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Research Articles: Behavioral/Cognitive

EEG correlates of preparatory orienting, contextual updating and inhibition of sensory processing in left spatial neglect.

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EEG correlates of preparatory orienting, contextual updating and inhibition of sensory processing in left spatial neglect.

Abbreviated title: Preparatory attention ERPs in spatial neglect

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We declare no conflict of interest

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Abstract

Studies with Event Related Potentials (ERPs) have highlighted deficits in the early phases of orienting to left visual targets in right-brain-damaged patients with left spatial neglect (N+). However, brain responses associated with preparatory orienting of attention, with target novelty and with the detection of a match/mismatch between expected and actual targets (contextual updating), have not been explored in N+. Here in a study in healthy humans and brain damaged patients of both sexes we demonstrate that frontal activity that reflects supra-modal mechanisms of attentional orienting (ADAN) is entirely spared in N+. In contrast, posterior responses that mark the early phases of cued orienting (EDAN) and the setting up of sensory facilitation over the visual cortex (LDAP) are suppressed in N+. This uncoupling is associated with damage of parietal-frontal white matter. N+ also exhibit exaggerated novelty reaction to targets in the right side of space and reduced novelty reaction for those in the left side (P3a) together with impaired contextual updating (P3b) in the left space. Finally, we highlight a drop in the amplitude and latency of the P1 that over the left hemisphere signals the early blocking of sensory processing in the right space when targets occur in the left one: this identifies a new electrophysiological marker of the rightward attentional bias in N+. The heterogeneous effects and spatial biases produced by localised brain damage on the different phases of attentional processing indicate relevant functional independence among their underlying neural mechanisms and improve the understanding of the spatial neglect syndrome.

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Significance statement

Our investigation answers important questions: are the different components of preparatory orienting (EDAN, ADAN, LDAP) functionally independent in the healthy brain? Is preparatory orienting of attention spared in left spatial neglect? Does the sparing of preparatory orienting have an impact on deficits in reflexive orienting and in the assignment of behavioural relevance to the left space? We show that supra-modal preparatory orienting in frontal areas is entirely spared in neglect patients though this does not counterbalance deficits in preparatory parietal-occipital activity, reflexive orienting and contextual updating. This points at relevant functional dissociations among different components of attention and suggests that improving voluntary attention in N+ might be behaviourally ineffective unless associated with stimulations boosting the response of posterior parietal-occipital areas.

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Introduction

Right brain damage (RBD) often produces a salient inability in orienting attention toward the left side of space, i.e. the "spatial neglect" syndrome. Neglect is frequently associated with parietal and frontal lesions and the loss of cross talk between these areas due to damage of underlying white matter connections (Mort *et al.,* 2003; Doricchi & Tomaiuolo, 2003; Thiebaut de Schotten *et al.,* 2005; Bartolomeo *et al.,* 2007; Doricchi *et al.,* 2008; Verdon *et al.,* 2009; Thiebaut de Schotten *et al.,* 2011). Past investigations have well established that in patients with neglect (N+) the N1 and P2 ERPs components evoked by targets in the left side of space show a relative increase in latency and reduction in amplitude (Verleger et al., 1996; Deouell et al., 2000; Di Russo et al. 2007). Both of these components mark early phases in attentional processing. The N1 originates in the intraparietal sulcus and reflects facilitation of sensory processing at attended spatial positions (Hillyard et al., 1998). The P2 reflects attentional re-activation of the occipital cortex (Di Russo et al., 2007). Nonetheless, other important components of orienting remain totally unexplored in N+. In healthy humans, voluntary orienting of attention guided by symbolic spatial cues, e.g. an arrow, presented at central fixation is associated with three preparatory ERPs components that have higher amplitude over the hemisphere contralateral to the expected target location (Eimer, 2014). The first component is an " Early Directing Attention Negativity" (EDAN) that occurs 200–400 ms post-cue in parietal-occipital areas. This component is interpreted as marking the early phases of the attentional shift toward the lateral position of the target (Harter et al., 1989; Nobre et al., 2000) or, alternatively, the spatial selection of task-relevant features in central visual cues that guide lateral shifts of attention (vanVelzen & Eimer, 2003). The second component is an "Anterior Directing Attention Negativity" (ADAN) that reflect supramodal mechanisms of attentional engagement in frontal areas and occurs 500–900 ms post-cue (Eimer et al., 2002; Praamstra et al., 2005). The third componenr is a "Late Directing Attention

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Positivity (LDAP; Harter et al., 1989; Hopf & Mangun, 2000) that marks the setting-up of facilitatory effects in posterior visual areas 500-1000 msec post cue. No study of these components is available in N+. This gap is relevant because, based on behavioural measures, voluntary orienting of attention is usually considered relatively spared in N+ and exploited for rehabilitation purposes (for review, see Natale *et al.,* 2005). In addition, studying the effects of localised brain damage can provides clues on the mutual functional reliance of these components in the normal brain, i.e. whether each of them can be independently suppressed by brain damage. The first aim of our study was to gain new insights in these issues.

Another relevant and poorly explored aspect of spatial neglect is whether the drop in the interest of N+ for events in the left space is also linked to defective evaluation of the novelty and the probabilistic distribution of sensory events in that space, i.e. contextual updating. In the healthy brain the P3a and P3b components reflect novelty detection and the updating of probabilistic occurrence of a stimulus based on its past exposures, respectively (Polich, 2007). The P3a is generated in frontal and cingulate dopaminergic structures (Daffner *et al.* 2000, 2003; Polich, 2007) while the P3b is generated in temporal-parietal areas innervated by norepinephrine and marks the categorization of stimuli as a function of their match or mismatch to expected ones (Polich, 2007; Doricchi et al., 2009; Macaluso and Doricchi 2013). Past studies in N+ have demonstrated an increment in the latency and a reduction in the amplitude of the P300 elicited by stimuli in the left space (Lhermitte et al., 1985; Verleger *et al.* 1996; Saevarsson *et al.* 2012). Nonetheless, despite the clear distinction between the functions played by the P3a and P3b no study has specifically explored these components in N+. The second main aim of our investigation was to fill this gap.

Finally, we exploited recent ERPs findings in healthy humans to identify a new marker of the pathological rightward attentional bias of N+ in a specific modification of the P1 component that originates from the joint activity of areas V3a and V4 and that reflects

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suppression of processing at non-attended spatial locations (Hillyard et al., 1998). Slagter et al. (2016) showed that validly cued visual targets evoke a larger P1 over the hemisphere contralateral to the non-stimulated side of space, thus marking the target-related blocking of sensory processing in this side of space. Here we verified whether the rightward bias of N+ is matched with reduced blocking of sensory input in this side of space, that is with reduced amplitude of the P1 over the left hemisphere when expected targets are presented in the left side of space.

Material & methods

Participants

Patients were consecutively screened for inclusion in the study on admission for physical and neuropsychological rehabilitation at the Fondazione Santa Lucia IRCCS (Rome). Patients with bilateral strokes, signs of dementia or history of previous neurological illness were excluded. Two groups of patients completed the experimental protocol and were included in final data analyses: twelve right-brain-damaged patients with left spatial neglect (N+) and thirteen right-brain-damaged patients without neglect (N-). In addition, fifteen age-matched healthy participants were tested as controls (C). Patients and participants were all right-handed and had normal or corrected-to-normal visual acuity. At the time of clinical and experimental examination, all patients were free from confusion and from temporal or spatial disorientation. Visual fields were tested with standard kinetic Goldmann perimetry. All patients had intact visual fields, with the exception of one N+ patient who suffered restriction of the left inferior quadrant with sparing of 10° around central fixation. N+ and N- patients did not differ in time elapsed from stroke onset ($F_{(1,11)} = 3$, $P = 0.23$; mean = 46 days). Age was equivalent among N+, N- and C ($F_{(2,22)} = 2.6$, $P = 0.32$; mean age: C = 53.2; N+ = 62.6; N- = 61.9 years). Clinical and demographic data are reported in Table 1. Patients and controls gave

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their informed consent for participating in the study that was approved by the Institutional Ethical Committee of the Fondazione Santa Lucia IRCCS.

Clinical assessment of neglect

Unilateral neglect was assessed with a battery composed of six standardized tests:

1. Line bisection: the task requires the bisection of five horizontal 200 mm lines. Each line is separately presented at the centre of a horizontally oriented A3 paper sheet. Rightward deviations from the true line centre are scored as positive deviations (in mm.) and leftward deviations as negative ones. The cut-off score for spatial neglect is 6.5 mm (Azouvi *et al.,* 2002).

2. Letter cancellation (Diller *et al*., 1974): the task requires the cancellation of target capital letters presented on a horizontally oriented A3 paper sheet. Letters are arranged in six rows. In each row, target letters (H) are intermixed with filler letters (total score range 0–104; 0–53 on the left side, 0–51 on the right side). The presence of neglect is indicated by a difference of four or more omissions between the contralesional and ipsilesional side of the sheet.

3. Line cancellation (Albert, 1973): the task requires the cancellation of short line segments that are arranged in scattered order and random orientation on an A3 paper sheet (total score range 0–21; 0–11 on the left side, 0–10 on the right side). Neglect is indicated by a difference of 1 or more omissions between the contralesional and ipsilesional side of the sheet.

4. Star cancellation (Halligan *et al.*, 1990): the task requires the cancellation of small stars that are presented on a A3 paper sheet interspersed with 52 large stars, 13 letters and 10 short words that act as distracters (total score = 54: 27 on the left side and 27 on the right side). Neglect is indicated by a difference of 3 or more omissions between the contralesional and ipsilesional side of the sheet.

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184 *5. Sentence reading test* (Pizzamiglio *et al.,* 1992): the score is the number of sentences red
185 without omissions/errors (score range 0–6). One or more omissions/errors in reading the
186 initial part of the sentence or of the words composing the sentence indicates left spatial
187 neglect.
188 *6. Wundt–Jastrow area illusion test* (Massironi *et al.*, 1988): the score is the frequency of
189 missed optical illusion when the two fans are oriented towards the contralesional or the
190 ipsilesional side of space (score range 0–20 in both cases). The performance is considered
191 pathologically biased when the contralesional vs. ipsilesional difference in the frequency of
192 missed illusions is higher than 2.
193 Patients who failed on at least two out of the six tests were classified as suffering left
194 spatial neglect. Clinical and demographic data of the N+, N- and C groups are reported in Table
195 1.
196
197 *** Insert Table 1 about here ***
198
199 *Lesion mapping.*
200 Individual 1.5 T MRI scans were corrected for inter-individual differences in brain size
201 and brain volume orientation, using a transformation into the standardized MNI space using
202 the software REGISTER
203 (http://www.bic.mni.mcgill.ca/ServicesSoftwareVisualization/Register). This program uses
204 more than five neuroanatomical landmarks to match individual brain volumes to the Colin-
205 MNI brain. Selection of damaged area in individual MRI scans registered in MNI space was
206 made through the DISPLAY mouse-brush,
207 (http://www.bic.mni.mcgill.ca/software/Display/Display.html) that allows colouring selected
208 voxels. This operation is accompanied by the simultaneous 3D view of brain volumes and the

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visualisation of the movements of the mouse-brush within the sagittal, axial, and coronal planes, thus optimising the identification of lesion landmarks. The probability maps of N+ and N- groups are reported in Fig. 1. In each experimental group, the MNI coordinates of the centroids of areas of maximal lesion overlap were defined using the command DISPLAY. To check whether peaks of lesion overlap highlighted in the N+ vs. N- subtraction encroached upon white matter pathways, we used the diffusion tensor imaging-based atlases by Thiebaut de Schotten *et al.* (2011) and by Oishi *et al.* (2008). White matter pathways were visualized using MRICron software (Rorden *et al.,* 2007). Using Tractotron software (Thiebaut de Schotten *et al.,* 2012; BCBtoolkit http://www.brainconnectivitybehaviour.eu).

Procedure and stimuli

Participants were tested with the head comfortably blocked by a chin rest, in a dimly lit, sound attenuated and electrically shielded room. Stimuli were presented on a video monitor (22 inch) at a viewing distance of 57.5 cm. Presentation of stimuli and recording of manual reaction times (RTs) was performed with E-prime software (Schneider *et al.,* 2002). The experiment included four experimental sessions that were run in different days and were separated by a one-two day interval. A total number of 280 Valid trials (140 with the target in the left side of space and 140 with the target in the right side), 120 Invalid trials (60 left side, 60 right side), 160 Neutral (80 left side, 80 right side), and 48 Catch trials (16 cue left side, 16 cue right side, 16 neutral cues) were administered during the four experimental sessions. An equal number of 152 (70 Valid, 30 Invalid, 40 Neutral and 12 Catch) trials were delivered in each session.

