

Cerebellar damage impairs detection of somatosensory input changes. A somatosensory mismatch-negativity study

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Several recent studies support the view that the cerebellum's contribution to sensory processing is not limited to movement regulation. In a previous paper (Restuccia D, Valeriani M, Barba C, Le Pera D, Capecci M, Filippini V, Molinari M. Functional changes of the primary somatosensory cortex in patients with unilateral cerebellar lesions. *Brain* 2001; 124: 757–68) we showed that the cerebellum influences somatosensory input processing at very early stages. The present study was aimed at verifying whether an analogous influence is also exerted at higher levels. For some time it has been known that in the auditory modality a specific event-related potential (ERP), that is, mismatch negativity (MMN), reflects preattentive detection of changes in the incoming stimulus by comparing the new stimulus with sensory memory traces. To test the cerebellar influence on the processing of incoming somatosensory stimuli we first verified whether the electrical stimulation of fingers, according to an 'oddball' paradigm within a stimulus-ignored condition, was able to elicit event-related components specifically linked to the preattentive detection of change. We analysed scalp responses obtained from eight healthy volunteers during frequent and rare electrical stimulation of the first and fifth finger of the left hand, respectively. To ensure that responses to deviant stimuli were due to changes in detection mechanisms, rather than to activation of new afferents, we also analysed responses to rare stimulation alone ('standard-omitted' condition). The 'oddball' stimulation was able to elicit a parieto-occipital extra negativity that was different in scalp distribution and latency from the N140 response to the 'standard-omitted' stimulation. We considered that this response was related to changes in detection mechanisms and labelled it somatosensory mismatch negativity (S-MMN). When the same procedure was applied to six patients with unilateral cerebellar lesions we found that the S-MMN was clearly abnormal after stimulation of the affected hand (ipsilateral to the affected cerebellar hemisphere). Earlier ERPs, as well as ERPs elicited during the 'standard-omitted' condition, were fully normal. Present data indicate that cerebellar processing is involved in preattentive detection of somatosensory input changes. In conclusion, this study demonstrates the reliability of S-MMN recordings and indicates that subjects with cerebellar damage may be impaired in the cortical processing of incoming somatosensory inputs.

Keywords: mismatch negativity; somatosensory evoked potentials; cerebellum

Abbreviations: ERP = event-related potential; ISI = interstimulus interval; MMN = mismatch negativity; S-MMN = somatosensory mismatch negativity

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Introduction

According to the classical interpretation of cerebellar function, the massive somatosensory (and, in general, sensory) input to the cerebellum is devoted exclusively to optimizing the fine regulation of voluntary movement. In fact, cerebellar lesions do not produce any apparent sensory deficit (Holmes, 1939). However, many recent studies support the hypothesis that the cerebellum acts as a general sensory acquisition controller (Bower, 2002). Pure sensory tasks, such as sensory discrimination (Gao *et al.*, 1996) or non-motor auditory or visual tasks (Jueptner *et al.*, 1995; Allen *et al.*, 1997), are able to activate cerebellar nuclei, as demonstrated by neuroimaging techniques. Recently, ‘fractured maps’ of the body were found in the cerebellum (Leergaard *et al.*, 2000) and climbing and mossy fibres’ cerebellar activation has been reported with magnetoencephalography in humans (Hashimoto *et al.*, 2003). On the basis of this finding, it is likely that the cerebellum participates in recognizing somatosensory stimuli by following a somatotopic map containing the respective representations of body parts organized according to a hierarchical and functional, not merely anatomical, subdivision. (Bower, 2002; Shumway *et al.*, 2005). Seen in this view, the cerebellum could play a major role in optimizing sensory processing without using sensory information to regulate voluntary movements. In line with cerebellar involvement in the cortical processing of somatosensory stimuli, we demonstrated that the cerebellum is able to modulate the excitability of the primary sensory cortex at very early stages of somatosensory input processing (Restuccia *et al.*, 2001). By analysing early latency somatosensory evoked potentials (SEPs) in patients with lateralized cerebellar lesions we were able to demonstrate that inhibitory circuitries, whose activation follows the primary depolarization of granular layer cells, are low-functioning in cerebellar patients. This strongly suggests that the cerebellum influences the activity of inhibitory circuitries in the primary somatosensory cortex, which, in turn, is thought to modulate receptive fields and to optimize cutaneous discrimination (Ebner and Armstrong-James, 1990). In this view it should be considered that patients with cerebellar lesions could have impaired cortical sensory processing. Somatosensory deficits, such as difficulty in weight perception (Holmes, 1917) or kinaesthesia (Grill *et al.*, 1994), are occasionally reported after cerebellar lesions and have been interpreted as a dysfunction in the early stages of somatosensory processing. In the last decade, the notion that the cerebellum participates in several high-level processes, such as motor learning, memory, planning and attention, has received increasing support (Appollonio *et al.*, 1993; Molinari *et al.*, 2002; Schmahmann, 2004). In different human brain lesion studies we showed that patients with cerebellar lesions can have high-level deficits not directly related to motor behaviour (Molinari *et al.*, 1997a, b, 2004; Silveri *et al.*, 1998; Leggio *et al.*, 1999, 2000). In particular, it was suggested that high-level impairment in sensory

processing explains the sensory dysgraphia observed after cerebellar damage (Silveri *et al.*, 1997).

