

Electrophysiological evidence for an early (pre-attentive) information processing deficit in patients with right hemisphere damage and unilateral neglect

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Summary

Patients with right hemisphere damage and contralesional neglect are often unaware of visual, auditory or tactile stimuli occurring on their left side. In an effort to understand the contribution of pre-attentive processes to this phenomenon, we examined the processing of the pitch, duration and spatial location of auditory stimuli using an electrophysiological probe, the mismatch negativity (MMN). This event-related brain potential indexes the integrity of cerebral processes that respond automatically to deviations from regularity in the acoustic environment. We compared the MMN elicited by right- and left-sided deviant stimuli in 10 patients with left unilateral neglect and 10 age-matched healthy volunteers, exploring an anticipated dissociation between the

processing of spatial localization of sounds and the processing of the other auditory dimensions. Across dimensions, the MMN elicited by deviance occurring to the left of the patients was reduced relative to that elicited by deviance occurring to the right. This effect was robust for spatial location, and less so for pitch, whereas the processing of stimulus duration was not significantly affected by the side of stimulation. In healthy subjects, deviance in either side elicited similar MMN. We suggest that an early deficit in detecting changes in the environment hampers the involuntary triggering of attention in those patients and discuss the specific role of encoding spatial location in the establishment of conscious awareness.

Keywords: unilateral neglect, mismatch negativity, event-related potentials, attention, awareness

Abbreviations: EOG = electro-oculogram; ERP = event-related potential; HL = hearing level; MMN = mismatch negativity

Introduction

Unilateral neglect is a frequent disabling sequela of right hemisphere damage (neglect of the right side of space, following left hemisphere damage, is a much less frequent phenomenon) (Halligan *et al.*, 1989). Patients suffering from neglect may fail to acknowledge, respond, orient to, or report stimuli and events occurring on the contralesional side of their personal or extra-personal space (Heilman *et al.*, 1993). Although most evident in the visual modality, neglect may also be exhibited in the auditory and the tactile modalities (e.g. De Renzi *et al.*, 1984, 1989; Gainotti *et al.*, 1989; Soroker *et al.*, 1997). In the related phenomenon of extinction, the failure to notice a stimulus occurs only when a competing stimulus is presented simultaneously more towards the side of the lesion (e.g. Heilman *et al.*, 1970; De Renzi *et al.* 1984;

Rapsack *et al.*, 1987). Despite their frequency and major significance for the patient's functional prognosis (Denes *et al.*, 1982; Katz *et al.*, 1999), the cognitive and neural deficits underlying neglect and extinction are still debated in the literature (cf. Marshall *et al.*, 1993).

The neglect phenomenon has been conceptualized mainly as a 'higher-order' deficit, resulting from a variety of difficulties in allocating attention, from a disruption of space representation or from specific damage to pre-motor circuits (for reviews, see Riddoch and Humphreys, 1987; Marshall *et al.*, 1993). Sensory-perceptual accounts have also been suggested (e.g. Denny-Brown *et al.*, 1952; Denny-Brown and Banker, 1954) but were not easy to defend, mainly because neglect manifestations were shown to exist even in the

absence of sensory stimulation (e.g. in imagery; Bisiach and Luzzatti, 1978; Bisiach *et al.*, 1979). The data on which the different accounts for neglect have been based consisted mostly of observations and measurements of patients' performance on a variety of behavioural tests. Using such measures, early processes, especially pre-attentive and unconscious ones, are relatively hard to investigate. In contrast, event-related potentials (ERPs) reflect event-specific on-going activity in the brain, and thus may open a window onto processes that are only addressed indirectly by conventional behavioural manipulations. In the present study, we used ERPs to address two main questions. (i) Are pre-attentive processes, located relatively early in the stream of stimulus processing, intact in neglect patients as expected by attentional and pre-motor theories? (ii) Is there a specific deficit in the encoding and use of spatial information related to an external event?

Initial electrophysiological findings showed that neglected visual and somatosensory stimuli elicited normal early cortical sensory-evoked potentials such as N1 (Vallar *et al.*, 1991). Likewise, Viggiano and colleagues found no difference in the amplitude of steady-state visual-evoked potentials elicited by stimuli presented in the contralesional (neglected) and the ipsi-lesional sides (Viggiano *et al.*, 1995). These results supported the hypothesis that early sensory processes are normal in neglect patients, suggesting that the failure is located at a higher level, perhaps in the access to conscious awareness (Vallar *et al.*, 1991). However, more recent studies cast doubts on this conclusion (for a recent review, see Deouell *et al.*, 1999).

In a visual cueing paradigm, Verleger and colleagues found a reduced N1 component at the right parietal recording sites in patients with right parietal damage (Verleger *et al.*, 1996). In addition, studies of steady-state visual-evoked potentials in neglect patients revealed longer latencies in response to stimuli in the left visual field compared with the right visual field, especially for the lower left quadrant (Spinelli *et al.*, 1994; Angelelli *et al.*, 1996; Spinelli and Di Russo, 1996; Pitzalis *et al.*, 1997). Furthermore, the prolongation of latency was evident when the features of the stimulus were adequate for activation of the magnocellular visual system (e.g. high temporal frequency of contrast reversal), but not when the features were appropriate for the activation of the parvocellular system (e.g. colour changes; Doricchi *et al.*, 1996; Spinelli *et al.*, 1996). These findings point to the possibility that neglect may be related to highly specific sensory deficits after all.

