Cortical Sources of Visual Evoked Potentials During Consciousness of Executive Processes

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Abstract: What is the timing of cortical activation related to consciousness of visuo-spatial executive functions? Electroencephalographic data (128 channels) were recorded in 13 adults. Cue stimulus briefly appeared on right or left (equal probability) monitor side for a period, inducing about 50% of recognitions. It was then masked and followed (2 s) by a central visual go stimulus. Left (right) mouse button had to be clicked after right (left) cue stimulus. This "inverted" response indexed executive processes. Afterward, subjects said "seen" if they had detected the cue stimulus or "not seen" when it was missed. Sources of event-related potentials (ERPs) were estimated by LORETA software. The inverted responses were about 95% in seen trials and about 60% in not seen trials. Cue stimulus evoked frontal-parietooccipital potentials, having the same peak latencies in the seen and not seen data. Maximal difference in amplitude of the seen and not seen ERPs was detected at about +300-ms post-stimulus (P3). P3 sources were higher in amplitude in the seen than not seen trials in dorsolateral prefrontal, premotor and parietooccipital areas. This was true in dorsolateral prefrontal and premotor cortex even when percentage of the inverted responses and reaction time were paired in the seen and not seen trials. These results suggest that, in normal subjects, the primary consciousness enhances the efficacy of visuo-spatial executive processes and is sub-served by a late (100- to 400-ms post-stimulus) enhancement of the neural synchronization in frontal areas. *Hum Brain Mapp* 30:998–1013, 2009. © 2008 Wiley-Liss, Inc.

Key words: executive functions; subliminal stimuli; awareness; visual evoked potentials (VEPs); LORETA; human cortex

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INTRODUCTION

Primary consciousness is an early process by which a conscious perceptive image of a sensory stimulus emerges by cortical activity, as opposed to parallel not conscious, automatic processing of the same stimulus. As a simple operational definition, here "visual primary consciousness" was considered as the process underlying immediate subject's self-report about an adequate visual stimulation given to himself or herself. In line with Pinker's [1997]

theoretical view, that report implies subjective phenomenal experience (sentience) and the ability to report on the content of short-term phenomenal/mental experience (access to information). It does not imply attributes of “secondary” consciousness that link external stimulus with episodes of own life and ethical implication of that experience.

A variety of visual stimuli is perceived and processed without any reportable consciousness [Holender, 1986; Kihlstrom et al., 1992; Merikle, 1982; Purcell et al., 1983; Reingold and Merikle, 1988]. Neural correlates of the conscious and unconscious visual processes have been studied in patients with unilateral brain lesions, particularly at the right posterior parietal cortex [Driver and Vuilleumier, 2001; Driver et al., 1997; Vallar et al., 1988]. During bilateral stimulations, these patients typically miss contralateral stimuli at the left visual hemifield (visual extinction), probably due to a pathological bias in visuo-spatial attention [Cocchini et al., 1999; Desimone and Duncan, 1995; Driver et al., 1997; Posner et al., 1984; Vallar et al., 1988] and abnormal processes in parieto-occipital cortical areas [Driver et al., 2001; Lhermitte et al., 1985; Marzi et al., 2000, 2001; Spinelli et al., 1994; Vallar et al., 1991; Verleger et al., 1996; Vuilleumier et al., 2001].

Uncontrolled effects of the brain lesion in “extinction” patients have required a confirmation of the mentioned findings in normal subjects [Brandeis and Lehmann, 1986; Kostandov and Arzumanov, 1977; Naatanen and Gaillard, 1983; Shevrin and Fritzel, 1968; Shevrin, 1992; Wong et al., 1994]. In the so-called oddball paradigm, normal subjects had to respond (i.e., movement or counting) after rare but not frequent stimuli of a sequence. During electroencephalographic (EEG) experiments, rare stimuli evoked a well-shaped late positive ERP peaking at about 300-ms post-stimulus (P300; P = positivity, 300 = 300-ms post-stimulus), which is supposed to reflect cognitive closure of the recognition processing and memory updating [Hillyard and Picton, 1987; Hillyard et al., 1971; Iragui et al., 1993; Smith et al., 1970]. Compared to the unconscious (subliminal) perception of the rare stimuli, the conscious one evoked parietal P300 having higher amplitude [Brandeis and Lehmann, 1986; Brazdil et al., 1998, 2001, 2002; Kostandov and Arzumanov, 1977; Shefrin et al., 1988; Shevrin, 1976]. This result suggested that primary consciousness is concomitant with enhanced temporal synchronization of post-synaptic potentials at the dendrites of cortical pyramidal neurons, as roughly revealed by the main generators of event-related potentials (ERPs). However, it might be argued that the movement or counting demands only impinged upon P300 of the trials with conscious perception of the rare supraliminal stimuli. This issue has been overcome by a recent high-resolution EEG study [Babiloni et al., 2006a] in which no oddball paradigm was used to study visual consciousness. Subjects were required the same motor response in the trials characterized by both conscious and unconscious perceptions (i.e., physical features of the stimuli were equal in all trials). Results

showed negative-positive visual-evoked potentials accompanying consciously and unconsciously perceived stimuli. Specifically, we observed posterior N1, P2 and P3 components, which peaked about from 100- to 300-ms post-stimulus; they were reasonably related to extraction-integration of visual features and the closure of the cortical processing according to previous evidence on these potentials [Herrmann and Knight, 2001; Kugler et al., 1993]. In the mentioned study [Babiloni et al., 2006a], cortical sources of the visual-evoked potentials were located in occipital BA 19 and posterior parietal BA 7. Furthermore, the source strength of the P3 was significantly stronger in consciously than unconsciously perceived cases. Authors concluded that these features of the parieto-occipital activation might relate to primary visuo-spatial consciousness [Babiloni et al., 2006a]. More recently, it has been shown that the repetitive transcranial magnetic stimulation of right or left posterior parietal area significantly reduced the percentage of visual stimuli consciously perceived in the same experimental condition, thus confirming the crucial contribution of that area in the conscious perception of visuo-spatial stimuli [Babiloni et al., 2006b].