In synthesis, experimental (Bower, 2002), neurophysiological (Teschke and Karhu, 2000; Restuccia *et al.*, 2001) and functional neuroimaging data (Blakemore *et al.*, 1999) support the idea that cerebellar activity influences somatosensory cortex activity. In particular Tesche and Karhu (2000), but see also the commentary by Ivry (2000), suggested that the cerebellum is capable of evaluating the predictability of incoming somatosensory sensory stimuli and, accordingly, of modulating the somatosensory cerebral cortex. To verify whether the cerebellum participates in somatosensory input processing and, more specifically, whether the presence/absence of cerebellar processing affects the somatosensory cortex’s ability to recognize the similarity/diversity of incoming inputs, we analysed the somatosensory mismatch negativity (S-MMN) component of event-related potentials (ERPs) in six patients with unilateral cerebellar lesions. Thus far, the mismatch negativity (MMN) response has been studied almost exclusively in its auditory modality, although some studies concerned also MMN elicited by visual (Nyman *et al.*, 1990; Alho *et al.*, 1992; Woods *et al.*, 1992; Tales *et al.*, 1999), olfactory (Pause and Krauel, 2000) and somatosensory (Kekoni *et al.*, 1997; Shinozaki *et al.*, 1998; Kida *et al.*, 2001, 2004b; Tamura *et al.*, 2004; Akatsuka *et al.*, 2005) modalities. When unattended, deviant acoustic stimuli are interspersed between regular, frequent acoustic stimuli; the deviant ones usually elicit a frontotemporal negative response in the 120–180 ms latency range, labelled MMN (Naatanen *et al.*, 1978; see also Naatanen and Escera, 2000 for review). According to Naatanen and Michie’s (1979) model, MMN is generated by an automatic cortical change-detection process in which a difference is found between current input and representation of the regular aspects of the preceding auditory input (see also Takegata *et al.*, 2001). This process can be achieved only if a memory representation of the standard input is available for comparison with the current input, and it is thought to reflect a distributed network involving auditory cortex, prefrontal cortex and parietal cortex (Alain *et al.*, 1998). Although auditory MMN has been consistently studied, the MMN response elicited by somatosensory stimulation has been seldom analysed (Kekoni *et al.*, 1997; Shinozaki *et al.*, 1998; Kida *et al.*, 2001, 2004b; Tamura *et al.*, 2004; Akatsuka *et al.*, 2005). Though all of the above-mentioned studies reported somatosensory ERPs elicited by changes in the characteristics of frequent stimuli, the reports are not completely consistent. Kekoni *et al.* (1997) used a vibratory mismatch paradigm and reported the presence of an S-MMN at 100–200 ms, while Shinozaki *et al.* (1998) reported mismatch positivity at 100–200 ms using a topographical mismatch paradigm. Although Kida *et al.* (2001) used a paradigm very similar to that of Shinozaki *et al.* (1998), they did not find any positivity in the 100–200 ms latency range. Instead, Tamura *et al.* (2004) adopted a

two-point discrimination paradigm and found a negative potential at ~140 ms. Finally, using a temporal discrimination protocol, Akatsuka *et al.* (2005) found a large positive component peaking at around 100–200 ms. We took into account the differences in the neurophysiological S-MMN patterns reported above and attempted to record an S-MMN response reliably in a control population. For this purpose we recorded scalp responses in eight healthy volunteers following electrical stimulation of the fifth left finger interspersed among frequent electrical stimulations of the left thumb ('oddball' paradigm). To ensure that the subjects' attention was not directed toward the stimulated hand, we kept the electrical stimulation just above the minimal sensory threshold and asked the subjects to read a novel very attentively because they would have to summarize it after the test. Moreover, to confirm that the MMN responses issuing from such a paradigm were not merely due to the intrinsic characteristics of the deviant stimulus, we also recorded responses elicited by the deviant stimulus alone, omitting the frequent stimulus ('standard-omitted' paradigm). A similar procedure was described in earlier reports (Kekoni *et al.*, 1997). Then, we studied S-MMN responses in six patients with unilateral cerebellar lesions. 'Standard-omitted' stimulation was also administered to three of the patients. Additionally, auditory MMN was recorded in two patients according to the technique described in a previous paper (Restuccia *et al.*, 2005).

Material and methods

Control subjects

We first studied eight healthy volunteers (ages ranging from 27 to 64 years, mean: 43.6, five males, three females). All of them underwent left-hand stimulation according to the following protocols.

'Oddball' stimulation

Electrical stimuli were delivered via ring electrodes placed on the finger (stimulating electrode proximal, placed above the proximal phalanx; anode placed above the distal phalanx). Frequent and deviant stimulations were delivered to the first and fifth left finger, respectively. Frequent and deviant stimulations were 80 and 20%, respectively. Two successive runs of 500 stimuli were delivered with 1000 ms of interstimulus interval (ISI). Traces from each run were superimposed to ensure reproducibility and then averaged. Stimulus intensity was adjusted just above the sensory threshold for each subject. Intensity for a 200 μ s stimulus duration ranged from 2 to 4 mA. Then, the subjects' attention was distracted by a simple task, that is, reading a novel. To limit ocular artefacts as much as possible, each line of the two-column book was 7.5 cm long, and the book was kept on a board 60 cm from the subjects' eyes, according to a previous report (Desmedt and Tomberg, 1989). Moreover, an electrooculogram (EOG) was carried out by means of an electrode placed on the lateral cantus of the right eye. We ensured that the subjects had been attentive to the reading task by asking them to summarize the novel briefly but exhaustively after the session. Recording electrodes were placed on 31 regularly spaced scalp locations (10–20 system). A reference electrode was

placed above the nose. Electrode impedance was kept <3000 Ω . Signal was filtered with a bandpass of 1–60 Hz; trials exceeding 40 μ V were automatically edited out from the averaging. Signals were further digitally filtered 'off-line' with a bandpass of 2–20 Hz. Baseline stabilization was ensured by subtracting the mean voltage during the 50 ms prestimulus period from the signal.

'Standard-omitted' protocol

The above procedure was repeated by omitting the frequent stimulation to the left thumb. For responses during the 'standard-omitted' protocol, the following components were recognizable in the 180 ms after stimulus onset: P45, N60, P100, N140 (Desmedt and Tomberg, 1989; Allison *et al.*, 1992). Owing to their high reproducibility and to the specific purposes of the present study, only the N60 and the N140, respectively recognizable within the 60–90 and 120–180 latency windows, were evaluated. Amplitudes were measured from the baseline, while latencies were measured at the recording site, where the response reached its maximum. The traces that issued from frequent stimulation in the 'oddball' paradigm were generally low-amplitude; therefore, most responses were questionable. For this reason the analysis was performed directly on difference traces obtained by subtracting frequent-stimulus ERPs from deviant stimulus ERPs. Latencies were compared by means of paired *t*-tests. Amplitude values were evaluated using one-way ANOVAs (analysis of variance). When significance was reached, *post hoc* analysis was performed by means of Tukey's tests. As regards analyses of topographical changes between 'standard-omitted' and 'oddball' conditions, we firstly considered electrode location \times condition interactions; however, by considering the low number of control subjects and the changes in the ERP amplitude across conditions (McCarthy and Wood, 1985), we also evaluated the amplitude ratio between Fz and Pz responses. For each subject, we thus calculated the amplitude of the negative response in the 120–180 ms latency range at Fz and Pz leads; then we calculated the Pz/Fz amplitude ratio. The ratio values in the different conditions were compared by means of paired Student's *t*-tests.