In the auditory domain, the N1 ERP component reflects the integrity of the early response of the primary tonotopic cortex to auditory stimuli. Another auditory ERP component, the mismatch negativity (MMN) (Näätänen *et al.*, 1978), may be particularly useful for exploring injured and intact parts of the perceptual system (cf. Mäkelä *et al.*, 1991; Aaltonen *et al.*, 1993; Woods *et al.*, 1993; Alain *et al.*, 1998; Wertz *et al.*, 1998). In a typical MMN paradigm, the subject is presented with a train of auditory stimuli, termed

'standards', which share at least one feature (e.g. they are all of the same pitch). Infrequently, stimuli differing from this common feature are presented (a 'deviant'). The electrophysiological response to the occurrence of this deviant stimulus consists of a negative shift in the waveform elicited by the deviant sounds, compared with the waveform elicited by the standard sounds. This negativity peaks between 100 and 250 ms after the onset of the deviant event, is maximal in frontocentral recording sites and, for most types of deviance, reverses polarity over the mastoid processes. It can be elicited by changes of simple physical (acoustic) properties such as frequency, intensity, duration and location of the sounds, by more complex features such as temporal order or phonetic value, and even by abstract features such as the direction of frequency glides (for reviews, see Näätänen, 1990, 1992; Näätänen and Alho, 1995). While there are initial findings suggesting a parallel to MMN in the visual and tactile modalities (Kekoni *et al.*, 1997; Shinozaki, *et al.*, 1998; Helzenfeld, 1999), the phenomenon has been investigated extensively and is well established only in the auditory modality.

Most importantly for the study of neglect, attention is not required for eliciting MMN, and MMN may be elicited in an unattended channel, even when attention is highly focused on a difficult task in another channel (e.g. Alho *et al.*, 1989, 1992; Näätänen, 1991; Näätänen *et al.*, 1993; but see Woldorff *et al.*, 1991). In fact, participants in a typical MMN experiment are asked to disregard all the sounds and concentrate on a diversionary (usually visual) task, such as reading a book, watching a movie or playing a video game. Consequently, it is assumed that MMN is associated with a pre-attentive mechanism which compares the current auditory input with memory traces formed by previous auditory inputs, and signals the occurrence of an infrequent change (Näätänen, 1990; Ritter *et al.*, 1995; for a somewhat different version of this assumption, see Winkler *et al.*, 1996). The pre-attentive detection of the change in the auditory input may then trigger a stimulus-driven involuntary shift of attention (Näätänen, 1990, 1992; Novak *et al.*, 1992; Schröger, 1996; Alho *et al.*, 1997; Escera *et al.*, 1998; Schröger and Wolff, 1998). Therefore, MMN may be used to probe the integrity of pre-attentive processes that may have a role in triggering involuntary switch of attention, a capacity that is apparently malfunctioning in neglect. To this end, we examined the MMN elicited by changes occurring on the left and on the right sides of patients with right hemisphere lesions and left side neglect. In addition, to conform to previous literature, we also examined the influence of side of presentation on the N1 component.

Furthermore, the MMN paradigm allows a targeted examination of the registration of specific auditory dimensions, comparing deviations that occur on the neglected (or extinguished) side with deviations occurring on the intact side. Previous studies suggested that the auditory memory traces involved in the elicitation of MMN are specific to individual features or to specific conjunctions of auditory

features (e.g. Schröger, 1995; Deacon *et al.*, 1998; for a review, see Ritter *et al.*, 1995). Consequently, a 'normal' MMN elicited by a deviance in a specific dimension is evidence that this particular dimension of the stimulus has been processed adequately by the system (cf. Aaltonen *et al.*, 1993; Deouell and Bentin, 1998).

The working hypothesis in the present study was that if behavioural manifestations of neglect result from an attentional or other higher order dysfunction, MMN should be comparable in response to deviants on both sides of the patient. Such symmetry was evident in studies of healthy subjects, under both dichotic and unilateral stimulation conditions (Deouell and Bentin, 1998; Deouell *et al.*, 1998). On the other hand, if a dysfunction at an early, pre-attentive stage of processing contributes to the emergence of neglect, MMN may be abnormal for deviants presented in the neglected side.

An additional hypothesis was that a lateralized deficit (if found) would be seen in response to stimuli deviating in features such as spatial location or timing, but not for non-contextual features such as pitch or intensity. Because neglect phenomena are associated with space, such a hypothesis might seem trivial. However, the fact that the deficit is related to a sub-region of space does not necessarily imply, *a priori*, a deficit in processing spatial attributes. The rationale on which the hypothesis was based is that encoding the spatial location and timing of an event are *sine qua non* for conscious awareness, for the simple reason that our cognitive system is not capable of acknowledging place-less or time-less events. In other words, sensory events that cannot be encoded spatiotemporally are probably rejected as irrelevant 'noise' or cognitively dissonant perturbations. The spatiotemporal encoding deficit hypothesis is consistent with the findings of Spinelli and her colleagues (Dorrichi *et al.*, 1996; Spinelli *et al.*, 1996) which point to a specific deficit of neglect patients in recruiting the dorsal stream of the visual system, responsible for processing spatiotemporal attributes of visual information. Indeed, a few studies showed that patients suffering from neglect exhibit a particular difficulty in localizing sounds (e.g. Ruff *et al.*, 1981; Bisiach *et al.*, 1984; Pinek *et al.*, 1989; Soroker *et al.*, 1997). However, the mechanism of this deficit has not been clarified. Finding electrophysiological evidence for a specific deficit in encoding spatial information outside the focus of attention may lend converging support to the hypothesis, based on performance data, that neglect is related to a deficit of representation of space (e.g. Bisiach and Berti, 1987) and suggest that this deficiency is not necessarily mediated by attention disorders. There is some indication that time coding is also affected in right brain-damaged patients (Vakil *et al.*, 1998), but the current study does not address this possibility directly. Although the manipulation of stimulus duration affects temporal attributes, it does not manipulate the contextual sense of timing (the question of 'when'). In fact, a previous study of right brain-damaged patients did not find a lateralized

deficit in MMN elicited by duration deviants (Woods *et al.*, 1993).

