



P300 in neglect

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HIGHLIGHTS

- Reduced P300 to contralesional targets relative to ipsilesional targets in neglect.
- P300 amplitudes correlate with scores and time in standard neglect tests.
- Results suggest a link between attentional dysfunction and impaired stimulus processing.

ABSTRACT

Objective: Attentional deficits have been thought to underlie hemispatial neglect. The present study investigates this using the P300 component of the event-related potential, which is assumed to reflect the allocation of attention.

Methods: We recorded the P300 and oddball detection performance from patients with neglect. Infrequent targets appeared either in the affected contralesional or the unaffected ipsilesional visual hemifield.

Results: Contralesional targets produced weaker average P300 responses than ipsilesional ones, but stronger responses than when only distractors were presented. In the affected hemifield, the difference in P300 amplitude between identified and missed targets was correlated with the miss rate. The number of missed contralesional targets for a given participant was positively correlated with the time required for completion of standard neglect tests.

Conclusions: The P300 not only reflects a general attentional impairment in neglect, but also varies as a function of the participants' awareness of individual stimuli.

Significance: The findings reflect an important link between attentional dysfunction and impaired stimulus processing in neglect and extinction.

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1. Introduction

Patients suffering from unilateral neglect may fail to notice or react to stimuli presented to their contralesional visual field (Heilman et al., 2003; Saevarsson et al., 2008). They ignore stimuli, such as a person approaching them from the left, or fail to react to other visual, tactile or auditory stimulation presented to their left. Neglect is usually caused by damage to areas involved in attentional allocation following stroke in the arteria cerebri media in the right hemisphere (Vallar, 1993).

Here we used event-related potentials (ERPs) in the electroencephalogram (EEG) to explore brain function in neglect. The P300 is a positive component in the ERP that is most commonly recorded in an oddball stimulus paradigm, where a series of trials with fre-

quent stimuli is interspersed trials with rare stimuli of a different type (Sutton et al., 1965). The P300 typically occurs around 300–600 ms following the onset of the rare stimulus, and is considered to be a blend of several subcomponents. Among those, the P3b is usually associated with an amplitude maximum at parietal scalp locations, while the P3a is marked by a more frontal amplitude maximum (Squires et al., 1975). Differences in the stimulation scheme and task demands modulate the contributions of these subcomponents to the P300 (Polich, 2007; Simons et al., 2001). Experiments aimed at recording the P3b usually employ a two-stimulus oddball paradigm, while the P3a is typically found in three-stimulus oddball experiments, where one of two types of infrequent stimuli is a novel, task-irrelevant, and unrepeated, stimulus, which is not necessarily associated with a task (the term “novelty P3” is therefore sometimes used for the P3a).

The P300 is known to be modulated by attention (e.g. Becker and Shapiro, 1980; Heinze et al., 1990; for review see Polich and

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Kok, 1995) and has subsequently even been used to measure the allocation of attention (e.g. Sawaki and Katayama, 2008). As a consequence, the P300 has been studied in different groups with neuropsychological disorders where attention has been found to be impaired, such as in Alzheimer's disease (Polich and Corey-Bloom, 2005), and has been suggested as a tool for assessing high-level visual impairments (Heinrich et al., 2010b), which may be related to attentional deficits.

While the P300 is modulated by attention, only a handful of studies have so far used the P300 to investigate the role of attention in neglect, possibly because of the difficulty to recruit participants that are able to participate in such experiments (see Deouell et al., 2000 for a discussion). Lhermitte and colleagues (1985) studied patients with visual neglect, and found some evidence that P300 amplitude was smaller if the target stimulus was presented on the neglected side compared to the non-neglected side. Using a cueing paradigm, Verleger et al. (1996) found a reduction of the P3b subcomponent in neglect patients, irrespective of stimulus location, and a frontal increase with a right cue and a left target, when compared to the responses of normal controls. Interestingly, Marzi et al. (2000) found that P300 responses in a participant with extinction were of similar size irrespective of whether the stimuli were consciously perceived or not, while earlier ERP components were reduced on trials where the stimulus was missed, a result in contrast to what was found by Lhermitte and colleagues. As reviewed by Deouell et al. (2000), the evidence is mixed regarding whether early "pre-attentive" ERP components are affected in neglect. In normal observers, attention may affect early components to some degree (e.g. Hoshiyama and Kakigi, 2001), which may, however, be the result of modulatory feedback from higher cortical areas.

The present study pursues two main aims. The first is to confirm the findings of Lhermitte et al. (1985; see also discussion in Deouell et al. 2000), for the affected side in neglect. The second goal is to elucidate whether such a difference would also be seen when missed stimuli on the neglected side are compared with recognized stimuli presented to this same side.

2. Methods

2.1. Participants

Six chronic stroke patients participated after providing informed written consent. All had lesions in areas supplied by the right arteria cerebri media. Fig. 1 shows tissue damage in red on horizontal (axial) sections for the individual patients. Table 1 provides biographical data and clinical descriptions of the participants. Extinction and visual field deficits were explored with standard confrontation techniques. All patients had intact visual fields, hemiplegia of the left side of their body, and were right handed. All measurements were made in the same experimental session with a few brief breaks in between. The experiments followed the tenets of the Declaration of Helsinki and were approved by the local review board.

2.2. Standard neglect tests

The presence of neglect was reconfirmed at the date of the ERP experiments by a series of standard neglect tests (Albert's, star, number and letter cancellation tests, and line-bisection and clock-drawing tasks; Halsband et al., 1985; Wilson et al., 1987). The search-based tests were scored according to percentages of crossed out targets on the left side. The free-hand drawing test was assessed based on the percentage of correct lines and their location in the drawing; each stroke on the left side of an image

was counted as a point, each omitted stroke was counted as a null point, and each clearly misplaced or distorted stroke was counted as half a point. The deviation of the line-bisection test was measured in millimeters and the deviation was scored in percentages, where 100% indicated perfect bisection.