For illustrative purposes, we performed the grand average of traces obtained from our control subjects in the different conditions. Then we obtained frozen maps showing the distribution of the responses over the scalp from grand-average traces by spline interpolation (Perrin *et al.*, 1987). We also calculated the Current Source Density (CSD) maps by means of the Laplacian transformation of the potential values without taking the reference electrode into account (Hjorth, 1991). CSD mapping allows identifying regions where current exits (current sources) or enters the head (current sinks), and may be particularly useful for studying the topography of responses peaking close to each other in time and space.

Patients

We studied six patients with unilateral lesions of the cerebellum. Before the test all patients underwent the following: (i) Clinical examination, comprising pinprick and joint-touch sensation examination. Cerebellar motor impairment was quantified using a modified version of Appollonio's (Appollonio *et al.*, 1993), which ranges from 0 (absence of any deficit) to 42 (presence of all deficits to highest degree); (ii) brain MRI; (iii) median nerve early latency SEPs. Using the procedure standardized in our laboratory (Restuccia *et al.*, 1992), we evaluated the latency of the brainstem P14 and particularly of the cortical N20 component to reveal any

dysfunction of the somatosensory subcortical ascending pathways. Patients’ clinical data are summarized in Table 1, and lesion extent in Fig. 1. In particular, four subjects had unilateral ischaemia and the remaining two had undergone surgery for haemangioma removal. A careful analysis of brain MRI, together with the absence of clear clinical involvement of joint and touch sensations and the normality of median nerve short-latency SEPs allowed us to exclude any significant involvement of ascending somatosensory pathways in the brainstem.

Auditory MMN was also recorded in two patients (2 and 4 in Table 1). The recording technique was the same described in a previous paper (Restuccia *et al.*, 2005), with the only difference of the task used to keep the attention away from the acoustic stimulation. Briefly, auditory stimuli were presented while subjects read a novel: auditory stimuli were sinusoidal tones (85 ms duration, 1 ms rise and 1 ms fall time, 85 dB SPL of intensity), presented binaurally via headphones. Standard 800 Hz tones and deviant 500 Hz tones were presented with a probability of 85 and 15%, respectively, with an ISI of 1 s. Patients underwent two successive blocks of ~500 acoustic stimuli. Each couple of blocks was superimposed to verify their reproducibility and then further averaged. ERPs were recorded from 31 scalp electrodes. EOG was monitored by an electrode placed in the outer cantus of the right

eye. An automatic artefact-rejection system excluded from the average all runs containing transients exceeding $\pm 65 \mu\text{V}$ at any recording channel. The nose served as reference for all electrodes. The analysis time was 500 ms, with a bin width of 970 μs . The amplifier bandpass was 0.1–100 Hz; ERPs were further filtered off-line with a bandpass of 1–20 Hz (24 dB roll off). Baseline stabilization was ensured by subtracting the mean voltage during the 50 ms prestimulus period from the signal. The N1 component was identified as a negative peak within 70–110 ms from the stimulus onset in frequent stimulus traces. Traces obtained by subtracting the standard stimulus ERP from the deviant stimulus ERP showed two successive deflections: auditory MMN (negative on frontal leads and peaking at ~110–140 ms) and P3a (positive on frontocentral leads and peaking within 200 and 300 ms).

Results
Control subjects
‘Standard-omitted’ protocol

Both N60 and N140 components were easily identifiable in all control subjects on the basis of their latency, polarity and distribution. The N60 response, recognized in the 60–90 ms latency window, was maximal at temporoparietal leads contralateral to the stimulated side. The N140 component, recognizable within the 120–180 ms latency window, was maximal at centroparietal recording sites, with a slight prevalence in amplitude on scalp regions contralateral to the stimulated side. Statistical evaluation of the N60 component revealed a significant amplitude difference among electrodes (one-way ANOVA, $P < 0.05$). *Post hoc* analysis (Tukey’s tests) revealed a significant difference ($P < 0.05$) between CP6, T4, FC6, T6 and C4 electrodes and the remaining ones. As far as the N140 component is concerned, its statistical evaluation did not reveal any significant difference among electrodes (one-way ANOVA, $P > 0.05$).

Table 1 Patients’ characteristics

Patient	Sex	Age (years)	Disease duration*	Clinical motor rating scale**
1	M	57	2 years	1.75
2	F	65	4 years	2.00
3	M	59	3 years	2.00
4	M	58	4 years	1.75
5	F	63	1 year	1.75
6	M	48	6 months	3.00

*From stroke (ischaemic/haemorrhagic lesion) or from intervention (tumour ablation);
**Appollonio *et al.*, 1993.

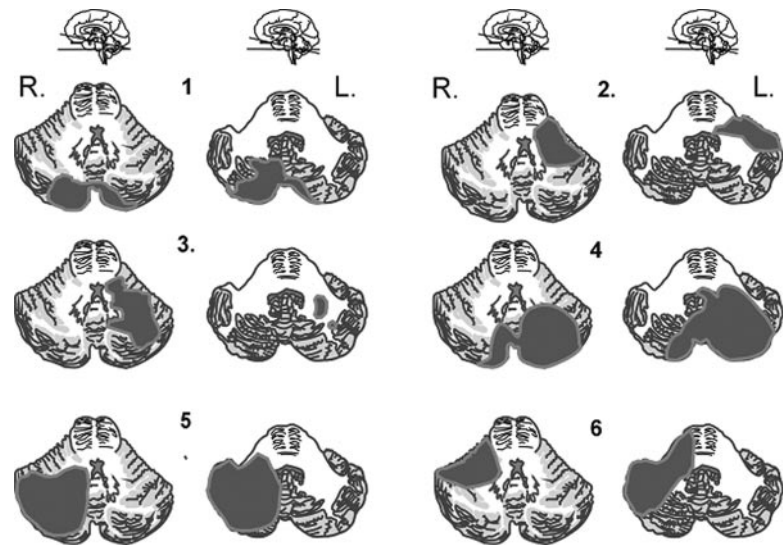


Fig. 1 Topography of cerebellar lesions in the six patients included in the study. R: right; L: left.

