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Lost in number space after right brain damage: A neural signature of representational neglect

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ABSTRACT

The human brain represents numbers along a mental number line, whose spatial nature was confirmed by studies of patients with visuospatial neglect. Here we describe a neural signature of neglect for the left ‘‘number space’’ by using a task that does not require manipulation of numbers. Patients were asked to discriminate an infrequent (‘‘one’’ or ‘‘nine’’) from a frequent spoken number word (‘‘five’’). P3b brain waves, elicited by infrequent stimuli and indexing cognitive processing, were delayed to targets on the left of the number line (‘‘one’’) compared to targets on the right (‘‘nine’’). The delay of P3b is thus a neural signature of the disorder of representational space.

1. Introduction

Numbers and space are inextricably linked in the history of mathematical thinking. The roots of this connection can be traced to the way the human brain represents numerical information, which appears to depend on a spatial layout where numbers are placed along a continuous, analogical, left-to-right oriented mental line (for review see Hubbard et al., 2005). Small numbers are represented on the left of the mental number line (MNL) and larger numbers are represented on the right.

The spatial nature of the MNL has been confirmed by neuropsychological studies of patients with left neglect (Hoeckner et al., 2008, this issue; Priftis et al., 2006; Rossetti et al., 2004; Vuilleumier et al., 2004; Zorzi et al., 2006; Zorzi et al., 2002), a disorder of spatial attention impairing awareness of the left side of space following right brain damage (for review see Halligan et al., 2003). Left neglect patients bisect a visually perceived line to the right of its true midpoint, as if they were not aware of the leftmost portion of the line, and show an identical pattern when asked to bisect a numerical interval (Priftis et al., 2006; Rossetti et al., 2004; Zorzi et al., 2006; Zorzi et al., 2002). They shift to the relative right (i.e., toward larger numbers) the midpoint of a spoken number interval (e.g., ‘‘What number is halfway between 1 and 9?’’ Patient’s answer: ‘‘7’’). Left neglect patients are also slower at judging the magnitude of smaller numbers (left on the MNL) than that of larger numbers (right on the MNL) in a number comparison task (Vuilleumier et al., 2004).

The spatial disorder for mental representations, known as representational neglect, was first described in the seminal work of Bisiach and Luzzatti (1978), in which neglect patients were asked to describe by memory a very familiar location

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(i.e., the Piazza del Duomo in Milan). Other cases of representational neglect were subsequently described (see review in Berti, 2004). However, establishing the presence of representational neglect is often difficult because it requires the availability of a location, with more or less the same number of features on either side, which is very familiar to the patient. Alternatively, one must make recourse to rather complex experimental procedures (e.g., Bisiach et al., 1979). Neglect for the left ‘‘number space’’ (Zorzi et al., 2002), instead, is a form of representational neglect that involves a well-defined and circumscribed domain that can be assessed using simple experimental tasks. The aim of the present study was to find a neural signature of this disorder.

In contrast to previous behavioural studies, which used number bisection or number comparison, we employed a much simpler task that did not require any mental manipulation of numbers. Patients performed an auditory oddball task, in which they discriminated an infrequent target stimulus from a frequent standard stimulus (i.e., non-target) and reported the occurrence of the target with a key-press response. The standard stimulus was the spoken number word ‘‘five’’, whereas the target stimulus was either ‘‘one’’ or ‘‘nine’’. Electrophysiological studies of the oddball paradigm show that the target stimulus elicits the P300 brain wave, a large, positive-going potential that is of maximum amplitude over the parietal electrode sites (P3b component), with a peak latency of about 300–350 msec for auditory stimuli. P3b latency reflects target stimulus evaluation and classification speed and it is rather independent from response generation processes and behavioural reaction time (for review see Polich, 2004, 2007).

The P3b wave is an important signature of cognitive processes, such as attention and working memory, and of their dysfunction in neurological disorders (Linden, 2005). Polich (2007) suggests that the P3b wave is associated with temporal–parietal activity that involves noradrenergic pathways (see also Nieuwenhuis et al., 2005). P300 peak's latency is negatively correlated with cognitive ability and attention allocation but it is positively correlated both with normal aging and dementia (Polich, 2004, 2007). Finally, P300 peak's latency for contralesional stimuli is increased in neglect patients (Lhermitte et al., 1985).

