Probing the circuits of conscious perception with magnetophosphenes

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Abstract: Conscious perception is theorized to involve a large-scale, coordinated activation of distant brain regions, a process termed "ignition" in the influential "Global Workspace Theory" of consciousness. Here, we provide evidence for the ignition process in humans by combining a magnetically-induced phosphene perception task with dense-electroencephalography. Functional cortical networks were identified and characterized using graph-theoretical analysis to quantify the impact of conscious perception on local (segregation) and distant (integration, key to ignition) processing. Conscious phosphene perception activated frequency-specific networks, each associated with a spatial scale of information processing: integration increased within an alpha-band functional network, *versus* a beta-band functional network for segregation. We speculate that such stimulus-induced modulation of the frequency-specific networks characterizing ignition could be exploited to assess non-invasively residual consciousness in minimally conscious patients.

Introduction

The characterization of the physiological mechanisms that enable conscious perception is the focus of intense, multi-disciplinary research efforts. As opposed to the question of the nature of consciousness itself (referred to as the "hard problem" of consciousness (*1*)), the identification and characterization of the physiological processes that enable the emergence and maintenance of consciousness (referred to as the "soft problem" of consciousness (*1*)) is more readily achievable. Two of the most widespread theories of consciousness, namely the Global Workspace Theory (GWT (*2-4*)), and the Integrated Information Theory (IIT (*5*)), share some key common points: 1) information processing is at the core of conscious processes, 2) conscious experience involves a sufficiently "complex" level of information processing, 3) information needs to be *integrated* at a large scale to be efficiently shared and processed. Another recent theory, the Kolmogorov theory of consciousness (*6*) (KT), also establishes links between the complexity of information processed by cortical networks and conscious processes. The idea that information processing coordinated between distant brain regions is essential has received considerable experimental support, notably from combined transcranial magnetic stimulation-electroencephalography (TMS-EEG) studies in disorders of consciousness (DOC) patients and healthy controls: during unconsciousness (e.g., deep sleep, propofol anesthesia or coma) TMS-evoked EEG responses fail to propagate in cortico-cortical networks and only induce local activation, while complex spatiotemporal responses are evoked at the brain-scale during wakefulness (*7*).

One of the processes proposed to enable the large-scale cortical activation associated with conscious processes is termed *ignition* in GWT, and consists of a sudden and coordinated large-scale recruitment of distant brain regions that can make information available to the global workspace, enabling information processing (*2*). Ignition has been identified using functional MRI (fMRI) in a variety of tasks, as reviewed by Dehaene and Changeux (*2*). A compelling example is that, during subliminal perception of words, the activated brain network is considerably less spatially extended than during conscious perception (*8*). Using EEG and magnetoencephalography (MEG), it has also been shown that large-scale activation occurs following an attentional blink task (*9*), with an associated increase of phase synchrony within the beta band. Invasive intracranial recordings have also been performed in humans using deep electrodes during exposure to masked/unmasked words, which revealed an increase in gamma power in distant sites associated with an increase in beta synchrony. In a recent experimental study, van Vugt et al. provided compelling evidence for the ignition process in monkeys, using intracranial electrodes during a phosphene perception task (*10*). Phosphenes are visual perceptions in the absence of light, and can triggered by electric stimulation (electro-phosphenes (*11*)) or magnetic stimulation (magneto-phosphenes (*12*)). In this study, van Vugt et al. performed intracranial stimulation of the visual cortex at different current intensities (sub-threshold vs. supra-threshold) and linked visual saccades with phosphene perception by monkeys. Consistent with predictions from GWT, large-scale brain activation was seen at the onset of phosphene perception.

In the present study, we aimed at inducing magnetophosphene perception to characterize non-invasively the associated ignition process in humans. Our study involved N=20 human subjects exposed to a 50 Hz magnetic field (MF) at 11 different flux density conditions given in a random order (5 mT steps ranging from 0 -sham- to 50 mT, each repeated 5 times for a total of 55 conditions), while dense-EEG (64 channels) was recorded. MF exposure was delivered

through a whole-brain exposure system designed and manufactured in-house (Fig. 1A). Large-scale functional connectivity was identified from dense-EEG using the EEG source connectivity method (*13*), and graph theoretical analysis were used to quantify local and global/distant processing, enabling the identification of a network of cortical regions. The study design is summarized in Fig. 1. Our hypothesis was that, during suprathreshold (conscious) magnetophosphene perception, a drastic increase in global/distant processing characteristic of ignition occurs, which should be detectable through an increase in network integration, quantified using graph theory based metrics.