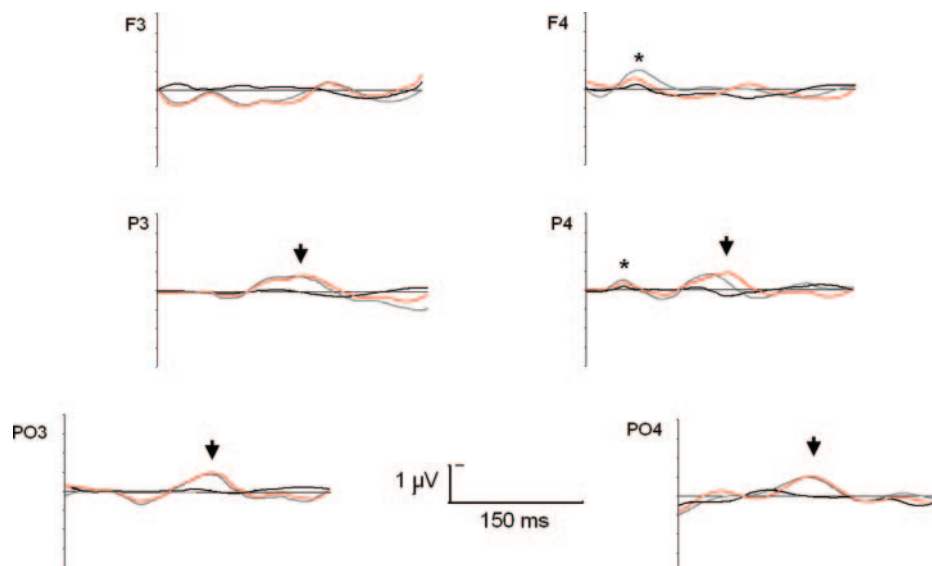


Fig. 2 Grand average of ERPs obtained in eight control subjects after stimulation of the left hand during the 'oddball' protocol. Black traces: frequent stimulation. Grey traces: deviant stimulation. Red traces: difference 'deviant-minus-frequent'. Negativity is upward. Traces after frequent stimulation are low-amplitude and poorly defined, and they only show a small N60 component (asterisk). Traces after deviant stimulation show a larger number of well-defined components, among which an N60 (asterisk) as well as an S-MMN (arrow) are clearly recognizable.

'Oddball' protocol

Responses to frequent stimulation during the 'oddball' protocol (Fig. 2) showed a low but reliable N60 component with inconstant and questionable later ERPs. The N60 component was very low but always recognizable. The N140 component was absent in five subjects and questionable in the remaining three owing to its very low amplitude. In contrast, waveforms issued from deviant stimulation in the 'oddball' paradigm always showed well-defined negative responses in the 60–90 ms and 120–180 ms latency windows. By analysing traces issued from the off-line subtraction of frequent traces from deviant ones, we recognized an N60 response in the 60–90 ms latency range, which was maximal at frontocentral leads contralateral to the stimulated side, and a negative component in the 120–180 ms latency window. This component was maximal in parieto-occipital regions, with a slight prevalence in amplitude on scalp regions contralateral to the stimulated side. Statistical evaluation of the N60 component revealed a significant amplitude difference among electrodes (one-way ANOVA, $P < 0.05$). *Post hoc* analysis (Tukey's tests) revealed a significant difference ($P < 0.05$) between CP6, C4, FC2, F4, F8 electrodes and the remaining ones. As far as the negative component in the 120–180 ms latency window is concerned, its statistical evaluation revealed a significant amplitude difference among electrodes (one-way ANOVA, $P < 0.05$). *Post hoc* analysis (Tukey's tests) revealed a significant difference ($P < 0.05$) between parieto-occipital leads and remaining ones.

'Standard-omitted' versus 'oddball' protocol

The grand average of traces obtained in the 'standard omitted' condition and the difference traces obtained by subtracting frequent-stimulus ERPs from deviant-stimulus ERPs in the 'oddball' conditions are shown in Fig. 3. The latency of the N60 component was significantly different between the two conditions (mean latency: 83 ms in 'standard-omitted' condition, 71 ms in 'oddball' condition. Paired t -test, $P = 0.04$). Visual analysis revealed a slight difference in its scalp distribution, since the N60 tended to be maximal at right temporoparietal leads in the 'standard-omitted' condition, while it was maximal at right fronto-central leads in the 'oddball' condition (Fig. 4). Statistical analysis (one-way ANOVA) revealed a significant difference among electrodes ($P < 0.01$) and between conditions ($P < 0.05$) but no interaction effects ($P = 0.99$), suggesting clear scalp distribution differences. As regards the comparison between components recorded in the 120–180 ms latency window in the 'standard-omitted' condition and in the 'oddball' condition, statistical analysis revealed a significant latency difference (mean latency: 144 ms in the 'standard-omitted' condition, 160 ms in the 'oddball' condition. Paired t -test, $P = 0.01$). Visual analysis revealed a clear difference in their scalp distribution. In the 'standard-omitted' condition it was widely distributed over all scalp regions and maximally in centroparietal regions of the right hemisphere; in the 'oddball' condition it was clearly maximal in parieto-occipital regions and was virtually absent at frontal leads (Fig. 3). Statistical analysis (one-way

