Anticipatory Cerebellar Responses During Somatosensory Omission in Man

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Abstract: The traditional view of cerebellum is a structure that modifies and synchronizes elements of motor performance. Recent evidence indicates that human cerebellum is involved in a wide range of nonmotor sensory and cognitive functions. A common feature in these diverse motor and nonmotor tasks may be the capacity of cerebellar neuronal circuits to process and anticipate sensory input with high temporal acuity. We present evidence supporting this hypothesis from measurements of the magnetic field at the scalp evoked by neuronal population activity in human cerebellum. Intermittent electrical stimulation of the finger and the median nerve elicited stimulus-locked cerebellar responses with oscillatory components at 6–12 Hz and 25–35 Hz. Sustained oscillatory activity followed random stimulus omissions, with initiation of cerebellar responses prior to the next overt stimulus. These responses indexed processing of temporal features of somatosensory input independent of motor performance or response. The refractory behavior of the responses suggested that a neuronal trace of the temporal pattern of somatosensory stimulation remained in cerebellar circuits for 2–4 s. The cerebellar activity elicited by violation of an established temporal pattern was enhanced when attention was directed to somatosensory stimuli, in concordance with recent imaging studies suggesting participation of cerebellum in attentional networks. The attentional enhancement of the cerebellar responses supports the salience of cerebellar activity in the processing of purely somatosensory input. The short-term maintenance of cerebellar templates for predictable sensory input may reflect a physiological substrate for fine-grained temporal tuning and optimization of performance in large-scale sensory and integrative systems. *Hum. Brain Mapping 9:119–142, 2000.* © 2000 **Wiley-Liss, Inc.**

Key words: cerebellum; somatosensory stimulation; brain rhythms; human; evoked responses; omission; timing; magnetoencephalography; MEG

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INTRODUCTION

Early clinical findings described negligible sensory impairment after cerebellar lesions, leading to a con-

sideration of cerebellum as a motor organ which is responsible for adjusting and synchronizing motor performance [Holmes, 1939]. In contrast to this classic view, anatomical, behavioral, lesion, and imaging studies indicate that in primates, the evolutionarily youngest lateral cortical areas are involved in a wide range of nonmotor, cognitive, and language functions [Ivry and Keele, 1989; Leiner et al., 1991; Middleton and Strick, 1995; Passingham, 1975; Schmahmann, 1991, 1997]. Recent fMRI studies have verified with remarkable spatial accuracy the involvement of cere-

bellar circuits in the processing of purely sensory information [Allen et al., 1997; Gao et al., 1996]. The main cerebellar output relay, the dentate nucleus, activates strongly in humans during a task that dissociates the acquisition and discrimination of sensory data from motor performance [Gao et al., 1996]. Magnetoencephalographic recordings show stimulation of afferent somatosensory tracts evokes responses in cerebellum that precede those in primary somatosensory cortex (SI), indicating immediate input of sensory information into human cerebellar circuitry [Tesche, 1996a; Tesche and Karhu, 1997a,b].

The role of cerebellum in sensory processing has remained elusive. Theoretical considerations of cerebellar functions suggest that the cerebellar neuronal assemblies provide short-term timing information which may be utilized by a variety of sensory, motor, and cognitive systems [Akshoomoff et al., 1997; Bower, 1997; Ito, 1984, 1997; Ivry, 1997; Keele and Ivry, 1990; Thach et al., 1992].

Attentional demands may contribute significantly to cerebellar activation independent of motor performance [Akshoomoff et al., 1997; Allen et al., 1997]. A broad concept of cerebellum as a predictor with high learning capacity has also been suggested [Keele and Ivry, 1990; Miall et al., 1993; Stein and Glickstein, 1992]. Experimentally, patients with cerebellar lesions have been shown to misjudge the duration of auditory stimuli [Ivry and Keele, 1989] and the velocity of a moving visual stimulus [Ivry and Diener, 1991]. The putative "sensory" role of cerebellum is thus particularly prominent during tasks that require short-term representation of accurate temporal information. Modern neurophysiological brain-imaging methods are well suited to address the order of activation and timing in neuronal networks and provide sufficient temporal and spatial resolution for the noninvasive monitoring of neuronal processing in large, synchronously active neuronal populations. Magnetoencephalographic (MEG) and electroencephalographic (EEG) recordings performed noninvasively at the scalp are utilized routinely to characterize current flow generated by postsynaptic activity in cortex with millisecond temporal resolution [for a review, see Hämäläinen et al., 1993].

Observation of cerebellar activity in man with traditional EEG methods has not been reported. Recently, cerebellar evoked MEG responses have been detected following somatosensory stimulation [Tesche, 1996a; Tesche and Karhu, 1997a,b] and associated with saccadic eye movements [Jousmâki et al., 1996a,b]. In this study, we monitored cerebellar and cortical MEG responses during stimulation of finger and hand with repetitive somatosensory stimuli containing various patterns of omissions. The motivation for the study was twofold. We presumed that if cerebellar networks are involved in the processing of sensory input, it is likely that the repetitive stimuli become represented by a local neuronal model of the input. Subsequently, if the cerebellar circuits participate in the recognition of the timing of perceptual input, any violation of the temporal predictions of the model, such as a sudden, unpredictable omission, may be manifest in changes in the spectral and/or temporal characteristics of the neuronal activation.

An omitted stimulation provides a momentary doubling of the time interval between stimuli (ISI), and thus a comparison of responses to the preceding and subsequent stimuli probes the duration and refractoriness of the local model for sensory input. Omission-related responses to randomly omitted stimuli also probe the ability of the network to recognize a fixed temporal interval between stimuli and to anticipate the subsequent stimulus following omission. Stimuli which are omitted on a predictable basis also result in a momentary doubling of the ISI, but responses to the omission *per se* may be quite different. The neuronal network may categorize the input as part of a more complex, but stereotypic temporal pattern. Thus, the neuronal activity in the epoch following an omission and the anticipatory activity associated with the first stimulus after omission may provide experimental support for theoretical considerations of cerebellum as a predictor, irrespective of the details of the task at hand [Ivry, 1997; Keele and Ivry, 1990; Miall et al., 1993; Stein and Glickstein, 1992].

A common feature supporting the diverse motor and nonmotor tasks associated with human cerebellar activation could be the capacity of cerebellar neuronal circuits to anticipate and process information whenever high temporal acuity and accuracy is required. We present evidence for this hypothesis from observation of evoked, stimulus-locked neuronal oscillations in normal human cerebellum. We observed oscillatory activity at 6–12 Hz and 25–35 Hz consistent with the known physiological frequencies of the two afferent systems to cerebellar cortex: the climbing and mossy fibers. Sustained activity followed the omission of stimuli and robust anticipatory enhancement of activity occurred prior to the first stimulus following an omission. Cerebellar responses sustained during regularly omitted stimuli were clearly smaller than those observed following random omissions, suggesting specific cerebellar involvement in the immediate processing of a deviance in the temporal pattern of stimulus presentation. Both anticipatory cerebellar ac-
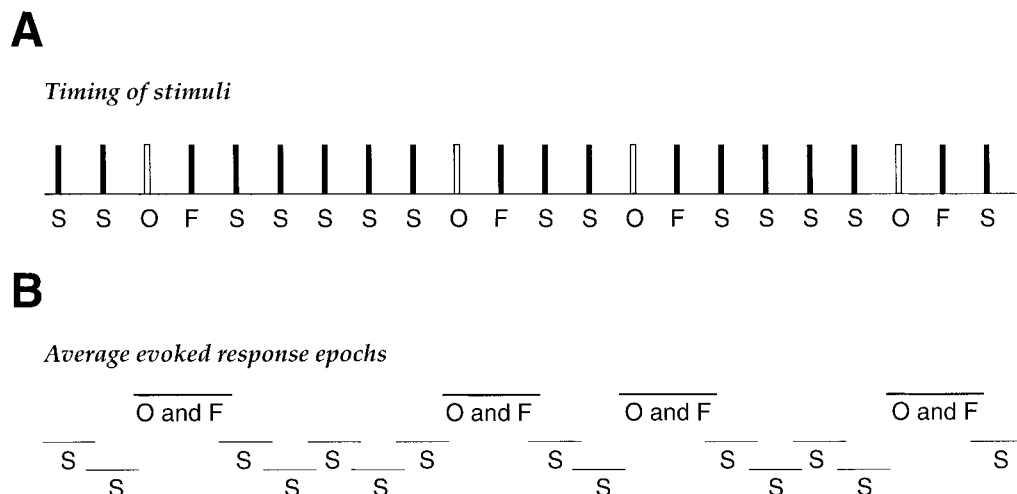
A

Timing of stimuli

S S O F S S S S S O F S S O F S S S S O F S

B

Average evoked response epochs

Figure 1.

A. Timing diagram for the stimulation of the median nerve by short pulses at a uniform rate. 15% of the stimuli are randomly omitted. An omitted stimulus, indicated by the letter O, is followed by a first stimuli after an omission, F, and then by subsequent stimuli with no intervening omission, S. **B.** Definition of the epochs utilized to calculate average evoked responses. Responses time-locked to the omissions and the first stimuli after omissions (O and F) are indicated by thick lines and responses to all stimuli except the first after omission (S) by thin lines.

tivity during omission and the magnitude of the first evoked response following an omission were strongly reduced when attention was directed outside the somatosensory system. Finally, the refractory behavior of cerebellar responses clearly differed from that observed in primary somatosensory cortex, suggesting separate timecourses for the maintenance of neuronal representations in these two structures.

MATERIALS AND METHODS

Nine right-handed normal volunteers (six males; age 25–49 years) participated in an ongoing study of evoked MEG responses to somatosensory stimulation [Tesche, 1996a,b; Tesche and Karhu, 1997a,b]. Seven of the subjects received unilateral median nerve stimulation through transcutaneous electrodes at the wrist. Five subjects received stimulation of the finger. Constant current pulses of 0.3 ms duration were delivered at steady interstimulus intervals (ISIs). In one set of studies, the train of pulses was interleaved with random omissions of 15% of the stimuli (Fig. 1A). In a second set of studies, cerebellar responses to regular (predictable) perturbations of the temporal order of stimulus presentation were investigated through application of a train of current pulses in which every fifth stimulus was omitted (Fig. 5A). Responses were recorded for stimuli with random omissions at ISIs of 0.5, 1, 2, and 4 s and for stimuli with regular omissions at ISI of 0.5 s. Pulse amplitudes for median nerve stimulation (4–6 mA) were individually adjusted to be completely painless but just above the motor threshold of the hand muscles innervated by the median nerve. Pulse amplitude for stimulation of index finger was 7–11 mA. No movement or motor responses were elicited by the finger stimuli. Between 450–1500 pulses were delivered separately both to the left and to the right wrist or the index finger. The attentional state of the subject was varied as follows. In the "attend" condition, subjects attended passively to the stimuli, with no counting or motor responses required, nor any other stimuli presented as distractors. In the "ignore" condition, subjects read a self-selected text. A structural MRI (1-T Siemens Magnetom system: recorded at the Helsinki University Central Hospital, Helsinki, Finland) was also performed on each subject.

Evoked scalp magnetic field patterns were recorded with a 122-channel MEG detector [Ahonen et al., 1993]. Subjects were seated inside a magnetically shielded room underneath a helmet-shaped array of sensors. Each sensor in the array detected a weighted sum of the magnetic signals generated by all current flow in the brain. A single planar-gradiometer sensor in the array was most sensitive to synchronized postsynaptic current flow of neuronal populations in nearby superficial fissural cortex. Subcortical and cerebellar sources of current flow in the brain were imaged by the ensemble of all the detectors [Tesche, 1997].

