Subcortical Interactions Between Somatosensory Stimuli of Different Modalities and Their Temporal Profile

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1Electromyography and Motor Control Unit, Neurology Department, Institut d’Investigació Biomèdica August Pi i Sunyer, and 2Department of Neurosurgery, Hospital Clínic, Universitat de Barcelona, Barcelona; and 3Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas, Instituto de Salud Carlos III del Ministerio de Sanidad y Consumo, Madrid, Spain

Submitted 28 March 2008; accepted in final form 26 June 2008

Costa J, Valls-Solé J, Valdeoriola F, Rumia J. Subcortical interactions between somatosensory stimuli of different modalities and their temporal profile. J Neurophysiol 100: 1610–1621, 2008. First published July 2, 2008; doi:10.1152/jn.90412.2008. Interactions between inputs of different sensory modality occur along the sensory pathway, including the thalamus. However, the temporal profile of such interaction has not been fully studied. In eight patients who had been implanted an intrathalamic electrode for deep brain stimulation as symptomatic treatment of tremor, we investigated the interactions between mechanical taps and electrical nerve stimuli. Somatosensory evoked potentials (SEPs) were recorded from Erb’s point, cervical spinal cord, nucleus ventrointermedialis of the thalamus, and parietal cortex. A handheld electronic reflex hammer was used to deliver a mechanical tap to the skin overlying the first dorsal interosseous cortex. A handheld electronic reflex hammer was used to deliver a mechanical tap to the skin overlying the first dorsal interosseous muscle and to trigger an ipsilateral digital median nerve electrical stimulus time-locked to the mechanical tap with a variable delay of 0 to 50 ms. There were significant time-dependent interactions between the two sensory volleys at the subcortical level. Thalamic SEPs were decreased in amplitude at interstimulus intervals (ISIs) from 10 to 40 ms with maximum effect at 20 ms (−42.8 ± 10.5%; P < 0.001). A similar decrease was also seen in the number and frequency of the high-frequency components of thalamic SEPs (−25 ± 4%). A smaller reduction (−18.1 ± 5.8%; P < 0.001) was present in upper cervical response at ISI = 20 ms. There were no changes in peripheral responses. Cortical SEPs were almost completely absent in some subjects at ISIs from 20 to 50 ms. There were no changes in SEP latencies. Our results indicate that significant time-dependent interactions between sensory volleys occur at the subcortical level. These observations provide further insight into the physiological mechanisms underlying afferent gating between sensory volleys of different modality.

INTRODUCTION

The human CNS selects relevant sensory inputs for processing among the whole bombardment of information constantly received (Burke et al. 1982). When inputs of different sensory modalities coincide in time, the expected cortical event related to one of the inputs is of reduced size compared with when the stimuli are applied separately. The interactions between inputs of different sensory modality take place in various sites along the sensory pathway, including the thalamic nuclei. However, the temporal profile of such interaction has not been fully studied. In particular, little is known about the interactions between simultaneous somatosensory inputs at a subcortical level. This phenomenon, known as afferent or sensory “gating,” has been demonstrated by recording the somatosensory evoked potentials (SEPs) from the scalp (Cheron and Borenstein 1991; Gandevia et al. 1983; Jones 1981). Afferent gating probably involves interactions between cortical and subcortical structures (Staines et al. 2002), although its precise mechanisms are still unclear. The participation of subcortical structures in the selection of information to be further processed has been recently recognized in a study of efferent gating: i.e., the effect induced by voluntary movements on the SEPs (Insola et al. 2004). However, the role of subcortical structures is less clear in the case of afferent gating (Klostermann et al. 2002a).

Implantation of deep brain stimulation (DBS) electrodes with therapeutic purposes provides a unique opportunity to carry out physiological studies about the function of deep brain structures in conscious humans. With this purpose, DBS electrodes have been used to study either the effects of stimulating the nearby structures and neural circuits (Ashby et al. 1999; Compta et al. 2006; Costa et al. 2006, 2007) or to record evoked potentials to stimulation of somatosensory afferent pathways (Hanajima et al. 2004a; Klostermann et al. 2006). DBS of the nucleus ventrointermedialis of the thalamus (Vim) is used for the symptomatic treatment of various types of tremor (Schaer et al. 2000). Such intrathalamic electrodes can pick up activity generated in nearby neuronal groups by synchronized afferent sensory volleys resulting from electrical stimulation of peripheral nerves (Hanajima et al. 2004a; Klostermann et al. 2006).

In the present study, we aimed at investigating the intrathalamic interference between two somatosensory volleys of different composition and to explore the temporal profile of such interaction. Mechanical stimuli are known to induce afferent volleys that can be recorded over the nerve or in the scalp in humans (Ackermann et al. 1992; Baba et al. 2001; Spitzer and Claus 1992) and there is some indirect evidence that they can interfere with other sensory processing (Pfurtscheller et al. 2001). Therefore we hypothesized that afferent volleys elicited by mechanical stimuli would interfere with the responses to the sensory inputs induced by electrical stimuli at various points along the somatosensory pathway and, specifically, at the intrathalamic level.