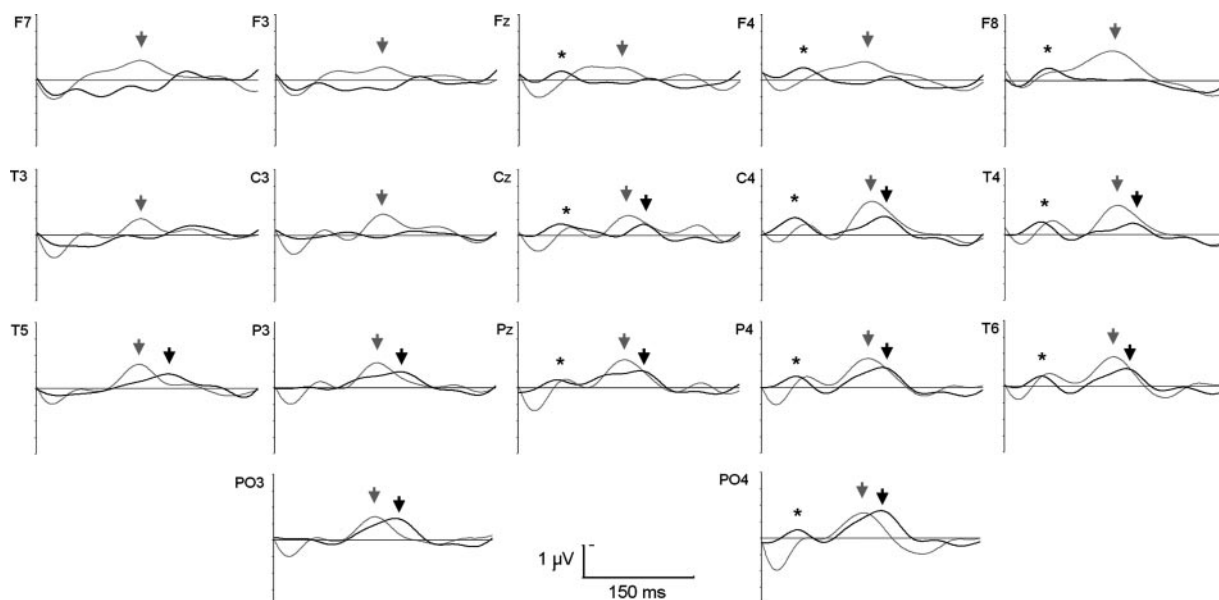


Fig. 3 Grand average of ERPs obtained in eight control subjects after stimulation of the left hand during 'standard-omitted' (grey traces) and 'oddball' (black traces) protocols. For the 'oddball' protocol, only difference traces (deviant–frequent) are shown. Negativity is upward. A clear N60 component is evident in right frontal and temporo-central regions in both conditions. Its latency occurs slightly later during the 'standard-omitted' protocol. In the 120–180 ms latency window, a negative response is evident in both conditions. During the 'standard-omitted' protocol, the negative component (N140) is widely distributed over the whole scalp and reaches its maximum over right centroparietal regions. In contrast, the S-MMN is virtually absent at frontal locations, reaching its maximum at parieto-occipital locations. Its latency occurs slightly later than the N140 in the 'standard-omitted' condition.

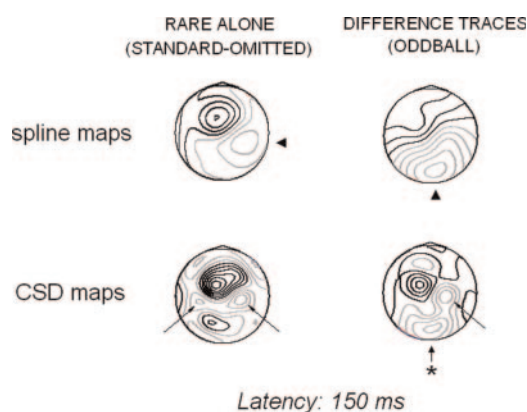


Fig. 4 Distribution maps calculated from the grand average of ERPs obtained in eight control subjects after stimulation of the left hand during 'standard-omitted' and 'oddball' protocols. Both spline and CSD maps were calculated in a latency value including both the N140 and the S-MMN component. Grey indicates the negative field; black, the positive field. Spline maps clearly show that the N140 reached its maximum over the right centroparietal regions, while the S-MMN component was almost exclusively distributed over parieto-occipital regions. CSD maps also show that the N140 distribution is well explained by two temporal sources (SII areas?), whereas the S-MMN may be generated by a right parietal (arrow) and a mid-occipital (asterisk) source.

ANOVA) revealed a significant difference among electrodes ($P < 0.01$) and between conditions ($P < 0.01$) but no interaction effects ($P = 0.99$), indicating a strong scalp distribution difference. The statistical comparison between

Pz/Fz amplitude ratios revealed a significant difference between 'standard-omitted' and difference traces issued from the 'oddball' conditions (Paired t -test, $P < 0.001$). Because of these differences, ERPs recorded in the 120–180 ms latency window in the two conditions were differently labelled, namely N140 in the 'standard-omitted' condition and 'S-MMN' in the 'oddball' condition.

Patients

All cerebellar patients underwent the 'oddball' protocol after successive stimulation of both hands. The 'standard-omitted' stimulation was also performed in three patients (2, 3 and 4 in Table 1) after successive stimulation of both hands. During the 'oddball' paradigm, stimulation of the unaffected side (hand contralateral to cerebellar lesion) always elicited well-defined N60 and S-MMN components (Figs 5 and 6). Stimulation of the affected side (hand ipsilateral to the cerebellar lesion) always elicited a well-defined N60 component. In contrast, the S-MMN was fully lacking in four patients (1–4 in Table 1; Figs 5 and 6). In the remaining two patients, residual negativity was still found in parieto-occipital regions contralateral to the stimulated side. However, the mean amplitude of this negativity at parieto-occipital leads (P4, Pz, P3, PO4, PO3, O2, O1) was extremely low ($0.11 \mu\text{V}$ in Patient 4 and $0.09 \mu\text{V}$ in Patient 5) when compared with the analogous amplitude value obtained in controls ($1.66 \pm 0.09 \mu\text{V}$). During the 'standard-omitted' paradigm stimulation of both the

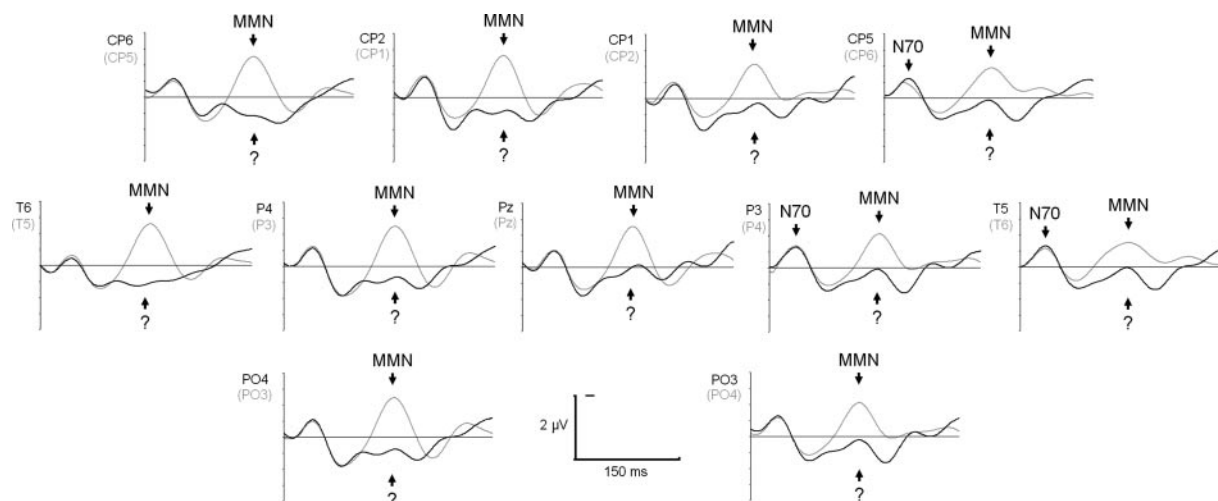


Fig. 5 ERPs obtained from Patient 3 during the 'oddball' protocol difference traces. Traces obtained after stimulation of the unaffected right hand (grey) are superimposed over those obtained after stimulation of the affected left hand (black). Corresponding leads are also superimposed (T5–T6, P3–P4, etc.). Negativity is upward. The S-MMN response is clearly lacking after affected hand stimulation.