We predicted that in left neglect patients the latency of P3b waves to the target number would be modulated by its relative position on the MNL. That is, P3b waves to targets located on the relative ‘‘left’’ of the standard number (i.e., ‘‘one’’) would be delayed compared to targets located on the relative ‘‘right’’ (i.e., ‘‘nine’’). This delay in the P3b wave would be the neural signature of neglect for the left ‘‘number space’’, and by extension for representational neglect in general.

2. Method

2.1. *Participants*

Six left neglect patients (mean age: 60 years) and six controls with right hemisphere lesions but without neglect (mean age: 61 years) gave informed consent to take part in the study according to the Declaration of Helsinki. Demographic, neurological, and psychometric data of participants are reported in Table 1. Peripersonal neglect (i.e., neglect within reaching space) was assessed using the Behavioural Inattention Test (Wilson et al., 1987). Extrapersonal neglect (i.e., neglect beyond reaching space) was assessed by means of verbal description and pointing toward objects in the neuropsychological assessment room. Selective omissions of objects in the left extrapersonal space were considered as a sign of extrapersonal neglect. Two left neglect patients (5 and 6) had a BIT score above the cut-off point, but they showed severe signs of extrapersonal neglect. All other left neglect patients showed both extrapersonal and peripersonal neglect.

2.2. *Stimuli*

The experimental stimuli were spoken number words presented binaurally via headphones at 75 dB above participants' hearing threshold. Targets were the numbers ‘‘one’’ and ‘‘nine’’, whereas the non-target was the number ‘‘five’’. Note that ‘‘one’’ is located on the relative left of ‘‘five’’ on the MNL, whereas ‘‘nine’’ is located on the relative right.

2.3. *Procedure*

Participants were tested in a sound-attenuated room. They were asked to ignore the non-target stimulus ‘‘five’’, but to press a key in response to the target stimulus ‘‘one’’ or ‘‘nine’’. Targets (20%) were presented randomly among

Table 1 – Demographic, neurological, and psychometric data of participants

	Left neglect patients						Controls					
	1	2	3	4	5	6	1	2	3	4	5	6
Sex	F	F	F	M	F	M	M	M	M	F	M	M
Age (years)	60	67	39	64	70	60	72	70	61	52	48	63
Education (years)	5	8	13	11	5	13	8	5	13	8	5	8
Handedness	R	R	R	R	R	R	R	L	R	R	R	R
Lesion site	OP	FP	BN	FTP	FTP	TP	C	FT, P	FT,P	FT	F	FP, BN
Lesion aetiology	HS	IS	HS	HS	IS	IS	HS	IS	IS	IS	IS	IS
BIT: cut-off $\leq$ 129/146	111	58	116	96	139	136	136	131	146	146	130	135
Extrapersonal neglect	+	+	+	+	+	+	−	−	−	−	−	−

M = male; F = Female; BN = basal nuclei; F = frontal; T = temporal; P = parietal; O = occipital; C = capsular; + = presence of extrapersonal neglect; − = absence of extrapersonal neglect; R = right; IS = Ischemic stroke; HS = Hemorrhagic stroke.

to-be-ignored non-targets (80%), in an oddball paradigm. The inter-stimulus interval (ISI) was 2.5 sec and the upper bound of one block of trials (session) was 90 stimuli. Each session was repeated twice. Thus, each target was presented on 36 out of 180 total trials. The order of the four sessions was randomised among participants.