Each trial started with the presentation of a central fixation cross (size: 1° × 1°) and two lateral boxes (size: 1° × 1°), one centered 4.5° to the left and the other 4.5° to the right of central fixation. This "Fixation" period lasted 800–1000 ms (uniform distribution) and was

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followed by a "Cue" period, lasting between 1800 and 2400 ms (uniform distribution). This relatively extended cue period was adopted to counteract any potential slowing in the engagement of attention in patients with RBD (Husain and Rorden, 2003) and favour the full deployment of spatial attention. In *directional* Valid and Invalid trials, at the beginning of the "Cue" period an arrow-cue pointing to the left or the right box was presented at central fixation. In this case, participants were asked to pay attention to the box indicated by the cue. In *non-directional* Neutral trials, the arrow was replaced by an "=" symbol. In this case, participants were instructed that the symbol indicated no specific side of space and that they had to wait for target presentation without paying attention to one of the two lateral boxes. At the end of the "Cue" period, a target-asterisk (size: 0.6° × 0.6°) was presented for 300 ms at the centre of one of the two boxes, with the central cue remaining on until target disappearance. Once the target and the cue disappeared, 2 sec were allowed for response ("Response" period). In each trial, participants were asked to detect the target by pressing a central button with their right index finger as soon as possible and to withhold response when no target was presented (Catch trials). On "Valid" trials, the target was presented in the box cued by the arrow. On "Invalid" trials, the target was presented in the box opposed to that cued by the arrow. It is worth noting that directional cues presented during Valid and Invalid trials were statistically informative of target location, because 70% of trials were Valid (280/400) and 30% were Invalid (120/400). On "Neutral" trials with non-directional cues, the target was presented with equal probability in one of the two boxes. The experiment also included *directional*-Catch and *non-directional*-Neutral Catch trials with no target presentation. Central fixation, boxes and targets were in white, cues in yellow. All stimuli were presented on a black background. Participants were required to hold their gaze on central fixation throughout the trial and try not to blink during the cue and target period. Eye movements were monitored with an infrared eye tracker (Tobii X120, sampling rate 8.3

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msec). The eye tracker allows the continuous and instantaneous check of gaze position within a notification window in the screen used by the experimenter. Using this window, the experimenter triggered the start of each trial only when the gaze of the participant was within an area of 1° around the central fixation point.

EEG recording and pre-processing

The EEG was recorded using a Brain Vision system from 64 electrodes placed according to the 10–10 system montage. All scalp channels were online referenced to the left mastoid (M1). Horizontal eye movements were monitored with a bipolar recording from electrodes at the left and right outer canthi. Blinks and vertical eye movements were recorded with an electrode below the left eye, which was referenced to site Fp1. The EEG from each electrode site was digitized at 250 Hz with an amplifier bandpass of 0.01–60 Hz, including a 50 Hz notch filter, and was stored for off-line averaging. Continuous EEG was recalculated against the average reference and successively segmented in epochs lasting 2000 ms for cue-locked analysis and 1000 ms for target-locked analysis. In both cases 200 ms before the events were used as baseline. Prior to computerized artefact rejection, ocular correction was performed accordingly to Gratton & Coles algorithm (Gratton *et al.,* 1983). Artefact rejection was performed prior to signal averaging in order to discard epochs in which deviations in eye position, blinks or amplifier blocking occurred. All epochs in which EOG amplitudes and EEG amplitudes were greater than ±60 mV were excluded from further analysis. On average, 4.9 %, 3.8 % and 4.2 % of the trials were rejected for violating these artefact criteria in the healthy subject, N- and N+ group, respectively. Notwithstanding this relatively low number of epochs discarded due to artefact in the EEG, the general high number of missed target in the N+ group (up to 62% of missed invalid targets in the left side of space, see Result section) and the marked inter-individual variance in the hit-rate as a function of target type (Valid, Neutral

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and Invalid) in N+ and N- patients, precluded the possibility of running separate ERPs analyses target- for hit and missed targets.

Statistical analyses

Clinical and demographical data.

To analyse clinical performance in the two Groups of patients, individual score of Line bisection and Sentence reading test were compared through an unpaired two-tailed T-test with p-level set to 0.05. Individual scores from Letter cancellation, Line cancellation, Star Cancellation and the Wundt-Jastrow Area Illusion task were entered in a Group (N-, N-) x Target Side (Left, Right) repeated-measures ANOVA.

Lesion analyses

First, lesion volume of the two groups of patients was compared through a one-way repeated-measure ANOVAs. Second, Descriptive and inferential statistical comparisons of lesion mapping were run by subtracting the probability map of the N- group from that of the N+ group and by comparing, with Fisher exact test, the frequency of damage occurrence at the centroids of the areas of maximal lesion overlap. Lesion probability maps resulting from this subtraction and the corresponding MNI coordinates of centroids of lesion overlaps are reported in Fig. 1.

Successively, we evaluated individual probability of disconnection of white matter pathways that included the peaks of lesion overlap highlighted in the N+ vs. N- subtraction. Individual probabilities were first entered in one-way N+ vs. N- repeated-measures ANOVA. In a second step, this ANOVA was run again using lesion volume as a covariate (ANCOVA).

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Behavioural performance and RTs.

Omissions: Due to the different frequency of Valid, Neutral and Invalid trials, individual percentage of omissions were initially submitted to arcsine transformation (Sheskin, 2003). Percentages were entered in a Group (C, N- and N+) x Trial type (Valid, Neutral and Invalid) x Target Side (Left, Right) repeated-measures ANOVA.

Reaction Times (RTs): Due to the high number of omissions of targets in the left side of space, RTs were analysed through two different procedures. First (Analysis A), only RTs provided by patients were considered in the analysis. Second (analysis B), in order to allow comparison with other recent RTs investigations in neglect patients (Reganchary *et al.,* 2011), omitted RTs were replaced with the maximum time allowed for response (2000 ms). In both analysis A and B, individual mean RTs were entered in a mixed Group (C, N- and N+) and Trial type (Valid, Neutral and Invalid) x Target Side (Left, Right) repeated-measures ANOVA.

ERP data.

Lateralized cue-related components

The three lateralized, long lasting and large-amplitude preparatory ERP components EDAN, ADAN and LDAP that were elicited by central spatial cues were averaged within six conventional ROIs (Kelly *et al.,* 2009): left frontal (FL: F7, FC5), right frontal (FR: F8, FC6), left posterior (PL: P7, CP5), right posterior (PR: P8, CP6), left occipital (LO: PO7, O1) and right occipital (RO: PO8, O2). In a first series of analyses, each component was analysed by entering individual data in a Group (C, N-, N+) x Cue Direction (Left, Right) x Hemisphere (Left, Right) repeated-measures ANOVA. The amplitude of these components were measured as mean activity with respect to a 200 ms pre-stimulus baseline in the following conventional time windows: EDAN (240–420 ms post-cue, PL and PR; Kelly *et al.*, 2010; Seiss *et al.*, 2009), ADAN

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(450–850 ms post-cue, FL and FR; Eimer *et al.*, 2002; Seiss *et al.*, 2009) and LDAP (500–1000 ms post-cue, PL and PR; Eimer *et al.*, 2002; Seiss *et al.*, 2009) in all groups.

Harter *et al.* (1989) and Nobre *et al.* (2000) pointed out that the ADAN and LDAP components can persist for the entire duration of the cue period up to target appearance. Based on this suggestion, in a second series of analyses we explored the development and maintenance of the ADAN and LDAP during the entire cue period adopted in the present study. To this aim, we re-analysed through the same series of repeated-measures ANOVAs, the ADAN and LDAP during the first half and the second half of the cue period that ranged from the onset of each component to the end of the cue period, i.e. 1800 ms, that was shared by the different cue durations that preceded target presentation. The ADAN was re-analysed within the 450-1125 ms and 1125-1800 ms time windows. The LDAP was re-analysed within the 500–1150 ms and 1150-1800 ms time windows.

Target-related components

P3a and P3b

The amplitude of P3a and P3b components was measured as the mean activity change with respect to a 200 ms pre-stimulus baseline in the following time windows: P3a 220 -380 ms, P3b 300 - 600 ms. Both components were analysed at the following pools of derivations: a) P3a: AFz, Fz, Fcz, F1, F2 (see Fig. 6) b) P3b: P1, P3, PO1, PO3, Pz, POz, Oz, P2, P4, PO2, PO4 (see Fig. 7). The selection of time windows and derivations used for the analysis of these large amplitude components were based on the results of previous studies (Polich, 2007; Saevarsonn *et al.,* 2012) and on visual inspection of scalp topographies. Individual data were entered in a Group (C, N- and N+) x Trial Type (Valid, Neutral and Invalid) x Target side (Left, Right) repeated-measures ANOVA. Latency peaks of the P3a and P3b components were estimated through an automatic peak-detection algorithm (Vision Analyzer 2.1.2) within the

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same time windows and electrode derivations used in amplitude analyses. All peaks identified by the software were further verified through visual inspection. Individual latencies were entered in a Group (C, N- and N+) x Trial Type (Valid, Neutral and Invalid) x Target side (Left, Right) repeated-measures ANOVA.

P1 and N1

Individual amplitudes and latency peaks of these small amplitude transitory ERPs components were estimated through an automatic peak-detection algorithm (Vision Analyzer 2.1.2) within specified time windows (P1: 90 – 200 ms; N1: 150 - 250 ms). Peak detection was carried out at electrode derivations, i.e. PO7/8, CP3/4, where these components showed maximal amplitude in the grand average of each experimental group (Di Russo *et al.,* 2007). Time windows and derivation are consistent with those used in the large majority of previous studies (see for example Slagter *et al.,* 2016; Lasaponara et al., 2011; Gonzalez *et al.,* 1994). All peaks identified by the software were further verified through visual inspection. Individual latency and amplitude P1 peaks were successively entered in a Group (C, N-, N+) x Target Side (Left, Right) x Hemisphere (Ipsilateral, Contralateral) repeated-measures ANOVA, while individual latency peaks of the N1 recorded over the hemisphere contralateral to target side were entered in a Group (C, N-, N+) x Target Side (Left, Right) repeated-measures ANOVA.

In a series of additional analyses, we investigated whether valid attentional cuing produced an increase in the amplitude of the P1 and N1 with respect to invalid cuing, i.e. sensory gain (Mangun & Hillyard, 1991). To this aim we initially calculated individual differential P1 and N1 waveforms between Valid and Invalid targets within each patient and participant. This served to partially control for the potential confounds that would have been produced if the contrast between Valid and Invalid targets would have been initially run between groups of patients with brain lesions differing in site and size. In a first step, through

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a series of one-sample t-test, we checked whether the mean differential amplitude of the P1 and N1 components was significantly different from zero in each experimental group. In a second step, differential P1 waveforms were entered in Group (C, N-, N+) x Target Side (Left, Right) x Hemisphere (Ipsilateral, Contralateral) repeated-measures ANOVA, and differential N1 waveform in a Group (C, N-, N+) x Target Side (Left, Right) repeated-measures ANOVA.

The influence of attentional cuing on peak-latencies was tested by entering individual P1 data in a Group (C, N-, N+) x Trial Type (Valid, Invalid) x Target Side (Left, Right) x Hemisphere (Ipsilateral, Contralateral) repeated-measures ANOVA, and N1 data in a Group (C, N-, N+) x Trial Type (Valid, Invalid) x Target Side (Left, Right) repeated-measures ANOVA for the N1.

Results

Clinical results

A series of between-group comparisons, showed that compared to N-, N+ patients had significant rightward spatial biases in all neglect tasks (see Table 1). N+ had a higher rightward bias during line bisection ($t_{(23)}$ = -4.1, P = 0.0003, unpaired t-test) and showed a higher number of left side omissions in the Sentence reading task ($t_{(23)}$ = 3.3, P = 0.002, unpaired t-test). In the Letter cancellation ($F_{(1,23)}$ = 16.5, P = 0.0004, η_p^2= 0.41), Line cancellation ($F_{(1,23)}$ = 10.4, P = 0.003, η_p^2= 0.31), Star Cancellation ($F_{(1,23)}$ = 22.8, P = 0.0000, η_p^2= 0.49) and in the Wundt-Jastrow Area Illusion task ($F_{(1,23)}$ = 18.3, P = 0.0002, η_p^2= 0.44), the performance of N+ differed from that of N- more for stimuli positioned in the left side of space than for stimuli positioned in the right side of space, as indexed by significant Group x Side interactions.