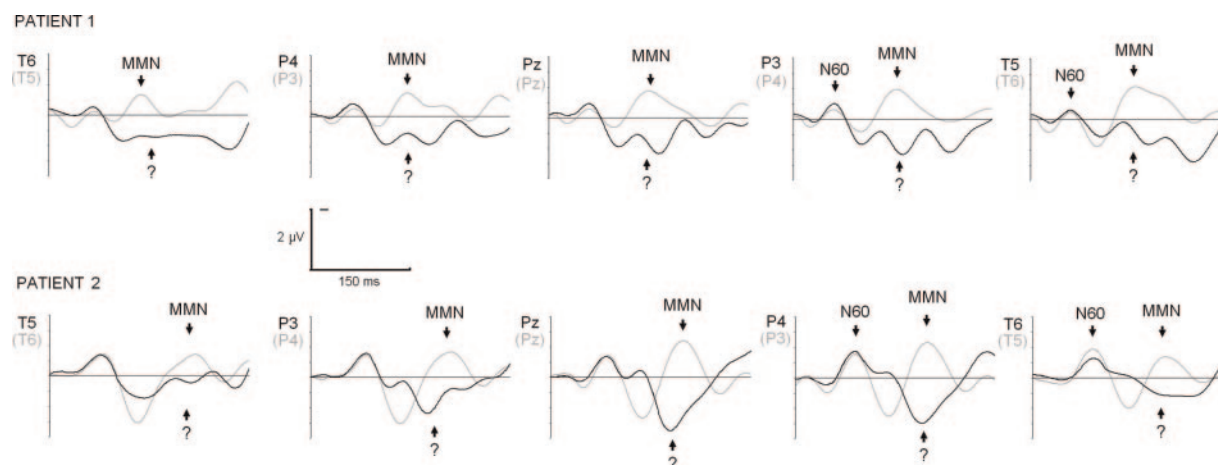


Fig. 6 ERPs obtained from Patients 1 and 2 during the 'oddball' protocol difference traces. Traces obtained after stimulation of the unaffected hand (grey) are superimposed over those obtained after stimulation of the affected hand (black). Corresponding leads are also superimposed (T5–T6, P3–P4, etc.). Negativity is upward. The S-MMN response is clearly lacking after affected hand stimulation.

affected and the unaffected sides elicited well-defined N60 and N140 components in all three patients who underwent the protocol (Fig. 7).

In the two patients who also underwent acoustic stimulation, a well-defined MMN response was evident at frontal regions, with a characteristic phase-reversal at posterior temporal leads (Fig. 8). The MMN peak amplitude measured at F3 and F4 location ranged between 1.2 and 1.6 μV , with an interside asymmetry never exceeding 10%.

Discussion

The two major findings of the present study can be summarized as follows:

- (1) In the unattended condition, deviant electrical somatosensory stimuli interspersed among frequent, regular

electrical somatosensory stimuli are able to elicit a negative parieto-occipital response, labelled as S-MMN, whose characteristics are very similar to those shown by the well-known auditory MMN.

- (2) The generation of S-MMN is clearly abnormal when a cortical hemisphere is lacking in cerebellar input.

Somatosensory MMN

In the somatosensory system, as well as in the auditory domain (Näätänen *et al.*, 2005), MMN can be defined as an electrical response evoked by a discriminable change in any regular (e.g. repetitive) somatosensory stimulation elicited also in the absence of attention. Thus defined, it is generally accepted, at least for the auditory modality, that MMN is generated by an automatic change-detection process in

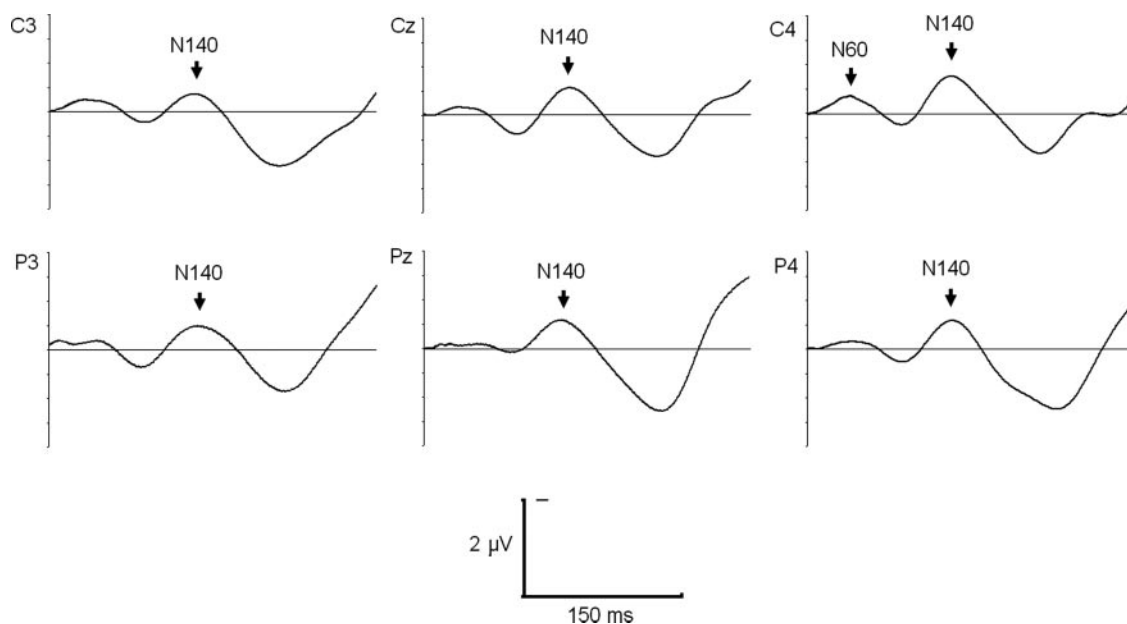


Fig. 7 ERPs obtained from Patient 3 during the 'standard-omitted' protocol stimulation of the affected side (left hand). Negativity is upward. Both N60 and N140 components are clearly recognizable.

