Neural dynamics of neglected targets in patients with right hemisphere damage

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1. Introduction

Damage to fronto-parietal networks in the right hemisphere (He et al., 2007; Thiebaut de Schotten et al., 2005) often impairs the perceptual processing of left-sided objects, and generates deficits which can range from mild asymmetries in response times to florid neglect for left-sided events, whereby patients behave as if the left part of the world did not exist anymore.
Importantly, visual unawareness in neglect patients is variable and fluctuates over time. As a consequence, at chronic post-injury stages, patients may vary from time to time gain awareness of visual stimuli, but they may miss the very same stimuli on other trials (Small and Ellis, 1994; Wade et al., 1988). In a similar way, healthy individuals often fail to see near-threshold stimuli which they readily detect at other times (Chica et al., 2011; Dehaene et al., 2006). Since stimulus salience remains constant, such performance fluctuations might correlate with the functional state of specific brain regions prior to stimulus onset (Fox and Raichle, 2007). Indeed, specific patterns of activated and deactivated brain regions before stimulus occurrence can determine the processing of subsequent stimuli. For instance, pre-stimulus fluctuations of oscillatory activity preceding target presentation, in order to obtain a sufficient number of trials corresponding to possible target presentation time (16 msec). Omissions ranged from 2 to 4 per side and per subject. We thereby decided to use the patients’ data as an internal control, by comparing detected and omitted targets.

2.2. Stimuli and procedure

A go/no-go task was used during MEG recordings. Patients were requested to produce speeded manual responses to target appearance and to refrain from responding to target-absent displays. Targets were asterisks .6 in diameter, displayed 3.8° to the left or to the right from a central fixation cross, presented inside one of the two lateral boxes with 1.3° long sides. Target duration was titrated in a pre-test session so that patients made a substantial number of omissions for left targets. For all patients target duration was set at 100 msec, except for patient 2, who required a 32-msec presentation time in order to show omissions for left-sided targets. Participants sat in the MEG recording room, about 90 cm away from a projection screen. They were required to maintain fixation throughout the trial and to respond to the target presence (go condition) as soon as possible, by pressing a response button with their right thumb, independently of the side of target presentation. When the two boxes appeared empty, participants had to refrain from responding (no-go condition). The response time window was fixed at 1500 msec and the intertrial interval varied randomly from 500 msec to 900 msec. In order to obtain a sufficient number of trials corresponding to left omissions to average out, without having to excessively increase the number of trials, we presented a higher number

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/age</th>
<th>Months since onset</th>
<th>Etiology</th>
<th>Locus of lesion</th>
<th>Bell cancellation (L/R hits, ( \text{max} = 15/15 ))</th>
<th>Letter cancellation (L/R hits, ( \text{max} = 30/30 ))</th>
<th>20-cm line bisection ( % ) deviation</th>
<th>Left visual extinction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/59</td>
<td>17</td>
<td>Ischemic</td>
<td>F, T, A, Pt, Pl, C, Th, I, P</td>
<td>13/13</td>
<td>22/29*</td>
<td>−3.0</td>
<td>−</td>
</tr>
<tr>
<td>2</td>
<td>F/52</td>
<td>30</td>
<td>Ischemic</td>
<td>F, T, I, Pt, P</td>
<td>13/15</td>
<td>27/29</td>
<td>−3.5</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>M/54</td>
<td>41</td>
<td>Ischemic</td>
<td>T, A, Pt, C, I, P</td>
<td>11/15*</td>
<td>28/30</td>
<td>+1</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>M/65</td>
<td>10</td>
<td>Hemorrhagic</td>
<td>I, Pt, Pl, C, Th</td>
<td>8/15*</td>
<td>28/30</td>
<td>+4.0</td>
<td>−</td>
</tr>
</tbody>
</table>

M: Male; F: Female. Locus of lesion: P, parietal; T, temporal; F, frontal; A, Amygdala; Pt, Putamen; C, Caudate; Pl, Pallidum; I, Insula; Th, Thalamus. Asterisks indicate pathological scores. Visual extinction test: presence (+) or absence (−) of visual extinction for left targets on double simultaneous visual stimulation. For line bisection, positive values indicate rightward deviations, negative values indicate leftward deviations of the subjective midpoint.
of left-sided than right-sided targets. Thus, each block consisted of 36 left-sided target, 27 right-sided target, and 21 no-target trials. Responses were classified as right hits, left hits (correct detection of targets presented in the right or in the left hemifield, respectively), left misses (omitted responses to left-sided targets) and correct rejections (no response to no-target trials). Each patient performed between 8 and 15 blocks (mean, 12 blocks), depending on individual fatigue levels during the session.