Aforementioned studies [Babiloni et al., 2006a,b] have revealed neural correlates of primary consciousness during a condition in which no mental operation was performed on the visual stimuli, except the recognition. Therefore, the results cannot be generalized to most of our experiences, which are characterized by the manipulation of sensory or mental representations within a working memory [Baddeley, 1992, 2003] as well as by (decisional) executive functions implying inhibition of impulsive responses and selection of the proper response [Baddeley, 1986; Botvinick et al., 1999; Carter et al., 1998; Collette et al., 2005; Luria, 1973a,b; MacDonald et al., 2000; McCarthy and Warrington, 1990; Milner, 1982; Pardo et al., 1990; Petrides et al., 1993; Raichle, 1998; Robbins, 1998; Roland, 1984, 1985; Shallice and Burgess, 1996; Stuss and Benson, 1986]. A typical experimental task probing these functions requires subjects to “invert” the side of the motor response with reference to the position of a visual stimulus, e.g., when left cue stimulus appears one must press right mouse button [Bialystok et al., 2005; Deecke et al., 1984; Kornhuber et al., 1995; Lang et al., 1986, 1988].

In general, the neural concomitants of executive processes include the interaction and integration of separable cerebral networks. Among them, prefronto-parietal networks would play a crucial role [Miyake et al., 2000], being involved in the top-down modulation of domain-specific sensory association areas towards task-relevant information processing [Gruber and Goschke, 2004]. Seminal studies using functional magnetic resonance imaging (fMRI) have shown that prefronto-parietal networks include dorsolateral prefrontal (Brodmann area 8-9, BA 8-9), lateral and medial premotor (BA 6L and BA 6M), and posterior parietal (BA 7, 40) areas [Cohen et al., 1997; D’Esposito et al., 1998, 2000; Pollmann and von Cramon, 2000; Postle and D’Esposito, 1999; Postle et al., 2000; Rowe

et al., 2000]. Interestingly, some nodes of these networks have been reported to be deeply implicated with primary consciousness [Christensen et al., 2006; de Lafuente and Romo, 2005; Ehrsson et al., 2005]. However, to date, the relationships among primary consciousness, working memory and prefronto-parietal networks are poorly known.

The aforementioned considerations and data raise at least two major issues: What is the role of visual consciousness during executive processes, and what is its neural substrate and timing? A possible starting point for the answers is the high-resolution EEG study quoted earlier [Babiloni et al., 2006a], which has shown that parietal-occipital sources of a late positive ERP component were higher in amplitude in the conscious than in the not conscious perception of a visuo-spatial cue stimulus with negligible executive processes. Given the well-known strict relationship between executive processes and fronto-parietal circuits, we hypothesize a frontalization of the ERP sources in the conscious compared to the not conscious perception associated with a mental manipulation of cue stimuli. To test this hypothesis, the present high-resolution EEG study investigated the relationship among primary consciousness, executive functions and sources of ERPs.

MATERIALS AND METHODS

Subjects

Experiments were performed on 13 healthy adult volunteers (eight males; mean age of 29.6 years ± 0.8 standard error, SE). They were right-handed, as revealed by Edinburgh Inventory ($69.3\% \pm 7.1$ SE) and had no previous psychiatric or neurological history. Their sight was normal or corrected-to-normal. All experiments were undertaken with the understanding and written consent of each participant, according to Code of Ethics of the World Medical Association [1997] and the standards established by the Author's Institutional Review Board. The study was approved by the local ethical committee.

Experimental Task

The subjects were seated in a comfortable reclining armchair, placed in a dimly lit, sound-damped and electrically shielded room. They kept their forearms resting on the armchairs, with the right index finger resting between two buttons of a mouse, connected to a computer monitor. The monitor of the computer was placed in front of them at a distance of about 100 cm.

For each subject, a preliminary procedure ascertained the individual threshold time (ms) of the cue stimulus. The cue stimulus was a white circle (diameter of about 0.5° of visual angle) appearing at 6° right or left side of the background central white cross (diameter of 0.5°). The cue stimulus was preceded and followed by a masking visual stimulus formed by two "Xs" (large about 0.8°), located at 6° right and left sides of the central white cross. The sub-

jects had to say "seen" any time they perceived the position of the cue stimulus. In detail, the procedure was as follows. The duration of the cue stimulus varied randomly trial-by-trial within the following values: 20, 40, 60, 80, 100, 120, 140 and 160 ms for 80 trials (10 for each duration value). The procedure was repeated seven times. The threshold time to be used during the EEG recordings was defined as the duration of the cue stimulus determining about 50% of correct stimulus detections within a series of 10 trials, in the majority of the seven repetitions of the procedure. Just before the EEG recording, this threshold time was systematically varied up and down (10 ms) for some preliminary trials, to verify the stability of that time based on subject's self-report. There was always a confirmation before the EEG recording of the threshold time of cue presentation, as indicated by the earlier preliminary procedure. Subject-by-subject, the mean threshold time of the cue stimulus was 113 ms (± 13.7 SE). It is worth noticing that the global correctness of the procedure for the determination of that threshold time was supported by a post hoc verification. Specifically, the recognition of the cue stimuli during the EEG recordings was of 48.7% (± 3.5 SE) on across subjects average.

Figure 1 illustrates a typical trial. The sequence of the visual stimuli was as follows: (i) background stimulus Xs lasting 5.5 s; (ii) cue stimulus "small circle" appearing on the right or left (50%) monitor side for the threshold time; (iii) masking stimulus Xs lasting about 2 s (i.e., 2 s minus the threshold time); (iv) go (target) stimulus lasting about 0.5 s. The go stimulus was a small green circle with a diameter of about 0.5° , which appeared in the center of the monitor. In the case in which the subject seen the cue stimulus, the subjects had to press the left mouse button if the cue stimulus appeared on the right monitor side, whereas they had to press the right mouse button if the cue stimulus appeared on the left monitor side. This was supposed to be sub-served by executive processes for the production of "inverted" responses. In the "not seen" trial, the subject was free to press the left or right mouse button. The computer receiving the mouse inputs registered the corresponding reaction time and the side of the button pressed. Immediately after the hand motor response, the subjects had to say seen if they had detected the cue stimulus (seen trial) or not seen if they had missed the cue stimulus (not seen trial). Noteworthy, subjects denied the use of mental verbal codes for the cue or go stimuli after the experiment. Verbal self-report was registered by a microphone connected to the mentioned computer as well as by the manual note of an experimenter. The experimenter controlled even that subjects watched the computer monitor during the task. Of note, the same presentation time and physical features (shape, position, luminance etc.) characterized the cue stimuli consciously perceived (seen trials) and those not consciously perceived (not seen trials). Therefore, these features cannot explain the reason why some cue stimuli were seen and others were consciously not seen.

