Neglect is a Spatial Failure of Alerting Mechanisms Required for Awareness: An ERP Study

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Abstract: In the present study, we describe a group of right brain-damaged (RBD) patients with neglect or extinction, most of them affected in all three (visual, auditory, somatosensory) modalities studied. We applied event-related potential (ERP) analysis to reveal the neural mechanisms underlying hemispatial neglect. ERPs to stimuli of all three modalities were determined for the patients with neglect/extinction at (sub)acute phase, and 3 and 12 months post-stroke. Our results demonstrated that N1 deflections in ERPs, reflecting fronto-parietal alerting mechanisms, were absent or diminished/delayed in neglect, and the waves became normalized with recovery from neglect. In somatosensory ERPs, similar changes were evident also in P1 deflections preceding the N1, reflecting activation of the secondary somatosensory cortex (SII).

We also demonstrated somatosensory ERPs of some of our patients who showed different responses elicited by low intensity electrical stimulation of the median nerve at the wrist depending on the location of the hands either in uncrossed anatomical position or crossed over the body midline to the other hemispace. Our results indicate that there are cases among patients with hemispatial neglect who do indeed show emergence or increment of responses to left-hand stimulation when the arm is crossed to the right hemispace.

Therefore, we propose that the mechanism underlying hemispatial neglect is the disruption of the flow of (location related) sensory information to awareness at the level of multimodal alerting mechanisms.

Keywords: Neglect, alerting, awareness, event-related potential, recovery, space.

INTRODUCTION

Event-related potential (ERP) components reflect alerting, orientation, stimulus detection and discrimination, and memory processes [1], and stimulus awareness [2]. ERPs thus provide a useful tool in determining the information processing stage and the cognitive components disturbed or preserved in neglect patients. So far, neglect and extinction have been studied with visual stimulation [3-9] with results showing that the information flow in neglect patients is interrupted after primary processing. Furthermore, Marzi *et al*. [10] have described visual P1/N1 decline in a right brain-damaged (RBD) patient with visual extinction, thus demonstrating the correspondence between P1/N1 and conscious visual perception. In line with these findings, Eimer *et al*. [11] have demonstrated reduced P60 and N110 responses and conscious perception in a patient with somatosensory extinction. Although extinction and neglect are not the same phenomenon [12], these results indicate the level, at which disturbances inhibit the conscious perception of the stimulus, and thus induce extinction/neglect (for a review, see [13]). Recently, Tarkka *et al*. [14] described amplitude decrement of auditory and visual N1 component as well as decrement or non-existence of mismatch negativity (MMN) responses (reflecting auditory sensory memory) to left-side stimulation in neglect patients.

There have been some interesting reports on ERP components related to stimulus awareness in normal subjects (for a recent review on visual awareness, see [2]), which may bear close resemblance to the mechanisms underlying neglect. Koivisto *et al*. [15] demonstrated the relation between visual awareness and posterior negative amplitude shift 130-320 ms after the stimulus in visual ERPs of normal subjects. Schubert *et al*. [16] demonstrated that conscious perception of somatosensory stimuli correlated with P100 and N140 amplitude enhancements in somatosensory ERPs. They concluded that early activation of the primary somatosensory cortex (SI) was not sufficient to warrant conscious stimulus perception. Thus, the level of conscious perception seems to require activation of the secondary somatosensory cortex (SII) reflected by P100 [17, 18], followed by activation of posterior parietal cortices reflected by N140 [19-21]. In their recent review on somatosensory awareness, Gallace and Spence [22] postulate that following primary processes (at SI), SII,

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insula, posterior parietal areas and temporoparietal junctions, and premotor cortices are involved in somatosensory awareness, or conscious perception of somatosensory stimuli.

The first aim of the present study was to measure ERPs to visual, auditory, and somatosensory stimuli in neglect patients as well as in healthy control subjects to further verify the mechanisms underlying hemispatial neglect. In addition, ERPs to stimuli of all three modalities were determined in the patients with neglect/extinction at the (sub)acute phase and 3 and 12 months post-stroke. We will describe a rather uniform decline of N1 (N140) waves in responses to stimuli of different modalities, associated with disturbed multimodal alerting mechanisms in (sub)acute hemispatial neglect, and the further normalization of the weakened N1 waves as neglect recedes.

Somatosensory hemineglect has provided excellent examples of the true spatial nature of neglect, that is, neglect being connected to the hemispace and not to the limb. Smania and Aglioti [23] found in a touch detection task that RBD patients with left hemispatial neglect detected left-hand stimulation with an accuracy of 36% in the uncrossed anatomical position, whereas crossing the arms resulted in a detection accuracy of 65% of the left-hand stimuli. Right-hand detection was 100% in the uncrossed anatomical position, and 99% in the crossed position. Moving the right arm into the neglected hemispace did not cause neglect of the stimuli. Thus, moving the neglected left arm into the right hemispace improves touch detection, whereas moving the non-neglected right arm into the neglected hemispace has no effect on touch detection.

Aglioti, Smania, and Peru [24] compared the ability of normal subjects, and left brain-damaged (LBD) and RBD patients with or without somatosensory extinction or somatosensory neglect to detect a light touch delivered to the left or right hand, or both hands simultaneously. The hands were either in the anatomical position or crossed over to the other hemispace. Normal subjects and patients without somatosensory extinction performed better when the hands were in the anatomical position than when they were in the crossed position. Patients with somatosensory extinction detected contralesional (left hand) stimuli with higher accuracy in the crossed than in the uncrossed anatomical position.

So far, there are two studies on the effects of trunk posture or arm position on ERPs of neglect patients and normal subjects. Spinelli and Di Russo [25] showed that trunk rotation to the left shortened the previously lengthened P100 latencies of visual evoked potentials to left visual field stimulation in left hemispatial neglect patients. Eimer *et al*. [26] demonstrated rather elegantly in normal subjects that cross-modal attentional links are not determined by hemispheric projections, but by common external locations. They showed that focusing attention to the hand, while in hands-uncrossed or -crossed position, modified the ERPs to spatial auditory or visual stimuli. The somatosensory evoked potential (SEP) was also strongly affected by hand positions, with delayed and smaller attentional effects for crossed than uncrossed hands. The authors concluded that this may reflect the combined influence of anatomical and external spatial codes within the somatosensory modality, while cross-modal links depend only on the latter codes.

All the studies mentioned above demonstrated the role of spatial factors in the perception of unilateral stimuli. In the present study, we demonstrate some patients with hemispatial neglect who show different somatosensory ERPs elicited by low intensity electrical stimulation of the median nerve at the wrist depending on the location of the hand either in the uncrossed anatomical position or crossed over to the other hemispace. Thus, we will show that among the patients with hemispatial neglect, there are cases that indeed show changes in somatosensory ERPs comparable to those demonstrated in previous behavioral studies.

MATERIALS AND METHODS

Control Group

Seven healthy, age-matched (46-68 years, mean age 56.6 years; 4 females, 3 males), right-handed subjects participated in auditory, visual, and somatosensory ERP measurements. All the control subjects were tested neuropsychologically and with the detection test in the same way as the patients (see Neuropsychological diagnosis).

Neglect Patients

The patients were recruited from the Turku University Hospital, where they were treated for stroke. The patient group consisted of 15 patients (46-69 years, mean age 57.6 years; 5 females, 10 males) with right hemisphere lesions and left hemispatial neglect. The detection test in all three modalities could be obtained from nine patients, and ERP measurements in

all three modalities from 13 patients. Five patients participated in follow-up ERP measurements either from (sub)acute or 3 months onward. The recordings from some patients, especially in the acute phase, were too noisy to be analyzed, or allowed too few trials for averaging. Grand averaging over the patient data was not possible due to large inter-individual differences. For these reasons, only the data from individual patients with clear ERP responses are reported.

The experiment was approved by the ethics committee of the Soutwestern Finland Hospital District. All procedures were carried out with an adequate understanding and written consent of the patients and healthy controls.

Neuropsychological Diagnosis

In patients, stroke locations were confirmed with computer tomography (CT) and magnetic resonance imaging (MRI), and the severity of stroke was assessed with the National Institute of Health (NIH) stroke scale [27]. The symptoms and severity of neglect were diagnosed with an extensive clinical battery of conventional paper-and-pencil type or non-conventional (behavioural) tasks such as subtests from the Behavioral Inattention Test (BIT) [28]. The neuropsychological features of the patients are described in full detail by Lindell *et al*. [29].

Visual and somatosensory sensory deficits were estimated during a routine neurological examination [27]. We also applied a somatosensory search board developed for measuring somatosensory and spatial aspects of neglect [29]. Hearing was tested with the standard hearing threshold method using similar 1000 Hz tones as applied in ERP recordings. Visual fields were tested with finger perimetry and the Goldmann perimetry method.

A behavioral stimulus detection test was performed in visual, auditory, and somatosensory modalities with similar stimuli used in ERP measurements, but with a longer (2.0 s) inter-stimulus-interval (ISI). Subjects were asked to verbally report the spatial location of each stimulus (right, left, or both). For most of the patients, 20-30 trials were enough to reveal the inability to detect the stimuli coming from the left. This was especially the case in the acute phase when many patients had great difficulties orienting to the task and the situation as a whole. At later stages, no such problems were usually encountered. Control subjects made no mistakes in the detection tests.