Methods

Subjects

Ten patients with right hemisphere damage, admitted to the Loewenstein Hospital (Ra'anana, Israel) for rehabilitation after stroke, were recruited for the study on the basis of the following inclusion criteria. (i) First occurrence of an ischaemic brain infarction, or a circumscribed parenchymal haemorrhage, as determined from history, physical examination and the acute-stage CT scan. (ii) Absence of marked mass effect (with possible unrecognizable distant structural damage) in the acute-stage CT scan. (iii) Negative neurological or psychiatric past history. (iv) Absence of significant cortical atrophy or leukoaraiosis. (v) A stable clinical and metabolic state. (vi) Cognitive status enabling full comprehension of task requirements. (vii) Manifestation of left-sided neglect in activities of daily living. (viii) Pure tone audiometry between 500 and 2000 Hz (the frequencies used in the experiment) revealing normal hearing at 20 dB hearing level (HL). There were seven males and three females at an age range of 34–68 years (mean 58.2 ± 10.57). All patients were right handed. Six patients suffered ischaemic infarction in the territory of the right middle cerebral artery, one patient (G.F.) suffered a right posterior cerebral artery infarction (with involvement of the posterior thalamus as well as cortical structures), two patients (N.M. and Z.Y.) had a right thalamic haemorrhage and one patient suffered haemorrhage in the right basal ganglia (G.H.). Examination took place during the hospitalization period, with time after the onset of stroke being 19–145 days (mean 52.3 ± 37.9). Demographic, clinical and lesion data of each patient are presented in Table 1. The control group consisted of 10 (eight males, two females) healthy right-handed hospital personnel and their family members who volunteered to participate in the study. Although the control subjects were on average slightly younger than the patients (age range 31–68 years; mean 52.9 ± 13.6), the difference was not significant ($P = 0.34$).

Tests for visual and auditory neglect/extinction

The patients were formally tested for neglect in the visual modality using the conventional part of the Behavioural Inattention Test (cut-off score 130, maximal score 146; Wilson *et al.*, 1987). At the time when the experiments were conducted, seven patients scored below the cut-off for normality in this test. Three patients (B.Y., G.H. and Z.Y.) with higher scores still manifested neglect in activities of daily living, and one of them (B.Y.) showed also motor neglect (Table 1). In the auditory modality, a phonetic discrimination task, sensitive for auditory neglect and extinction, was used (Soroker *et al.*, 1997). In this task, the

Table 1 Demographic, clinical and lesion data of patients

Patient	Age/ sex	Motor deficit	Sensory loss	Visual field deficit	Time after onset	BIT score	Auditory extinction (%Lt./%Rt.)	Lesion site	Lesion type
Z.A.	58/F	++	+	E	19	111	97/3	T, P, F, BG, IC, CSO	I
H.S.	34/F	+	+e	E	34	125	55/0	T, P, F, BG, CSO	I
B.Y.	67/M	+	-	-	25	132*	17/0	T, P, F	I
G.H.	54/M	+	++	E	40	141	50/0	BG	H
C.Y.	62/M	+	e	E	19	59	75/22	IPL, BG, GIC	I
B.S.	49/M	++	+	E	145	81	97/3	T, P, F	I
G.F.	68/F	++	++	LHHA	55	34 [†]	72/19	O, P, Post. Th	I
N.M.	58/M	++	++	E	78	34	59/0	Th, PLIC, PVWM	H
D.Y.	64/M	++	+	E	83	123	100/0	T, P, F	I
Z.Y.	68/M	+	-	-	25	137	75/0	Th	H

Motor deficit: ++, left hemiplegia; +, left hemiparesis. Sensory loss: ++, hemianaesthesia; +, hemihypoesthesia; e, extinction on bilateral simultaneous stimulation. Visual field deficit: LHHA, left homonymous hemianopsia; E, extinction of left-sided stimuli on bilateral simultaneous stimulation. Lesion site: BG, basal ganglia; CSO = centrum semi-ovale; F, frontal; GIC, genu of internal capsule; IPL, inferior parietal lobule; LN, lenticular nucleus, P, parietal, PLIC, posterior limb of internal capsule; PVWM = peri ventricular white matter; T, temporal; Th, thalamus. Lesion type: I, ischaemic; H, intra-cerebral haemorrhage. Time after onset: interval in days between the stroke and the ERP recording. BIT, Behavioural Inattention Test, patient score near the time the ERP recordings were conducted. *Also significant motor neglect; [†]without letter cancellation—illiterate patient.

subjects were presented randomly with 36 natural syllables played with an intensity of 75 dB (sound pressure level) from a loudspeaker located 60° to their left, 36 syllables played from a loudspeaker located 60° to their right and 36 pairs of syllables, played simultaneously from the left side and the right side loudspeakers. The subjects were required to say first whether the sound was on their left, right or both sides, and then to try to identify the syllable or syllables heard (da, ba, pa, za, va, na, ma, ra, ka, la, ga or ta). The control subjects did not show extinction in any of the trials. In contrast, all patients showed auditory extinction, with all but one extinguishing >50% of left-sided stimuli in conditions of bilateral simultaneous stimulation (mean detection rate: 30.3 and 95.3%, for left- and right-sided stimuli, respectively; Table 1). In all patients, the rate of identification of left-sided syllables was worse than that of the right-sided syllables presented simultaneously (mean identification rate: 25 and 61%, for left- and right-sided stimuli, respectively). In addition to extinction, seven of the 10 patients also had signs of unilateral auditory neglect, as evidenced by erroneously identifying, at least once, left-sided sounds as coming from the right. Such errors were never found in the control subjects.

All subjects gave an informed consent to participate in the study. The research was approved by the local Helsinki committee in the Loewenstein Rehabilitation Hospital and by the corresponding committee of the Israeli Ministry of Health.

Stimuli

Standard stimuli

The standard stimuli were harmonic tones composed of 600 Hz fundamental frequency and two harmonics (1200 and 1800 Hz). The intensities of the harmonics were reduced by a factor of 2 and 4, respectively, compared with the intensity of the fundamental frequency. The stimuli were 75 ms long, with 5 ms rise and fall time. They were presented via a loudspeaker placed, in different blocks, either 60° to the right or 60° to the left of the subject's mid-sagittal plane, 90 cm from the centre of the subject's head. The stimulus onset asynchrony was random, ranging between 385 and 415 ms.

