventing ringing artifacts due to anti-aliasing filter automatically applied prior to downsampling (1000 Hz). Traces were subsequently visually inspected to reject trials contaminated with large amplitude artifacts. A first round of independent component analysis (ICA) (FastICA, Hyvärinen & Oja, 2000) with automated component selection was performed on the entire dataset to remove the tail-end of the TMS-evoked muscle activity (threshold 8 μV, time window 11–30 ms) and electrical charge artifacts. Before the second ICA, which intended to remove residual artefactual components, data were bandpass filtered (zero-phase, fourth order Butterworth band-pass) between 1 and 100 Hz and band-stop filtered between 48 and 52 Hz. The second run of the automated component selection screened also for blinks (threshold 2.5 z-scores, electrodes Fp1, Fp2) and lateral eye movements (threshold 2 z-scores, electrodes F7, F8), persistent muscle activity (threshold 60% of the total power, 30–100 Hz) and electrode noise (threshold 4 z-scores). Note that, to improve component decomposition, interpolated data around TMS were substituted for constant amplitude values (i.e. zeros) prior to each ICA and interpolated again thereafter. A last visual inspection, blind to the experimental conditions, was also carried out with the aim of rejecting traces with possible remaining artifacts. Finally, data were low-pass filtered (20 Hz) and baseline corrected (from −100 to −5 ms pre TMS).

TMS-evoked potentials (TEPs) were then calculated by averaging the resulting good epochs for each stimulation site, separately for trials where the patient reported perceiving a phosphene (hereafter called "phosphene-present" trials/condition) and those where TMS did not elicit any visual percept (hereafter called "phosphene-absent" trials/condition).

2.5. Statistical analysis

To characterize the spatio-temporal dynamics of the TEPs, two measures were calculated: The Global Mean Field Power (GMFP) and the Global Dissimilarity index (GDI). These two indexes are reference-independent measures providing complementary information on the strength of neural activity at a given time-point and on the location and orientation of underlying generators of neural activity recorded at scalp level at a given time-point (Michel & Murray, 2012).

To obtain the overall amount of electrical activity induced by TMS, the Global Mean Field Power (GMFP) was computed at each time-point in the series. GMFP is calculated as the root mean-squared value of the signal across all electrodes (average reference) divided by the number of electrodes (Lehmann & Skrandies, 1980; Michel & Murray, 2012). GMFP reflects the amount of synchronous (coherent) activity at a given time-period within the epoch: the higher the GMFP, the higher the synchrony and consistency of activity across observations. We computed three GMFP from 100 ms before to 400 ms after TMS: on the average of all trials, i.e. regardless of the patient's response (Fig. 2, purple line), on the average of phosphene-absent trials (Fig. 3, blue line) and on the average of phosphene-present trials (Fig. 3, red line). For each condition, the 95% confidence interval (CI) of the mean of the distribution was calculated.

To quantify the stability of successive topographic maps (microstates) over time, the Global Dissimilarity index (GDI) was computed. GDI is calculated as the root mean square of the difference of two maps normalized by the GMFP. This measure is calculated for each time-point along the epoch and it ranges between 0 and 2, where 0 refers to topography stability and 2 to topography inversion. This measure is inversely related to the spatial correlation between two maps and it makes possible to assess topographical similarity/dissimilarity between successive maps and, thus, to isolate period of topographic stability over time, the so-called functional microstates of activity (Lehmann, 1987). We computed three GDI from 100 ms before to 400 ms after TMS: on the average of all trials, i.e. regardless of the patient's response (Fig. 2, purple line), on the average of phosphene-absent trials (Fig. 3, blue line) and on the average of phosphene-present trials (Fig. 3, red line). For each condition, the 95% confidence interval (CI) of the mean of the distribution was calculated.

These two indices were calculated using the MATLAB function eeg_gfp implemented by Darren L. Weber under the terms of the GNU General Public License.

In order to assess statistical significance of the phosphene present/absent effect, for each of the stimulated sites, the difference in amplitude for the two conditions (phosphene-present|phosphene-absent) was analyzed by means of a non-parametric Monte Carlo percentile two-tailed bootstrap simulation (Efron & Tibshirani, 1993; Oruc et al., 2011). We created a simulated data distribution with 10,000 re-sampled sets of raw data with replacement. A p-values of 0.05 was used as the significance level and false-discovery-rate (FDR) correction was applied to control for multiple comparisons (Murray, Brunet, & Michel, 2008). Since we cannot predict which trial in the sequence would result in a phosphene-present or absent outcome and, more importantly, that the two conditions did not result in the same number of trials, before running the bootstrap analysis, the order of trials was randomized within each of the two conditions (phosphene-present/phosphene-absent) and the size of the resample data corresponded to the lower number of trials between the two conditions.