The MEG signals were bandpass filtered at 0.03–330 Hz and sampled at 1 kHz. Two average evoked re-

sponses were computed on line: one time-locked to the presentation of stimuli and the other to the omission of stimuli. A vertical electrooculogram was used to reject epochs contaminated by eye movements and blinks from the on-line averages (rejection limits ± 150 μV). Averaged evoked responses to all stimuli except those occurring immediately following an omitted stimulus were calculated off-line. The epochs contained in the evoked response averages to the omission of stimuli and the first stimulus following omission (O and F) and for all stimuli except the first after an omission (S) are indicated in Figure 1B. Data recorded for subjects N4, N7, N8, and N9 included in addition all raw data for the 122-channels of MEG, the vertical EOG, and stimulus markers. Additional averaged evoked MEG responses for these were calculated off-line triggered on the EOG recordings of spontaneous blinks (EOG > 80 μV).

Calculation of the distribution of current flow in the brain from neurophysiological responses observed at the scalp requires additional information beyond that available from MEG and/or EEG data. We determined sites of localized cortical responses to the stimuli using conventional equivalent current dipole (ECD) analysis. Short-oriented current segments were used to approximate the locations and orientations of sources previously identified with activation following stimulation of the hand (for a review of standard MEG methods for cortical source analysis [Hämäläinen et al., 1993]). From 3 to 6 ECDs were determined for each subject from a least-squares fit to the data for sources in primary somatosensory cortex SI, secondary somatosensory cortex SII, and precentral and posterior parietal cortex [Forss et al., 1996]. A subject-specific spherical model for the conducting volume of the brain determined from the subject's individual MR images was utilized in this analysis. MEG data from subsets of 34 planar gradiometer detectors that were located directly over the corresponding fissural cortex was used in the determination of the individual ECD parameters (goodness-of-fit > 90%). The baselines for the sensors were fixed from 100 to 5 ms before the anticipated stimuli.

Responses with more complex field patterns were observed at 120–420 ms following the omission of an expected stimulus (Fig. 2A). These responses were largest in detector channels located over right frontal cortex, but also involved sensors located over left frontal and parietal areas (median nerve stimulation for subjects N1–N7: the magnitude of the SSP vector for distributed activity in MEG channels located over right hemisphere > left hemisphere for 18/23 projections). Although a detailed discussion of the distrib-

uted cortical omission responses is outside the scope of the present work, it is important to include this activity explicitly in the analysis to avoid misassignment of these responses to deeper brain structures. For this purpose, it was sufficient to characterize these quite distributed responses directly as patterns of signal strengths recorded in the array [Tesche et al., 1995]. The distributed responses were included along with the ECD sources as SSP components of the cortical responses to the stimuli and omissions.

Blinks represent a very common disturbance of MEG recordings. Blinks generate both movement-related artifacts and neuronal responses in cortex and cerebellum. Epochs containing blinks were rejected from the on-line averaged evoked responses for subjects N1–N3, N5, and N6 with an EOG rejection limit of 150 μV. Blink responses were identified explicitly in data for subjects N4, N7, N8, and N9. Prominent MEG signals were recorded during the blink in sensors located near the face. These blink artifacts were characterized by the topography of the signals recorded in the array at the time of the peak EOG response. A previously identified cortical response in posterior parietal cortex [Hari et al., 1994] was characterized by an ECD determined from the blink-triggered evoked responses at 100 ms following the peak EOG activity. The blink-related MEG "artifact" and posterior parietal source were included explicitly along with the other cortical components in the analysis of data for these subjects.

Access to subcortical neuronal populations was obtained by the incorporation of *a priori* physiological information into the analysis of the MEG data [Tesche, 1996a,b]. Anatomical features of the individual subject's brainstem and cerebellum were obtained from the subject's MR images. Magnetic field patterns and the corresponding signal topographies determined in the 122-channel array were calculated for a simulated pulse of activity generated by a single dipolar current flow located at various sites in cerebellar vermis, dentate, or fissural cortex or in inferior olivary nuclei for comparison with the measured data. The simulations utilized a subject-specific single-compartment boundary-element model for the conducting volume of the brain determined from each subjects' MR images [Hämäläinen and Sarvas, 1989].

The simulated data demonstrated that the coverage of the present 122-channel system was sufficient to distinguish responses from a dipolar source of ~5 nAm located at midline cerebellum near vermis from dipolar activity generated at lateral displacements of > 1 cm for averaged evoked responses of ~200 trials. This result implies that, although it is possible to observe activity with good signal-to-noise in these

brain areas, identification of responses with individual structures, such as dentate or fastigium, is not appropriate with the present array. Waveforms derived from MEG and/or EEG data for any dipolar generator, be it in superficial cortex or cerebellum, may include activity generated at sites adjacent to the exact location of the putative source or may correspond to more distributed current flow. We report waveforms for patterns of responses in the MEG array that are identified by the locations and orientations of the cortical and subcortical dipolar current sources, but, as in all analyses of MEG data, verification of a specific source model and ensuing results requires additional information beyond that available from the MEG recordings.

The characterization of cortical, subcortical, and distributed responses share a common description as patterns of signal intensities in the array. We utilized signal-space projection (SSP) [Ilmoniemi and Williamson, 1987; Tesche et al., 1995; Uusitalo and Ilmoniemi, 1997] as a common framework for a multicomponent analysis of the data. Individual SSP components were identified by the corresponding signal topographies for each of the ECD sources, the more distributed omission-related responses, the blink artifact, and for the subcortical generators in cerebellum or brainstem. Waveforms for all cortical and distributed components plus one of the subcortical generators were derived from the MEG data in a multicomponent analysis from a pseudoinverse of the corresponding source matrix [Tesche et al., 1995]. It is important to include all cortical responses explicitly in the multicomponent analysis to avoid misassignment of these responses to deeper brain structures. This procedure was repeated for all of the subcortical generators. The relative amplitudes of peak responses in the waveforms obtained from the measured data for the set of subcortical generators were compared with results calculated in a similar fashion from simulated data to determine if the choice of a specific subcortical generator would be consistent with the simulated results [Tesche and Karhu, 1997b].

Amplitude spectra of the averaged evoked SSP waveforms were calculated over 0.5 s epochs spaced at 0.02 s intervals following stimuli and omissions. The magnitude of stimulus-locked oscillations in alpha-range (6–12 Hz) was determined by bandpass-filtering and subsequently squaring the individual SSP evoked response waveforms. The filter settings were selected individually for each subject and component for an analysis of gamma-range activity by centering a 10-Hz passband on the peak spectral amplitude observed between 25–45 Hz. The filtered and squared waveforms were then lowpass filtered (alpha-range at

10 Hz, gamma-range at 25 Hz) and subsequently averaged over a set of 200-ms epochs. Alpha-range: epoch DF from 0 to 200 ms after the presentation of the first stimulus after omission and epoch DS from 0 to 200 ms after the presentation of the subsequent stimuli. Gamma-range: epoch DF from 100 ms before to 100 ms following the presentation of the first stimulus after omission and epoch DS from 100 ms before to 100 ms following the presentation of the subsequent stimuli. Omission-related responses: epoch DO from the instant of stimulus omission to 200 ms following omission, and epoch DA from 200 ms prior to the instant of the presentation of the first stimulus following omission. Responses DO, DA, and DF were normalized with respect to the response DS for each subject and SSP component. Averages were computed across subjects for activity in SI. Responses for cerebellum were computed by averaging across subjects and over both orientations V_x and V_t.

The evoked response waveforms contain contributions from neuronal population activity within the human brain and also contributions from various ambient and sensor-related noise sources. These noise sources were assumed to be uncorrelated with the brain signals. We characterized this system noise for each source by recording data with the array for the same number of trials and sampling frequency/filter settings when the subject was not present ("empty-room" data) [Tesche et al., 1995]. Only features which had amplitudes exceeding the corresponding system noise by at least 3 SD were accepted for further analysis. For the statistical analysis of the relative magnitude of responses, the amplitudes were normalized with respect to the amplitude of the averaged response to all stimuli except the first one after an omission at 0.5 s ISI (S). The statistical significance of the differences of magnitude of the averaged evoked responses was calculated by comparing stimulus- and omission-locked activity separately for each SSP component and frequency-range (Students t-test, paired, two-tailed). Responses to finger stimulation showed substantial intersubject variability. In these trials, both cerebellar orientations V_x and V_t were used separately for the comparison of evoked responses to random vs. regular and attended vs. nonattended stimuli (Wilcoxon signed-ranks test).

Approval for this study was obtained from the ethical committee of the Helsinki University Hospital (Helsinki, Finland). Informed consent was obtained from all subjects following explanation of the nature and possible consequences of participation in these measurements. A preliminary report of this inves-
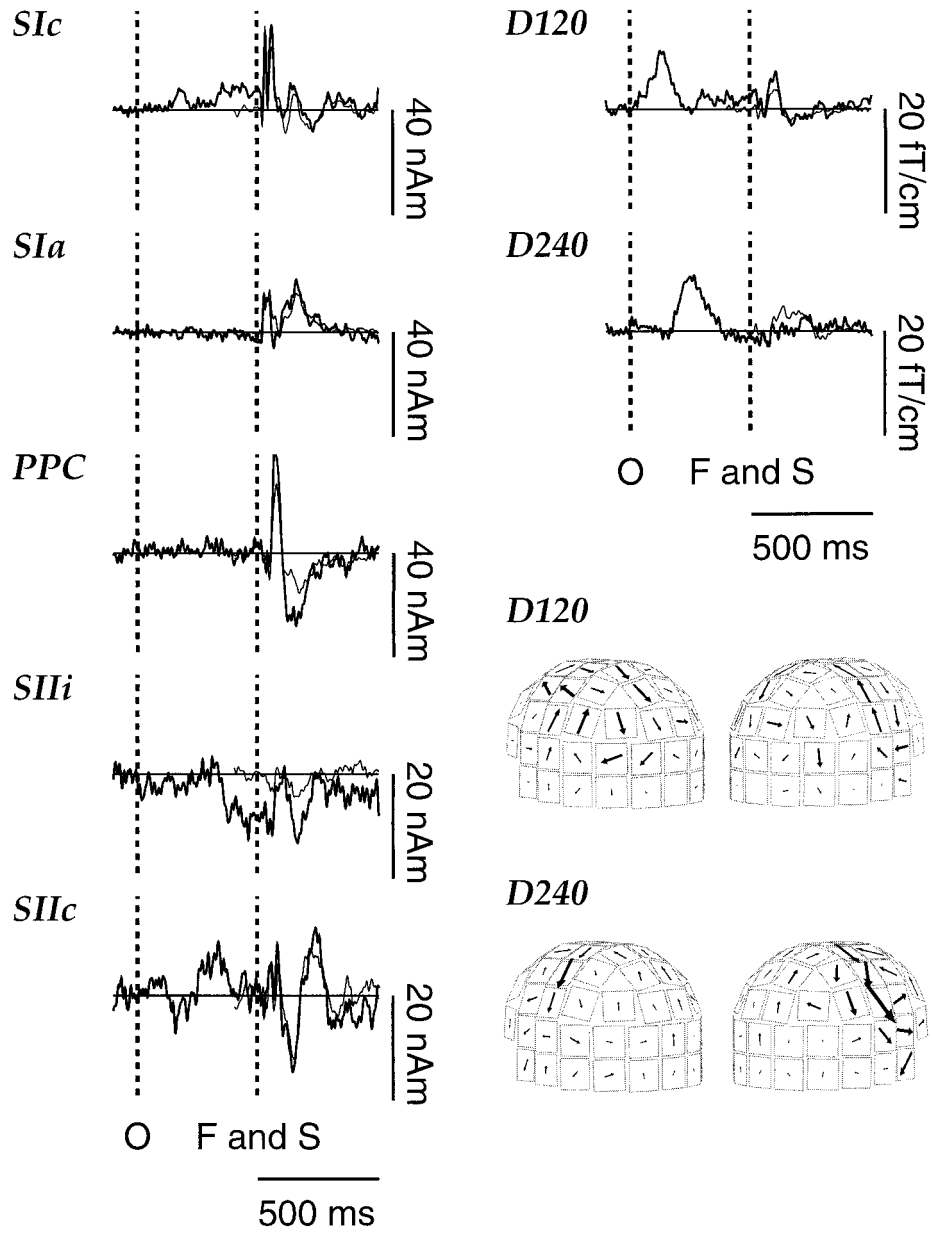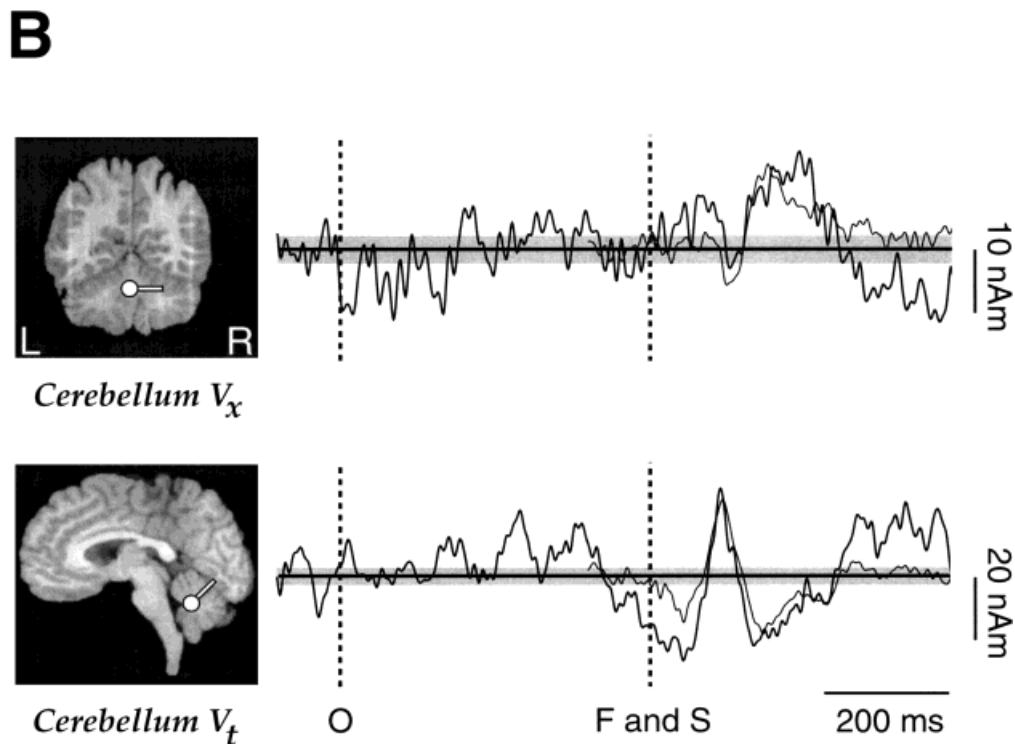
A