Figure 1.

The sequence of events during a trial was: (i) cue stimulus appearing on the right or left monitor side for the threshold time giving about 50% of stimulus recognition; (ii) masking stimulus lasting about 2 s (i.e. 2 s minus the threshold time); (iii) go stimulus lasting about 0.5 s. The go stimulus was a green circle with a diameter of about 0.5°, which appeared at the center of the monitor. A masking stimulus lasting 5.5 s was delivered between go and subsequent cue stimulus. Subjects had to click the left mouse button if the cue stimulus appeared on the right monitor side, whereas they had to click the right mouse button if the cue stimulus appeared on the left monitor side (inverted response). The computer receiving mouse inputs registered the corresponding reaction time and the side of the mouse button clicked. After hand motor response, subjects had to say seen if they had detected the cue stimulus (seen trial) or not seen if they had missed the cue stimulus (not seen trial). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

EEG Recordings

During the experimental task, EEG data were recorded (Grass neurodata amplifiers and home-made data acquisition software; bandpass: 0.1–100 Hz, sampling rate: 256 Hz) from 128 electrodes placed according to an augmented

10–20 system. Linked ear lobes served as an electrical reference and electrode impedance was kept lower than 5 kOhm. A spatial digitalization of the electrodes was made for each subject by a magnetic digitizer (Polhemus fast-track), which allowed confirming the comparable position of homologous scalp electrodes across subjects (less than 1 cm of inter-subject error, on average). Vertical and horizontal electrooculographic activity was also recorded with the same features of the EEG data, to monitor eye movements and blinking. In parallel, involuntary and voluntary (following the go stimulus) hand motor responses were assessed by collecting electromyographic activity from extensor digitorum muscle of both arms. This allowed the control of involuntary and mirror hand movements for the selection of artifact-free EEG trials. Acquisition time for all data was set from –1 s to +5.5 s after the onset of the cue stimulation. On average, 160 trials for each subject were recorded.

Behavioral Data Analysis

Behavioral data analysis was mainly aimed at verifying the possibility that the verbal command (click the mouse button opposite to the position of the cue stimulus) induced executive processes and inversion of the motor response even when the perception of the cue stimulus was unconscious (seen trials). The working hypothesis was that this was the case.

ANOVA analysis for repeated measures served to evaluate that hypothesis. It was predicted that the percentage of inverted responses (i.e., opposite side of the cue stimulus and mouse button press) would be higher in the seen than in the not seen trials. Furthermore, it was predicted that the percentage of the inverted responses would be higher than that of the not inverted ones not only in the seen but also in the not seen trials, as an effect of unconscious executive processes. The ANOVA design included the factors condition (seen, not seen), side of visual stimuli (left, right), and response (inverted, not inverted). Mauchly's test evaluated the sphericity assumption. The correction of the degrees of freedom was made by Greenhouse–Geisser procedure. Duncan test was used for post hoc comparisons ($P < 0.05$).

Preliminary EEG Data Analysis

EEG single trials contaminated by blinking, eye movements and involuntary motor acts during the cue stimulation were rejected off-line. For the EEG data analysis, the artifact-free trials were classified in seen and not seen trials.

Artifact-free EEG data at the individual montages were then interpolated by a spline function [Babiloni et al., 1995], in order to obtain potentials at 105 electrode sites of an augmented 10–20 system. These electrodes were disposed over a 3D template head model digitized at the Brain Imaging Center of the Montreal Neurological Insti-

tute (<http://www.bic.mni.mcgill.ca/>). The head model was co-registered to Talairach atlas [Talairach and Tournoux, 1988]. This made the electrode position across subjects consistent for the subsequent data analyses. The potentials at these 105 electrodes were then averaged within the across the trials into two classes: the class of the seen trials and the class of the not seen trials to form the ERPs. Noteworthy, the same number of seen and not seen trials was selected in each subject, so that the ERPs for the two classes could be correctly compared in amplitude. The number of the trials for each subject and condition (seen and not seen) was 79 ($5 \pm \text{SE}$). That number in individual data sets included a same number of left and right-sided cue stimuli. The low amount of trials did not allow the separate ERP analysis of left and right-sided cue stimuli. Of note, one individual data set was rejected, since the visual evoked potentials could not be clearly recognized with respect to the background noise. Therefore, further data analyses were performed in the remaining 12 subjects. In these subjects, a standard pre-stimulus baseline (from $-1,000$ ms to cue stimulus onset) was used as a reference to measure the amplitude at the peak of the typical components of the visual ERPs following the cue stimuli, namely N1, P2 and P3 peaks [Babiloni et al., 2006a].

Cortical Sources Analysis of the ERPs

A popular technique called “low-resolution electromagnetic brain topography” (LORETA) was used for the source analysis of the ERPs [Pascual-Marqui et al., 1994, 1999, 2002; <http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm>]. LORETA computed 3D linear solutions (LORETA solutions) for the EEG inverse problem within a three-shell spherical head model including scalp, skull and brain compartments. The brain compartment was restricted to the cortical grey matter/hippocampus and was co-registered to the Talairach probability brain atlas, digitized at the Brain Imaging Center of the Montreal Neurological Institute [Talairach and Tournoux, 1988]. This compartment included 2,394 voxels (7 mm resolution), each voxel containing an equivalent current dipole. The activity of each BA of interest was computed averaging the radial component (z-component) of the current density of all voxels having the same polarity (positive or negative) of the ERP component analyzed, namely we considered all negative voxels for the analysis of N1, and all positive voxels for the analysis of P2 and P3.

Statistical Analysis

The ERP latency and amplitude (dependent variables) were analyzed by ANOVAs for repeated measures. Mauchly's test evaluated the sphericity assumption. Correction of the degrees of freedom was made by Greenhouse-Geisser procedure when appropriate. Duncan test was used for post hoc comparisons ($P < 0.05$).