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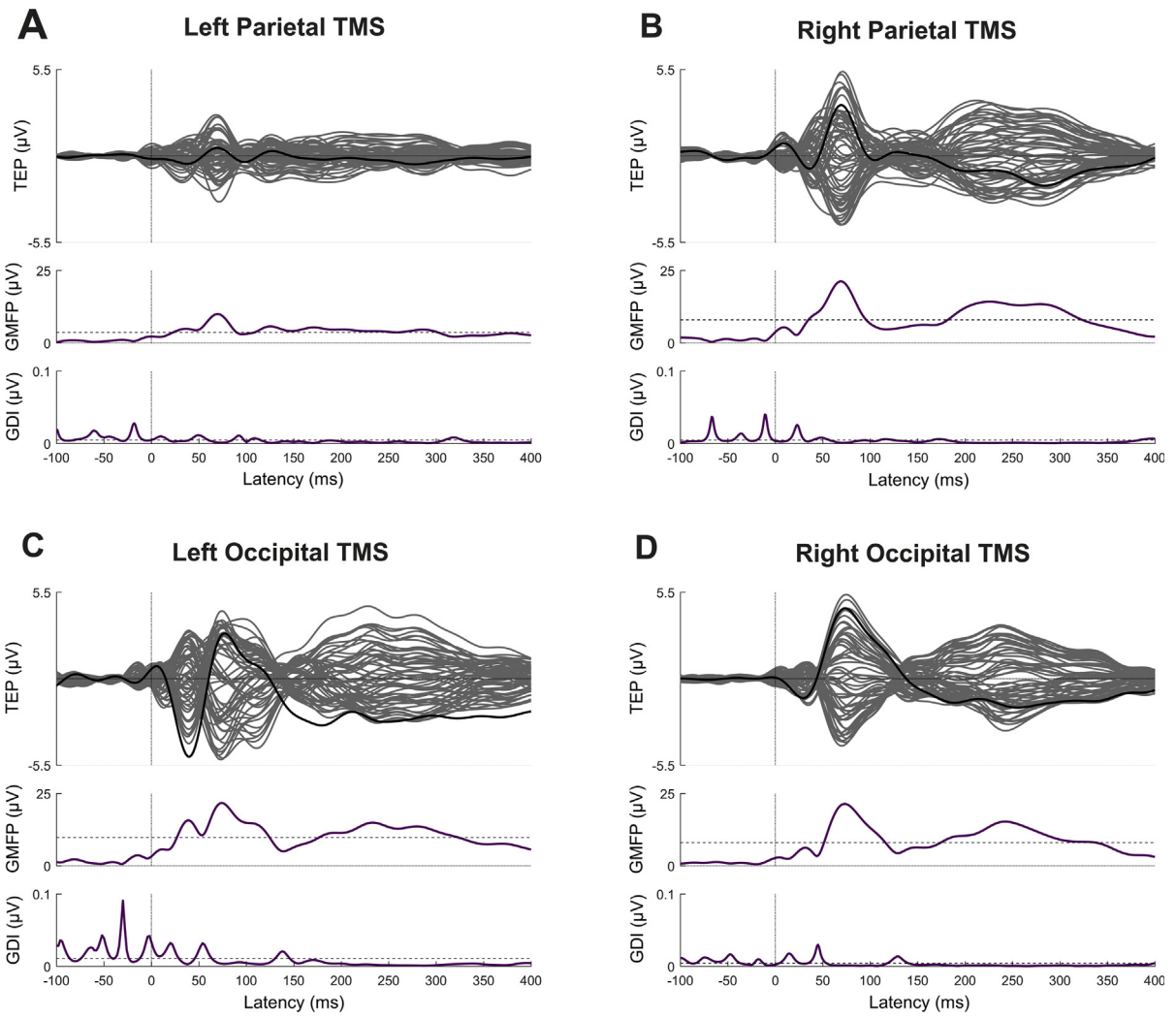

Fig. 2. Results regardless the patient's phosphene report for each stimulated site. Upper panel: Butterfly plots from −100 to 400 ms (each line is the average of an electrode). The black line corresponds to the electrode underlying the TMS coil. Middle panel and bottom panel: Respectively Global Mean Field Power (GMFP) and Global Dissimilarity index (GDI) plotted in purple. The dashed lines in the middle and lower panels represent the 95% confidence interval of the mean of the distribution. (A) Left parietal TMS. (B) Right parietal TMS. (C) Left occipital TMS. (D) Right occipital TMS.

3. Results

3.1. Phosphene threshold functions

The stimulated sites for patient AM are shown in Fig. 1C. Patient AM could experience phosphenes, described as brief, static and mostly greyish or white patches, when TMS was applied over both occipital and parietal cortices in both hemispheres. Interestingly, in all the four stimulation sites, the patient reported to perceive the phosphenes in his upper (blind) visual field.

Phosphene threshold intensity was reached at 72% of the MSO for the left occipital site, at 73% of the MSO for the right occipital site, at 83% of the MSO for the left parietal site and at 80% of the MSO for the right parietal site. As previously described (Bagattini et al., 2015; Mazzi et al., 2014) the two phosphene thresholds for the parietal cortices appeared to be higher than the occipital phosphenes thresholds. More importantly, patient AM could reliably report the presence of a phosphene, as assessed by the evidence that the reports of a phosphenes increased as the stimulation intensity increased and that these reports fitted well with cumulative Weibull psychometric functions (Fig. 1D).