METHODS

Subjects

We studied eight patients, five with parkinsonian tremor and three with essential tremor (Table 1), undergoing chronic DBS of the
TABLE 1. Patients undergoing DBS of the thalamus (Vim)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>H &amp; Y</th>
<th>Disease Duration, yr</th>
<th>Side</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>M</td>
<td>PD</td>
<td>2.5</td>
<td>8</td>
<td>R/L</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>PD</td>
<td>3.0</td>
<td>11</td>
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</tr>
<tr>
<td>3</td>
<td>71</td>
<td>M</td>
<td>PD</td>
<td>3.0</td>
<td>9</td>
<td>R/L</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>F</td>
<td>PD</td>
<td>3.0</td>
<td>14</td>
<td>R/L</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>M</td>
<td>PD</td>
<td>2.5</td>
<td>9</td>
<td>R/L</td>
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<tr>
<td>6</td>
<td>57</td>
<td>F</td>
<td>ET</td>
<td>NA</td>
<td>7</td>
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<td>8</td>
<td>47</td>
<td>M</td>
<td>ET</td>
<td>NA</td>
<td>8</td>
<td>R/L</td>
</tr>
</tbody>
</table>

H & Y, mean Hoehn and Yahr “off” stage; PD, Parkinson’s Disease; ET, Essential Tremor; R, right; L, left; NA, not applicable.

thalamus. None of the patients had sensory complaints and all had normal upper-limb nerve conduction studies. DBS electrodes were implanted in the Vim and were left externalized for up to 3 days to assess the clinical efficacy of stimuli and to confirm electrode localization by magnetic resonance imaging (MRI), before the definitive DBS stimulator was implanted in a second surgery. Patients were all examined during that period and parkinsonian patients were evaluated in overnight “off medication” condition. Because of the postoperative microthalamotomy effect (Kondziolka and Lee 2004), patients experienced a significant improvement of tremor at this moment. All patients gave informed consent to the study protocol, which conformed to the standards set by the Declaration of Helsinki (last modified in 2004) and was approved by the Ethics Committee of the Hospital Clinic of Barcelona.

Vim targeting and surgical procedures

The target was identified by MRI and located stereotactically. Electrodes were implanted uni- or bilaterally into the Vim (Medtronic 3389; Minneapolis, MN). For electrode placement, standard Vim positions from the stereotactic brain atlas by Schaltenbrand and Wahren (1977) were referred to the individual AC–PC line (the straight sagittal connection between anterior and posterior commissure). Theoretic anatomic targeting parameters for Vim were placed 14 mm lateral to the AC–PC line (x coordinate), 6 mm posterior (y coordinate), and 0 mm ventral to the midcommissural point (z coordinate). These standard coordinates were adjusted for each case with respect to the individual thalamic height and AC–PC length. Intraoperative electrode localization was tested by microelectrode recording of spontaneous neuronal activity and activity evoked by physical examinations. The decision on electrode placement was made after on-site evaluation of the effects of macrostimulation (Molinuovo et al. 2003).

The macroelectrodes used have four platinum–iridium cylindrical surfaces (1.27-mm diameter; 1.5-mm length) and a contact-to-contact separation of 0.5 mm. Contact 0 was the most caudal and contact 3 was the most rostral. An adapted Medtronic switch was used to connect all four leads to external amplifiers of an electromyograph (Mystro5Plus; Oxford Instruments, Surrey, UK) using appropriate setup for the recording of SEPs.

Median nerve SEPs and gating paradigm

In control trials, SEPs were elicited by contralateral median nerve stimulation delivered to the digital cutaneous branches of the middle finger (third digit) through a pair of metal ring electrodes: the anode was placed over the distal phalanx and the cathode over the proximal phalanx (a square-wave pulse with duration of 0.2 ms and intensity threefold the individual sensory threshold and always below pain threshold, at 5 Hz). In test trials we applied mechanical stimuli at a rate of about 2 Hz to the ipsilateral dorsal first interosseous muscle through a handheld electronic reflex trigger hammer (TH-920310; Vickers Medical, Surrey, UK), with a contact area of 1.5 cm², which was synchronized with the sensory nerve stimulus. The interstimulus time intervals (ISIs) between the mechanical and the electrical stimuli varied between 0 (both stimuli given simultaneously) and 50 ms, in 10-ms steps. The force used in the mechanical stimulus was that necessary to generate a gentle tendon tap at the metacarpophalangeal joint, which produced a tiny movement of the second finger. Control and test trials were applied in random order.

Thalamic and surface recordings

Subjects lay relaxed on a comfortable bed in an air-conditioned room (24°C). Recordings of thalamic SEPs were performed from the four contacts of the DBS electrode (Th0, Th1, Th2, and Th3) contralateral to the stimulation site using monopolar and bipolar configurations. For monopolar configurations, each electrode contact was referred to Fz (midfrontal). For bipolar configurations, each electrode contact was referred to the adjacent one, leading to three derivations (Th0–Th1; Th1–Th2; Th2–Th3). The reference electrode was always the first of each pair.

Responses were amplified and averaged “on-line.” For a better measurement of latency and amplitude of thalamic SEPs, we used a frequency band-pass of 5 to 500 Hz, intended to cut off most of the high-frequency oscillations (HFOs) recently described in thalamic recordings (Hanajima et al. 2004b; Klostermann et al. 1999, 2000, 2002a,b). In three subjects, we also evaluated changes in HFOs by measuring the number of reproducible negative peaks in recordings in which the high-frequency cutoff was increased to 5,000 Hz.