Figure 2

Figure 2

Figure 2.

Determination of cortical and subcortical evoked response waveforms from a multicomponent Signal-space (SSP) analysis of the MEG data (left median nerve stimulation, subject N1). Responses time-locked to the omissions and the first stimuli following omissions (O and F) are indicated by thick lines and responses to all stimuli except the first after omission (S) by thin lines (filter 0.03–85 Hz). The vertical dashed lines indicate the anticipated, but omitted, stimuli (O) and the first and all subsequent stimuli (F and S). **A.** Examples of averaged evoked response waveforms for cortical responses. On the left: the amplitudes of current flow as a function of time for neuronal activity for equivalent current dipole sources (ECDs) obtained from a least-squares fit to the data. Sources are located in contralateral primary cortex, SIc and SIa, in posterior parietal cortex, PPC, and in ipsilateral and contralateral second somatosensory corteciies, $SIIi$ and $SIIc$. On the right, the amplitudes of responses as a function of time for two prominent nondipolar patterns observed in the MEG array. The topographies of the responses, $D120$ and $D240$, were identified at 120 and 240 ms following the omission of anticipated stimuli. The arrows on the helmet-shaped arrays indicate the local values of the magnetic field gradients for the $D120$ and $D240$ components. The sensors located over the left (right) hemispheres are shown on the left (right) sides of the figures. SSP waveforms computed for current sources located in cerebellum and brainstem were calculated for each deep dipolar source in combination with all the SSP components shown in Figure 2A. These locations are indicated on the MR images as dots and current flow orientations as short tails. **B.** Waveforms derived from the MEG data for two "probe" sources located near cerebellar vermis with orientations V_x and V_t. The rms MEG system noise for responses (O and F) is indicated by the horizontal shaded area (200 trials). The system noise is reduced by 42% for the responses to the subsequent stimuli (S). **C.** Evoked response waveforms (O and F) calculated from the data as the location of the probe source is moved from the midline site c to sites (d and e) in lateral cerebellum and (f) in brainstem (orientation V_t). The line-types for the waveforms indicate the locations of the probes. **D.** Waveforms calculated using the same multicomponent SSP analysis for six sets of simulated data. Each simulation consisted of a single pulse of activity of unit strength located at one of the sites (a–f). Each nested set of four waveforms for the probes (c–f) is identified by one of the locations (a–f). The relative magnitudes at each latency of the four probe waveforms shown in (C) are to be compared for consistency with those of the nested set of four simulated SSP waveforms shown for each of the sites (a–f) in D. See p. 126 for parts C and D.
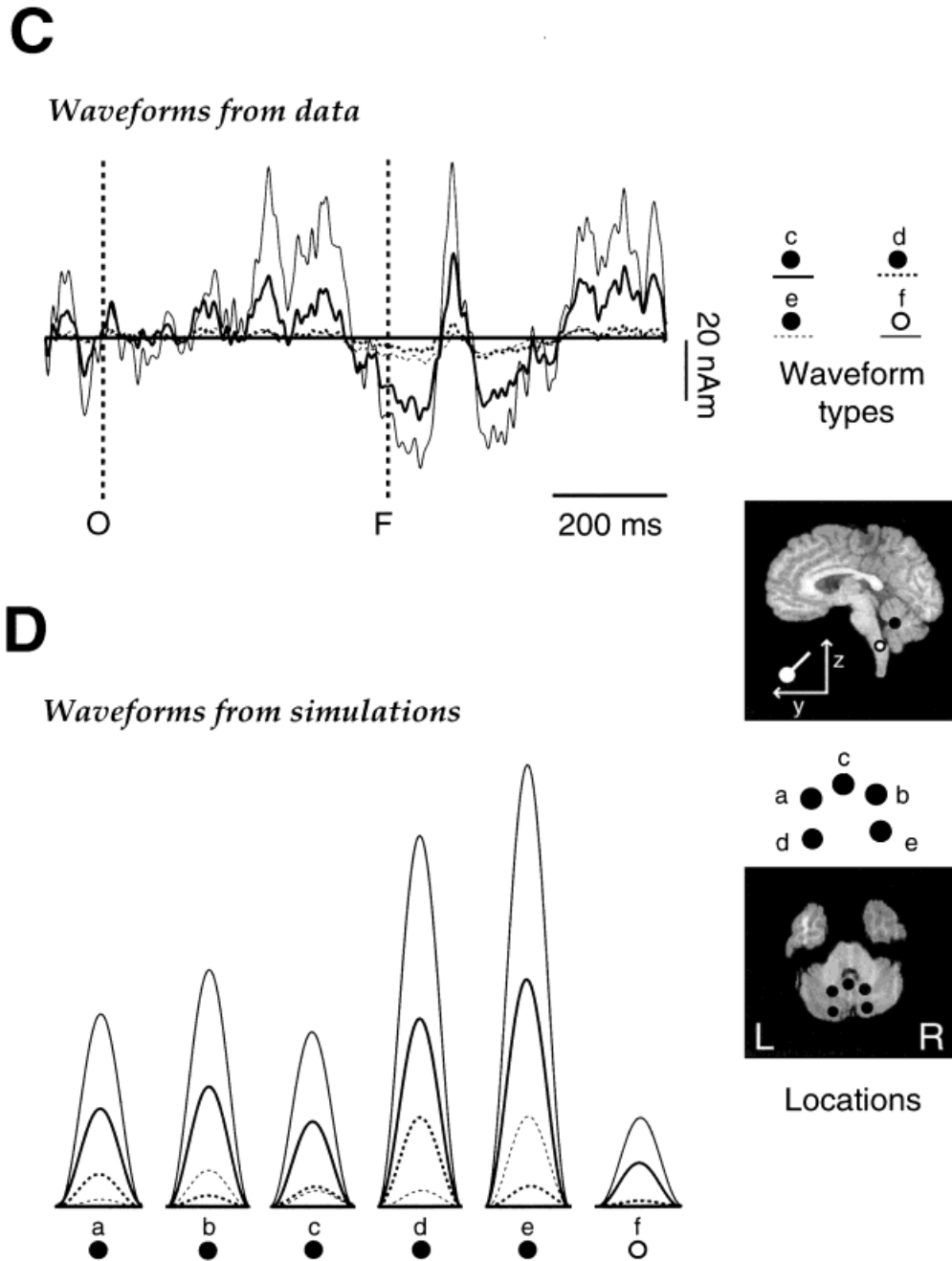
C

Waveforms from data

D

Waveforms from simulations

Locations

Figure 2

tigation has been published previously in abstract form [Tesche and Karhu, 1997a].

RESULTS

Averaged evoked response waveforms

Waveforms for activity in neocortex and cerebellum showed time-locked neuronal population responses both to the presentation and the omission of somatosensory stimulation. Traces shown in Figure 2A and B for subject N1 illustrate these results. Figure 2A shows SSP waveforms for evoked responses to left median nerve stimulation with random omission of stimuli for two adjacent locations in contralateral somatosensory cortex, SIc and SIa, for ipsilateral, SIIi, and contralateral, SIIc, second somatosensory cortex, for a source in contralateral posterior parietal cortex, PPC, and for

two distributed topographies defined at 120 and 240 ms after omitted stimuli, D120 and D240.

Figure 2B shows SSP waveforms for two orthogonal orientations, V_x and V_t, of a dipolar current source generator located near cerebellar vermis (Talairach coordinates 0, −60, −18) [Talairach and Tournoux, 1988]. We have previously demonstrated that the first response to the afferent somatosensory volley in cerebellum is well-represented in SSP waveforms defined by a generator at this location [Tesche and Karhu, 1997b]. In the present study, waveforms for responses captured by this generator show both prominent oscillatory activity in the epoch between omitted stimuli and the subsequent first stimuli following omission, and a slow shift of activity initiated about 100 ms prior to the anticipated first stimulus following an omission. The slow shift continues with enhanced amplitude immediately following the first stimulus following omission. Features in the first 200 ms following median nerve stimulation occur with different amplitudes at various latencies for each of the two orientations of current flow. This shifting of orientation is indicative of the representation of several different neuronal populations in the evoked response waveforms subsequent to the initial ~16 ms response. Both omission-related and evoked response features which exceed the rms system noise by at least a factor of 3 are represented in the waveforms.

Omission-related responses and responses following the first 16-ms activation may involve more widespread activation or cerebellar areas other than those adjacent to vermis. We investigated this possibility by computing a series of waveforms for "probe" generators at various subcortical sites. Figure 2C shows the dependence of the SSP waveforms derived from the median nerve stimulation data on the location of the probe generator in midline cerebellum (location c), more lateral areas (locations a, b, d, e) and in brainstem (location f). The waveform morphologies are quite similar for midline generators c and f, and show common features, though with reduced amplitude, for the lateralized sources d and e. Simulation for generators at intermediate points show a smooth interpolation between these waveforms. This is an important observation. The implication is that we can investigate evoked response features and oscillatory phenomena with a SSP projection derived from a dipolar current source, even if the underlying neuronal current distribution is considerably more widespread or involves differential activation of several areas within cerebellum.

The nested set of waveforms which are derived from the MEG data for a family of probe generators

(Fig. 2C) also contain useful information about the distribution of the underlying neuronal activity. We can compare the pattern of the amplitude of these responses at a given latency with predictions from a specific model for the underlying current distribution. A nested set of predicted waveforms are shown in Figure 2D. A pulse of activity was located at one of the sites a–f. MEG signals were computed for each current pulse. The corresponding nested set of probe waveforms was then calculated from the simulated data using exactly the same analysis utilized for the responses shown in Figure 2C. We show 4 probe waveforms for the actual data, and 4 probe waveforms for the simulated data in this example, although simulation with a finer grid of points yields a similar result.

