

Title:

Transient and steady-state responses to mechanical stimulation of different fingers reveal interactions based on lateral inhibition

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ABSTRACT

Objective: Simultaneous tactile finger stimulation evokes transient ERP responses that are smaller than the linear summation of ERP responses to individual stimulation. Occlusion and lateral inhibition are two possible mechanisms responsible for this effect. The present study disentangles these two effects using steady state somatosensory evoked potentials (SSSEP). Simultaneous stimulation on adjacent and distant finger pairs with the same and different stimulation frequencies are compared.

Methods: The index finger (IF), middle finger (MF) and little finger (LF) were mechanically stimulated with a frequency of 18, 22 or 26 Hz. Stimulation was applied for each finger separately, and for the IF (18 Hz) in combination with each other finger for all frequencies. IR was calculated for the P60 component and the SSSEP amplitude.

Results: Significant interactions were found in both the P60 response and in the SSSEP response. Stimulation of adjacent finger combinations caused more interaction than distant finger combinations. No difference was found between stimulation of two fingers with the same or a different frequency.

Conclusion: Our results indicate that lateral inhibition is mainly responsible for the interaction effect.

Significance: These observations provide further insight in the mechanisms behind interaction between somatosensory inputs.

INTRODUCTION

When part of the body is stimulated by tactile vibration at a particular frequency, a periodic electrophysiological brain response is elicited in the EEG activity. This response, called the steady-state somatosensory evoked potential (SSSEP), has the same frequency components as the driving tactile stimulus and sometimes also higher harmonics. The largest response amplitudes are typically observed for stimulation frequencies near 20 Hz (Muller et al. 2001, Tobimatsu et al. 1999). Simultaneous stimulation of the left and right index finger with two different frequencies elicits a SSSEP with both frequency components and spatial attention to one of the tactile stimulation sites can modulate this response (Giabbiconi et al. 2004). Attending to one of several stimulus trains results in an increase of the SSSEP amplitude of the frequency of the attended stimulus relative to the unattended stimuli.

Several studies using event related potentials (ERP) and fields (ERF) have described an interaction effect when two tactile stimuli are applied simultaneously (Biermann et al. 1998, Gandevia et al. 1983, Hoechstetter et al. 2001, Ishibashi et al. 2000). For a linear system, the response to two simultaneously applied stimuli should be equal to the sum of the responses to each stimulus separately. These studies have shown that the amplitudes of the event related potential (ERP) and field (ERF) components following simultaneous stimulation are in general smaller than the arithmetic sum of the amplitudes for separate stimulation. This process is known as sensory gating. Similar interaction effects have been found using electrical nerve stimulation (Ishibashi et al. 2000, Okajima et al. 1991) or using a combination of stimuli with different sensory or sensorimotor modalities (Abbruzzese et al. 1980, Cheron et al. 1991, Kakigi 1986). Several studies have shown that this deviation from linear addition is related to the physical distance between the two stimulation sites. The interaction is stronger when adjacent fingers are stimulated compared to simultaneous stimulation of non-adjacent fingers of the same hand (Biermann et al. 1998, Hsieh et al. 1995, Ishibashi et al. 2000, Tanosaki et al. 2002). These interaction effects have most often been described in finger or hand stimulation but have also been observed for other parts of the body (Kakigi et al. 1985, 1986, Naka et al. 1998).

Two neuronal mechanisms have been proposed to underlie this interaction effect. Gandevia et al. (1983) argued that the interaction effect might reflect occlusion at a subcortical or cortical level due to convergence of sensory inputs. A neuron responding to both stimulations separately might respond less vigorously in the condition of simultaneous stimulation. The total EEG response will then be less than the sum of the individual

responses. The second mechanism suggested to play a role is active lateral inhibition (Gandevia et al. 1983, Tanosaki et al. 2002). Two neuronal assemblies simultaneously activated by stimulation of two fingers might inhibit each other by lateral inhibition. Both hypotheses can explain the effect of distance between stimulation sites, because both convergence and lateral inhibition are stronger for stimulation of neighboring sites than for stimulation of more distant sites because of the somatotopically organized sensorimotor cortex. However, the timeframe in which these mechanisms operate is different. For occlusion the limiting factor is the refractory period of action potentials, which is about 1 or 2 ms. Therefore, only responses to spike inputs arriving within a few ms will be affected by occlusion. Lateral inhibition is mediated by a different mechanism involving inhibitory processes at a much longer time frame. The observation that the N20m response to paired stimulation is reduced for inter-stimulus intervals (ISI) shorter than 120-150 ms has been attributed to infield inhibition (Gardner 1984) or lateral inhibition (Forss et al. 1995). Furthermore, there are some indications that lateral inhibition is most likely responsible for the interaction effect (Costa et al. 2008, Huttunen et al. 1992). However, to our knowledge no study was able to clearly disentangle the two mechanisms.