Results

As expected, participants did not perceive any phosphene in the sham condition (0 mT), and the perception of magnetophosphenes began with a probability of perception of 0.28 at a threshold value of 20 mT when the entire head was stimulated by the homogeneous 50 Hz sinusoidal signal, as assessed by perception button-press self-reports. It is worth noting that, at the maximal MF flux density value used (50 mT), the probability of magnetophosphene perception was close to 1 (0.96). The resulting magnetophosphene perception curve as a function of the MF flux density results in a sigmoid-like function, as can be seen in Fig. 2 (lower panel), similarly to the curve obtained in monkeys with increasing intracranial stimulation current values (*10*). The comparison between these two curves is direct: intracranial current injection results in an electric field that depolarizes neighboring neuronal elements; while MF exposure also induces an electric field in brain tissue per Maxwell-Ampere's law of magnetic induction. One difference is that, in the present study, retinal cells instead of visual cortex cells are modulated by the induced electric field. As detailed in the Methods section, each functional network reconstructed in each of the 55 conditions featured 68 ROIs, and the participation and clustering coefficients quantifying *integration* (global) and *segregation* (local) processing respectively, were computed for each frequency band (theta, 4-7 Hz; alpha, 8-12 Hz; beta, 13-30 Hz). Gamma-band networks could not be estimated due to the need to filter the EEG from 50 Hz stimulation contamination. In the following, all *p*-values were corrected for multiple comparisons using the False Detection Rate (FDR) method.