Anatomical results

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N+ patients had larger lesion than N- ones ($F_{(1,23)}$ = 12.7, P = 0.002, η_p^2= 0.42). The lesion probability maps resulting from the subtractions between N+ and N- showed three areas of 78% lesion overlap in N+ and no overlap , i.e. 0%, in N- patients (Fischer exact test, P = 0.0003). A first anterior peak of lesion overlap was located in the frontal operculum (MNI coordinates: 30, 26, 8; Peak 1 in Fig. 1). A second peak was located in the anterior segment of the arcuate fasciculus (MNI coordinates: 34, -19, 22; Peak 2 in Fig. 1). Finally a third peak was found in cortical and subcortical structures around the Temporal Parietal Junction (Peak 3 in Fig. 1. Heschl gyrus: 43, -22, -1 and 42, -24, 10; Posterior sector of the Superior Temporal Gyrus: 44, -28, 4; Planum temporale: 45, -32, 9; Posterior segment of the Arcuate Fasciculus also close to the Inferior Longitudinal Fasciculus: 38, -35, 11 and 35, -36, 12).

The N+ vs. N- comparison run on individual probabilities of disconnection defined by the Tractotron software showed higher probability of disconnection in the N+ group in each of the tracts highlighted in the study of lesion overlap (Anterior segment of the Arcuate Fasciculus: N+ = 89%, N- = 46%, $F_{(1,23)}$ = 4.93, P = 0.04, η_p^2= 0.22; Posterior segment of the Arcuate Fasciculus: N+ = 83%, N- = 44%, $F_{(1,23)}$ = 5.41, P = 0.03, η_p^2= 0.24; Inferior Longitudinal Fasciculus: N+ = 83%, N- = 36%, $F_{(1,23)}$ = 6.6, P = 0.01, η_p^2= 0.28). When the same comparisons were run taking into account lesion volume as covariate, no significant difference was found between N+ and N-. This result illustrates that lesion volume increases the probability of white matter disconnection and of the presence of spatial neglect.

*** Insert Figure 1 about here ***

Behavioural results

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Omissions.

N+ made more omissions (37.3%; Group effect: $F_{(2,37)} = 22.8$; $P = 0.0000$, $\eta_p^2 = 0.55$) than N- (15.5 %, $P = 0.0006$) and C (4.3 % $P = 0.0000$). The ANOVA highlighted a significant Group x Trial Type x Target Side interaction ($F_{(4,74)} = 2.6$; $P = 0.03$, $\eta_p^2 = 0.13$). This triple interaction was further analysed through two ANOVAs comparing C with N+ and N- groups separately. The Group (C, N-) x Trial type (Valid, Neutral and Invalid) x Side of target (Left, Right) ANOVA showed that N- made more omissions than C (Group effect: $F_{(1,26)} = 23$ $P = 0.0000$, $\eta_p^2 = 0.46$). A significant Group x Target Side interaction showed that compared to C, in the N- group omissions were more frequent for targets in the left side of space ($F_{(1,26)} = 15.1$, $P = 0.0006$, $\eta_p^2 = 0.36$; Left side: N- = 20%, C = 3%; Right side: N- = 10%, C = 4%) and that this happened independently of Trial Type (Group x Trial Type x Target side interaction, $F_{(2,52)} < 1$, P = n.s). The Group (C, N+) x Trial type (Valid, Neutral and Invalid) x Side of target (Left, Right) ANOVA showed that compared to C, N+ made more omissions ($F_{(1,25)} = 36.5$, $P = 0.0000$, $\eta_p^2 = 0.59$) and that this omissions were more frequent in the left side of space ($F_{(1,25)} = 34.2$, $P = 0.0000$, $\eta_p^2 = 0.57$; Left side: N+ = 51%, C = 3%; Right side: N+ = 23%, C = 4%). Most important, a significant Group x Trial Type x Target side interaction ($F_{(2,50)} = 3.4$, $P = 0.03$, $\eta_p^2 = 0.12$) showed that compared to C, in N+ omissions in the left side of space increased as a function of trial type: they were less frequent with valid targets (38%) intermediate with neutral targets (52%) and reached the highest level with invalid targets (62%). This result highlight the reorienting deficit suffered by N+ patients (Posner *et al.*, 1984). Finally, we compared the performance of N+ and N- patients through a Group (N+, N-) x Trial Type (Valid, Neutral and Invalid) x Side of target (Left, Right) ANOVA. N+ made more omissions than N- patients ($F_{(1,23)} = 9.3$, $P = 0.005$, $\eta_p^2 = 0.28$). A Group x Target side interaction ($F_{(2,46)} = 7.4$, $P = 0.01$, $\eta_p^2 = 0.24$) showed that compared to N-, N+ made more omissions in the left side of space though not in the right side (Left side: N+ = 51%, N- = 20%, Bonferroni post-hoc test $P = 0.0003$; Right side: N+ = 23%, N-

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457 = 10%, *P* = 0.53). We also found a significant triple Group x Trial Type x Target Side
458 interaction ($F_{(2,46)}$ = 3.8, *P* = 0.02, η_p^2= 0.14). Separate Group x Trial Type ANOVAs run for the
459 left and right side of space showed that compared to N-, in N+ omissions in the left side of
460 space grew up as function of Trial Type (Group x Trial Type interaction: F = 4.1, *P* = 0.02; N+:
461 Valid = 38%, Neutral = 52%, Invalid 62%; N-: Valid = 16%, Neutral = 19%, Invalid 24%). A
462 similar interaction was not present when targets were presented in the right side of space
463 (Group x Trial Type interaction: F < 1).
464
465 *RTs.*
466 *Analysis A*. A significant Trial Type effect showed the presence of attentional benefits, i.e. RTs
467 advantage for Valid as compared to Neutral targets, and costs, i.e. RTs disadvantage of Invalid
468 as compared to Neutral targets ($F_{(2, 74)}$ = 25.9, *P* = 0.0000, η_p^2= 0.41; Valid = 510 ms, Neutral =
469 547 ms, Invalid = 568 ms: Bonferroni post-hoc comparisons *P* = 0.01 and *P* = 0.03 for Costs
470 and Benefits respectively). A Group x Target Side interaction ($F_{(2,37)}$ = 4.7; *P* = 0.01, η_p^2= 0.20)
471 showed that compared to C, N+ had slower responses to targets presented in the left side of
472 space, though not for those in the right side (Left: C = 511.2 vs. N+ = 568.5, *P* = 0.03; Right: C =
473 507.8 vs. N+ = 569, *P* = 0.11). RTs of N- were comparable to those of C in both sides of space.
474 No significant difference was found between N+ and N-.
475
476 *Analysis B*. N+ had slower RTs (1100 ms) as compared to both C (500 ms *P* = .0001) and N-
477 patients (800 ms *P* = .003; Group effect: $F_{(2,37)}$ = 19.3; *P* = 0.0000, η_p^2= 0.51). A significant Trial
478 Type effect showed the presence of attentional benefits and costs ($F_{(2, 74)}$ = 34, *P* = 0.0000, η_p^2=
479 0.47; Valid = 701 ms, Neutral = 783 ms, Invalid = 865 ms: Bonferroni post-hoc comparisons *P*
480 = 0.01 and P = 0.003 for Costs and Benefits respectively). A Group x Target Side interaction
481 ($F_{(2,37)}$ = 14.2; *P* = 0.0000, η_p^2= 0.43) highlighted that compared to C, N+ had slower responses

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to target appearing both in the left and in the right side of space (Left: C = 511.2 vs. N+ = 1323.5, *P* = 0.0000; Right: C = 507.8 vs. N+ = 899.1, *P* = 0.0000). Conversely, when compared to N-, N+ had slower RTs for targets in the left side of space while the same difference did not reach significance for targets in the right side of space (Left: N- = 886.1 vs. N+ = 1323.5, *P* = 0.0000; Right: N- = 689 vs. N+ = 899, *P* = 0.055). Compared to C, N- had slower responses for targets in the left side of space (Left: C = 511 vs. N- = 886, *P* = 0.001; Right: C = 507 vs. N- = 689, *P* = 0.12).

*** Insert Figure 2 about here ***

Electrophysiological results

Cue-related ERPs

Grand-average of cue-related EDAN, ADAN and LDAP components elicited by cues pointing to the left or the right side of space in the six ROIs (FL, FR, PL, PR, OL and OR) are illustrated in Figs. 5, 6, 7 for C, N- and N+ participants respectively.

EDAN

The Group x Cue Direction x Hemisphere interaction was significant ($F_{(2,37)}$ = 3.4, *P* = .04, η_p^2= 0.14). Bonferroni post-hoc comparison showed that in C the EDAN was present both over the left and over the right hemisphere (Left hemisphere: cue in the contralateral direction = -.96 μV, cue in the ipsilateral direction = -.60 μV, *P* = 0.03; Right hemisphere: cue contralateral = -.54 μV, cue ipsilateral = -.12 μV, *P* = 0.03). In N- the EDAN was present over the left hemisphere (cue contralateral = 13 μV, cue ipsilateral = 64 μV; *P* = 0.02) while over the right hemisphere there was a non-significant reversal of the component, with relative higher voltage for the cue in the contralateral direction (cue contralateral = 75 μV, cue ipsilateral = 35 μV). No EDAN was present in N+.

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These results suggest that N+ suffer a general and space-independent deficit in the early phases of the attentional shift and/or the spatial selection of cue-features that guide lateral shifts of attention. In contrast, N- patients display this deficit only for cues pointing in the contralesional direction, i.e. leftward.

ADAN

The Group x Cue Direction x Hemisphere ANOVA highlighted the bilateral presence of the ADAN in all Groups (Cue Direction x Hemisphere interaction: $F_{(1,37)} = 37$, $P = 0.0000$, $\eta_p^2 = 0.50$). There was also a significant main Group effect ($F_{(2,37)} = 3.7$, $P = 0.03$, $\eta_p^2 = 0.16$). Bonferroni Post-hoc comparisons showed that this was due to general higher negativity in N+ as compared to C (-.67 μV vs. .27 μV, $P = 0.02$).

First Half of the Cue Period. The Group x Cue Direction x Hemisphere ANOVA highlighted bilateral ADAN in all Groups (Cue Direction x Hemisphere interaction: $F_{(1,37)} = 9$, $P = 0.004$, $\eta_p^2 = 0.19$).

Second Half of the Cue Period. The Group x Cue Direction x Hemisphere interaction was significant ($F_{(2,37)} = 4.8$, $P = 0.01$, $\eta_p^2 = 0.20$) and highlighted a bilateral ADAN in C (Left hemisphere: cue contralateral = .27 μV, cue ipsilateral = .53 μV, $P = 0.05$; Right hemisphere: cue contralateral = -.26 μV, cue ipsilateral -.40 μV, $P = 0.002$), though no significant ADAN in N- (Left hemisphere: cue contralateral = .30 μV, cue ipsilateral = .59 μV, $P = 0.54$; Right hemisphere: cue contralateral = .16 μV, cue ipsilateral .47 μV, $P = 0.41$) and N+ (Left hemisphere: cue contralateral = -.06 μV, cue ipsilateral = -.46 μV, $P = 0.42$; Right hemisphere: cue contralateral = .62 μV, cue ipsilateral .37 μV, $P = 0.62$).

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These findings highlight sparing of supramodal frontal mechanisms of attentional engagement in all groups of patients.

LDAP

The Group x Cue Direction x Hemisphere interaction was significant ($F_{(2,37)}$ = 3.4, P = 0.04, η_p^2= 0.13) Bonferroni Post-hoc comparisons showed that in C the LDAP was present in both hemispheres (Left hemisphere: cue contralateral = .44 μV, cue ipsilateral = -.18 μV, P = 0.006; Right hemisphere: cue contralateral = .18 μV, cue ipsilateral -.33 μV, P = 0.02), while in N- it was only found over the right hemisphere (Left hemisphere: cue contralateral = .34 μV, cue ipsilateral = .11 μV, P = 0.43; Right hemisphere: cue contralateral = .14 μV, cue ipsilateral = -.43 μV, P = 0.01).

First Half of the Cue Period. The Group x Cue Direction x Hemisphere interaction was significant ($F_{(2,37)}$ = 3.5, P = 0.04, η_p^2= 0.14). Bonferroni Post-hoc comparisons showed that in C the LDAP was present in both hemispheres (Left hemisphere: cue contralateral = .11 μV, cue ipsilateral = -.30 μV, P = 0.0000; Right hemisphere: cue contralateral = .09 μV, cue ipsilateral -.47 μV, P = 0.0001), while in N- it was only found over the right hemisphere (Left hemisphere: cue contralateral = .35 μV, cue ipsilateral = .008 μV, P = 0.26; Right hemisphere: cue contralateral = .61 μV, cue ipsilateral = -.01 μV, P = 0.04). No LDAP was found in N+ (Right hemisphere P = 0.57; Left hemisphere P = 0.17).