Stimuli

Visual stimuli were yellow light emission diode (LED) flashes with a duration of 100 ms. Two LEDs were set at a 50 cm distance in front of the subject at a 40° angle from the gaze line when looking straight ahead. Auditory stimuli were 1000 Hz tones delivered *via* two speakers located at a 25 cm distance from the ears at a 90° angle. Unilateral sounds were applied with loudness of 84 dB, and bilateral loudness was 78 dB to balance the subjective loudness between unilateral and bilateral stimulation. Somatosensory stimuli were electric pulses with a pulse width of 0.1 ms delivered to the median nerve at the wrist using disposable electrodes attached to the skin above the nerve. The intensity was set individually just below the threshold for eliciting a thumb twitch, first for the intact ipsilesional side and then at about the same intensity contralesionally.

ERP Measurements

ERP was recorded at the Department of Clinical Neurophysiology, Turku University Hospital. Subjects were lying in a half sitting position on a hospital bed in a dimly lit laboratory room, and instructed to relax and direct their eyes to the fixation point during stimulus presentation. ERPs were recorded to visual, auditory, and somatosensory stimulus sequences. All stimulus sequences contained 600 stimuli: 200 left, 200 right, and 200 bilateral stimuli presented in random order. The ISI was 500 ms (from onset to onset) in all stimulus sequences. Somatosensory ERP was recorded twice always in the same order, first with the arms in the uncrossed anatomical position resting by the subject's side, and then with the arms crossed on the chest, with the hands extending to the contralateral hemispaces. It was not allowed to look at the arms during the electroencephalogram (EEG) measurements. The experiment including preparation for EEG recordings and stimulus presentation for each modality lasted altogether about 1.5 h.

Twenty Ag/AgCl electrodes were placed on the scalp according to the international 10-20 system (Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, Pz, P3, P4, Oz, O1, O2, T7, T8, P7, P8). The electrodes were referenced to linked earlobes and the right arm was used as the ground. Electrode impedances were kept below 5 kΩ. Continuous EEG was recorded with the NeuroScan systems (Charlotte, NC) including a SynAmp amplifier (×30,000). The sampling rate was 400 Hz and a bandpass filter was set at 0.1-40 Hz. The

notch filter was set at 50Hz. Eye movements were recorded with two electro-oculogram (EOG) electrodes placed below the left eye (EOGL) and at the canthus of the right eye (EOGR). Since we used the same EEG recording parameters for all three modalities, early somatosensory components (20-80 ms) were not visible due to low digitization rate and narrow bandpass.

Continuous EEG data were divided offline into 500 ms epochs including a 50 ms prestimulus baseline. Baseline correction was performed and epochs with artefacts (deflections exceeding ±70 μV) were rejected using EOG and Fp electrodes as criteria. Epochs were further checked visually for any remaining obvious artifacts. Accepted epochs were averaged separately for the stimulation side (right, left, bilateral), and arm position (uncrossed, crossed) for somatosensory stimuli. The averaged responses were further digitally filtered (bandpass 1-20 Hz). Peak latencies of the ERP components were measured in the average waveforms, and mean amplitudes were calculated in single trials at a 10 ms interval centered at the peak latencies of the corresponding ERP components to provide 95% confidence intervals (CI) for individual patient data. The control group data were tested with one-sample t-tests whether the amplitudes of ERP components were significantly different from zero (one-tailed).

Statistical Analysis

Conventional P1, N1, and P2 components were considered for visual and auditory modalities. For the somatosensory modality, the ERP components of special interest were P50, P100, and N140, followed by late positivity [17]. P50 and P100 have been proposed to originate from the SI and SII, respectively. For

Table 1: Average Peak Latencies (ms) and Amplitudes (μV) of Main ERP components (P1, N1, P2) from Individual Control Subject Data

		P3			P4		
		P1	**N1**	**P2**	**P1**	**N1**	**P2**
Visual	Right	128 0.2	213 -1.1	295 0.7	148 0.1	213 -0.8	293 0.8
	Left	123 0.4	200 -0.8	295 0.6	118 0.3	203 -0.8	320 0.5
	Both	120 0.5	198 -1.0	378 1.0	125 0.6	195 -1.1	383 0.7
			C3			C4	
		P1	N1	P3	P1	N1	P3
Auditory	Right	73 1.1	140 -3.2	260 1.7	70 1.1	133 -2.8	255 1.5
	Left	65 0.9	135 -2.7	223 1.4	65 1.3	133 -3.3	223 1.3
	Both	73 1.1	135 -2.2	218 1.2	73 1.1	135 -2.2	218 1.3
Somatosensory (uncrossed)	Right	73 2.0	105 -1.9	218 0.8			
	Left				73 1.6	103 -2.3	250 1.4
	Both	73 0.7	100 -2.2	233 1.3	75 0.9	103 -2.1	253 1.5
Somatosensory (crossed)	Right	73 1.9	105 -2.3	213 1.0			
	Left				75 2.1	105 -2.0	248 1.3
	Both	75 1.3	103 -2.1	230 1.5	75 1.6	105 -2.1	245 1.6

comparability with the other modalities, we use here the nominations P1 for P100, N1 for N140, and P2 for late positivity.

The C3 and C4 channels placed at the left and right central scalp areas, respectively, were chosen for auditory and somatosensory data analysis, and posterior P3 and P4 channels at the left and right parietal areas, respectively, were chosen for visual data. For the control group, peak latencies and amplitudes of the ERP components were measured in the grand average waveforms across subjects (Table **1**), and mean amplitudes were calculated for each subject at a 10 ms interval centered at the peak latencies of the corresponding grand average (Table **2**). The control group data were tested with one-sample

Table 2: Mean amplitudes (μV, ± SD) of main ERP components (P1, N1, P2) in the control group. Amplitudes that are significantly different from zero in the direction of their polarity according to one-sample t-tests (one-tailed) are marked in bold, and t- and p-values are listed below the amplitude.

		P3			P4		
		P1	**N1**	**P2**	**P1**	**N1**	**P2**
Visual	Right	0.2 ± 0.4	**-1.1 ± 0.8**	**0.7 ± 0.9**	0.1 ± 0.3	**-0.8 ± 0.8**	**0.7 ± 0.8**
	t	0.969	-3.521	2.067	1.258	-2.370	2.381
	p	0.185	0.006	0.042	0.128	0.028	0.028
	Left	0.3 ± 0.6	**-0.8 ± 0.3**	**0.6 ± 0.8**	0.3 ± 0.5	**-0.8 ± 0.4**	0.5 ± 0.7
		1.526	-7.680	2.026	1.728	-4.868	1.941
		0.089	<0.0005	0.045	0.068	0.002	0.050
	Both	**0.5 ± 0.6**	**-1.0 ± 0.3**	**1.0 ± 0.4**	**0.5 ± 0.4**	**-1.0 ± 0.7**	**0.7 ± 0.4**
		2.183	-8.628	7.610	3.315	-3.744	4.576
		0.036	<0.0005	<0.0005	0.008	0.005	0.002
			C3			C4	
		P1	N1	P2	P1	N1	P2
Auditory	Right	**1.0 ± 0.9**	**-3.2 ± 0.9**	**1.7 ± 0.9**	**1.1 ± 0.6**	**-2.8 ± 0.8**	**1.5 ± 1.0**
		3.108	-9.169	4.861	4.903	-9.406	4.093
		0.011	<0.0005	0.002	0.002	<0.0005	0.003
	Left	**0.9 ± 0.8**	**-2.7 ± 0.5**	**1.4 ± 0.9**	**1.3 ± 0.8**	**-3.3 ± 0.7**	**1.3 ± 0.8**
		2.852	-13.594	4.017	4.092	-13.148	4.238
		0.015	<0.0005	0.004	0.003	<0.0005	0.003
	Both	**1.1 ± 0.6**	**-2.1 ± 0.7**	**1.2 ± 0.8**	**1.0 ± 0.5**	**-2.2 ± 0.9**	**1.3 ± 0.7**
		4.731	-8.488	4.026	5.530	-6.424	5.169
		0.002	<0.0005	0.004	0.001	0.001	0.001
Somatosensory (uncrossed)	Right	**1.9 ± 1.5**	**-1.8 ± 1.4**	0.8 ± 1.1			
		3.228	-3.299	1.829			
		0.009	0.008	0.059			
	Left				**1.5 ± 0.5**	**-2.2 ± 1.4**	**1.4 ± 0.6**
					7.526	-4.212	6.236
					<0.0005	0.003	0.001
	Both	0.6 ± 1.4	**-2.1 ± 1.5**	**1.3 ± 1.0**	**0.8 ± 0.8**	**-2.0 ± 1.5**	**1.5 ± 1.4**
		1.144	-3.639	3.430	2.607	-3.382	2.958
		0.148	0.006	0.007	0.020	0.008	0.013
Somatosensory (crossed)	Right	**1.8 ± 1.3**	**-2.2 ± 1.3**	**1.0 ± 0.9**			
		3.793	-4.516	3.154			
		0.005	0.002	0.010			
	Left				**1.9 ± 0.9**	**-1.9 ± 1.3**	**1.3 ± 0.7**
					5.492	-3.809	5.227
					0.001	0.005	0.001
	Both	**1.2 ± 1.0**	**-2.0 ± 1.2**	**1.5 ± 1.5**	**1.5 ± 0.7**	**-2.0 ± 1.5**	**1.6 ± 1.1**
		3.232	-4.422	2.614	5.635	-3.550	3.876
		0.009	0.002	0.020	0.001	0.006	0.004

t-tests whether the amplitudes of the ERP components were significantly different from zero (one-tailed depending on polarity, P or N).