2.3. ERP stimuli and task

P300 recordings were performed employing a standard random-sequence oddball paradigm (Fabiani et al., 2000). On trials with frequent stimuli circles appeared at the left and right of the fixation cross at an eccentricity of 8° (Fig. 2), measured from the center of the circle. Trials with infrequent stimuli had one of the circles replaced by a triangle. Stimulus probabilities were 80% for the frequent bilateral distractors and 10% for each of the two unilateral target stimuli (left and right triangles; triangles never appeared on both sides on the same trial). These values are in the range known to be efficient for recording P300 responses (Heinrich and Bach, 2008). Although the P300 in normal subjects does not depend on the randomness of the target stimuli (Heinrich et al., 2009), this factor could be potentially relevant in the case of neglect as the predictability of the target stimuli could potentially modulate the participants attention in the respective trials. Therefore, targets in the present study appeared on randomly selected trials in the sequence of stimuli. The diameter of the circles and the height of the equilateral triangles were 2.1°. The time between the onsets of two consecutive trials was 2.5 s and the stimuli were presented for 53 ms. The short presentation duration was within the limits proposed by recent guidelines (Duncan et al., 2009), and short enough to make the task difficult to perform, especially when the target appeared on the contralesional side, and ensured that the participants could not employ compensatory strategies. Mell et al. (2008) compared 53 and 93 ms presentation durations in healthy subjects and found that P300 amplitude did not differ between presentation durations.

The stimuli were black with a Weber contrast of 99% on a white background that remained constant across trials and inter-trial intervals. They were presented on a Philips GD 402 monochrome CRT monitor at a viewing distance of 50 cm. The participants were instructed to respond to the stimuli as quickly and accurately as possible by pressing the left (red) button of a two-button response box when they detected a triangle (target stimulus) on either side of the fixation point, and by pressing the right (black) button if they saw no triangle on the screen (non-target stimulus or missed targets).

2.4. ERP recording and analysis

The EEG was recorded from six scalp locations at the midline (Oz, Pz, Cz, and Fz) and temporal areas on the scalp (T7 and T8), according to standard nomenclature (American Clinical Neurophysiology Society, 2006), referenced to linked ears. The ground electrode was attached to the wrist. The signal was digitized at a rate of 500 Hz after being bandpassed at 0.1–70 Hz. Artifacts were rejected based on a 100- μ V threshold criterion (Odom et al., 2010).

Prior to the P300 experiment, bilateral pattern reversal visual evoked potentials (VEPs; Michelson contrast 50%, check size 1.2°, 100 trials per participant) were recorded from each subject to confirm the functioning of the experimental setup and the integrity of the early visual pathways.

In the P300 experiment, a total of 1043–1365 artifact-free trials were recorded per subject, spread over 6–7 recording runs with short breaks in between. Artifact rates (proportion of trials) in individual subjects ranged from 4.8% to 20.1%, with the exception of one subject who produced 46.9% artifacts whose data were not included in the ERP analyses. Looking at experimental conditions,

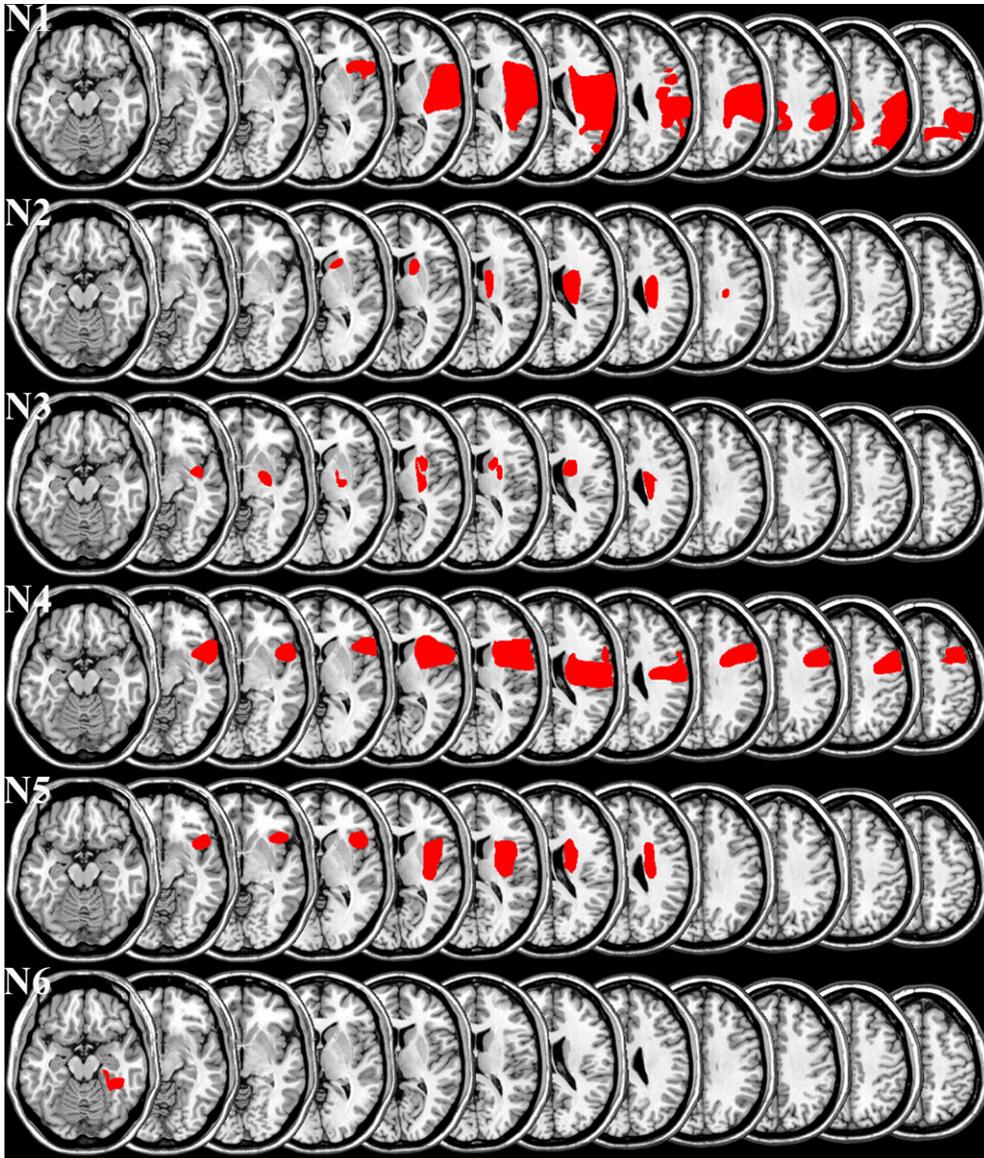


Fig. 1. The horizontal (axial) sections corresponding to lesions (shown in red) in the right hemisphere (reversed neurological convention) for the six patients.