Second Half of the Cue Period. The Group x Cue Direction x Hemisphere interaction was significant ($F_{(2,37)}$ = 4.6, P = 0.01, η_p^2= 0.19) and highlighted a bilateral LDAP in the C (Left hemisphere: cue contralateral = -.18 μV, cue ipsilateral = -.71 μV, P = 0.0003; Right hemisphere: cue contralateral = -.70 μV, cue ipsilateral -.01 μV, P = 0.0003) and in the N-

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group (Left hemisphere: cue contralateral = .41 μV, cue ipsilateral = -.34 μV, P = 0.04; Right hemisphere: cue contralateral = .50 μV, cue ipsilateral -.26 μV, P = 0.04). No LDAP was present in N+ (Left hemisphere: cue contralateral = .34 μV, cue ipsilateral = -.28 μV, P = 0.76; Right hemisphere: cue contralateral = .49 μV, cue ipsilateral .26 μV, P = 0.84).

These results suggest preserved setting-up of facilitatory effects in posterior visual areas of both hemispheres in HC and N- patients, though delayed over the left hemisphere in the latter group, and bilateral loss of these facilitatory effects in N+.

*** Insert Figure 3, 4 and 5 about here ***

Target-related ERPs

Grand-average of target-related ERPs in the C, N- and N+ groups are illustrated in Fig. 6, 7, 8 and 9 respectively.

P300

P3a

Latency

No significant main effect or interaction was found in the analysis of latency peaks (All $F < 2$ and all $P > 0.10$).

Amplitude

The triple Group x Trial Type x Target side interaction was significant ($F_{(4,74)} = 6.6$, $P = 0.0001$, $\eta_p^2 = 0.26$). Post-hoc comparisons pointed out that compared to C and N-, N+ had reduced P3a in response to Left Invalid targets (N+ = -1.1 μV, C = 1.6 μV, P = 0.003; N+ = -1.1

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581 μV, N- = 1.1 μV, *P* = 0.01) and increased P3a for Right Invalid target (N+ = 3.1 μV, C = 1.2 μV, *P*
582 = 0.04; N+ = 3.1 μV, N- = .93 μV, *P* = 0.02). No difference was found between C and the N- (all *P*
583 > 0.58). The Target side main effect and the Group x Target side interaction were also
584 significant (Both F > 6.2 and both *P* < 0.004): both of these effects are explained by the
585 increased amplitude of the P3a in response to right Invalid targets in N+ highlighted by the
586 triple Group x Trial Type x Target side interaction (see above and Figure 6). All other main
587 effects and interactions were not significant (All F < 2 and all *P* > 0.13). In line with previous
588 studies run in elderly adults with the Posner task (Curran et al., 2001), in the sample of HC
589 tested in our study the amplitude of the P3a was not enhanced by invalid cuing (though see
590 below significant validity effects for the P3b). Dissociations between P3a amplitude and
591 validity effects in the Posner task were also described in the young children (Flores et al.,
592 2010). All together these results show that changes in the amplitude or latency of the P3, are
593 not necessarily linked to changes in the detection or speed of detection of invalid or other
594 types of attentional targets.
595 These data suggest exaggerated novelty reaction to targets in the right side of
596 space and reduced novelty reaction for those in the left side in N+ patients.
597
598 *P3b*
599 *Latency*
600 The analysis of latency peaks revealed a significant Group x Trial type x Target side
601 interaction ($F_{(4,74)}$ = 3.2, *P* = 0.01, η_p^2= 0.18). This interaction pointed out that, independently
602 of target side, in HC the P3b response to Invalid targets was delayed both as compared to
603 Valid and Neutral targets (Invalid = left 500ms, right 496 ms; Neutral = left 427 ms, right 425
604 ms; Valid = left 424 ms, right 426 ms; all *P* < 0.0001). In contrast, in N- no significant
605 difference in latency peak was found as a function of target type or target side. Finally, in N+

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606 the latency peak of the P3b was anticipated for left Valid targets (384 ms) as compared both
607 to left Neutral (537 ms) and left Invalid (494 ms) targets (all $P < 0.0001$): this effect was
608 superimposed on a general drop in the amplitude of the P3b in response to target in the left
609 side of space (see below). In N+ no difference in latency peak was observed among Valid,
610 Neutral and Invalid targets presented in the right side of space (all $P > 0.11$).
611
612 *Amplitude*
613 A significant Group x Target Side interaction was found ($F_{(2,37)} = 3.8$, $P = 0.03$, $\eta_p^2 =$
614 0.17). Bonferroni post-hoc comparisons showed that in N+ the amplitude of the P3b was
615 reduced in response to targets in the left side of space as compared to those in the right side
616 (Left =1.9 μV, Right 3.3 μV, $P = 0.005$). No comparable difference was observed in HC and N-
617 (all $P > 0.46$). The Group x Trial type interaction was also significant ($F_{(4,74)} = 2.9$, $P = 0.04$, $\eta_p^2 =$
618 0.13). This showed that the amplitude of the P3b was higher for Invalid as compared to Valid
619 and Neutral trials in HC (Invalid = 4.6 μV vs. Valid = 3.4 μV, $P = 0.005$; Invalid = 4.6 μV vs.
620 Neutral = 3.4 μV, $P = 0.02$; see Fig. 7). The same difference was not observed in N- and N+
621 groups (all $P > 0.33$). All others main effects and interactions were not significant (All $F < 2.3$
622 and all $P > 0.19$).
623 These results suggest that N+ suffer defective processing and updating of the
624 probabilistic occurrence of behaviourally relevant sensory events in the left side of space.
625
626 *** Insert Figure 6 and 7 about here ***
627
628 ***Early target related components (P1 and N1)***
629 *P1*
630 *Latency*

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In line with the results of previous studies (Slagter et al., 2016; Lasaponara et al., 2017), a significant Group x Target Side x Hemisphere triple interaction ($F_{(2,37)}$ = 57.2, P = 0.0000, η_p^2= 0.75) highlighted that when targets were presented in the right side of space, the P1 recorded over the ipsilateral right hemisphere was delayed by about 45-50 ms with respect to the P1 recorded over the left hemisphere (all P-values = 0.0000). This result was present in all experimental groups (see Fig. 8). In contrast, when targets were presented in the left side of space, the P1 recorded over the ipsilateral left hemisphere was delayed, with respect to its contralateral counterpart, by 45-50 ms in HC and N- (all P-values = 0.0000) though not in N+. In N+, a reversed latency pattern was found so that the P1 recorded over the contralateral right hemisphere followed by about 60 ms, rather than anticipated, the P1 recorded over the ipsilateral left hemisphere (197 ms vs. 135 ms; P = 0.0000). In N+ the latency of this contralateral P1 was also significantly longer than in HC (197 ms vs. 120 ms; P = 0.0000) and N- (197 ms vs. 114 ms; P = 0.0000).

Amplitude

A significant Group x Target Side x Hemisphere triple interaction ($F_{(2,37)}$ = 7.1 P = 0.002, η_p^2= 0.27) showed that in all groups, targets presented in the right side of space evoked larger P1 amplitude over the ipsilateral right than over the contralateral left hemisphere (all P-values < 0.01). When targets were presented in the left side of space, in HC the amplitude of the P1 was higher over the ipsilateral hemisphere (ipsilateral P1: .57 μV vs. contralateral P1: .27 μV, P = 0.01) while no significant difference between ipsilateral and contralateral P1 amplitude was found in N- (ipsilateral P1: .23 μV vs. contralateral P1: .34 μV, P = 0.37). In N+ the amplitude pattern was reversed and a larger P1 was found over the contralateral right hemisphere when targets were presented in the left side of space (ipsilateral P1: .22 μV vs. contralateral P1: .64 μV, P = 0.003).

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This set of analyses show that N+ suffer reduced inhibition of sensory processing in the right space when targets occur in the left one.

Valid minus Invalid difference waves (sensory gain).

T-tests revealed that independently of Target side and Hemisphere, in HC the amplitude of the differential P1 waveform between Valid and Invalid targets was significantly different from zero, (all $t_{(14)} > 4.8$, all $P < 0.0002$). This shows conventional sensory gain in HC. In N- differential waveforms were significantly different from zero only for right targets (both $t_{(12)} > 2.8$, all $P < 0.01$) while in N+ no sensory gain was found for the P1 evoked by left or right targets (all $t_{(11)} < 0.76$, all $P > 0.45$). When individual differential waveforms were entered in a Group (C, N-, N+) x Target Side (Left, Right) x Hemisphere (Ipsilateral,Contralateral) repeated-measures ANOVA, a significant Group x Target Side interaction ($F_{(2,37)} = 4.9$ $P = 0.01$, $\eta_p^2 = 0.20$) showed higher sensory gain in HC as compared to both N- and N+ in response to left targets (HC = 0.41μV vs. N- = 0.03 μV, $P = 0.0008$; HC = 0.41 μV vs. N+ = 0.06 μV, $P = 0.002$). No difference was found for left tragets between N- and N+ (N- = 0.03 μV vs. N+ = 0.06 μV, $P = 0.79$). For right targets, sensory gain was higher in HC as compared to N+ (HC = 0.38 μV vs. N+ = 0.14 μV, $P = 0.03$), though no difference was found between HC and N- (HC = 0.38 μV vs. N- = 0.45 μV, $P = 0.47$). For right targets N- showed higher sensory gain than N+ (N- = 0.45 μV vs. N+ = 0.14 μV, $P = 0.008$). No effect of attentional cuing was found in the latency peaks of the P1 component (All $F < 2.6$ and all $P > 0.12$).

N1

Latency

A significant Group x Target Side interaction ($F_{(2,37)} = 9.4$, $P = 0.0004$, $\eta_p^2 = 0.33$) pointed out that in HC there was no latency difference between the N1 evoked by targets in the left or

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the right side of space (Left target: 202.4 ms vs. Right target: 209 ms, $P = 0.50$). In contrast, in N- the N1 evoked by targets in the right side of space was slightly delayed as compared to that evoked by targets in the left side (Left target: 192.8 ms vs. Right target: 226.7 ms, $P = 0.02$). In N+, the N1 was found only over the left hemisphere in response to targets presented in the right side of space. The latency of this N1, 215 ms, was equivalent to those found in HC and N-.

Amplitude

A significant Group effect ($F_{(2,37)} = 15.8$, $P = 0.0001$, $\eta_p^2 = 0.46$) showed that the N1 was larger in HC as compared to both N- and N+ (all *P*-values < 0.001). No negative peak was found in the N1 latency time window in N+.

Valid minus Invalid difference waves (sensory gain).

In HC, the amplitude of the differential waveform between Valid and Invalid targets was significantly different from zero, independently of target side (both $t_{(14)} > -6.1$, all $P < 0.0001$). In N- differential waveforms were significantly different from zero only in response to right targets ($t_{(12)} > -15.3$, all $P < 0.0000$). No significant differential waveforms were found in N+ (both $t_{(11)} < 1.8$, both $P > 0.1$). When individual differential waveforms were entered in a Group (C, N-, N+) x Target Side (Left, Right) repeated-measures ANOVA, a significant Group x Target Side interaction ($F_{(2,37)} = 3.3$ $P = 0.04$, $\eta_p^2 = 0.15$) showed larger differential waveforms in HC as compared to both N- and N+ in response to left targets (HC = -1.1 μV vs. N- = -0.03 μV, $P = 0.000$; HC = -1.1 μV vs. N+ = 0.32 μV, $P = 0.000$). No significant difference was found between N- and N+ (N- = -0.03 μV vs. N+ = 0.32 μV, $P = 0.06$). Also in the case of right targets, differential waveforms were larger in HC as compared to both N+ (HC = -1.5 μV vs. N+ = 0.18 μV, $P = 0.000$) and N- (HC = 1.5 μV vs. N- = -0.93 μV, $P = 0.0008$). Nonetheless, at variance with left targets, N- showed larger differential waveforms in response to right targets as compared

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706 to N+ (N- = -0.93 μV vs. N+ = 0.18 μV, $P = 0.000$). Valid attentional cuing produced no change
707 in the latency peaks of the N1 component (All $F < 1$ and all $P > 0.35$).
708
709 *** Insert Figure 8 and 9 about here ***
710
711 *Caveats on the interpretation of ERPs findings in brain damaged patients.*
712 A full interpretation of ERPs modifications after brain damage would imply
713 establishing the roles played by the anatomical/functional disruption of ERPs neural sources
714 and/or by the altered propagation of normally generated EEG signals through the damaged
715 neural tissue. This is a largely open issue. A few modelling studies (see Cohen et al., 2015)
716 have suggested that ischemic stroke should induce higher resistivity in damaged neural tissue
717 resulting in higher potentials in the damaged compared to the healthy hemisphere.
718 Haemorrhagic strokes should induce lower resistivity in the damaged tissue and lower
719 potential in the damaged hemisphere. In addition, it is also important to note that although
720 some cortical areas play a primary role in the production of specific ERPs components, most
721 components arise from the joint activation of multiple secondary cortical sources (see Linden
722 et al., 2005). Thus a cautious interpretation of defective ERPs components in our sample of
723 patients is that brain damage modified specific ERPs components either by disrupting,
724 anatomically or functionally, the activity of their corresponding main generators and/or by
725 disturbing the coordinate activation of multiple ERPs sources. For exploratory purposes,
726 based on available reviews of the literature, we have superimposed the coordinates of the
727 sources of the different ERPs components examined in the present study, on the lesion maps
728 of N- and N+ participants. The only potentially relevant finding of this purely exploratory
729 investigation is that the portion of the insular cortex that participate as a secondary source in
730 the generation of the P3A (Bledowsky et al., 2004) was lesioned in 55% of N+ patients while

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no lesion involvement was found in N-. In contrast, in both groups there was an equal 20% lesion involvement of the inferior parietal generators of the P3B, despite larger disruption of the P3B response to left targets in N+, and an equivalent 10% lesion involvement of precentral areas participating in the generation of the ADAN (Praamstra et al., 2005) that was maintained in both groups. These preliminary observations suggest that both direct damage of cortical ERPs sources and disturbed interaction among different cortical areas should be considered in interpreting alterations of ERPs after brain damage.