For neglect patients, mean amplitudes of ERP components of individual patients were compared to t-distributions derived from control group sample statistics [30, 31] to determine whether they fall in the 95% range ($p > 0.05$) centered at the 'normal' control group mean. The formula for the test was

$$t_{n-1} = \frac{x^* - \bar{x}}{s\sqrt{\frac{n+1}{n}}}$$

where x^* is the patient's score, $\bar{x}$ and s are mean and standard deviation (SD) of the scores of the control sample, and *n* is the size of the control sample.

RESULTS

Control Group

Left, right, and bilateral stimulation mostly elicited significant ERP responses in terms of mean amplitude in visual and somatosensory (both arms-crossed and -uncrossed) modalities and all in the auditory modality in the control group (Table **1**). Visual grand average ERPs elicited by stimuli applied to the left, right, or both hemifields contained the same components (Figure **1**). The most prominent waveform was the N1 deflection of -0.9 μV, peaking at 203 ms latency. The N1 was preceded by a P1 deflection of 0.4 μV at 127 ms peak latency, which was most prominent to bilateral stimulation (0.5 μV). The N1 was then followed by a P2 component, which was largest to bilateral stimulation (0.9 μV), peaking at 380 ms latency.

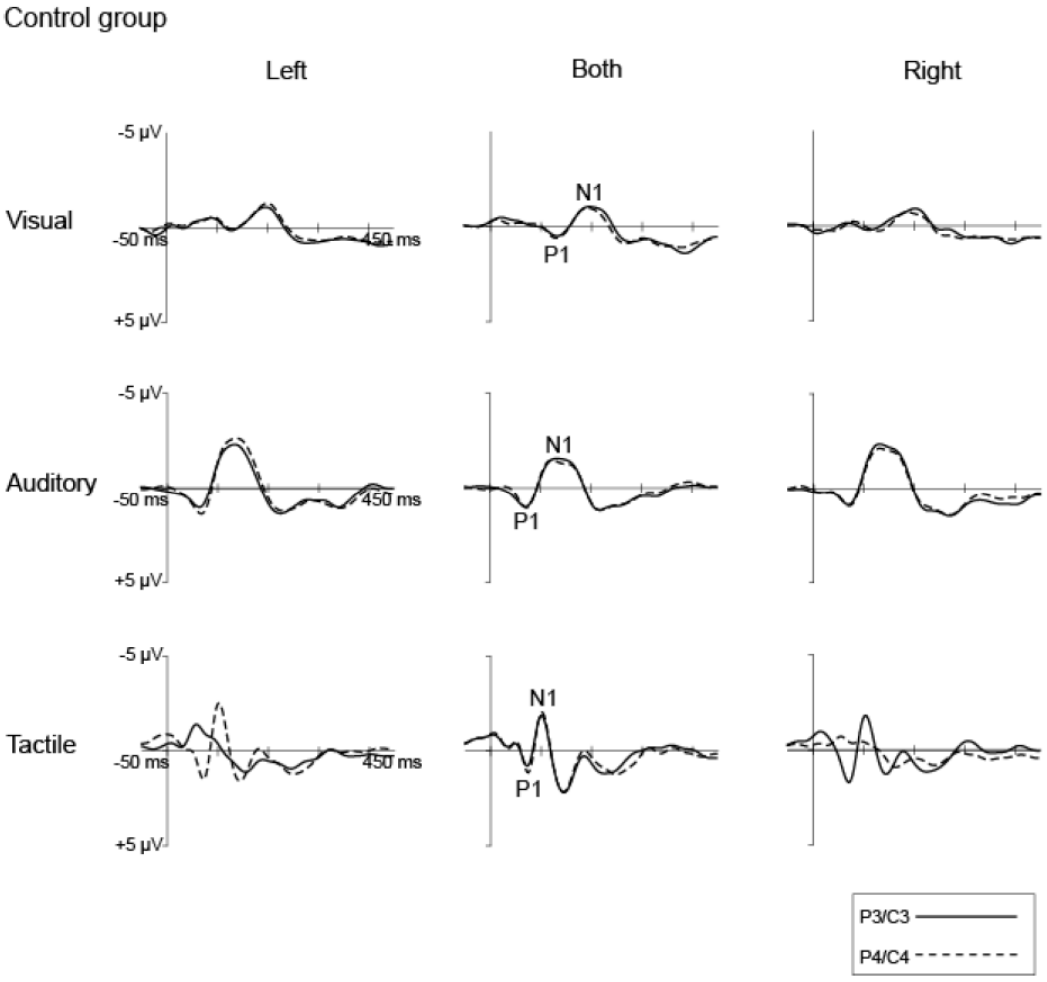

Figure 1: Control group's average ERPs to visual stimuli measured at P3 and P4, and auditory and somatosensory stimuli at C3 and C4. Stimuli were delivered to the left hemifield/wrist, right hemifield/wrist, or to both simultaneously. For visual and auditory ERPs, P1 and N1 deflections are marked; for somatosensory ERPs, P50, P100 (P1) and N140 (N1) deflections are marked. The scale (±5 μV) and the analysis period (50 ms prestimulus and 450 ms poststimulus period) are the same for each modality.

Auditory grand average ERPs were symmetrical on both hemispheres (Figure **1**). The N1 deflections of 2.7 μV, peaking at 135 ms latency, were elicited fronto-centrally. The N1 was preceded by a small P1 wave of 1.1 μV at 70 ms peak latency, and then followed by a small P2 wave of 1.4 μV, peaking at 233 ms latency. The ERPs were similar in all stimulus conditions, but curiously, the N1 amplitudes were slightly smaller in responses to bilateral than to unilateral stimulation.

In contrast to the visual and auditory responses, somatosensory grand average ERPs demonstrated clear-cut effects of the stimulation site and hemisphere (Figure **1**). Stimulation of the right and left median nerves produced the largest responses on the contralateral recording sites, regardless of the arm position, while bilateral stimulation produced similarly large responses bilaterally. Early positive deflections P50 and P100/P1 peaking here at 40 and 74 ms, respectively, were followed by a prominent N140/N1 wave of -2.1 μV, peaking already at 103 ms. The short onset and peak latencies of all these deflections reflect electrical stimulation of the median nerve at wrist instead of the slow onset mechanical stimulation of the skin and underlying mechanoreceptors in the fingers [17]. The N1 deflections were followed by a P2 component of 1.3 μV, peaking at 236 ms latency.

Multimodality of Neglect Reflected in both Behavior and ERPs

Some Individual Cases of Hemispatial Neglect/Extinction

The current study found no case of unimodal neglect. All nine patients studied with the detection test had visual neglect in both neuropsychological and visual detection tests. Evaluation of the degree of visual neglect was based on the neuropsychological tests. Seven patients had neglect symptoms in all three sensory modalities tested, whereas the two remaining patients did not show neglect in either auditory or somatosensory modality.

Patient #05 in Acute Phase: Multimodal Neglect with Decline of Corresponding N1 Responses

The patient was a 52-year-old right-handed male who had suffered a subcortical hemorrhage affecting the right capsula interna and parts of the putamen. At the acute phase, he showed strong visual neglect in the conventional BIT tests. A partial left hemianopy was found with the finger perimetry 14 days after the stroke. Hearing threshold was within normal limits. He had severe deficits in the sensation of pain, touch, and posture in the left side of the body. The only symptom he experienced in the acute phase was the paralysis of left limbs. ERP measurements were performed first in the acute phase (17 days post-stroke), and during ERP recordings, he could only report the stimuli delivered to the right median nerve.

The patient demonstrated severe visuospatial neglect in neuropsychological test. He was not able to find any lines in the left hemispace in the line cancellation test. The visual detection test showed that he did not notice the LED flashes in the left visual field. He heard all the auditory stimuli in the auditory detection test but reported them as coming from the right side. Thus, the patient did not neglect the left-side auditory stimuli themselves but the hemispace where they were presented (for a review on different types of auditory neglect, see [32]). The somatosensory search test indicated mild difficulties in searching for objects in the left hemispace. In the somatosensory detection test, he could not report any of the left stimuli even if asked to pay special attention to the left wrist, indicating also the possible presence of hemianesthesia.