Ag–AgCl surface electrodes (9-mm diameter) were placed on ipsilateral Erb’s point, CS2 (second cervical spine), and contralateral C PC (centroparietal), referenced to Fz, in accordance with the International 10–20 system. Impedances were kept <$5 kΩ. Bipolar derivations of Erb-Fz, CS2-Fz, and C PC-Fz were used to record N9, N13, and N20, respectively.

Responses to two consecutive series of 512 stimuli were averaged, and superimposed to check reproducibility. The mean between the two averages was used for data analysis.

Data analysis

All recordings were printed and analyzed off-line independently by two of the authors (JC and JVS). The mean values obtained from these two measurements were used for statistical analysis. Statistical data analyses of thalamic SEPs were done considering the largest response in both bipolar and monopolar recordings in control trials. In bipolar recordings, we determined the electrode pair showing phase reversal, considered as a sign suggestive that SEPs were generated within the thalamus. In monopolar recordings, we considered only the most representative response (i.e., the largest response in control trials) because it should be the closest to the sensory relay nucleus of the thalamus (the ventrocaudalis nucleus).

Latencies were measured to the peak of the largest positive (ThP1) and negative (ThN1) phases and amplitudes were determined peak to peak. All values are expressed as mean ± SD.

Latencies and amplitudes were measured in all control and test trials at every ISI. To quantify the effect of the conditioning stimuli, we determined the ratio between test and control trials for each parameter. We analyzed the results by grouping all data on the same ISI from all patients. In the three subjects in whom we used a higher-frequency cutoff, we evaluated the HFOs by determining their frequency (mean interval between reproducible negative peaks). No statistical analysis was performed in these data due to the small number of subjects.

Distribution and homogeneity of the results were analyzed with the Kolmogorov–Smirnov and Levene tests, respectively. Statistical analysis was performed with repeated-measures one-factor ANOVA for
determining the effects of ISI and recording site on the latency and amplitude of the EPs. Bonferroni post hoc test was used to explore the nature of significant differences. Statistical analyses were done with SPSS 13.0 for Windows. The level of significance was set at \( P = 0.01 \) to correct for multiple comparisons.

**RESULTS**

No patient reported any pain or discomfort during or after the experiments. The clinical DBS benefit was reflected by a decrease of 58% ± 23% in the total tremor score postoperatively \( (P < 0.001) \). Postsurgical MRI confirmed that the planned electrode location was met (Fig. 1).

**Thalamic SEPs**

**MONOPOLAR RECORDINGS.** Monopolar recordings disclosed SEPs with a first major positive wave (ThP1) and a second negative wave (ThN1). There were no significant intraindividual differences in the latencies of SEPs recorded from electrode contacts 0 to 3 (one-factor ANOVA; \( P > 0.42 \) for all comparisons). However, in both control and test trials, there was a gradient toward shorter latencies in caudal electrode contacts, with a nonsignificant mean difference between Th0 and Th3 of 0.2 ± 0.2 ms.

In four subjects, there were significant individual differences in SEP amplitudes recorded from the four electrode contacts in control trials, which were significantly larger in Th0 and Th1 (closest to the AC–PC line) than those in Th2 and Th3, with a mean difference of 2.1 ± 1.3 \( \mu \)V \( (P < 0.05) \). In the other four subjects, who did not exhibit differences in SEP amplitude between the four thalamic electrode contacts in recordings from control trials, the anteroposterior distance from AC–PC (\( \beta \)-angle) was higher (>77°), indicating that electrodes were relatively more perpendicular to the AC–PC line.

In test trials, there was a significant reduction in SEP amplitude at ISIs between 10 and 40 ms, with the largest difference occurring at an ISI of 20 ms \( (0.59 ± 0.09, P < 0.001) \) (Figs. 2A and 3A). A small positive wave \( (2.1 ± 1.4 \mu \text{V}) \) was recorded in four subjects at a mean peak latency of 26.4 ± 2.9 ms after the mechanical stimulus (Fig. 3B).

The mean amplitude decrease of thalamic SEPs was similar between the four electrode contacts across all ISIs tested (one-factor ANOVA; \( P > 0.21 \) for all comparisons). Considering the most representative response for each subject (i.e., the largest thalamic response in control trials), results were also very consistent across all ISIs (Fig. 2A).

**BIPOLAR RECORDINGS.** Bipolar recordings showed phase reversal in all subjects at the electrode contacts closest to the AC–PC line (Th0 or Th1 in all subjects). A significant amplitude reduction was seen at ISIs between 10 and 40 ms, with the largest difference occurring at an ISI of 20 ms \( (0.57 ± 0.10, P < 0.001) \), similar to the findings described in the previous point for monopolar recordings (Figs. 2B and 3A). There were no differences in the amplitude reduction of the SEPs measured from bipolar and monopolar recordings (one-factor ANOVA; \( P > 0.37 \) for all comparisons).