The ANOVA analysis of the latency was performed for each ERP component (N1, P2, P3). The ANOVA design included the factors condition (seen, not seen; independent variable) and electrode site (AFz, Fz, FCz, Cz, CPz, Pz, POz, Oz, C3, C4; note that the restriction to a subset of midline and central electrodes was due to the relatively low number of subjects). The percentage of the inverted responses in the seen and not seen conditions was used as a covariate.

The same ANOVA design served for the evaluation of the ERP amplitude (N1, P2, P3). In line with a previous study [Babiloni et al., 2006a], the planned statistical testing evaluated the working hypothesis that ERP amplitude is higher in seen than in not seen trials, with no difference in latency.

The regional LORETA solutions (dependent variable) were analyzed by ANOVA for repeated measures as well. To minimize the repetition of the statistical test, the ANOVA analysis only tested LORETA solutions relative to the ERP components showing clear statistically verified amplitude differences between seen vs. not seen ERPs. For these components, the ANOVA design included the factors condition (seen and not seen), hemisphere (left, right), and lobe of interest (frontal, central, parietal and occipital). The percentage of inverted responses in the seen and not seen conditions were used as covariates, to support the explanation that ERP-source differences between the seen and not seen trials strictly depended on primary consciousness of executive processes rather than on executive processes per se. The planned statistical testing evaluated the working hypothesis of a specific ERP source pattern for the executive processes accompanying the conscious perception of the cue stimulus (seen trials) as contrasted with the ERP source pattern relative to the not consciously perceived cue stimulus (not seen trials). The confirmation of the working hypothesis would imply that frontal-parietal LORETA solutions are stronger in amplitude in the seen than in the not seen ERPs.

RESULTS

Behavioral Results

Reaction time to the target stimuli was 649 ms (± 114 SE) for the seen trials with inverted responses, 607 ms (± 76 SE) for the seen trials with not inverted responses, 753 ms (± 111 SE) for the not seen trials with inverted responses and 781 ms (± 122 SE) for the not seen trials with not inverted responses. The ANOVA analysis of the reaction time showed a main effect of the factor condition (seen, not seen), indicating that the reaction time was faster ($F(1,11) = 6.1334$, $P < 0.05$) in the seen than in the not seen trials, regardless of the kind of responses (inverted, not inverted). Conscious perception of the cue stimuli was associated with enhanced sensorimotor information processing in the present experimental conditions.

The inverted responses (i.e., left cue stimulus, right mouse button) were 93.5% (± 2.3 SE) in the seen trials and 59.6% (± 2.7 SE) in the not seen trials. The ANOVA analysis of the percentage of inverted responses resulted in a statistically significant ($F(1,11) = 125.36$; $P < 0.00001$) interaction between the factors such as Condition (not seen, seen) and response (inverted, not inverted). Planned post hoc comparisons showed that the percentage of the inverted responses was higher in the seen than in the not seen trials ($P < 0.0001$). Furthermore, the percentage of the inverted responses was higher than that of the not inverted responses not only in the seen ($P < 0.000065$) but also in the not seen ($P < 0.001$) trials. Effective executive processes as probed by inverted responses characterized not only the consciously perceived cue stimuli but also the consciously not perceived cue stimuli.

Spatio-Temporal Evolution of the ERPs

Figure 2 plots grand average ($N = 12$) waveforms of the scalp not seen and seen ERPs, recorded at representative midline and central electrodes (AFz, Fz, FCz, Cz, CPz, Pz, POz, Oz, C3, C4). Noteworthy, the peak latencies were practically identical in the not seen and in the seen ERPs. On average, these peak latencies were measured at +167 ms (± 3 SE), +292 ms (± 8 SE) and +423 ms (± 20 SE) post-stimulus. The corresponding ERP peaks were named N1, P2 and P3, respectively. The difference in amplitude between the seen and the not seen ERPs started from about 100- to 200-ms post-stimulus and reached maximum values at the P3 peak (which should not be confused to classical P300 waveform relative to oddball paradigms).

The results of the ANOVA analysis showed no statistically significant difference in the latency of the N1, P2 and P3 components between the seen and the not seen ERPs. The ANOVA analysis of the ERP amplitude (N1, P2, P3) included the factors region of interest (frontal, central, parietal and occipital) and hemisphere (left, right). The dependent variable was the mean ERP amplitude across all the electrodes within the region of interest. It was observed a statistical main effect condition for the P3 component ($F(1,11) = 11.02$; $P < 0.006$), showing that this component was generally higher in amplitude in the seen than in the not seen ERPs over the whole scalp. To reduce the number of multiple-comparisons, LORETA source analysis was focused only on this component.

P3 Sources Computed by LORETA

Figure 3 maps the grand average ($N = 12$) of LORETA solutions (i.e., current density at cortical voxels), modeling the distributed ERP sources of not seen and seen at the P3 peak. Main P3 sources were estimated in frontal (BA 8), central (BA 6), parietal (BA 7) and occipital (BA 19) regions. These sources appeared to be greater in magnitude in the seen than in the not seen P3.

Figure 2.

Grand average ($N = 12$) waveforms of event-related potentials (ERPs) recorded at representative midline electrodes (AFz, Fz, FCz, Cz, CPz, Pz, POz, Oz, C3 and C4 sites of 10–20 system). These potentials were obtained averaging separately not seen, and seen trials. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The ANOVA analysis of the P3-LORETA solutions showed a statistically significant ($F(1,11) = 14.05$; $P < 0.0032$) main effect for the factor Condition (not seen, seen), indicating that the magnitude of the LORETA solutions was globally greater in the seen than in the not seen P3 with no statistically significant hemispherical lateralization. Furthermore, there was a statistically significant interaction between the factors Condition and Lobe of interest ($F(3,33) = 2.74$; $P < 0.05$). Figure 4 (top) plots grand mean ($N = 12$) of the LORETA P3 solutions at the cortical regions of interest and the results of the mentioned interaction. The LORETA solutions were stronger in amplitude in the seen than in the not seen P3 at dorsolateral prefrontal (BA 8; $P < 0.000033$), lateral premotor (BA 6; $P < 0.000037$), posterior parietal (BA 7; $P < 0.000295$) and extrastriate occipital (BA 19; $P < 0.035348$) regions of interest. Of note, these differences were especially evident at the dorsolateral prefrontal and lateral pre-motor regions of interest.