Table 1
Biographical and clinical information.

Participant	Gender	Age in years	Months between stroke and ERP recordings	Frontal and occipital lesions	Ocular and cephalic deviation to the right	Extinction to the left side revealed by standard confrontation techniques
N1	F	64	68	--	- +	-
N2	F	48	32	--	++	-
N3	M	72	44	--	--	-
N4	M	69	69	+ -	++	+ ^a
N5	M	58	57	+ -	++	-
N6	F	84	19	--	++	+

The “+” and “-” symbols refers to presence of a particular lesions or symptoms.

^a Indicates a minor indication for extinction. Patient N1 was not included in the ERP analysis (see text).

artifact rates (median across subjects) were between 12.3% and 14.1% for all combinations of stimulus type and button response, except for false alarms (0.0%) and right misses (2.8%), for which very few trials were recorded in the first place.

Due to the probabilistic nature of the stimulation, the randomness of artifacts, and differences in the endurance of the participants, the probabilities of 80% for the non-targets stimuli and

10% for either of the target stimuli resulted in a variable number of artifact-free trials in the individual recordings, for each participant, with the minimum numbers being 888 for the non-target stimuli, 67 for the left targets, and 80 for the right targets.

We had considered adjusting the task difficulty individually for each participant by adjusting the presentation duration, thereby equalizing the fraction of detected target stimuli between

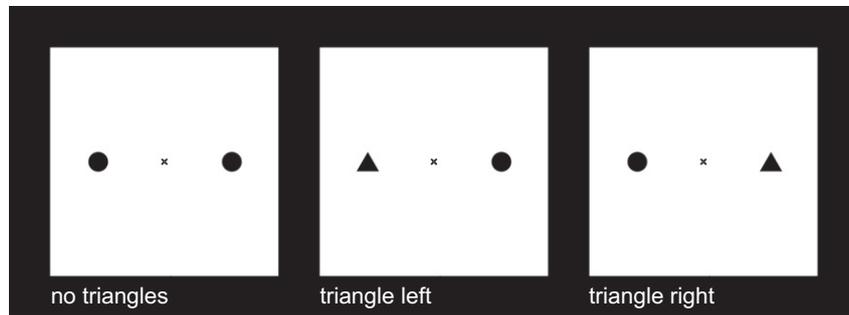


Fig. 2. Left: frequent (non-target) stimulus. Center and right: infrequent (target) stimuli. Circles and triangles were located at an eccentricity of 8°.

Table 2

Performance on the standard neglect tests and the oddball task.

Participant	Average accuracy on the standard tests (%)	Average time for neglect test completion (s)	Missed left targets in the oddball task ^a (%)	Missed right targets in the oddball task ^a (%)	False alarm rate (non-target stimuli) (%)
N1	60	56	88	2.7	0.3
N2	76	51	49	34	1.0
N3	74	90	85	12	0.1
N4	76	44	35	21	0.6
N5	84	44	16	1.1	0.0
N6	58	82	89	29	0.1

^a Response “non-target” instead.

participants. However, we decided against this, as (a) the initial assessment of the participants’ performance would reduce the time available for the ERP recordings, given the time limitations imposed by the participants’ general state, (b) having differences in stimulation between subjects would make it more difficult to interpret the results, and (c) it would become impossible to compare task performance during the P300 recordings to the results of the standard neglect tests.

Because the P300 is a slow-wave component, a low-pass filter with a cut-off frequency of 10–30 Hz, and even lower, has been used in previous studies (for instance Duncan-Johnson and Donchin, 1979; Verleger et al., 1996; Bernat et al., 2001; Bledowski et al., 2004) to reduce noise. By using a 20-Hz cutoff frequency during off-line analysis, i.e. a moderately low value within the above range, we ensured that no relevant responses would be suppressed; the use of a digital Fourier-based filter avoided latency shifts. Trials were sorted by experimental condition, and averaged according to standard techniques. The detailed analysis focused on the Pz electrode, where the P300 usually reaches its maximum (Katayama and Polich, 1996; Picton, 1992), in order to reduce the effects of multiple testing in the statistical assessment.

2.5. Statistical testing

Within the general scope of the study, several individual a priori hypotheses were tested as described in Section 3. The directionality of these hypotheses was based on the expected impact of neglect on the different measures extracted from the data. A correction for multiple testing was applied where necessary when one hypothesis consisted of several sub-hypotheses.

3. Results

3.1. Behavioral results

Generally, participants were able to perform the tasks well. With a frequency of 8–81% (the latter subject was the one excluded from the EEG analysis, see below), most typically 10–15%, subjects

pressed the button for target trials only after erroneously pressing the button for non-target trials. This happened more often with left targets than right targets, although the difference was not quite significant (two-sided Wilcoxon test, $P = 0.063$). Because of this response pattern, we refrained from analyzing reaction times and ignored the first button press if a second button press was recorded. Table 2 provides an overview of both the oddball behavioral data and the results of the standard tests for neglect. The numbers for the oddball behavioral data in Table 2 are based on the trials included in the ERP results, i.e. trials with EEG artifacts excluded. We verified that the inclusion of artifact trials would not change these data substantially.