2.3. MEG recordings and data analysis

Continuous MEG signals were collected by using a whole-head MEG system with 151 axial gradiometers (CTF Systems, Vancouver, Canada) at a sampling rate of 1250 Hz and a low-pass filter at 300 Hz. Head localization with respect to MEG sensors was measured at the beginning of each run by using coils placed at the nasion and at the left and right pre-auricular points. Vertical and horizontal electrooculogram (EOG), finger electromyogram (EMG) and electrocardiogram (ECG) were simultaneously recorded. Vertical and horizontal EOG signals were used to detect blinks and saccades. Electromyogram signals from the right finger were collected to monitor for the potential occurrence of sub-threshold button presses. Electrocardiogram signals were recorded to correct for the cardiac artifact if needed. Data preprocessing, analysis, and final visualization were performed using in-house software (http://cogimage.dsi.cnrs.fr/logiciels/). Data were high-pass filtered at 1 Hz and the timing of visual stimulus onset was corrected with respect to the refresh delay of the projector (+25 msec, measured on-line with a photodiode).

Fig. 1 – Lesion reconstructions and overlap map. (A) Lesion reconstructions for each patient on the axial sections of the Montreal Neurological Institute (MNI) standard brain in radiological convention. MRcron software (http://www.mccauslandcenter.sc.edu/mricro/mricron/index.html) was used to generate lesion overlay plots for all patients. (B) Overlap map showing the degree of involvement of each voxel in the lesions of the patient group (n = 5), normalized to the MNI template. The number of overlapping lesions is indicated by color-coded increasing frequencies from blue (n = 1) to red (n = 5). There was damage to gray matter regions (right putamen and cortical parietal and/or frontal sites), and to the right internal capsule in three patients. All patients showed damage to the external capsule, consistent with an impact on the most anterior part of the inferior-fronto occipital fasciculus, whose disconnection has previously been associated with signs of spatial neglect (Urbanski et al., 2008, 2011).
2.4. Artifact rejection

The EOG was calibrated in a separate recording block in which patients made voluntary saccades toward both the precise locations of the stimuli in the screen and half of this distance. The rejection threshold for eye movements corresponded to a deflection of $\pm 50 \mu V$ in $\pm 50$ msec on the horizontal EOG trace, corresponding to a deviation of $2^\circ$ of visual angle from fixation (target at $3^\circ$B). Eye blinks were easily detectable on the vertical EOG traces and were removed using a rejection threshold of $90 \mu V$. Thus, trials contaminated by eye movements (22%), eye blinks (16%), or muscular artefacts (17%) were rejected off-line upon inspection of the unfiltered EOG and MEG traces. This high rate of rejection was expected since brain-damaged patients find it particularly difficult to maintain immobility (muscular artefacts) and long-time concentration (blinks and saccades). Because the right hemispheric lesions induced large perturbations on neuromagnetic signals, we focused our analysis on the left, unimpaired hemisphere. Additionally, 13 perturbed MEG sensors [MEG left frontal (MLF): 11-12-21; MEG left temporal (MLT): 11-12-21-22-31-41-42; MEG midline frontal (MZF): 01; MEG midline central (MZC): 01] were also discarded from the final analysis.

2.5. Time–frequency (TF) analysis

A TF wavelet transform (Tallon-Baudry et al., 1997) was applied to each trial at each MEG sensor by using a family of complex Morlet wavelets ($m = 10$), resulting in an estimate of oscillatory power at each time sample between 10 and 60 Hz in 1-Hz steps. The TF signal power data from $–500$ to $–300$ msec before stimulus onset were used as baseline. An index of signal power, defined at each time sample and each frequency, as the increase or decrease of spectral power relative to fixation baseline in logarithmic decibel units $[\log(\text{TF}/\text{TF}_{\text{baseline}})]$ was considered as the measure of interest for all TF analyses. Indeed, log-transformed TF data approach a normal distribution, which allowed us to use standard parametric tests such as paired $t$-tests to assess the reliability of the observed effects (Kiebel et al., 2005).