P3-LORETA CURRENT DENSITY

Figure 3.

Grand average of LORETA solutions (i.e., current density at cortical voxels) modeling the distributed sources for P3 component of the ERPs. These solutions refer to the ERPs formed by seen and not seen trials ($N = 12$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Control Analyses

To clarify whether subjects chose the response to not seen cue stimuli upon internal criteria (i.e., preference for the response to the right or left mouse button; number of preceding responses on each side), we compared the num-

ber of right and left mouse responses in the seen vs. not seen trials in all subjects. The ANOVA analysis included the factors condition (seen, not seen) and side of mouse button (left, right). The results showed no statistically significant effect including the factor condition ($P > 0.6$), in line with the control hypothesis that the variable in question did not affect the results. In all subjects, we also compared the number of sequences of two, three and four consecutive responses at the same mouse button in the

Figure 4.

Top: Grand means ($\pm$ SE) ($N = 12$) of LORETA P3 solutions for the factors condition (not seen and seen), hemisphere (right and left), and lobe of interest (prefrontal BA 8, premotor BA 6, posterior parietal BA 7, occipital BA 19). Bottom: grand means ($\pm$ SE) of not seen and seen LORETA solutions, which represented significant interaction between the factors condition and lobe of interest. P3 source strength was used as dependent variable. The ANOVA analysis included factors such as condition, hemisphere, and lobe of interest. Duncan post hoc testing indicated that LORETA solutions were stronger in amplitude in seen than not seen P3 sources ($P < 0.001$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

seen vs. an in the not seen trials. The ANOVA analysis included the factors condition (seen, not seen) and consecutive mouse response (two, three, four). The results showed no statistically significant effect including the factor condition ($P > 0.6$), in line with the control hypothesis that the variable in question did not affect the results.

To evaluate the meaning of different reaction time in the seen and in the not seen trials, we performed a control behavioral experiment in a sub-group of 13 subjects. In this experiment, there were two conditions. In the first condition, the task was the same of the main experiment (the inversion motor task). In the second condition, the task required no inverted motor response to the subjects (no inverted motor task). Specifically, the visual cue stimulus (same features of the inverted task) was followed by a go stimulus (small green circle) that appeared on the right or left (50% of probability) side of the central white cross. The subjects had to press the left (right) mouse button if the go stimulus appeared on the left (right) monitor side. Therefore, the motor response was strictly related to the side of the target; furthermore, it had to be executed at the same side of the target stimulus. We performed an ANOVA analysis of the difference between the reaction time of the seen and not seen trials, separately for the two conditions (inverted and no inverted motor tasks). It was observed that the difference in reaction time between the seen and the not seen trials in the inverted condition ($71 \text{ ms} \pm 17 \text{ SE}$) was similar ($P < 0.74$) to the difference in reaction time between the seen and the not seen trials in the non-inverted condition ($63 \text{ ms} \pm 10 \text{ SE}$). These results suggest that it is unlikely that the difference in reaction time of the seen and not seen trials depended on different internal criteria related to the inversion task. Rather, it may depend on less efficient processes related to the processing of stimuli not consciously perceived in the framework of executive processes.

To evaluate whether subjects based decisions relative to not seen stimuli on a guess, we performed another control behavioral experiment in the earlier sub-group of 13 subjects. In this new experiment, 33.3% of the trials presented no cue stimuli at all (no cue), while the remaining trials were presented at the left (33%) or right (33%) side of the monitor. Results showed that the mean percentage of seen self-reports for the no-cue trials (false positive responses) was of 2.38% ($\pm 0.88 \text{ SE}$). These results were in line with the control hypothesis that subjects' self-report was substantially reliable in the present experimental conditions.

The percentage of inverted responses was higher in the seen than in the not seen ERPs, so that the percentages of the inverted responses were used as covariates in the aforementioned ANOVA analysis. To better account for this possible confound, a control analysis was performed. For each individual subject, the same percentage of trials with inverted responses (on average, about 89%) was averaged to form both seen and not seen ERPs. Furthermore, the EEG trials were selected to have practically equal mean reaction time in the seen (556 ms $\pm$ 83.5) and not seen (584 ms $\pm$ 86.9) trials. The P3 amplitude still prevailed in the seen than

Figure 5.

For each individual subject ($N = 12$), the same percentage of trials with inverted responses was averaged to form both seen and not seen ERPs. Furthermore, the EEG trials were selected to have practically equal mean reaction time in the seen and not seen trials. Grand average waveforms of event-related potentials (ERPs) recorded at representative midline electrodes (AFz, Fz, FCz, Cz, CPz, Pz, POz and Oz sites of 10–20 system). These potentials were obtained averaging separately not seen, and seen trials. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

in the not seen ERPs (see Fig. 5). Therefore, the percentage of the inverted responses and the reaction time to go stimuli did not affect the difference in magnitude of the P3 in the seen and in the not seen ERPs.

Furthermore, an ANOVA analysis of P3-LORETA solutions was performed on the data related to the control analysis in which each subject had the same percentage (on average, about 89%) of trials with inverted responses and equal mean reaction time in the seen and not seen trials (see Fig. 6). The ANOVA analysis of these P3-LORETA solutions again showed a statistically significant interaction between the factors condition and lobe of interest ($F(3,33) = 3.04$; $P < 0.04$). Figure 7 plots the results of this interaction. The LORETA solutions were stronger in amplitude in the seen than in the not seen P3 at dorsolateral prefrontal

Figure 6.

Grand means ($\pm$ SE) of not seen and seen LORETA solutions, which represented the significant interaction between the factors condition and lobe of interest. P3 source strength was used as dependent variable. The ANOVA analysis included factors such as condition, hemisphere, and lobe of interest. Duncan post hoc testing indicated that LORETA solutions were stronger in amplitude in seen than not seen P3 sources in dorsolateral prefrontal (BA 8; $P < 0.007$) and lateral premotor (BA 6; $P < 0.008$) regions of interest. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

(BA 8; $P < 0.007$) and lateral premotor (BA 6; $P < 0.008$) regions of interest, in line with the results of the main LORETA analysis.

