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Neural dynamics of visual awareness investigated by means of Fast Optical Imaging and EEG

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SOMMARIO

Nell’ambito delle neuroscienze cognitive, una delle questioni ancora molto dibattute riguarda la ricerca dei correlati neurali della consapevolezza (NCC – Neural Correlates of Consciousness, Koch, 2004). Nonostante siano stati impiegati numerosi sforzi per cercare di rispondere a questa domanda, le teorie esistenti forniscono risposte contrastanti. L’eterogeneità delle interpretazioni fornite può dipendere da un problema metodologico, dato che fino ad oggi gli studi volti ad investigare tali correlati hanno impiegato tecniche che possono raggiungere una buona precisione solamente o a livello spaziale o temporale, rivelandosi inadeguate per indagare le dinamiche spazio-temporali relative alla visione consapevole.

I seguenti studi mirano a chiarire la controversa ricerca dei correlati neurali della consapevolezza, in particolare della consapevolezza visiva, proponendo approcci innovativi che permettono di andare oltre questi problemi metodologici.

Il primo studio, utilizzando tecniche quali EEG ed EROS (Event-Related Optical Signal), ha lo scopo di dipanare le dinamiche spazio-temporali che si verificano quando uno stimolo visivo entra in coscienza. Per fare ciò, l'attività cerebrale dei partecipanti viene registrata mediante EEG ed EROS durante l'esecuzione di un compito di discriminazione. L'EEG permette di indagare i correlati elettrofisiologici della consapevolezza visiva e di identificarne l’ esatta tempistica, mentre l'EROS permette di individuare quali regioni cerebrali sono coinvolte quando lo stimolo viene consapevolmente percepito e il loro ordine di attivazione. I risultati mostrano che, quando lo stimolo entra in coscienza, un'attivazione sostenuta nel Lateral Occipital Complex (LOC) viene elicitata. Questo suggerisce che tale regione cerebrale potrebbe rappresentare un affidabile correlato neurale di coscienza. È interessante notare che questa attivazione sostenuta si verifica all'interno della finestra temporale di VAN (Visual Awareness Negativity), che è generalmente considerato un solido correlato elettrofisiologico della consapevolezza visiva, corroborando l'idea che LOC potrebbe servire come il generatore corticale di VAN.

Nel secondo studio, il segnale EEG viene scomposto in componenti indipendenti mediante ICA (Independent Component Analysis), al fine di identificare le sorgenti neurali che contribuiscono in modo significativo ai correlati ERP della consapevolezza visiva (VAN e LP) e il loro decorso temporale. Dai risultati emerge che i generatori corticali di VAN sembrano risiedere in regioni posteriori del cervello, che comprendono la corteccia occipitale e temporale. Diversamente, LP sembra riflettere una combinazione di più sorgenti distribuite su zone frontali, parietali e occipito-temporali.

Complessivamente, i risultati presentati nel seguente lavoro forniscono nuove evidenze circa la ricerca dei correlati neurali della consapevolezza visiva.

ABSTRACT

The search for the Neural Correlate of Consciousness (NCC, Koch, 2004) is one of the unresolved problems of cognitive neuroscience. Although great efforts have been made to seek to answer this fundamental question, theories about the neural basis of consciousness provide different and competing answers. The heterogeneity of the NCCs interpretations could be due to a methodological gap since so far studies trying to unveil the neural correlates of visual awareness have employed techniques that can reach a high level of resolution only in one dimension (i.e., space or time) resulting to be inadequate to investigate the spatio-temporal dynamics related to conscious vision.

The following studies aim to elucidate the controversial search for the neural correlates of visual awareness, by proposing innovative and cutting-edge approaches that allow to move beyond these issues.

In the first study, availing of EEG and EROS (Event-Related Optical Signal) techniques we seek to unravel the spatio-temporal dynamics occurring when a visual stimulus enters consciousness. To do so, participants' brain activity is recorded during the performance of a discrimination task by means of EEG and EROS in separate sessions. EEG allows to investigate the electrophysiological correlates of visual awareness and to identify their exact timing, while EROS permits to disentangle which brain regions and in what order of activation are involved when the stimulus is reported as consciously perceived. Results revealed that when the stimulus entered the consciousness, it elicited a sustained activation in LOC, suggesting that this brain region could represent a reliable neural correlate of consciousness. Interestingly, this sustained activation occurred within the temporal window of VAN (Visual Awareness Negativity), corroborating the idea that LOC could serve as the cortical generator of VAN, which is typically considered a reliable marker of conscious vision.

In the second study, EEG signal was decomposed into maximally independent components by means of ICA (Independent Component Analysis) in order to unveil the cortical generators and the time-courses of independent neural sources

that significantly contribute to the ERP correlates of visual awareness (i.e., Visual Awareness Negativity and Late Positivity). It emerged that the neural sources of VAN seem to be localized in posterior brain regions, including occipital and temporal cortex, while LP seems to reflect a combination of multiple sources spread over frontal, parietal and occipito-temporal cortex.

Overall, the present results provide innovative insights into the search for the neural correlates of visual awareness.

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GENERAL INTRODUCTION

Consciousness is one of the most intriguing topics debated in neuroscience research. Due to its multifaceted nature, it is difficult to provide an exhaustive definition (Zeman, 2005), but we generally refer to consciousness (or awareness) as the set of subjective experiences that we have when we are awake. Because of the heterogeneity of the concept of consciousness, different classifications have been proposed, in order to distinguish between different aspects of this complex theme.

A first important distinction is between the *state* of consciousness (i.e., awake, asleep, in a coma) and the specific *content* of the conscious experience. This first and fundamental distinction discerns between being aware and being aware of something. Furthermore, regarding the specific content of consciousness, another central distinction may be made between *phenomenal* consciousness, referring to the immediate, proper, nonverbal subjective experience, and *access* (or *reflective*) consciousness, which refers to the subsequent selection and manipulation of the contents of phenomenal consciousness for further cognitive processes (Block, 1995). In recent years, the majority of studies about consciousness focused on the search for its neural correlates (NCCs), defined as those neural mechanisms that are necessary and sufficient for the generation of a specific conscious percept (Koch, 2004). In general, the most widely used approach to assess such NCCs consists of contrasting brain dynamics associated with conscious experience and dynamics that do not correlate with awareness. To do so, usually participants are presented with a stimulus that they only sometimes consciously perceive. This allows to experimentally manipulate the conscious experience of the participant and to sort Aware (i.e., “seen”) and Unaware trials (i.e., “unseen”) according to the participant’s subjective report, while keeping constant the physical characteristics of the stimulus. Thus, differences emerging when contrasting the two conditions are attributable to awareness-related processes.

Although the application of this useful paradigm (known as contrastive analysis, Baars, 1988) allowed neuroscientists to widely investigate the NCCs, so far research has reached controversial conclusions. Because of their excellent temporal resolution, electrophysiological measures have been extensively employed in addressing this issue. Research on ERPs suggests that principally two components can be considered as the electrophysiological markers of visual awareness: an early negative deflection, peaking around 200 ms after the stimulus onset at occipito-temporal sites, named Visual Awareness Negativity (VAN) and a later enhanced positivity (called Late Positivity, LP), occurring at centro-parietal electrodes in the P3 time window (Koivisto & Revonsuo, 2003, 2010). Although VAN and LP are often regarded as if they are both related to aware vision, converging evidence suggests that these two electrophysiological components reflect different processes. It has been shown, in fact, that the amplitude of LP is affected by post-perceptual processes occurring after the stimulus has entered the consciousness (Förster et al., 2020; Mazzi et al., 2020), suggesting that this component does not reflect activity strictly related to consciousness. However, despite EEG achieves a very high temporal resolution, its spatial resolution is very poor and it affords very restricted insights into the spatial distribution of the neural processes that underlie consciousness. For this reason, relatively few attempts to localize the cortical source of VAN and LP have been made. Furthermore, neuroimaging techniques such as MRI, although providing a good spatial resolution, do not represent a suitable methodology to investigate the spatio-temporal unfolding of brain activity occurring when a stimulus enters the consciousness because their temporal resolution is in the order of several seconds.

The present thesis aims to shed further light on the controversial search for NCCs. Given the lack in literature of significant attempts to localize the neural bases of conscious vision, here we sought to unveil the neural generator(s) of the electrophysiological signature of conscious vision by proposing innovative and alternative methodologies to investigate them.

In the first study, availing of a cutting-edge approach, which combines Event-Related Optical Signal technique with EEG, we investigated with a millisecond resolution the temporal unfolding of brain areas showing great activation within the temporal window of VAN. We thus drew significant inferences about the possible cortical generator(s) of the well-known VAN component.

In the second study, taking advantage of the ICA approach, which allows to decompose the EEG signal into maximally independent components (ICs), we could investigate the spatiotemporal dynamics of the brain sources underlying the ERP correlates of conscious vision. Each IC, in fact, represents a temporally and functionally independent source of the EEG signal, with a specific scalp distribution and a specific amplitude at each time point (Onton et al., 2006; Onton & Makeig, 2006).

Overall, the two studies presented in the present work allow to move beyond the existing literature, extending the current knowledge about the neural correlates of visual awareness.