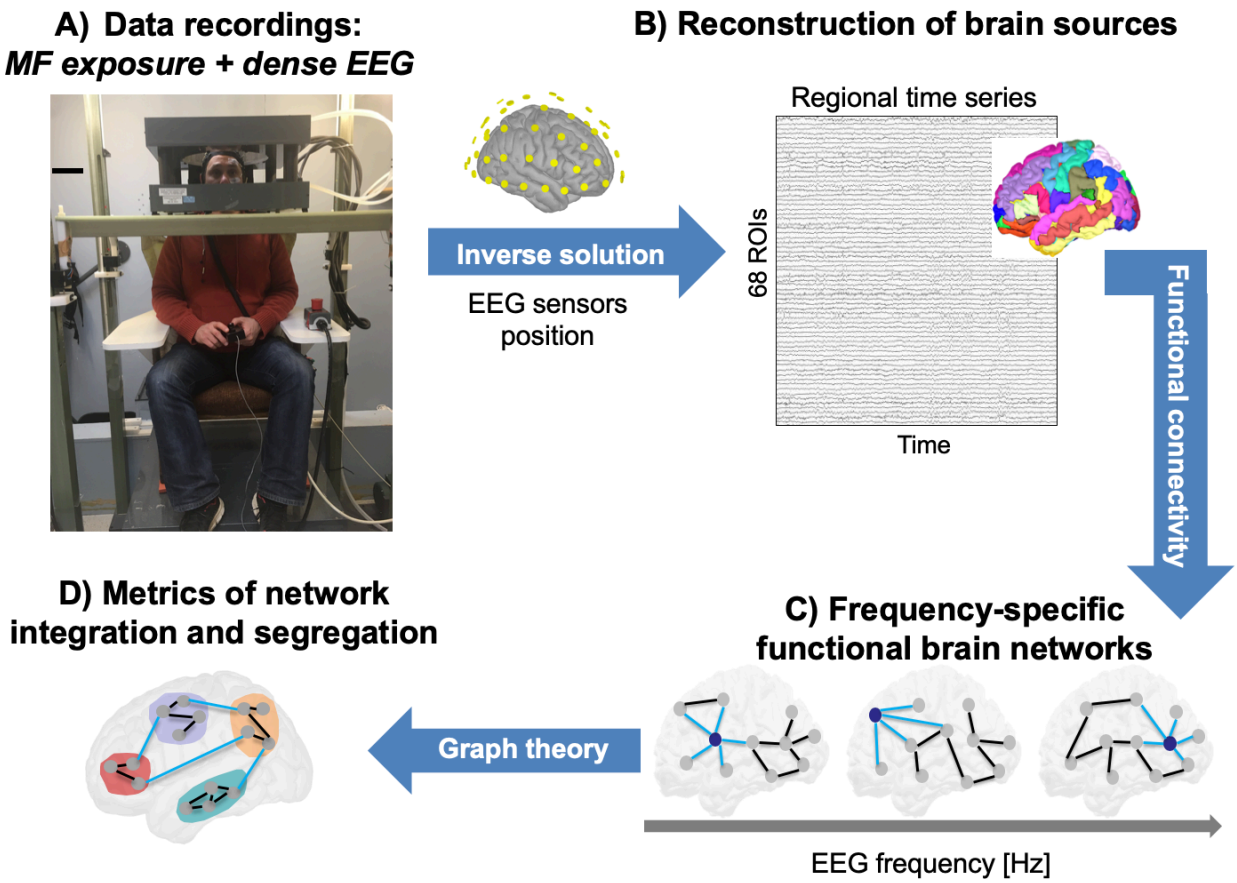

Fig. 1. Study design and data analysis pipeline. A) MF exposure setup (water-cooled Helmoltz coils, in-house design and engineering, see Methods for details) used to induce magnetophosphene perception. Subjects could report magnetophosphene perception using a button press. Dense-EEG (64 channels, MRI compatible cap) was recorded throughout the entire experiment. **B)** Source activity was reconstructed for the 68 regions of the Desikan-Killiany atlas. **C)** Frequency-specific functional networks were computed for the theta, alpha and beta frequency bands. **D)** Metrics from graph theory were used to quantify segregation and integration (local and global processing, using clustering and participation coefficients, respectively).

First, brain structures for which integration (quantified by the participation coefficient) was correlated with the MF flux density were almost exclusively within the alpha band (see Fig. 2, right panel). More specifically, there were structures involved both in "subliminal" (i.e., 50 Hz MF exposure below the perception threshold) and suprathreshold magnetophosphene perception. These regions involved DMN (Default Mode Network) structures such as the right rostral anterior cingulate (p=0.0012) and left parahippocampal gyrus (p=0.0116); a structure from the VIS (visual) network (left fusiform, p=0.0089); and a DAN (Default Attention Network) structure (left pars triangularis, p=0.007). The left pericalcarine cortex (p=0.0052, visual cortex area), right enthorinal (p=0.0085), right frontal pole (0.0085), and right paracentral (p=0.0092) were also involved.

Regions correlating specifically with the perception curve involved a DMN region (left precuneus, p=0.001), two regions from the DAN (left pars orbitalis and left pars opercularis, p<0.001), and a region from the SAN (Salience Attention Network), namely the right

supramarginal gyrus (p<0.001). Interestingly, the right supramarginal gyrus has been previously identified as involved in phosphene perception in humans using intracranial stimulation (*14*). The left temporal pole, p < 0.001, the left frontal pole, p=0.0026 and left inferior parietal, p<0.001 were also involved.