In order to evaluate whether the frontalization of the above LORETA solutions for the consciousness perception was confounded by the percentage of inverted responses, we performed a further control experiment in a sub-group of five subjects. In this experiment, there were three conditions. In the first condition, the task was the same of the main experiment (cue-based inverted). In the second condition, the task required not inverted motor response to the subjects as described in the above behavioral control experiment (no inverted motor task). Finally, the third condition was similar to the second condition with the difference that the subjects were asked to invert the response to the target stimulus (target-based inverted). Specifically, they had to press the right (left) mouse button after the left (right) monitor side target stimulus. According to the main experiment results, the percentage of the seen trials was 48%, 44% and 45% for the “cue-based inverted”, “no inverted” and “target-based inverted” task, respectively. In the cue-based inverted task, the percentage of the inverted responses was 93% in the seen trials and 73% in the not seen trials. As expected, the percentage of the inverted responses for both seen and not seen trials was 100% in the target-based inverted task (note that the subjects always consciously perceived the target stimulus, so that he/she had no difficulty to invert the motor response). Figure 7 shows the seen and not seen P3-LORETA solutions for the BAs of interest, in

Figure 7.

Grand means ($\pm$ SE) ($N = 5$) of LORETA P3 solutions for the factors condition (not seen and seen), task (cue-based, target-based and not inverted task), and lobe of interest (prefrontal BA 8, premotor BA 6, posterior parietal BA 7, occipital BA 19). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

this control experiment. It is noted that the amplitude of P3-sources is globally higher in the seen than in the not seen ERPs. Furthermore, the frontal and central P3-LORETA solutions seem to be higher in amplitude in the seen ERPs including inverted responses (cue-based and target-based inverted motor tasks) compared to that with no inverted responses. These results further corroborated those of the main data analysis.

As a further control, we repeated the source data analysis with the traditional LORETA approach. The P3 activity of each BA of interest was indexed averaging the square root of the sum of squares of the x , y and z components of the LORETA current density for all voxels. The ANOVA analysis of these P3-LORETA solutions confirmed ($F(3,33) = 2.92$; $P < 0.0484$) the results previously obtained only considering the radial component (z -component) of the dipole current density.

DISCUSSION

Primary Consciousness During Visual Executive Processes

To probe visual executive processes, we asked the subjects to invert the side of the motor response to go stimulus with reference to the side of the cue stimulus (i.e., left cue stimulus/right mouse button etc.). The percentage of the inverted responses indexed these processes. This kind of executive task has been repeatedly used in previous neurophysiological studies focused on the control of impulsive motor actions and on the maintenance of the proper operative set [Bialystok et al., 2005; Deecke et al., 1984; Kornhuber et al., 1995; Lang et al., 1986, 1988], as important aspects of the executive functions [Collette et al., 2006]. The behavioral results of the present study showed a preponderance of the inverted response in the seen over not seen trials. Furthermore, there was a preponderance of the inverted over not inverted response also in the not seen trials. The enhancement of the inverted motor responses in the not seen trials was interpreted as due to an unconscious processing of the visual cue stimuli and to an automatic implementation of the executive set (inversion). As such, the present results are in line with previous evidence on the unconscious elaboration of not seen stimuli [Babiloni et al., 2006a,b; Ivanoff and Klein, 2003; McCormick, 1997].

It has been repeatedly demonstrated that the intensity of cortical neuronal responses varies from one trial to the next, even when a sequence of physically identical stimuli is presented [Dean, 1981; Geisler and Albrecht, 1997; Shadlen and Newsome, 1998; Softky, 1993]. According to a simple model of the decision process [Ress and Heeger, 2003], a previous study has shown that the cortical neuronal activity, as revealed by (LORETA) ERP sources, was higher in magnitude when the observers responded seen rather than not seen to threshold visuo-spatial stimuli [Babiloni et al., 2006a]. In the present study, we tested the hypothesis that peculiar (LORETA) frontal-parietal ERP sources

characterize the primary consciousness during visuo-spatial executive processes. The results showed that the visual cue stimulation evoked three major ERP components such as N1, P2 and P3, which had the same peak latencies in both not seen and seen trials. Extending previous suggestions [Babiloni et al., 2006a; Shevrin, 2001], these results hint that conscious and unconscious visuo-spatial executive processes are associated with a similar temporal evolution of the cortical neural correlates, as revealed by the ERP waveforms (i.e. the sequence of the negative-positive peaks). Compared to the primary unconscious processes, the conscious ones would not be characterized by longer information processing, at least in the period examined. In contrast, there was a marked difference in amplitude between the ERPs accompanying seen and not seen trials. These differences started from about 100- to 200-ms post-stimulus, and reached the maximum amplitude and statistical significance at the P3 peak (about 400-ms post-stimulus). The (LORETA) source analysis of the P3 peak showed a maximum regional activity in dorsolateral prefrontal, lateral premotor, posterior parietal and extrastriate occipital areas. That activity was greater in amplitude in the seen than in the not seen trials; the maximum difference of the P3 peak sources was detected in dorsolateral prefrontal and in lateral premotor areas. This was true in dorsolateral prefrontal and premotor cortex even when percentage of the inverted responses and reaction time were paired in the seen and not seen trials.