The simulated data for sources a, b, d, and e show rather dissimilar waveform amplitudes for probe locations d and e (heavy and light dashed lines), whereas the waveforms for the probes d and e are almost identical for simulated midline sources at c and f. The latter pattern of waveform amplitudes is most consistent with that shown in Figure 2C at all latencies for system noise levels as indicated in Figure 2B. We conclude that a single strongly lateralized source is not consistent with the present data. In contrast, an approximately midline, or bilateral, source distribution is consistent with the data. This distribution of activity is also consistent with cerebellar anatomy. Mossy fibers enter the cerebellum rostrally and many of them cross the midline and distribute bilaterally, with spinocerebellar fibers occupying an intermediate position in lobules [Voogd and Glickstein, 1998]. Thus, utilization of the same midline generator used in the previous study of short-latency somatosensory responses [Tesche and Karhu, 1997b] seems to adequately capture the morphology of the underlying activity also at other latencies, with the caveat that activation of cerebellar nuclei and brainstem structures may also contribute to the SSP waveforms.

Figure 3 shows responses to left and right median nerve stimulation for subjects N2–N6 for cerebellar components V_x and V_t. Common features across all seven subjects (13/14 stimulated hands) included evoked response peaks to the first stimulus following omission and to subsequent stimuli that exceeded the system noise by at least 3 SD. Responses following omission of stimuli showed alpha-range oscillatory activity. Slow prestimulus shifts following omission were detected in cerebellar SSP responses for five of the seven subjects (N1, N2, N4, N5, and N7).

Activity in primary somatosensory cortex following both the first stimulus following an omission and also all other stimuli began with a brisk stereotypic re-
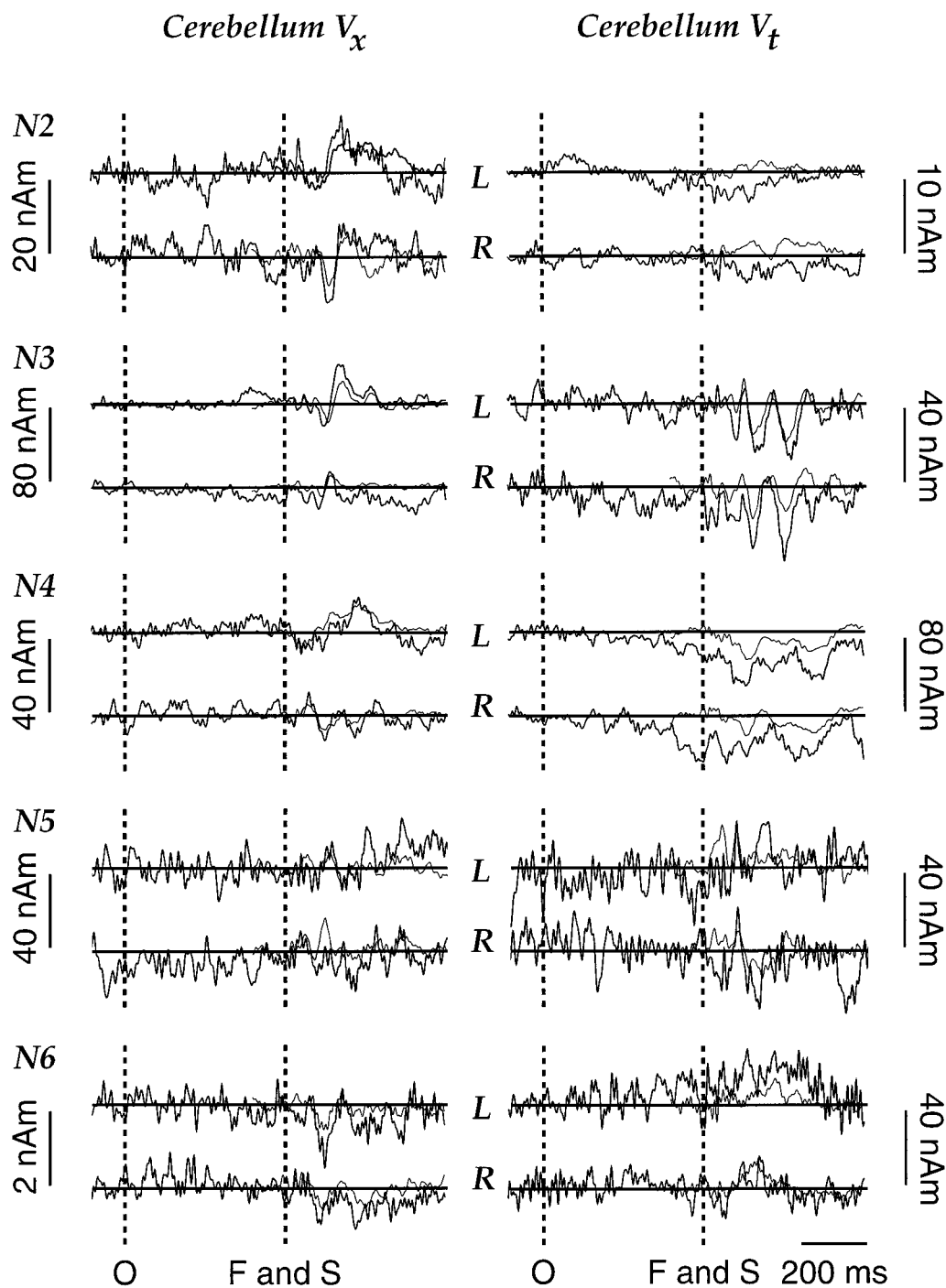
Cerebellum V_x Cerebellum V_t

Figure 3.

Averaged evoked responses to left median nerve stimulation at 2 Hz (15% random omissions) for subjects N2–N6. The locations and orientations of the dipolar current sources for cerebellar components V_x and V_t are as shown in Figure 2B. Responses to the omissions and first stimuli after omissions are indicated by the thick lines and to the subsequent stimuli by the thin lines (filter 0.03–85 Hz).

sponse at about 20 ms. A characteristic, well-known pattern of neuromagnetic responses to somatosensory input followed at latencies of 35 ms, 45 ms, 60–80 ms, and around 100 ms [Hari et al., 1993]. Interestingly, although all subjects showed distributed cortical responses following omissions that corresponded to the D120 and D240 components in subject N1, neither these responses nor those for SI showed the slow shifts of activation in the 100 ms preceding the first stimulus following omission that were characteristic of the cerebellar responses. The responses shown in Figure 2A for subject N1, component SIc, which are the most prominent examples, are steplike in time rather than a slow shift of increasing amplitude. Responses in other cortical areas during the omission epoch were more complex, and will not be described in detail in this report.

Spectral components of cortical and cerebellar responses

Figure 4A shows amplitude spectra of the averaged evoked responses during the omissions and the first stimuli after omission for contralateral SI and cerebellar SSP component V_t (subject N1). The time-course of the corresponding evoked response waveforms are shown on the right. These traces display spectral features indicative of stimulus-locked fast neuronal oscillations at 20–60 Hz which are clearly different for SI (spectral peak at ~35 Hz) and for cerebellum (spectral peak at ~28 Hz). On average, peak spectral amplitudes in all subjects for gamma-range oscillatory activity occurred from 35–45 Hz in contralateral SI and from 25–35 Hz in cerebellum. Interestingly, prominent cerebellar and cortical activity was also observed in the amplitude spectra at 6–12 Hz in all subjects.

Averaged evoked responses were bandpass filtered, squared and subsequently low-pass filtered to extract a measure of the amplitude of activity in specific frequency bands as a function of time (*c.f.* waveforms shown in Fig. 4B and C). This procedure identifies the strength of oscillatory components which are phase-locked to the stimuli. Figure 4 B shows that cerebellar SSP waveforms contain stimulus-locked gamma-range activity which enhances significantly for the first stimulus after an omission compared to responses to all other stimuli. This enhancement does not occur for gamma-range activity in SI. Moreover, the gamma-range oscillatory activity in cerebellum to anticipated stimuli is sustained during the omission epoch. The bar graphs show the average across subjects of the time-averaged gamma-range responses to the first stimuli after omission, ΔF, to the subsequent stimuli,

ΔS, and for the omission epoch, ΔO and the anticipatory epoch, ΔA. Gamma-range responses in epochs ΔO and ΔA are on the same order as those to the subsequent stimuli in cerebellum, but not in SI.

Figure 4C shows results for alpha-range activity. Omission-related cerebellar activity in epoch ΔO is on the order of that to subsequent stimuli with enhancement of responses during epoch ΔA, and a further increase of activity to the first stimulus after an omission. Although the SI responses also show alpha-range activity in the epochs ΔO and ΔA, these responses are significantly less than those to both the first and subsequent stimuli. In contrast to the cerebellar responses, enhanced responses to the first stimuli after an omission in SI are not significantly larger than those to the subsequent stimuli.

Dependence on interstimulus interval and attention

A series of interstimulus interval experiments were performed for median nerve stimulation on subjects N4 and N7 and for finger stimulation on subjects N3, N4, N7, N8, and N9. Median nerve was stimulated with 15% randomly omitted stimuli at ISI's of 0.5, 2 and 4 s and finger at ISI's of 0.5, 1, 2 and 4 s. An additional set of stimuli were utilized to probe cerebellar responses to the predictable omission of somatosensory stimulation. Figure 5A shows a repeating pattern of four stimuli and one omission for ISI of 0.5 s. The temporal duration of the pattern is 2.5 s. Figure 5B shows results for cerebellar SSP component V_x for the ISI study with random omissions, and also for stimuli with a regular pattern of omissions. The waveforms show prominent phase-locked alpha-range oscillations in the 500 ms epoch immediately preceding the first stimulus after omission for stimulation with random omissions at ISI's of 0.5, 2, and 4 s. However, the oscillatory activity during this epoch appears strongly reduced for stimulation with regular omissions at ISI of 0.5 s.