STUDY 1

1. Introduction

One of the most intriguing questions for cognitive neuroscience is to unveil the neural mechanisms occurring when a visual percept enters the consciousness. The neural processes serving visual awareness, in fact, have long been debated and still remain unclear. The most used method to investigate the neural correlates of visual awareness is the so-called “Contrastive Analysis” (Baars, 1988), which consists in manipulating the visibility of a stimulus across trials, while keeping constant its physical properties. In this way, it is possible to experimentally manipulate the conscious experience of the participant and to sort Aware (i.e., “seen”) and Unaware trials (i.e., “unseen”) according to the participant’s subjective report. Then, trials are contrasted allowing for the segregation of brain activity correlating with conscious perception. The combination of this paradigm with neuroimaging and electrophysiological techniques allowed neuroscientists to widely investigate the neural correlates of consciousness (hereafter “NCCs”). Electroencephalography (EEG), thanks to its good temporal resolution, represents a useful tool to investigate the temporal dynamics involved in conscious vision. In particular, examining the Event Related Potentials (ERPs) allows to investigate brain activity locked to a specific event (i.e., the onset of the stimulus) with a millisecond resolution. Several ERPs studies contrasting Aware and Unaware conditions suggested that two components can be considered as the principal electrophysiological markers of visual awareness: the Visual Awareness Negativity (VAN) and the Late positivity (LP) (Koivisto & Revonsuo, 2003, 2010; Renate Rutiku et al., 2016). VAN is an early negative deflection, peaking around 200-250ms at occipito-temporal sites. LP occurs at centro-parietal electrodes in the P3 time window (i.e., around 300-500 ms after the presentation of the stimulus). According to a large body of literature, VAN is considered a more reliable ERP correlate of visual awareness than LP since the latter seems to reflect post-perceptual processes (Förster et al., 2020; Koivisto et al., 2006; Mazzi et al., 2020; Pitts et al., 2014). Because of the poor spatial resolution of EEG, it is, however, difficult to localize the cortical generator of the signal and, thus, the brain areas directly involved in the emergence of aware vision remain to be defined. In this respect, source localization and neuroimaging studies may help in shedding light on the neuroanatomical bases of visual awareness. However, literature does not converge towards a univocal perspective, and the debate about the brain regions responsible for rising conscious percepts still remains unanswered. According to a large body of literature, visual awareness is served by a frontal network, as suggested by the Global Workspace Theory (Dehaene & Changeux, 2011; Dehaene & Naccache, 2001). On the other hand, several pieces of evidence argue for a posterior localization of the NCCs, suggesting that conscious vision arises in a posterior "hot zone" which includes temporal, occipital, and parietal cortices (Boly et al., 2017; Koch et al., 2016; Koivisto et al., 2018).

The heterogeneity of the interpretations of the NCCs could be due to a methodological gap since studies trying to unveil the neural correlates of visual awareness employ techniques that can reach a high level of resolution only in one dimension (i.e., space or time) resulting to be inadequate to investigate the spatio-temporal dynamics related to conscious vision. Electrophysiological techniques provide accurate information about the timing of activations, but cannot precisely localize the generator of such activations. On the contrary, neuroimaging methods afford high spatial resolution, but their temporal resolution is at best few seconds, so that information about the temporal order of activations is lacking. To overcome this issue, it could be revealing to investigate NCCs with a method able to integrate temporal and spatial information, thus allowing to determine the relative timing of activation of specific brain areas. In this respect, fast optical imaging represents a very advantageous tool. Over recent years, a relatively novel approach, known as Event-Related Optical Signal (EROS) or Fast Optical Signal (FOS) has begun to be employed to investigate brain functions (Parisi et al., 2020; Toscano et al., 2018). Its main advantage is that it can combine a temporal resolution of milliseconds with a sub centimeters spatial resolution (Baniqued et al., 2013; Gratton et al., 1995; Gratton & Fabiani, 2010) thus providing spatio-temporal information about brain functions (Gratton et al., 1997; Gratton &

Fabiani, 1998, 2001). Basically, it works by shining light through the scalp and the skull by means of optical fibers and then detecting the changes in the light scattering properties that are known to be directly related to neural activity. The noteworthy advantages provided by EROS can help in shedding further light on the search for NCC allowing to investigate the anatomical substrate of the above-mentioned electrophysiological markers of visual awareness. In particular, since EROS and EEG have comparable temporal resolutions (Barinaga, 1997), it could be compelling to investigate with this very promising technique which brain regions are active in the specific time window of the VAN, and interestingly their order of activation.

In the present study, we thus adopted a combined approach, in which electrophysiological data and EROS data were recorded during a forced-choice discrimination task. We then sorted trials in Aware (stimulus seen) and Unaware (stimulus unseen) conditions according to the subjective report of participants. The logic was to administer the same experiment to the same sample in two separate sessions, i.e., EROS session and EEG session. The advantage provided by this multi-modal approach was two-fold: first, thanks to the strength of EROS technique in integrating accurate information at the highest achievable spatial and temporal resolution, it has been possible to achieve comprehensive knowledge about the spatio-temporal dynamics underlying visual awareness with a level of accuracy that has never been reached so far. Second, combining information provided by EROS with EEG results allowed us to investigate with a millisecond resolution the temporal unfolding of brain areas showing great activation within the exact temporal window of VAN, enabling us to draw significant inferences about the possible cortical generator(s) of the well-known VAN component.

2. Methods

2.1 Experiment 1

2.1.1 Participants

A total of forty-one healthy adults (16 males, mean age ± standard deviation: 23.5 ± 2.8) were recruited from the university community. They all were right-handed and reported normal or corrected-to-normal vision and no history of neurological or psychiatric disorders. They gave their written informed consent before taking part in the experiment and all were naïve to the experimental hypothesis. All participants received compensation for their participation.

The study was carried out according to the principles laid down in the 2013 Declaration of Helsinki and approved by the local Ethics Committee.

In order to maintain an equal number of trials in both the conditions (i.e., aware and unaware) we discarded data from participants (17) reporting a proportion of awareness equal or superior to 75%.

The final sample was thus composed of twenty-four participants (10 males, mean age ± standard deviation: 23.8 ± 3.2).

2.1.2 Stimuli

The stimuli were Gabor patches (diameter of 2°) created using a custom-made Matlab script (version R2017b; the MathWorks, Inc., Natick, MA).

As shown in Figure 1, Gabor patches could be horizontal (90° - catch trials), with the right side of the stimulus oriented upwards (orientation <90°) or downwards (orientation >90°). Gabor patches were presented for 100 ms at an eccentricity of 3.5° from the fixation cross along the vertical meridian and of 2° along the horizontal meridian, i.e., in the lower right quadrant of the screen. The orientation of the stimuli to be used in the experimental session for each participant was determined by means of a subjective perceptual threshold.

2.1.3 Perceptual Threshold Assessment

Participants were tested in a dimly illuminated room, sitting in front of a 17 in. LCD monitor (resolution 1920x1080, refresh rate of 144 Hz) placed at a viewing distance of 57 cm, with head laying on an adaptable chin rest with forehead support so that eyes could be aligned with the center of the screen.

The goal of the threshold assessment was to identify, for each participant, two stimuli (one oriented upward and one oriented downward) that the subject reported to be aware of about 50% of the times. These stimuli were then used in the experimental task, together with the horizontal one (catch).

The subjective perceptual threshold was measured using the method of constant stimuli, where Gabor patches with different degrees of orientation were randomly presented: six different degrees of inclination for stimuli oriented upwards (from the easiest to the most difficult: 87°, 87.5°, 88°, 88.5°, 89°, 89.5°) and six for stimuli oriented downwards (from the easiest to the most difficult: 93.5°, 93°, 92.5°, 92°, 91.5°, 91°).

All the stimuli, as well as the catch stimulus (90°), were presented 30 times each.

The task was the same to that of the main experiment and it consisted in a 2-alternative forced-choice orientation discrimination task, followed by the assessment of the perceptual awareness (2-alterantives “YES-NO” response).

2.1.4 Experimental procedure

Before taking part in the study, participants underwent a structural magnetic resonance imaging (MRI), in order to obtain structural images of the brain to be subsequently co-registered with functional data (see below for more detailed information).

The experiment lasted approximately four hours and it was composed of two identical sessions performed on the same day, one after the other, preceded by the assessment of the subjective perceptual threshold. The two sessions were identical except for the EROS montages specifically devised to obtain better coverage of the brain areas of interest (see below for more detailed information).

2.1.5 Main Experiment

The experimental paradigm is shown in Figure 1. The task was a 2-alternative forced-choice discrimination task, in which participants had to discriminate the orientation of a Gabor patch, followed by the assessment of the awareness, by means of a question appearing on the screen. Each trial began with the presentation of a central black fixation cross, followed 500 ms later by a sound presented for 150 ms, notifying participants of the onset of the stimulus.

As the stimulus appeared, participants had to discriminate as fast and as accurately as possible its orientation, by pressing one of two buttons of a response box (one if perceived upwards and another one if perceived downwards), while maintaining the gaze on the central fixation cross throughout the block (in case of catch trials, i.e. a horizontal stimulus, participants were instructed to answer by choosing randomly one of the two buttons). After that, participants were asked to report whether they had seen or not the orientation of the stimulus, by answering a question with the same response box.

The question persisted on the screen until participant answered. Each experimental session was composed of 10 blocks, for a total of 20 blocks per participant. Each block consisted of 60 trials (25 upward, 25 downward and 10 horizontal), resulting in a total of 1200 trials per participant. Participants could rest during inter-block intervals and could initiate the next block by pressing a key.

The experiment was programmed and administered using E-Prime 2.0 software (E-Prime Psychology Software Tools Inc., Pittsburgh, PA, USA).

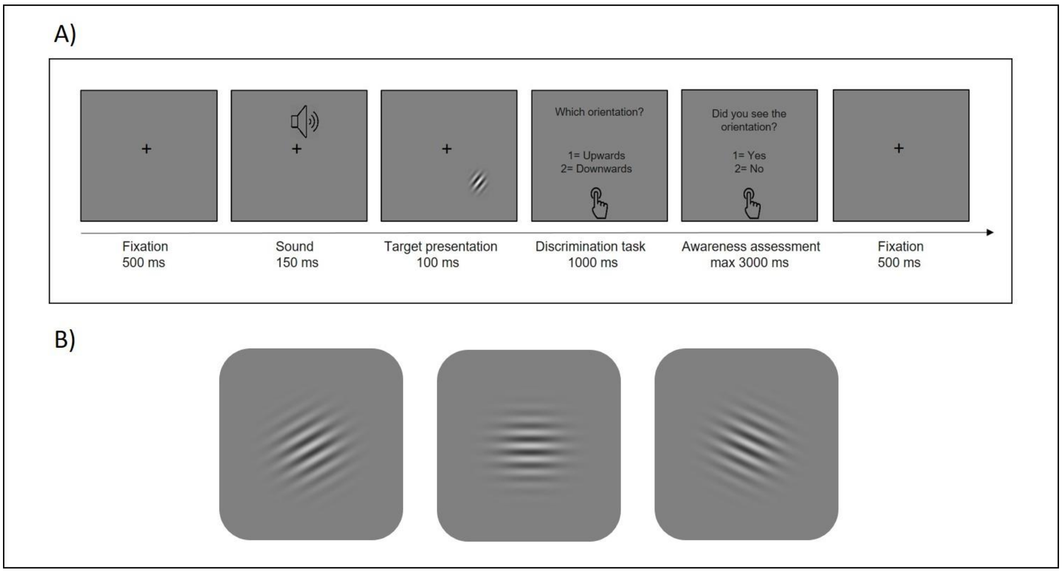

Figure 1. Trial procedure and stimuli. A) Experimental procedure: a central fixation cross was presented for 500 ms, followed by a warning acoustic tone lasting 150 ms. Then, the stimulus was presented for 100 ms and participants were asked to discriminate its orientation (Discrimination task) and then to report whether they had seen or not the orientation (Awareness assessment). B) Stimuli: stimuli were Gabor patches which could be slightly upward or downward oriented.