The earlier results suggest that the primary consciousness during visuo-spatial executive processes is associated with ERP cortical sources having peculiar spatial (frontal-parietooccipital) and time [peak at about +400-ms post-stimulus) features, when compared to the ERP cortical sources related to mere primary visuo-spatial consciousness (parieto-occipital ERP sources peaking at about +300-ms post-stimulus; Babiloni et al., 2006a). In the same vein, the present results extend those of several field studies. First, fMRI has shown that a stimulus interference paradigm induced the failure of primary visual consciousness together with a depression of the activation in anterior cingulate, medial prefrontal and frontopolar regions [Feinstein et al., 2004], while a visual-somatosensory perceptual illusion was strictly related to the activation of premotor cortex [Ehrsson et al., 2004, 2005]. Second, EEG studies have reported that frontal-parietal P300 was higher in amplitude after subliminal rare than frequent stimuli of oddball paradigms; it was also higher after seen (conscious perception) than not seen (subliminal perception) rare stimuli [Brazdil et al., 1998, 2001, 2002; Shevrin, 2001]. Third, frontal ERPs and regional cerebral blood flow increased in magnitude in executive tasks requiring inverted motor responses [Lang et al., 1988]. Fourth, there was an amplitude increase of the P3 (300- to 400-ms post-stimulus) during visually cued continuous performance tasks probing perseverance/inhibition conflict with respect to control conditions [Kirmizi-Alsan et al., 2006]. Fifth, a posterior P3 (350- to 600-ms post-stimulus) was elicited by

visual feedback cues that confirmed subject's set for a motor response, whereas a frontally distributed P3 potential (300- to 400-ms post-stimulus; Barcelo, 2003) was induced by visual feedback cues directing a shift in that set. Sixth, P3 amplitude was related to attentional processes during a pursuit-tracking task in which the subjects had to track a target cross with a mouse-controlled cursor [Hill and Raab, 2005]. The results of the present study suggest that late frontal sources of ERPs are related to conscious experience of visual stimuli during executive processes. As such, they complement previous findings showing that late parieto-occipital sources of ERPs were associated with mere conscious experience of visuo-spatial stimuli [Babiloni et al., 2006a]. Taken together, these results collectively corroborate the theory of "micro-consciousnesses," posing that different attributes of primary consciousness are associated with the activity of specialized cortical areas [Zeki, 2003, 2004, 2005]. It can be speculated that here late frontal sources of ERPs reflect the enhanced synchronization of neural populations implied in the mental manipulation of visual stimuli for proper motor responses. Enhancement of neural synchronization may increase the chance that underlying information processing emerges in the competition with parallel brain processes.

Of note, the experimental design of the present study did not allow disentangling the respective role of the late frontal neural synchronization in the emergence of primary consciousness and executive processes. To this aim, a proper experimental design should assure that processes of executive control were systematically manipulated during both conscious and not conscious perceptions. This was not the case of the current research. In the present experimental conditions, percentage of inverted response and reaction time differed in the consciously perceived (seen) and not consciously perceived (not seen) stimuli, namely there were higher percentage of inverted motor responses and shorter reaction time during the seen than not seen stimuli. However, a provisional confirmation of the present results came from control data analyses. It was shown that prefrontal and premotor (LORETA) sources generated a P3 higher in amplitude in seen than not seen trials, regardless the difference in reaction time and percentage of the inverted motor responses between the consciously and not consciously perceived stimuli. This agrees with the fact that P3 was recorded immediately after the cue stimuli, whereas the motor responses were performed after the target stimuli (i.e. about 2 s later).

A striking result of the present study was that the early visual evoked potentials (up to 100- 200-ms post-stimulus) presented similar spatial-temporal features in seen and not seen trials. This result supported the idea that the main neural correlates of conscious perception emerge at later stages and higher levels of sensory processing, in line with several field studies summarized in the following [Crick and Koch, 1995, 2003; Crick et al., 2004; Fang and He, 2005; Koch, 1998, 2004; Libet, 1999, 2003; Sergent et al., 2005]. First, it has been shown that not consciously per-

ceived somatosensory stimulations induced early (20- to 50-ms post-stimulus) evoked potentials in primary somatosensory cortex [Ray et al., 1999], and that threshold somatosensory stimulations elicited high-frequency EEG oscillations with similar features for consciously and unconsciously perceived stimuli, in primary somatosensory cortex along 150-ms post-stimulus [Meador et al., 2002]. Second, the detection without recognition of threshold auditory stimuli was associated with the modulation of early N1 component (peak around 100-ms post-stimulus), whereas stimulus recognition other than detection was concomitant with the modulation of the P3 [Parasuraman and Beatty, 1980]. Third, visuo-spatial stimulation induced a prominent occipital and/or parietal activation not only in normal subjects [Brandeis and Lehmann, 1986; Brazdil et al., 1998, 2001, 2002; Kostandov and Arzumanov, 1977; Ress and Heeger, 2003; Sergent et al., 2005; Shefrin et al., 1988; Shevrin, 1976] but also in patients suffering from deficits of visual primary consciousness, namely subjects with "visual extinction" [Driver, 1996; Driver and Mattingley, 1998; Driver et al., 1997, 2001; Heilman et al., 1997; Lhermitte et al., 1985; Marzi et al., 2000; Robertson et al., 1997; Spinelli et al., 1994; Vallar et al., 1991; Verleger et al., 1996; Vuilleumier et al., 2001]. Fourth, late single-neuron activity (after about 100-ms post-stimulus) was selectively suppressed in monkey's primary visual cortex when the stimuli were not consciously perceived [Super et al., 2001]. Furthermore, the neuronal firing in premotor but not primary somatosensory cortex was related to monkey's conscious perception of threshold somatosensory stimuli [de Lafuente and Romo, 2005].

The earlier interpretation of the present results should be considered with extreme caution. Primary consciousness is not an instantaneous mental experience to be related to the instantaneous peak of a local neural concomitant (e.g., the P3 of visual evoked potentials). Rather, it reasonably emerges from relatively long integrative neural processes (i.e. hundreds of milliseconds), implying reciprocal information flux and temporal synchronization among different brain regions [Tononi, 2001, 2004]. The understanding of these neural processes implies the use of various methodological approaches, probing the time (duration), frequency (brain rhythms) and spatial (topography of the network) domains of such a complex phenomenon. Instead, our analysis was limited to just one neural concomitant of the phenomenon (ERP sources). Therefore, the present results cannot confute the hypothesis that the primary consciousness during executive processes is associated with subtle very early (i.e., before 100-ms post-stimulus) neural processes in primary sensory cortex. Indeed, such a hypothesis is corroborated by recent fMRI evidence documenting that the responses of primary visual cortex were stronger in seen than not seen trials [Ress and Heeger, 2003]. In addition, magnetoencephalographic recordings have shown that the primary somatosensory consciousness was associated with phase-locked oscillations at extended alpha range (8–14 Hz) in somatosensory, frontal

and parietal regions before 100-ms post-stimulus [Palva et al., 2005a].