2.4. ERP recording and data analysis

We used a standard procedure for recording ERPs (Picton et al., 2000). The EEG was recorded from cup silver/silver-chloride electrodes placed at frontal (Fz), central (Cz), and parietal (Pz) sites, according to the international 10–20 system. Electrodes were all referenced to linked earlobes. The electroculogram (EOG) was recorded from an electrode at SO2 (inferior and lateral to the right eye) that was also referenced to linked earlobes. A ground electrode was positioned on the forehead. The three electroencephalogram channels (EEG) and the single EOG channel were amplified by SynAmps (NeuroSoft, Inc.). All impedances were kept below 5 kΩ. Channels were band-pass filtered between .15 Hz and 35 Hz and digitised (16-bit resolution) at 1000 Hz sampling rate for each channel. Notch filter was set on. Every recorded single-sweep epoch, synchronized with the stimulus, began 100 msec before the stimulus onset, up to 1000 msec after the stimulus trigger signal, for a total amount of 1100 msec. Thus, 1100 sampled points per channel were available after every stimulus to detect the presence of the P300. Trials were artefact rejected at ±100 μV for a 1100 msec epoch.

Correct trials for each numerical condition were averaged. After artefact rejection, 95% of the trials were included in the analysis. ERPs were smoothed off-line using a low-pass filter at 15 Hz. ERPs' waveforms were plotted with upward deflections indicating positive potentials. From each participant's averaged data, amplitudes and latencies were manually peak-picked by two electrophysiology experts who were blind as to the patient's group membership (i.e., neglect *vs* controls). The P3b was picked as the largest positive peak between 300 msec and 700 msec at Pz.

2.5. Design

Independent variables were manipulated within a mixed factorial design. Group was the between-participants factor with two levels (left neglect patients *vs* control patients without neglect). The within-participants factor was number with two levels (''one'' *vs* ''nine''). The dependent variables were reaction time (RT, in msec), P3b latency (in msec), and P3b amplitude (in μV).

3. Results

3.1. RT analysis

Median RTs for each target number (one *vs* nine) were introduced into a two-way mixed analysis of variance. Control patients without neglect were significantly faster (mean RT: 584 msec) than left neglect patients (mean RT: 647 msec), $F(1,10) = 5.67$, $p < .05$. Both the main effect of number and the interaction group by number were not significant (both Fs < 1).

3.2. Latency analysis

P3b latencies to the ''left'' number (''one'') and to the ''right'' number (''nine'') were significantly different for left neglect patients (mean latencies: 510 msec *vs* 480 msec; see Fig. 1 and Table 2). In contrast, performance of control patients without neglect was not affected by number magnitude (mean latencies: 493 msec *vs* 498 msec). Median P3b latencies for each participant and target number (one *vs* nine) were introduced into a two-way mixed analysis of variance. The main effects of group and number were not significant (group: $F(1,10) < 1$, *ns*; number: $F(1,10) = 3.26$, *ns*). The interaction group *x* number was significant ($F(1,10) = 6.39$, $p = .03$) and was further investigated through simple effect analyses. For control patients without neglect (see Fig. 1), the comparison between P3b latencies for one and nine was not significant, $t(5) = -.48$, *ns*, two-tailed. In contrast, left neglect patients had significantly delayed P3b latencies for ''one'' with respect to ''nine'', $t(5) = 3.22$, $p = .023$, two-tailed.

3.3. Amplitude analysis

Median amplitudes for each target number (''one'' *vs* ''nine'') were introduced into a two-way mixed analysis of variance. Neither the main effects (group, number) nor the interaction were significant (all Fs < 1).

4. Discussion

We observed an effect of number magnitude in the P3b latencies of left neglect patients performing a numerical oddball task. In contrast, right brain damaged patients without neglect did not show any effect. P3b latencies in neglect patients were influenced by the number's relative position on the MNL, with an advantage for the number on the ''right'' (i.e., ''nine'') in comparison to the number on the ''left'' (i.e., ''one''). Because the oddball paradigm is in itself devoid of any spatial component, the spatial asymmetry we have found must be attributed to the spatial nature of the MNL.

The latency shift in the ERP wave was not mirrored by significant changes in amplitude or in RTs. The dissociation between P3b latency and RTs is not surprising because the P3b reflects target stimulus evaluation and classification speed and it is rather an independent form of response generation processes and behavioural reaction time (for review see Polich, 2004, 2007). P3 amplitude is known to be affected by overall task difficulty (i.e., resources allocation), uncertainty (i.e., whether the stimulus is a target or non-target), and target probability (see Luck, 2005, for review). Since these factors played no role in our study, the absence of differences in amplitude between neglect patients and controls suggests that the specific difficulty in neglect patients is not tied to the initial coding of numbers. In contrast, the significant divergence in P3b latencies can be attributed to processing differences at the stage of number categorization (i.e., activation of the MNL and comparison between target and standard).