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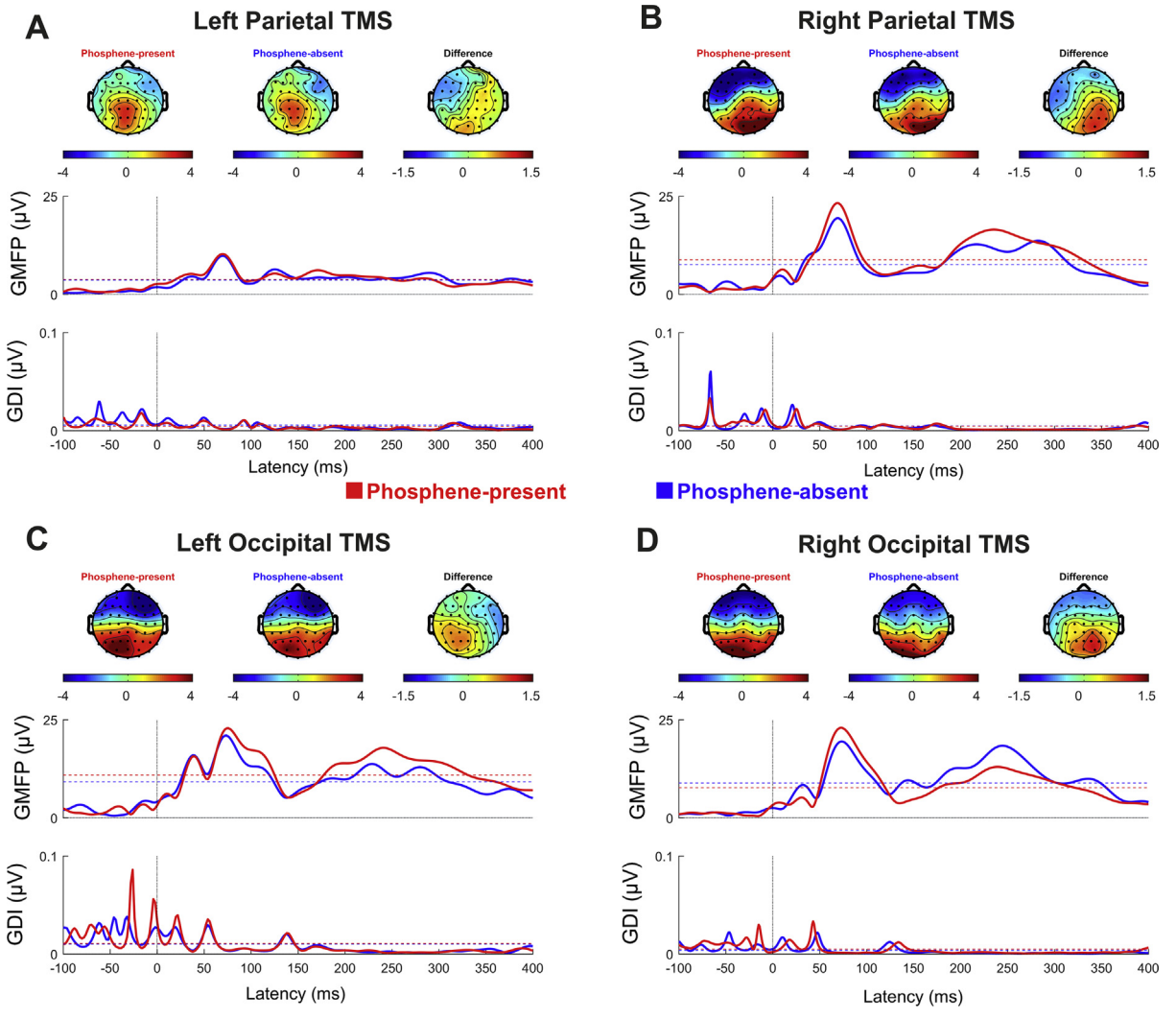

Fig. 3. Results considering phosphene-present trials versus phosphene-absent trials for each stimulated site. Upper panel: Scalp topographic distributions of the TMS evoked activity (μV) displayed for phosphene perception, absence of phosphene and the difference between the two, computed in correspondence of the maximum GMFP (considered independently from the phosphene report). Middle panel and bottom panels: respectively Global Mean Field Power (GMFP) and Global Dissimilarity index (GDI) plotted in red (phosphene-present condition) and blue (phosphene-absent condition). Dashed lines in the middle and lower panels represent the 95% confidence interval of the mean of the distribution. (A) Left parietal TMS. (B) Right parietal TMS. (C) Left occipital TMS. (D) Right occipital TMS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2. Left parietal TMS

Stimulating the left parietal cortex (P3), patient AM reported phosphenes in 59% of the trials (N = 214) and in the remaining 41% of trials (N = 146) no percepts were reported. Following the artifact rejection, trials for phosphene-present condition were 170 and 114 for phosphene-absent condition. Considering the butterfly plot in Fig. 2A (upper panel) a main deflection at around 70 ms following the TMS pulse can be identified. This component reflects a period of overall strength of the electric field as confirmed by the greatest GMFP peak (9.976 μV) which is located within the same time-range (70 ms) and whose value is greater than the 95% of the confidence interval (dashed line, Fig. 2A, middle panel). Values of the Global Dissimilarity index (Fig. 2A, lower panel) are correspondingly very low (not exceeding the 95% of the confidence interval, dashed line), therefore supporting the idea of a moment of quasi-stability of consecutive maps. The FDR corrected bootstrap comparison performed between the two conditions reveals that the earliest latency where to find a significant difference ($p < 0.05$) in TEPs amplitude between phosphene-present trials and phosphene-absent trials is in the time window from ~70 ms to ~90 ms after TMS. The effect was detectable at occipito-parietal and central scalp electrodes (O1, PO7, PO3, P7, P3, P1,

TP7, T7, C5, C3) in the stimulated hemisphere, as also highlighted in the difference topographic map depicted in Fig. 2A, upper panel.

Examining data divided on the basis of patient's reports, the maximal GMFP peaks can be found again in the same time period, characterized by high neural synchronization and they appear to be temporally overlapped (maximal phosphene-present GMFP peak = 10.282 μV at 70 ms after TMS and maximal phosphene-absent GMFP peak = 9.816 μV at 70 ms after TMS, Fig. 3A, middle panel) though higher in amplitude when perceiving a phosphene. Once again, both the two conditions exceed the 95% of the confidence interval of the epoch distribution, confirming high neural coherence. Accordingly, also the GDI was lower than the 95% of the confidence interval for both phosphene-present and phosphene-absent conditions, thus being indicative of the presence of a microstate in neural activity.