We first tested the relation between the fraction of missed left targets in the ERP experiment and the results of the standard neglect tests. At the single-test level, we found a significant correlation with both the time required by individual participants to perform the standard tests (Kendall’s $\tau = 0.82$, one-sided $P = 0.045$), and with the percentage correct score on those tests (Kendall’s $\tau = -0.55$, one-sided $P = 0.0098$). Both are significant with a sequential Bonferroni correction (Holm, 1979). For completeness (not included in this Bonferroni correction), we also assessed the right targets. The participants missed some of these, but much less often than they missed left targets (median 16.7% vs. 67.1%, $P = 0.016$, one-sided Wilcoxon test). The fraction of missed right targets was neither significantly correlated with the fraction of missed left targets (Kendall’s $\tau = 0.20$, two-sided $P = 0.57$) nor with the time required to perform the standard tests (Kendall’s $\tau = 0.066$, $P = 0.85$) or its percentage correct score (Kendall’s $\tau = 0.00$, two-sided $P = 1.00$).

3.2. ERP results

The P100 responses to checkerboard stimuli, measured at the Oz position, were in the expected range for all participants as verified prior to the P300 recordings (Fig. 3). Amplitudes ranged from 4.0 to 9.9 μV and latencies from 88 to 114 ms. There was no evidence of a double peak in any of the participants (curves not shown), which could have resulted from differences in the ascending visual pathways. In the P300 recordings, participant N1 pro-

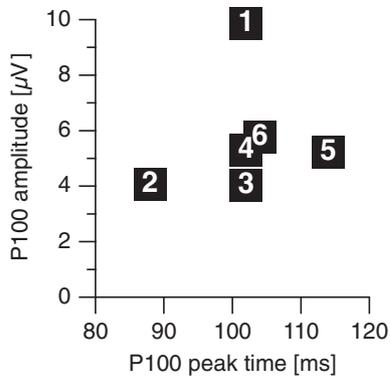


Fig. 3. P100 amplitude and latency as obtained at the Oz electrode with a standard checkerboard reversal stimulus. All subjects were in the expected range.

duced a large number of ocular artifacts that appeared to be partly time-locked to the stimuli. This participant was excluded from the ERP analysis.

3.2.1. Analysis by stimulus type

Trials were pooled by stimulus type only (frequent bilateral distractors, left targets, and right targets, i.e. not taking into account the button response of the participant), and the respective grand means are depicted in Fig. 4. In the P300 time range the response is lower for frequent (non-targets) compared to infrequent (target) stimuli in both hemifields. Left hemifield targets produced lower responses than right targets, as can be seen in the difference traces (Fig. 5). This is also reflected by the amplitude maxima in the 300–800 ms time window at the Pz electrode in all individual participants (Fig. 6 left) and was confirmed by one-sided *t* tests (non-target vs. left target, $P = 0.0067$; non-target vs. right target, $P = 0.0055$; left target vs. right target, $P = 0.011$; all significant at a family-wise α of 0.05 with Bonferroni correction). Peak times (Fig. 6 right) did not show a clear effect of the critical manipulations (one-sided

tests; non-target vs. left target, $P = 0.062$; non-target vs. right target, $P = 0.078$; left target vs. right target, $P = 0.25$). In all stimulus conditions, right-side temporal responses (T8 electrode) are smaller than left-side side (T7) temporal responses (Fig. 4).

We performed *t* tests for each time point (Fig. 7) to obtain a better estimate of the temporal and spatial characteristics than maxima-based tests provide, albeit without correction for multiple testing. The results are consistent with the maxima-based tests, and in addition suggest no significant difference between the two infrequent stimuli (left target vs. right target) at the Fz electrode, irrespective of the large absolute responses. Although the basic P300 effect was consistent between subjects, there is some interindividual variability in curve shape (Fig. 8). It is noteworthy that the response of participant N6, who showed strong symptoms of extinction, differs most from those of the other participants, although we cannot draw strong conclusions from this individual case.

3.2.2. Analyses by behavioral response

The trials with left targets were split up into two response conditions, depending on whether the participants detected the targets or missed them. The grand mean P300 amplitude was larger for detected targets than for missed targets (Fig. 9). The effect on maximum amplitudes of individual participants (Fig. 10) supported this trend, but was not statistically significant (one-sided *t* test, $P = 0.093$). However, for participants who missed many left targets, the P300 amplitudes for recognized targets were larger than those for missed left targets (Kendal's $\tau = 0.80$, $P = 0.025$, one-sided). The participants did not show a consistent pattern of differences between maximum amplitudes seen for recognized left targets and those for recognized right targets (two-sided *t* test, $P = 0.92$). However, even when missed, left targets resulted in a larger P300 than non-target trials (two-sided *t* test, $P = 0.045$). The amplitude obtained with correctly recognized left targets was not significantly correlated with the fraction of missed left targets (Kendal's $\tau = 0.40$, $P = 0.16$, one-sided).

