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## Cutaneous stimulation of the digits and lips evokes responses with different adaptation patterns in primary somatosensory cortex

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### Abstract

Neuromagnetic evoked fields were recorded to compare the adaptation of the primary somatosensory cortex (SI) response to tactile stimuli delivered to the glabrous skin at the fingertips of the first three digits (condition 1) and between midline upper and lower lips (condition 2). The stimulation paradigm allowed to characterize the response adaptation in the presence of functional integration of tactile stimuli from adjacent skin areas in each condition. At each stimulation site, cutaneous stimuli (50 ms duration) were delivered in three runs, using trains of 6 pulses with regular stimulus onset asynchrony (SOA). The pulses were separated by SOAs of 500 ms, 250 ms or 125 ms in each run, respectively, while the inter-train interval was fixed (5 s) across runs. The evoked activity in SI (contralateral to the stimulated hand, and bilaterally for lips stimulation) was characterized from the best-fit dipoles of the response component peaking around 70 ms for the hand stimulation, and 8 ms earlier (on average) for the lips stimulation. The SOA-dependent long-term adaptation effects were assessed from the change in the amplitude of the responses to the first stimulus in each train. The short-term adaptation was characterized by the lifetime of an exponentially saturating model function fitted to the set of suppression ratios of the second relative to the first SI response in each train. Our results indicate: 1) the presence of a rate-dependent long-term adaptation effect induced only by the tactile stimulation of the digits; and 2) shorter recovery lifetimes for the digits compared with the lips stimulation.

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## Keywords

magnetoencephalography; somatosensory evoked fields

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## 1. Introduction

Response adaptation, defined as a change in the neuronal responsiveness determined by a recent history of stimulation, has been extensively studied along different levels of the somatosensory pathway. Converging evidence from evoked response studies using repetitive somatosensory stimulation of the upper limb indicates a clear trend toward increasingly larger sensitivity to stimulus repetition at progressively higher levels of processing. The first-order afferent volleys in the human peripheral nerves undergo observable changes with stimulus repetition only at very short inter-stimulus intervals (ISIs), and full recovery occurs as soon as 5 ms after a stimulus (*e.g.* Buchtal and Rosenfalck, 1965; Reisin et al, 1988). Cervically-recorded somatosensory evoked potentials (SEP) components, which reflect synaptic activity in the spinal dorsal horn, exhibit response attenuations for ISIs as long as 60 ms (Kaji and Sumner, 1987). Responses in the cuneate nucleus and medial lemniscus (Wiederholt, 1978) show apparent attenuation at ISIs as long as 100 ms in barbiturate-anesthetized cats. Slightly longer recovery times (up to 150 ms) were reported for the thalamus and thalamocortical radiation components in human (Emori et al, 1991) and animal studies (Wiederholt, 1978). Finally, recovery intervals for primary somatosensory (SI) response components have typical values ranging from 200 to 250 ms. Components considered to be generated within the *upper* layers of area 3b (P30/N30) and area 1 (N35) are more susceptible to attenuation induced by repetitive electrical stimulation than earlier components (N20 and P25) which are mainly associated with afferent invasion of the *middle* layers in areas 3b and 1, respectively (Alisson et al, 1962, Tomberg et al, 1989; Tiihonen et al, 1989; Huttunen and Homberg, 1991).

This type of adaptation, which occurs and fades out rapidly, has been typically studied using intermittently delivered pairs or regular trains of brief stimuli presented at different stimulus onset asynchronies (SOAs). It was however observed that prolonged stimulation with electrical or vibrotactile conditioning stimuli can also produce longer lasting forms of adaptation at subcortical and cortical levels. Conditioning over times ranging from tens of seconds to tens of minutes can induce a prolonged depression in the responsiveness of cuneate neurons in cats (O' Mara et al, 1988), or can lead to attenuation of the cortical response to subsequent test stimuli in humans over periods lasting as long as 40 min (*e.g.* Macefield and Burke, 1991). Along with data from paired and train stimulation studies reviewed previously, such observations suggest that the adaptation mechanisms at higher processing levels may involve short-term neuronal plasticity which can develop and persist over a large range of temporal scales.

Although it is intuitive to consider that cortical somatosensory adaptation inherits some effects of adaptation from lower levels within the sensory pathway, several studies have demonstrated that it relies substantially on intra-cortical dynamics (Lee and Whitsel, 1992; Lee et al., 1992, Whitsel et al, 1989). Cortical adaptation has attracted special attention, given the link between the evoked cortical responses and the physical and subjective (perceived) characteristics of the stimuli (Hashimoto et al, 1988; Hashimoto et al, 1992; Jones et al., 2007). Assessing perceptual judgments about stimuli with conditioning paradigms has therefore contributed to elucidating more characteristics and the functional role of cortical adaptation. Long-lasting (10 min) electrical stimulation of the finger was found to induce patterns of cortical adaptation that replicate closely the time course of hypaesthesia (Macefield and Burke, 1991). Furthermore, whereas adaptation impairs

detection of a liminal vibrotactile stimulus, it improves the intensity and frequency *discrimination* of supraliminal stimuli with physical parameters that are close to those of the adapting stimulus (Goble and Hollins, 1993; Goble and Hollins, 1994), and enhances the spatial localization of a subsequent tactile stimulus (Tannan et al., 2006). Similar relationships between adaptation and enhancement of discriminative ability have been also reported in auditory (von Békési, 1960) and visual modalities (Greenlee and Heitger, 1988), suggesting the existence of a general principle of sensory adjustment to repetitive stimulation.