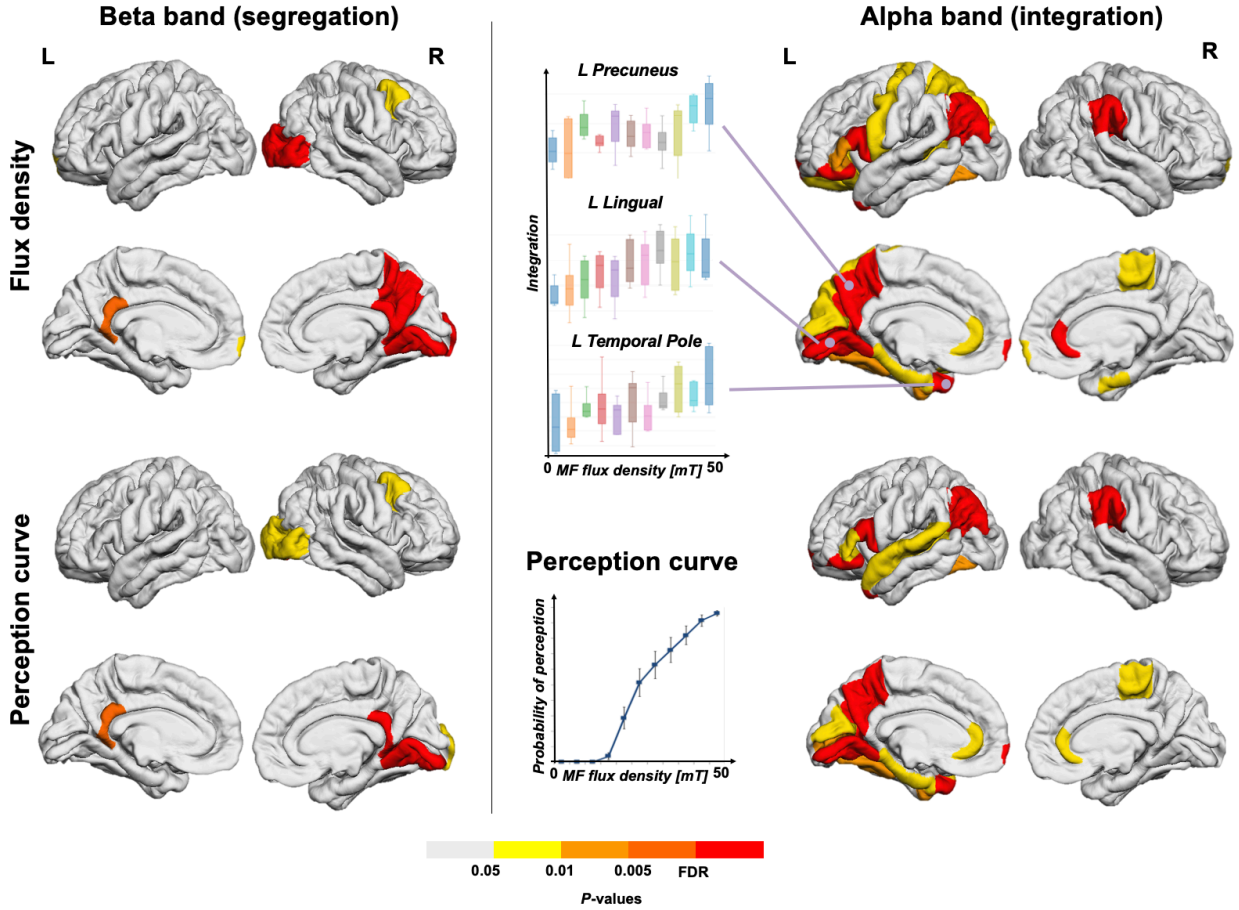

Fig. 2. Left panel. Segregation results in the beta-band functional network (linear trend, flux density sub-panel; correlated with perception reports, perception curve sub-panel). Results are presented for each hemisphere. **Right panel**. Integration results in the alpha-band functional network (linear trend, flux density sub-panel; correlated with perception reports, perception curve sub-panel). Results are presented for each hemisphere. The increase in integration with flux density is shown for three regions of interest (left precuneus, left lingual and left temporal pole), along with the perception probability curve for magnetophosphene from subjective reports (N=20 subjects).

Second, magnetophosphene perception was associated with an increase in segregation (local processing) almost exclusively in a beta functional network, as illustrated in Fig. 2 (left panel). More specifically, the network segregation increased (both for "subliminal" and conscious perception) in the right lingual cortex (p<0.001, VIS), within DMN regions (right precuneus, p=0.0018; and left/right isthmus cingulate, p=0.0019 and p<0.001 respectively) and a DAN region (right caudal middle frontal gyrus, p=0.0031). In the case of conscious (suprathreshold)

perception, only the right lingual cortex and right isthmus cingulate ($p < 0.001$) specifically showed significant correlation with the perception curve in terms of beta network segregation.