Left visual field stimulation only elicited a late low-amplitude negative wave (P4: -1.7 μV, 293 ms, t_6 = -2.046, p = 0.087) (Figure **2**). It could be interpreted as a delayed N1 wave because of its fronto-central distribution. Right visual field stimulation elicited a normal-shaped but delayed N1 deflection contralaterally (P3: -2.6 μV, 247 ms, t_6 = -1.711, p = 0.138). Bilateral stimulation elicited an enlarged N1 wave (P3: -5.3 μV, 238 ms, t_6 = -12.704, p < 0.0005). No clear-cut earlier or later waves could be observed. Auditory responses were quite obscure in all stimulus conditions. The N1 could be identified at normal latencies in the left hemisphere to right-side stimulation (C3: -5.2 uV, 108 ms, t_6 = -2.096, p = 0.081). No earlier or later waves could be identified. Recognizable responses to somatosensory stimuli were mainly seen on the left hemisphere. There was a clear-cut difference between stimulation sites in somatosensory ERPs: Only small early deflections, normally preceding the N1 deflections, could be seen to left-side stimuli (C3: -1.3 μV, 40 ms, n.a.), whereas very large P1 (C3: 4.2 uV, 53 ms, t_6 = 1.441, p = 0.200), N1 (C3: -7.2 uV, 110 ms, t_6 = -3.521, p = 0.013), and P2 (C3: 5.6 uV, 252 ms, t_6 = 4.016, p = 0.007) deflections were elicited by right-side stimuli. P2 deflections were also recognizable on the right hemisphere.

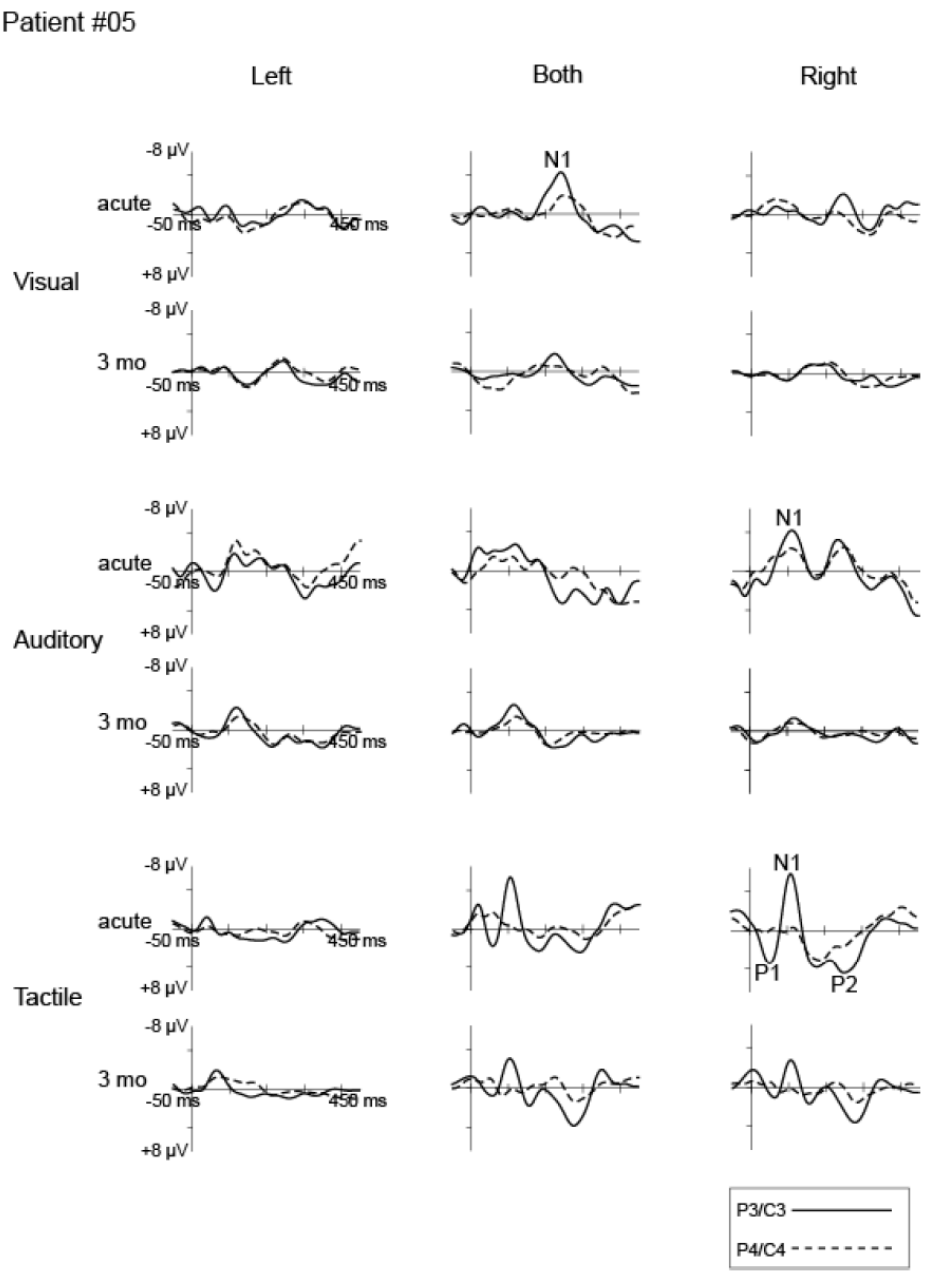

Figure 2: Patient #05: ERPs to visual, auditory, and somatosensory stimuli measured in A. acute phase (17 days post-stroke) and B. 3 months post-stroke. The scale and analysis periods are the same for all responses.

To summarize, visual ERPs were consistent with the neuropsychological status: Left visual field stimulation barely elicited N1 waves, whereas the N1 was rather normal, even though delayed, to right-side and bilateral stimuli on the left hemisphere. Interestingly, the N1 response to bilateral visual stimulation was about twice as large as that to right-side stimulation, suggesting that left stimuli were also processed at some level. The appearance of auditory responses, even though rather obscure, is consistent with the detection test results showing that the patient did detect the left as well as the right sounds even though he was not aware of the left hemispace. Finally, the clear-cut difference in P1, N1, and later waves in the responses elicited by left- and right-side somatosensory stimulation again coincided well with neglect and possible hemianesthesia in the somatosensory modality.

Patient #14 in Subacute Phase: Multimodal Neglect and Decline of N1 Responses

The patient was a 46-year-old male with right fronto-parietal lesion (involving inferior parietal lobe) due to middle cerebral artery infarction. In the subacute phase

(37 days post-stroke), he had mild to moderate neglect including personal neglect. As shown by the detection test, he also demonstrated neglect in auditory and somatosensory modalities.

Right visual field stimulation elicited ERPs with distinct N1 deflections over the left contralateral hemisphere (P3: -1.1 μV, 153 ms, t_6 = -0.006, p = 0.996) (Figure **3**). These responses were comparable to those elicited by simultaneous stimulation of both hemifields. In contrast, left visual field stimulation elicited only small-amplitude posterior responses with a smaller N1 (P4: -0.5 μV, 151 ms, t_6 = 0.613, p = 0.562). Visual P1 deflections were rather small or absent in all conditions. More distinct auditory ERPs with N1 deflections were again obtained to auditory stimuli applied to the right hemifield (C3: -1.7 μV, 143 ms, t_6 = 1.497, p = 0.185) and bilaterally (C3: -1.2 μV, 175 ms, t_6 = 1.320, p = 0.235) than when the stimuli were applied to the left hemifield (C3: -0.4 μV, 160 ms, t_6 = 4.097, p = 0.006). Again, auditory P1 deflections were rather obscure in all stimulus conditions. Finally, the most striking difference between stimulation sites was seen in the somatosensory modality. Left median nerve stimulation elicited almost no response, whereas right-side and bilateral stimulation produced prominent somatosensory ERPs with large early positive peaks (Right, C3: 3.6 μV, 44 ms, t_6 = 1.072, p = 0.325; Bilateral, C3: 3.2 μV, 46 ms, t_6 = 1.783, p = 0.125) followed by large N1 deflections (Right, C3: -2.8 μV, 78 ms, t_6 = -0.656, p = 0.536; Bilateral, C3: -1.6 μV, 76 ms, t_6 = 0.284, p = 0.786), especially on the left hemisphere. To summarize, the patient demonstrated a close correlation between left hemispatial neglect in all three modalities and deterioration of corresponding ERPs. The most striking effect was seen for N1 waves in all modalities, and also for P1 in SEPs.