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**FIG. 1.** Target (nucleus ventrointermedius of the thalamus [Vim]) location. Postoperative T1-weighted magnetic resonance imaging (MRI) images in one representative subject showing the exact position of the electrodes in the Vim and its anatomical relations with surrounding structures. On top are the corresponding slices from the anatomic stereotactic atlas of Schaltenbrand and Wahren (1977). In the bottom are the atlas slices superimposed to the postoperative MRI images. From right to left: axial, coronal, and sagittal plan, all AC–PC (anterior–posterior commissure) aligned (small white circles). The white arrow points to the target (Vim).
The small positive wave recorded in four subjects after the mechanical stimulus did not show phase reversal in bipolar recordings (Fig. 3B).

**HIGH-FREQUENCY COMPONENTS.** The mean number of negative peaks recorded in control trials was 8.7 ± 1.8 (range, 6–13) with a mean frequency of 971 ± 14 Hz (range, 890–1,197). In test trials, the number and frequency of negative peaks decreased dramatically in all three subjects. At the ISI showing the most marked amplitude reduction in the SEP low-frequency component (20 ms), the mean number of negative peaks was reduced to 5.2 ± 1.5 (range, 3–8) with a mean decrease of 240 ± 37 Hz (−25.1 ± 4.3%) in HFO frequency (Fig. 4).

**Effects of mechanical conditioning stimuli on thalamic and surface SEPs**

Table 2 shows the mean and SD latency values in control and test trials for all recording sites and ISIs tested. The effects of mechanical stimuli on latency of the response were not significant in any of the recordings at any ISI. Statistical values were as follows: N9, F(6,49) = 0.2, P = 1.0; N13, F(6,49) = 0.5, P = 0.8; ThP1, F(6,49) = 0.7, P = 0.7; ThN1, F(6,49) = 0.8, P = 0.6; bipolar Th, F(6,49) = 0.6, P = 0.5; and N20, F(6,49) = 0.3, P = 0.9.

Table 3 shows the mean and SD amplitude values in control and test trials for all recording sites and ISIs tested. No significant differences were found between control and test trials regarding the mean amplitude of N9 [F(6,49) = 0.67; P = 0.7]. In contrast, significant differences were found when comparing cervical, thalamic, and cortical SEPs between control and test trials: N13, F(6,49) = 27.9, P < 0.001; ThP1–N1, F(6,49) = 21.2, P < 0.001; bipolar Th, F(6,49) = 20.7, P < 0.001; and N20, F(6,49) = 78.8, P < 0.001. Post hoc analysis showed a significant SEP amplitude decrease at ISIs between 10 and 40 ms for N13 and bipolar Th (P < 0.003 for all comparisons), and at ISIs between 10 and 50 ms for N20 (P < 0.001 for all comparisons).

The ratio of EPs amplitude between test and control trials was significantly different when comparing all recording sites across each ISI. Statistical values were as follows: ISI 0 ms, F(3,28) = 26.9, P < 0.001; ISI 10 ms, F(3,28) = 37.1, P < 0.001; ISI 20 ms, F(3,28) = 176.9, P < 0.001; ISI 30 ms, F(3,28) = 138.3, P < 0.001; ISI 40 ms, F(3,28) = 112.3, P < 0.001; and ISI 50 ms, F(3,28) = 201.9, P < 0.001.

Post hoc analyses showed that the amplitude decrease was larger for N20 than that for bipolar Th, N13, and N9, at ISIs between 0 and 50 ms (P < 0.01 for all comparisons). Also, SEP amplitude decrease was larger for bipolar Th than that for N13 at ISIs between 10 and 40 ms, and N9 at ISIs between 0 and 40 ms (P ≤ 0.01 for all comparisons).

Figure 5 shows the ratio between SEP amplitude in test and control trials for each recording site across all ISIs. Figure 6 shows recordings taken from a representative subject at the ISI showing the most marked SEP amplitude reduction (20 ms).

**Comparison between mechanical and electrical conditioning stimuli**

In view of the preliminary results obtained with mechanical stimulation, we decided to examine in the last three subjects enrolled in the study the effects of applying two identical electrical digital (third digit) median nerve stimuli separated by 20 ms. The characteristics of these stimuli were identical to the electrical stimuli used in the mechanical gating paradigm and recordings were done from the same places. There were no significant changes in SEP amplitude recorded from Erb (1.0 ± 0.01; P > 0.05), CS2 (0.99 ± 0.02; P > 0.05), or thalamic (1.01 ± 0.02; P > 0.05) electrodes with this paradigm. On the other hand, cortical SEP showed significant attenuation (0.58 ± 0.07; P < 0.01). In comparison with the results obtained in mechanical conditioned responses, both thalamic and cortical SEPs were significantly less attenuated in paired electrical stimulation paradigm (P < 0.01 for both comparisons). Figure 7 shows recordings taken from a representative subject.

**DISCUSSION**

To the best of our knowledge, ours is the first study on the temporal profile of the interaction between sensory inputs of...
different modalities taking place at the intrathalamic level. Our results show inhibitory actions of inputs induced by mechanical taps on the sensory volley elicited by digital nerve electrical stimuli, with the following main points.

1) Regarding location, our results indicate that significant afferent or centripetal interference (gating) takes place at a subcortical level.

2) Regarding quantitation, a small but significant percentage of gating (~20%) is already present at or below the medulla and >40% of gating is documented at a thalamic level.

3) Regarding temporal profile, the afferent gating is time dependent, with a peak at about 20 ms after the mechanical stimulus.