The aim of this study was to investigate the interaction between responses to tactile stimulation of nearby and distant fingers at various stimulation frequencies to see whether we could discriminate between the two possible mechanisms for non-linear interaction. In order to do this, we started with investigating whether the non-linear interaction effect observed in ERPs and ERFs can also be observed in the steady-state response, which might be important for SSSEP-based applications. For example, simultaneous stimulation with different frequencies has been suggested as a method for finger representation mapping (Bardouille et al. 2008, Diesch et al. 2001, Pollok et al. 2002). Furthermore, the SSSEP, and more specifically its attentional modulation property, has been used in a brain computer interface (BCI) (Muller-Putz et al. 2006, Zhang et al. 2007). In a BCI the goal for the subject is to intentionally modify a brain signal that can be detected by a computer and then translated into a useful output for interaction with the environment (van Gerven et al. 2009). By attending to one of several tactile stimuli with a particular frequency, the SSSEP at this frequency is expected to be enhanced. The computer then can detect this modulation and thus can 'read' which finger was attended. Müller-Putz et al. (2006) showed that with this type of BCI classification rates can be achieved in the range between 53 and 88%.

To disentangle the interaction effects due to occlusion and lateral inhibition, we applied tactile stimuli simultaneously and slightly shifted in time on adjacent and distant fingers. For

simultaneous stimulation we used the same stimulation frequency for both fingers. We also used two different stimulation frequencies on two fingers, because then most tactile stimulus taps do not arrive at the same time. We hypothesized that if occlusion is causing the interaction effect, the interaction will be stronger when identical stimulation frequencies are used than when different stimulation frequencies are used. If lateral inhibition is responsible for the interaction, this interaction will be similar when equal or different stimulation frequencies are used.

METHODS

Participants

Nine healthy volunteers (age range: 21 to 34 yr, 5 male, 4 female) participated in this experiment. All subjects were healthy and none of the subjects was ever diagnosed with any neurological disorder. The experiment was approved by the ethical committee of the faculty of social sciences at the Radboud University Nijmegen.

Stimuli/Materials

Piezo-electrical Braille stimulators were used to mechanically stimulate the fingertips. Four Braille stimulators were situated on five stacked discs forming a cylinder, which the subjects could grasp with the right hand (see Figure 1). Each Braille stimulator had two rows with four pins each. We used square-wave pulses which pushed all pins out by about 0.5 mm. The frequency of stimulation varied per condition (see Table 1). Each disc could be rotated to ensure full contact of the Braille stimulators with the finger tips. In this experiment only the second, third and fifth Braille stimulators were used, stimulating the index finger, middle finger and little finger.



Figure 1. Braille stimulators are placed inside five stacked disks. The disks of the cylinder could be rotated individually to adjust optimal placement of the Braille stimulators on the fingers of the subject, when he grasped the cylinder.

The standard method for looking at interaction effects is by comparison of the responses to simultaneous stimulation of two fingers with the sum of the responses to separate stimulation of each finger. As a control stimulus, the index finger (IF) of the right hand was stimulated at 18 Hz. An interfering stimulus was applied to another finger on the same hand separately or simultaneously with the control stimulus. To test for a spatial proximity effect the index finger was stimulated together with the middle finger (MF) and the little finger (LF). To investigate an effect of stimulation frequency, three frequencies (18, 22 and 26 Hz) were used as interfering stimuli. Table 1 gives an overview of all stimulation conditions.

Table 1. Overview of the various stimulus combinations in this study. The control stimulus (S1) corresponds to stimulation of the index finger at 18 Hz and is the same in each condition. The interfering stimulus (S2) is specific for each combination. The simultaneous stimulation (SIM) corresponds to the combination of S1 and S2. IF, MF and LF refer to index finger, middle finger and little finger, respectively. The number after IF, MF and LF refers to the stimulation frequency. ADJ = adjacent (i.e. simultaneous stimulation of index finger and middle finger), DIST = distant (i.e. simultaneous stimulation of index finger and little finger), SAME = same stimulation frequency, DIFF = different stimulation frequency.