Discussion

Preparatory orienting of attention: cue-related responses

The first new finding of our study is that during preparatory voluntary orienting of attention N+ patients show normal ADAN over frontal derivations in both hemispheres together with a complete bilateral drop of the LDAP over posterior occipital derivations. ERPs studies have pointed out that the ADAN develops independently of sensory modality, thus marking an amodal mechanism of attention. In contrast, the LDAP develops in response to visual stimuli or to the use of visual references (Eimer, 2014): this is suggested by the absence of the LDAP in congenitally blind participants (Van Velzen *et al.,* 2006) and during tactile attention tasks (Gherri *et al.,* 2016). Our data show that amodal preparatory attentional engagement is preserved in N+ though this is not followed by the setting-up of corresponding facilitatory effects in posterior visual areas. This dissociation sheds light on the functional basis of dissociations that past investigations in neglect have documented both in the study of reflexive and voluntary orienting and in the effects of different rehabilitation protocols. Several authors have argued that compared to deficits in reflexive orienting, N+ would have relatively spared voluntary orienting of attention that can be exploited for rehabilitation (for review, see Bartolomeo and Chokron, 2002; Natale *et al.,* 2005). Marzi and co-workers (Natale

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et al., 2005) offered a more articulated view of this by showing that when targets are presented at a fixed position in left space, so as to favour the exploitation of such regularity and the voluntary focusing of attention at this position, N+ show faster RTs to detected targets though no change in the frequency of hits and misses when compared to targets presented at variable positions. These authors concluded that although voluntary orienting of attention can be relatively preserved in neglect patients, this produces no effect on their basic reflexive visual spatial deficits. The ADAN/LDAP dissociation that we have documented in our study clarifies the functional basis of the findings by Marzi and co-workers and supports their conclusions. Sturm and co-workers (Sturm *et al.,* 2006; Thimm *et al.,* 2006; Thimm *et al.,* 2008) have demonstrated that while neglect rehabilitation through visual optokinetic stimulation produces a significant enhancement of the BOLD response in posterior visual areas, i.e. cuneus, rehabilitation focused on the voluntary management of attention enhances activation in frontal areas with no equivalent effects on posterior visual ones. Our results highlight a similar functional independence between frontal and posterior components of attentional orienting and suggest that rehabilitation of voluntary attention in N+ might be ineffective unless associated with sensory stimulation boosting the response of posterior attentional visual areas. N+ also showed a bilateral drop of the EDAN: this finding could highlight a general slowing of attentional reactivity in lateral orienting (Harter et al., 1989; Nobre et al., 2000) or in the selection and analysis of task-relevant features in central cues (vanVelzen & Eimer, 2003). The bilateral drop of the EDAN is in line with the presence of non-spatially lateralised deficit of attention in spatial neglect (Husain *et al.,* 1997). To summarise, concomitant preservation of the ADAN and suppression of the EDAN and LDAP in spatial neglect suggests relevant functional independence among anterior and posterior preparatory components of attention that are related to the use of central spatial cues. Current studies in healthy participants point out that the ADAN can develop without the ensuing development of

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781 the LDAP (Gherri *et al.,* 2016) but whether a normal development of the LDAP over the
782 posterior extrastriate cortex must be necessarily preceded by the ADAN, remains to be
783 explored.

784 Interestingly, N- patients showed normal bilateral ADAN and LDAP, although over the
785 left hemisphere the onset of the LDAP was delayed to the second part of the cue period. One
786 plausible interpretation of the faster development of the LDAP over the damaged hemisphere
787 is that it reflected compensatory mechanism counteracting residual contralesional attentional
788 deficits. In N-, these residual deficits were evident both during the processing of central cues,
789 when a drop of the EDAN over the right hemisphere was present, and at the moment of target
790 detection when N- showed a higher number of left target omissions as compared to healthy
791 controls.

792 Anatomical findings confirmed the role of parietal-frontal white matter disconnection
793 in the pathogenesis of spatial neglect (Doricchi and Tomaiuolo, 2003; Thiebaut de Schotten et
794 al., 2005; Verdon et al., 2009). Poor parietal-frontal connectivity can probably account for the
795 ADAN/ LDAP and ADAN/EDAN uncouplings that we have specifically highlighted in N+. In
796 addition, hypoactivation of subcortical structures adjacent to the damage like the pulvinar,
797 might also contribute to reduced attentional modulation of preparatory responses in the
798 visual areas (Green et al., 2017).

799

800 *Target related responses: late attentional processing and contextual updating*

801 In N+ the P3a recorded over frontal derivations was abnormally reduced in response
802 to infrequent invalid targets in the left side of space and abnormally enhanced in response to
803 equivalent targets in the right side. At variance with the P3a, the P3b component was reduced
804 for all types of targets presented in the left side of space though not enhanced for those in the
805 right side of space. This shows that N+ suffer down-regulation of novelty detection (P3a) and

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806 contextual updating (P3b) for events in the left side of space and up-regulation of novelty
807 detection with normal contextual updating for events in the right side. This deficits might
808 importantly contribute to the reduced interest of N+ for events in the contralesional space
809 and suggest the importance of investigating further whether N+ can learn and exploit
810 contextual contingencies that govern the distribution in space of behavioural targets
811 (Bartolomeo *et al.,* 2001; Geng and Behrmann, 2002) and rewards (Malhotra *et al.,* 2013;
812 Lecce *et al.,* 2015).

813 Concomitant down-regulation of the P3a in response to left targets and up-regulation
814 in response to right ones suggests push-pull inter-hemisheric competition while in the case of
815 the P3b only selective contralesional down-regulation was found. Differences in competitive
816 hemispheric processing might be rooted in different patterns of inter-hemispheric
817 connectivity, though available anatomical evidence does not yet provide sufficient evidence in
818 favour of this conclusion (Catani and Thiebaut de Schotten, 2012; Caminiti et al., 2013; Joliot
819 *et al.,* 2015). Different spatial preferences of the cortical areas implicated in the generation of
820 the P3a and P3b might also contribute to different types of inter-hemispheric competition. In
821 humans, the right IFG-MFG is sensitive to the novelty of invalidly cued targets though no
822 lateral spatial preference is currently reported in this area (Shulman *et al.,* 2009; Doricchi *et*
823 *al.,* 2010). In contrast, we have recently demonstrated that the left TPJ responds preferentially
824 to invalid targets in the right side of space (Dragone *et al.,* 2015; Silvetti *et al.,* 2016). This
825 spatial preference might determine the selective down regulation of the P3b response to
826 targets in the left side of space after right brain damage. Down-regulation of
827 electrophysiological responses mediated by the frontal lobes, i.e. P3a, to contralesional stimuli
828 and up-regulation of responses to ipsilesional ones is also in line with a number of previous
829 observations. Vuilleumier *et al.* (1996) have described sudden remission of left spatial neglect
830 due to an initial right parietal stroke when a second stroke in the frontal area of the left

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hemisphere reduced the ipsilesional bias caused by the first stroke. Reduction of ipsilesional hyperattention in neglect is also produced by TMS inactivation of the left frontal cortex (Olivieri et *al.,* 1999). More recently, Rastelli *et al.* (2013) showed that in patients with left spatial neglect omissions of visual targets in the left side of space is systematically anticipated by up-regulated synchronization of beta MEG activity over frontal areas in the left hemisphere. The results of our study expand on this evidence and show that inter-hemispheric push-pull competitive mechanisms also affect the late phases of attentional processing reflected in P3a and P3b responses.

Target related responses: early attentional processing and the P1-related inhibition of the unstimulated side of space

Comparisons between P1 and N1 components evoked by valid and invalid targets, demonstrated bilateral loss of sensory gain produced by valid cuing in N+ and loss of sensory gain for targets appearing in the left side of space in N-. It is interesting to note that in N+ bilateral drop of sensory gain was matched with bilateral drop of cue-related preparatory EDAN and LDAP components over posterior visual areas, while in N- preserved gain for targets in the right side of space was matched with preserved EDAN and LDAP over the left hemisphere. In contrast, in N- loss of sensory gain for targets in the left side of space was matched with preserved LDAP and loss of EDAN on the right hemisphere. Whether this finding suggests that normal development of sensory gain in the processing of visual targets depends on maintenance of both EDAN and LDAP preparatory components remains matter for future investigations.

Like in previous studies (Verleger et al., 1996; Deouell et al., 2000; Di Russo et al. 2007), in N+ we found suppression of the N1 and preservation of the P1 component evoked by left side targets over the right hemisphere. In line with the data by Slagter and co-workers

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(2016), in healthy controls the P1 appeared first over the hemisphere contralateral to the target and then in that ipsilateral to the target where it displayed greater amplitude. In contrast, in N+ the hemispheric distribution in the amplitude and latency of the P1 evoked by left side targets was entirely altered. In this case the P1 evoked over the ipsilateral left hemisphere was smaller, rather than larger, and anticipated, rather than followed, the P1 recorded over the contralateral right hemisphere. This finding points out concomitant delayed response to validly cued targets in contralesional left side of space and poor target-related inhibition in the sensory processing of the unstimulated ipsilesional right side. This pattern in the hemispheric distribution of the P1 response identifies a new electrophysiological marker of hyperattention for the right side of space in spatial neglect and shows further that voluntary engagement of attention does not entirely counteract basic deficits in the automatic processing of contralesional targets (Natale *et al.,* 2005; see also Bartolomeo et al., 2001). The reduction in the amplitude of the P1 evoked over the left hemisphere by left side targets was also matched with a relative reduction of its latency and with a relative increase in the latency of the P1 over the right hemisphere. Future studies should clarify whether these changes in the latency of P1 are linked to pathological changes in callosal connectivity (see Slagter *et al.,* 2016; Lasaponara *et al.,* 2017), which can be anatomically and functionally disrupted in neglect patients (Lunven *et al.,* 2015). In line with our findings, in a recent ERPs study Martin Arevalo et al. (2016) demonstrated that in healthy humans adaptation to leftward-deviating prismatic lenses produces left spatial neglect-like behaviours together with a reduction in the amplitude of the left hemispheric P1 response to left side targets.

In conclusion, the results of our study provide new insights on the attentional impairments suffered by N+ and suggest that in the healthy brain the components of

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880 preparatory attention mediated by frontal and parietal-occipital areas have a degree of
881 functional independency.
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Figures and Tables captions.

Table 1. Clinical and demographic group data of right brain damaged patients with left spatial neglect (N+), without left spatial neglect (N-) and healthy controls (HC*).*

Figure 1: (**A**) Overlay of lesions in RBD patients without left spatial neglect (N−), with left spatial neglect (N+) and lesion probability maps resulting from the N+ minus N- subtraction (range of 5-80% or 50-80%). Areas of maximal lesion overlap resulting from the subtraction (differential overlap = 78%) are highlighted by numbered red circles. (**B**) Anatomical details of areas of maximal lesion overlap numbered in panel A. 1: frontal operculum (MNI coordinates: 30, 26, 8); 2: anterior segment (purple) of the Arcuate Fasciculus (red) (MNI coordinates: 34, -19, 22); 3: Posterior sector of the Superior Temporal Gyrus - Planum temporale (MNI coordinates 45, -32, 9; 44, -28, 4; 43, -22, -1; 42, -24, 10.); Posterior segment (orange) of the Arcuate Fasciculus (red) and Inferior Longitudinal Fasciculus (blue) (MNI coordinates 38, -35, 11 and 35, -36, 12).