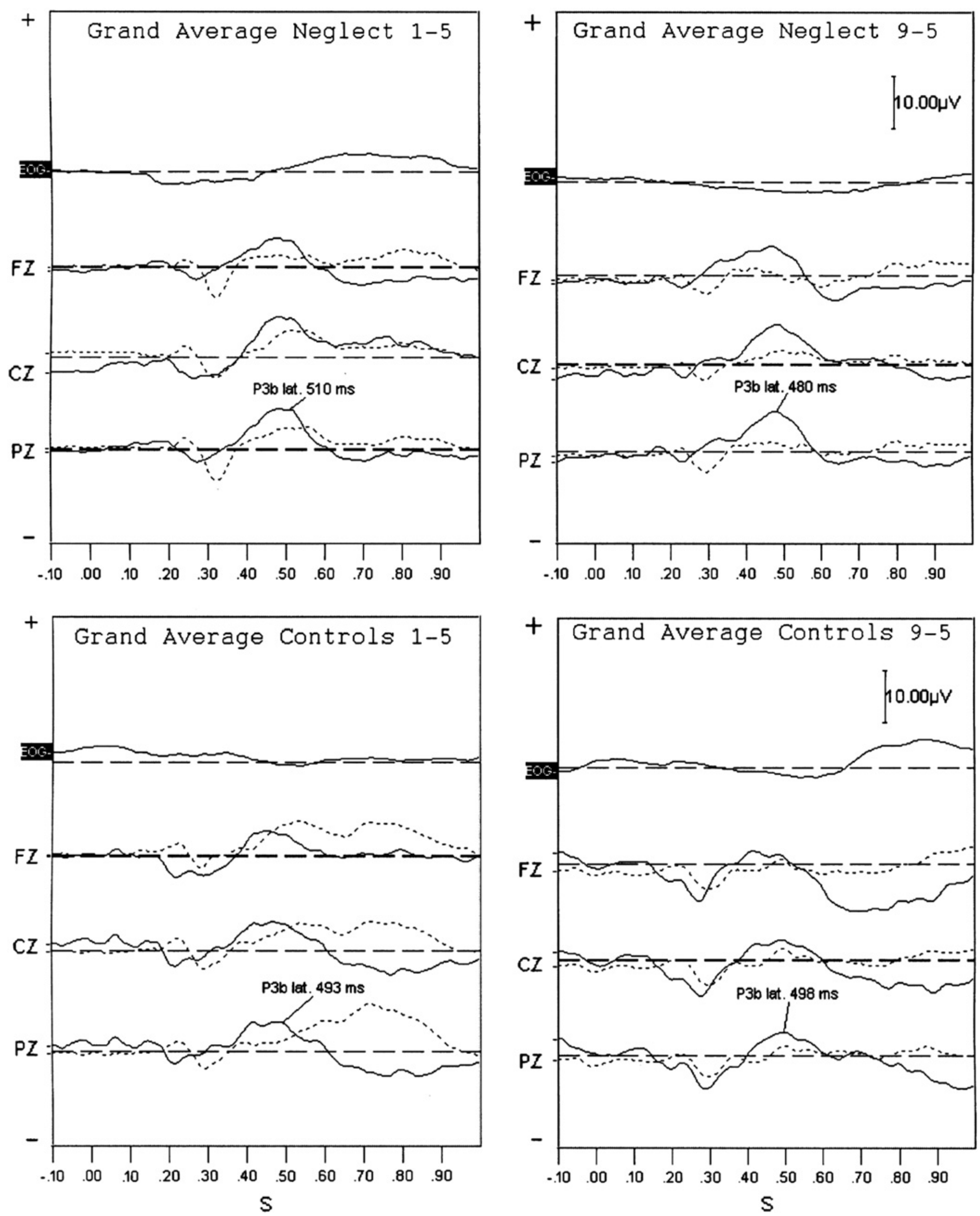

Fig. 1 – Grand averaging of P3b latencies. Dotted lines represent waves related to the standard stimulus (i.e., five), whereas continuous lines represent waves (i.e., the P3b) related to the target stimulus (i.e., one or nine). EOG: electroculogram.