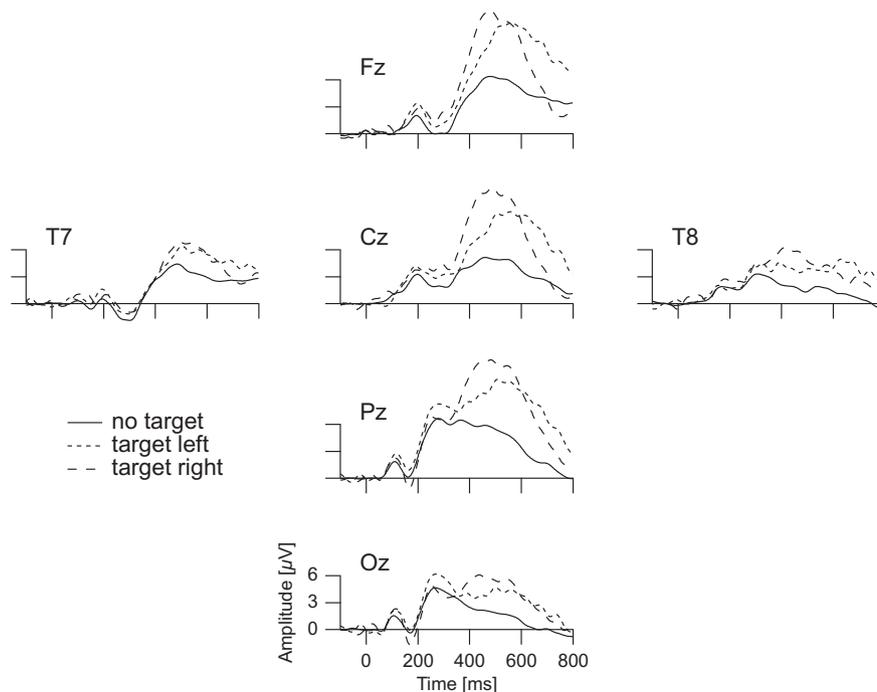


Fig. 4. Grand mean ERPs obtained with all three stimuli (irrespective of the participants' response). The largest responses were obtained with right targets. Left targets produced intermediate amplitudes, and non-target stimuli produced the smallest amplitudes.

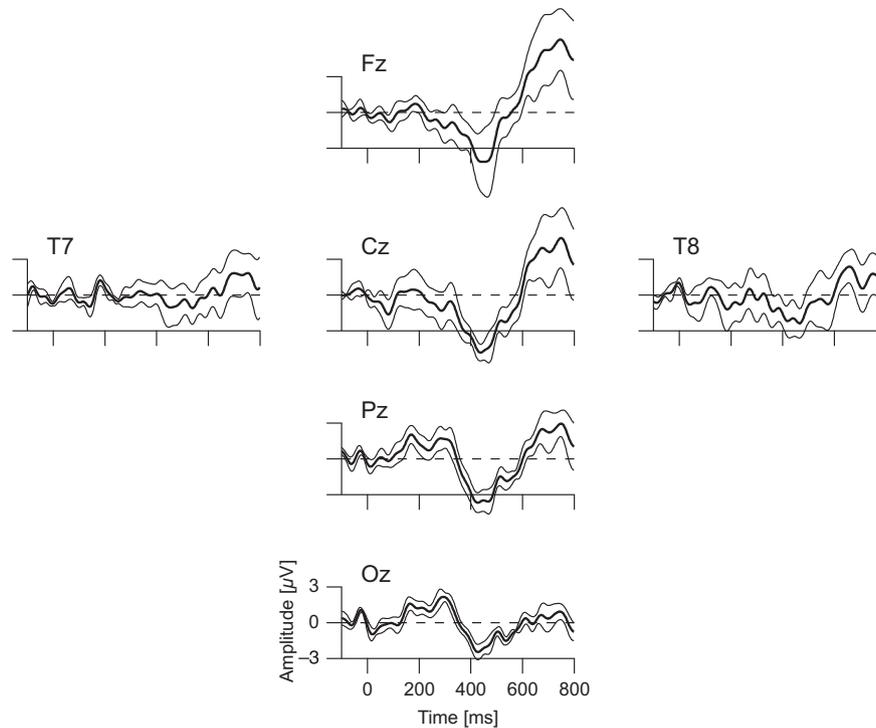


Fig. 5. Grand mean difference traces (thick lines denote responses to right targets subtracted from responses to left targets), with the standard error of the mean shown as bracketing thin lines. The negative deflection around 400–500 ms post-stimulus indicates that the responses to the left targets in this time range were smaller than the responses to the right targets.

Furthermore, we tested whether there was a difference between recognized left targets and recognized right targets at the Fz electrode, possibly reflecting a frontal P3a effect. No significant difference between the respective responses (paired t test, $P = 0.69$; Wilcoxon test, $P = 1.00$) was, however, found.

4. Discussion

The main findings of the present study are fourfold.

- I. On average, P300 amplitude was smaller for left targets than for right targets.
- II. Participants with higher miss rates showed a larger difference in P300 responses between detected and missed left targets.
- III. Missed left targets produced a larger P300 than the non-target frequent trials.
- IV. Participants who scored lower on standard neglect tests and required more time to complete them, missed left targets more frequently in the oddball task. This most likely indicates stronger neglect symptoms and attentional deficits.

Importantly, the reduced P300 amplitude for left targets (both missed and detected pooled) confirms earlier findings by Lhermitte and colleagues (1985). On the one hand, this reduction can be explained by the large number of missed targets. On the other hand, this finding could not be predicted with certainty since a subjectively lower number of targets (largely irrespective of the true number of targets) is usually associated with a larger P300 response elicited by those targets that were detected (Duncan-Johnson and Donchin, 1977). We found evidence for this latter pattern, since the response amplitude for detected left targets increased significantly as the number of missed left targets increased.

As a trend, the P300 elicited by recognized left targets was larger than the one elicited by left targets that were missed, but this

was not statistically significant. However, the trend is corroborated by the finding that the P300 response to detected left targets is positively correlated with the miss rate. Importantly, the response to the missed left targets was still larger than that to the frequent stimuli, suggesting that the missed targets elicited a response despite never reaching full consciousness. This is reminiscent of the finding by Bernat et al. (2001) that subliminal stimuli may elicit a P300, although the responses in that study were smaller than those in the present study. Our findings suggest that some stimulus information reaches a sufficiently high level of processing to elicit a moderately large average P300, even when the target stimuli are missed. The actual size of the response may be a matter of likelihood. For instance, if processing were unreliable for contralateral stimuli, a P300 would be elicited on some trials but not others. This would be consistent with experiments in normal subjects that suggest that the P300 is typically either elicited with full amplitude, or is completely absent, but does not occur with intermediate amplitude. For instance, Bonala et al. (2008) have shown that intermediate response sizes resulting from certain local stimulus probabilities are actually the result of the reduced likelihood that a P300 is generated at all, rather than a reduction of the P300 amplitude in those trials where a P300 is present. Wilkinson and Seales (1978) have demonstrated with auditory stimulation that missed infrequent stimuli elicit small P300 responses similar to frequent stimuli. It is unclear whether the gradual change in P300 amplitude found in experiments where the discriminability of the target stimuli was manipulated (Polich, 1987) is also a result of the likelihood of P300 generation.