2.1.6 Optical recording

Brain activity of each participant was recorded throughout the experiment, concurrent with behavioral data acquisition, by using two synchronized Imagent frequency domain systems (ISS, Inc., Champaign, IL). Continuous fast optical data were collected using the ISS Corporation “Boxy” program. Near-infrared light (830 nm) was carried to the scalp by means of 32 light emitters (laser diodes).

Light was modulated at 110 MHz and multiplexed through the sets of sources every 25.6 ms, resulting in a sampling rate of 39.0625 Hz. Light that scattered through the head and returned to the scalp surface was detected by eight 3-mm fiber-optic bundles, connected to photomultiplier tubes. Fast Fourier transforms were applied to the current reaching the photomultiplier tubes in order to compute three measures: DC intensity (i.e., Direct Current, the mean amount of light detected), amplitude (i.e., Alternating Current, the amplitude of light modulation) and phase delay, that is changes in the transit time of light. Since in this study we were interested in the fast-optical signal, we analyzed only changes in phase delay data, converted into picoseconds delay.

Both light emitters and detectors were held in place using a custom-built helmet. To minimize interferences, before placing the optical fibers on the head, the hair was moved so that the fibers could reach the scalp.

Two helmets of different sizes were available, in order to better adhere to the head of the participant: one 55-56 cm large, usually used for women, and one 57-58 cm large. For each helmet, two different montages (i.e., the combination of light sources and detectors) were developed, so that to provide a dense coverage of the regions of interest (Figure 2A shows the brain regions covered by the montages).

Because of the high number of optical fibers to place, EROS montages were created using a specific program (NOMAD, Near-Infrared Optode Montage Automated Design) implemented in Matlab, useful to place sources and detectors at optimal distances (minimal distance 17.5 and maximum distance 50 mm, (Gratton et al., 2000) while avoiding cross-talks between channels. Thus, each montage was to permit each of the 8 detectors to detect light from up to 16 sources, providing a total of 128 potential channels per session. As mentioned before, each montage was recorded in a separate session, and the order was counterbalanced across participants.

After finishing the EROS sessions, the location on the scalp of each source and detector, as well as the remaining scalp locations, in relation to the nasion and fiducial points (both crus of helix) were digitized with a neuro-navigation software (SofTaxic, E.M.S., Bologna, Italy) combined with a 3D optical digitizer (Polaris Vicra, NDI, Waterloo, Canada). Successively, such digitized scalp locations were co-registered with the individual MRI of each subject, using a dedicated software package (OCP, Optimized Co-registration Package, MATLAB code) developed by Chiarelli and colleagues (Chiarelli et al., 2015).

As mentioned above, before taking part in the experiment, participants underwent a structural MRI, which took place at the Borgo Roma Hospital in Verona, by means of a 1.5 Tesla Philips scanner with a standard 15-channel head coil. A whole brain high-resolution 3D T1-weighted image with magnetization-prepared rapid acquisition gradient echo (MPRAGE) was acquired. The acquisition parameters were the following: phase encoding direction= anterior to posterior, voxel size= 0.5 × 0.5 × 1 mm, Repetition Time= 7.7 ms, Echo Time= 3.5 ms, field of view= 250 × 250 mm, flip angle= 8°.

2.1.7 Data Analysis

Behavioral data

Raw data were processed by means of scripts created on Matlab (version R2017b; the MathWorks, Inc., Natick, MA). According to the subjective awareness report, trials were sorted into the two experimental conditions (i.e., Aware and Unaware conditions). For each participant, trials with no response as well as trials with reaction times lower than 150 ms and higher than 3 standard deviations were excluded from the analysis. Data were successively analyzed with IBM SPSS Statistics for Windows, version 22: paired sample t-tests were applied to compare the behavioral performance (i.e., the Accuracy) and the mean reaction times (RTs) between Aware and Unaware conditions.

EROS data

Continuous optical data were pre-processed using a dedicated in-house software, P-POD (Pre-Processing of Optical Data, run in MATLAB, version R2013b). Full and detailed description of the pre-processing procedure is in depth described in Parisi et al., 2020. The pre-processing steps included a) normalization of data, in which data were corrected for phase wrapping, de-trended to remove low-frequency drifts and baseline corrected; b) pulse correction, i.e., heart beats artifacts removal by using a regression algorithm (Gratton & Corballis, 1995); c) filtering of data by means of a band-pass filter which allows frequencies between 0.5 Hz and 15 Hz. After that, data were segmented into epochs time-locked to the onset of the stimulus and averaged separately for each subject, condition, and channel. Each epoch comprised a period from 486 ms before the stimulus onset to 998 ms following the stimulus onset, resulting in an epoch lasting 1484 ms. Statistical analyses on functional data were then computed on averaged data with an in-house software package (Opt-3d; (Gratton et al., 2000)), which allowed to analyze and graphically display the fast optical signal. To compute statistics, data from channels whose diffusion paths (bananas) intersected a given voxel were combined (Wolf et al., 2014). Phase delay data were spatially filtered with an 8-mm Gaussian kernel. t-Statistics were calculated across subjects for each voxel, converted into Z-scores and corrected for multiple comparisons using random field theory (Kiebel et al., 1999; Worsley et al., 1995). Subsequently, *Z*-scores were weighted and orthogonally projected onto the lateral surface of a MNI template brain, according to the physical homogenous model (Arridge & Schweiger, 1995; Gratton, 2000).

Regarding the investigated Regions of Interest (ROIs), they are shown in Figure 2B and their coordinates are listed in Table 1. ROIs were identified in the occipital and in the left temporo-parietal lobes, based on both the inspection of the functional data and previous literature on perceptual awareness.

Thus, we selected as ROIs the primary visual cortex (V1), the extra-striate visual cortex (V3), specifically the portion included in the cuneus (Brodmann Area 19), the superior parietal lobe (SPL), the lateral occipital complex (LOC) and motor areas (MAs) including supplementary motor area, premotor and motor cortex. As the EROS data were projected on the surface of the brain, ROIs were defined by a 2-dimensional box-shaped structure: depending on the visualization of the data (coronal or sagittal) y or x coordinates are missing, respectively. In order to better define ROIs boundaries and to avoid the overlapping of different ROIs, we referred to the Yale online search tool (https://bioimagesuiteweb.github.io/webapp/mni2tal.html). The same tool was also used to estimate the Brodmann's areas encompassed by each ROI.

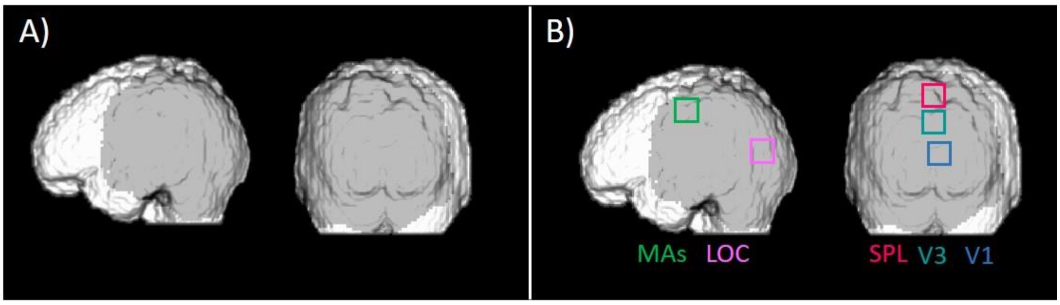

Figure 2. Covered area and ROIs. A) The gray area represents the area covered by the montages. B) Colored squares represent the selected ROIs for EROS and Granger analyses. Their coordinates are reported in Table 1.

Region	*Projection*	*Coordinates*			*Involved Ba*
MAs	Sagittal	y =	-29	9	4
		z =	38	58	
LOC	Sagittal	y =	-86	-66	19
		z =	4	24	
SPL	Coronal	x =	-10	10	7
		z =	46	66	
V3	Coronal	x =	-10	10	19
		z =	25	45	
V1	Coronal	x =	-5	15	17
		z =	5	25	

Table 1. MNI coordinates of selected ROIs

2.2 Experiment 2

2.2.1 Participants

In Experiment 2, we recruited the same participants as Experiment 1, in order to test the same sample in both experiments. All but four participants accepted to take part in the second experiment, so a total of 20 participants were tested in Experiment 2 (8 males, mean age ± standard deviation: 24.4 ± 3.5). Data from 4 participants were discarded because of behavioral reasons (awareness equal to or higher than 75%), so that the final sample was composed of 16 participants (7 males, mean age ± standard deviation: 24.7 ± 3.6). All of them gave a new written informed consent before taking part in the experiment. The study was carried out according to the principles laid down in the 2013 Declaration of Helsinki and approved by the local Ethics Committee.

2.2.2 Experimental Procedure

The experimental procedure was the same as Experiment 1, with the difference that the EEG experimental session consisted of a single session divided into 10 blocks of 60 trials each, thus providing a total of 600 trials per subject. To verify that fixation was maintained during the task, on-line monitoring of the eye movements was performed by an infrared camera.