3. Results

On average, patients omitted 37.4% of left-sided targets and 9.6% of right-presented targets (Table 2). All patients omitted more left-sided targets than right-sided targets. On average, patients (excluding patient 3) were 88 msec slower to respond to left-sided targets than to right-sided targets. Patient 3 was 69 msec faster for left-sided than for right-sided targets, but he had also a very large number of left omissions (89.4%).

To explore intrinsic brain activity prior to stimulus occurrence, we analyzed the oscillatory MEG activity engaged during the pre-stimulus period. We focused our analysis on the left, unimpaired hemisphere, to avoid the perturbations induced by the vascular lesions on neuromagnetic signals from the right hemisphere. To determine a region of interest (ROI) in time, frequency and space without a priori assumptions, we first looked for elevated power on the signal averaged across all experimental conditions, before stimulus onset (Fig. 2). This perusal revealed the presence of a robust pre-stimulus low beta synchronization in left frontal sensors during the first 250 msec prior to target onset, between 13 and 17 Hz. We averaged power in this TF of interest ($–250$–0 msec, 13–17 Hz) and selected the 10 sensors showing the largest power (MLF: 23-32-33-42-43-44-45-52; MLC: 12-13, see Fig. 2) as a ROI for subsequent statistical analysis.

We then averaged power between $–250$ and 0 msec, 13–17 Hz, over the 10 left frontal sensors separately in the four experimental conditions, to test whether pre-stimulus activity predicted stimulus detection or omission. Left frontal pre-stimulus beta power was much larger when left-sided targets were missed than when left-sided targets were correctly detected, or in the no-target or right hits conditions (Fig. 3A). The difference in mean pre-stimulus beta activity between left omissions and left or right hits was statistically significant (left hits vs left misses, $t = –3.1, d.f. = 4, p = .036$; right hits vs left misses, $t = –5.6, d.f. = 4, p = .004$). The difference between left misses and correct rejections on no-target trials was also significant ($t = 3.46, d.f. = 4, p = .025$), suggesting that the pattern of synchronization observed before left misses was not simply related to a simple lack of motor response. Finally, the left frontal pre-stimulus activity in the “left misses” condition could be observed in each of the five patients included in the study (Fig. 3B). The $–250$–0 msec, 13–17 Hz left prefrontal activity was larger in the “left misses” condition than in any other condition in all patients (Table 3).

The topography of the effect, with a maximum over prefrontal scalp sensors, called for a control of eye movements. As mentioned in the Methods section, we had discarded from analysis any trial contaminated with eye movements larger than $2^\circ$ of visual angle. However, smaller saccades could have gone undetected. We therefore analyzed EOG channels in the $–250$–0 msec and 13–17 Hz frequency ranges.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Misses (%)</th>
<th>FA (%)</th>
<th>RT (msec)</th>
<th>Number of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>1</td>
<td>20.2</td>
<td>7.1</td>
<td>13.9</td>
<td>453</td>
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<td>13.5</td>
<td>16.1</td>
<td>623</td>
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<td>5</td>
<td>15.6</td>
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<td>1.9</td>
<td>593</td>
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<tr>
<td>Mean</td>
<td>37.4</td>
<td>9.6</td>
<td>11.9</td>
<td>525</td>
</tr>
</tbody>
</table>

Table 2: Percentage of target omissions, false alarms (FA) and mean response times (RT) for each patient; number of trials analyzed after the artifact rejection procedure for each condition and patient.
band, and compared beta activity in left hits and left misses, on both vertical and horizontal EOG channels. Paired t-tests did not reveal any significant difference between conditions (all p values >.3), thereby suggesting that an oculomotor interpretation of our findings was unlikely. Last, we tested whether the effect reported here could have already been present in the baseline (−500 to −300 msec). A statistical analysis of the uncorrected −500 to −300 msec, 13−17 Hz TF window over the 10 frontal sensors of interest did not reveal any significant difference between conditions (all p values >.5).