Deviant stimuli

There were three types of deviant tones in each block: (i) pitch deviants, with fundamental frequency and harmonics reduced by 10% relative to the standard; (ii) duration deviants, with stimulus duration reduced from the standard 75 ms to 25 ms; and (iii) location deviants, with source location (on each side of presentation) 30° medial to the source of the standard. The intensity of all stimuli (standard and deviants) was 75 dB (sound pressure level).

Procedure

The experiment was performed in a sound-attenuated and echo-reduced chamber. The patient was monitored

continuously with a closed-circuit video camera, which allowed monitoring of head position and gaze direction. The EEG was recorded in one or two sessions (each on a separate day), determined by the patient's clinical condition. The subjects were seated in their wheelchair to which a headrest had been attached. They were shown a movie (either a nature movie or Charlie Chaplin's 'The circus') presented silently on a computer monitor, and instructed to ignore any sounds. The part of the screen on which the movie was presented extended a visual angle of 5° on each side of the mid-sagittal plane, at a distance of ~100 cm from the subject's eyes. Ten blocks of 500 stimuli were presented, with a few minutes break between blocks. The blocks alternated between left-sided and right-sided stimulation. In each block, 350 tones (70%) were standard while the remaining 150 stimuli were deviants, equally divided between the three types of deviance. Thus, the relative frequency of each deviant type was 0.1. Standard and deviant tones were presented in a pseudo-random order (different for each subject and block) with two constraints: the first was that at least two standard tones preceded each deviant tone and the second was that two consecutive deviants should never be of the same type. As a consequence of these constraints, the local probability of a specific type of deviant was 0.09 at the most.

EEG recording and averaging

The EEG was recorded from 32 tin electrodes referenced to the tip of the nose. The recording sites were based on the 10–20 system with 12 additions (FT7, FC5, FC3, TP7, CP5, left mastoid, FT8, FC6, FC4, TP8, CP6 and right mastoid). All electrodes were mounted on a custom-made cap (ECI), except for the mastoid electrodes. The electro-oculogram (EOG) was recorded with two electrodes, one located at the outer canthus of the right eye and the other at the infraorbital region of the same eye.

The EEG was sampled continuously at 250 Hz, amplified $\times 20\,000$ with an analogue band-pass filter of 0.1–100 Hz, and stored for off-line analysis. For ERP averaging, the EEG was divided into epochs of 436 ms each, starting 48 ms before the stimulus onset. Epochs with EEG or EOG exceeding $\pm 100\ \mu\text{V}$ were excluded from the averaging. The epochs were averaged separately for each stimulus type. The baseline was adjusted by subtracting the mean amplitude of the pre-stimulus period of each ERP from all the data points in the epoch.

Data analysis

The amplitude and latency of N1 were evaluated by detecting the most negative peak between 70 and 130 ms on the waveforms elicited by the standard stimuli, following digital filtering with a band pass of 1–30 Hz ($-3\ \text{dB}$). For MMN analysis, difference waveforms were calculated by subtracting the ERPs elicited by standard trials from those elicited by deviant trials in the same block. The difference waveforms

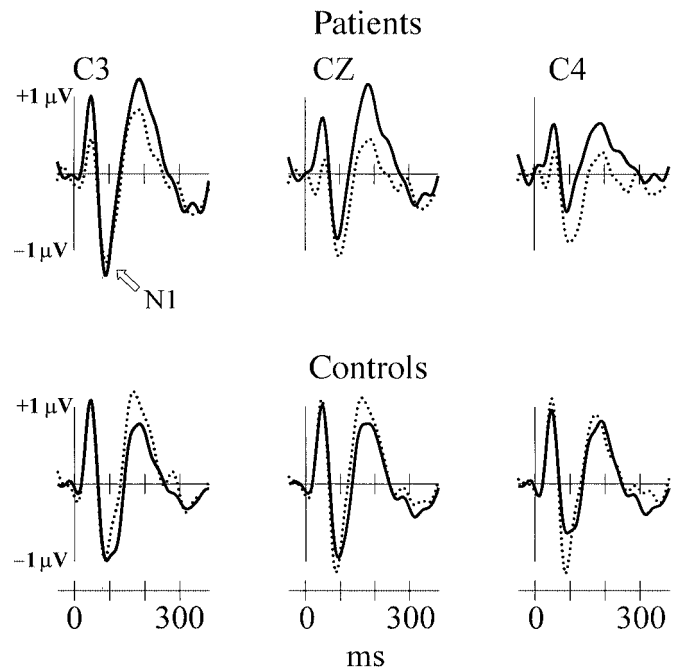


Fig. 1 Response to standard tones in patients and controls at central electrodes. Dotted lines = stimuli on the left; continuous lines = stimuli on the right.

were digitally filtered with a narrow band-pass of 1–12 Hz (Sinkkonen, 1998). The amplitude and latency of the MMN were measured at Fz on the most negative peak between 100 and 250 ms after stimulus onset. Since MMN related to the types of deviance used in the current study is characterized by a polarity inversion between Fz and the mastoid sites, the analysis was repeated after digitally re-referencing the data to the averaged mastoids. This process highlights the MMN over partially overlapping N2b components that are negative at both the Fz and the mastoids (Schröger, 1998). This procedure was deemed especially important in this study because initial visual inspection of the patients' data revealed that in some cases the mastoid positivity was more conspicuous than the frontal negativity. All the statistical analyses were done within subjects. Differences between conditions were assessed by a two-way ANOVA (analysis of variance) with dimension (pitch, duration or location) and side of stimulation (left or right) as factors, followed by planned comparisons between left and right stimulation within each dimension. The Greenhouse–Geisser procedure was applied where necessary.