Most of the knowledge about somatosensory cortical adaptation in humans comes from studies using stimulation of the upper limb. Comparatively, less knowledge has been gained about other body structures, and in particular, about the trigeminal somatosensory pathway (Murray et al., 2001). The current study compares the response adaptation in primary somatosensory cortical areas of the fingers and lips to investigate potential differences that can be due to distinct functional specialization of these structures, using magnetoencephalographic (MEG) recordings of somatosensory evoked fields (SEFs). A core assumption of the study is that salient aspects of distinct functionality would likely be revealed using stimulation strategies that replicate as closely as possible the frequent conditions in which the somatosensory input from these structures must be processed. First, we use tactile stimulation instead of the electrical stimulation used by most previous studies. The electrical stimulation bypasses the sensory receptors of the skin and engages undifferentiated afferent and motor efferent fibers, increasing the risk of abnormal afferent interactions (mostly due to lateral inhibition), which are not triggered by mechanically delivered stimuli (Willis and Coggeshall, 1991), and which can influence adaptation at subcortical and cortical levels. Second, the tactile stimulation was delivered simultaneously to the glabrous skin at the tips of digits I, II and III (thumb, index and middle finger) in one condition, and at midline between the vermilion surface of the upper and lower lips (simultaneously stimulating both lips) in a second condition of the experiment. The simultaneous stimulation strategy was chosen to replicate behaviorally natural conditions that require *functional integration* of tactile stimuli from skin areas of adjacent digits or from upper and lower lips. Previous studies have indicated that in the presence of simultaneous somatosensory stimulation at multiple sites considerable interaction occurs at different levels along the sensory pathway (Okajima et al, 1991; Huttunen et al, 1992; Gandevia et al, 1983; Hsieh et al, 1995). These interactions were observed in the subcortical sensory relay nuclei (including the cuneate nucleus and the sensory thalamic nucleus), and were predominant within regions of the primary somatosensory cortex. In particular, the higher inhibitory interaction in cortical area 3b observed for simultaneous stimulation at *adjacent* fingers compared with *distant* fingers (Hsieh et al, 1995; Biermann et al, 1998) has been hypothesized to reflect important aspects of functionality related to the simultaneous use of adjacent digits in frequent tasks.

The glabrous skin of the fingertips and lips is characterized by a high density of mechanoreceptors, accompanied by high cortical magnification factors (defined as the ratio between the area of representation in the primary somatosensory cortex to the area of the skin), which are considered to be determinant for the relatively high tactile acuity of these structures (Van Boven and Johnson, 1994; Sathian and Zangaladze, 1996). On the other hand, whereas sensory information from the fingertips is frequently required when small objects are inspected or manipulated, signals from the lips mechanoreceptors in humans primarily subserve the sensorimotor regulation of oral behaviors involving contact between the lips, teeth or tongue tip, such as speech, chewing and swallowing (Barlow, 1987; Johansson et al., 1988a; Nordin and Hagbarth, 1989; Trulsson and Essick, 1997). Whether such distinct functional properties of the digits and lips SI cortical areas are associated with

different response adaptation patterns is unknown and it defines the primary research question of the current study.

## 2. Methods

### 2.1. Subjects, stimuli, and data acquisition

Somatosensory evoked fields were recorded from 14 female subjects without known neurological conditions who agreed to participate in the study. Informed consent was obtained from all subjects prior to participation in the experiment. The study was approved by the University of Kansas Medical Center Institutional Review Board. Data from 3 subjects were discarded due to a low signal-to-noise ratio in some conditions of the experiment. The remaining 11 participants (mean age: 26 years, 3 months  $\pm$  4 years, 5 months) were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971).

The pneumatic-cutaneous stimuli were delivered using a servo-controlled pneumatic amplifier that modulated the intraluminal pressure of a silicone Soothie™ pacifier receiver in a repeating 6-pulse sequence, which yielded a 275  $\mu$ m deflection of the nipple cylinder with each pulse. With these settings, the cylinder can apply a light pressure stimulus to the skin surface during each deflection. The membrane displacement had a rise-time of 24 ms (defined as the time interval between the 10% and 90% of the maximum displacement) and a duration of 50 ms (measured between the half maximum displacement on the rising and falling slopes of the pressure wave). All latencies reported in this study are referenced to the point of 10% of the maximum deflection following stimulus onset (correcting for a 17 ms mechanical response delay between the trigger to the pneumatic servo and the onset of nipple deflection).

Each MEG experiment was divided into two sessions. In one session, the stimulus probe was positioned at midline between the vermilion surface of the upper and lower lips. After placement, the probe was secured in position with a fabric band strap adjusted around the head for proper fit. In the other session, the stimulus probe was placed at the glabrous surface of the hand, between the thumb, index and middle finger. After placement of the stimulus probe, the three fingers were surrounded with a narrow band strap applied over the nails to restrict movement. Each session comprised three successive runs. In each run, the 6-pulse stimuli were delivered in blocks of 125 trials with a constant stimulus onset asynchrony of 125, 250 or 500 ms, respectively (corresponding to stimulation rates of 8 Hz, 4 Hz and 2 Hz). The pulse duration and the inter-trial interval (5 sec, measured from the last stimulus in one trial to the first stimulus in the next) were constant across runs. The order of the three runs in each session as well as the order of the two sessions was randomized across subjects.

The temporal distribution of the stimuli was chosen to allow the characterization of the adaptation patterns over two time-scales. First, we aimed to investigate what will hence-to-forth be referred to as short-term adaptation, based on the response changes to serial pulses within trains and their dependence on SOA. Second, we aimed to test for the presence of any rate-dependent long-term adaptation effects, with recovery periods exceeding the inter-train interval of 5 sec, which would be reflected as changes in the responses to the first pulse in each train.

MEG signals were recorded in a magnetically shielded room using a whole-head CTF 151-channel system with axial gradiometers sensors (5 cm baseline). Two bipolar (vertical and horizontal) EOG channels were simultaneously recorded to identify the trials affected by ocular artifacts and eye blinks. The head position with respect to the sensor array was

determined by feeding current into three localization coils placed at nasion and left and right pre-auricular points, respectively. Data were recorded in continuous mode using a sampling rate of 600 Hz and a pass-band of 0-150 Hz. Magnetic resonance imaging (T1-weighted MRI) scans were performed for all participants immediately after the MEG experiment using registration landmarks placed at the localization coils positions. The total experiment duration (including the preparation and the short breaks between runs) was approximately 2 hours.