Figure 2: (**A**) Time course of events during Directional (Valid, Invalid), Non-directional (Neutral) and Catch experimental trials. Duration of events is reported in ms. (**B**) Behavioural performance of healthy controls (HC; blue), RBD patients with left spatial neglect (N+; green) and patients without neglect (N−; red) in the Posner task: average percentages of omissions with Valid, Neutral and Invalid targets. Uncorrected average RTs to Valid, Neutral and Invalid targets (see Methods, analysis “a”); corrected average RTs to Valid, Neutral and Invalid targets (omissions are replaced with maximal time allowed for response = 2000 ms; see Methods, analysis “b”). Bars indicate S.E.

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Figure 3: (**A**) Cue-related ERPs components recorded in Healthy Controls (HC) during directional trials with arrow-cues pointing to the left (black line) or the right (red line). ERPs recorded over the left and the right hemisphere, are reported separately for the anterior, occipital and posterior pools of derivations (see Methods). Conventional time windows used for the analysis of lateralized responses associated to attentional orienting (i.e. EDAN, ADAN and LDAP) are highlighted by grey squares (full squares = significant difference between ipsilateral and contralateral waveforms; empty squares = non-significant difference). Horizontal bars below the ADAN and LDAP highlight the first and second half of the cue period (see Methods). Asterisks indicate a significant difference between ipsilateral and contralateral waveforms in the corresponding half of the cue period (**B**) Scalp topographic maps representing the amplitude of differential "Cue-Right minus Cue-Left" waveforms.

Figure 4: (**A**) Cue-related ERPs components recorded in RBD patients without left spatial neglect (N-) during directional trials with arrow-cues pointing to the left (black line) or the right (red line). (**B**) Scalp topographic maps representing the amplitude of differential "Cue-Right minus Cue-Left" waveforms.

Figure 5: (**A**) Cue-related ERPs components recorded in RBD patients with left spatial neglect (N+) during directional trials with arrow-cues pointing to the left (black line) or the right (red line). (**B**) Scalp topographic maps representing the amplitude of differential "Cue-Right minus Cue-Left" waveforms.

Figure 6: (**A**) Mean amplitude of the P3a response to left and right Valid, Neutral and Invalid targets in the three experimental groups (HC, N-, N+); Bars indicate S.E. (**B**) Grand-average of target-related ERPs in response to Invalid targets presented in the left (black) and in the right

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(red) side of space in the three experimental groups (HC, N-, N+). Time windows used for analyses are highlighted by grey squares (full squares = significant difference; empty squares = non-significant difference). (**C**) Mean amplitude of P3b response to left and right targets in the three experimental groups (HC, N-, N+); Bars indicate S.E. (**D**) Grand-average of P3b responses to targets presented in the left (black) and in the right (red) side of space in the three experimental groups (HC, N-, N+). Time windows used for analyses are highlighted by grey squares (full squares = significant difference; empty squares = non-significant difference).

Figure 7: (**A**) Mean amplitude of the P3b response to left and right Valid, Neutral and Invalid targets in the three experimental groups (HC, N-, N+); Bars indicate S.E. (**B**) Grand-average of target-related ERPs in response to Valid (black), Neutral (dashed blue) and Invalid (red) targets presented in the left and in the right side of space in the three experimental groups (HC, N-, N+). Time windows used for analyses are highlighted by grey squares (full squares = significant difference; empty squares = non-significant difference). Vertical bars represent latency peaks estimated through the semi-automatic peak detection algorithm (see Methods).

Figure 8. Grand-average of early P1 and N1components recorded over the left and over the right hemisphere in response to ipsilateral (red) or contralateral (black) left and right targets. Top panel Healthy Controls, middle panel RBD patients without left spatial neglect (N-), bottom panel RBD patients with left spatial neglect (N+). Note that, at variance with the other groups, in N+ the P1 recorded over the contralateral right hemisphere in response to left targets (bottom left panel) follows, rather than foregoes, the P1 recorded over the ipsilateral left hemisphere.

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Figure 9. (**A**) Mean Valid > Invalid differential amplitude and relative scalp topographies, of the P1 component evoked by the Left and the Right targets over the ipsilateral and contralateral hemisphere in the healthy controls (HC; blue), RBD patients with left spatial neglect (N+; green) and patients without neglect (N−; red). Bars indicate S.E. (**B**) Mean Valid > Invalid differential amplitude and relative scalp topographies, of the N1 component evoked by the Left and the Right targets over the contralateral hemisphere in the healthy controls (HC; blue), RBD patients with left spatial neglect (N+; green) and patients without neglect (N−; red). Bars indicate S.E.

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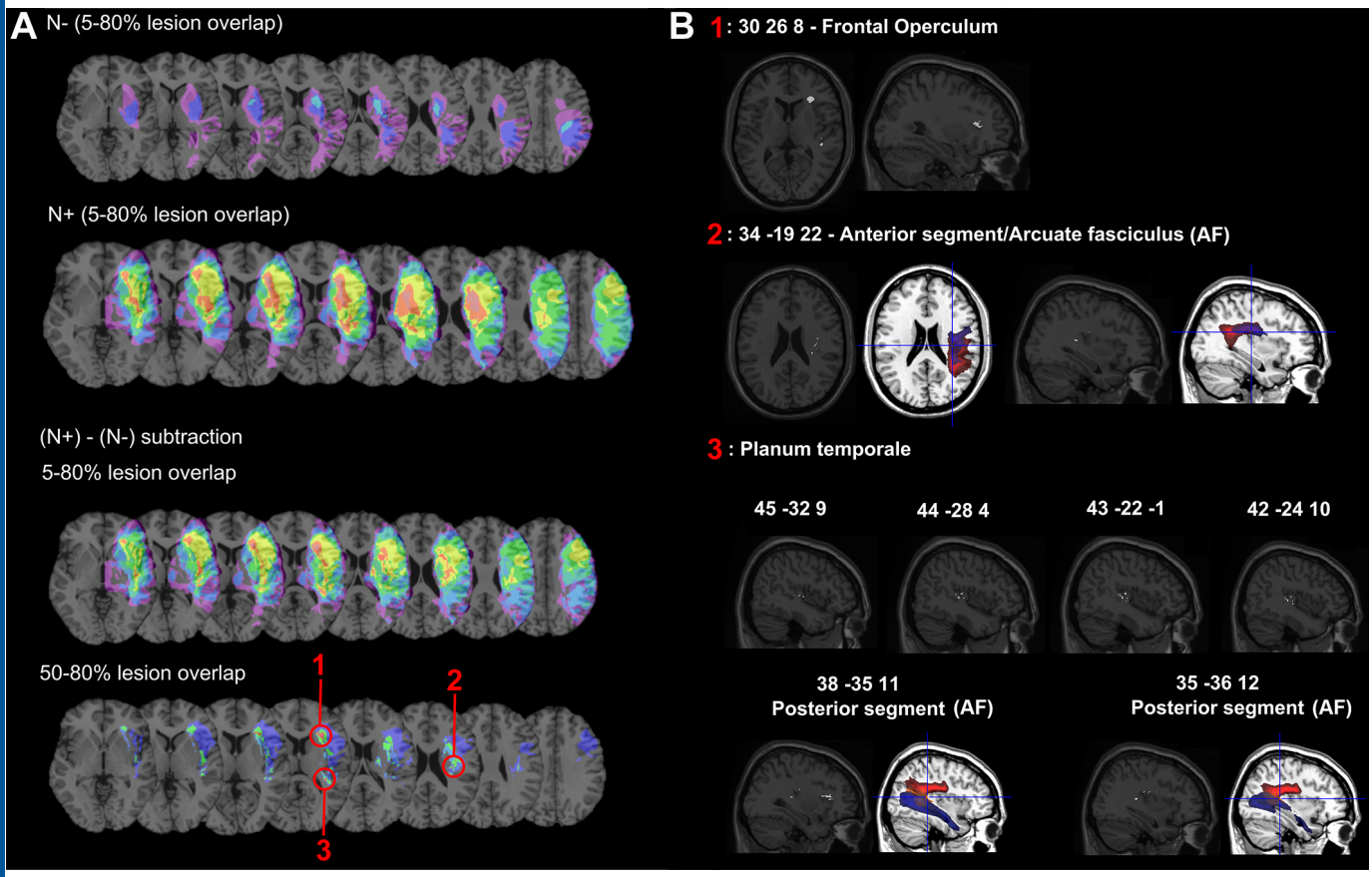

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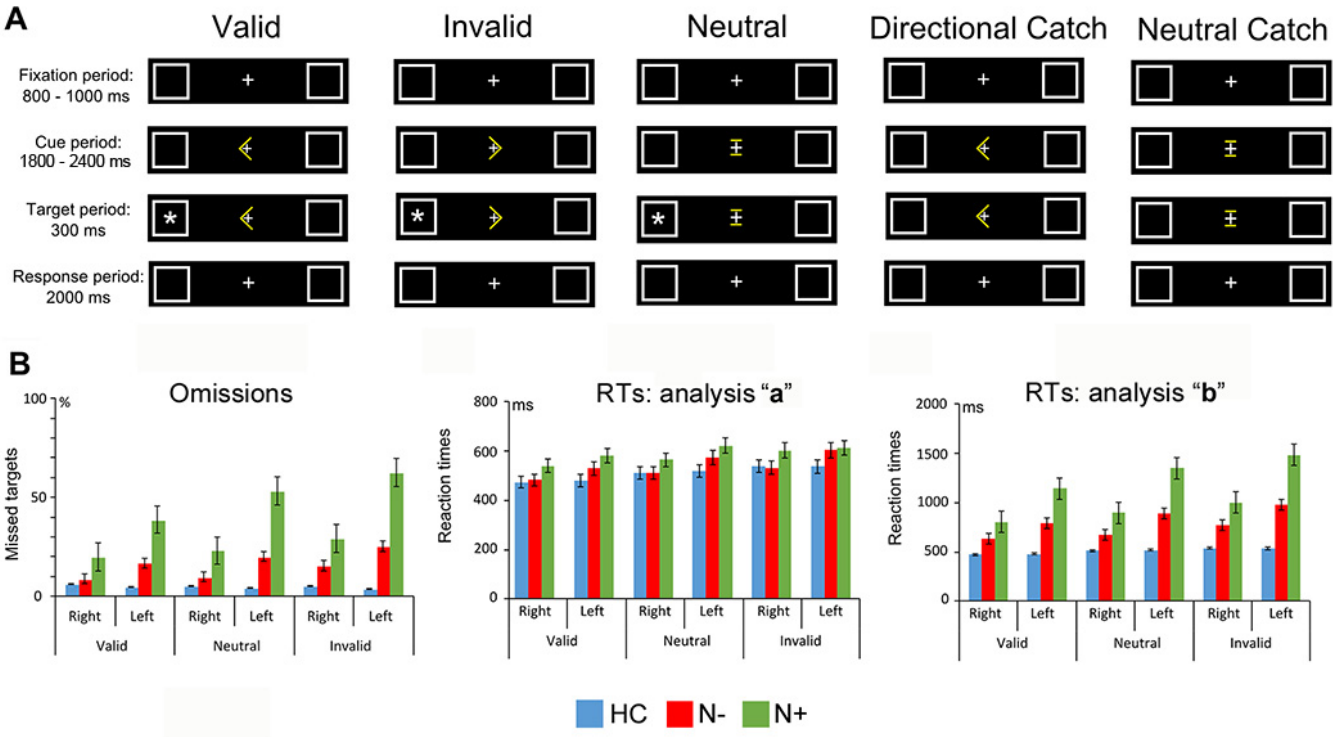