Patient #06 after 3 Months: Visuo-Somatosensory Neglect and Decline of Corresponding N1 Deflections

This 49-year-old right-handed male participated in the ERP study 88 days post-stroke. He had a large brain lesion in the right hemisphere extending to the temporal, parietal, and occipital lobes in the regions of the medial cerebral artery (internal carotid artery infarction). He had, consequently, a severe left-side paralysis and the somatosensory sensibility was

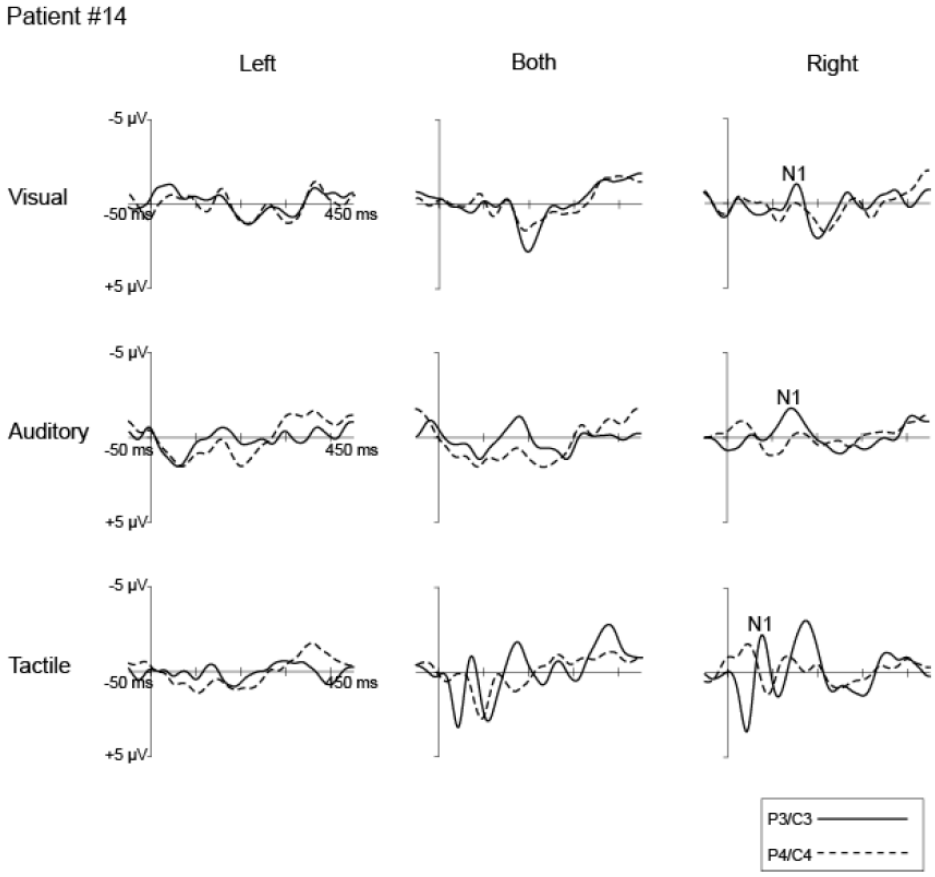

Figure 3: Patient #14: ERPs to visual stimuli measured at P3 and P4, and auditory and somatosensory stimuli at C3 and C4. The scale and the analysis period are the same for all modalities/responses.

remarkably weakened on the side contralateral to the lesion, particularly in the upper limb. The patient did not have any primary deficits in the visual fields.

The patient demonstrated mild visual and severe somatosensory, but no auditory neglect. He had no problems in hearing and locating the tones in the auditory detection test. In the somatosensory search test, he was not able to find any objects in the left hemispace. The somatosensory detection test revealed that sensations elicited by the left-side stimuli were weaker, indicating also a primary somatosensory deficit.

Left visual field stimulation elicited only a small N1 deflection (P4: 0.6 μV, 90 ms, t_6 = 3.050, p = 0.022) (Figure **4**) but nevertheless a normal fronto-centrally distributed P2 wave (P4: 2.5 μV, 355 ms, t_6 = 2.777, p = 0.032). Right visual field as well as bilateral stimulation evoked large N1 waves that were abnormally large over the left scalp (Right, P3: -3.4 μV, 205 ms, t_6 = -2.620, p = 0.040; Bilateral, P3: -3.7 μV, 213 ms, t_6 = -7.948, p < 0.0005), while P2 waves were largest to the bilateral visual stimuli (P4: 3.2 uV, 313 ms, t_6 = 5.776, p = 0.001). No clear P1 deflections were seen in any of the stimulus conditions. All auditory stimuli elicited rather normal N1 responses, but the largest responses were obtained at the left hemisphere to right-side stimulation (C3: -2.3 μV, 147 ms, t_6 = 0.881, p = 0.412). Rather clear P1 deflections were seen over the left hemisphere to left- (C3: 1.6 μV, 95 ms, t_6 = 0.844, p = 0.431) and right-side (C3: 1.3 μV, 65 ms, t_6 = 0.279, p = 0.789) stimulation. Right-side somatosensory stimulation elicited distinct P1 (C3: 1.1 μV, 56 ms, t_6 = -0.465, p = 0.658) and N1 waves (C3: -3.0 μV, 95 ms, t_6 = -0.787, p = 0.461) over the left normal hemisphere, whereas the following P2 wave was seen over both hemispheres, but it was far larger over the left normal hemisphere (C3: 5.5 μV, 230 ms, t_6 = 3.932, p = 0.008). Corresponding to behavioral findings, that is, partial hemianesthesia plus neglect, left median nerve stimulation elicited rather flat responses. The ERP response to bilateral stimulation was surprisingly similar to the responses to right-side stimulation.

To summarize, neuropsychological and detection tests revealed neglect in visual and somatosensory modalities. In addition, ERPs to both visual and

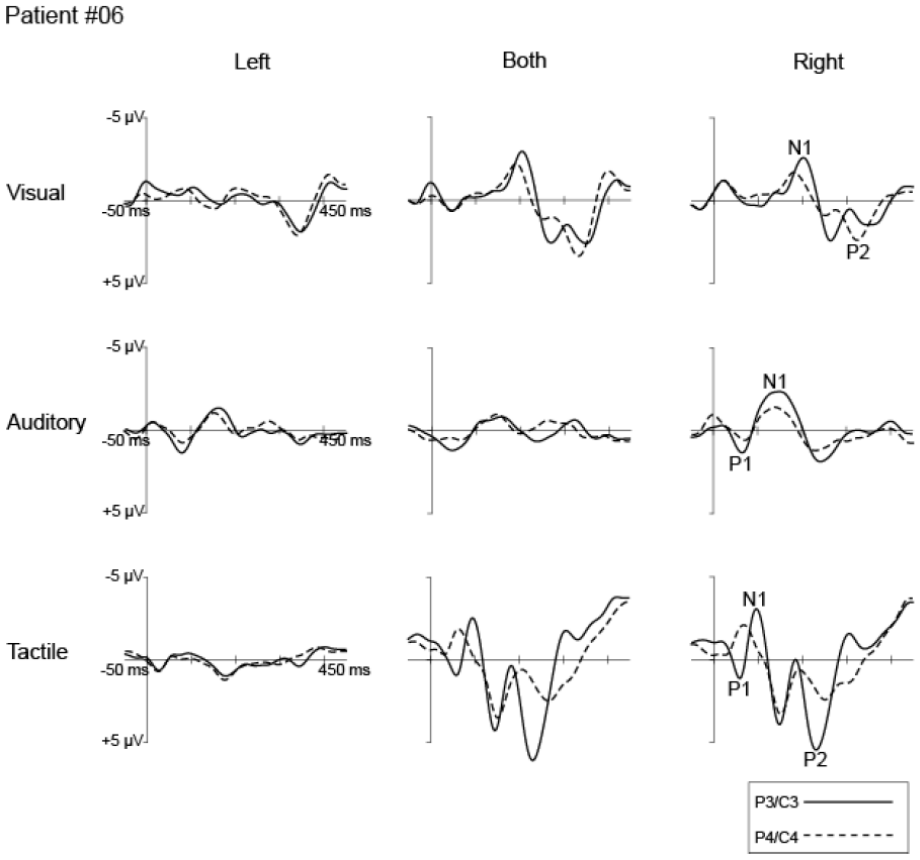

Figure 4: Patient #06: ERPs to visual, auditory, and somatosensory stimuli measured 3 months post-stroke. The scale and the analysis period are the same for all modalities/responses.

somatosensory contralesional stimuli were distinctly abnormal, the N1 and also somatosensory P1 deflections being absent or greatly diminished in the responses to stimuli applied to the left neglected side. In visual ERPs, later P2 waves were present.

Recovery from Neglect

Patient #05 71 Days Post-Stroke: No Visual Neglect, Altered Auditory Perception, somatosensory Extinction, and Corresponding P1 and N1 Responses

In 71 days, the patient had recovered quite remarkably from neglect, and performed well on the neuropsychological tests. He had no visual neglect anymore, and auditory and somatosensory performances demonstrated fluctuating right and left extinction (or confusion), but no neglect. During the visual detection test, he could see and locate all visual stimuli. He showed auditory extinction, reporting, surprisingly, that bilateral stimuli are coming from the left side or from the front. He could weakly sense somatosensory stimuli in the somatosensory detection test only when stimulus intensity at the left wrist was increased. He had trouble in bilateral somatosensory stimulation, reporting sometimes 'left' and sometimes 'right', demonstrating fluctuating somatosensory extinction.