The current results represent an important extension of previous findings. For instance, Vuilleumier et al. (2001) reported that implicit visual learning is independent of awareness of previous stimulus exposure in extinction and neglect. Rees et al. (2000) demonstrated activation in the visual cortex for extinguished stimuli in an fMRI study (see Driver et al., 2001 for a comprehensive overview). Russo et al. (2008) studied visual evoked potentials in

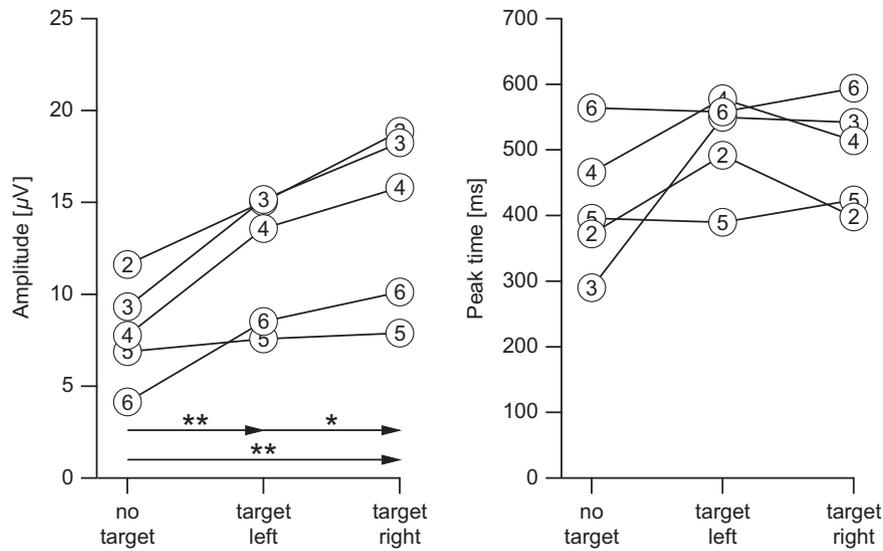


Fig. 6. Left: maximum Pz amplitudes in the 300–800 ms time range for the five patients included in the ERP analysis. Numbers refer to participants as in Table 1. For all participants, the smallest amplitude was found for non-target stimuli, followed by left targets. The largest amplitudes were obtained with right targets. Asterisks indicate the significance level (** and * indicate a familywise α of 0.01 and 0.05, respectively). Right: the corresponding peak times do not show a consistent effect.

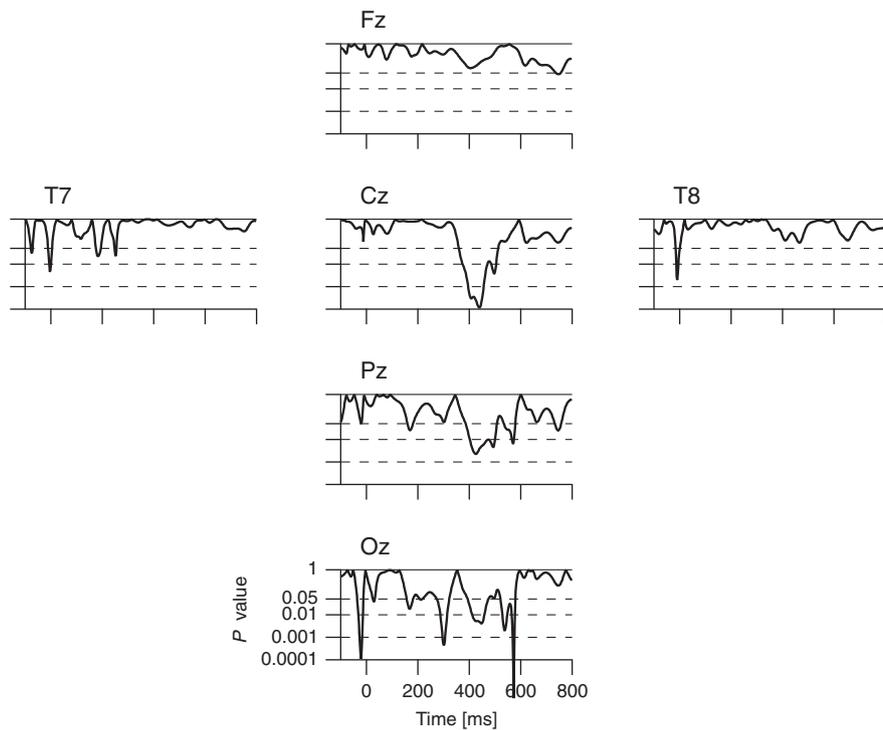


Fig. 7. *P* values from point-wise *t* tests for the grand mean difference between ERPs to left and right target stimuli. Small *P* values are predominantly found at Pz and Cz between 400 and 600 ms. However, at Oz, small *P* values already occur around 300 ms.

neglect. They found bottom-up processing around 130 ms at the intraparietal sulcus level and top-down feedback in striate and extrastriate areas in the range 140–220 ms to be defective. Surprisingly, Marzi et al. (2000) found the P1 and N1 components to be absent with bilateral stimulation in a patient with extinction symptoms. The present study also has the following notable links to studies on visual priming in neglect patients and healthy subjects. Saevarsson colleagues (2008; see also Kristjánsson et al., 2005) showed how priming of targets and distractors proceeded normally (e.g. Kristjánsson and Driver, 2008; see Kristjánsson

and Campana, 2010, for review). Such priming shows that there is considerable processing of missed stimuli in the neglected visual field even though the observers are unaware of the stimuli (see also Driver and Vuilleumier, 2001). This agrees well with findings from fMRI which indicate that priming causes activity modulations in early visual areas (Geng et al., 2006; Kristjánsson et al., 2007). Consistent with these results, the current study shows that even though the participants were unaware of the rare target stimuli there was still considerable processing of those stimuli as the P300 component for the missed left targets shows.