3.3. Right parietal TMS

When stimulating the right parietal cortex (P4), phosphenes were reported in 50% of the trials (N = 179) while in the other half of the trials nothing was seen (N = 181). Preprocessing steps reduced the total amount of trials to 156 for phosphene-presence condition and to160 for phosphene-absent condition.

TEPs waveform are characterized by two deflections, the first at about 70 ms while the second one around 240 ms following TMS, as shown by the butterfly plot in Fig. 2B (upper panel, electrode P4 highlighted in black). GMFP data (Fig. 2B, middle panel) in correspondence with these two components exceed the 95% of the confidence interval of the whole data distribution and the maximal GMFP peak (21.270 μV) matches with the latency of the first deflection (69 ms after TMS). At the same time, the corresponding GDI data (Fig. 2B, lower panel) are extremely low (not exceeding the 95% of the confidence interval, dashed line). Taken together, these two indices indicate high global synchronization and a period of stable spatial distribution of TEPs.

Moreover, when comparing the two conditions (phosphene-present vs. phosphene-absence) with a 10000 resampling bootstrap and correcting results with FDR, the earliest difference is found from ~50 ms to ~80 ms after the TMS onset, and this effect is topographically located at occipito-parietal and central scalp electrodes (O2, PO4, PO8, P2, P4, P6, P8, CP2, CP4, CP6, TP8, C2, C4) ipsilateral to the stimulated hemisphere. The maximum general GMFP time point corresponding to 69 ms (at which power maps are shown in Fig. 3B, upper panel) also represents the biggest GMFP value for both the conditions taken separately (phosphene-present max GMFP = 23.244 μV and phosphene-absent max GMFP = 19.402 μV, both values exceeding the 95% of the confidence interval) with a higher amplitude for trials in which conscious visual percepts were reported. Moreover, scalp distribution maps of the two conditions reflect a quasi-stable landscape (i.e. with a Global Dissimilarity Index lower than the 95% of the confidence interval; Fig. 3B, lower panel), thus being indicative of the presence of a microstate in neural activity.

3.4. Left occipital TMS

When stimulating the left occipital cortex (O1), AM reported perceiving a phosphene in 41% of the trials (N = 149), while single-pulse TMS did not elicit a phosphene in the remaining 59% of trials (N = 211). After pre-processing the EEG data, the phosphene-present and phosphene-absent conditions resulted in 102 and 139 trials, respectively.

Fig. 2C (upper panel) show the butterfly plot of the TEPs waves evoked by left occipital stimulation regardless of the patient's response, where each wave corresponds to one electrode and the electrode underlying the TMS coil is depicted in black. As it can be seen, two main deflections can be detected, one around 70 ms after TMS and a later one at about 240 ms after TMS. These two deflections reflect high neural coherence in the time series, in which the GMFP exceeds the 95% of the confidence interval of the entire distribution of data. Importantly, the highest amount of synchrony in the neural activity, as measured by the GMFP (maximal GMFP peak of 21.705 μV at 74 ms after TMS), corresponds to the earlier deflection (Fig. 2C, middle panel). Within the same time-period the Global Dissimilarity index remained low (not exceeding the 95% of the confidence interval, dashed line in Fig. 2C, lower panel), thus indicating a moment of stability in the topography of the effect (i.e. a microstate).

Importantly, as assessed by the FDR-corrected bootstrap tests, the earliest latency in which a significant difference ($p < 0.05$) in TEPs amplitude between phosphene-present and phosphene-absent patient's reports can be found from ~60 ms to ~90 ms after TMS in the stimulated hemisphere at centro-parietal scalp electrodes (PO3, P3, P1, CP5, CP3, CP1, C5, C3, C1). The topography of the phosphenes present/absent effect can be seen in Fig. 3C as scalp intensity maps and it corresponds to the time-period showing the highest GMFP for both phosphene-present (maximal GMFP peak of 22.831 μV at 76 ms after TMS) and phosphene-absent (maximal GMFP peak of 20.966 μV at 74 ms after TMS) trials (Fig. 3C, upper panel), i.e. when neural coherence is the highest, with higher synchronous activity for the generation of awareness (phosphene-present trials) than for unconscious processing (phosphene-absent trials). Also in this case, in this time-period the GMFP of the two conditions exceed the 95% of the confidence interval of the entire epoch distribution, thus indicating high neural coherence. Moreover, in the same time-period, the topographies of both conditions showed to pertain to a quasi-stable landscape (i.e. with a Global Dissimilarity Index lower than the 95% of the confidence interval; Fig. 3C, lower panel), thus being indicative of the presence of a microstate in neural activity.

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3.5. Right occipital TMS

TMS stimulation of the right occipital cortex (O2) resulted in the perception of a phosphene in 54% of the trials (N = 194), while in the remaining 46% of trials (N = 166) the patient could not perceive anything. Following the EEG preprocessing, a total of 166 trials for the phosphene-present condition and 128 trials for the phosphene-absent condition were used to compute each average.

The butterfly plot (Fig. 2D, upper panel) depicting averaged TEPs in all electrodes while stimulating O2 (in black) regardless of phosphene report, highlights two main deflections due to TMS: the first around 70 ms and the second at about 240 ms after the TMS pulse onset. They both reflect a period of high global neural coherence as indicated by a corresponding value of GMFP greater than the 95% of the confidence interval of the entire distribution of data (black dashed line, Fig. 2D, middle panel). In addition, the first deflection represents the moment within the whole epoch with the highest synchronization (maximal GMFP peak of 21.380 μV at 73 ms after TMS) and at the same time, a low value of the Global Dissimilarity Index (not exceeding the 95% of the confidence interval, dashed line in Fig. 2D, lower panel), thus, identifying a microstate (i.e. stable spatial distribution of TEP in that specific moment).