Results

N1

Figure 1 displays the average response elicited by left- and right-sided standard tones around the vertex. For both patients and healthy subjects, the N1 at Cz was somewhat larger for stimuli presented on the left side than for those presented on the right side, but this difference was not statistically significant. In the control group, the N1 was larger over the

hemisphere contralateral to the side of stimulation as validated by a significant interaction in ANOVA with hemisphere (left–C3/right–C4) and side of stimulation (left/right) as factors [$F(1,9) = 28.1, P < 0.0001$]. No significant main effects were found in this analysis. In contrast, the patient group elicited a larger N1 at C3 (over the intact left hemisphere) than at C4 (over the damaged right hemisphere) in response to both left- and right-sided stimuli, resulting in a significant main effect of hemisphere [$F(1,9) = 7.22, P < 0.05$]. Neither the side of stimulation effect, nor the interaction between side of stimulation and hemisphere were significant. Although throughout this study we stress the within-subject comparison rather than across-groups comparisons, note that there were no significant differences between the control group and the patient group in the amplitude of N1, regardless of the side of stimulation or the hemisphere over which it was measured. Thus, the main difference between patients and control subjects was in the inter-hemispheric distribution of N1.

MMN

Controls

Figure 2 (lower row) presents the differential responses to stimuli presented on the left and on the right side of the subjects, separately for each dimension. MMN was elicited for all the dimensions tested (pitch, duration and location) and for stimulation on either side of the patient. ANOVA showed a significant effect of dimension [$F(2,18) = 6.12, P < 0.01$, Greenhouse–Geisser epsilon = 0.7556], whereas the side of stimulation effect and the interaction between the two effects were not significant. *Post hoc* comparisons revealed that the pitch MMN and the location MMN amplitudes did not differ significantly, whereas the duration MMN was larger than both [$F(1,9) = 7.75, P < 0.03$]. The planned comparisons between left- and right-sided stimulation within each dimension revealed no effect of the side of stimulation for any dimension studied. In fact, the amplitudes were very similar across sides (Table 2 and Fig. 3). Re-referencing the data to the averaged mastoids did not change the pattern of results or the significance of any of the effects. In fact, the amplitudes of MMN across the sides of stimulation became almost identical nominally.

Patients

Figure 2 (upper row) presents the differential responses to stimuli presented to the left and the right sides of the patients for all three dimensions. Evidently, the MMN was larger when the auditory stimuli (both standard and deviant) occurred on the right of the patient. ANOVA with side of stimulation and dimension of deviance as factors confirmed that this difference was significant, both when the dependent variable was the peak MMN amplitude at Fz [$F(1,9) = 8.362, P < 0.02$] and when the responses were averaged over a more extended group of frontal electrodes (Fz, F3, F4, F7

and F8) and the mean value was used as dependent variable in the ANOVA [$F(1,9) = 11.644, P < 0.001$]. In contrast to N1, there was no significant difference between the MMN over the right and left hemispheres.

The planned comparisons revealed that the difference between the MMN to deviants presented to the right and left side was highly significant for location deviance [$t(9) = 3.80, P < 0.005$], marginally significant for pitch deviance [$t(9) = 2.35, P = 0.043$] and not significant for duration deviance [$t(9) = 0.8, P = 0.44$]. Furthermore, a non-parametric approach showed that the MMN was not detected reliably in all subjects and conditions. For location deviance, MMN was detected in nine out of 10 patients for right-sided stimuli, and in only four patients when the stimuli were on the left side (two of these patients suffered from temporoparietal infarcts and two from haemorrhage affecting the right basal ganglia or thalamus). For pitch deviance, MMN could be detected in eight patients in response to right-sided stimuli and in six patients in response to left-sided stimuli. For duration deviance, MMN could be detected in nine patients when the stimuli were on the right, and in eight patients when the stimuli were on the left. Thus, the non-parametric analysis is in line with the above parametric analysis of the amplitudes. To summarize this point, right hemisphere damage affected mostly the MMN elicited by contralesional location deviance, followed by deviance in pitch, and least affected the MMN in response to deviance in duration.

Visual inspection of the data revealed that in some patients the MMN was characterized by a relatively conspicuous mastoid positivity (Fig. 2). Thus it is possible that measuring only the Fz site or around it underestimated the deviance effect. Indeed, re-referencing the data to the averaged mastoids changed the results somewhat, although keeping them within the trends revealed in the more conventional measurement (Fig. 3). ANOVA with side of stimulation and dimension as factors revealed that the dimension effect was significant [$F(2,18) = 6.602, P = 0.07$, Greenhouse–Geisser epsilon = 0.7084], whereas the side of stimulation effect only approached significance [$F(1,9) = 4.390, P = 0.066$]. *Post hoc* comparisons revealed that, as in the control group, the dimension effect resulted from a larger duration-related MMN than both MMN elicited by location and pitch-related MMN [$F(1,9) = 9.562, P < 0.02$]. The latter two MMNs did not differ.

Following the re-referencing procedure, the planned comparisons of MMN across sides of stimulation within each dimension revealed a significant side effect only for location deviance in the patient group. The location deviance elicited a significantly larger MMN when the stimuli were on the right of the patient than when the stimuli were on the patient's left [$-1.23 \mu\text{V}$ versus $-0.41 \mu\text{V}$, $t(9) = 2.41, P < 0.05$]. Thus, in both the 'conventional' method and after re-referencing to the mastoids, the MMN elicited by contralesional deviance in location was deficient. The effect of brain damage on the pitch-related MMN was not robust, and duration MMN seems not to be affected by the side of stimulation.