## 2.2. MEG data analysis

**Data pre-processing**—The recorded MEG signals were band-pass filtered between 1.5 Hz and 50 Hz using bi-directional 4<sup>th</sup> order Butterworth filters, to remove the sustained fields that occurred during the stimulus trains and to facilitate the identification of the transient response components. Epochs starting 1.0 sec before the first pulse and ending 1.0 sec after the last pulse in each trial were visually inspected to discard trials containing eye blinks or movement artifacts. The remaining artifact-free trials (not less than 90 for each subject/condition) were averaged separately for each run and the DC was offset using the pre-stimulus period as a baseline.

To improve the robustness of the subsequently computed source estimators, the averaged datasets for each subject and stimulation site were decomposed using a PCA-filtered ICA algorithm (EEGLAB *software*, Delorme and Makeig 2004). The PCA filtering step was applied to reduce the data dimensionality, so that an appropriate statistical measure of independence could be achieved by the subsequent ICA, which was used to segregate the contribution of SI to the overall magnetic field.

**Source reconstruction**—The source reconstruction was performed in CURRY (Compumedics Neuroscan) using a spherically symmetric volume conductor model fitted to each individual subject's skull segmented from the MRI data. The source space was defined as a regular grid of points throughout the brain volume (average distance between points was 4 mm). The components of interest were localized using a two-step source reconstruction algorithm. First, a current density analysis using sLORETA (Pascual-Marqui, 2002) was performed to identify the spatial peaks of activity corresponding to the SI activity. sLORETA uses the standardization of a minimum norm inverse solution, and does not require a priori information about the number of active sources. Second, a location constrained dipole analysis was performed to obtain estimates of the direction and strength for each active brain region. The number of dipoles was set based on the number of spatially distinct sources retrieved by sLORETA. The dipole fitting procedure allowed characterizing the source strengths using current units rather than the statistical measures reported by sLORETA.

## 2.3. Assessment of SI adaptation patterns

Dipole locations, peak strengths and peak latencies were the main variables of interest used for the statistical analysis, with explicit comparisons between stimulation site (lips vs. digits) and stimulation rate (SOA). The statistical analysis was performed using GraphPad Prism 5 software (GraphPad Software, Inc.).

**Long-term adaptation**—We hypothesized that the presence of long-term adaptation effects (defined in this study as those effects which persist for more than the 5 sec inter-train interval) and their possible dependence of the stimulation rate will be reflected as changes in the response amplitude to the first stimulus in each train. Repeated-measures ANOVAs on the amplitudes of the responses to the first pulse in each train were conducted separately for the digits and lips stimulation conditions. When a main effect was present, Bonferroni

multiple-comparison tests were carried out on the corresponding data from paired sets of stimulation rates.

**Short-term adaptation**—Based on the observation that the maximal decrement in the response amplitude occurs with the second response in each train (see *Results* section), a quantitative measure of response adaptation in SI was derived from the set of suppression ratios of the second response relative to the first response for each stimulation rate, i.e.

$\alpha(SOA) = \frac{A_2^{SOA}}{A_1^{SOA}}$ . The values of the suppression ratios,  $\alpha(t)$ , in each stimulation condition were fitted by an exponentially saturating function of the form  $f(t) = 1 - e^{-Kt}$ . This model was used in previous neuromagnetic studies to characterize the cortical response recovery (e.g. Lü et al, 1992a; Lü et al, 1992b; Uusitalo et al., 1996; Hamada et al., 2002) and was also representative for the observed recovery trajectories in our study. The lifetime value, defined as  $t_{50\%} = 0.693/K$ , which represents the estimated SOA for which the response reaches 50% of the maximum was subsequently compared between the digits and lips stimulation conditions. In a first approach, a non-linear least-squares regression was applied globally across subjects to fit the parameters of the model, and the estimated lifetimes were compared between the stimulation conditions using an extra sum-of-squares F-test. In a second approach, the response suppression curves were determined independently for each subject and condition, and the sets of lifetime values for the digits and lips stimulation were subsequently compared using a two-tailed, paired *t*-test.

### 3. Results

#### 3.1. Neuromagnetic SEFs to cutaneous pulse trains

Figure 1 exemplifies the averaged SEF data for the digits (panel a) and lips (panel b) stimulation in the 500 ms SOA condition. Each pulse stimulus in the train produced prominent responses with a time-varying morphology indicating the existence of multiple SEF sources peaking at different latencies. For the digits stimulation (panel c), the dominant component peaks in this example at 67 ms. Subsequent pulses within the train evoke similar SEFs, although with different relative amplitudes of the various components. For the lips stimulation (panel d) the dominant component peaks at 58 ms. As for the digits stimulation, the dominant peak is also followed by several late components with different temporal morphologies and spatial patterns of magnetic field (it must be noted that for both digits and lips stimulation conditions not all subjects showed exactly the same sequence of late response components).

The results obtained by analyzing the independent component (IC) that segregated the most robust response waveform (consistently present in all subjects), i.e. peaking around 70 ms (digits stimulation) and around 60 ms (lips stimulation), are reported in this study. For the digits stimulation, this component is characterized by a markedly dipolar pattern (figure 2a) essentially confined to a sub-array of sensors covering the left hemisphere (contra-lateral to the stimulation site). The magnetic field pattern and the orientation of the underlying source closely match those of the response components generated at 30-35 ms in EEG and MEG recordings during electrical stimulation of the median nerve (Renvall et al, 2005). These components are considered to be mainly generated by the activity in superficial layers of the primary somatosensory cortex (McLaughlin and Kelly, 1993), which follows immediately after the initial afferent invasion in the *middle* cortical layers. Previous MEG studies have indicated underlying generators confined mainly to cytoarchitectonic area 3b (Simões et al, 2001; Renvall et al, 2005), with possible contribution from area 1 in the anterior crown of the postcentral gyrus. The latency difference between corresponding components elicited by electrical versus tactile stimulation can be ascribed to differences in the stimulation modality

as well as to temporal differences in stimulus characteristics such as rise-time and duration. For lips stimulation, the magnetic field explained by the corresponding component is characterized by two dipolar patterns, each expanding across a sub-array of sensors covering one hemisphere and indicating the presence of bilateral neural generators (figure 2b).