Finally, to test whether differences between left hits and left misses could be due to vigilance fluctuations, following standard knowledge (Niedermeyer and Lopes da Silva, 1993) we measured alpha amplitude (8−12 Hz, −250 to −50 msec before stimulus onset), over the nine sensors over the left cortex 49 (2013) 1989−1996

Fig. 2 — TF analysis of MEG activity average across conditions and participants. TF activity of the mean of patients and conditions over left hemisphere sensors: Frontal (F), Central (C), Temporal (T), Parietal (P), and Occipital (O). Time 0 corresponds to target onset. A peak of energy can be observed before stimulus onset in the beta range (black rectangle, −250−0 msec and 13−17 Hz). This activity peaks at left frontal sensors, as shown on the topographical map. The 10 sensors displaying the largest power in the TF window of interest are highlighted by black circles. Oscillatory activity is expressed in logarithmic power units relative to baseline (relative power). Ant: Anterior, Post: Posterior.

Fig. 3 — TF mean of pre-stimulus MEG activity across conditions and individual data. (A) 3D head representation of the pre-stimulus (from −250 msec to 0 msec) oscillatory activity (from 13 Hz to 17 Hz) in each condition. (B) 3D head representation of the pre-stimulus beta activity in the Left Misses condition for each patient. The 10 selected sensors are highlighted and the color bar represents the frequency of oscillatory activity expressed in logarithmic power units relative to baseline (relative power).
hemisphere showing maximal power on data averaged across all experimental conditions. None of the pairwise comparison between experimental conditions revealed any significant difference (all comparisons, p > .2). In particular, pre-stimulus alpha level over the left hemisphere did not distinguish between left hits and left misses (paired t-test, t(5) = −1.46, p > .21). Although signal quality over the right hemisphere was poorer than over the left hemisphere, we nevertheless applied the same procedure and selected the nine sensors displaying the largest alpha power in the 8–12 Hz, −250 to −50 msec time window, to specifically test the hypothesis that left misses could be due to larger alpha oscillations over contralateral sensory regions. Right alpha power was similar for left hits and left misses (t(5) = −1.43, p > .22), and in general did not differ between conditions (all pairwise comparisons, p > .1).

4. Discussion

Our results established the time course and the localization in the brain of events leading to target omission in a group of right brain-damaged patients. In these patients, target misses had a neural signature of their own, likely to correspond to an active neural process supporting omissions of response and resulting neither from eye movements nor from fluctuations in vigilance. For the first time, we were able to correlate neglect episodes with ongoing brain activity before stimulus presentation. Such episodes were associated with a pre-stimulus build-up of low beta synchrony operating on anatomically intact left frontal regions in the contralesional hemisphere. We had to focus our analysis on the left hemisphere, to avoid the perturbations induced by the vascular lesions on neuro-magnetic signals from the right hemisphere. As a consequence, we cannot exclude that similar pre-stimulus neural oscillatory activity could also have occurred over unimpaired right areas. Nevertheless, independent support to the hypothesis that left frontal activity may have a bearing on left visuospatial neglect comes from the case report of a patient with right parietal damage and left neglect, who abruptly recovered after a subsequent lesion in the left lateral frontal cortex (Vuilleumier et al., 1996). Similarly, in another study on right brain-damaged patients (Oliveri et al., 1999), single pulse transcranial magnetic stimulation over the left frontal cortex decreased the number of left tactile extinctions induced by the simultaneous electrical stimulation of the right and left fingers. More generally, our finding that left omissions are preceded by a specific pattern of activity in the ipsilateral, healthy hemisphere, supports network-based models of neglect, which postulate that this condition does not directly result from focal brain damage, but depends on dysfunction of large-scale brain networks within and across the two hemispheres (Bartolomeo et al., 2012, 2007; Corbetta and Shulman, 2011; Doricchi et al., 2008; Kinsbourne, 1970; Mesulam, 1999; Thiebaut de Schotten et al., 2012; Urbanski et al., 2011).

Thus, in brain-damaged patients, not only can target misses be related to lack of the appropriate brain events (Vuilleumier et al., 2001), but they can also result from specific patterns of brain activity, during a time period crucial for normal preparatory states. Contralateral suppression of beta-band oscillations before target presentation seems required for awareness of visual targets (Schubert et al., 2009), and has been associated to faster responses to subsequently presented tactile stimuli, probably as a consequence of orienting of attention in time or in space (van Ede et al., 2011). Although neglect signs likely result from the interaction of several deficits, impaired orienting of spatial attention has often been stressed as prominent in neglect (Bartolomeo, 2007). Left frontal activity patterns could here be a correlate of inappropriate rightward orienting of spatial attention during the pre-stimulus period, resulting in inadequate preparation of the brain to respond to left-sided targets (see Chica et al., 2012a).