Notably, while magnetophosphene perception was mainly restricted effects within alpha- and beta-band functional networks, a limited number of brain structures displayed increased integration within the theta (left pars triangularis, $p<0.001$; right middle temporal, $p=0.001$) and beta (left precuneus, $p<0.001$) bands. Furthermore, regarding the network segregation, an effect was also identified in a single region (right superior frontal gyrus, $p<0.001$) of the alpha functional network.

Discussion

Magnetophosphene perception increases as a function of the increasing level of magnetic stimulation, which results from the induced electric fields modulating retinal neurons (*15*) signaling. This increase in magnetophosphene perception induced in healthy humans volunteers results in an increase of information integration at the brain-scale. Conscious perception was tracked using participants' subjective reports increased with gradually increasing stimulus strength. The increase of information integration was observed mostly in visual- and DMN-related regions, and also in a few frontal regions. To our knowledge, this is the first use of EEG source-space networks to characterize the increase of integration information as a consequence of conscious visual perception. These results confirm the recent study by van Vugt et al. (*10*) who identified the ignition process in monkeys, also using a phosphene perception paradigm (although stimulation was delivered intracranially, as opposed to non-invasively in the present study). Taken together, these results provide further support for the ignition process that was conceptualized in GWT. Another originality of this study is that we characterized the functional networks involved in the biological effect occurring at the lowest known level of *in situ* electric field, which is why magnetophosphene perception is at the core of international guidelines for the general public and workers regarding the safety of electromagnetic fields exposure (*16, 17*).

One limitation of our study is that the whole brain was exposed to the delivered MF, which leaves open the possibility that some identified brain regions were not necessarily associated with phosphene perception, but rather with neuromodulation from the MF. This whole head exposure protocol was chosen since it was the most effective to generate phosphenes perception non-invasively, which was the most important required feature at this initial stage of evaluating if brain networks would react to this perception. Next developments will use a more focal stimulus targeting the eyeball. That being said, the levels of MF flux density in this study are known to activate the retina only, since the perception of magnetophosphenes is the biological effect occurring at the lowest known MF flux density. This is indeed for this reason that the international guidelines protecting the general public and workers from the adverse effects from electromagnetic fields exposure are based, for extremely low-frequency fields (< 300 Hz), on the perception of magnetophosphenes (*16, 17*). Another limitation is that, since we used a 50 Hz stimulus, we were not able to investigate gamma-band functional networks. This 50 Hz frequency was selected because it is reported to be effective in triggering phosphenes perception (phosphene perception decreases as the stimulus frequency increases), although the related contamination of EEG signals involves filtering and thereby prevents investigation of gamma-related processes.

In addition to a contribution in terms of the fundamental mechanisms of consciousness, we also suggest that our experimental paradigm could form the basis of a novel protocol to assess the level of consciousness in DOC patients. While a rather cumbersome experimental setup was used in this study, it would be possible to simplify it by using scalp (surface) electrodes placed on the temples and with an adapted level of delivered electrical current. Since the perception of phosphenes from scalp electrodes originates from stimulation of the retina (*18*) such a protocol would bypass the cornea, which can be a cause of impaired vision in DOC patients and prevents the use of visual stimulation protocols. This has some similarities with recently developed TMS-based techniques that evaluate the complexity of evoked dense EEG responses (see for example the Perturbational Complexity Index, PCI (*7*)), which is associated with a certain level of information integration within the cortico-cortical network. Our results support the possibility to use the ignition process as a marker of the consciousness level using non-invasive recordings of brain activity, through a stimulation protocol involving induced currents considerably lower than those used with TMS, which has practical implications.

Another more fundamental implication of these results is that changes in frequency-specific functional networks appear directly dependent on their spatial extent of information processing: during magnetophosphene perception, distant information processing increases mostly within the alpha band, while local information processing increases mostly within the beta band. This result is consistent with other studies pointing the role of low-frequency oscillations for distant communication between brain regions, while higher frequency rhythms would rather contribute to stimulus encoding itself (*19*). Therefore, our results bring further support to the framework conceptualizing information flow and processing between brain structures as an interplay between slow and fast oscillations, each associated with a "range" for information processing.