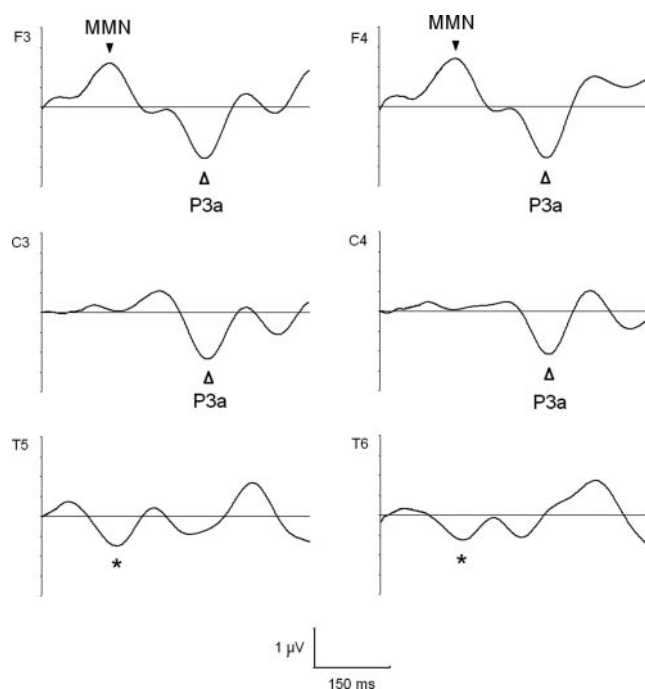


Fig. 8 Patient 4, auditory ERPs, 'oddball' protocol, difference traces (deviant–frequent). Negativity is upward. Both F3 and F4 recordings show a well-defined and symmetrical MMN response, with a clear phase-reversal at posterior temporal leads. Frontocentral recordings also show a well-defined P3a response.

which a discordance is found between input from the deviant event and sensory-memory representation of the regular aspects of the preceding stimulation (Näätänen *et al.*, 2005). This mechanism is thought to rely on different

circuits than those sustaining the N140 wave observed during repetitive regular stimulation. Thus, to define the negative component observed in the 120–180 ms latency window after deviant stimulus as S-MMN we must be assured that this wave is not a variant of the N140 wave. In fact, it can be hypothesized that differences in the cortical activity recorded depend on variations of the N140 wave due to changes in the characteristics of the stimulus and not to activation of different neural circuits.

Differences in stimulation rate are able to alter N140. It is well known that stimulation rate is critical in affecting ERPs (Ritter *et al.*, 1968). In fact, some differences between 'standard-omitted' and 'oddball' ERPs in our control subjects can be ascribed to stimulation rate differences. For example, the N60 component occurs significantly later in the 'standard-omitted' protocol than in the difference traces obtained during the 'oddball' protocol. Frequent traces in the 'oddball' condition were poorly defined, but invariably showed a small N60 component contributing to the final waveform in difference traces. The N60 component may be an amalgam of two separate subcomponents ('N60' and 'N70' in Barba *et al.*, 2002), probably generated in the frontocentral and suprasylvian cortex, respectively. Since the later 'N70' subcomponent is highly sensitive to stimulus rate, conceivably the overall higher stimulus rate in the 'oddball' protocol could have reduced this later subcomponent and enhanced the earlier 'N60' subcomponent (Barba *et al.*, 2002). In contrast, effects related to stimulus rate do not fully explain the specific characteristics of the S-MMN we found in the 'oddball' paradigm. As described above, the contribution of frequent stimuli to difference traces in the 120–180 ms latency window is minimal or absent since

frequent stimulation does not elicit any reliable negative response in this latency range. Therefore, if the large negativity we observed in the ‘oddball’ protocol is exclusively due to the lower rate of deviant stimuli, one might expect such a response to be almost identical to the one obtained in the ‘standard-omitted’ protocol. In contrast, the two protocols gave origin to very different responses in the 120–180 ms latency range. ‘Standard-omitted’ stimulation gave origin to a negative response widely distributed over the entire scalp, reaching its maximum over the centro-parietal regions contralateral to the stimulated side. A CSD map of grand-average traces from control subjects clearly showed two lateralized sources, suggesting the bilateral activation of SII areas. Therefore, this response, labelled ‘N140’ in the present study, is very similar to Garcia-Larrea *et al.*’s (1995) ‘N120’ response, which is characterized by its distribution, consistent with its origin in the second somatosensory area, and by its insensitivity to spatial attention. Also, Kida *et al.* (2004a) described a similar bitemporal scalp distribution for a temporal subcomponent of the N140 response. On the other hand, difference traces showed clearly that the S-MMN response was virtually present only in the parieto-occipital regions. Although no clear interaction effects were found between the two conditions, evaluation of the Pz–Fz amplitude ratio clearly demonstrated a significant difference between N140 and S-MMN scalp distributions.

Another factor that has to be considered to ascertain the independence of MMN from variations of the N140 wave is attention and, possibly, interactions between attention and stimulus rate changes.

Recently Kida *et al.* (2004b) found that the N140 amplitude was significantly larger during ‘standard-omitted’ than during ‘oddball’ conditions. They explained this finding by hypothesizing a stronger orienting effect against a ‘silent’ background during the ‘standard-omitted’ condition. This hypothesis was based on the presence of a clear P3a component, which is thought to reflect an actual attention shift toward the deviant stimulus (Escera *et al.*, 1998; Knight and Scabini, 1998). This was not the case in our control subjects since P3a was lacking in difference traces issued from the ‘oddball’ paradigm (*see* Figs 2 and 3). Furthermore, in our control subjects the S-MMN response occurred significantly later than the N140 elicited by the ‘standard-omitted’ stimulation. This finding lends further support to the hypothesis that these two responses reflect different processes. The specificity of the S-MMN and its difference from the N140 wave is clearly demonstrated also by the clear-cut differences in the cerebellar influences on the two waves. While cerebellar damage blocks or greatly reduces S-MMN, it is completely unable to modify the N140 response. This finding is particularly relevant because it demonstrates that different neural circuits sustain the two waves.

Further considerations are needed to explain differences with previous reports on S-MMN. Our findings are very