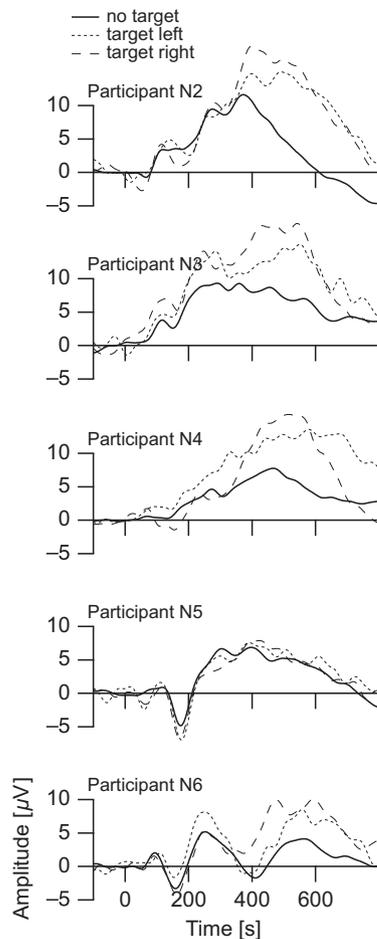


Fig. 8. ERPs (Pz electrode) of individual participants to all three stimulus types, sorted from top to bottom by the magnitude of the response to frequent stimuli. The numbering of the participants is identical to Table 1. While the largest amplitude was consistently found with right targets, there was considerable variability in curve shape and in the differences between stimuli.

Regarding the effects on the P300, some potentially confounding factors need to be considered. The first one is the intrusion of motor responses into the ERP, which may occur when the subjects press a button. While we cannot completely exclude that this plays a role, it is unlikely to be an important factor. This assertion is based both on previous research (Verleger et al., 2006) and on the design of the experiment, where the participants had to press a button on *all* trials, which kept this factor constant over the critical comparisons. Reaction time patterns were not consistent between subjects, regarding both absolute times and the relative timing for different stimuli. The interindividually consistent P300 effects are thus not simply a result of reaction time differences. Similarly, the frequency with which subjects first pressed the wrong button before they corrected their response differed substantially between subjects without affecting the consistent P300 effects. A second factor is a potential cognitive left/right bias introduced by the orientation of the button box. However, this should not affect the correlation between the miss rate and the amplitude of the P300 to contralateral targets. Regarding the left/right comparisons, an effect opposite to the one found would be expected if there had been a cognitive link between the buttons and the target stimuli on the respective sides.

Another potential confounder is a variation in temporal jitter between conditions. More temporal jitter of the P300 response between single trials would, most likely, result in a broader, but also shallower, peak. The data in Fig. 8 does not suggest that this is the

case, however, as there is no inverse relationship between the width of the P300 peak and its amplitude.

Although there is no evidence that subjects failed to fixate during the experiment, it is worth evaluating possible effects of eye movements on the outcome of the study. An intrusion of electrical signals (electro-oculogram) is unlikely to be picked up to a sizable degree at the Pz electrode, especially given the linked-ears reference. If eye movements were predominantly triggered in one stimulus condition, the stimulus would have already entered cortical processing before the eye movement was executed and would therefore hardly be affected by the eye movement.

A systematic effect of eye movements on stimulus perception is also unlikely, as the eye movement would have to be triggered by a certain stimulus (for instance a rare one). However, the stimulus would then already have entered cortical processing and it is unlikely that the P300 would be affected.

We should furthermore consider whether the P300 effects are possibly an epiphenomenal consequence of processing differences at earlier processing stages. Indeed, Fig. 7 shows some significant effects (not corrected for multiple testing) preceding the P300. On the one hand it should be noted that the respective *P* values are only moderately small and may thus be a spurious result of multiple testing. On the other hand, a direct link between early effects and the P300 is unlikely, considering that previous studies (e.g. Bonala et al., 2008) have shown that the P300 varies independently of earlier components. This is further corroborated by the finding that both at Pz (Fig. 8) and Oz (not shown) the polarity of the effects around 200 ms varies between subjects, without determining the P300 effect. This interindividual difference between the even earlier responses is expected, given that responses to flash stimuli vary between individuals (Odom et al., 2010) and cortical anatomy affects the response topography with stimuli displayed on different sides of the visual field differentially. The general response asymmetry between the left and right temporal electrodes, which does not depend on the stimulus condition, is most likely a consequence of the brain damage itself. The more positive deflection at the left temporal electrode would also be compatible with a leftward movement of the eyes. However, given the linked-ears reference, the difference between traces appears to be larger than one would expect. It is also not obvious why leftwards eye movements would be more frequent than rightwards movements.

Lastly, we need to take into account that various neuropsychological factors such as brain lesions may result in different symptoms for different patients (e.g. Karnath et al., 2003; Verdon et al., 2009). For instance, it has been speculated that extinction and neglect, rather than being fundamentally distinct, represent different points on a continuum with extinction being a less serious form of neglect (Robertson, 1992, see however Pavlovskaya et al., 2007). Also, neglect can affect both hemifields (*bilateral neglect*) although the more contralesional a target is located, the likelier it is to be neglected (Kinsbourne, 1987). In light of this, our current findings call for further studies where the P300 in different forms of neglect and extinction would be compared and these other factors would be controlled for. For instance, an experimental condition with bilateral target presentation may help to differentiate between extinction and neglect.

Lacking novel stimuli, the stimulus sequence used here was not designed to elicit P3a responses. Nevertheless, there was a sizable P300-like response at the Fz electrode. One may wonder whether the left targets, as far as they were recognized despite the neglect, would be perceived as novel by the participants. If so, frontal responses to left targets should be larger than those to right targets. As the results show, this was not the case.