Prominent phase-locked 6–12 Hz oscillatory activity followed random omissions of both median nerve and finger stimulation. Figure 5C shows bar graphs for alpha-range responses time-averaged over omission epochs ΔO and ΔA, and epochs ΔF following the first stimulus after omission and ΔS following the subsequent stimuli for finger stimulation (average of subjects N3, N4, N7, N8, and N9). Responses to the first stimuli after omissions were clearly larger than the responses to subsequent stimuli for random omissions (finger stimulation $P < 0.01$), but were reduced when the train of stimuli was interrupted by a regular, pre-
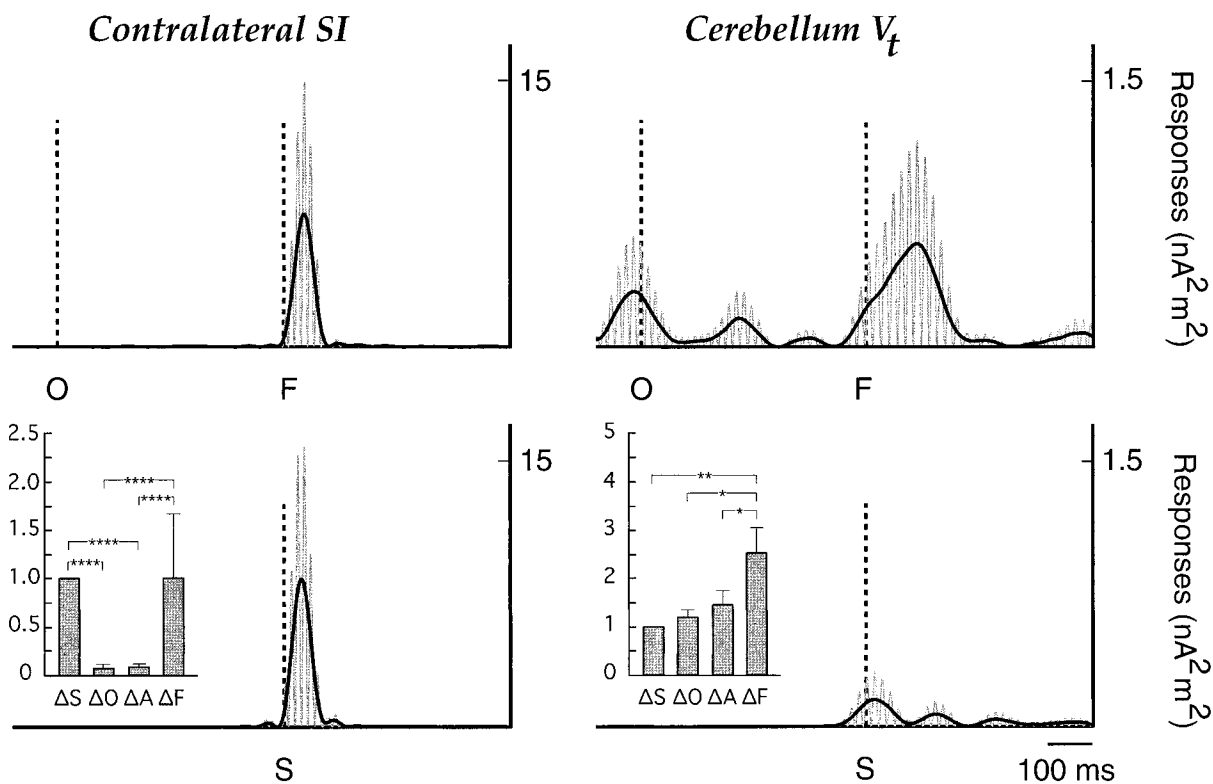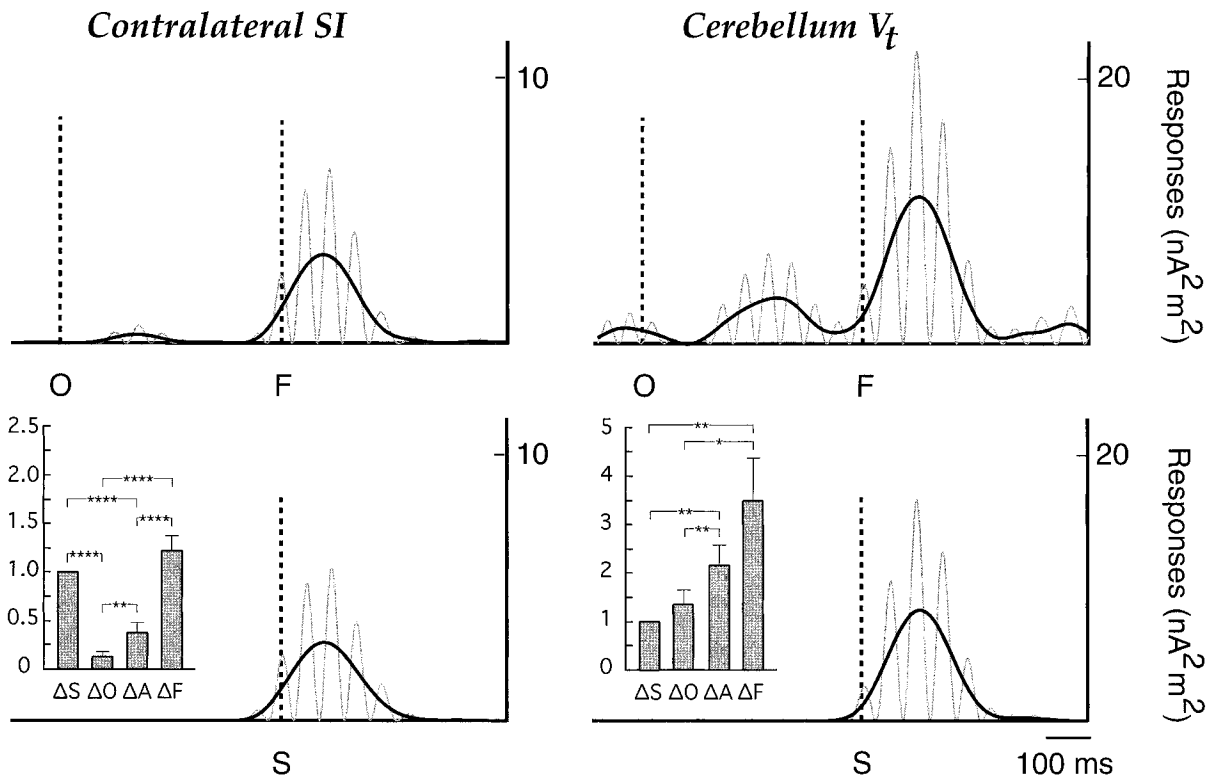
A
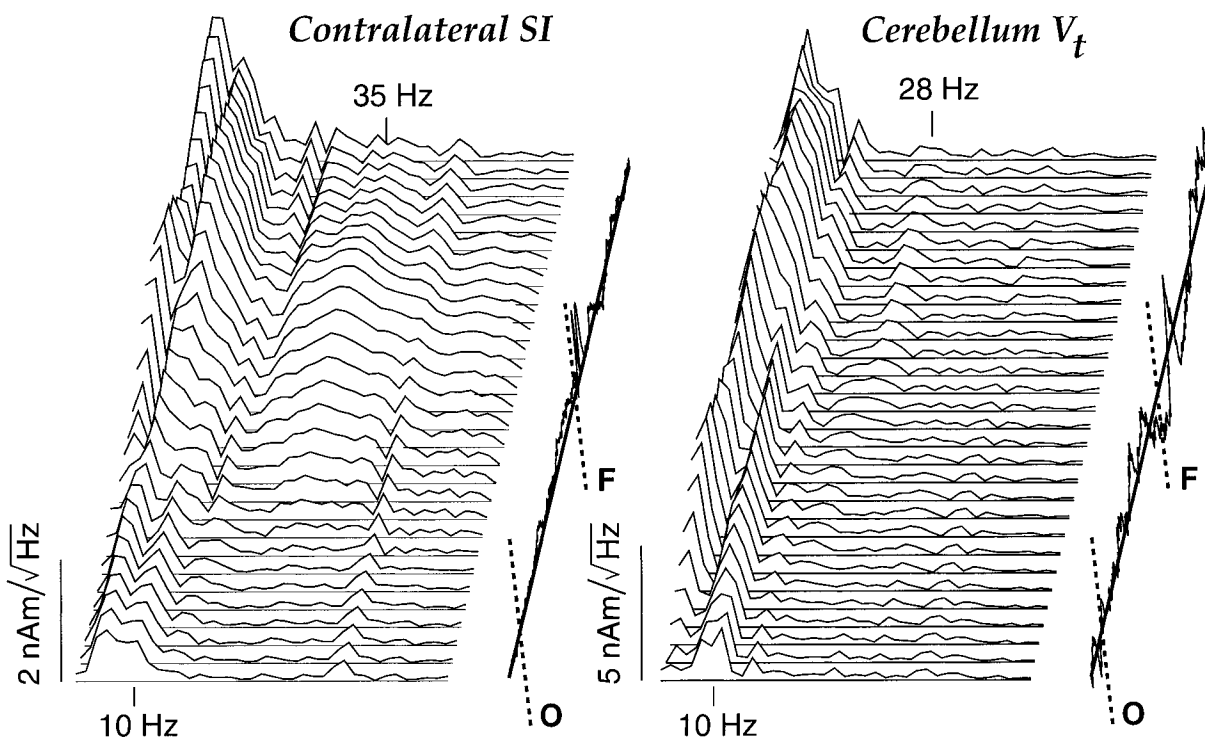
B

Figure 4

C

Figure 4

A. Amplitude spectra of the averaged evoked responses to omissions and to the first stimuli after omissions for contralateral SI and the cerebellar component V_t (subject N1). The corresponding evoked response waveforms are shown on the right. Spectra were computed from 520-ms epochs at successive intervals of 20 ms, with the first (bottom traces) beginning 100 ms before the omitted stimuli and the last (top traces) terminating 480 ms after the presentation of the first stimuli after omissions. **B.** Gamma-range responses to omissions and to the first stimuli after omissions (upper traces) and to all other stimuli (lower traces) for contralateral SI and the cerebellar component V_t. The averaged evoked responses have been bandpass filtered and squared (light curves) and subsequently lowpass filtered (heavy curves) to display the amplitude of oscillatory activity time-locked with stimulus presentation. Results shown are for subject N1 with bandpass filter setting 25–45 Hz (SI) and 25–35 Hz (V_t). The bar graph inserts show the grand average over all subjects and both hemispheres of the amplitudes of the lowpass-filtered curves for activity in SI and cerebellum averaged over 0–200 ms following the omitted stimuli (ΔO) and over 300–500 ms following the omitted stimuli (ΔA), just prior to the subsequent stimuli. The averages for first stimuli after omissions (ΔF) and for all other stimuli (ΔS) were averaged over 100 ms prior to 100 ms following these applied stimuli. **C.** Alpha-range activity for omissions and for the first stimuli after omissions (upper traces) and for the subsequent stimuli (lower traces) for contralateral SI and cerebellar V_t. The bandpass filter setting was 6–12 Hz.

dictable pattern of omissions. Alpha-range activity during the ΔO and ΔA was also suppressed for regular omissions compared to values for random omissions at 0.5 s ISI (regular *vs.* random ΔO, $P < 0.01$; ΔA, $P < 0.05$). However, there was a trend of relative enhancement of activity during ΔA for regular omissions.

Figure 5D shows the magnitude of alpha-range responses to the stimuli as a function of the elapsed time (ET) since the previous stimulation (random stimulus omissions). The amplitudes of the alpha-range cere-

bellar responses to the first stimuli after omissions were strongly enhanced when compared to those of the subsequent stimuli with comparable elapsed time (*i.e.* ET = 4 s; responses to first stimuli in trials with 2 s ISI are larger than responses to subsequent stimuli in trials with 4 s ISI). A similar trend of cerebellar refractory behavior was visible in gamma-range responses. Interestingly, there was no significant enhancement of the first median nerve evoked responses after omission at the longest ET of 8 s as compared to those at ET of 4 s for either alpha- or gamma-range activity. The
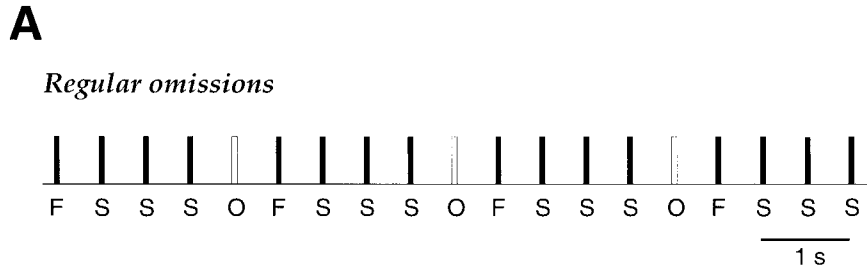
A

Regular omissions

F S S S O F S S S O F S S S O F S S S

1 s

Figure 5.

A. Timing diagram for the stimulation of the median nerve by short pulses (duration 0.2 ms) at ISI of 0.5 s with a regular omission of 20% of the stimuli. **B.** Waveforms for cerebellar component V_x (subject N7) for evoked responses to right median nerve stimulation with the temporal patterns shown in Figures 1A and 5A. Responses time-locked to the omissions and the first stimuli after omissions (O and F) are indicated by thick lines and responses to all stimuli except the first after omission (S) by thin lines (filter 0.03–45 Hz). The vertical dashed lines indicate the instant of anticipated, but omitted, stimuli (O) and the applied stimuli (F and S). **C.** Bar graphs for alpha-range (6–12 Hz) cerebellar activity for random and regular patterns of finger stimulation (ISI 0.5 s). Error bars show the standard error of mean. **D.** Above: alpha-range evoked responses to median nerve stimulation for cerebellum and contralateral SI as a function of the elapsed time since the previous stimulus for subjects N4 (open circles and squares) and N7 (solid circles and squares). Below: the averaged evoked responses to finger stimulation for subjects N3, N4, N7, N8, and N9. Error bars show the standard deviation. Responses to the subsequent stimuli, ΔS, (solid lines, circles), and first stimuli after omissions, ΔF, (dashed lines, squares) at all ISIs are normalized to the response ΔS for ISI of 0.5 s.

plateau of response enhancement was reached for finger stimulation at ET of 2 s. In general, the refractory pattern in cerebellum suggests several different time-courses for the recovery of evoked responses and, in particular, dissociates the behavior of the responses to the first stimuli vs. those to subsequent stimuli. In contrast, the alpha-range responses in SI showed no consistent enhancement of responses to the first stimuli after omissions compared to the subsequent for the same ET.