Indeed, spatial orienting requires the integrated activity of brain networks with prefrontal and parietal cortical nodes (He et al., 2007; Nobre, 2001; Thiebaut de Schotten et al., 2005), a coordination that could also rely on beta-band oscillatory synchrony (Buschman and Miller, 2007; Gross et al., 2004). For example, the left frontal eye field has been proposed as a causal determinant of the interactions between spatial attention and conscious perception (Chica et al., 2012b). More generally, baseline shifts in attention preceding stimulus onset can modulate sensory areas and could potentially result from top–down signals from prefrontal regions (see, e.g., Kastner et al., 1999). Other studies in healthy people have shown that differential increases in coupling between frontoparietal areas and visual areas prior to a stimulus can determine its subsequent access to awareness in attentional blindness tasks (Poultos et al., 2006), and could also support an interpretation in terms of asymmetric top–down signals.

Finally, the dorsolateral prefrontal cortex (especially in the left hemisphere: Heekeren et al., 2008), with its neighboring motor and premotor regions, has been proposed to be important in accumulating sensory evidence to compute a decision variable (Heekeren et al., 2008). Prefrontal neurons can actively encode perceptual decisions not only about the presence, but also about the absence of a stimulus (Merten and Nieder, 2012). A left hemisphere “absence” system might receive inconsistent or degraded information from the lesioned right hemisphere. A dysfunctional “absence” system might explain why some neglect patients, when asked to press a button when a visual stimulus is presented and another one when no stimulus occurs, may be faster to produce erroneous “absent” responses for stimuli presented on the left side than correct judgments of absence when no stimulus is presented (Laeng et al., 2002; Mijovic’-Prelec et al., 1994). It is thus possible that inappropriate left prefrontal

<table>
<thead>
<tr>
<th>Patient</th>
<th>No target</th>
<th>Right hits</th>
<th>Left hits</th>
<th>Left misses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−0.02</td>
<td>−0.001</td>
<td>0.002</td>
<td>0.199</td>
</tr>
<tr>
<td>2</td>
<td>−0.006</td>
<td>−0.057</td>
<td>−0.023</td>
<td>0.048</td>
</tr>
<tr>
<td>3</td>
<td>0.073</td>
<td>0.035</td>
<td>0.131</td>
<td>0.141</td>
</tr>
<tr>
<td>4</td>
<td>0.074</td>
<td>0.007</td>
<td>−0.001</td>
<td>0.192</td>
</tr>
<tr>
<td>5</td>
<td>0.037</td>
<td>0.026</td>
<td>0.012</td>
<td>0.105</td>
</tr>
<tr>
<td>Mean</td>
<td>0.031</td>
<td>0.002</td>
<td>0.024</td>
<td>0.137</td>
</tr>
</tbody>
</table>
activity in neglect patients contributes to their lack of exploration/detection of left-sided events, especially when the left frontal lobe does not receive appropriate input from more posterior or contralateral regions (Bartolomeo et al., 2007). Thus, left frontal activity may not only be beneficial to conscious target detection (Chica et al., 2012b; Dehaene and Changeux, 2011), but also detrimental to it.

In sum, our results provide information not only about the cerebral location but also about the timing of synchronization events leading to target omissions in right brain-damaged patients. Our observation might be a starting point to manipulate brain activity in order to reverse the conditions leading to episodes of visuospatial neglect. For example, EEG-triggered transcranial magnetic stimulation could be used, as done elsewhere (Oliiveri et al., 1999), to artificially desynchronize on a trial-to-trial basis, left frontal oscillatory patterns, and by doing so increasing left target detection rates. For the time being, the pre-stimulus signature we observed can only be considered distinctive of post-stroke focal cerebral damage patients as those participating in this study. Further research in intact individuals will clarify if similar mechanisms could be extended to episodic absence of target report in intact participants, and manipulated to boost detection rates.

Acknowledgments

We thank Jean-Didier Lemarechal and Denis Schwartz for technical assistance. This work was supported by the Institut National de la Santé et de la Recherche Médicale (INSERM), Project RBM 04-37, by EU FP6 and ANR project eraNEURON BEYONDVIS to AV-C and PB, by PHRC Regional Neglect to AVC-C and PP-D, and by a Translational Research grant from the Assistance-Publique-Hôpitaux de Paris to PB.

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