The differences between participants regarding the number of trials that were recorded for a given condition have two effects. First, they affect the signal-to-noise ratio of the ERPs. The

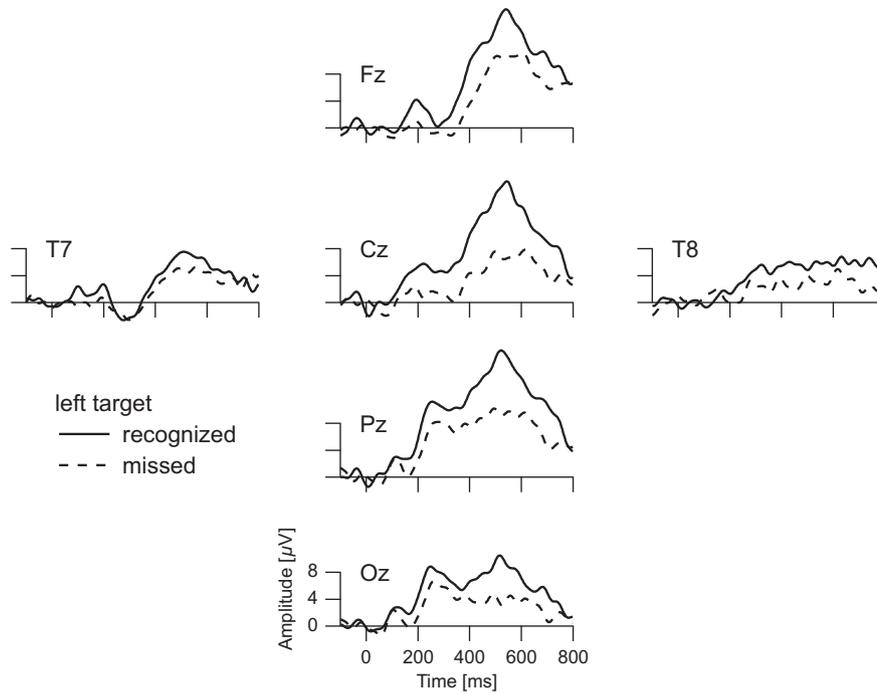


Fig. 9. Grand mean ERPs for recognized and missed left targets. Recognized targets produced substantially larger responses in the P300 time range.

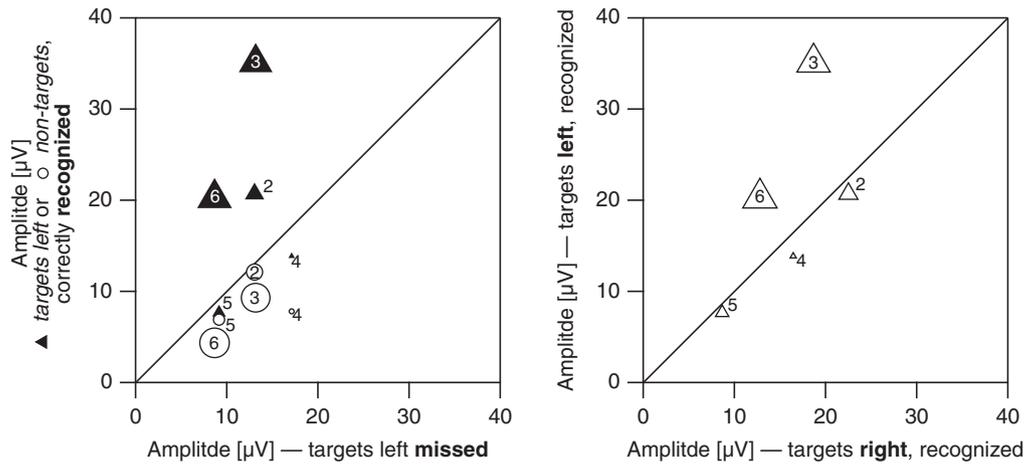


Fig. 10. Maximum amplitudes of individual participants in the 300–800-ms interval (Pz electrode). Marker size indicates the fraction of targets missed. The numbers correspond to the participant numbers in Table 1. Left pane, triangle markers: recognized left targets (ordinate) vs. missed left targets (abscissa). Most participants, in particular those that missed many left targets, produced larger amplitudes. Left pane, circle markers: non-target stimuli (ordinate) vs. missed left targets (abscissa). In non-target trials, amplitudes were smaller than in trials with missed left targets. Right pane: recognized left targets (ordinate) vs. recognized right targets (abscissa). There is no simple pattern, although those participants that missed the left targets at least tended to produce similar amplitudes in both conditions, while those with more missed targets produced larger responses with left than with right targets. The largest responses for recognized left targets were obtained for those subjects that missed most of the left targets.

consistency of the results between subjects and outcome of the statistical testing suggests that this was not a problem in the present study. Second, because we refrained from equalizing interindividually the relative number of trials obtained for different response conditions (cf. Section 1), we can assess the correlation between the results of the P300 responses, the fraction of missed targets, and the standard neglect tests. In addition to the link between P300 amplitude to contralesional targets and subject performance (see above), we found an interesting correlation between the fraction of missed left targets and the time needed to perform the standard neglect tests. If the latter measure is taken as an index

of individual processing speed, this may mean that these participants were more likely to miss a stimulus because they did not process the stimuli fast enough to cope with the presentation timing. Such an impediment may be due to difficulties in allocating attention, and these participants may indeed simply be suffering from stronger neglect than the others. This may have important implications for the assessment and therapy designs (Rengachary et al., 2009; Saevarsson et al., 2011). Similarly, the frequency of the missed left targets correlated, unsurprisingly, with the error rate on the standard tests. Rossit et al. (2009) have found lesions in occipito-temporal areas to be strongly associated with reduced

accuracy in delayed leftward pointing and anterior frontal damage to be related to movement slowing. These areas may contribute to the differences in the time required to perform the classical neglect tests.

To conclude, P300 has the potential to be a helpful addition to standard assessment tools for visual attention deficits. Importantly, the present study sheds light on how the P300 to contralesional visual events in an oddball task is correlated with standard measurements of neglect. Further, the P300 to contralesional targets depends substantially on whether the targets were seen or not. These findings pinpoint an important link between attentional factors and stimulus processing in unilateral neglect and extinction, and hopefully the direction of causality will be demonstrated in future studies.

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