Alternative Explanations and Results of the Control Analyses

The results of the present study cannot be accounted by the relative percentage of inverted responses in seen and not seen trials. The same is true for the reaction time to go stimuli as a rough reflection of the general attention during the events. In fact, the same results were still found when the percentage of inverted responses and the mean reaction time were paired in seen and not seen ERPs. Of note, the frontalization of the P3 sources during the seen trials was observed even in a control condition (target-based inverted motor task) in which the inversion of the motor task was 100% in both seen and not seen trials. Therefore, it is unlikely that the frontalization of the P3-sources during the seen trials merely depended on the percentage of the inverted responses.

The present results cannot be accounted by a different motor planning in the two conditions. The transient ERPs of interest were evoked by the cue stimuli and preceded the target stimuli of about 1.5 s, while the motor commands were executed after the target stimuli.

The results of this experiment were unlikely provoked by some peculiar internal decisional criteria during not seen trials such as key preference or balancing the number of responses on each side. Indeed, the results of a control analysis showed no differences between seen and not seen trials in the side of the motor responses and in the sequence of consecutive responses at each side.

One may argue that the present results might be affected by an unreliable subjects' self-report. We do not know exactly if all not seen stimuli were really missed and if all seen trials were really perceived. Part of the not seen and seen reports could be affected by subject's perceptive or response uncertainty. This problem has been extensively discussed in the implicit perception literature [for recent reviews see Hannula et al., 2005; Pessoa, 2005]. In the case of forced binary choice, subjects' report (i.e. seen vs. not seen) may be influenced by subjective response criteria about confidence on the perception or response. For example, if subjects consciously perceived just some part of the not seen cue stimuli, these trials were mixed with truly unconsciously perceived trials. As a consequence, the same cortical regions could be activated [with lesser degree which would result in the lower amplitude of ERPs Hillyard et al., 1971]. In line with this possibility, evidence derived from signal detection theory (e.g. confidence ratings) has shown that visual consciousness should be considered as formed by two partially overlapped curves of probability, centered at the following subjective experiences: "surely perceived" and "surely not perceived". A certain rate of false seen and false not seen would be represented in the halfway of these experiences. The subject's response confidence is an important issue, since it has

been reported that P3 amplitude is smaller with trials in which the stimulus is perceived less confidently [Hillyard et al., 1971]. To quantify the global confidence of the subjects' report, we performed a control behavioral experiment in a sub-group of 10 subjects. The results showed that for the no-cue trials, the mean percentage of seen self-reports was very low (less than 3%), confirming that the subjects' self-report was substantially reliable in the present experimental conditions. Anyway, at the present stage of research, one should be very cautious in the interpretation of "not seen" trials as the "unconscious" ones.

An important methodological remark is the different complexity of the cerebral processes in the seen and not seen trials. Execution of a response is typically more difficult in the case of self-generated (not seen trials) than cue-related behavior (seen trials). This was confirmed by the present results showing that the reaction time was longer for the not seen than seen trials. When compared to the standard approaches of signal detection theory, the present approach has the disadvantage that rate of subjects' response confidence could not be quantified, and that the differences of the P3 amplitude between not seen and seen trials might not entirely be ascribed to primary consciousness and executive functions in the main experiment. However, the present approach has several advantages that can contribute to the field understanding, together with other complementary approaches. First, ERPs following seen and not seen cue stimuli were not affected by self-reflexive cognitive processes related to the subjective evaluation of the degree of own perceptive or response uncertainty. Second, the same stimulus was given in all trials, so that neural synchronization to the physical properties of the stimulus was equal in association with both seen and not seen trials. Third, the similar frequency of seen and not seen experience paired the attentional effects of "novelty" in the two classes of trials.

CONCLUSIONS

Human executive processes are mainly sub-served by frontal-parietal cortices. Does visual consciousness exert a role in these processes? What is the timing of its neural substrate within fronto-parietal systems? In the present study, the percentage of inverted motor responses (i.e. left cue stimulus, press of the right mouse button) indexed simple executive processes at the basis of a visuo-spatial task. The inverted responses were about 95% in the seen trials and about 60% in the not seen trials. Cue stimulation evoked frontal-parietooccipital potentials having the same peak latencies in the seen and in the not seen trials. Maximal difference in the amplitude of the seen and not seen ERPs was detected at about +400-ms post-stimulus (P3 peak). The P3 peak (LORETA) sources were higher in amplitude in the seen than in the not seen trials in dorsolateral prefrontal, premotor, and parietooccipital areas. This was true in dorsolateral prefrontal and premotor cortex

even when percentage of the inverted responses and reaction time were paired in the seen and not seen trials. These results suggest that in normal subjects, the primary consciousness enhances the efficacy of visuo-spatial executive processes and is sub-served by a late enhancement of the neural synchronization in frontal cortex. The primary visual consciousness of the executive processes would mainly emerge by a relatively late information process (100- to 400-ms post-stimulus) within frontal cortical areas responsible for different functions such as motor planning and executive manipulation of information.

A conclusive interpretation of the present results in terms of neural synchronization of pyramidal cortical cells should be supported by future investigations evaluating the phase locking and coherence of brain oscillations, especially at alpha, beta and gamma rhythms [Babiloni et al., 2005; Palva et al., 2005b]. Furthermore, future investigations should study the thalamocortical and cortico-cortical interactions related to the primary visual consciousness as opposed to executive processes [Lamme et al., 2002; Tononi, 2001, 2004]. For this purpose, a promising approach might be the use of intracerebral stereo EEG in epilepsy patients during the pre-surgical monitoring of cerebral functions [Babiloni et al., 2004; Kuba et al., 2003; Rektor et al., 2002, 2003] and paradigms in which the primary visual consciousness can be manipulated by stimulus features [Babiloni et al., 2006b; Brazdil et al., 2001; Moradi et al., 2005]. Finally, repetitive transcranial magnetic stimulation might test the hypothesis of a causal role of dorso-lateral prefrontal, premotor and parietooccipital areas in the primary consciousness during visuo-spatial executive processes [Babiloni et al., 2006b].

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