2.2.3 EEG recording

The EEG activity was continuously recorded through a BrainAmp system (Brain Products GmbH, Munich, Germany–Brain Vision Recorder) provided with 59 Ag/AgCl electrodes mounted on an elastic cap (EasyCap, GmbH, Herrshing, Germany), placed according to the 10-10 International System. Four additional electrodes placed at the left and right canthi and above and below the right eye were used for monitoring blinks and eye movements. Signal was referenced online to the right mastoid (RM) and electrode AFz served as ground. Data were recorded at a sampling rate of 1000Hz and the impedance of all the electrodes was kept below 5 KΩ.

2.2.4 Data Analysis

Behavioral data

Behavioral data were analyzed in the same manner as in Experiment 1.

EEG data

The analysis of EEG data was performed with MATLAB (version R2020b; the MathWorks, Inc., Natick, MA) scripts created ad-hoc based on functions from the EEGLAB toolbox (v2020.0, Delorme & Makeig, 2004). The EEG signal was first resampled to 250 Hz. Continuous raw data were filtered offline using zero-phase Hamming windowed sinc FIR high-pass and low-pass filters (cut-off frequencies: 0.1 and 90 Hz, transition bandwidth: 0.2 and 20 Hz). To remove line noise, a notch filter (cut-off frequencies: 49.5 and 50.5 Hz, transition bandwidth: 1 Hz) was applied. After that, channels with bad signal were identified and removed by means of the *clean_channels* EEGLAB function, using a correlation threshold of .5 (mean number of channels removed across participants: 1.25).

To submit a clean dataset to the independent component analysis (ICA) algorithm and to facilitate the recognition and removal of artifacts, we created a temporary dataset to which a different pre-processing had been applied (Winkler et al., 2015). Specifically, the following pre-processing steps were implemented: a) a high-pass filter at 1 Hz (cut-off frequency: 0.5 Hz, transition bandwidth: 1 Hz) was applied; b) data were segmented into epochs ranging from -1150 to 1250 ms with respect to the stimulus onset; c) artifactual epochs were detected and removed by means of improbability and kurtosis criteria (SD > 5 for local threshold and SD > 3 for global threshold).

After these steps, ICA was computed through the FastICA algorithm (Hyvärinen, 1999) on this temporary dataset, in order to correct for blinks, eye movements and muscular activity based on scalp topography, evoked time course and spectral distribution. The solution of the ICA was then applied to the original dataset (the one with the removed bad channels and already segmented into epochs from -1150 ms to 1250 ms).

Data were subsequently low-pass filtered at 40 Hz (cut-off frequency: 45 Hz, transition bandwidth: 10 Hz) and removed channels were interpolated using a spherical spline method (Perrin et al., 1989). All scalp channels were then offline re-referenced to the linked mastoids (RM-LM) and baseline correction was applied from -450 ms to -150 ms before the stimulus onset.

Only trials with RTs > 150 ms and < 3 SD were included in further analysis. Subsequently, we applied an automatic procedure to detect artifactual epochs based on extreme values (±125 μV), abnormal trend in data (maximal slope allowed = 50 μV/epoch and minimal R2 allowed = .3), and improbability and kurtosis criteria (SD > 5 for local threshold and SD > 3 for global threshold). This procedure was carried out together with the Trial by Trial (TBT) plugin of EEGLAB, that allows to automatically reject and interpolate channels on an epoch-by-epoch basis. In particular, an epoch was removed if it had more than 6 bad channels, otherwise channels were interpolated.

Finally, the resulting epochs were sorted into the two experimental conditions, Aware and Unaware (average epochs included: 268.5 and 204, respectively), and statistical analyses were applied. ERP waveforms were averaged separately for the two conditions and paired-sample t-tests were computed on all time points and electrodes between aware and unaware conditions.

Finally, data were thresholded using temporal clustering and only clusters of activity lasting longer than 30 ms were taken into account.

3. Results

3.1 Experiment 1

3.1.1 Behavioral results

Raw data were processed by means of scripts created on Matlab (version R2017b; the MathWorks, Inc., Natick, MA). According to the subjective awareness report, trials were sorted into the two experimental conditions (i.e., Aware and Unaware conditions). Aware trials represented on average 60.00% of the trials. Paired sample (two-tailed) t-test revealed, as expected, that the *Accuracy* was significantly greater for Aware trials (M = 90.55%) than Unaware trials (M = 45.07%; $t_{(23)} = 15.689$, $p < 0.001$), suggesting that in the Aware condition participants could properly discriminate the orientation of the stimulus.

Conversely, mean RTs for Aware (565.11 ms) and Unaware condition (568.86 ms) were not statistically different ($t_{(23)} = -.480$, $p = .636$), indicating that there ~~is~~ was no difference in the responsiveness between the two conditions.

3.1.2 Functional Results

In order to highlight the spatiotemporal dynamics underlying aware vision, neural activity occurring in Aware trials was contrasted with neural activity occurring during Unaware trials.

As shown in Figure 3A, the Aware vs Unaware contrast showed a significant increase of activation 76 ms after the presentation of the stimulus in the lateral occipital complex (LOC) ($z = 3.05$; $z\ crit = 2.71$), followed by increased activity in the superior parietal lobule (SPL) at 102 ($z = 2.60$; $z\ crit = 2.22$) probably reflecting top-down processes of allocation of attention towards the attended stimulus. Subsequently, LOC revealed greater activation in a time window ranging from 153 to 307 ms. Specifically, activity reached the statistical significance at 179 ms ($z = 2.54$; $z\ crit = 2.53$), 230 ms ($z = 2.72$; $z\ crit = 2.66$) and 281 ms ($z = 3.26$; $z\ crit = 2.50$). The sustained and recurrent activity highlighted in this area reflects the conscious identification of the stimulus, as also suggested by the high accuracy reported by participants at behavioral level. LOC, in fact, is an extra-striate area which is known to be involved in object recognition (Grill-Spector 2001, 2003). Later on, activity in LOC was followed by significant activity in the primary visual cortex (V1) at 460 ms ($z = 2.75$; $z\ crit = 2.32$) and 486 ms ($z = 2.73$; $z\ crit = 2.36$), which in turn was followed by greater activity in motor areas (including supplementary motor area, premotor and motor cortex) ($z = 3.25$; $z\ crit = 2.63$) at 537 ms.

3.1.3 Granger Causality

Granger causality (G-causality) analysis was performed in order to better understand the flood of activity occurring in the investigated areas. G-causality, in fact, allows to unveil the predictive interaction between activity in different brain areas at different time-points, thus revealing patterns of activation not highlighted by conventional EROS analyses.

ROIs resulted significantly active in EROS analysis were used as seeds, as well as ROIs whose activity was predicted by G-causality analysis. Granger causality analysis (Figure 3B) revealed that neural processes relating to conscious perception were characterized by a sustained and recurrent activation of LOC and striate and extra-striate visual areas. The stream of activation, in fact, principally originated in LOC and subsequently spread towards visual and motor areas. In particular, early activation of LOC resulted to be predictive of activity in both striate and extra-striate visual areas. Specifically, LOC at 76 ms was predictive of activity in SPL and V3 at 127 ms, as well as of activity in LOC at 383 ms and motor areas at 460 ms. Activity in motor areas at 460 was also predicted by activity in LOC at 153 and 179 ms. Then, activity in SPL at 102 ms was predictive of activity in extra-striate visual areas like V3 at 127 ms and LOC at 153 and 383 ms. Activity in LOC at 230 ms resulted to predict activity in visual areas, more in detail in extra-striate visual areas (V3) at 255 ms and 332 ms, and in the primary visual cortex at 332 and 460 ms. Moreover, activity in V1 at 332 ms was in turn predictive of activity in V3 at 460 ms.

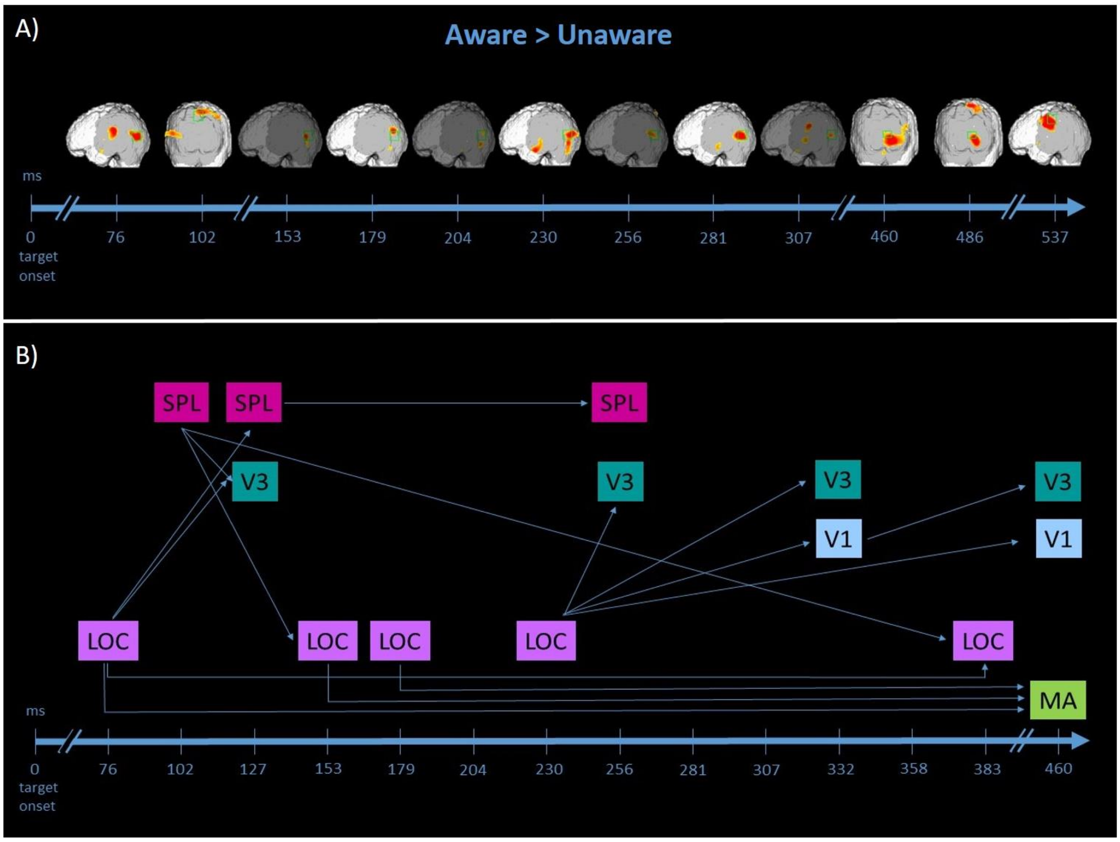

Figure 3. EROS and Granger causality results obtained contrasting Aware and Unaware conditions. A) EROS results. Saturated images represent significant statistical parametric maps of the z-score difference computed between Aware and Unaware trials. Shaded maps represent marginally-significant effects. B) Granger causality results. For this analysis, ROIs resulted significantly active in EROS analysis were used as seeds, as well as ROIs whose activity was predicted by G-causality analysis. Each arrow represents a significant predictive link between the respective brain regions.