The patient showed more normal (Figure **2**, cf. Figure **1**) visual responses with P1, N1, and P2 waves in all stimulus conditions, with only delayed peak latencies (242 ms for N1) of the waves to left visual field stimulation as a marker of receding neglect. The peak latencies of the N1 deflection to right-side stimulation were shorter (155 ms over the left hemisphere) than in the acute phase. Compared to the acute phase, the N1 on the left healthy hemisphere was now diminished, that is, normalized for right-side (P3: -1.0 μV, 178 ms, t_6 = 0.108, p = 0.917) and bilateral (P3: -1.8 μV, 230 ms, t_6 = -2.300, p = 0.061) stimulation. Thus, recovery from visual neglect coincided with the appearance of more distinct responses with shorter latencies to left-side stimulation, and reduction of the pathologically large N1 amplitudes in responses to right-side and bilateral stimulation. Auditory ERPs demonstrated rather normal N1 deflections, elicited with both left (C4: -1.7 μV, 123 ms, t_6 = 2.220, p = 0.068) and right (C3: -1.7 μV, 123 ms, t_6 = 1.497, p = 0.185) auditory stimuli. Thus, there is no direct counterpart for the right-biased/fluctuating extinction in auditory perception. Somatosensory ERPs showed no recognizable waves to left stimuli, whereas the responses to right and bilateral stimuli became rather normal. Responses to left stimulation were flat with only some early deflections being observable. Right-side and bilateral stimuli elicited left hemisphere responses with the same identifiable deflections as in the acute phase, but the P1 (Right, C3: 1.1 uV, 73 ms, t_6 = -0.465, p = 0.658; Bilateral, C3: 1.1 μV, 73 ms, t_6 = 0.348, p = 0.740), N1 (Right, C3, -3.7 uV, 105 ms, t_6 = -1.242, p = 0.261; Bilateral, C3: -3.7 μV, 105 ms, t_6 = -1.032, p = 0.342), and P2 (Right, C3: 4.3 uV, 278 ms, t_6 = 2.933, p = 0 026; Bilateral, C3: 4.2 μV, 278 ms, t_6 = 2.620, p = 0.040) waves were of rather normal size compared to the exaggerated deflections in the acute phase.

To summarize, visual ERPs were consistent with the recovery process: When the neglect symptoms had decreased, visual ERPs had also evidently normalized. However, left stimuli were still processed more slowly than right ones. Despite the fluctuating right-left extinction shown by the patient after 71 days, auditory ERPs seemed rather normal at this time. Left-side somatosensory stimulation still elicited a surprisingly flat response, although the patient was, according to the somatosensory detection test, aware of at least some of the stimuli delivered to his left wrist. Apparently, the patient had recovered from neglect in a little over 2 months – he had no difficulties in exploring the left hemispace when blindfolded in the somatosensory search test – but due to possible primary somatosensory deficits, ERPs to left stimuli had remained as pathological as in the acute phase.

Patient #16 in Acute Phase and 3 Months Post-Stroke: Reappearance of Visual Perceptions and Visual N1

The patient was a 68-year-old male who had a parietal damage involving the inferior parietal lobule and inferior parieto-temporal junction, and extending to the somatosensory cortex. His neuropsychological status was assessed at the acute phase and after 3 months (and further 12 months), finding severe neglect involving personal neglect and then very slight or no neglect, respectively. He demonstrated a remarkably good recovery from neglect with corresponding changes in visual ERPs. Unfortunately, only visual ERP follow-up was available in this case.

There was a large difference in visual responses to right- and left-side stimuli in the acute phase (Figure **5**). Right-side stimulation elicited large P1 (P3: 0.9 uV, 98 ms, t_6 = 1.559, p = 0.170), N1 (P3: -2.9 uV, 155 ms, t_6 = -2.052, p = 0.086), and P2 (P3: 4.2 uV, 229 ms, t_6 = 3.482, p = 0.013) deflections especially on the left intact hemisphere. Also clear responses, although of

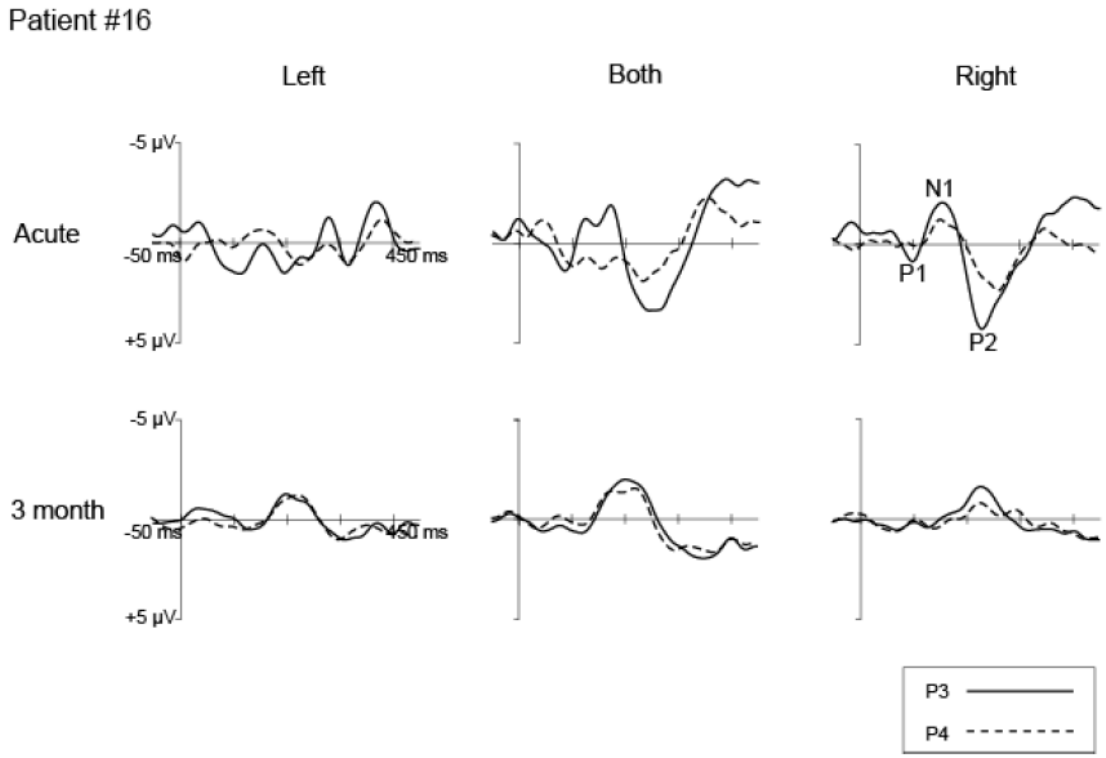

Figure 5: Patient #16: Visual ERPs measured at acute phase and 3 months post-stroke, measured at P3 and P4.

far smaller amplitude, could be seen to left-side stimulation. This difference coincided well with neglect. After 3 months, the left neglect had receded, and rather similar responses were seen on both hemispheres, regardless of the side of stimulation.

Space and Neglect: Evidence from Somatosensory ERPs

Control Group

Control group's average somatosensory ERPs responses to electrical pulses delivered to the right and left median nerve, and bilaterally at the wrist when the arms were in uncrossed anatomical and crossed position are provided in Figure **6**. There was a mismatch between arms-crossed and -uncrossed conditions at around 140 ms: less positive in the arms-crossed condition.

Patient #05: Emerging ERP to Left-Hand Stimulation in Right Hemispace

See above for clinical description of the patients.

Somatosensory ERPs evoked by unilateral stimulation of the right hand in the uncrossed position (Figure **7**) showed distinct responses with prominent P1 (C3: 4.5 µV, 53 ms, t_6 = 1.625, p = 0.155), N1 (C3: -9.7 µV, 108 ms, t_6 = -5.148, p = 0.002), and P2 (C3: 4.0 µV, 248 ms, t_6 = 2.683, p = 0.036) waves over the contralateral left hemisphere. In contrast, responses to left hand stimulation in the uncrossed position were absent, which coincides with the patient's inability to sense electric pulses. Responses to bilateral stimulation resembled those caused by unilateral right-hand stimulation: P1 (C3: 3.0 µV, 53 ms, t_6 = 1.647, p = 0.151), N1 (C3: -6.8 µV, 103 ms, t_6 = -2.974, p = 0.025), and P2 (C3: 2.7 µV, 290 ms, t_6 = 1.252, p = 0.257).

In the crossed position, responses evoked by right-hand stimulation resembled those evoked in the uncrossed position: P1 (C3: 2.8 µV, 55 ms, t_6 = 0.695, p = 0.513), N1 (C3: -8.8 µV, 115 ms, t_6 = -4.812, p = 0.003), and P2 (C3: 4.1 µV, 253 ms, t_6 = 3.423, p = 0.014). In contrast, left-hand stimulation with the hand now in the right hemispace evoked a large negative wave at 160 ms peak latency, followed by a distinct P2 wave. The response was most prominent over the intact left hemisphere (C3: N1, -3.8 µV, 160 ms, t_6 = -1.171, p = 0.286; P2, 4.0 µV, 293 ms, t_6 = 3.313, p = 0.016) and decreased in amplitude over to the injured right hemisphere. The N1 (C3: -7.5 µV, 123 ms, t_6 = -4.309, p = 0.005) evoked by bilateral stimulation in the crossed position was comparable to that elicited in the uncrossed position.