Figure 6A shows the average effect of attention on the omission-related responses for subjects N4 and N7 during median nerve stimulation and for subjects N3, N4, N7, N8 and N9 during right index finger stimulation. The waveform shows an example of responses for component V_t (subject N7). Oscillatory alpha-range activity followed both random omission of stimuli and the first stimuli after omission during passive attention to the stimuli. This activity was strongly diminished when the subject was reading a book. The bar graphs for alpha-range responses shows this very prominent suppression of both omission- and first stimulus-related activity (attended vs. non-attended, all epochs, ΔO, ΔA, ΔF; $P < 0.01$). In particular, the response amplitudes to the first stimuli after omissions, F, were decreased by a factor of 10 when attention was consciously directed outside the sensory system.

Figure 6B compares both contralateral SI and cerebellar V_t evoked responses to unilateral finger stimulation with those following median nerve stimulation

in the passive attention condition. Interestingly, both SI and cerebellar waveforms show similarities in the evoked response features for the purely sensory input (finger stimulation) and sensory input with accompanying induced movement of the muscles of the hand (median nerve stimulation).

Blinks are a common contaminant of MEG data. Blinks are associated with both a movement-related artifact and with activation of neuronal populations in the brain. Since there are no previous reports of the overall magnitude or waveform morphology for blink-related MEG responses in human cerebellum, we studied explicitly the contribution of blinks to the cerebellar SSP components for subjects N4, N7, N8 and N9. Figure 7 shows an example of evoked responses averaged time-locked to spontaneous blinks recorded during the intermittent somatosensory stimulation. The initial deflection observed at 0–200 ms in the averaged EOC recordings was closely mirrored by a similar deflection in the waveform for a movement artifact recorded in MEG channels immediately posterior to the eyes. In this subject, a source was also identified in posterior parietal cortex (Hari, et al., 1994), with activity at about 200 and 300–500 m. The SSP waveform for activity which was captured by the midline cerebellar generator V_t showed substantial responses during a similar timeframe for all three studied subjects. The contribution of these responses to evoked activity time-locked with stimulus presentation may be negligible if the blinks are uncorrelated with stimulus presentation. Figure 7 shows a contri-
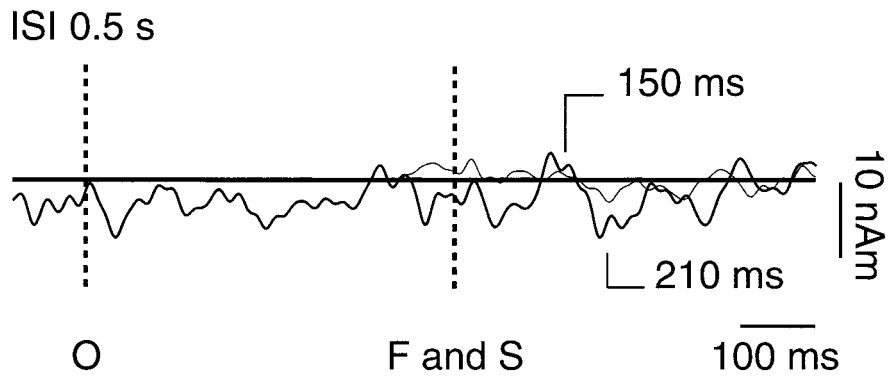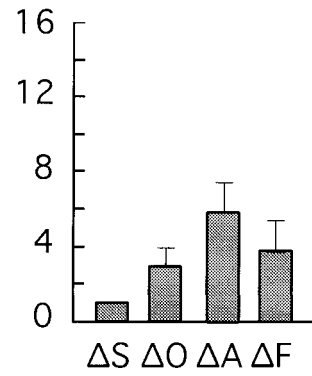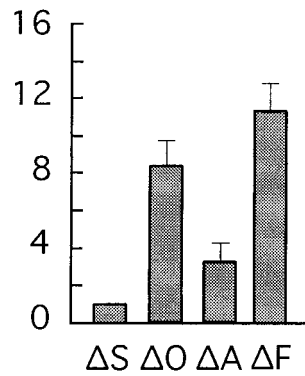
B

Random omissions

ISI 0.5 s

ISI 2 s

ISI 4 s
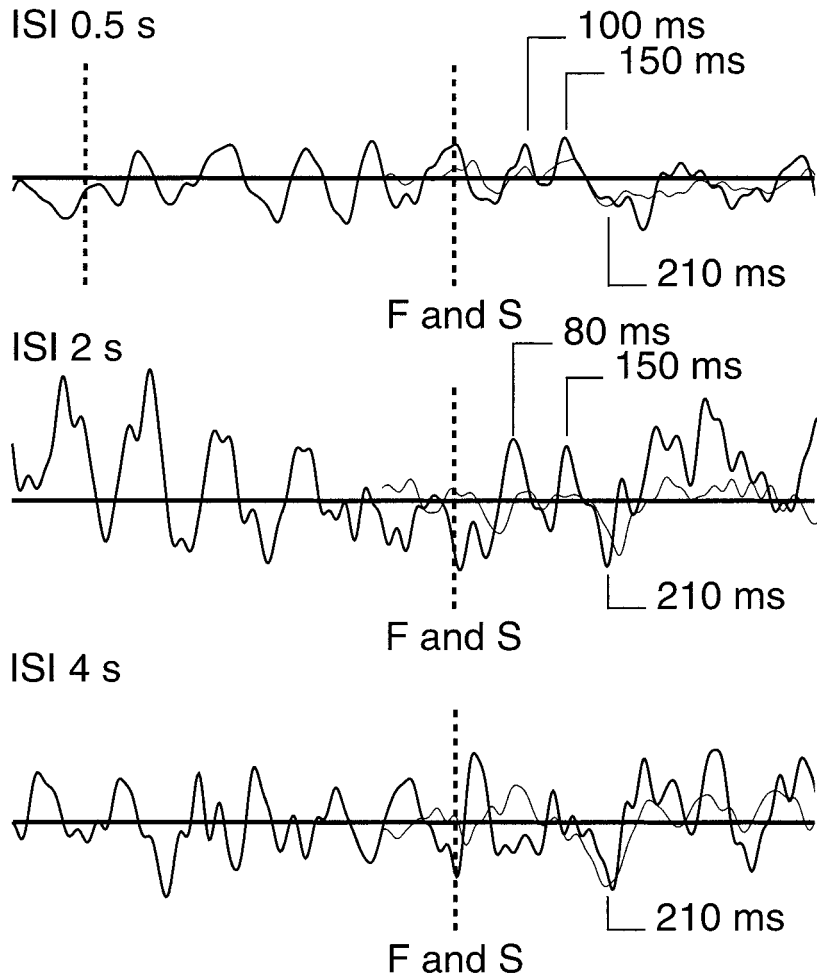
Regular omissions

ISI 0.5 s

Figure 5

C
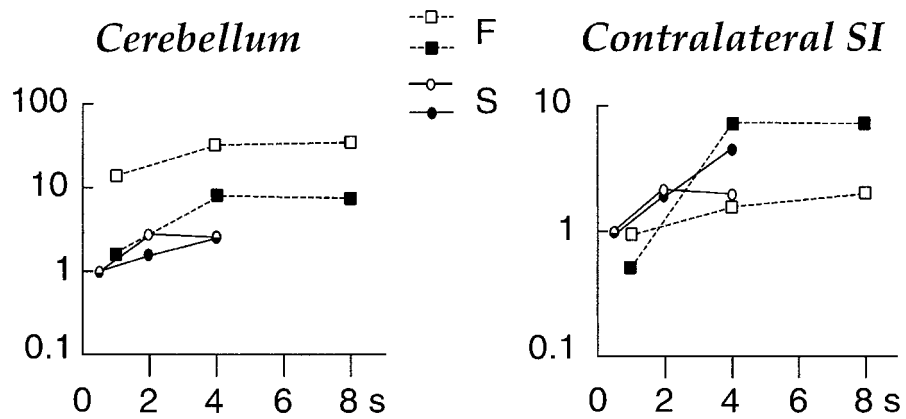
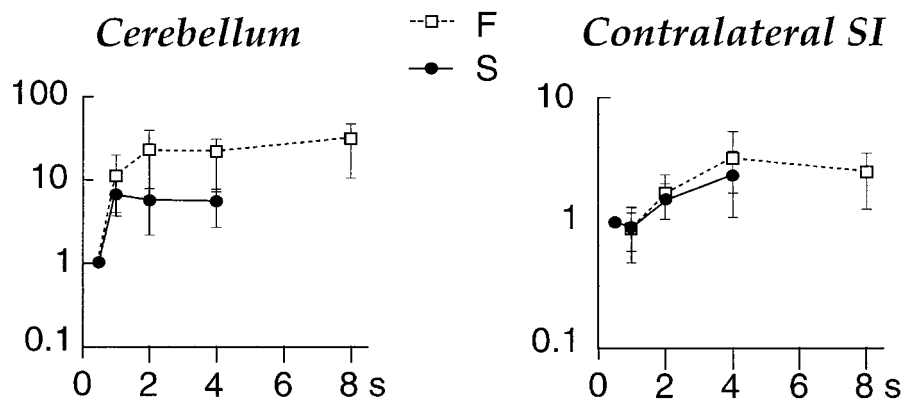## *Random*   *Regular*

MEDIAN NERVE

D

FINGER

Figure 5

bution of blink-evoked neuronal activity to the cerebellar waveform of ~0.8 nA m. It is important to note, however, that although artifacts related to lid or eyeball movement may not contaminate MEG cerebellar waveforms directly, the substantial amplitude (~40 nA m) of blink-related neuronal responses in cerebellum must be identified and/or eliminated for accurate interpretation of cerebellar data.

DISCUSSION

We investigated the congruence between the observed MEG responses and known properties of neuronal activity in neocortex and cerebellum. We compare the spectral content of the observed evoked oscillatory activity at 6–12-Hz and 25–35-Hz with the known physiological frequencies of the two afferent systems to cerebellar cortex: the climbing and mossy fibers. Anticipatory cerebellar activity observed during stimulus omission is compared with similar sustained activity detected in *in vitro* cerebellar preparations. The refractory behavior of the cerebellar responses to somatosensory stimuli is contrasted with that of somatosensory cortex: separate timecourses for the transient neuronal representations in these two structures support independent generation of the MEG responses. Finally, we relate the observed modulation of cerebellar responses by attention to results of recent fMRI studies. The functional significance of the observed cerebellar responses are then discussed with reference to the task of anticipation and processing of the temporal content of somatosensory input.

Generators of cerebellar signals

Extracranial detection of brain activity with neurophysiological methods requires both synchronous activation of a neuronal population and at least some degree of spatial orientation in the resultant current flow. In all parts of the cerebellar cortex, the neuronal elements and their synaptic connections are arranged similarly in a three-dimensional lattice. In fact, this basic structure appears to be common to all vertebrates [Llinas and Hillman, 1969; Llinas and Walton, 1990].