Interestingly, the first significant difference revealed comparing with a bootstrap approach (FDR correction) the TEPs amplitude between phosphene-present and phosphene-absent can be seen from ~60 ms to ~90 ms after the TMS. This difference was detectable ipsilaterally to the stimulation at occipito-parietal scalp electrodes (O2, PO4, PO8, P2, P4, CP2) as shown in Fig. 3D (upper panel). The same latency also corresponds to the highest GMFP for both phosphene-present (maximal GMFP peak of 22.935 μV at 73 ms after TMS) and phosphene-absent (maximal GMFP peak of 19.453 μV at 73 ms after TMS) trials, where we can observe a higher synchronous activity for the generation of awareness (phosphene-present trials) than for unconscious processing (phosphene-absent trials). Once again, the GMPF values corresponding to this range of time (~60–90 ms) are greater than the 95% of the confidence interval of the entire epoch distribution, also when considering trials split for the two conditions, thus, confirming high neuronal coherence. It has finally to be noted that the scalp potential maps of the two conditions exhibited low GDI values (i.e. not exceeding the 95% of the confidence interval), indicating the presence of a microstate in neural activity.

4. Discussion

The present paper aimed at investigating the spatio-temporal dynamics of the awareness of occipital and parietal phosphenes. To do this we used a TMS-EEG interactive co-registration approach (Miniussi & Thut, 2010). This methodology allowed us to elicit phosphenes by stimulating V1/V2 and IPS sites and, thanks to the EEG signal recording, to uncover cortical reactivity and connectivity (Ilmoniemi et al., 1997; Miniussi & Thut, 2010) correlating with the presence or absence of phosphenes. Moreover, we applied this methodology to a patient with altitudinal hemianopia resulting from a bilateral lesion of the occipital cortex. Previous works (Bagattini et al., 2015; Mazzi et al., 2014) already studied phosphenes awareness in hemianopic patients, however, patient AM's lesion (i.e. involving occipital cortex bilaterally but not completely, thus spearing the lower portion of his visual field) offered the possibility to investigate, in a damaged brain, the neural processes correlating also with occipital phosphenes. Moreover, to study this patient also offered the possibility to apply the same methodology to both hemispheres and to show whether, as suggested by data reported in literature (Cavézian et al., 2010; Chokron, Perez, & Peyrin, 2016), lesion side can lead to different impairments.

In the present paper we, thus, stimulated both the occipital and the parietal cortices in both hemispheres while concurrently recording EEG signal. In line with previous data (Bagattini et al., 2015; Mazzi et al., 2014), patient AM could reliably assess the presence of a phosphene elicited by parietal stimulation. As a novel evidence, patient AM could also reliably report phosphenes while his occipital cortex was stimulated. Moreover, the threshold for phosphene detection was higher for parietal than for occipital TMS, again in line with previous reports (Bagattini et al., 2015; Fried, Elkin-Frankston, Rushmore, Hilgetag, & Valero-Cabre, 2011; Mazzi et al., 2014). Importantly, for both the occipital and parietal stimulation sites, in both hemispheres, it was possible to find a cluster of electrodes in posterior sites, ipsilaterally to stimulated hemisphere, reliably showing differential activity for the presence vs. absence of the perception of phosphenes. Moreover, this differential activity peaked, for all sites of stimulation, at an early time window, i.e. around 70 ms after TMS.

The present data thus showed that: (1) we cannot establish a clear difference between hemispheres in the generation of the perceptual awareness of phosphenes as no clear evidence of either timing and topography can be found among the stimulated sites; (2) neural activity differentially correlates with the presence or the absence of a conscious experience in occipital and parietal sites at the same time window and (3) the earliest time window showing differential activity for conscious vs. unconscious processing is at an early time-period after stimulation.

The present results, in our opinion, have, thus, several important implications. Firstly, they corroborate previous evidence (Bagattini et al., 2015; Mazzi et al., 2014) on the independence of the occipital and parietal cortices in the generation of phosphenes. Indeed, to postulate the need for recurrent processing feeding back to V1 in the emergence of awareness (Lamme, Supèr, & Spekreijse, 1998), one needs to find that stimulation of an area hierarchically higher than V1 would correlate with awareness in a later time window than stimulation of V1. Following Lamme's model, in fact, additional time would be needed for neural activity to travel back to V1 from IPS and ignite conscious processing, thus leading to a later latency for phosphene perception after IPS stimulation than after V1 stimulation. This additional time has been broadly quantified

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in about 40 ms after the time of activity in higher-order areas (Lamme, 2001). Despite in the present paper we did not find such a large difference, we tested whether the activity in parietal cortex was later in time than that in occipital cortex. We thus preformed non-parametric Monte Carlo percentile one-tailed bootstrap simulations on the latency of the peak of activity within the temporal window of 50–100 ms after TMS between parietal and occipital electrodes during parietal and occipital stimulation respectively. Different tests were performed, for each hemisphere, on the general activity recorded on the scalp, i.e. regardless of patient's subjective reports (Fig. 2), and on the activity obtained considering the presence/absence of a phosphene. These analyses did not show any differences (all $p > 0.05$) in latency for the parietal and occipital electrodes in all the conditions tested. Importantly, the lack of significant differences with respect to the timing of the neural activity differentially correlating with the presence/absence of a phosphene can let us conclude that the time window for the emergence of occipital and parietal phosphenes is the same, thus ruling out any involvement of feedback to V1 in perceptual awareness (Ffytche & Zeki, 2011; Silvanto, 2014). The present results, thus, argue for the existence of different gatekeepers for the emergence of awareness (Moutoussis & Zeki, 2002) in different (posterior) areas of the brain. These data are in line with accumulating findings showing that neural correlates best correlating with perceptual awareness are "primarily localized to a posterior cortical hot zone" (see for a review, Koch et al., 2016), which includes occipital, temporal and posterior parietal cortices.