similar to those reported by Kekoni *et al.* (1997) and Kida *et al.* (2004b), because in both studies an extra negativity in the 100–200 ms latency range was reported after deviant unattended stimulation in the ‘oddball’ condition. Both studies did not find a clear predominance of the S-MMN at posterior leads; however, this scalp distribution may have been underestimated owing to the limited number of recording sites. Differences in the number of recording sites and in particular the low coverage of the parieto-occipital locations may explain why previous studies did not find a mismatch-related response at posterior leads, but do not explain why in the present study no frontal S-MMN was found. A possible (and very likely) explanation is related to the recording technique we used. In the present study, the reference electrode was located over the nose. Such a recording technique obviously allows a reduction in amplitude of frontal responses. Further studies are needed to definitively clarify the precise localization of the S-MMN generator, possibly using a mastoid reference electrode or a dipolar source analysis that minimizes the influence of the reference electrode location. Other studies (Shinozaki *et al.*, 1998; Akatsuka *et al.*, 2005) reported the presence of extra positivity in the 100–200 ms latency window, which might reflect a process of mismatch detection. As before, also in these two studies no recordings were performed at parieto-occipital locations where S-MMN is recorded. Furthermore, a key reason for the discrepancies between these results and the present one may lie in the stimulus frequency utilized. In the present study, the ISI was 1000 ms; as a matter of fact, in the study of Shinozaki *et al.* (1998), when ISI was 1000 ms, positivity vanished and a frontal negativity was found in the 100–200 ms latency window, according to other similar studies (Kekoni *et al.*, 1997; Kida *et al.*, 2004b). Interestingly, Kida *et al.* (2004b) found that the positivity in the 100–200 ms latency range (which they labelled, according to the previous literature, as P100) was enhanced for deviant stimuli in an oddball protocol, thus suggesting that it could, at least in part, reflect a mismatch-detection process. Looking at our present data, the P100 in control subjects seems enhanced after deviant rather than after frequent stimulation during the oddball paradigm (Fig. 2), while it seems reduced during the ‘rare-alone’ protocol (Fig. 3). This should suggest a possible role of some mismatch-detection mechanisms in the generation of the P100 component. However, differently from the S-MMN, the P100 does not show an unequivocal abnormality in cerebellar patients (*see* Figs 5 and 6). In conclusion, the mere visual analysis of traces suggests that different mechanisms, not only mismatch-related, participate in the building of the P100 component, so that its behaviour is hardly utilizable in analysing ERP changes in cerebellar patients. Further analysis on data obtained from healthy subjects is necessary to definitively assess the actual generation mechanism of the P100 component, which is, however, out of the main aim of the present paper.

Cerebellum and S-MMN

As described above, S-MMN was clearly abnormal in our cerebellar patients despite the fact that N60 (in both protocols) and N140 (in the ‘standard-omitted’ protocol) as well as auditory MMN, at least in the two subjects tested, were fully normal. This is a strong indication that the cerebellum plays a role in mechanisms generating the S-MMN and that subjects with cerebellar damage may be altered in their capacity to correctly process somatosensory information at cortical level.

MMN is generated by an automatic change-detection process in which a discordance is found between input from the deviant event and sensory memory representation of the regular aspects of the preceding stimulation (Naatanen *et al.*, 2005). One of the classical ideas about cerebellar functioning is that the cerebellum acts as a comparator. This function described to explain the ability of the cerebellum to smooth motor activity by comparing the so-called efferent copy of the planned movement with the sensory feedback produced by the actual movement (Marr, 1969; Albus, 1971; Ito, 1990). Interactions between mossy and climbing systems, the so-called base and teaching lines, are considered the structural base for such comparisons as well as the key element involved in the temporal discrimination required for somatosensory associative learning (Ito, 2005). In different models the cerebellum was considered instrumental in anticipating temporal sequences of repeated events (Ivry, 1996). Furthermore, magnetoencephalographic studies showed that the cerebellum is capable of signalling changes in the rate of a somatosensory input particularly by signalling the absence of a predictable event (Teschke and Karhu, 2000). Finally, cerebellar lesions impair intracortical processing of somatosensory stimuli without affecting the arrival of the somatosensory volley to SI (Restuccia *et al.*, 2001). Taken together, the data reported above identify the cerebellum as the ideal structure for detecting ‘discordances between the input from the deviant event and the sensory memory representation of the regular aspects of the preceding stimulation’ (Naatanen and Michie, 1979), at least for the somatosensory system. Support for this hypothesis comes from many sources. The role of the cerebellum in learning to make predictions is stressed in vestibular ocular reflex (Coenen, 1996, cited by Sailer *et al.*, 2005) and in eye-hand coordination (Sailer *et al.*, 2005). The importance of the cerebellum in working memory processing is stressed by functional RMN (Kirschen *et al.*, 2005; Ravizza *et al.*, 2006) and clinical data (Silveri *et al.*, 1998; Ravizza *et al.*, 2006). The key role of the cerebellum in the sensory processing required for procedural learning is evidenced in clinical (Molinari *et al.*, 1997b) and functional imaging studies (Ellerman *et al.*, 1994).

Although appealing and supported by data from various sources, the hypothesis that the cerebellum is the site where constant and deviant stimuli are compared has yet to be confirmed. In particular, this hypothesis has to be tested in different models that question the role of the

cerebellum in making predictions and in comparing old and new stimuli.

Different studies indicated that cognitive and/or behavioural anomalies observed in cerebellar patients may be related to anomalies in processing of incoming sensory stimuli (Molinari *et al.*, 1997b; Bower, 2002; Katz and Steinmetz, 2002; Schmahmann, 2004), and it has been proposed that these anomalies might influence the predictive control of cognitive processes (Ito, 2005). Present findings, indicating that cerebellar damage might impair recognition of differences among somatosensory stimuli, are in line with this hypothesis. It still remains to be elucidated whether cerebellar damage will also affect MMN processing in other sensory domains. Present control data on auditory MMN seems to indicate that the detection of novelty/difference in incoming auditory inputs is preserved in cerebellar patients. Nevertheless, this study was aimed to analyse strictly unilateral somatosensory inputs. According to the auditory MMN recording procedure we used, auditory stimuli are projected bilaterally to the neocortex, and thus the present patient group, with unilateral cerebellar lesion, was not apt to provide a definite answer. Similarly, to analyse the visual domain will require a dedicated study especially because the existence of a visual MMN is still a matter of debate (Pazo-Alvarez *et al.*, 2003).

In conclusion, the present findings indicate that the preattentive detection of deviant somatosensory stimuli is impaired in cerebellar patients; thus they support the hypothesis that cerebellar processing is required for detecting the novelty of an incoming somatosensory stimulus providing key elements for understanding the pathophysiology of cerebellar motor, cognitive and behavioural symptoms.

As regards the putative clinical utilization of S-MMN recordings in cerebellar patients, the present finding of a clear-cut and unequivocal ERP abnormality speaks in favour of a possible utilization of this technique, also keeping in mind that clear ERP abnormalities have been found in patients with slight clinical symptoms. A field of particular interest, where S-MMN analyses may have important clinical implication, is that of cerebellum-related behavioural disorders. Autism and schizophrenia in particular have been often considered to be associated with cerebellar anomalies (Penn, 2006; Bigelow *et al.*, 2006), and abnormalities of the auditory MMN have been reported in both conditions (Gomot *et al.*, 2006; Oades *et al.*, 2006). Present data indicate S-MMN as a useful tool for further addressing cerebellar functionality in these groups of patients.

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