Indeed, P3b latency is related to the time required to categorize a stimulus and is not affected by post-categorization processes such as those involved in response selection and execution (see Luck, 2005). Thus, our findings are in accordance with those of other studies suggesting that the association between number and space is not restricted to the stage of response selection (Casarotti et al., 2007; Fischer et al., 2003; Salillas et al., 2008, this issue; Stoianov et al., 2008, this issue).

There is mounting evidence that number processing causes shifts of visuospatial attention in healthy participants (Casarotti et al., 2007; Fischer et al., 2003; Salillas et al., 2008, this issue). More interestingly, spatial attention can directly influence number processing tasks such as number comparison and parity judgment (Stoianov et al., 2008, this issue). The latter finding suggests that spatial attention is routinely involved in number processing tasks and it is consistent with the bias in ‘‘number space’’ shown by neglect patients (Priftis et al., 2006; Rossetti et al., 2004; Vuilleumier et al., 2004; Zorzi et al., 2006; Zorzi et al., 2002). Indeed, this left–right bias is congruent with the way spatial attention is deployed in left neglect (Làdavas et al., 1990), resulting in hypoattention for the relative left space and hyperattention for the relative right space. Thus, the effect of neglect on number processing can be attributed to the impairment of spatial attention mechanisms that are involved in the mental exploration and manipulation of the number line (Priftis et al., 2006).

Our results suggest that the repeated presentation of the standard stimulus (i.e., ‘‘five’’) leads to the automatic

Table 2 – P300b latency, amplitude, and RTs of each participant

	Latency		RT		Amplitude	
	1	9	1	9	1	9
Neglect						
1	550	540	693	678	2.13	3.66
2	490	460	723	626	20.83	14.86
3	510	460	548	639	16.7	10.55
4	540	510	657	624	12.39	12.31
5	510	450	550	595	14.95	15.18
6	460	460	686	745	6.03	15.21
Mean	510	480	643	651	12.17	11.96
Controls						
1	530	580	577	488	5.15	10.15
2	450	460	574	629	18.24	10.73
3	570	560	618	533	14.51	13.63
4	460	470	580	650	12.99	12.31
5	520	500	564	568	13.19	16.92
6	430	420	588	644	16.02	16.26
Mean	493	498	584	585	13.35	13.33

activation of its magnitude representation, which corresponds to engaging attention to a specific spatial position on the MNL. Thus, the processing of the small target (‘‘one’’) would be delayed because attention must be shifted to the left of the reference point. In contrast, processing the large target (‘‘nine’’) might even benefit from the hyperattention towards numbers that are located on the right of the reference. A similar pattern was observed by Vuilleumier et al. (2004) in number comparison RTs. Note that the explicit magnitude comparison task employed by Vuilleumier et al. might have affected RTs more than our oddball task where the comparison was only implicit. Moreover, in Vuilleimer et al.’s study neglect predominantly affected the number immediately preceding (i.e., to the left of) the reference but not the more distant numbers. In other words, the effect of neglect on RTs was not observed for all ‘‘left’’ numbers but it was limited to those close to the reference. Accordingly, the absence of RT effects in our study could be attributed to the fact that the target numbers were far from the reference (i.e., ‘‘one’’ and ‘‘nine’’ *vs* ‘‘five’’).

In conclusion, we showed that the P3b wave is a neural signature of neglect for the left ‘‘number space’’ and of a disorder of representational space (i.e., representational neglect) in general. Notably, our findings mirror those of Lhermitte et al. (1985) in the perceptual domain. Thus, ERP recordings during the numerical oddball paradigm could provide an objective assessment of representational neglect in clinical practice.

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