3.2 Experiment 2

3.2.1 Behavioral results

Behavioral results of Experiment 2 followed the same trend as behavioral results of Experiment 1. Aware trials represented on average 57.06% of the trials. Also in this case, *Accuracy* for Aware trials (M = 87.76%) was significantly greater than Unaware trials (M = 55.05%; $t_{(15)} = 13.360$, $p < 0.001$) and the paired sample (two-tailed) t-test did not reach the statistical significance ($t_{(15)} = -1.152$, $p = .267$) when comparing mean RTs of Aware trials (595.87 ms) with mean RTs of Unaware trials (603.87 ms).

3.2.2 EEG Results

The average number of epochs taken into account in the two experimental conditions after epochs rejections was respectively 269 for Aware condition and 204 for Unaware condition.

In line with previous ERPs studies, Aware trials elicited a significant VAN at posterior electrodes, followed by a more widespread LP (Figure 4). More in detail, VAN resulted to be significant in electrode O1 between 240 and 268 ms and between 308 and 338 ms, in electrode PO7 between 160 and 200 ms, between 236 and 272 ms and between 296 and 424 ms. In electrode PO8 VAN resulted significant from 360 to 392 ms, in electrode P7 from 160 to 252 ms and from 268 to 424 ms, and in electrode P5 from 156 to 280 ms and from 300 to 396 ms. Moreover, electrodes P8 and CP5 showed significant VAN, respectively between 332 and 392 ms and between 180 and 256 ms. Finally, VAN was significant also in electrode CP3 between 176 and 208 and between 220 and 256 ms, in electrode C5 between 220 and 252 ms, and in electrode FC5 between 192 and 240 ms.

LP resulted to be significant in all electrodes (except for C6 electrode) in a temporal window ranging from 484 and 664 ms.

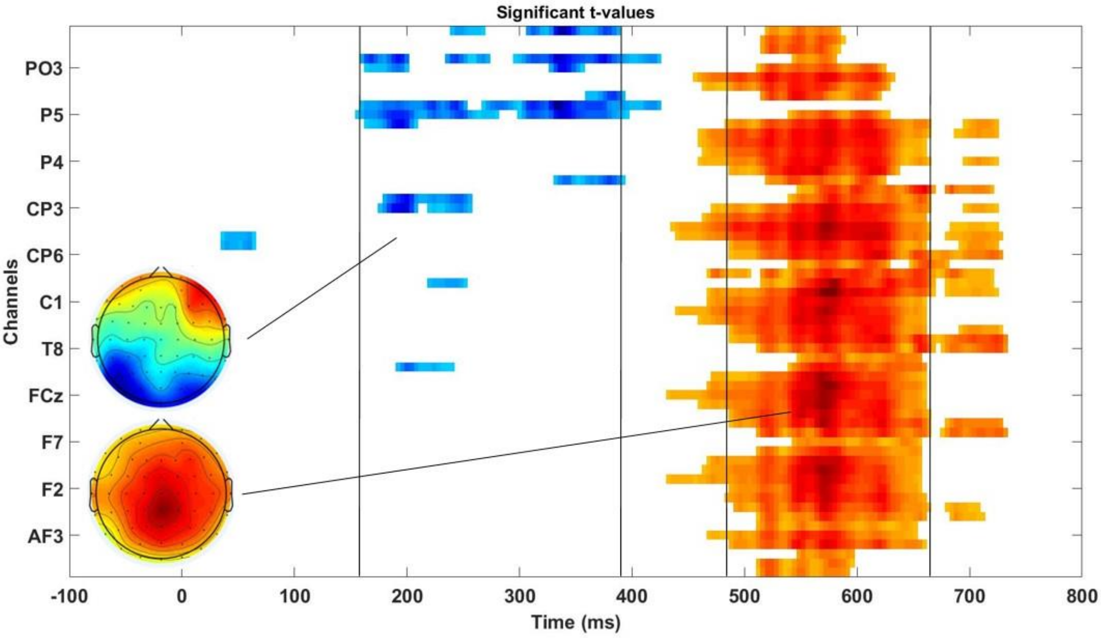

Figure 4. Raster plot representing results from a paired t-test between Aware and Unaware conditions. Data were thresholded using temporal clustering where only clusters of activity lasting longer than 30 ms were taken into account. The scalp distribution maps on the left represent the voltage difference between conditions in VAN (blue) and LP (red) time-windows respectively.

4. Discussion

The present study sought to shed further light on the neural correlates of perceptual awareness, by disentangling the spatio-temporal dynamics occurring when a stimulus enters consciousness. To do so, we adopted a combined approach in which participants' brain activity was recorded during the performance of a discrimination task by means of EEG and EROS techniques in separate sessions. The advantage of this approach was two-fold: EEG allowed to investigate the electrophysiological correlates of visual awareness and to identify/determine their exact timing, while with EROS it has been possible to disentangle which brain regions and in what order of activation were involved when the stimulus was reported as "seen". Thanks to the worthwhile opportunity provided by EROS technique of combining both high spatial and high temporal resolution, it was possible to investigate both the neural correlates and the timing of conscious perception. Specifically, we were interested in tracing the time-course of activation of specific brain areas occurring in the time range of VAN, since a large body of literature agrees that this is the earliest and most reliable marker of conscious vision. Although VAN and LP are often regarded as if they are both related to aware vision, converging evidence suggests that these two electrophysiological components reflect different processes. While VAN is barely affected by neural processes not directly related to awareness, it has been shown that the amplitude of LP is affected for example by attention (Koivisto & Revonsuo, 2008), working memory load (Koivisto et al., 2018b), the requirement of report (Koivisto et al., 2016), and other neural processes that occur at later stages of the stimulus processing (Mazzi et al., 2020).

Overall, our electrophysiological results replicated the typical pattern commonly reported in visual awareness literature: Aware trials elicited a larger early negativity when compared to Unaware ones in the N2 time window at posterior electrodes. This difference (VAN) was followed by a significant LP peaking at centro-parietal sites in the P3 time-range.

Concerning the functional results, interestingly, in the time window of the VAN, significant activity was observed in the lateral occipital complex, an extra-striate area involved in object recognition (Grill-Spector et al., 2001). This was also reflected in the behavioral performance, which was significantly above chance level in Aware trials. In Aware condition, in fact, participants could discriminate the orientation of the Gabor patch, while in the Unaware condition the performance was at chance level, indicating that participants were not discriminating the orientation of the stimulus. EROS findings suggest not only that LOC plays a crucial role in the conscious perception of a visual stimulus, but also that this specific area could serve as a proper correlate of visual awareness. This is consistent with previous MEG source localization studies (Liu et al., 2012; Vanni et al., 1997) that identified LOC as the cortical generator of VAN. Moreover, as highlighted by Granger causality results, it is interesting to note that the sustained activity in LOC was predictive of later activity in striate and extra-striate visual areas. Granger causality, when combined with EROS analysis, is a very powerful tool since it allows to explore the predictive interaction between different brain areas at different time-points (Roebroeck et al., 2005). In this respect, the present findings can help in shedding light on a controversial issue, regarding the role of the primary visual cortex in visual awareness. A large body of literature, indeed, suggests that V1 plays a direct and crucial role in conscious perception, by engaging recurrent circuits with extra striate areas (Lamme & Roelfsema, 2000). According to this perspective, feedback projections from extra striate areas to V1 are necessary for visual awareness to arise. On the other hand, several pieces of evidence suggest that V1 is not part of the NCC, since visual awareness originates in a wider posterior zone, which includes temporal, occipital, and parietal cortices (Boly et al., 2017; Koch et al., 2016).

In the present study, EROS results showed that activity in V1 occurs late (i.e., 460 ms after the presentation of the stimulus) and Granger analysis results suggest that V1 activity is reflecting feedback contribution from extra striate areas since it is predicted by activity in LOC occurring earlier. In line with previous literature claiming that V1 per se is not sufficient to give raise to a conscious experience (Rees et al., 2002), these findings suggest that the primary visual cortex does not constitute part of the NCCs. EROS results, in fact, showed that when contrasting Aware and Unaware conditions, early activity in V1 is not observed, but it emerges only later, when the feedback sweep is coming back from extra striate areas. According to the basic logic of contrastive analysis approach, for which common neural processes occurring in both conditions cancel each other out, activity in V1 is present both in the Aware and in the Unaware condition, suggesting that it is not directly involved in the emergence of visual awareness. Its role, in fact, would be that of providing essential visual input and carrying it toward extra-striate areas.

Furthermore, another interesting aspect highlighted by Granger analysis is that early activity in LOC was predictive also of later activity in motor areas. Motor areas are responsible both for the motor response and for the preparation of the response. Specifically, the supplementary motor area (SMA) and the pre-motor areas are known to play an important role in the internal preparation of the movement (Cunnington et al., 2002) while primary motor cortex (M1) is involved both in the preparation and in the execution of the motor response (Richter et al., 1997).