### 3.2. Spatio-temporal reconstruction of the somatosensory SI activity

For the digits stimulation condition, sLORETA retrieves activity confined to the hand primary somatosensory cortex (SI) over the contralateral (left) parietal region, i.e. in regions extending from the fundus of the central sulcus to the anterior wall and the crown of the postcentral gyrus (exemplified in figure 2a, lower panels). This most likely indicates neuronal generators in proximal neuronal populations from hand areas 3b and 1. For the lips stimulation condition, sLORETA retrieved bilateral regional activations, within the somatosensory cortex of the left and right hemispheres (figure 2b). The results of the second step of source reconstruction (*i.e.* sLORETA constrained dipole fitting) are exemplified in figure 3. For the digits stimulation condition, dipoles were consistently localized in the anterior wall of the postcentral gyrus. For the lips stimulation, dipoles were localized within the central sulcus, and in the left hemisphere they were shifted laterally and inferiorly compared to the digits stimulation condition. It must be noted that for the 8 Hz stimulation rate, the peak identification was sometimes strained by the very low amplitude of the responses to the later pulses in the train (exemplified in figure 3a). In those cases, the peaks with the same polarity and with the closest latency to the expected latency of the SI response were used for analysis (marked with small arrows in fig. 3a).

A comparison between the dipole locations (summarized in Table 1) for the digits versus lips stimulation using a two-tailed paired *t*-test ( $df=10$ ) on each of the three Cartesian coordinates of the corresponding *left hemisphere* sources showed a significantly different localization of the source evoked by the lips stimulation relative to the hand SI along all three directions: laterally ( $\Delta x=-5.2$  mm,  $t=3.7$ ,  $p=0.004$ ), anteriorly ( $\Delta y=6.9$  mm,  $t=3.3$ ,  $p=0.008$ ), and downwardly ( $\Delta z=-11.2$  mm,  $t=6.9$ ,  $p<0.0001$ ). The results are in agreement with the somatotopic organization of the primary somatosensory cortex (Penfield and Rasmussen, 1968), with the lips represented towards the base of the postcentral gyrus, *i.e.* more laterally, anteriorly and inferiorly with respect to the hand S1. The localization of the lips SI is also consistent with data reported in previous MEG studies of trigeminal somatosensory evoked fields (Nevalainen et al, 2006). No significant differences were observed between the coordinate values of the left and right sources evoked by labial stimulation when *absolute* values of the *x* coordinates were considered (with the *x*-axis going from left to right through pre-auricular points), demonstrating that they were essentially symmetric with respect to the midsagittal plane.

### 3.3. SI adaptation patterns

In the bilabial stimulation condition, no consistent difference in the amplitudes of the left and right sources was observed across subjects. Hence, the synchronous strengths of the two sources were averaged to yield a common measure of S1 evoked activation for this condition. The strategy was used throughout the analysis of the long- and short-term adaptation patterns described in the following sections.

**Long-term adaptation**—Figure 4 (panels *a* and *b*) illustrates the mean amplitude of the responses (dipole strengths) to the *first* pulse in the train for each stimulation rate and site. The response amplitude appeared to decrease progressively with increasing stimulation for digits stimulation, but not for lips stimulation. Repeated measures ANOVAs performed separately for each stimulation site on the amplitude of responses to the first pulse in each train indicated a significant main effect of stimulation rate for the digits stimulation ( $F=5.22$ ,

$p=0.015$ ). Follow-up Bonferroni multiple-comparison tests carried out on data from paired sets of stimulation rates indicated a significant difference between 2 Hz and 8 Hz stimulation rates ( $t=3.2$ ,  $p=0.016$ ), whereas the differences between 2 Hz and 4 Hz, as well as between 4 Hz and 8 Hz responses lacked significance ( $t_s<1.76$ ,  $p_s>0.11$ ). In contrast, no significant effect of stimulation rate was observed for the amplitude of the first responses in the train for the lips stimulation condition ( $F=0.45$ ,  $p=0.64$ ). These results indicate that a rate-dependent long-term adaptation effect, lasting for more than the inter-train interval of 5 sec, was induced by the digits stimulation, whereas no such effect was detected for the lips stimulation in the range of stimulation rates used in our study.

To test for the presence of rate-dependent long-term adaptation effect on the response latencies, a  $3 \times 2$  repeated measures ANOVA was performed, with the stimulation rate (2, 4, and 8 Hz) and stimulation site (digits vs. lips) as independent variables and the latency of the response to the first stimulus in each train as the dependent variable. This test indicated a significant main effect of stimulation site ( $F=23.1$ ,  $p<0.001$ ), but no significant effect of stimulation rate or rate-by-site interaction. These results are explained by a significantly shorter latency of the cortical response evoked by the lips ( $63.2 \pm 8.4$  ms) compared with the digits stimulation ( $71.3 \pm 5.9$  ms), with mean values estimated from the pooled data across subjects and stimulation rates. A shorter response latency for the lips stimulation is consistent with the shorter conduction delay for the trigeminal pathway. Based on these results, we conclude that no rate-specific long-term adaptation effects were reflected in the response latencies.

**Short-term adaptation**—Panels c-e in figure 4 show the averaged peak amplitudes at different stimulation rates as a function of serial position within the pulse train, for the two stimulation sites. Individual differences in the absolute response amplitude for both digits and lips stimulation, which can be related to neuroanatomical differences in the extension of the receptive fields (Geyer et al., 2000) or to physical factors such as subject variability in the orientation of current sources relative to local radial direction, were removed by normalizing the source strengths with the amplitude of the first response in the train for each subject/condition. The averaged data across subjects indicate a general trend for the lips stimulation to evoke responses with a more pronounced decay of the relative amplitude as compared to the digits stimulation, particularly for the 2 Hz and 4 Hz stimulation rates. A similar observation holds for the second response in the train at 8 Hz, while the amplitude of the following responses in this case remains generally low and shows a slight oscillatory behavior. A similar oscillatory behavior with the serial position subsequent to the second response in the train was present in the data reported by Angel et al. (Angel et al., 1985).