4) Regarding underlying physiological mechanisms, our results suggest active inhibition processes within the somatosensory system, featuring a significant reduction of intrinsic thalamic neuronal activity since the afferent interactions affected in similar ways the cell populations generating both slow components and HFOs of thalamic SEPs.

5) Regarding normal CNS function, selection of relevant sensory information from multiple concurrent sources involves time-locked interactions between the thalamus and the primary sensory cortex.

Although the results were very consistent among all subjects of our study they were obtained in patients with Parkinson’s disease or essential tremor, and thus some of the findings and hypothesized mechanisms may not apply to the general population. In addition, other potential biases emerge from the experimental general conditions such as the relatively small amplitude of cortically generated potentials possibly due to cerebral edema in the postoperative period (Hanajima et al. 2004a; Insola et al. 1999).

**Responses from intrathalamic recordings**

The responses recorded in our study from Vim are similar in shape to the intrathalamic SEP components previously reported (Hanajima et al. 2004a,b, 2006; Insola et al. 1999, 2004; Morioka et al. 1989). We also found small differences in the amplitude of the thalamic SEPs according to the depth and distance from the AC–PC line with phase reversal at around the AC–PC line (Hanajima et al. 2004a,b). It is generally agreed that the slow potentials recorded in thalamic nuclei from 14 to 22 ms of latency result from a positive field generated by...
excitatory postsynaptic potentials (EPSPs) in the ventrocaudalis nucleus (VC) induced by lemniscal somatosensory inputs (Hanajima et al. 2004a, 2006; Insola et al. 2004; Klostermann et al. 2002b). Potentials recorded from the Vim are probably due to volume conduction from VC (Hanajima et al. 2004a).

High-frequency, low-amplitude wavelets are superimposed to slow components of thalamic SEPs (Hanajima et al. 2004a,b, 2006; Klostermann et al. 1999). Both low- and high-frequency components reflect locally restricted near-field activity (Hanajima et al. 2004b, 2006; Klostermann et al. 2002b), probably generated in local neuronal firing within somatosensory relay thalamic nuclei. The function of the HFOs may be to synchronize and perhaps prolong important inputs, thus increasing the signal-to-noise ratio (Hanajima et al. 2004b). We have mainly focused our study in the slow components because of the important intra- and interindividual variability of HFOs and the difficulties in establishing uniform criteria for measuring latency and amplitude (Hanajima et al. 2006; Klostermann et al. 1999, 2002b).

Our subjects showed a similar amplitude decrease of the SEPs (in both monopolar and bipolar recordings) and reduction of the frequency of the HFOs in test trials with respect to control trials. These results support that the modulation of the SEPs was actually occurring within the thalamus.

Subcortical afferent gating

Only a few studies have addressed the mechanisms and locus of afferent gating using intrathalamic recordings in humans (Hsieh et al. 1995; Klostermann et al. 2002a). Hsieh et al. (1995) investigated the interaction between volleys arising from simultaneous electrical digital stimulation of hand fingers. When the second and third fingers were simultaneously stimulated the cortical N20, the P17 (recorded from VC), and the N16 (recorded from cuneate nucleus) showed an amplitude decrease of 10.220.33.5 on September 3, 2017 http://jn.physiology.org/ Downloaded from

<table>
<thead>
<tr>
<th>SEP Latencies, ms</th>
<th>Intrathalamic (Vim) Recordings</th>
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<tbody>
<tr>
<td></td>
<td>Monopolar</td>
<td>Bipolar</td>
</tr>
<tr>
<td></td>
<td>P1</td>
<td>N1</td>
</tr>
<tr>
<td>N9</td>
<td>10.2 ± 0.7</td>
<td>14.5 ± 0.7</td>
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<tr>
<td>N13</td>
<td>10.2 ± 0.8</td>
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<tr>
<td>0 ms</td>
<td>10.3 ± 0.8</td>
<td>14.5 ± 1.0</td>
</tr>
<tr>
<td>10 ms</td>
<td>10.3 ± 0.8</td>
<td>14.5 ± 0.8</td>
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<tr>
<td>20 ms</td>
<td>10.2 ± 0.7</td>
<td>14.4 ± 0.8</td>
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<tr>
<td>50 ms</td>
<td>10.2 ± 0.8</td>
<td>14.5 ± 0.9</td>
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</tbody>
</table>

Values are means ± SD. For simplicity, values in control trials represent the grand mean in all ISIs. P1 and N1 refer to the mean values found in the largest monopolar recording in each subject. Th refers to the mean peak latency of the largest response in bipolar recordings in each subject.