In our study, participants were asked to respond by pressing a button on a response box even if they could not see the orientation of the stimulus, therefore motor preparation and response were present in both the experimental conditions. For this reason, one could expect that when contrasting Aware and Unaware trials, common neural processes shared by both conditions would cancel each other out. Interestingly, EROS results showed that Aware trials elicited a significant increase of activity in motor areas if compared to Unaware trials. Moreover, Granger analysis revealed that activity in motor areas 460 ms after the stimulus onset was predicted by earlier activity occurring in LOC, exclusively for Aware condition. This increased activity in motor areas occurring in the Aware condition could be due to the fact that when the stimulus was seen, a specific answer had to be given (i.e., a specific finger had to be moved in order to press the correct button), while when the stimulus was unseen, participants were asked to respond randomly, by pressing indifferently one of the two buttons on the response box. Thus, in Aware condition the motor response was goal-driven and triggered by awareness, while in Unaware condition motor response was merely an aimless movement.

Taken together, the results presented here show that when a stimulus enters consciousness it elicits a sustained activation in LOC, if compared to when the same stimulus does not reach awareness. Granger causality results highlighted also that activity in LOC predicted activity both in striate and extra-striate areas and in motor areas. Moreover, combining EROS and EEG results allowed to unveil that the sustained activation in LOC occurred in the temporal window of VAN, which is considered the electrophysiological signature of visual awareness. This, along with previous literature, suggests that LOC could represent a reliable neural correlate of consciousness, endorsing the idea that visual awareness is served by a wide posterior “hot zone”, rather than by V1 exclusively.

Overall, the present findings provide interesting insights into the neural correlates of conscious vision. The combination of EROS and Granger causality with EEG offered the possibility to achieve a comprehensive and innovative picture of the mechanisms underlying visual awareness.

STUDY 2

This experiment was carried out at the University of Turku under the supervision of Professor Henry Railo.

1. Introduction

Ever since consciousness gained more relevance in the field of science, neuroscientists have tried to outline the neurophysiological substrates that underlie it by searching for the neural correlate of consciousness (NCC). One of the main lines of study searches for the NCC that underlies the emergence of conscious visual experience. Due to their high temporal resolution, event-related potentials (ERP) measured using electroencephalography (EEG) provide excellent means to examine this question (Luck, 2014). These studies have revealed scalp recorded electrophysiological signatures of conscious vision, but the neural processes that generate these two correlates are not completely clear. Here, we sought to shed light on the spatio-temporal distribution of neural sources that contribute to the ERP correlates of conscious vision.

The most widely used approach to investigate NCC consists of presenting participants with a stimulus that they only sometimes consciously perceive. This allows contrasting the brain activity associated with “subjectively seen” and “unseen” stimuli while keeping the objective, physical stimulus constant. This procedure allows detecting the neural processes that are involved in visual awareness, although processes that are not specifically linked with conscious vision are likely also present (Aru et al., 2012). Processes that co-vary with conscious perception, but are not likely part of the mechanism that enables conscious perception can be roughly categorized into two classes: processes that contribute to perception, but take place before conscious perception (e.g., prestimulus activity (Britz et al., 2014)), and processes that causally link with visual conscious perception (e.g., cognitive processes and behavioral response-related processes).

ERPs provide a useful tool to examine the temporal dynamics involved in conscious vision. In particular, it allows to investigate brain activity time-locked to a specific event (i.e., the onset of the stimulus) with a millisecond resolution. The comparison between the Aware and Unaware conditions has revealed two major ERP correlates of conscious vision: the “visual awareness negativity” (VAN), and “late positivity” (LP). The VAN is an early, negative amplitude difference, typically peaking around 200 ms after the stimulus onset in occipito-temporal sites. The LP occurs at centro-parietal electrodes in the P3 time window (i.e., around 300-500 ms after the presentation of the stimulus) (Dehaene & Changeux, 2011; Koivisto & Revonsuo, 2003, 2010; Mashour et al., 2020). According to a large body of empirical studies, VAN is considered as the earliest reliable ERP correlate of aware visual perception whereas the LP may reflect “post-perceptual” processes occurring after the stimulus has entered the consciousness (Förster et al., 2020). While VAN is known to be localized over occipito-temporal sites, LP is thought to reflect several different cognitive processes such as identifying, naming and reporting the stimulus, and its topography is widely distributed over multiple cerebral sources spanning occipital, parietal, temporal, and frontal cortices (Dehaene & Changeux, 2011; Koivisto & Revonsuo, 2010; Volpe et al., 2007). In this regard, debate continues over how crucial frontal areas are for conscious perception: because of its involvement in cognitive functions such as attention and working memory, the prefrontal cortex is sometimes argued to play an essential role in conscious perception (Del Cul et al., 2009, Odegaard et al., 2017). In contrast, several pieces of evidence suggest that frontal and prefrontal cortices may be neither necessary nor sufficient for consciousness (Boly et al., 2017; Raccah et al., 2021), suggesting that the NCC are localized in posterior cortical regions, including occipital, parietal and temporal lobes (Koch et al., 2016; Mazzi & Savazzi, 2019).

Source localization studies localize the cortical generator of VAN in occipito-temporal areas (Koivisto & Revonsuo, 2010; Liu et al., 2012; Veser et al., 2008), while LP seems to relate to a wider network, distributed over fronto-parietal and temporal areas (Antoine Del Cul et al., 2007; Volpe et al., 2007). Given that ERPs are the summed activity of multiple distinct sources, correlates such as VAN and

LP may at a given time-point include a combination of consciousness-related sources, instead of being localized to a single area. Moreover, sources with opposite polarities may cancel each other out, rendering them invisible in the average ERP signal (Luck & Kappenman, 2012). Theories about the neural basis of consciousness typically argue that conscious perception involves recurrent activity across multiple areas, suggesting that correlates such as VAN and LP are a combination of multiple sources. This is especially true for LP, which according to the Global Neuronal Workspace Theory of consciousness, involves co-organized activity across widely distributed cortical areas (Dehaene & Changeux, 2011). While early correlates are typically argued to be driven by posterior areas, it remains possible that early activity in frontal areas also correlates with consciousness if a sufficiently sensitive source separation is utilized (Kapoor et al., 2022; Knotts et al., 2018; Thompson & Schall, 2000).

During recent years, source separation approaches such as independent component analysis (ICA) have been developed to uncover sources contributing to average ERPs. In ICA, EEG is decomposed into maximally independent components (ICs) equal to the number of the recording electrodes (Onton & Makeig, 2006). Each IC represents a temporally and functionally independent source of the EEG signal, with a specific scalp distribution (which is constant over time), and a specific amplitude at each time point (Onton & Makeig, 2006; Onton et al., 2006). This allows investigation of source level activity and allows isolating ICs that underlie the average ERP wave. The aim of the present study was to characterize the locations and time-courses of independent neural sources that significantly contribute to the ERP correlates of visual awareness. We expected to identify components that significantly contribute to VAN and LP, but hypothesized that source separation might also uncover correlates that are not visible in scalp recorded ERPs.

2. Methods

2.1 Participants

Analyses presented in this study were performed on data acquired in a previous study (Railo et al., 2021), and data collected as part of a EEG course organized at the University of Turku (same paradigm and EEG methodology as in Railo et al., 2021). In the current study, data from 35 healthy participants (mean age ± sd = 24.14 ± 3.52, range 19-36) were analyzed. All participants were students at the University of Turku, and reported no neurological disorders. All of them gave their written informed consent in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of the Hospital District of Southwest Finland.

2.2 Experimental procedure and Stimuli

The target stimuli were low contrast Gabor patches (diameter 6.5°, frequency 0.7 cycle/degree) which were presented to the left or right hemifield (about 5° from fixation on horizontal meridian) for 16.6 ms. In addition, the experiment included catch trials where no stimulus was presented (1/6th of all trials). The intensity of the low contrast stimuli was individually determined using a QUEST staircase (Watson, 2017), so that stimulus intensity was near 50% of subjective detection threshold.

The stimulus was presented after a fixation period ranging from 668 to 1332 ms across trials. Participants were asked to report the location of the target (left vs. right), and to subjectively rate the visibility of the stimulus by means of a four-steps scale (Figure 1a). The scale was composed of the following four alternatives: 0) "did not see stimulus at all", 1) "not sure but possibly saw something", 2) "pretty sure I saw it", 3) "saw the stimulus clearly". A total of 400 trials was collected per participant (divided into 10 blocks of 40 trials).

2.3 EEG

2.3.1 Recording

EEG data were recorded with a 64-channel EEG system at a sampling rate of 500Hz. Impedance was kept near 5 kΩ. Electrode Fz served as on-line reference, and the ground electrode was placed on the forehead of the participant.

2.3.2 Preprocessing

EEG data were preprocessed with MATLAB (version R2017b; the MathWorks, Inc., Natick, MA) using functions from the EEGLAB toolbox (v2020.0, Delorme & Makeig, 2004).

Continuous raw data were first resampled to 250 Hz, and filtered using a high-pass filter at 1 Hz (cut-off frequency .5 Hz, transition bandwidth: 1Hz), followed by a low pass filter at 40 Hz (cut-off frequency 45Hz, transition bandwidth: 10Hz). *Clean_channels* EEGLAB function with a correlation threshold of .5 was used to remove channels with a bad signal (mean number of channels removed across participants = 1.61; SD = 1.84). After that, data were re-referenced to the average of all electrodes and cut into epochs ranging from -500 to 900 ms with respect to the stimulus onset. To remove epochs containing artefacts, ICA was computed using the extended Infomax runICA algorithm (Bell & Sejnowski, 1995), and trials contaminated by artefactual components were removed using the EEGLAB function *pop_jointprob* (SD = 5 for both local threshold and global threshold). Baseline correction was then applied on the pre-stimulus period (from -500 ms to 0 ms), and ICA was computed again. Subsequently, the dipolar source of each component was localized using the DIPFIT plug-in (v3.3). The dipole localization was based on an average MRI, and electrode locations were co-registered based on standard channel coordinates. Because individual MRIs and subject-specific channel location information were not available, the accuracy of spatial localization in the present study is limited. Components with a residual variance of more than 15%, and those labelled as not-brain-based with a probability of >50% were automatically identified by means of the *ICLabel* plugin and removed. In total, 379 ICs (average number of ICs across participants =10.8) were selected as brain ICs. Finally, missing channels were interpolated for each participant using a spherical method using the EEGlab function *pop_interp*.