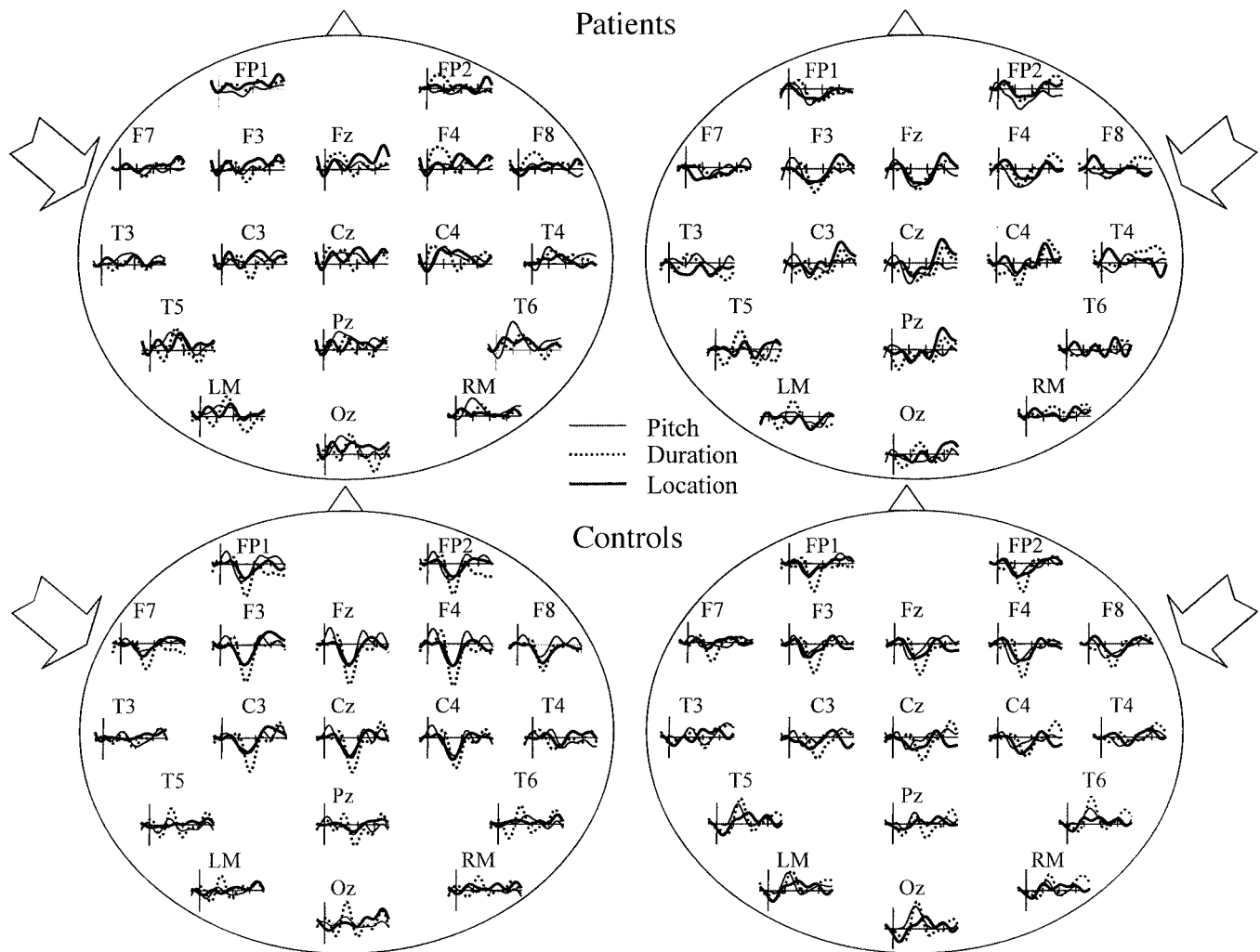


Fig. 2 Difference waveforms calculated by subtracting the response to the standards from the response to each type of deviance. A representative subset of the 32 recording sites is displayed. The location of the recording sites within the schematic heads represent only roughly the relative location of the electrodes on a flattened recording cap. The upper two 'heads' depict data from the patients group, the lower two depict the equivalent data from the normal controls. For each head, the large arrow represents the direction from which the sounds were presented.

Discussion

Unlike other major neuropsychological disturbances, such as aphasia, agnosia, apraxia or amnesia, unilateral neglect is not easily associated with one, well-defined, cognitive domain. Is it a problem of perceiving an event, of attending to it, of being conscious of it, of initiating a response towards it or a combination of deficiencies? In the present study, we investigated a possible bottom-up link between perception and attention in patients suffering from left auditory extinction and/or neglect. The probes were auditory ERP components, which are associated with pre-attentive processes (N1 and MMN) and with processes that interface pre-attentive and attention-related mechanisms (MMN). These ERPs were elicited in a 'passive' condition, while the subject was watching a movie and was not required to report, respond or make any decision. Therefore, the results of this study added information that was not available in standard analyses of patients' overt performance.

The magnitude of N1 elicited by standard stimuli presented to the left or to the right of the patient did not differ, nor was it different from that elicited in the normal control group. This result is in line with previous ERP reports in the visual and somatosensory domains that found no difference between the early electrophysiological responses to stimuli presented in the neglected and the intact sides (Vallar *et al.*, 1991; Viggiano *et al.*, 1995). The finding of a smaller N1 over the right hemisphere than over the left hemisphere, regardless of stimulus side, a pattern which contrasts with the normal contralateral predominance of N1 (Näätänen and Picton, 1987), may be interpreted as correlating with neglect patients' tendency to perceive left (contralesional) stimuli as originating from the right (ipsi-lesional) side. However, this interpretation is qualified by the fact that hemispheric asymmetries in scalp recordings of brain-damaged patients may be a consequence of altered conductivity of the damaged brain tissue situated between the electrical generator and the

recording scalp electrode, rather than of genuine diminution of the source (e.g. Abboud *et al.*, 1996). Indeed, attenuation of N1 over the damaged hemisphere was found in patients with either right or left hemisphere temporoparietal lesions (Alain *et al.*, 1998), but whether these patients with left- or right-sided damage exhibited extinction or neglect was not reported in those studies.