FIG. 4. Changes in the high-frequency components of the thalamic SEPs. Left: control trials (median nerve electrical stimulus only [�]). Right: test trials (mechanical stimulus [▲] followed by the median nerve electrical stimulus [�] at the interval of 20 ms). Monopolar (Th 1) recordings from 2 subjects using a higher-frequency cutoff (5,000 Hz). Note the presence of the high-frequency components of the SEP recorded within the thalamus superimposed to the low component and the reduction of the number of negative peaks and frequency of the high-frequency oscillations (HFOs).
TABLE 3. Mean SEP amplitudes in control and test trials at different ISIs

<table>
<thead>
<tr>
<th>SEP Amplitudes, μV</th>
<th>Vim Recordings</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Monopolar (P1–N1)</td>
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<tr>
<td>Control trials</td>
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<td>Test trials at different ISIs</td>
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<td>5.6 ± 1.6</td>
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</table>

Values are means ± SD. For simplicity, values in control trials represent the grand mean in all ISIs. P1 and N1 refer to the mean values found in the largest monopolar recording in each subject. Th refers to the mean amplitude of the largest response in bipolar recordings in each subject.

attenuation of 27, 20.6, and 10.4%, respectively, without changes in the latency of these responses. Because of similar amplitude reduction in the SEPs recorded from the thalamus and cuneate nucleus when digits II and III, and digits II and V were stimulated, the authors suggest that the neuronal cells representing the receptive field of sensory inputs at these levels are arranged in clusters. Klostermann et al. (2002a) studied a different gating paradigm consisting of complete muscle relaxation by succinylcholine in narcotized patients undergoing DBS. SEPs evoked by median nerve electrical stimulation at the wrist were recorded directly from the ventrolateral thalamus in only two patients. Under complete muscle block there was a clear thalamocortical dissociation, with a significant increase in the amplitude of the cortical N20 component (17%) and a significant decrease in the responses recorded from the subthalamic nucleus (STN) and thalamus (−9%). In addition, thalamic HFOs showed no consistent change except for a nonsignificant reduction in burst amplitude. On the other hand, in a study of motor gating, Insola et al. (2004) showed that voluntary movement of the wrist reduces the amplitude of the low- (−30%) and high-frequency SEPs recorded from STN and globus pallidus internus, and suggested that the centrifugal effect of movement also acts at the subcortical level, whereas the centripetal gating occurs only within the cerebral cortex.

Taken together, these results suggest that interaction of inputs from somatosensory stimuli occurs predominantly in the primary somatosensory cortex, whereas the thalamus and other subcortical structures are not responsible for significant afferent gating effects. However, none of these studies evaluated the influence of time in the interaction between somatosensory stimuli of different modalities. In fact, our results are in accordance with the findings reported if we consider only short ISIs.

Muscle afferents activated by mechanical tendon taps

Our mechanical stimulus was intended to hit the first dorsal interosseous muscle and produce a tendon jerk at the metacarpophalangeal joint. We considered this a convenient muscle, innervated by the ulnar nerve with overlapping skin innervated by the superficial radial nerve. Muscle afferents in the upper limb may have a suppressive effect on the responses to cutaneous fiber activation (Halonen et al. 1988). Since we were electrically stimulating the median nerve we consider unlikely any contribution to the inhibitory phenomena related to peripheral nerve function. Although short-latency cortical SEPs to electrical stimuli depend on the integrity of the posterior column pathways and are primarily mediated by large myelinated cutaneous afferents (Abbruzzese et al. 1980; Allison et al. 1991; Halonen et al. 1988), we applied the electrical stimuli to the digital nerve fibers to avoid any possible contribution from muscle afferents.

A weak phasic tendon tap is a selective stimulus for the primary sensory endings of muscle spindles (Burke et al. 1983; Cohen and Starr 1985a; Cohen et al. 1985; Murthy et al. 1978; Stuart et al. 1970), which were probably the most important type of mechanoreceptors activated in our study (Burke et al. 1983, 1988; Macefield 2005; Macefield et al. 1989). A brief phasic stretch of a muscle activates Ia afferents with a latency of 2 to 5 ms due to the time needed for propagation of the percussion wave and muscle spindle signal transduction (Cohen et al. 1985; Paintal 1959). The afferent volley thus generated is probably composed of a relatively long-lasting burst of impulses from a number of receptors. In fact, the duration of the afferent response in transcutaneous ulnar intraneurinerve record-
ings at the wrist after a tendon tap applied to the first interosseous muscle is in the range of 10 to 15 ms (Hagbarth and Vallbo 1968; Jacobi et al. 1970; Murthy et al. 1978). Similar observations have been reported for the compound sensory nerve action potentials (SNAPs) to air-puff stimulation (Hashimoto et al. 1991). Such desynchronization of the afferent volley is probably the cause of the small size of the SNAPs to mechanical stimuli causing a small indentation of the skin (Baba et al. 2001). A similarly desynchronized volley has been reported for the T-wave elicited in the soleus muscle by tendon tapping (Burke et al. 1983), suggesting that tendon tapping generates relatively long-lasting small EPSPs in the motoneurons. Thus a...
number of impulses occurring within the 20 ms after the mechanical stimulus are expected to reach the CNS, producing a near-synchronous discharge from a number of receptors. This time profile of the mechanical desynchronized volley is probably responsible for the time interval interactions found in our study.

Early cortical SEPs elicited by tendon taps and muscle stretch result from activation of primary muscle spindle endings, without significant contribution from joint, ligament, tendon, or skin mechanoreceptors (Ackermann et al. 1992; Cohen and Starr 1985a,b; Cohen et al. 1985; Morita et al. 1998; Pratt et al. 1979; Starr et al. 1981). Compared with SEPs evoked by electrical nerve stimulation, SEPs elicited by mechanical taps have smaller amplitude and shorter latency (Cohen and Starr 1985a; Cohen et al. 1985) probably due to the desynchronization of the afferent volley and to the relatively more proximal location of the receptors activated with tendon taps because the fastest muscle afferents from the upper limbs do not conduct more rapidly than the fastest cutaneous afferents of the digital nerves (Macefield et al. 1989).