Repeated measures one-way ANOVAs have been performed on the amplitude data from each stimulation site and rate to test for changes in response amplitude with the serial position of the stimuli within trains. This analysis indicated a main effect of serial position for the digits stimulation at each rate: 2 Hz ( $F=2.42$ ,  $p=0.048$ ), 4 Hz ( $F=3.91$ ,  $p=0.005$ ) and 8 Hz ( $F=33.31$ ,  $p<0.001$ ). Similarly, a main effect of serial position was present for the lips stimulation at each rate: 2 Hz ( $F=10.94$ ,  $p<0.001$ ), 4 Hz ( $F=12.1$ ,  $p<0.001$ ) and 8 Hz ( $F=33.97$ ,  $p<0.001$ ). For the lips stimulation condition, Bonferroni multiple-comparison tests indicated that the response amplitude to the first stimulus was significantly higher ( $p_s<0.05$ ) than each of the response amplitudes to subsequent stimuli (2-6) in the trains, at each stimulation rate. In turn, the paired comparison indicated that response amplitudes for stimuli 2-6 in each train were not significantly different from each other. For the digits stimulation condition, the response amplitude to the first stimulus in the train was significantly higher than the amplitudes of responses to subsequent stimuli (2-6) at 4 Hz and 8 Hz; for the rate of 2 Hz, the response amplitude to the first stimulus was significantly higher than the amplitude of the response to the last stimulus (6) in the train, but it was not



different from the amplitudes of the responses to stimuli 2-5. Regarding the differences in the amplitude of the responses to stimuli 2-6 in each hand stimulation run, the only significant difference was found between the amplitudes of the 2nd and 3rd responses for the digits stimulation at 4 Hz. This finding indicates that the rebound reflected in the noticeable increase in amplitude of the third compared to the second response (see figure 4) was significant across subjects.

A similar analysis was also carried out to test for changes in the response latencies with the serial position within the trains. This analysis showed no significant changes in response latencies with the serial position for the 2 Hz and 4 Hz stimulation rates at each stimulation site. However, it indicated a significant main effect of serial position at the 8 Hz stimulation rate, for both digits ( $F=4.29$ ,  $p=0.003$ ) and lips stimulation ( $F=6.68$ ,  $p<0.001$ ). Bonferroni multiple-comparison tests showed that at 8 Hz, latencies of the last four responses (3-6) for the digits stimulation condition were significantly longer (10.2 ms on average) than the first response latency. Similarly, at the 8 Hz stimulation rate, the latencies of the last three responses (4-6) for the lips stimulation condition were significantly longer (13.3 ms on average) than the first response latency.

Analysis of the response amplitudes demonstrated that the maximal decrement in amplitude generally occurs with the second response in each train. Further *incremental* attenuation with the serial position is small for the subsequent peaks, leading to a small cumulative attenuation effect that is seen only for the 2 and 4 Hz stimulation rates (figure 4, c-e). The observation that much of the response attenuation occurs between the first and second stimuli in the train is in agreement with previous reports of response suppression at the population level (e.g. Angel et al., 1985; Tomberg et al., 1989) or in single upper-layer cortical neurons (e.g. Lee et al, 1992). Following this observation, a quantitative measure of short-term response recovery in SI was estimated from the set of suppression ratios of second relative to first response amplitudes at each stimulation rate, as explained in *Methods*. Global fitting of the data from all subjects (figure 4, f, g) indicated a  $t_{50\%}$  value of 124.7 ms for the digits stimulation ( $r^2=0.59$ ), with the 95% confidence interval from 103.4 to 157.0 ms. For the lips stimulation, the lifetime of the response recovery had a longer value of 167.9 ms ( $r^2=0.44$ ), with the 95% confidence interval from 129.6 ms to 238.5 ms. The follow-up comparison using an extra sum-of-squares F-test indicated that the difference between the lifetimes for the digits vs. lips stimulation did not reach significance ( $F(1, 64)=2.9$ ,  $p=0.09$ ), with the mention that this test does not make explicit use of data pairing.

In a second analytic approach, lifetime values were fitted individually for each subject data (figure 4, h). In this case, the mean lifetime value for the digits stimulation was 130.7 ms ( $SD=40$  ms). As in the previous approach, the mean lifetime of the response recovery for the lips stimulation was longer, i.e. 166.3 ms ( $SD=57.9$  ms). The set of individual lifetime values in each stimulation condition passed a Kolmogorov-Smirnov normality test (KS distances of 0.21 and 0.19 for the digits and lips stimulation, respectively), and they were subsequently compared using a two-tailed, paired t-test. The results indicated that the difference between the recovery lifetimes was significant at the 0.05 level ( $t=2.7$ ,  $p=0.02$ ). Furthermore, a significant Pearson correlation coefficient ( $r=0.66$ ,  $p=0.014$ ) was observed between the lips and digits recovery lifetimes, indicating that a longer recovery in one stimulation modality was accompanied by longer recovery in the other stimulation modality, and therefore pairing was significantly effective.

As seen in figure 3, the responses from SI exhibit biphasic waveforms after each stimulus pulse, with the initial (upward) deflection followed by a broader component of opposite polarity. This raises the possibility that for stimulation with very short SOAs (e.g. corresponding to 8 Hz stimulation rate in our study) the initial upward response to the

second pulse (and the subsequent ones) in the train can be reduced in amplitude only because it overlaps temporally with the downward component of the response to the preceding pulse. To test the likelihood of such a simple linear summation of the responses accounting for the data, we applied for each subject and stimulation site a linear predictive model using the first response (selected from 0 to 500 ms) in the 2Hz train. These responses were added with their delayed versions (shifted in time with 125 ms) and the suppression ratios derived from the linearly predictive model were subsequently compared across subjects with the suppression ratios measured on the real data. The results showed that the ratios predicted by the model (digits stimulation:  $0.89\pm 0.18$ ; lips stimulation:  $0.81\pm 0.17$ ) were considerably higher than the ones obtained from the measured data (digits stimulation:  $0.42\pm 0.19$ ; lips stimulation:  $0.25\pm 0.22$ ). Using a paired *t*-test, these differences between the predicted and real data were found to be significant ( $t=10.37$ ,  $p<0.0001$  for the digits stimulation, and  $t=7.16$ ,  $p<0.0001$  for the lips stimulation). Thus, we conclude that the short-term adaptation analyzed in our study cannot be explained by the simple linear summation model and other significant neuronal interactions underlie the observed attenuation of the second relative to the first response.