2.3.3 IC clustering

The resulting 379 brain ICs were grouped into clusters using a k-means clustering method implemented in EEGlab. Components were clustered based on dipole location, dipole orientation and ERPs. Importantly, the data were divided into the Aware (visibility rating = 1,2,3) and Unaware (visibility rating = 0) experimental conditions after the clustering. On average, the number of epochs included in the analyses was 107 (SD=35.92) for Aware and 105 (SD=38.18) for Unaware condition. The default number of clusters suggested by EEGlab (i.e., *k* value) was 11, but it was manually adjusted to 13 after visual inspection of the initial clustering result. On average, each cluster was composed of 35.2 ICs. Outliers ICs (35 ICs, threshold = 3 SD)—that is, ICs that were not assigned into any one of the 13 clusters—were grouped in an auxiliary cluster, which was not included in the analysis. For statistical analyses, ICs of each participant (within a cluster) were averaged together.

2.3.4 Statistical analyses

Before clustering, ERP waveforms were averaged separately for Aware and Unaware conditions and paired-sample t-tests were computed on all time points and electrodes. The p-values were corrected for multiple comparisons using Benjamini-Hochberg false-discovery rate procedure (Groppe et al., 2011) implemented in Matlab. Subsequently, data were grouped into clusters and within each cluster, ERPs were averaged separately for the two experimental conditions. Visual inspection of clusters suggested Aware vs Unaware differences resembling the VAN-LP pattern, including a transient early and later more sustained difference. Statistical analysis was focused on these time-windows. Paired-sample t-tests (FDR-corrected) were computed between the Aware and Unaware conditions. Moreover, since we were interested in quantifying the contribution of each cluster to the average ERP, we calculated for each cluster the percent variance accounted for (*pvaf*, which compares the variance of the whole data minus the back-projected component to the variance of the whole data) using the *std_envtopo* (v4.10) EEGlab function.

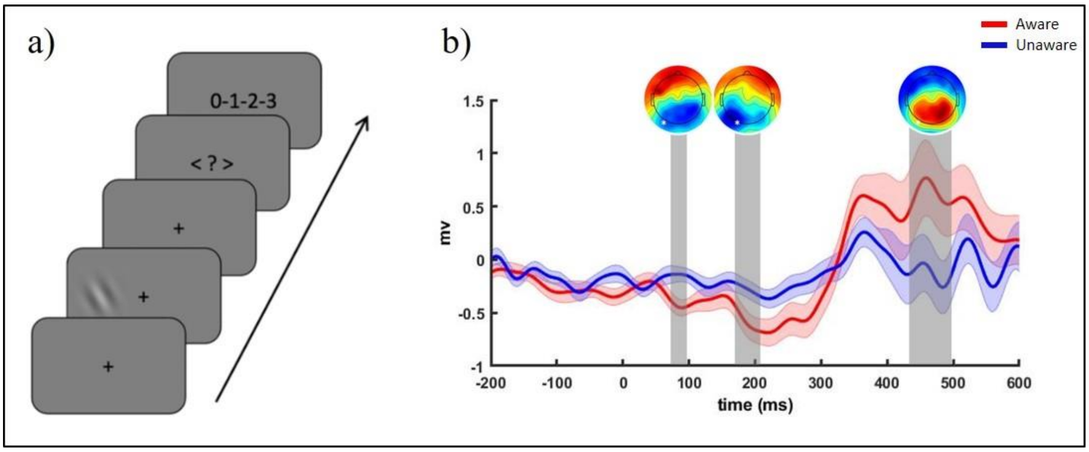

Figure 1: Experimental procedure and ERP results. A) Schematic presentation of a single experimental trial. B) Grand-average of ERPs computed for Aware and Unaware conditions at channel O1 (marked with a white star). The shaded area of the waveforms represents the SEM. Significant time-windows are highlighted in grey.

3. Results

The behavioral results showed that participants reported perceiving the stimulus on average in 50% of trials, and that performance in the location discrimination task scaled with participants' awareness of the stimulus. We refer the reader to Railo et al., 2021 where these analyses are reported in detail.

As expected, the grand average ERP showed both the VAN and the LP. Figure 1b shows the grand average ERP for the Aware and Unaware conditions at electrode O1. Paired-sample t-test (FDR-corrected) between Aware and Unaware trials revealed that at electrode O1 VAN was significant in 2 different temporal windows: between 80 and 100ms, and between 180 and 208 ms, while LP was significant between 444 and 500 ms.

To examine the independent brain sources that contribute to the scalp recorded ERPs, and possibly correlate with conscious vision, we next analyzed the clusters of ICs. Only clusters with more than 15 components were included into statistical analyses (clusters numbers 1, 2, 6, 7, 9, 10, 11, 12, 13). Excluded clusters contained on average 6 ICS (SD= 5.83). Figure 2 displays the ERP of each cluster, as well as the locations of individual ICs within the cluster. The clusters localized to different areas of the brain. For example, Cluster 1 localized to anterior parietal/posterior frontal areas, and Cluster 2 to temporal cortex. Visual inspection of the event-related responses suggested that especially in later time-windows (i.e., > 300 ms), the Aware and Unaware conditions differed. However, also earlier time-windows showed differences between the conditions, albeit smaller in amplitude (e.g., Clusters 2 and 12).

Aware vs Unaware epochs were contrasted within each cluster in the selected time-windows using FDR-corrected paired-sample t-tests. The results are reported in Table 1. The last column of the table shows the percent variance accounted for (pvaf) by each component at each temporal window. As shown in Table 1, many clusters showed statistically significant differences in the late time-windows (i.e., >300 ms after the stimulus presentation), and a few clusters also showed earlier differences. The earliest difference between Aware and Unaware conditions ~~is~~ was observed -108–100 ms in parietal regions. Also, cluster 2 showed a broad, early effect (32–212 ms), and also two later effects in temporal cortex. Clusters 7, and 12 showed a mid-latency (roughly 150–260 ms) effect in occipito-temporal regions, in a time window corresponding to VAN in the scalp recorded grand average ERP. Finally, a later difference between Aware and Unaware conditions was observed in most of the clusters, spanning frontal, parietal, temporal and occipital regions.

Many clusters explained about 20–35% of variance in the grand-average ERP.

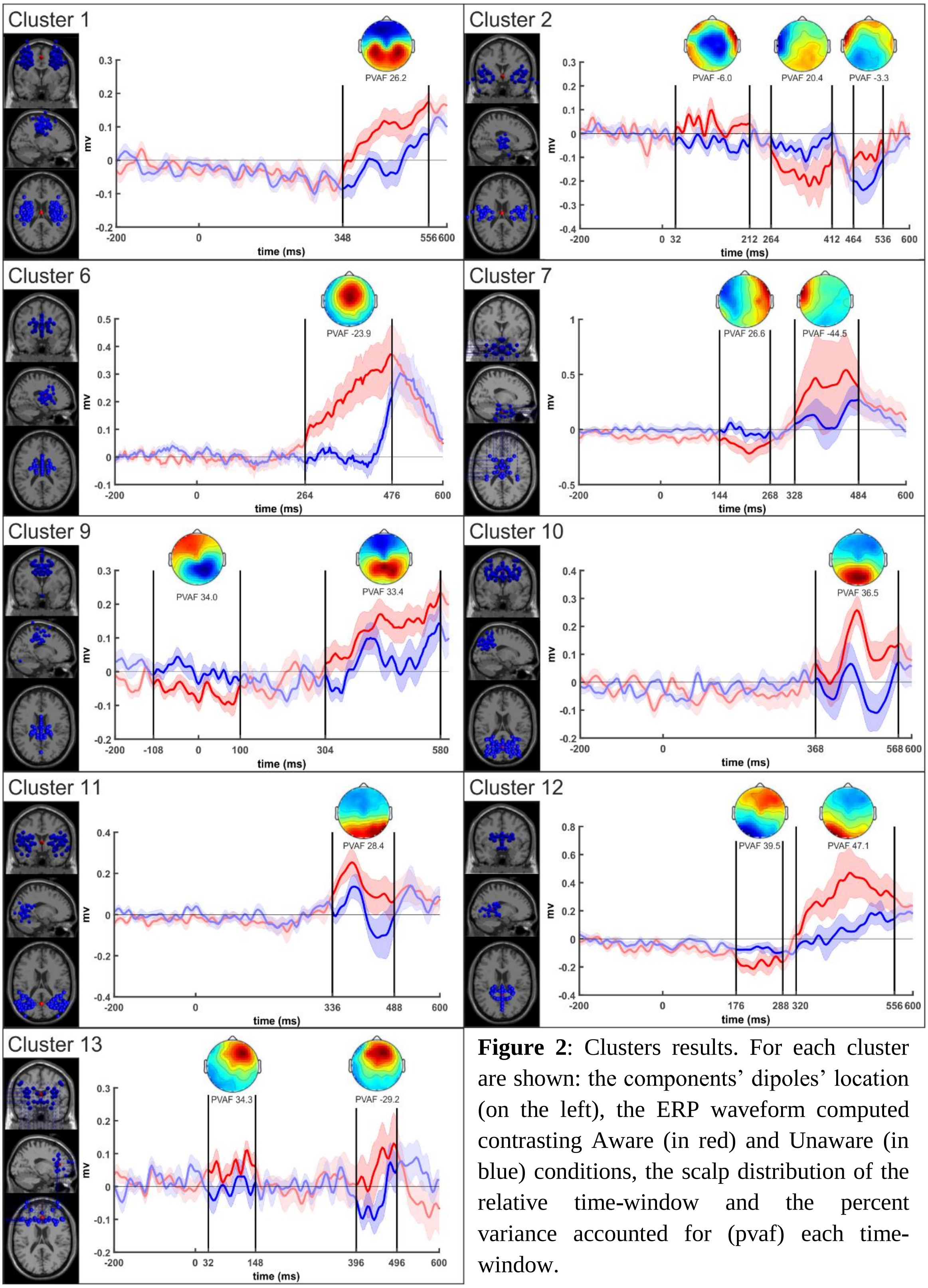

Figure 2: Clusters results. For each cluster are shown: the components' dipoles' location (on the left), the ERP waveform computed contrasting Aware (in red) and Unaware (in blue) conditions, the scalp distribution of the relative time-window and the percent variance accounted for (pvaf) each time-window.