Secondly, the present data and those of the same kind already present in literature (Bagattini et al., 2015), argue for an early stage of processing to be responsible for the emergence of awareness. The time window in which differential neural activity, able to distinguish between the presence and the absence of perceptual awareness (i.e. a phosphene), can be found is around 70 ms after stimulation of the cortex. This time window is in line with previous findings using the same TMS-EEG co-registration approach both with healthy participants and hemianopic patients (Bagattini et al., 2015) and it corroborates evidence in favor of early correlates of visual awareness found in ERP studies (e.g. Bachmann, 2009; Koivisto & Revonsuo, 2010; Railo, Koivisto, & Revonsuo, 2011). In this respect, it must be noted that a direct comparison between TEPs and ERPs latencies can only be speculative (Bagattini et al., 2015). Indeed, in the case of phosphenes, the percept is generated in the cortex, thus lacking all the subcortical processing reaching to it. To make a direct comparison between TEPs and ERPs latencies one would, thus, need to postulate that the timing of neural processing reaching the cortex from the retina for real stimuli, which is of about 40–80 ms, would be the same for phosphenes. Although caution should be taken to make a strict parallel between activity induced by TMS and that induced by real stimuli, a latency of 70 ms in TEPs could, then, correspond to a latency of about 150 ms in ERPs (i.e. 70 ms after cortical direct stimulation plus the time needed for activity to reach the cortex from the retina).

Moreover, the added value provided by the TMS-EEG interactive approach stands on its power to reveal causal effects induced by TMS on the reactivity and connectivity of the stimulated cortex. In this respect, although we adopted a contrastive approach (i.e. we contrasted conditions in which patient AM reported seen a phosphene with those in which he reported the absence of it), which has its known limitations (Aru, Bachmann, Singer, & Melloni, 2012), we believe that, thanks to the capabilities of the TMS-EEG interactive approach to directly "read" the state of the cortex under stimulation and its functional network of connected areas, and the use of patients, we can reliably infer the earliest moment in time correlating with the emergence of awareness (NCC) as something different from the consequences (NCC-co) of awareness, i.e. post-perceptual processes.

Finally, the present data add further evidence on the possibility to generate conscious percepts in the blind field of hemianopic patients by means of TMS. In line with previous attempts (Bagattini et al., 2015; Mazzi et al., 2014), the stimulation of the lesioned hemisphere (in patient AM, bilaterally as the lesion was bilateral) could induce conscious percepts. Importantly, differently from data already present in literature (Silvanto, Cowey, & Walsh, 2008; Silvanto et al., 2007), in which the perception of phosphenes was elicited by bilateral stimulation only, in the present paper and in previous ones (Bagattini et al., 2015; Mazzi et al., 2014), unilateral stimulation of the cortex was sufficient to elicit conscious percepts (see for a discussion, Silvanto, 2014, 2015). These results are important as they highlight the significance of the study of patients with visual field defects to gain more information on the neural processes responsible for the generation of perceptual awareness.

In conclusion, our results demonstrate the valuable role that can be played by the combination of a TMS-EEG interactive co-registration approach (Miniussi and Thut, 2010) with the use of patients with visual field defects in the field of perceptual awareness. Moreover, the present data and those already present in literature (Bagattini et al., 2015) corroborate evidence in ERP studies (e.g. Bachmann, 2009; Koivisto and Revonsuo, 2010; Railo, Koivisto, & Revonsuo, 2011) in favor of early correlates of visual awareness and suggest that several posterior areas in the brain can serve as early gatekeepers (Moutoussis and Zeki, 2002) of perceptual awareness in the human brain.

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References

Abrahamyan, A., Clifford, C. W. G., Ruzzoli, M., Phillips, D., Arabzadeh, E., & Harris, J. A. (2011). Accurate and rapid estimation of phosphene thresholds (REPT). *PLoS ONE, 6*(7). http://dx.doi.org/10.1371/journal.pone.0022342.

Anand, S., & Hotson, J. (2002). Transcranial magnetic stimulation: neurophysiological applications and safety. *Brain and Cognition, 50*(3), 366–386. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12480484.

Aru, J., & Bachmann, T. (2009). Boosting up gamma-band oscillations leaves target-stimulus in masking out of awareness: Explaining an apparent paradox. *Neuroscience Letters, 450*(3), 351–355. http://dx.doi.org/10.1016/j.neulet.2008.11.063.

Aru, J., Bachmann, T., Singer, W., & Melloni, L. (2012). Distilling the neural correlates of consciousness. *Neuroscience and Biobehavioral Reviews*. http://dx.doi.org/10.1016/j.neubiorev.2011.12.003.

Bachmann, T. (2009). Finding ERP-signatures of target awareness: Puzzle persists because of experimental co-variation of the objective and subjective variables. *Consciousness and Cognition, 18*(3), 804–808. http://dx.doi.org/10.1016/j.concog.2009.02.011.

Bagattini, C., Mazzi, C., & Savazzi, S. (2015). Waves of awareness for occipital and parietal phosphenes perception. *Neuropsychologia, 70*. http://dx.doi.org/10.1016/j.neuropsychologia.2015.02.021.

Cavézian, C., Gaudry, I., Perez, C., Coubard, O., Doucet, G., Peyrin, C., ... Chokron, S. (2010). Specific impairments in visual processing following lesion side in hemianopic patients. *Cortex, 46*(9), 1123–1131. http://dx.doi.org/10.1016/j.cortex.2009.08.013.