#### 4. Discussion

The patterned pneumatic tactile stimuli applied to the glabrous skin of the fingertips and lips were shown to be effective in evoking cortical SEF responses in human SI, allowing for a comparative study of the induced cortical adaptation. Our results indicate that the adaptation patterns were different in the corresponding primary somatosensory areas with respect to two aspects: first, we observed a rate-dependent long-term adaptation effect induced by tactile stimulation of digits but not of the lips; second, we observed a different short-term recovery function between the two conditions, with shorter recovery lifetimes for the digits stimulation.

In a previous MEG study using electrical stimulation of the median nerve (Hamada et al., 2002), the mean estimated lifetime of the response recovery in SI was 110 ms (ranging between 50 ms and 200 ms across a group of five subjects). The mean lifetime value estimated in our study using tactile stimulation of the digits is similar to the mean value reported in that study, with slight differences likely arising in part from the different stimulation techniques used in the two studies. In contrast, no knowledge on the short-term cortical recovery functions has been previously gained using trigeminal somatosensory pathway stimulation.

Previous studies have hypothesized that the lifetime of the short-term cortical recovery functions can be linked to the duration of a *sensory memory* (e.g. Lü et al, 1992a; Uusitalo et al., 1996), also referred to as an *activation trace*. Auditory (Lü et al, 1992b) and somatosensory studies (Hamada et al., 2002) have shown that longer lasting activation traces (corresponding to longer recovery functions) are typically induced in *secondary* compared to *primary* sensory areas. These findings have been interpreted to indicate longer lasting integrative processes taking place in secondary sensory areas, and have been linked to a functional role that includes maintenance and integration of more temporally or spatially dispersed inputs. Our study has not focused on the activity evoked in secondary somatosensory cortex, primarily because the responses evoked in these areas were not robust and consistent across subjects using tactile stimulation. However, based on the hypothesis proposed by those previous studies, the different short-term recovery functions we observed for the digits and lips SI areas might be due to differences in receptive fields as well as to differences in the temporal scales over which the corresponding tactile information is integrated. The relative incidence of neurons with convergent inputs from multiple oral structures has been shown to be high in primary somatosensory areas in monkeys (Toda and

Taoka, 2004). These neuronal populations include a substantial number of neurons with bilateral and bimaxillary receptive fields from both upper and lower lips (with receptive fields primarily extending over the corresponding sites of the lips that come into contact when the jaw closes), or with composite receptive fields covering combinations of oral structures, such as lips, tongue and gingiva. Moreover, whereas temporal integration of sensory information from the thumb, index and middle fingers is frequently required when small objects are inspected (*e.g.* for texture detection) or manipulated (to provide feedback information that supports motor tasks, *e.g.* in precision grasping tasks), signals from the lips mechanoreceptors subserve the sensorimotor regulation of oral behaviors (Barlow, 1987; Johansson et al., 1988a; Johansson et al., 1988b; Nordin and Hagbarth, 1989; Nordin and Thomander, 1989; Rath and Essick, 1990; Trulsson and Essick, 1997). Afferents in the lips respond not only to contact with environmental objects, but most frequently to contacts between lips, teeth, or tongue tip, which accompany movements associated with speech, chewing and swallowing. Tactile input from the upper and lower lips has been hypothesized to support feedback information during such motor tasks (Gracco and Abbs, 1985, 1988; Barlow, 1998; Estep and Barlow, 2007). Under this assumption, motor control of orofacial movements during speech and of digits during fine manipulation would be dependent on continuous monitoring of superficial and deep mechanoreceptive sensory input. Single-neuron recordings in behaving monkeys have shown that the primary somatosensory area in particular may indeed play an important role in orofacial (Lin et al., 1994; Sessle et al., 2005) and hand/digit motor control (Liu et al., 2008; Gardner et al., 2007; Salimi et al., 1999; Wannier et al., 1991). Whereas the transient tactile inputs to the digits during active exploration or manipulation of small objects likely require fast integration over brief temporal intervals, tactile input to the lips associated with orofacial behaviors repeats and must be eventually maintained and integrated in primary sensory cortices or higher order cortical areas over slightly longer intervals. In support of this hypothesis are kinematic observations on the normal rhythms of orofacial movements associated with speech and mastication, where tactile input to the lips can be linked to the normal syllable or jaw cycle rates ranging from DC to 5 Hz (Barlow and Stumm, 2009).

The temporal distribution of the stimuli used in our study allowed segregation of a long-term adaptation effect that was present only for the digits stimulation and it was reflected in the rate-dependent amplitude changes of the response to the first stimulus in the train. This indicates that the lifetimes of short-term recovery functions for the hand SI (*i.e.* which are estimated from the ratios of second to first response amplitudes in each train) inherently incorporate these long-term adaptation effects. Hence, the shorter lifetimes observed for the digits stimulation reflect the interplay between physiological adaptation mechanisms that span different time-scales. Although additional studies are necessary to address this question satisfactorily, it is conceivable that the interplay between long- and short-term cortical adaptation may play a role in optimizing the detection of small, fast transient tactile stimuli during active exploration (such as for the discrimination of size, texture or shape) or fine object manipulation. Previous studies have indeed indicated that neuronal mechanisms underlying longer-lasting adaptation to vibro-tactile stimuli sub-serve an improved discrimination of supraliminal stimuli, at the expense of elevated thresholds for detection of liminal stimuli (Goble and Hollins, 1993; Goble and Hollins, 1994). Questions of interest that can be addressed in future studies are: (1) if/how these types of psychophysical correlates of adaptation are associated with long- and short-time adaptation in SI, as estimated from non-invasive SEF recordings; (2) if similar psychophysical results are obtained with somatosensory stimuli that are delivered to skin areas other than that of the hand; or (3) if/how such relationships would be altered in neurological conditions that produce selective loss of tactile sensitivity.