Both types of afferents activated in this study are conducted through the posterior column pathway, have a synaptic relay in the cuneate nucleus, and ascend with the medial lemniscus to the thalamus. Some upper-limb muscle afferents ascend along the spinocebellar tract with a relay through the cerebellum (Burke et al. 1981; Phillips et al. 1971). It is well established that group Ia afferents from spine endings project to a different area of the sensorimotor cortex than cutaneous afferents (Gandevia and Burke 1988; Gandevia et al. 1984; Starr et al. 1981). Functionally, the projection of muscle afferents to the cortex has been considered a feedback pathway through which motor output can be regulated (Burke et al. 1981).

Two main criticisms may apply to the mechanical stimulus used in our experiment. First, a mechanical stimulus applied to the dorsum of the hand, causing a small movement of the metacarpophalangeal joint, can potentially activate a wide variety of mechanoreceptors, in particular skin mechanoreceptors such as Pacinian corpuscles (supplied by fast-adapting type II afferents) that are the most sensitive cutaneous receptors to distal stimuli (Johnson 2001). However, sensory nerve action potentials recorded over the ulnar nerve at the wrist after application of a tendon tap at the first dorsal intersosseous space do not depend on inputs from either the skin or tendons (Murthy et al. 1978). The second criticism to our mechanical stimulus is that its strength was not monitored. Therefore we had a certain amount of variability in the afferent response due to the variable strength of the applied mechanical stimuli. However, our results were reproducible intra- and interindividually. Angular incidence and site of stimulation are known not to have any relevant influence in SEPs (Cohen et al. 1985). Moreover, stimulus intensity and rise time of the mechanical stimulation do not directly correlate with SEP amplitude (Cohen et al. 1985; Gandevia et al. 1982; Spitzer and Claus 1992).

All these arguments fit well with the temporal profile of the interactions in our study, where the most significant gating was found at an ISI of 20 ms. In addition, the small thalamic responses to mechanical stimuli that were present in four subjects are also in accordance with the generation of a poorly synchronized discharge because of the inconsistency of these responses in the subjects studied, its small amplitude, its similarity in different monopolar recordings, and the absence of phase reversal with bipolar recording. This response probably represents a far-field potential and not a SEP originated within the thalamus.

**Interactions between two consecutive afferent volleys elicited by electrical median nerve stimulation**

Studies that evaluated the excitability of the CNS by studying the recovery function of SEPs with the electrical paired stimulation technique of the median nerve found a significant attenuation of P14 and cortical SEPs in normal subjects. At an ISI of 20 ms the N20 component shows an amplitude decrease of ≤50% and recovers at ISIs of >100 ms (Frasson et al. 2001; Mochizuki et al. 2003). The mechanisms involved in this modulation at the dorsal column lemniscus medialis system (P14, N20) are thought to depend on the postsynaptic potentials probably mediated by interneurons within the ventroposterolateral (VPL) nucleus (Araki et al. 1997; Frasson et al. 2001). However, at very short ISIs (<10 ms) N20 is not identified, whereas P30 is recognized following the second stimulus (Hoshiyama and Kakigi 2002). Thus the recovery function of the SEP components is not simply determined by the number of synapses interposed between the stimulus site and the generator source of the response in the CNS, but there might be a structural or functional process of low-cut filtering in the primary sensory cortex.

In our study, recordings from the three subjects in which we evaluate the effects of paired median nerve electrical stimulation showed significant N20 inhibition, but no changes in thalamic or cervical SEPs at an ISI of 20 ms. Similar results were reported by Klostermann et al. (2000) with intrathalamic recordings at ISIs of 10 and 20 ms, and by Araki et al. (1997) with upper cervical recordings. HFOs recorded from intrathalamic electrodes in PD patients completely recovered at an ISI of 20 ms, whereas HFOs recorded in the scalp recovered only 53% (Klostermann et al. 2000). This dissociation between cortical and subcortical responses may be due to longer refractory periods for cortical SEP generators because of accumulating response delays in serial synaptic transmissions (Klostermann et al. 2000). Taken together, these results indicate that mechanisms other than refractoriness of the circuit should be responsible for the significant inhibition of the SEPs observed with mechanical conditioning stimuli. We should keep in mind, though, that our study was done in patients with Parkinson’s disease and essential tremor who might have an abnormal suppression of SEPs (Mochizuki et al. 2003; Restuccia et al. 2003).

**Interactions between muscle and cutaneous afferent volleys**

As in previous studies of either afferent or efferent gating (Abbruzzese et al. 1980, 1981; Burke et al. 1982; Cohen and Starr 1987; Hsieh et al. 1995; Insola et al. 2004; Jones et al. 1989; Klostermann et al. 2002a; Tapia et al. 1987), there were no changes in the latencies of any subcortical or cortical responses, nor in the amplitude of the braunal plexus response (N9), indicating that the gating effect is mediated only by central structures. In particular, an interaction between lemniscal and spinocebellar inputs has been suggested to occur at a thalamic level (Gandevia et al. 1983; Okajima et al. 1991).
Others (Cohen and Starr 1985b) have suggested that inhibition due to a presynaptic effect of the Ia input may occur even at a spinal level. In fact, active inhibitory mechanisms between afferent volleys from upper limbs are well documented at this level (Jankowska and Padel 1984; Walmsley et al. 1987). Our results are in full agreement with these previous reports and bring direct evidence for the participation of subcortical structures in afferent gating beginning at or below the medulla.