Chokron, S., Perez, C., & Peyrin, C. (2016). Behavioral consequences and cortical reorganization in homonymous hemianopia. *Frontiers in Systems Neuroscience, 10*, 57. http://dx.doi.org/10.3389/fnsys.2016.00057.

Cowey, a., & Walsh, V. (2000). Magnetically induced phosphenes in sighted, blind and blindsighted observers. *NeuroReport, 11*(14), 3269–3273. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11043562.

Crick, F., & Koch, C. (2003). A framework for consciousness. *Nature Neuroscience, 6*(2), 119–126. http://dx.doi.org/10.1038/nn0203-119.

Del Cul, A., Baillet, S., & Dehaene, S. (2007). Brain dynamics underlying the nonlinear threshold for access to consciousness. *PLoS Biology, 5*, 2408–2423. http://dx.doi.org/10.1371/journal.pbio.0050260.

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods, 134*(1), 9–21. http://dx.doi.org/10.1016/j.jneumeth.2003.10.009.

Efron, B., & Tibshirani, R. J. (1993). An Introduction to the Bootstrap. *Refrigeration and Air Conditioning, 57*(57), 436. http://dx.doi.org/10.1111/1467-9639.00050.

Ffytche, D. H., & Zeki, S. (2011). The primary visual cortex, and feedback to it, are not necessary for conscious vision. *Brain, 134*(1), 247–257. http://dx.doi.org/10.1093/brain/awq305.

Fried, P. J., Elkin-Frankston, S., Rushmore, R. J., Hilgetag, C. C., & Valero-Cabre, A. (2011). Characterization of visual percepts evoked by noninvasive stimulation of the human posterior parietal cortex. *PLoS ONE, 6*(11). http://dx.doi.org/10.1371/journal.pone.0027204.

Hyvärinen, A., & Oja, E. (2000). Independent component analysis: Algorithms and applications. *Neural Networks, 13*(45), 411–430.

Ilmoniemi, R. J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H. J., Näätänen, R., & Katila, T. (1997). Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *NeuroReport, 8*(16), 3537–3540. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9427322.

Kammer, T., Puls, K., Erb, M., & Grodd, W. (2005). Transcranial magnetic stimulation in the visual system. II. Characterization of induced phosphenes and scotomas. *Experimental Brain Research. Experimentelle Hirnforschung. Expérimentation Cérébrale, 160*(1), 129–140. http://dx.doi.org/10.1007/s00221-004-1992-0.

Keel, J. C., Smith, M. J., & Wassermann, E. M. (2000). Letter to the Editor. A safety screening questionnaire for transcranial magnetic stimulation. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 112*, 720. http://dx.doi.org/10.3111/13696998.2014.909438.

Knight, R., Mazzi, C., & Savazzi, S. (2015a). Assessing the effects of physical and perceived luminance contrast on RT and TMS-induced percepts. *Experimental Brain Research, 233*(12). http://dx.doi.org/10.1007/s00221-015-4419-1.

Knight, R., Mazzi, C., & Savazzi, S. (2015b). Shining new light on dark percepts: Visual sensations induced by TMS. *Experimental Brain Research, 233*(11). http://dx.doi.org/10.1007/s00221-015-4381-y.

Koch, C., Massimini, M., Boly, M., & Tononi, G. (2016). Neural correlates of consciousness: Progress and problems. *Nature Reviews Neuroscience, 17*(5), 307–321. http://dx.doi.org/10.1038/nrn.2016.22.

Koivisto, M., & Revonsuo, A. (2010). Event-related brain potential correlates of visual awareness. *Neuroscience and Biobehavioral Reviews, 34*(6), 922–934. http://dx.doi.org/10.1016/j.neubiorev.2009.12.002.

Lamme, V. A. F. (2001). Blindsight: The role of feedforward and feedback corticocortical connections. *Acta Psychologica, 107*(1–3), 209–228. http://dx.doi.org/10.1016/S0001-6918(01)00020-8.

Lamme, V. A. F., Supèr, H., & Spekreijse, H. (1998). Feedforward, horizontal, and feedback processing in the visual cortex. *Current Opinion in Neurobiology*. http://dx.doi.org/10.1016/S0959-4388(98)80042-1.

Lehmann, D. (1987). Principles of spatial analysis. In A. Gevins & A. Remond (Eds.), *Handbook of electroencephalography and clinical neurophysiology*. *Methods of analysis of brain electrical and magnetic signals* (1, pp. 309–354). Amsterdam: Elsevier.

Lehmann, D., & Skrandies, W. (1980). Reference-free identification of components of checkerboard-evoked multichannel potential fields. *Electroencephalography and Clinical Neurophysiology, 48*(6), 609–621. http://dx.doi.org/10.1016/0013-4694(80)90419-8.

Marg, E., & Rudiak, D. (1994). Phosphenes induced by magnetic stimulation over the occipital brain: Description and probable site of stimulation. *Optometry and Vision Science, 71*(5), 301–311. http://dx.doi.org/10.1097/00006324-199405000-00001.

Marzi, C. A., Mancini, F., & Savazzi, S. (2009). Interhemispheric transfer of phosphenes generated by occipital versus parietal transcranial magnetic stimulation. *Experimental Brain Research, 192*(3). http://dx.doi.org/10.1007/s00221-008-1496-4.

Mazzi, C., Mancini, F., & Savazzi, S. (2014). Can IPS reach visual awareness without V1? Evidence from TMS in healthy subjects and hemianopic patients. *Neuropsychologia, 64*. http://dx.doi.org/10.1016/j.neuropsychologia.2014.09.026.