The observed differential SI adaptation patterns as a function of stimulation site may be partly attributable to the contributions of different peripheral sensory innervations of the fingers and lips (Barlow 1987; Johansson et al., 1988b).. In particular, along with the rapidly adapting (RA) mechanoreceptor afferents, the trains of cutaneous stimuli used with our paradigm are likely to co-activate Pacinian (PC) afferents in the fingers. Animal studies using metabolic mapping and optical intrinsic signal imaging have shown that PC afferent drive has a suppressive/inhibitory effect on SI responsivity during tactile stimulation, which can be mediated by their corresponding thalamocortical projections terminating selectively in layers I-II of SI or via inhibitory cortico-cortical interactions between SII and SI (Tommerdahl et al., 1999; Tommerdahl et al., 2005). Since the PC response is absent in the perioral skin (Barlow, 1987), one might expect the fingers' evoked response to experience a different pattern of adaptation. However, since the current study was not specifically designed to test this hypothesis., a more precise characterization of the role of PC afferents to the human SI adaptation patterns requires additional studies using stimulation methods that are optimized for their selective engagement.

Finally, two limitations of the current study must be acknowledged. First, the lifetimes of short-term recovery functions in SI have been derived from the suppression ratios at three stimulation rates. Although additional stimulation rates might have improved the robustness of estimating lifetime values, this was prevented by the need to record MEG data with somatosensory stimulation of two different sites (digits vs. lips), while keeping the overall duration of the experiment within acceptable limits for the participants. Second, the tactile stimulation was delivered in our experiment simultaneously at the tips of thumb, index and middle fingers, or at midline between upper and lower lips, to replicate behaviorally natural conditions that require functional integration of inputs from adjacent skin areas in each stimulation modality. Given the relatively long duration of the experiment, it was not possible to characterize precisely the specific role of each factor indicated by previous studies (Gandevia et al., 1983; Biermann et al, 1998) to be involved in the functional integration of tactile input, such as the number of stimulated skin sites (*i.e.* three sites for the digits and two sites for the lips) and their proximity, to the observed adaptation patterns. A typical approach to address this issue implies additional recordings for each stimulation site, with stimuli independently delivered to each of the functionally related areas (Okajima et al, 1991; Huttunen et al, 1992; Hsieh et al, 1995), or with stimuli delivered simultaneously at multiple skin sites in each condition (*i.e.* digits vs. lips) while varying the number and proximity of the stimulated sites. The potential change in the adaptation patterns with a systematic variation of these factors awaits therefore the results of future studies.

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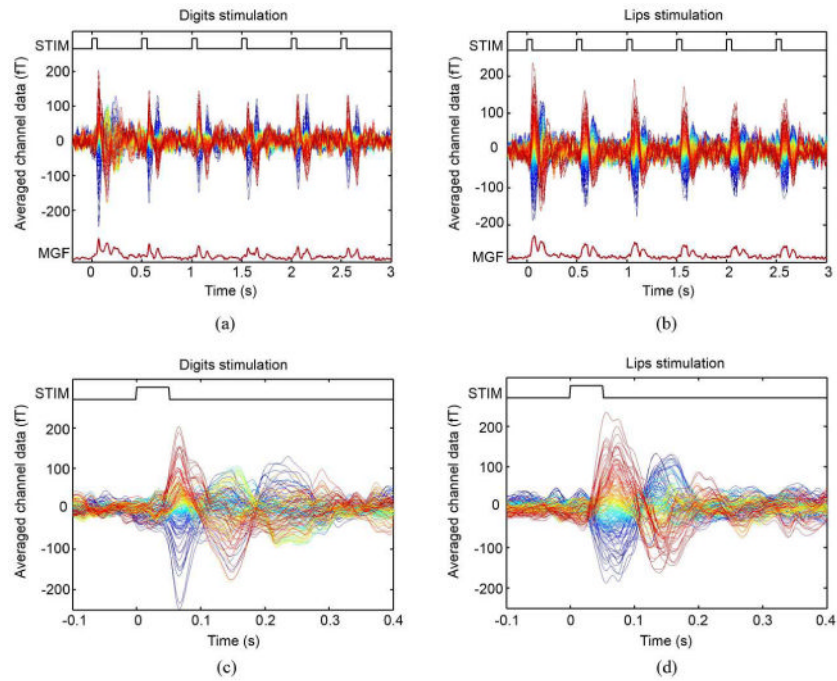
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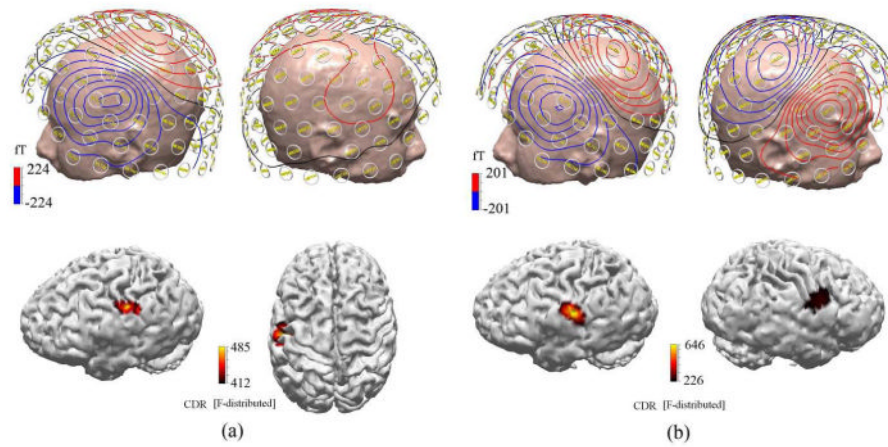
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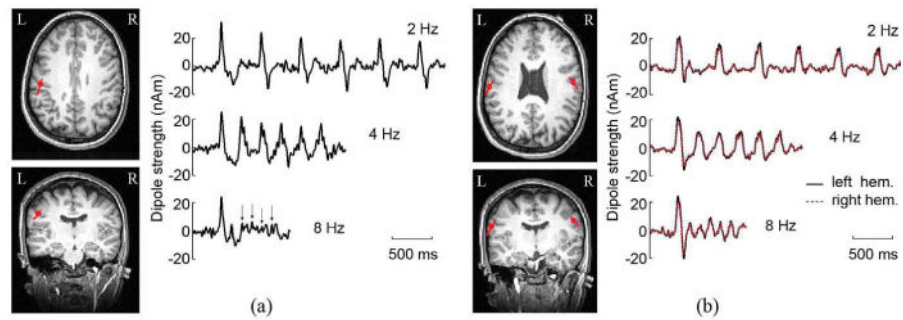