For all three dimensions of deviance, the MMN was elicited quite consistently when the deviance occurred to the right of the patient. When the deviant stimulus was on the left, the MMN for pitch and spatial location was significantly reduced (or even absent in some patients). This pattern of MMN deficits suggests the existence of a rather early, albeit selective, deficit in the stream of auditory processing in right

hemisphere-damaged patients with neglect. Yet, the specific conditions under which the MMN is elicited (e.g. Näätänen *et al.*, 1989; Winkler and Näätänen, 1993; Joutsiniemi *et al.*, 1998), as well as the dissociation of the generators of MMN from those of the earlier occurring N1 (e.g. Hari *et al.*, 1984; Scherg *et al.*, 1989; Giard *et al.*, 1990; Tiitinen *et al.*, 1993; Kropotov *et al.*, 1995; Levänen *et al.*, 1996; Opitz *et al.*, 1999; for a review, see Alho, 1995), suggest that the MMN is not simply a result of a more robust response of non-refractory neurons in the primary auditory cortex to the deviant sound. Indeed, the deviant feature may be abstract. For example, in one study, the standard stimuli were pairs of tones in which the second tone in the pair was higher in pitch than the first, while the absolute pitch and intensity of the pairs varied from trial to trial. Thus, the only repetitive feature was the temporal relationship of the two pitches in a pair. MMN was elicited by a deviance from this abstract regularity, i.e. by reversing the order of the high and low tones in some pairs (Saarinen *et al.*, 1992). Such data indicate that the MMN is indeed associated with the detection of 'rule breaking' in a more general sense. In line with this view of MMN, it is conceivable that the deficient MMN found in neglect patients in the present study is associated with an impairment in pre-attentive detection of deviations from regularity in the auditory environment when this deviation occurs on the left.

The difficulty in eliciting an adequate contralesional mismatch detection process in our patients may be related directly to the essential feature of unilateral neglect, the fact that significant events fail to attract attention reflexively when they occur in the contralesional side. This conjecture is supported by several lines of evidence connecting the process underlying the MMN to involuntary attention shifts (Näätänen and Michie, 1979; cf. Naatanen, 1990, 1992). For example, the MMN is time-locked to later attention-related components of ERPs (Novak *et al.*, 1992); the emergence of MMN elicited by deviants in an unattended channel is correlated with decrements in performance in the attended channel, a sign of transient reduction in attention (Schröger, 1996; Schröger and Wolff, 1998); and finally, the recently described inter-hemispheric distribution of anterior sources of MMN (Deouell *et al.*, 1998; see also Giard *et al.* 1990) resembles the distribution of cerebral attention mechanisms found using other imaging methods (e.g. Corbetta *et al.*, 1993).

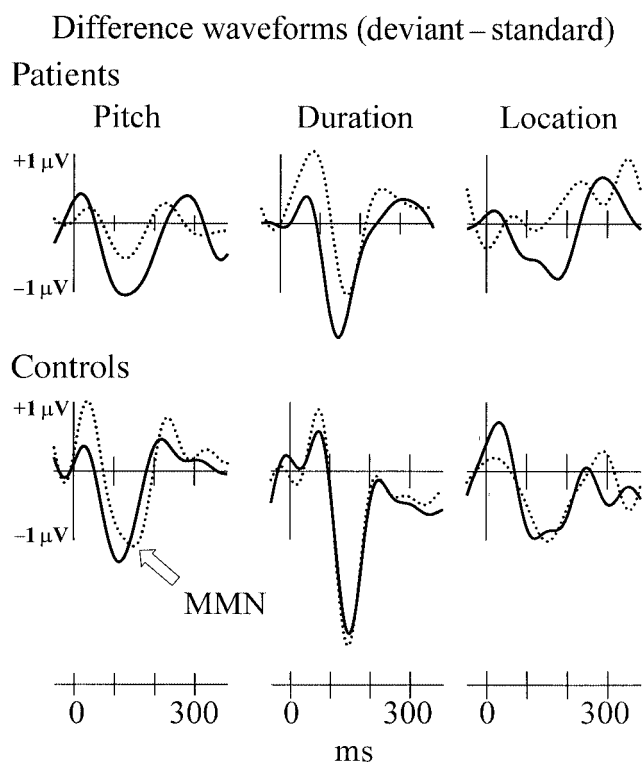


Fig. 3 Differential response (see legend to Fig. 2) at Fz to tones deviating in their pitch, duration or spatial location, occurring to the left or to the right of the subject. Data are referenced to the averaged mastoids. Dotted lines = stimuli on the left; continuous lines = stimuli on the right.

Table 2 Peak amplitude (in microvolts) of the MMN at Fz, and the P-value of the t-test comparing left and right side stimulation for each dimension

	Pitch			Duration			Location		
	Left	Right	P	Left	Right	P	Left	Right	P
Nose reference									
Controls	-1.41	-1.16	0.46	-2.18	-2.02	0.67	-1.28	-1.125	0.68
Patients	-0.50	-1.24	0.043	-0.99	-1.47	0.44	-0.45	-1.12	0.004
Mastoid reference									
Controls	-1.58	-1.63	0.82	-2.65	-2.67	0.97	-1.32	-1.36	0.917
Patients	-0.97	-1.46	0.173	-1.40	-2.17	0.22	-0.41	-1.23	0.039

From a theoretical perspective, keeping adequate surveillance of space outside the focus of attention is a necessary condition for efficient performance of the attention mechanism. Without such pre-attentive parallel monitoring of 'out of focus' information, attention would be fixed rigidly to a once selected target or location, instead of being shifted flexibly, as needed, when new and potentially more important events occur. Posner and his colleagues (Posner *et al.*, 1984, 1987) suggested that left visual neglect following right parietal damage stems from inability to disengage attention from an attended location on the right, in order to relocate it on a target object positioned more to the left, and that thalamic damage may hamper the 'engagement' of attention on the new target location. There is some evidence that the 'disengagement' failure may relate to locations cued by auditory events as well (Farah *et al.*, 1989; but see Buchtel and Butter, 1988). The present MMN results suggest that neglect patients may suffer from a deficient bottom-up process (signalled by MMN) that normally serves to 'call' for attention resources to be disengaged and relocated to an event whose perception has been accomplished by the sensory system (signalled by early evoked potentials such as N1). This deficit may contribute to and aggravate concomitant higher order deficits in these patients, leading to different manifestations of the lateralization bias characteristic of neglect. Furthermore, the present results indicate that this early deficiency is expressed differently while processing different stimulus dimensions.