Michel, C. M., & Murray, M. M. (2012). Towards the utilization of EEG as a brain imaging tool. *NeuroImage, 61*(2), 371–385. http://dx.doi.org/10.1016/j.neuroimage.2011.12.039.

Miniussi, C., & Thut, G. (2010). Combining TMS and EEG offers new prospects in cognitive neuroscience. *Brain Topography, 22*(4), 249–256. http://dx.doi.org/10.1007/s10548-009-0083-8.

Moutoussis, K., & Zeki, S. (2002). The relationship between cortical activation and perception investigated with invisible stimuli. *Proceedings of the National Academy of Sciences of the United States of America, 99*(14), 9527–9532. http://dx.doi.org/10.1073/pnas.142305699.

Murray, M. M., Brunet, D., & Michel, C. M. (2008). Topographic ERP analyses: A step-by-step tutorial review. *Brain Topography*. http://dx.doi.org/10.1007/s10548-008-0054-5.

Oruc, I., Krigolson, O., Dalrymple, K., Nagamatsu, L. S., Handy, T. C., & Barton, J. J. (2011). Bootstrap analysis of the single subject with event related potentials. *Cognitive Neuropsychology, 28*(5), 322–337. http://dx.doi.org/10.1080/02643294.2011.648176.

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Pins, D., & Ffytche, D. (2003). The neural correlates of conscious vision. *Cerebral Cortex (New York, N.Y. : 1991), 13*(5), 461–474. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12679293.

Pitts, M. A., Padwal, J., Fennelly, D., Martínez, A., & Hillyard, S. A. (2014). Gamma band activity and the P3 reflect post-perceptual processes, not visual awareness. *NeuroImage, 101*, 337–350. http://dx.doi.org/10.1016/j.neuroimage.2014.07.024.

Railo, H., Koivisto, M., & Revonsuo, A. (2011). Tracking the processes behind conscious perception: A review of event-related potential correlates of visual consciousness. *Consciousness and Cognition, 20*(3), 972–983. http://dx.doi.org/10.1016/j.concog.2011.03.019.

Rogasch, N. C., Sullivan, C., Thomson, R. H., Rose, N. S., Bailey, N. W., Fitzgerald, P. B., ... Hernandez-Pavon, J. C. (2016). Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: A review and introduction to the open-source TESA software. *NeuroImage*. http://dx.doi.org/10.1016/j.neuroimage.2016.10.031.

Rutiku, R., Martin, M., Bachmann, T., & Aru, J. (2015). Does the P300 reflect conscious perception or its consequences? *Neuroscience, 298*, 180–189. http://dx.doi.org/10.1016/j.neuroscience.2015.04.029.

Salminen-Vaparanta, N., Noreika, V., Revonsuo, A., Koivisto, M., & Vanni, S. (2012). Is selective primary visual cortex stimulation achievable with TMS? *Human Brain Mapping, 33*(3), 652–665. http://dx.doi.org/10.1002/hbm.21237.

Sergent, C., Baillet, S., & Dehaene, S. (2005). Timing of the brain events underlying access to consciousness during the attentional blink. *Nature Neuroscience, 8*, 1391–1400. http://dx.doi.org/10.1038/nn1549.

Silvanto, J. (2014). Is primary visual cortex necessary for visual awareness? *Trends in Neurosciences*. http://dx.doi.org/10.1016/j.tins.2014.09.006.

Silvanto, J. (2015). Why is "blindsight" blind? A new perspective on primary visual cortex, recurrent activity and visual awareness. *Consciousness and Cognition, 32*, 15–32. http://dx.doi.org/10.1016/j.concog.2014.08.001.

Silvanto, J., Cowey, A., Lavie, N., & Walsh, V. (2007). Making the blindsighted see. *Neuropsychologia, 45*(14), 3346–3350. http://dx.doi.org/10.1016/j.neuropsychologia.2007.06.008.

Silvanto, J., Cowey, A., & Walsh, V. (2008). Inducing conscious perception of colour in blindsight. *Current Biology*. http://dx.doi.org/10.1016/j.cub.2008.08.016.

Tagliabue, C. F., Mazzi, C., Bagattini, C., & Savazzi, S. (2016). Early local activity in temporal areas reflects graded content of visual perception. *Frontiers in Psychology, 7*(APR). http://dx.doi.org/10.3389/fpsyg.2016.00572.

Tapia, E., Mazzi, C., Savazzi, S., & Beck, D. M. (2014). Phosphene-guided transcranial magnetic stimulation of occipital but not parietal cortex suppresses stimulus visibility. *Experimental Brain Research, 232*(6). http://dx.doi.org/10.1007/s00221-014-3888-y.

Taylor, P. C. J., Walsh, V., & Eimer, M. (2008). Combining TMS and EEG to study cognitive function and cortico-cortico interactions. *Behavioural Brain Research, 191*(2), 141–147. http://dx.doi.org/10.1016/j.bbr.2008.03.033.

Thielscher, A., Reichenbach, A., Uğurbil, K., & Uludağ, K. (2010). The cortical site of visual suppression by transcranial magnetic stimulation. *Cerebral Cortex (New York, N.Y. : 1991), 20*(2), 328–338. http://dx.doi.org/10.1093/cercor/bhp102.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalography and Clinical Neurophysiology - Evoked Potentials, 108*(1), 1–16. http://dx.doi.org/10.1016/S0168-5597(97)00096-8.

Please cite this article in press as: Mazzi, C., et al. Markers of TMS-evoked visual conscious experience in a patient with altitudinal hemianopia. *Consciousness and Cognition* (2017), http://dx.doi.org/10.1016/j.concog.2017.01.022