**Figure 1.** Neuromagnetic SEF for the digits (a) and lips (b) stimulation using stimulus trains with 500 ms SOA. The single red traces in the upper panels show the mean global field (MGF) computed across the whole channel array. The corresponding responses to the first pulse in the trains are displayed in panels (c) and (d).



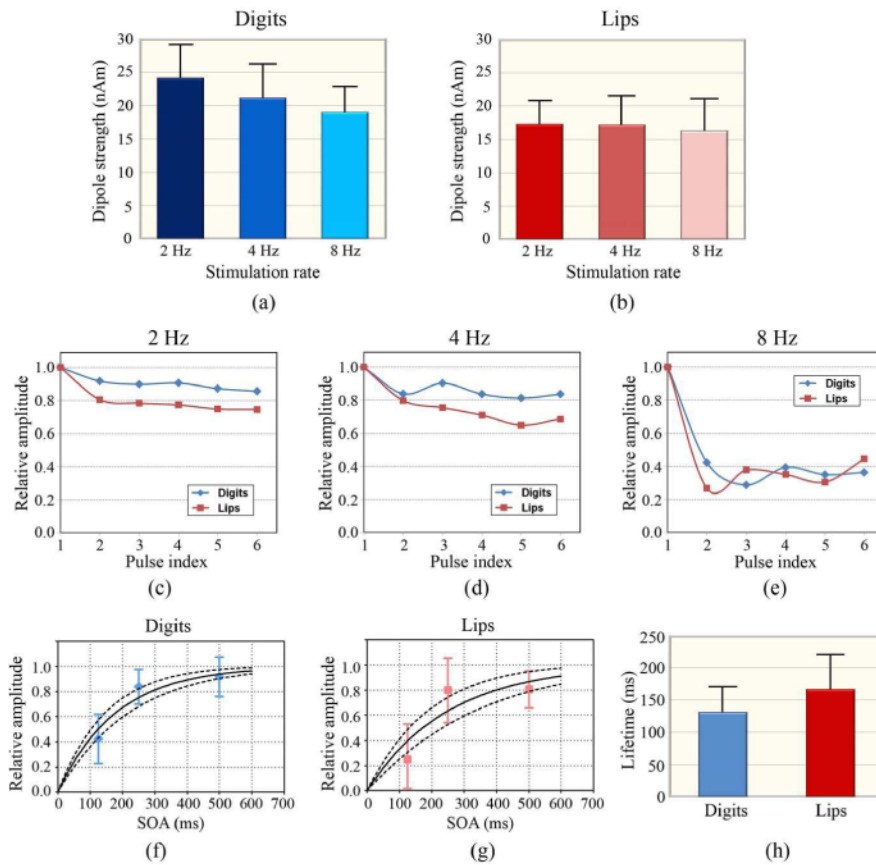


**Figure 2.** Magnetic field maps are shown in the upper panels at the peak latency of the SI response for the digits (a) and lips (b) stimulation conditions. The lower panels illustrate the corresponding results of current density analysis (sLORETA). The activity maps are shown on the cortical surface at the peak response to the first stimulus in the trains at 2 Hz, and are clipped at 75% of the spatial maximum of each source.



**Figure 3.**

Constrained dipole solutions for digits (a) and lips (b) stimulation. Dipoles locations and orientations are shown in orthogonal (axial and coronal) MRI slices. The dipole strengths across time are illustrated for each stimulation rate. Small arrows in panel a are used to aid visualization of the responses to the late stimuli at 8 Hz.



**Figure 4.** Adaptation effects in primary somatosensory cortex. Panels (a) and (b) show the absolute amplitude of the responses to the first pulse in the trains for the digits and lips stimulation, respectively, from runs with different stimulation rates. Panels (c)-(e) illustrate the mean relative peak amplitudes across subjects. The peak amplitudes were normalized in respect to the amplitude of the first response in the train for each subject/condition. Panels (f) and (g) show the results of the global fitting for the suppression ratios at different SOAs. Dotted lines mark the 95% confidence bands. Panel (h) shows the mean lifetime values when the model was fitted individually for each subject. Bars illustrate the standard deviations.

**Table 1**

S1 source locations (mean  $\pm$  standard deviations across subjects) are expressed in a Cartesian system of coordinates based on external landmarks on the scalp, with the x-axis going from left to right through pre-auricular points, y-axis from the back of the head to nasion, and z-axis pointing towards the vertex.

Digits stimulation			Lips stimulation					
Left hemisphere			Left hemisphere			Right hemisphere		
x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)	x (mm)	y (mm)	z (mm)
Mean	-44.9 $\pm$ 4.7	13.4 $\pm$ 12.7	90.7 $\pm$ 5.3	-50.1 $\pm$ 3.4	20.3 $\pm$ 12.7	79.5 $\pm$ 5.4	49.5 $\pm$ 5.4	23.1 $\pm$ 12.6
SD								78.3 $\pm$ 7.4