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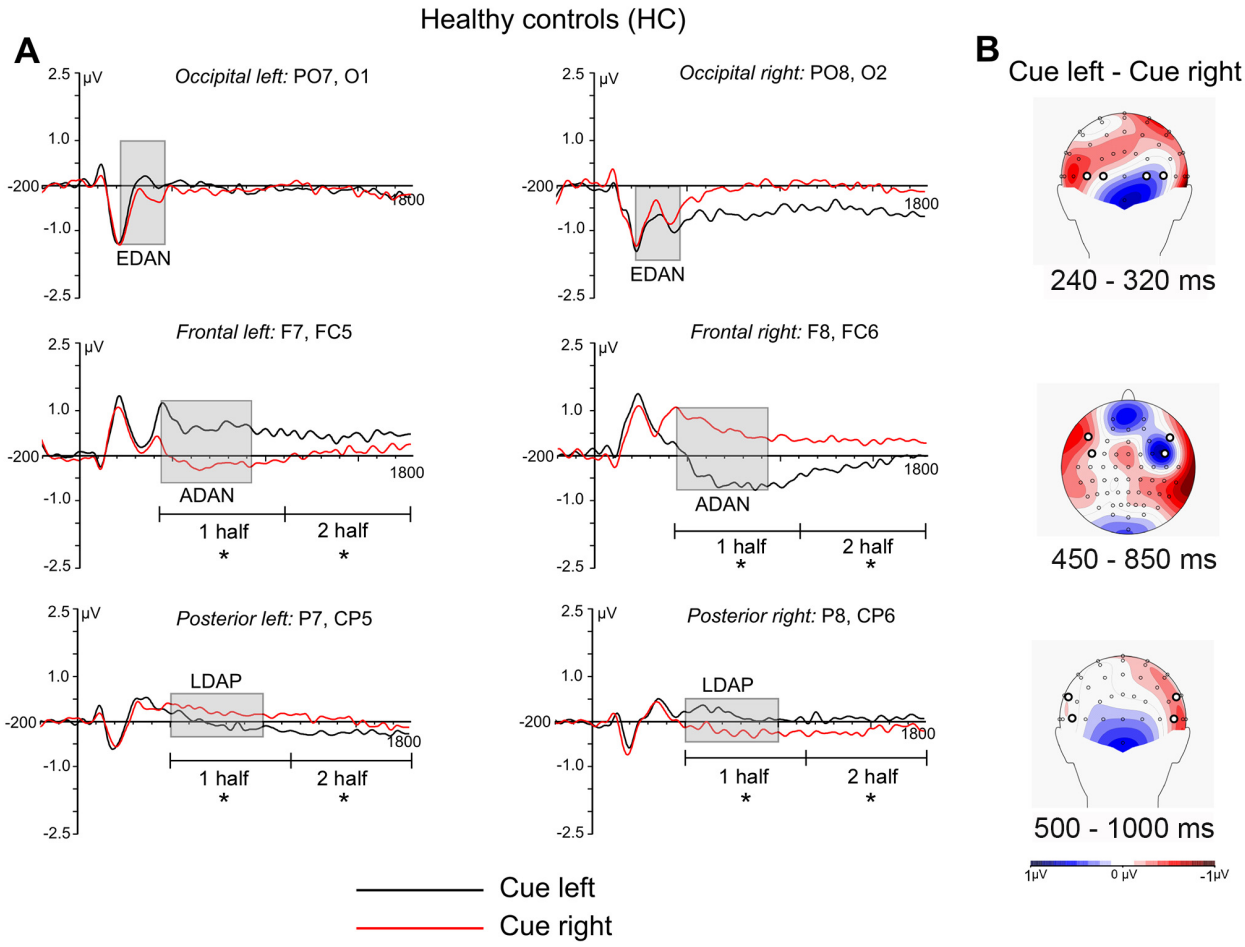

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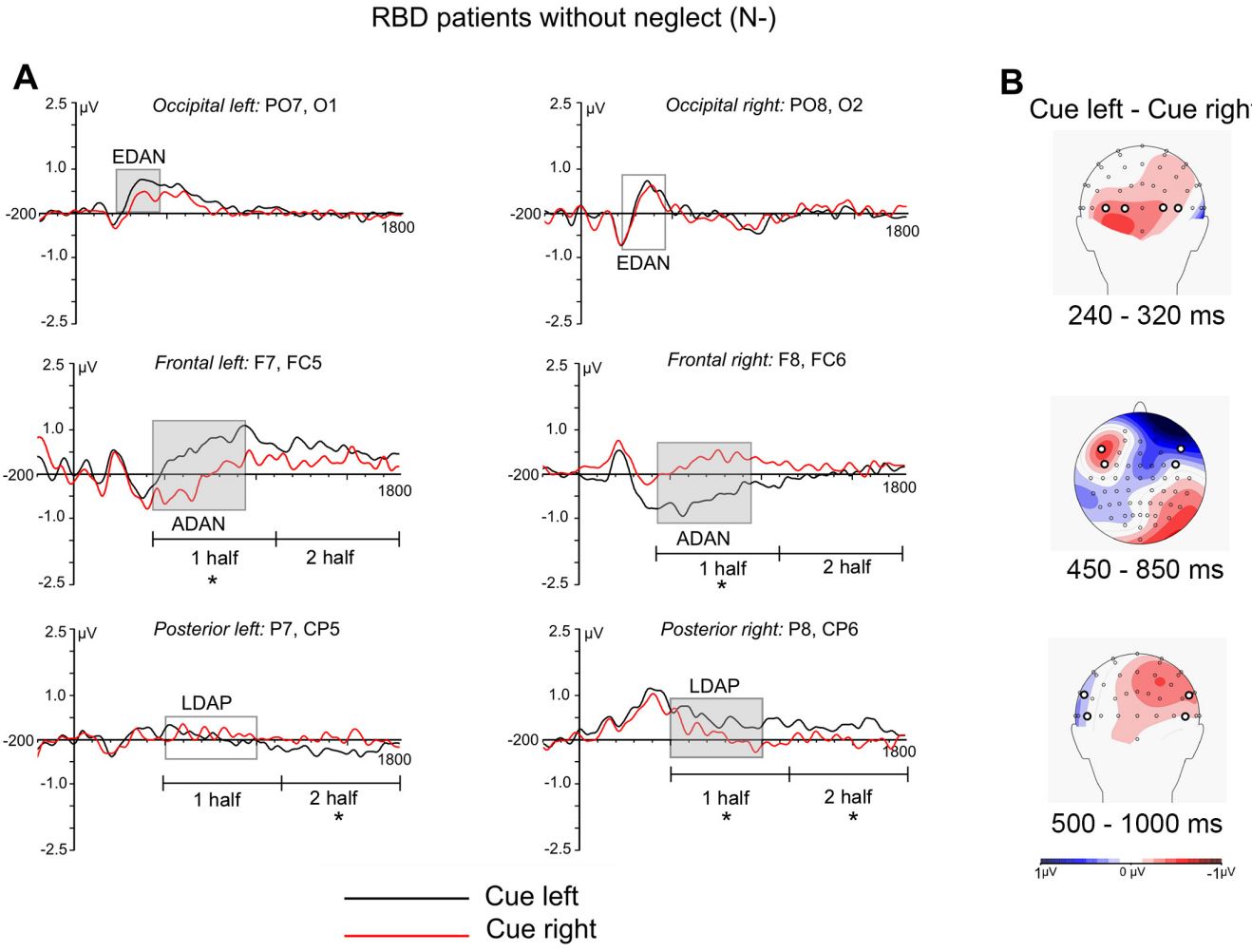

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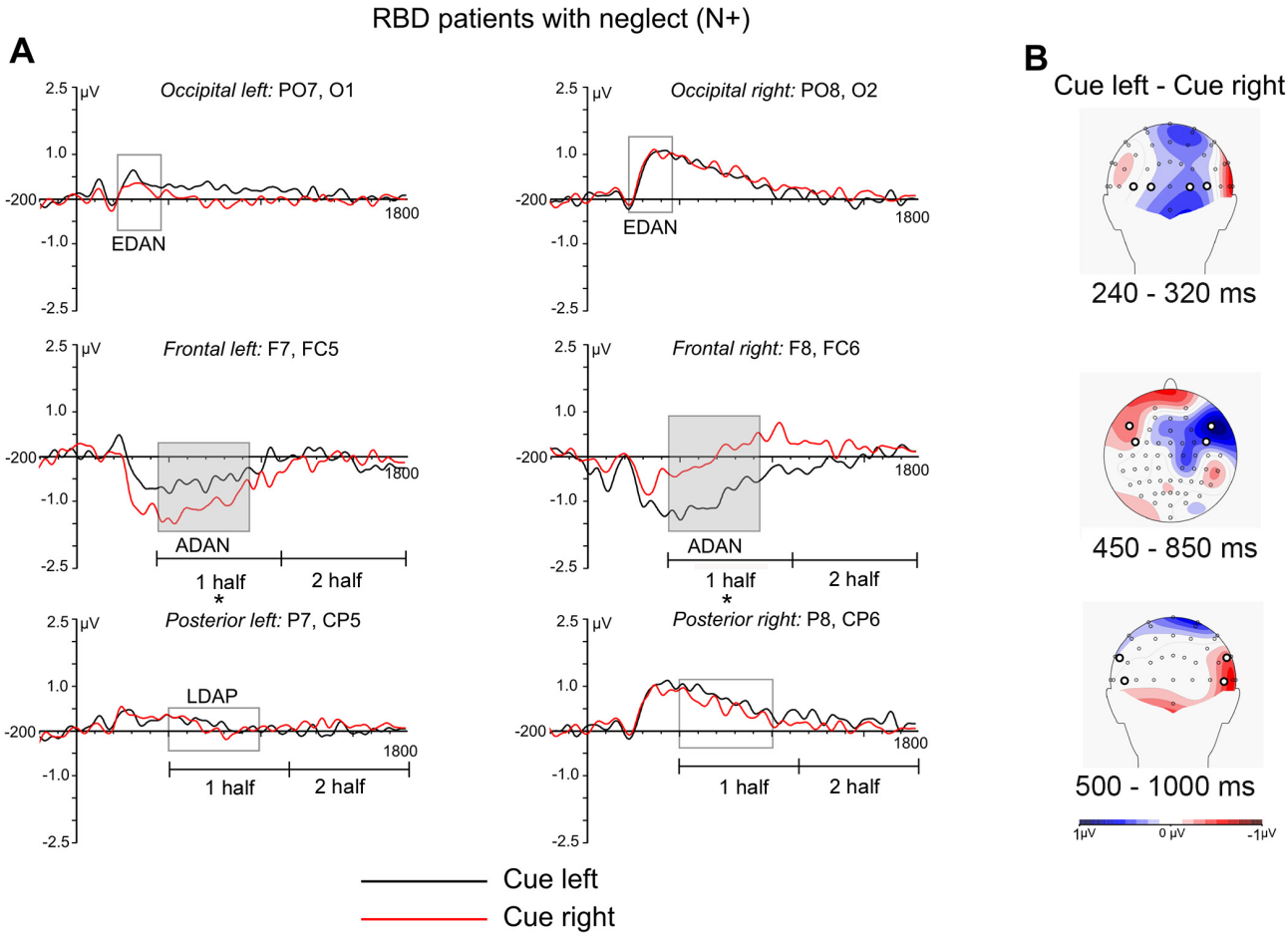

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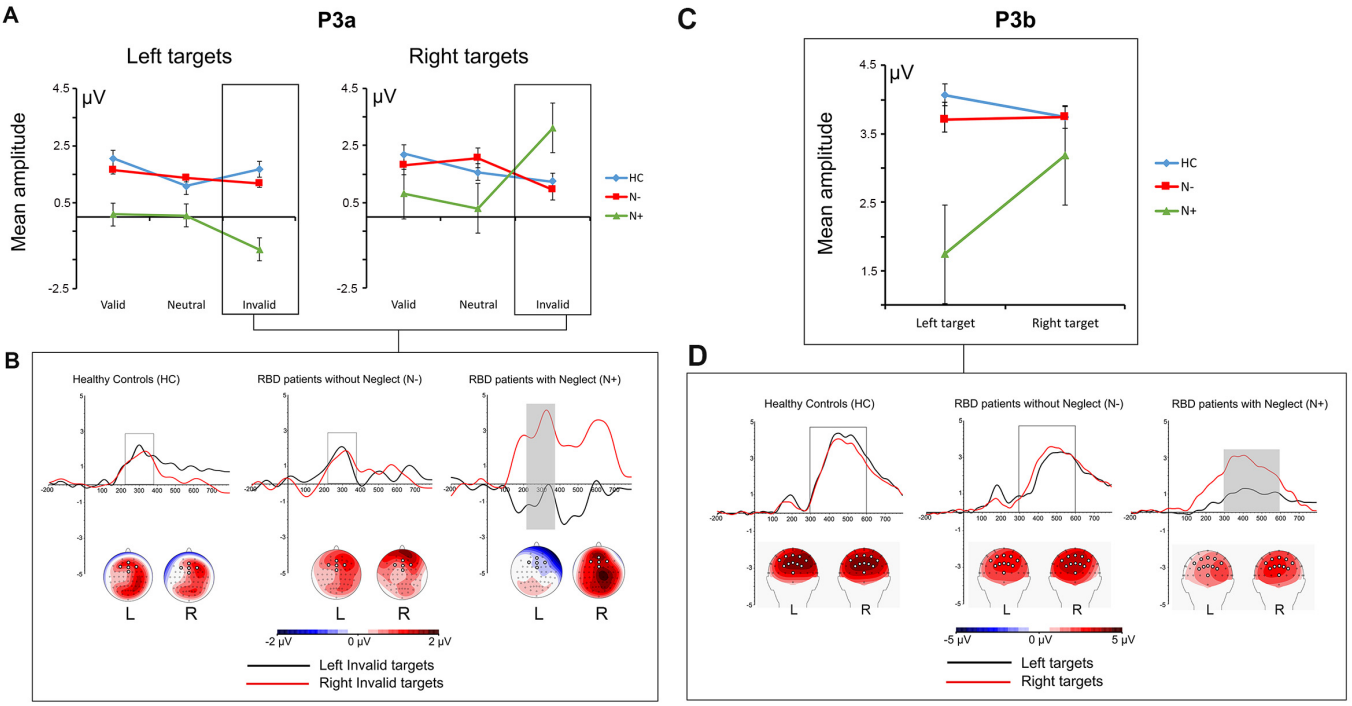