Purkinje cells have been shown to be principal generators of strong transient cerebellar magnetic fields in stimulated *in vitro* preparations of flattened turtle cerebellar cortex [Okada et al., 1988; Okada and Nicholson, 1988]. Stimulation of the right peduncle with a 50 μs electric pulse generated an effective current dipole moment of 1.5 nA m in 6 mm² of active tissue [Okada, et al., 1988]. Human cerebellar cortex is a highly con-

voluted, continuous sheet with surface area of about 5,000,000 mm². Scalp MEG recordings detect magnetic signals from both primary currents generated by synchronous post-synaptic activity in this vast array of highly organized neural elements and also activity generated by return currents in the surrounding conducting medium. We report amplitudes of primary current flow on the order of 10–50 nA m for a localized dipolar approximate of the cerebellar activity. This variability of response amplitude between subjects may reflect the influence of the extensive foliation of cerebellar cortex. Although in many instances the active area for a neocortical source may be confined to one wall of a single cortical fissure, the active area of cerebellar cortex during this task is most probably distributed across many folia. Thus, although the ratio of human to rat cerebellar cortex might suggest activation of 1/15,000–1/125,000 of the cortical neuronal population, an exact estimate of the area of the involved cerebellar cortex from the amplitude of the evoked responses is difficult.

In man, the first cerebellar MEG response to somatosensory input is mediated by spinocerebellar tracts, and is most probably due to post-synaptic current flow in Purkinje cells of spinocerebellar folia [Tesche and Karhu, 1997]. However, cerebellar cortex cannot be considered to be the only potential source of neurophysiological signals. Brainstem nuclei are well-known generators of early EEG evoked responses to sensory input, and thalamic responses to afferent somatosensory input have been reported also for MEG recordings [Rossini et al., 1988; Tesche, 1996]. Dentate and other cerebellar nuclei as well as cerebellar cortex must be considered as possible generators both of MEG signals observed subsequent to the first cortical response to the afferent volley, and to activity observed in the interval following stimulus omission.

Somatic sensory information reaches cerebellar cortex mainly through mossy fibers which terminate on granule cells. The Purkinje cells are excited subsequently by granule cells through axons which are organized into sheets of parallel fibers [Eccles et al., 1966; Eccles et al., 1966]. The characteristic frequency (on average 30–40 Hz) of simple spikes mediated by the mossy fiber system can be modulated effectively by the other afferent system, the climbing fibers [Lou and Bloedel, 1992; Sato et al., 1992]. A single afferent climbing fiber makes hundreds or thousands of synaptic contacts with a single Purkinje cell, causing a strong excitatory all-or-none response [Eccles, et al., 1966]. Rather large functionally specific groups of climbing fibers may become activated synchronously [Llinas and Yarom, 1986; Sato, et al., 1992], thus form-
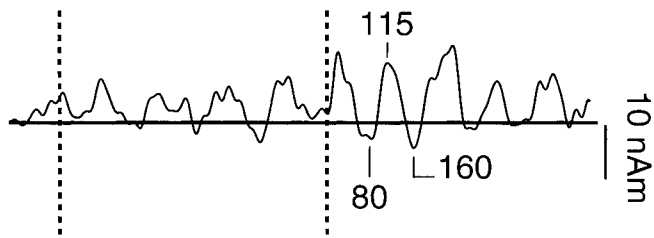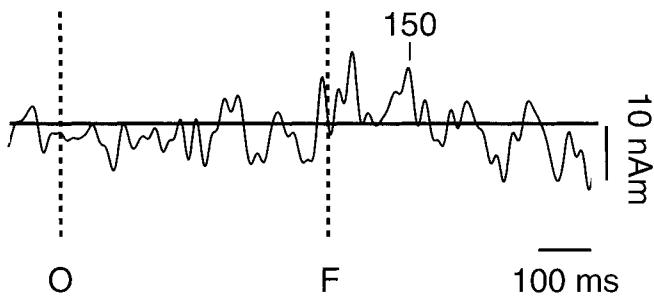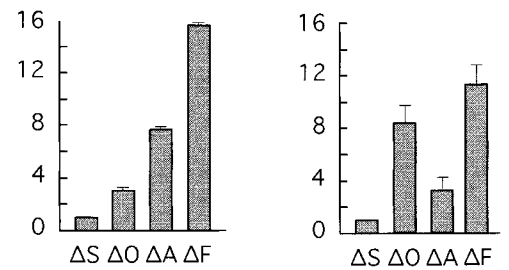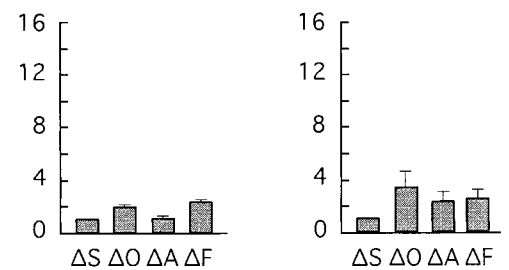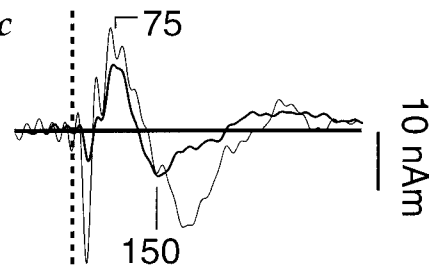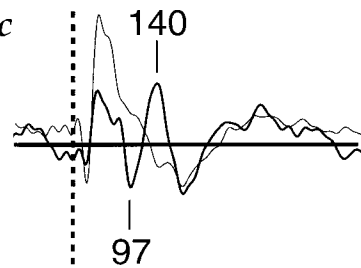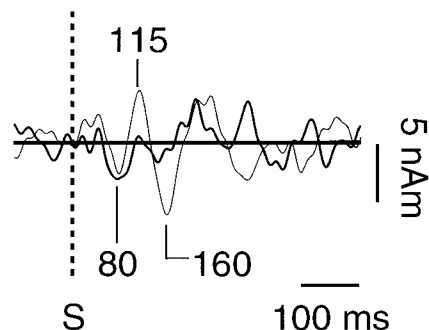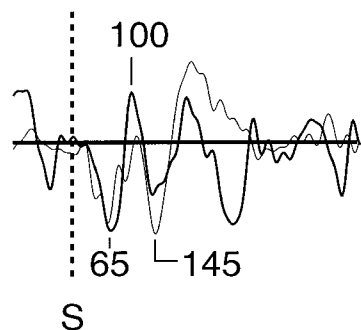
Figure 6

ing an ideal substrate for neurophysiological detection. Furthermore, inferior olivary nuclei, with intrinsic 6–10 Hz oscillatory properties [Llinas and Yarom, 1986], may provide climbing fiber input to cerebellum with resultant oscillations at sites and of magnitudes which are determined by the degree of neuronal membrane de- and hyperpolarization caused by preceding parallel fiber activity [Hounsgaard and Mitgaard, 1988].

Several properties of the signals reported here are consistent with these known properties of neuronal activity in cerebellum. Evoked oscillatory activities at 6–12-Hz and 25–35-Hz are congruent with the known physiological frequencies of the two afferent systems to cerebellar cortex: the climbing and mossy fibers. Thus the physiological frequencies observed at the single cell level in the cerebellar afferent systems are consistent with the spectral content of the cerebellar neuronal population responses to somatosensory stimulation reported here.

Functional significance of slow shift of responses

The observed slow shift of cerebellar evoked responses which was initiated in the omission epoch and preceded an overt, expected stimulus closely resembles in morphology two cortical evoked responses that are interpreted as anticipatory activations: the "bereitschaftpotential", or readiness potential, which precedes voluntary movement [Kornhuber and Deecke, 1964], and the "contingent negative variation", which precedes a cued stimulus requiring motor action [Walter et al., 1964]. The initial discovery of these cortical slow shifts in EEG recordings created much interest in their participation to network behavior as correlates of expectancy and attention. Early work in cats led to a suggestion that slow shifts are signs of enhanced neuronal activity in frontal cortical areas, mesenchephalic reticular formation and mediothalamic-frontocortical systems [Skinner and Yingling, 1977]. The significance of slow activity has been attributed to the control of involuntary vs. focused attention and to the expectancy of a cue stimulus.

The exact neuronal mechanism underlying the slow shifts have remained somewhat unclear, although excitatory postsynaptic potentials (EPSP's) are considered to be likely candidates [Mitzdorf, 1985]. To our knowledge, there are no reports of stimulus-locked slow shifts in primate cerebellum. However, very prominent and long lasting magnetic fields of several seconds duration, probably representing postsynaptic activity, have been detected in *in vitro* cerebellar preparations [Okada and Nicholson, 1988]. Even though the present tools do not allow determination of the underlying neural mechanism, indirect evidence from earlier cortical recordings, the anticipatory nature of the shift and previous speculations of cerebellar generators lead us to speculate that the observed slow shifts may be a correlate of cerebellar expectancy elicited by PSPs in Purkinje cell networks.

Functional significance of gamma-range oscillatory neuronal activity

Neuronal population oscillations accompany an imposing variety of cerebral functions across species. Coherent oscillations which involve widespread cortical areas have been associated with binding of stimulus features both within [Gray and Singer, 1989] and between hemispheres [Engel et al., 1991], with temporal coding [Singer, 1993], selective attentional enhancement of neuronal activity [Tiitinen et al., 1994] and sensorimotor integration [Murthy and Fetz, 1992]. For example, Murthy and Fetz report synchronous 20- to 40-Hz field-potential oscillations in sensorimotor cortex of awake behaving rhesus monkeys during exploratory and manipulative hand movements involving attention to tactile input [Murthy and Fetz, 1996a; Murthy and Fetz, 1996b]. Oscillations occurred both in pre- and post-central cortex, including synchronized activity between left and right motor cortex with negligible phase shift during bimanual manipulations. Single-unit burst activity was commonly seen in synchrony with the field potential oscillations, suggesting a role for gamma-range oscillations in the facilitation of interactions between relevant elements of a distrib-

Figure 6.

Waveforms for cerebellar component V_t (subject N7) for evoked responses to stimulation with the temporal pattern shown in Figure 1A (ISI 0.5 s). **A.** Waveforms for stimulation of right index finger when the subject was passively attending to the stimuli (*Attend*) and reading a book (*Ignore*). Responses are shown time-locked to the omissions and the first stimuli after omissions (O and F). **B.** Bar graphs for alpha-range (6–12 Hz) cerebellar activity during attended and nonattended stimulation of median nerve (subjects N4 and N7) and right finger (subjects N3, N4, N7, N8, and N9) (ISI 0.5 s, random omissions). Error bars show the standard error of mean. **C.** Waveforms for contralateral SIc and cerebellar V_t components for stimulation of index finger (thick lines) and median nerve (thin lines) (filter 0.03–45 Hz). Responses are shown to the left and right stimulation for all stimuli except the first after an omission (S).
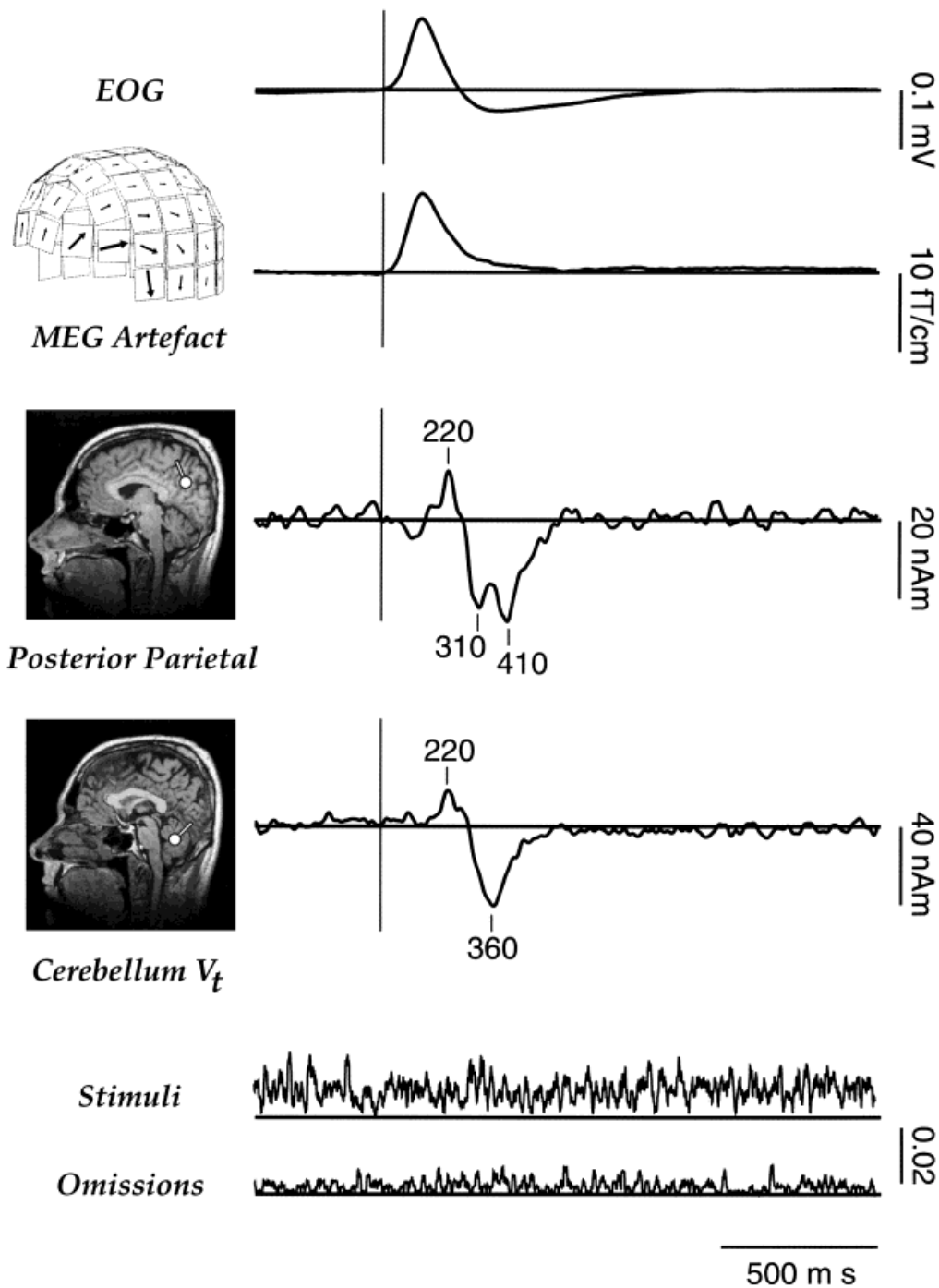
Figure 7.