A further aspect is that motor gating of upper-limb SEPs, compared with gating of lower-limb SEPs, appears to be more selective for the nerve being stimulated as well as the muscle being contracted (Cohen and Starr 1987; Morita et al. 1998; Tapia et al. 1987). This suggests that SEP AM is specific to movement of fingers supplied by the stimulated nerve, such that during these movement trials muscle afferents would be active as well. In our study, there was significant gating between muscle and cutaneous afferents from different nerves. This lack of selectivity of afferent gating suggests a more widespread inhibitory effect of mechanical stimuli than of hand voluntary movement. Possibly, voluntary movement goes with a rather high selectivity of changes in motor cortex excitability that would influence the expression of gating.

It is well known that relative timing and size of the conditioning and test volleys are critical factors for the interaction between sensory inputs from different modalities (Burke et al. 1982). Cortical SEPs evoked by electrical stimulation of the tibial nerve are significantly depressed if preceded by a conditioning stimulus such as a tendon tap of the biceps femoris (Morita et al. 1998). Similar results occur with SEPs evoked by an Achilles tendon tap when preceded by sural nerve electrical stimuli. Activation of muscle spindles by ipsilateral hand vibration induces a marked decrease of the amplitude of the N17 (thought to reflect the activity of the thalamocortical radiation) and N20 components of the cerebral SEP evoked by median nerve stimulation at the wrist or fingers (Abbruzzese et al. 1980; Cohen and Starr 1985b; Hoshiyama and Kakigi 2000), and a nonsignificant decrease of N13 (Abbruzzese et al. 1980).

Two major neurophysiological mechanisms have been described for afferent gating: active inhibition and occlusion due to convergence at relay nuclei (Abbruzzese et al. 1981; Burke et al. 1982; Chapman and Beauchamp 2006; Gandevia et al. 1983, 1984; Hsieh et al. 1995; Jones 1981; Jones et al. 1989; Klostermann et al. 2002a; Morita et al. 1998). Occlusion through convergence cannot be completely ruled out. If the same subpopulation of neurons is activated by two different afferent inputs, the response to afferent volleys arriving simultaneously will be less than the sum of the responses to each input given in isolation (Burke et al. 1982). In the context of our study, such convergence could result in refractoriness (Morita et al. 1993), synaptic transmission depression (Hultborn et al. 1996), or occlusion in various nuclei along the sensory pathway and the cortex (Jones et al. 1989; Klostermann et al. 2002a). However, electrical conditioning stimuli did not cause significant attenuation of the thalamic SEPs at an ISI of 20 ms, when the inhibitory effect of mechanical stimuli was at its peak. Although these results suggest that attenuation of SEPs after conditioning mechanical stimuli is due to an active inhibitory process, we cannot rule out completely the contribution of other forms of inhibition at the intervals not tested. Thalamic responses induced by mechanical stimuli have longer latencies than those induced by electrical stimuli and the possibility exists that the two responses have different relative refractory periods. A careful study of the effects of mechanical and electrical conditioning stimuli would be needed through a range of ISIs to determine the exact role of refractoriness in suppressing the SEPs. This was not the objective of our study and thus we can only speculate that, theoretically, ISIs longer than the one studied here (20 ms) would go with a more complete recovery of SEP amplitude rather than with more inhibition.

There is segregation of the cerebellar and dorsal columnar inputs to motor (ventrolateral nuclei complex) and sensory (VPL nucleus pars caudalis) regions of the thalamus, respectively (Sakai et al. 1996). Our results suggest that important active inhibitory processes take place at the thalamic level. Two types of inhibitory GABAergic neurons operate in the thalamus: reticular and small local-circuit neurons that contain synaptic vesicles in their dendrites (Govindaiah and Cox 2006) and thus can be pre- and postsynaptic. The reticular nucleus and its GABAergic axons have an inhibitory effect over all thalamic nuclei (Cox et al. 1997) and about 50% of reticular nucleus neurons synapse with ventrolateral interneurons dendrites. This condition results in very complex neural inhibition in thalamic and thalamocortical circuits (Govindaiah and Cox 2006; Schofield and Huguenard 2007).

The functional significance of afferent or sensory gating may be interpreted in terms of perceptual filtering, i.e., the reduction of processing of, and distraction by, irrelevant or repetitive stimuli (Braff et al. 1992). According to Graham’s theory of protection of preattentive processing (Graham 1992), a conditioning stimulus initiates two automatic processes, an increase in general arousal for identification of the lead stimulus and the triggering of an inhibitory process aimed at protecting the CNS preattentive sensory processing from the disrupting effects of any new stimulus (Blumenthal 1999; Reijmers and Peeters 1994). In conclusion, our results provide direct evidence that sensory information processing involves time-locked interactions between subcortical structures and primary sensory cortex that are probably relevant to human behavior and function.

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DISCLOSURE

The authors do not have any potential conflict of interest.

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