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Materials and Methods

Experimental protocol

This study was approved by the Health Sciences Research Ethics Board of Western University (London, ON, Canada) under the reference HSREB#18882. A total of N=20 healthy volunteers were recruited (age: 23.4 +/- 1.4, 10 males and 10 females). Study participants had no cardiovascular, neurological or visual system disorder. They were equipped with a 64 MRI-compatible EEG cap (Maglink, Compumedics-Neuroscan, US). Subjects were asked to seat in the chair placed below the MF exposure device and the coils where lowered so they had their head centered in the device for the duration of the experiment. EEG was continuously recorded, and subjects were asked to remain eyes closed for the duration of the experiment. An adaptation time to the darkness of the room of 5 minutes was present at the beginning of the exposure sequence. The 55 MF exposure conditions were then randomly delivered through a custom-made LabView (National Instruments, USA) program, had a duration of 5 seconds each, and were separated by 5 seconds. Each time that the participant began to perceive magnetophosphenes, he/she had to press as fast as possible on a button-press directly synchronized with the EEG acquisition system.

MF exposure device and physical principles

The MF exposure device was used to deliver whole-brain exposure, and consisted in "Helmoltz-like" coils designed and manufactured in-house. The mean diameter of each coils was 50 cm and their width 7.3 cm, and coils were separated by 20 cm. Water cooling (0.8 L/min) was performed through the squared hollow wire, in order to prevent from any coil heating. MRI gradient amplifiers (MTS corporation, USA) were used to power each coil (up to 200 A_{rms} capability). The experimental setup was Medical Grade approved by the Canadian Standard Association (CSA). The MRI gradient amplifiers driving a 50 Hz current through the coils, which per Maxwell-Ampere's law generated an homogeneous 50 Hz MF at the level of the head and eyes, which resulted in an induced electric field at the same frequency in these exposed biological structures. Therefore, the MF exposure non-invasively generates induced fields and current in the brain and retinal tissues at 50 Hz.

EEG acquisition and processing pipeline

64-channel EEG was acquired at a sampling frequency of 10 kHz. EEG data was imported in Matlab, and band-pass filtered (3-35 Hz) to remove artefacts present in the signal due to the MF exposure at 50 Hz. For each EEG recordings, the 55 EEG epochs (11 MF exposure conditions, each repeated 5 times) were extracted and imported in the Brainstorm Matlab package (*20*). EEG data was downsampled to 1 kHz, visually inspected for the quality of each epoch, and bad channels were interpolated using neighboring electrodes within a 5-cm radius. Brain regional time series (68 regions of interest) were reconstructed using the weighted minimum norm estimate (wMNE). The functional connectivity between the 68 regional time series was computed using the Phase Locking Value (PLV) method, using EEGNET (*20, 21*), for each condition, in three different frequency bands (theta, 4-7 Hz; alpha, 8-12 Hz; beta; 13-30 Hz). This resulted for each subject, in each of the three frequency bands, in 55 68x68 PLV matrices (one per MF condition).

Characterization of functional networks

The PLV matrices were then analyzed using graph theoretical functions from the Brain Connectivity Toolbox (*22*), and more specifically the clustering coefficient and the participation coefficient to quantify network segregation and integration, respectively. At the group level, this resulted in a clustering and participation matrix for each ROI in each of the 55 MF conditions, for each frequency band. For each frequency band, the Pearson correlation between the clustering/participation matrix and the reported perception curve was computed using Matlab and the False-Detection Rate (FDR) method was used to account for multiple comparisons.

Statistical analysis

The participation/clustering curves were correlated with the MF flux density curve (linear from 0 to 50 mT) and the phosphene perception curve (probability of perception between 0 and 1, computed for each condition as the number of button presses divided by the number of repetitions, i.e. 5). The linear trend associated with increasing MF flux density was assessed using the Jonckheere-Terpstra test (implemented in Matlab, The Mathworks, USA) with correction of the significance threshold using the FDR. The correlation with the (non-linear) perception curve was assessed using a linear correlation (Matlab, The Mathworks, USA) corrected using FDR.