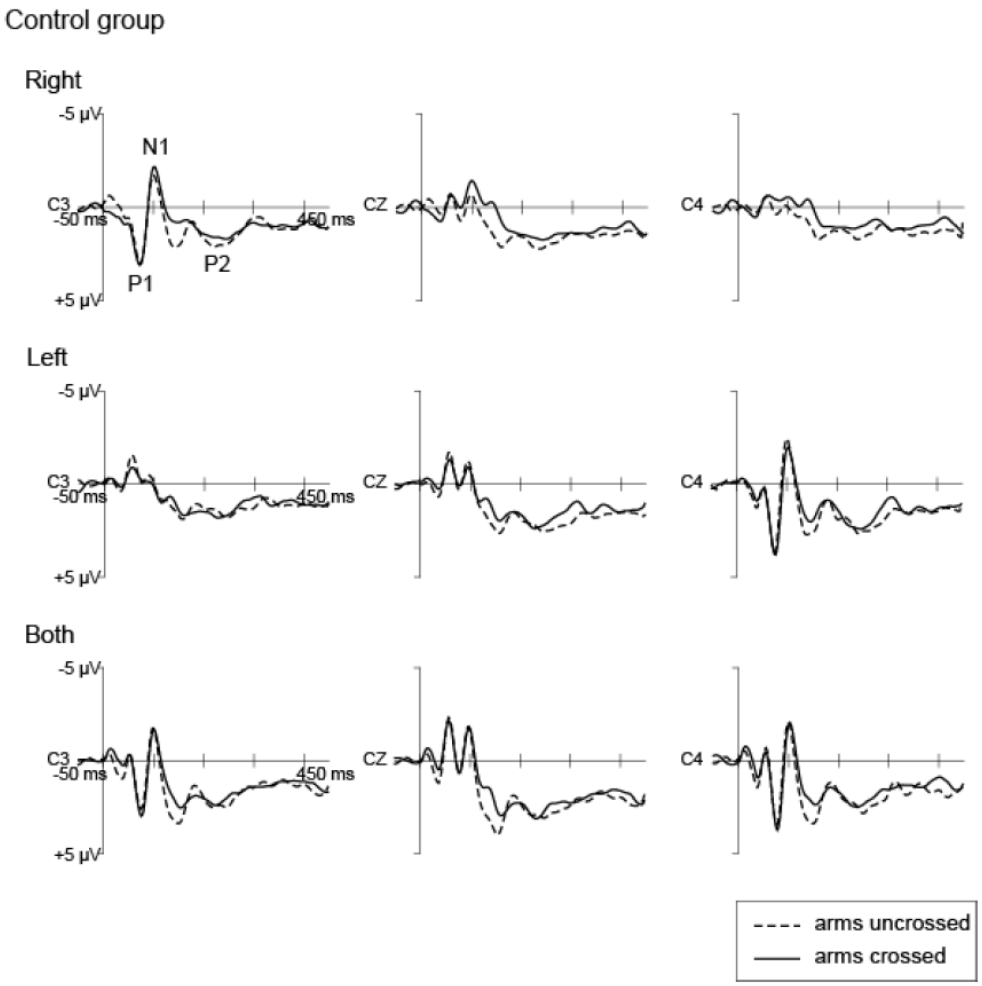

Figure 6: Control group's average somatosensory ERPs recorded at C3, Cz, and C4 to electrical pulses delivered randomly to right and left median nerve and bilaterally at the wrist when the arms were straight, that is, in uncrossed anatomical position (dotted traces), and when the arms were crossed (continuous traces). The scale was ±5 µV and the analysis period was 50 ms prestimulus and 450 ms poststimulus period.

The patient's ERPs were also measured after 3 months. By that time, the patient no longer showed neglect symptoms. Responses to right-hand stimulation had become normal, and crossing the arms no longer changed responses to left-hand stimulation.

Patient #15: Emerging ERP to Left-Hand Stimulation in Right Hemispace

The patient was a right-handed male and had a cortical hemorrhage in the middle of the right parietal lobe near the Sylvian fissure at the age of 65. The patient had left hemianesthesia and left visual field deficit. This caused general inattention: The patient omitted targets in cancellation tasks on both sides. The patient started the cancellation tasks from the right side, which is an abnormal searching strategy not seen in healthy controls. He had no motor deficits but touch sensations on the left palm were weak. He was able to report stimulation of the right hand correctly, but did not report bilateral stimulation and recognized no left stimulation. He said that stimuli on the left arm 'were different', but after crossing his arms, the left stimuli felt the same as the right ones.

Stimulation of the right hand in the uncrossed position resulted in contralateral responses with P1 (C3: 4.3 µV, 45 ms, t_6 = 1.503, p = 0.184), N1 (C3: -4.0 µV, 84 ms, t_6 = -1.438, p = 0.201), and P2 (C3: 1.7 µV, 206 ms, t_6 = 0.769, p = 0.471) deflections (Figure **8**). Responses to similar stimulation while keeping the right hand in the left hemispace were almost identical: P1 (C3: 3.9 µV, 47 ms, t_6 = 1.495, p = 0.186) and N1 (C3: -3.9 µV, 85 ms, t_6 = -1.244, p = 0.260). In contrast, stimulation of the left hand in the uncrossed position resulted in flat responses with only some negativity at 100 ms latency. Crossing the left arm into the right hemispace then produced a very large N1/P2 response (C4: N1, -4.7 µV, 112 ms, t_6 = -1.968, p = 0.097; P2,

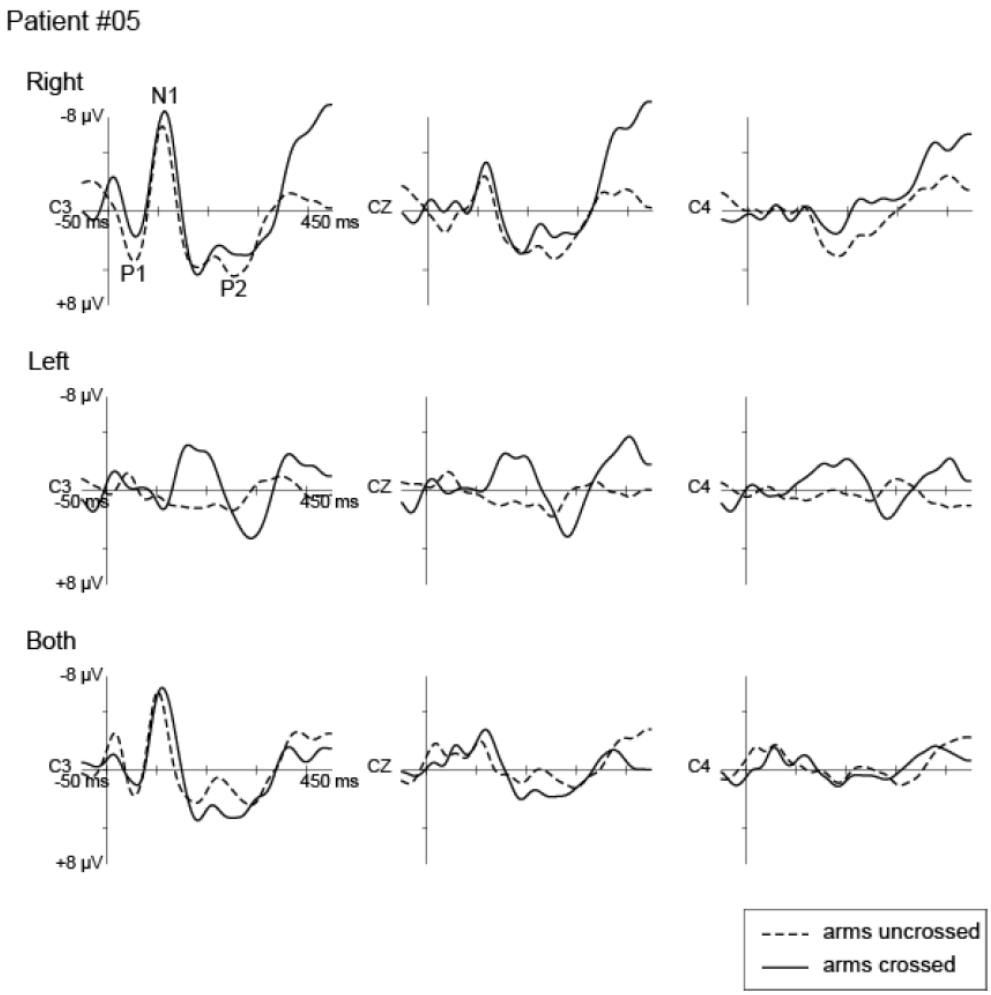

Figure 7: Patient #05: Somatosensory ERPs recorded at C3, Cz, and C4 when arms were in uncrossed (dotted traces) or crossed (continuous traces) position.

9.9 µV, 204 ms, t_6 = 11.856, p < 0.0005). It was largest over the contralateral injured hemisphere, being barely noticeable over the ipsilateral normal hemisphere. Responses to bilateral stimulation were almost identical to those elicited by right-hand stimulation in the uncrossed position (Bilateral, Uncrossed, C3: P1, 4.8 µV, 48 ms, t_6 = 3.351, p = 1.256; N1, -3.6 µV, 85 ms, t_6 = -1.256, p = 0.256) and left-hand stimulation in the crossed position (Bilateral, Crossed, C4: N1, -4.6 µV, 122 ms, t_6 = -1.661, p = 0.148; P2, 11.6 µV, 211 ms, t_6 = 8.913, p < 0.0005).