Cluster number	Temporal windows (ms)	p-value (fdr corrected)	Pvaf (%)
1	348-556	.0008*	26.02
2	32-212	.0047*	-6
	264-412	.0663	20.4
	464-536	.0076*	-3.3
6	264-476	.0007*	-23.9
7	144-268	.1012	26.6
	328-484	.2237	-44.5
9	-108-100	.0003*	34
	304-580	.0039*	33.4
10	368-568	.0000*	36.5
11	336-488	.0041*	28.4
12	176-288	.0237*	39.5
	320-556	.0367	47.1
13	32-148	.0932	34.3
	396-496	.1486	-29.2

*= statistically significant after FDR correction

Table 1: Results of FDR-corrected paired-sample t-tests computed contrasting Aware and Unaware conditions within each cluster in the reported time-windows.

4. Discussion

ERP correlates of conscious vision have identified two major correlates of visual awareness (VAN and LP). While scalp recorded ERPs display excellent time resolution, the sources of VAN and LP remain open. This is an important open question as theories of consciousness make different predictions about the location and the timing of consciousness-related activity in the brain (Seth & Bayne, 2022).

The present study aimed at characterizing the neural dynamics underlying conscious visual perception, by decomposing ERPs into independent components. This allowed us to identify and localize signal sources that significantly contribute to the electrophysiological correlates of conscious perception.

Overall, in keeping with previous electrophysiological literature, the scalp recorded grand average ERPs contrasting Aware and Unaware trials highlighted a significant difference in the N2 amplitude (i.e., VAN), followed by a significant difference in the P3 amplitude (i.e., LP). Results concerning the independent components clusters showed that activity of sources in many different cortical areas correlated with consciousness. In contrast to a serial, bottom-up driven process, the results suggest that the earliest differences between Aware and Unaware conditions were observed in parietal/frontal (cluster 9, between -108 and 100 ms) and temporal (cluster 2, between 32 and 212 ms) regions. Also, early activity in prefrontal cortex correlated with conscious perception (cluster 13, between 32 and 148ms), but this effect did not reach statistical significance. This early wave of activity was followed by correlates of conscious vision in occipito-temporal regions in a time-window corresponding to the typical VAN time-window (cluster 2 until 212 ms, cluster 7, between 144 and 268 ms, cluster 12, between 176 and 288). Finally, clusters spread over frontal, parietal, temporal and occipital areas displayed late differences in the P3 time-window.

Overall, these results are in accordance with previous source localization studies that identify the cortical generator of VAN in occipito-temporal brain regions (Liu et al., 2012; Vanni et al., 1997). Clusters 2, 7 and 12 revealed that the dipoles of components showing differences in the N2 amplitude when Aware and Unaware conditions were contrasted were localized in occipito-temporal areas, corroborating the idea that visual awareness correlates with activity in a posterior "hot zone" (Koch 2016, Boly e Tononi 2017, Koivosto 2018, Mazzi Savazzi 2019). According to a common interpretation, this activity may therefore reflect the formation of conscious visual perception (Koivisto et al., 2016; Koivisto & Grassini, 2016). While this early activity is often put forward as the correlate of "phenomenal" consciousness, Railo et al., 2015 have argued this time-window may also support some basic forms of "conscious access".

Dipoles of components reflecting differences in the P3 amplitude were spread over frontal, parietal and occipito-temporal cortex, supporting the idea that this component family has neural generators in wide-ranging cortical areas. According to a large body of literature, LP does not reflect neural processes purely related to subjective awareness of visual stimuli (Förster et al., 2020; Mazzi et al., 2020), but it is rather involved in later stages of processing such as processing task-relevant stimuli (Pitts et al., 2012, 2014; Shafto & Pitts, 2015), decision making (Koivisto & Grassini, 2016; Tagliabue et al., 2019), or processes related to reporting the contents of conscious perception (Koivisto et al., 2016). Whether these correlates reflect cognitive consequences of conscious perception, or higher forms of conscious processing is debatable (R. Rutiku et al., 2015). That is, it is possible that while VAN reflects the emergence of conscious visual perception, higher order cognitive processing of these visual contents is enabled by later stages (Dehaene & Changeux, 2011).

Early activity observed in fronto-parietal areas in clusters 9 and 13 are so early (<150 ms after stimulus onset) that they are outside the time-windows typically considered to directly enable conscious perception. These components may therefore reflect top-down mechanisms that are not strictly related to the conscious experience, but that occur before the stimulus enters the consciousness. Activity in fronto-parietal areas has been associated with visuospatial attention mechanisms (Corbetta et al., 2008; Parisi et al., 2020; Vossel et al., 2014). In particular, it has been proposed that attentional orienting towards specific locations is served by a bilateral fronto-parietal network, including the intraparietal sulcus (IPS), the superior parietal lobule (SPL) and the frontal eye fields (FEF) (Corbetta et al., 2000, 2008). Since in the present study participants were asked to report on which side of the screen the stimulus was presented, it is likely that they were covertly allocating their attention towards a location where the stimulus could appear. Thus, allocation of attention may have helped to facilitate the entry of the visual input in visual awareness, without directly enabling conscious vision. That said, one could also argue that these early effects reflect proper conscious vision. While VAN latency is typically around 200 ms after stimulus onset, studies also show that VAN sometimes onsets around 100 ms (Koivisto et al., 2005, 2009; Koivisto & Revonsuo, 2008). Although visual attention modulates responses in the same time-window as VAN, the awareness related effect seems to emerge independently of attention (Koivisto et al., 2005, 2006; Koivisto & Revonsuo, 2007). Also, in the present study the onset of scalp-recorded VAN was before 100 ms. Therefore, it remains possible that the earliest fronto-parietal clusters also contributed to early conscious perception. This possibility is intriguing because it could indicate that fronto-parietal areas provide key top-down modulation which enables consciously accessing simple visual features rapidly (see, Railo et al., 2015). Arguably, the large diameter visual stimuli, and simple location detection task employed in the present study were key to observing the early VAN as these visual features/tasks may be efficiently processed, enabling rapid conscious perception (Jimenez et al., 2021; Kouider & Dehaene, 2007).

Overall, the approach adopted in the present study helped elucidate the controversial search for the NCC. Decomposing the EEG signal into its maximally independent components helped unveil cortical sources underlying the ERP waveform. It emerged that, while LP seems to reflect a combination of multiple sources distributed among frontal, parietal and occipito-temporal cortex, VAN generators are localized in posterior areas including occipital and temporal cortex. Moreover, the results revealed early effects in fronto-parietal regions, which may play a role in the emergence of visual awareness, but their contribution needs to be thoroughly investigated. In conclusion, these results provided further significant information about the spatio-temporal aspects of neural dynamics involved in conscious vision, highlighting that IC clustering is a useful tool when investigating the neural correlates of conscious perception.

GENERAL CONCLUSIONS

In the controversial search for the NCCs, the present studies provided significant insights into the spatio-temporal unfolding of neural activity occurring when a visual stimulus enters the consciousness. Interestingly, for the first time, it has been possible to combine extremely accurate spatial information deriving from EROS with equally accurate temporal information deriving from ERPs analysis, making it possible to investigate which brain regions are involved when VAN occurs. Moreover, ICA approach permitted to isolate all the independent signal sources that underlie the ERP waveform, allowing to identify and localize the components that significantly contribute to the ERPs that correlate with visual awareness

Due to the employment of these cutting-edge approaches, it was possible to move beyond the existing literature, providing innovative insights into the search for the neural correlates of visual awareness.

Specifically, present results are particularly interesting regarding the localization of such neural correlates. Results of the EROS-EEG experiment revealed that Aware trials elicited an increased activity of the LOC, an extra-striate area involved in object recognition. Interestingly, this activity occurred in the same time-window of VAN, identified in the EEG experiment, suggesting that LOC could effectively serve as a correlate of visual awareness. These results are consistent with previous MEG source localization studies (Liu et al., 2012; Vanni et al., 1997) that identified LOC as the cortical generator of VAN. Moreover, similar results were found in the second experiment, which suggest that VAN generators are localized in posterior areas including occipital and temporal cortex.

Taken together, the present results suggest that visual awareness is served by posterior brain regions. In particular, the lateral occipital complex seems to play a key role in giving rise to conscious visual experiences. However, the present results cannot rule out a possible contribution of frontal areas. The limited number of optical fibers in our EROS equipment, in fact, were not sufficient to cover frontal cortex, not permitting to examining its involvement in conscious perception. Further investigation should thus try to overcome this limitation, by extending EROS recording to frontal areas, in order to explore their role in giving rise to conscious visual experiences.

Overall, the findings reported in the present work allow to broaden the current knowledge about the spatio-temporal dynamics involved in generating conscious percepts. In particular, the Granger causality results presented in the first study, provide innovative and extremely interesting insights about the neural networks involved when a visual stimulus enters the consciousness, highlighting the stream of activations triggered by conscious perception. On the other side, the clusters analysis proposed in the second study helps in elucidating the scalp distribution of the neural sources related to aware vision.

In conclusion, due to the above-mentioned theoretical implications, the present findings are of interest not only for research about visual awareness, but also for future research about consciousness in other sensory modalities. Several pieces of evidence, in fact, suggest that when contrasting conscious and unconscious auditory stimuli, they elicit the same negative difference in the N2 time window (Auditory Awareness Negativity, AAN) and the same later positive difference (LP) (Eklund & Wiens, 2019). Future studies may try to elucidate whether VAN and AAN share the same cortical substrate.

Moreover, deepening the knowledge about the neural correlates of visual awareness may contribute to develop new rehabilitation techniques for patients with brain damage resulting in a loss of conscious vision.

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