The presumed link between spatiotemporal aspects of experience and conscious awareness (e.g. Marcel, 1983) led us to predict that neglect patients would be more impaired in processing the spatial location than other stimulus attributes. This hypothesis was supported by the robustness of the side of stimulus effect on the MMN elicited by deviance in spatial location (across patients) compared with that elicited by deviance in pitch or duration. In fact, when both the frontal negativity and the mastoid positivity manifestations were taken into account, the MMN difference favouring the right- over the left-sided presentation was significant only for deviance in spatial location.

An analogous dissociation of spatiotemporal processing from the processing of other stimulus dimensions was found in the visual modality. The visual ERP results obtained by Spinelli and her colleagues (Dorrichi *et al.*, 1996; Spinelli *et al.*, 1996) pointed to a specific deficit in processing information which taps the dorsal but not the ventral visual pathway in the neglected side. The dorsal pathway is engaged in processing spatiotemporal characteristics of visual stimuli, whereas the ventral pathway analyses intrinsic stimulus features, such as colour, shape, etc. (e.g. Mishkin *et al.*, 1983). Although such cortical segregation in human audition is less well established, the present MMN results, taken together with those of Spinelli *et al.* (Spinelli *et al.*, 1996) and Dorrichi *et al.* (Dorrichi *et al.*, 1996) in the visual system, support the existence of a specific deficit in early, automatic, processing of spatial information in neglect patients in the

auditory as well as in the visual modality. It is not clear whether this is a demonstration of independent modality-specific spatial representations concomitantly injured, a supramodal spatial framework (as suggested by Farah *et al.*, 1989) or a reliance of the auditory system on a primarily visual spatial system that was damaged. Examination of the way in which visual information influences the MMN elicited by auditory stimuli could shed light on this question (cf. Calamaro *et al.*, 1995; Soroker *et al.*, 1995 who demonstrated audio-visual interaction in patients' performance).

The specific deficit in processing spatial information suggested by the convergence of ERP results may contribute to the representational theories of neglect that suggest, based on performance data, that neglect stems from a damage to the representation of outer space in the brain (e.g. Bisiach and Berti, 1987). The reduced or missing MMN for deviance of location may be a consequence of a difficulty in encoding the spatial location of a stimulus within a distorted spatial framework. Alternatively, it may result from an early failure of forming a memory trace for the spatial properties of the perceived events. In the latter case, even if the 'representation of space' were to be intact, stimuli could not be mapped to it. In any case, the present MMN results provide strong evidence that spatial attributes (more than other attributes) corresponding to events on the contralesional side are either not encoded, or at least that their encoding is not useful, and that the deficit is probably independent of attention. This particular deficiency may provide a clue for understanding the lack of awareness of the left hemispace in neglect.

Spatial information has a crucial role in both attention mechanisms and conscious awareness (e.g. Bisiach *et al.*, 1979; Treisman and Gelade 1980; Cutting, 1981; Marcel, 1983; Bisiach, 1992; Dennet and Kinsbourne, 1992). As Bisiach suggested on the basis of neglect performance (Bisiach, 1992), conscious awareness of a stimulus cannot be separated from a potential response to it, and such a pre-motor component necessitates, of course, a spatial framework for motor programming (cf. Rizzolatti and Gallese, 1988). On a conceptual/epistemological basis, it seems reasonable to assume that the nervous system, which developed to know a world where events occur in a clear spatial framework, can consciously acknowledge external events only if they carry spatiotemporal information. From a cognitive point of view, spatial information may serve as an anchor for binding the diversity of sensory events into a coherent experience. For example, according to the feature-integration theory, separate features of perceived stimuli are processed pre-attentively and in parallel, whereas the attention-demanding process of feature conjunction necessitates spatial information (e.g. Treisman and Gelade, 1980). In fact, within this framework, illusory conjunctions of features (Treisman and Schmidt, 1982; Cohen and Ivry, 1989) may be taken as a demonstration of the necessity to assign some spatial information (even if erroneous) to a perceptual event, in order to be aware of it and to respond to it. Several studies of neglect patients have indicated that neglected stimuli are perceived implicitly as

far as a categorical level (e.g. Volpe *et al.*, 1979; Marshall and Halligan, 1988; Berti and Rizzolatti, 1992; Berti *et al.*, 1992; McGlinchey-Berroth *et al.*, 1993). Successful encoding of some features while failing to encode the spatiotemporal features of an external event may explain this dissociation between perception and awareness.

That neglect has been much more difficult to demonstrate in the auditory than in the visual or tactile modalities might be a consequence of the fact that in audition, especially in free field, left-sided stimuli reach the ears from both sides, so that a (erroneous) 'location tag' may be attached to the stimulus and allow its recognition. The fact that patients tend to err in localizing auditory stimuli to the right of the true source is in line with this idea. In addition, Calamaro and colleagues showed that producing the illusion that a phoneme was delivered from the right, while it was actually produced by a speaker on the left of the subject, improved the detection and identification of the phoneme (Calamaro *et al.*, 1995). This could be a result of artificially providing the left-sided stimulus with an erroneous place tag on the right. By this account, a necessary (if not sufficient) condition for conscious awareness of an external event is that this event will have a sort of 'location tag' attached to it.

In conclusion, the present results point to an early, pre-attentive deficit contributing to neglect. This deficit may be related to a failure to link perceived sensory events to the attentional system, causing an inability to switch attention to stimuli on the contralesional side. The robust effect of side of presentation on the MMN induced by deviance in spatial location and the absence of reliable side effects for deviance in pitch and duration support the idea that processing spatial location is a pre-requisite for conscious awareness.

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