DISCUSSION

Our results demonstrate that hemispatial neglect of the stimuli coming from the left hemispace or applied to the left hand coincided with the absence or delay, and abnormality of the N1 wave in all three modalities. This shows a general, modality-independent dysfunctioning of the cognitive processes reflected by N1. Our data further show that recovery from neglect, that is, re-establishment of the ability to consciously perceive the stimuli from the neglected hemispace, coincides with the reappearance and normalization of N1 deflections in responses to left-side stimulation, which coincides with the results on visual evoked potentials in Di Russo *et al*. [33]. In somatosensory ERPs, corresponding changes were also observed in P1 deflections immediately preceding the N1 deflections.

These results, based on a rather small group of patients, but with rather homogeneous ERP findings, strongly point to the alerting system reflected by the N1 [34] as underlying mechanisms of hemispatial neglect. This is in line with the hypotheses that the elevated arousal threshold [35], reduced alertness [36], and disturbances in involuntary triggering of attention [37] or in circuit breaking by a behaviorally relevant stimulus [38] are the mechanisms underlying neglect. It should be underlined, however, that alerting may be only one, although very strong, candidate for the neglect mechanism among different cortical, and subcortical

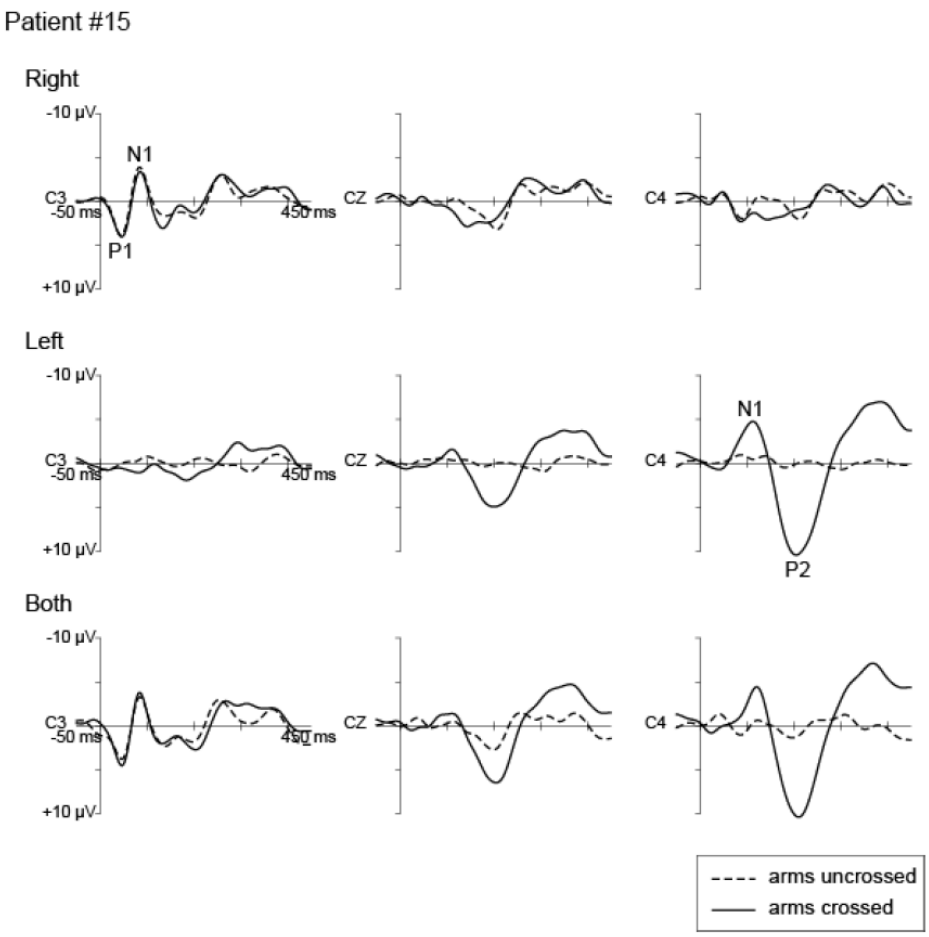

Figure 8: Patient #15: Somatosensory ERPs recorded at C3, Cz, and C4 when arms were in uncrossed (dotted traces) or crossed (continuous traces) position.

injuries with variable neglect and/or extinction outcomes [12, 39]. Our results, however, demonstrate the uniformity of the changes in ERPs as a function of severity of neglect in both multi- and unimodal data and in between- and within-subject comparisons. Finally, stimuli applied to the non-neglected side tended to elicit even pathologically large amplitude responses in the acute phase. The amplitudes returned to normal as a function of time and recovery. These amplitude fluctuations probably reflect imbalance in activation levels between the hemispheres right after the stroke, and regaining of balance as a function of time and recovery.

Marzi *et al*. [10] previously described the correspondence between conscious perception of visual stimuli and occurrence of P1/N1 deflections in an RBD patient with extinction. According to them, the visual P1/N1 complex is modulated by spatial attention, the P1 having extrastriatal generators, and the N1, wider frontal and parietal mechanisms. Verleger *et al*. [7] also described reduction of early negativity specifically for the extinguished stimulus (left targets preceded by right cues) in a group of RBD patients. Correspondingly, Eimer *et al*. [11] have demonstrated reduced somatosensory P60 and N110 responses and conscious perception in a patient with somatosensory extinction. In the present study, a correspondence between the N1 and conscious perception of the stimuli could be obtained for all three modalities studied. Somatosensory ERPs were the most uniform and replicable responses in our patients, and the P1 was most distinct in somatosensory ERPs in the form of P100 deflections, preceding the N1, or N140 [17]. In the present somatosensory ERPs, the occurrence of the N1 was usually tied to that of the P1, and as far as we know, the somatosensory P100 reflects activation of the SII [17], and is vulnerable to, for example, stimulus repetition [19, 20] and attention [18]. In this way, the present results on somatosensory neglect and P1/N1 responses correspond closely to those of Marzi *et al*. [10] on visual extinction and P1/N1 responses, and also to those of Eimer *et al*. [11] on somatosensory extinction and P1/N1 responses.

Koivisto *et al*. [15] have recently demonstrated the relation of attention, awareness, and ERP appearance within the visual system of healthy subjects (for a review, see [2]). Their results showed unequivocally that the earliest indication of visual awareness was associated with a posterior negative amplitude shift 130-320 ms after the visual stimulus. Interestingly, Schubert *et al*. [16] demonstrated that conscious perception of somatosensory stimuli correlated with P100 and N140 amplitude enhancement. They concluded that early activation of SI was not sufficient to warrant conscious stimulus perception. The level of conscious perception seems to require activation of at least the SII, reflected by P100/P1 responses [17, 18]. The SII activation, corresponding to extrastriatal origins proposed for visual P1 responses [10], are then followed by N140/N1 responses [17] with more parietal origins [21]. Finally, Gallace and Spence [22] recently postulated a model of somatosensory awareness, according to which SII, insula, posterior parietal areas and temporoparietal junctions, and premotor cortex are involved in the body schema and somatosensory awareness, or conscious perception of somatosensory stimuli. In conclusion, based on the previous studies on RBD patients with neglect and extinction, healthy subjects with varying degree of stimulus awareness, and the present findings on acute neglect and recovery, we propose that there exists a close connection between the mechanisms of hemispatial neglect/extinction, stimulus awareness, and P1/N1 responses.

The space-dependency of the emergence and/or size of somatosensory ERPs could be demonstrated in some of our patients. We described a few patients with left hemispatial neglect, who showed distinct, even though mostly rather abnormal, ERPs to electrical stimulation of the median nerve of the left wrist only when the arm was crossed to the right non-neglected hemispace. In these patients, right median nerve stimulation produced similar ERPs independent of the position of the arm in either hemispace. These cases indeed demonstrate that the effects of crossing the arms are not an epiphenomenon but a true, albeit not readily explained, phenomenon. Moreover, these phenomena were seen in only some neglect patients, and receded with receding neglect symptoms.

The most dramatic changes in somatosensory ERPs were seen in N1/P2 waves, which refer to arousal and orienting mechanisms (for a review, see [13]). However, in some patients, changes were seen especially in P1 deflections, being connected to SII activation [17, 40]. The SII areas have wide callosal connections, and are proposed to be involved in somatosensory working memory processes and body schema [40]. These different mechanisms may give rise to the changes in ERPs seen sometimes over the left intact and right injured hemispheres.

In hemineglect patients, gaze direction and trunk orientation can influence the boundaries of the neglected regions of space [41], and head tilt can influence body coordinates [42]. Weiskrantz and Zhang [43] reported a neglect case in whom somatosensory deficits improved if the participant touched her own left hand with the right hand. All these phenomena deal with modifications of the neglected vs. non-neglected space. So far, there is only one study in left hemispatial neglect patients, in which modification of brain responses (ERPs) has been demonstrated. Spinelli and Di Russo [25] showed that trunk rotation to the left shortened the previously lengthened P100 latencies of visual evoked potentials to left visual field stimulation. In normal subjects, Eimer *et al*. [26] demonstrated the effects of spatiality, that is, the effects of attention focused on the hand in uncrossed or crossed position on the ERPs to spatial auditory and visual stimuli in the same or different hemispace. All these studies with the present results verify the existence of the strong spatial component in our subjective perceptions as well as the ERPs reflecting the brain processes involved.

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