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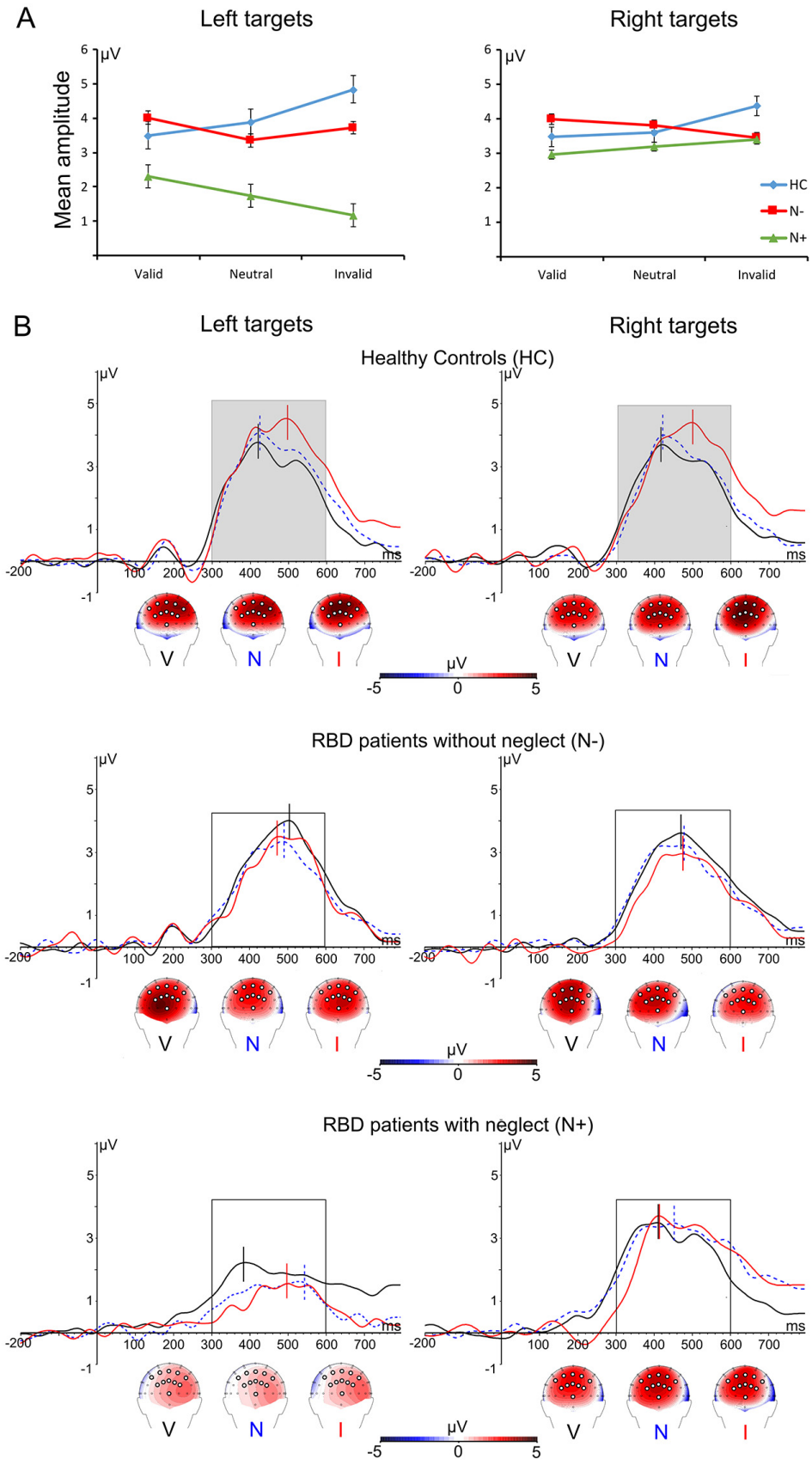

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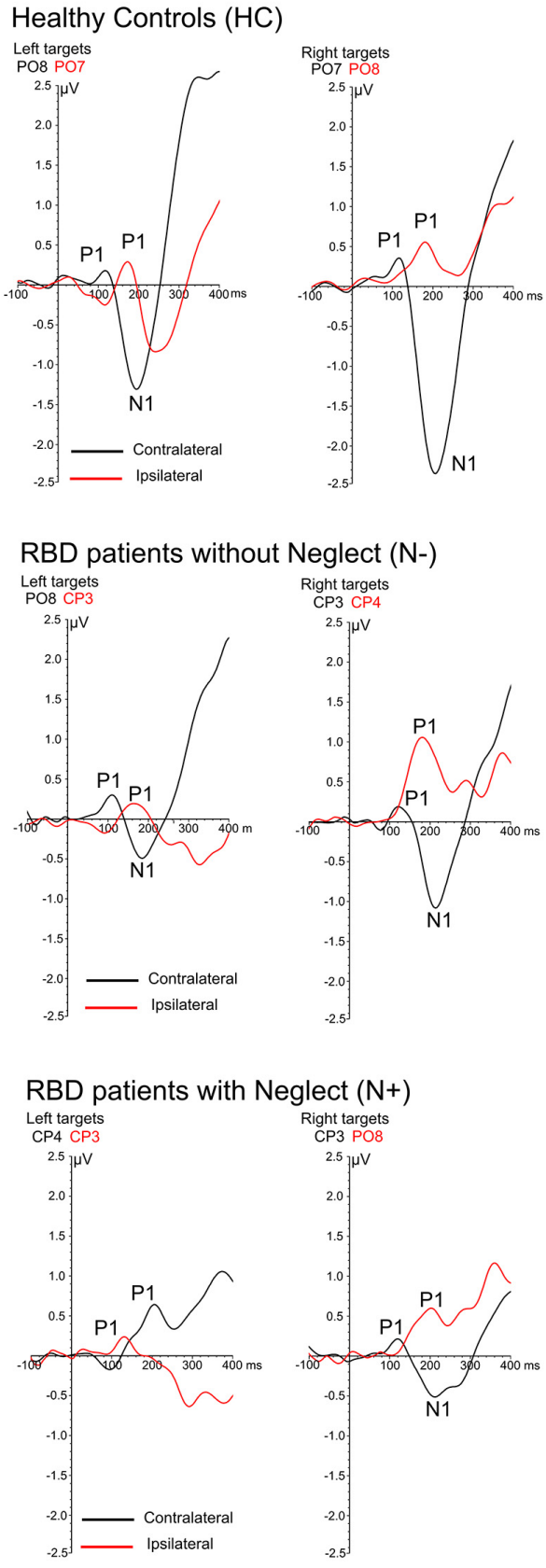

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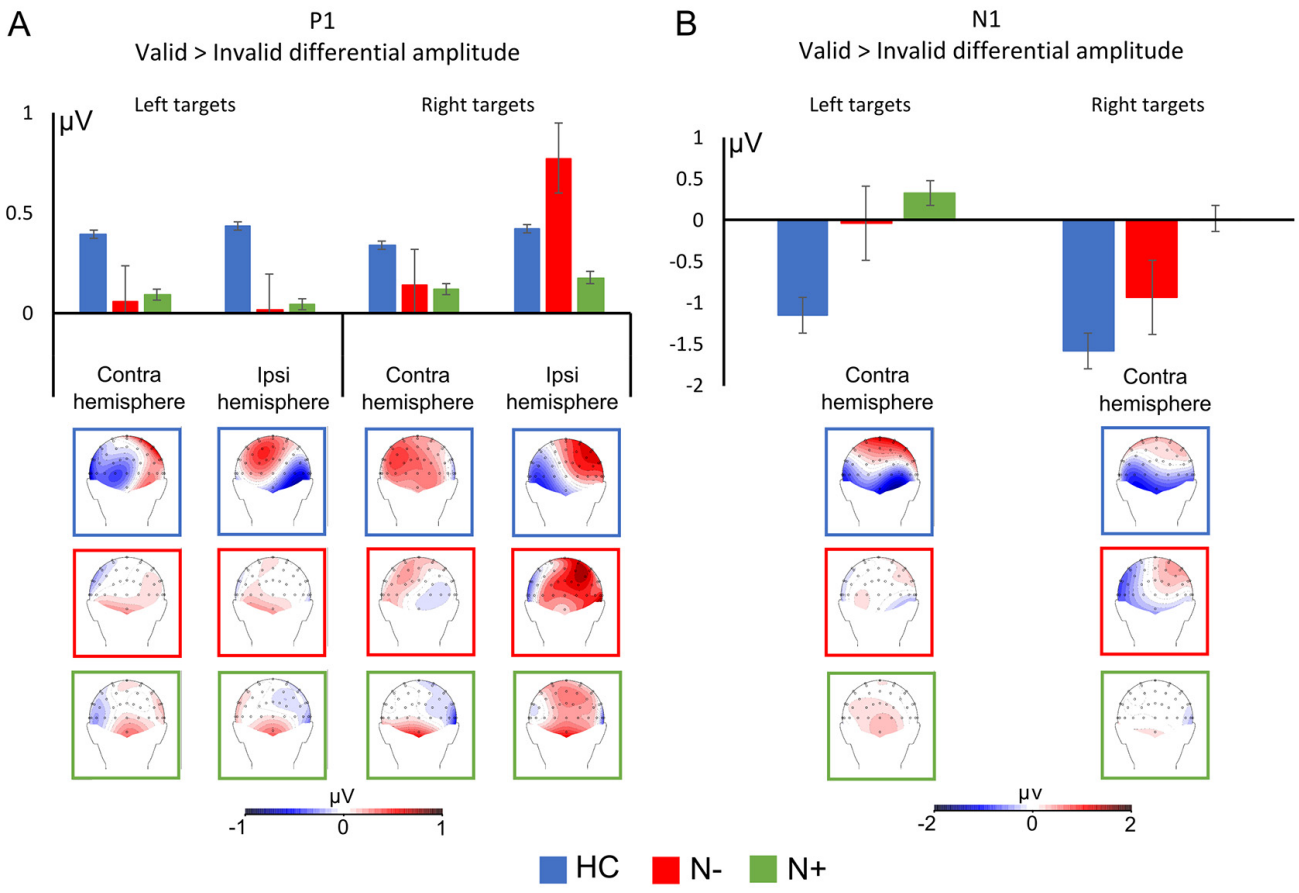

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Clinical and demographic data of patients and healthy controls

Patients Case	Sex	Age (years)	Stroke onset (months)	Line bisection (200 mm) rightward deviation (mm)	Letter cancellation		Line cancellation		Star cancellation		Sentence reading test (Max = 6)	Wundt-Jastrow illusion (unexpected responses)	
					Left	Right	Left	Right	Left	Right		Left	Right
RBD patients without neglect (N-)													
n = 13													
Mean	M=10	61.9	1.3	-0.25	51(53)	48.6(51)	10.9(11)	10(10)	26.2(27)	25.7(27)	5.9(6)	0.2(20)	0.1(20)
S.D.	F=3	9.3	0.47	2.8	2.7	5.5	0.2	0	1	1.8	0.2	0.5	0.5
RBD patients with neglect (N+)													
n = 12													
Mean	M=8	62.6	1.7	23.2	19(53)	28(51)	6.2(11)	8.3(10)	9.2(27)	15.5(27)	3.1(6)	10.1(20)	0.5
S.D.	F=4	10.4	0.36	19.9	20.5	21.2	5.1	2.4	11.1	8.6	2.9	8.1	1.1
Healthy controls (HC)													
n = 15													
	M=8	53.2											
	F=7	11.1											