Waveforms for evoked responses averaged time-locked to the onset of vertical electrooculogram (EOG) recordings of spontaneous blinks (598 evoked responses, subject N7, trigger: EOG > 80 μV). MEG sensors located close to the front of the head show activity coincident with the initial peak of the EOG signal. Evoked response waveforms are also shown for an ECD source in posterior parietal cortex and for cerebellar component V_t. The system noise is on the order of the linewidth of the horizontal axes (filter 0.03–45 Hz). The uniformity of the timing of the blinks with respect to the stimuli and associated omissions is shown at the bottom of the figure. Each median nerve stimulation and omission of stimuli is represented by a 10-ms pulses of unit amplitude: the figures show the average of all pulses for 2344 median nerve stimulations and the associated omissions.

uted population of cells. Facilitation in the absence of movement-specificity indicated that the gamma-range activity may represent a neural correlate of attention during a demanding sensorimotor activity, and electrical stimulation of the thalamic reticular nucleus is known to evoke gamma-range oscillations in somatosensory cortex [Mcdonald et al., 1998]. In cortical somatosensory circuits, gamma-range oscillations may thus be associated both with the binding of cell assemblies together and as a correlate of attentional demands.

MEG studies show that cerebellar evaluation of somatosensory input in man is initiated in parallel with cortical processing in primary somatosensory cortex [Tesche, 1996; Tesche and Karhu, 1997b]. In the present study, we found stimulus-locked 35-45-Hz oscillations in primary somatosensory cortex and 25-35-Hz activity in cerebellum during the first 100 ms of the processing of the repetitive somatosensory inputs. Cerebellar gamma-range activity was sustained during the omission and enhanced significantly for the first stimulus after omission. Most remarkably, the gamma-range activity in cerebellum began to enhance in all subjects and for both hands approximately 100–50 ms *prior* to the onset of each anticipated stimulus following an omission.

Single cell studies in primates show that object-slip perturbations of a hand-held object have a powerful effect on cerebellar cortical neurons at a mean latency of about 50 ± 14 ms. This effect of slip was visible on simple spike discharges which emerged at roughly the same frequency range as the gamma-range activity observed in the present study. Interestingly, the majority of the responding cells in monkey reacted to cutaneous input [Duggs and Smith, 1992]. A comparison of somatosensory evoked responses in man and monkey [Arezzo et al. 1981] indicates that the latency of these responses are consistent with the latency of the stimulus-induced cerebellar responses reported here.

Gamma-range activity associated with initial processing of repetitive, stereotypic input may represent or facilitate a functional connectivity of relevant populations within a "fractured" cerebellar somatotopy, and thus may have features in common with the cortical gamma-range activity [Gray and Singer, 1989; Engel, et al., 1991; Murthy and Fetz, 1996a; Murthy and Fetz, 1996b]. Interestingly, we found that gamma-range oscillations in primary somatosensory cortex were strongly suppressed during the omission epoch compared to the stimulus-related activity and showed no enhancement or anticipatory features prior to or during the subsequent stimulus. The dissociation of cerebellar and SI gamma-range responses during the

epoch following an omission and also the ISI dependence of the responses in this band suggest that these oscillations may subserve quite different processing of sensory inputs in the two structures. In particular, the cerebellar gamma-range oscillations may reflect a neural correlate of the representation of a temporal pattern of sensory events with a predictive quality which is specific to cerebellum, rather than to primary cortical somatosensory networks. The clear enhancement of gamma-range activity towards the end of an omission period and during the first stimulus after an omission suggests that the underlying cell assembly is particularly sensitive to a sudden violation of the temporal prediction established by previous stimuli. The dissociation between the refractory behavior of the cerebellar responses in gamma- and alpha-range to frequently repeated stimuli and to those following an omission may evidence the recruitment of additional neuronal populations for the processing of sensory input following a sudden omission of anticipated stimuli.

Functional significance of alpha-range oscillatory neuronal activity

The prominent, stimulus-locked alpha-range oscillations may reflect involvement of cerebellar cortico-nuclear circuits in the processing of temporal features of sensory input independent of motor performance or response. Both cerebellar and SI responses showed alpha-range activity following stimulus omission, although the amplitudes of the SI responses were significantly smaller than the cerebellar responses when compared to the corresponding stimulus-related activity. Recent observations in the rat show synchronization of 7-8 Hz oscillations in cerebellum during attentive immobility, with movement coincident with cessation of the oscillatory activity [Hartmann and Bower, 1998]. The oscillations were synchronized both within and between cerebellar hemispheres, suggesting that coherent activity at this frequency may be a dynamic property of the entire somatosensory network. However, our results demonstrate that the cerebellar alpha-range activity is much more sensitive to temporal patterning of somatosensory input than the corresponding cortical activity, and thus may represent at least in part a correlate of timing functions attributed to cerebellar circuits conjointly with the gamma-range activity.

Cerebellar alpha-range activity is modulated by stimulus intervals and attention

The amplitudes of cerebellar responses to the first stimuli following omissions, in particular, both gam-

ma- and alpha-range were strongly enhanced when compared to the subsequent stimuli for the same elapsed time (ET) since the last overt stimulus. In contrast, the responses in SI showed no consistent enhancement. Omission-related responses in alpha-range were of much larger amplitude following random omissions than following regular omissions. Markedly, there was no significant enhancement of the first cerebellar responses evoked by median nerve stimulation following omission at the longest ET of 8 s as compared to those at ET of 4 s. The plateau of enhancement of the cerebellar responses caused by finger stimulation was reached between 2 s and 4 s stimulus intervals. These patterns of refractory behavior in cerebellum suggests several different timecourses for the recovery of evoked responses and, in particular, dissociate the behavior of responses to first stimuli after a random omission from responses to frequent stimuli or a regular pattern of stimuli.

EEG and MEG observations in diverse cortical neuronal populations show that population responses to regularly delivered stimuli recover from the refractory period caused by preceding stimulus as a logarithmic function of ISI. The dependence of the amplitude of the population response on ISI is strongest for short ISIs. The amplitude reaches a plateau value at ISIs that range from 2–15 s for cortical responses [Hari et al., 1993; Lu et al., 1992; Ritter et al., 1968; Uusitalo et al., 1996]. The breakpoint (plateau) of the ISI effect is often taken as a marker for duration of functional neuronal representation, or sensory memory trace, in a neuronal assembly.

Interestingly, several lines of behavioral evidence indicate that features of events can be estimated accurately for a temporal epoch of up to 3 s [for a review, see Pöppel, 1997]. For example, the duration of randomly presented visual stimuli can be reproduced precisely to the limit of about 3 s. If a subject is asked to synchronize a sequence of auditory stimuli with finger movements, the stimuli are anticipated by a few tens of milliseconds also up to interstimulus intervals of about 3 s. It has been suggested that an automatic mechanism of temporal integration may "tag" several successive stimuli into perceptual units of 2–3 s duration [Pöppel, 1997]. The congruence between these behavioral observations and the present findings on the ISI dependence of cerebellar oscillatory responses supports the concept of cerebellar involvement in the evaluation and integration of temporal information during sensory events [Ivry, 1988; Jueptner et al., 1995, 1996; Meck, 1996]. However, fine-grained multimodal measurements are required, as well as measurements at ISIs longer than 8 s to verify this hypothesis. More-

over, the timecourse of response recovery for regularly presented, stereotypic stimuli as well as stimuli requiring motor action may be considerably different.

In the present study, the alpha-range cerebellar responses during an omission and those elicited by the first stimuli were clearly diminished when attention was consciously directed outside the somatosensory system. The anticipatory slow shift of averaged cerebellar evoked responses was similarly suppressed. Slow shifts of activity in cortical and subcortical neural networks has been attributed both to the control of involuntary vs. focused attention and to the expectancy of a cue stimulus [Skinner and Yingling, 1977]. Presuming that cerebellum participates to the control of attentional networks as suggested by recent imaging studies [Akshoomoff et al., 1997; Allen et al., 1997], we hypothesize that cerebellar stimulus-locked alpha-range activity may index the level of expectancy and attention in cerebellar neuronal populations.

CONCLUSIONS

Recent theoretical considerations of cerebellum advocate an integrative view of local and large-scale cerebellar neuronal circuits that do not necessarily distinguish between the functional properties required for motor, sensory, or "cognitive" activity. For example, cerebellar microcircuits may produce local models for error corrections for both motor and cognitive tasks [Ito, 1997] that, when combined, produce coordination of activity in other parts of the brain. Cerebellum may be involved in monitoring and adjusting the acquisition of sensory data [Bower, 1997] and in controlling attentional resources [Akshoomoff et al., 1997]. A common feature in these diverse motor and nonmotor tasks may be the capacity of cerebellar neuronal circuits to anticipate and process any input with high temporal acuity and to time multiple simultaneous tasks [Ivry, 1997].

We present physiological evidence in support of this hypothesis from the observation of evoked, stimulus-locked neuronal oscillations in intact human cerebellum that showed robust anticipatory enhancement to somatosensory input. The involvement of cerebellar circuitry in the processing of purely sensory input was evidenced by the similar dependence of the oscillatory responses on the timing of the somatosensory input both for stimuli associated with induced movement and for stimulation that generated no detectable motor activity. Sustained oscillatory responses following omission of anticipated stimuli provided further support for cerebellar processing of the

temporal pattern of input, independent of motor performance or response.

The anticipatory increase of coherent neuronal population activity reported here provides direct experimental evidence for the broad theoretical concept of human cerebellum as an adaptive predictor which is capable of extracting and sustaining a template for temporal information from diverse sensory and motor input [Ito, 1984; Ivry, 1997; Keele and Ivry, 1990; Thach et al., 1992]. Identification of a role for oscillatory phenomena in the recognition of temporal relationships, whether related to perceptual tasks requiring accurate representation of temporal information, motor coordination, or learning of temporal associations, may provide a mechanism for the involvement of cerebellum in cerebral processing that requires temporal monitoring and tuning of large-scale neuronal networks.

ACKNOWLEDGMENTS

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