Interaction Combination	Stimulation Condition		
	S1	S2	SIM
ADJ_SAME	IF18	MF18	IF18 & MF18
ADJ_DIFF_22	IF18	MF22	IF18 & MF22
ADJ_DIFF_26	IF18	MF26	IF18 & MF26
DIST_SAME	IF18	LF18	IF18 & LF18
DIST_DIFF_22	IF18	LF22	IF18 & LF22
DIST_DIFF_26	IF18	LF26	IF18 & LF26

Electrophysiological recordings

EEG was recorded with 256 (5 subjects) or 64 (4 subjects) sintered Ag/AgCl active electrodes referenced to the mean of all electrodes. The EEG signals were amplified using a Biosemi ActiveTwo AD-box and digitized at a sampling rate of 2048 Hz. To ensure good recordings, values for offset amplitude and jitter in offset were kept below 25 mV and 0.2 mV, respectively.

Data was preprocessed off-line to remove artifacts using the following steps. First the data was down-sampled from 2048 Hz to 512 Hz. Then EEG channels, which had artifacts, were identified for rejection for each trial. Criteria for rejection were based on thresholds for

offset amplitude (~ 35 mV), power around the 50 Hz bin ($6 \mu\text{V}^2$) and the maximum derivative of the signal (150 mV per sample). In some channels there was leakage of the tactile stimulation signal into the EEG signal. This was obvious when an electrical artifact of the tactile stimulation signal was observed in the EEG with a negligible latency, too small for neuronal conduction delays. In order to detect these channels, we have used tactile pseudo random noise codes (Farquhar et al. 2008, Marmarelis et al. 1978) to measure the time lag of the stimuli at each channel. These codes have an autocorrelation equal to zero, except at time lag zero. Regression analysis of the EEG with the stimulation code peaks at the time delay of the presented noise code in the EEG. Channels with signals that are significantly correlated to the stimulus with a small time delay were removed from further analysis. After bad channel removal the signals were re-referenced to an average over the remaining channels. Subsequently, the 256 electrode data was spatially down-sampled to the standard 10-20 layout (Jasper 1958) with 64 electrodes using spherical spline interpolation (Perrin et al. 1989). A set of frontal and occipital electrodes was removed from the 64 electrode data for further analysis because of eye-movement artifacts and large alpha waves, which obscured an accurate estimate of the ERP responses. The position of the remaining electrodes that have been used in this study are indicated by black dots in Figure 4. Finally linear trends were removed from the data.

Procedure

After electrode placement subjects were seated in an electrically shielded room in front of a computer screen. Subjects were instructed to look at a fixation cross during the recordings to avoid eye movements as much as possible. The data was recorded in four blocks. In the first two blocks only the reference frequency (18 Hz) was used (conditions ADJ_SAME and DIST_SAME). The other four conditions were tested in the last two blocks. Each block consisted of 8 sequences with 32 or 36 trials each. A trial consisted of a rest period of 0.5 seconds and a stimulation period of 2.5 seconds. In some of the rest periods the pins of one Braille cell were moved in and out once. Subjects were instructed to count how many of these short stimuli in the rest periods occurred within one sequence. This task was only used to assure that subjects paid attention to the tactile stimuli. A schematic overview of three successive trials is shown in Figure 2. To mask any sound produced by the stimulators, pink noise was played over loudspeakers, both during the rest and stimulation period. Each stimulation condition was repeated 64 times. The order of trials was randomized.

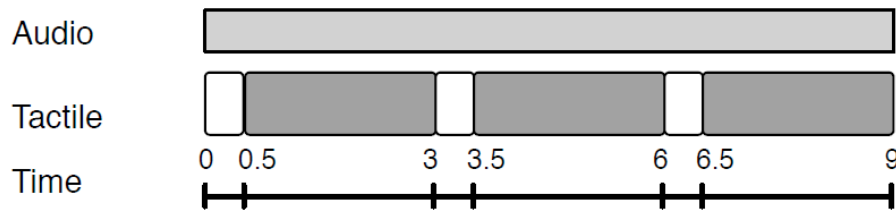


Figure 2. Schematic overview of three trials. The audio track consists of pink noise, which was adjusted per subject to the minimum sound level that masked the sound of the tactile stimulators. In the tactile stimuli there is a stimulation period of 2.5 seconds (dark grey area) and a rest period (white area) in which there was no tactile stimulation.

Data analysis

Data signals were analyzed using Matlab 7.4.0 (The Mathworks, Natick, MA). Because we were interested in non-linear interactions for simultaneous stimulation of two fingers compared to the amplitude of responses to separate stimulation of these fingers, an interaction ratio was calculated. This interaction ratio was defined as the ratio of amplitude of the ERP in the simultaneous stimulation, and the arithmetic sum of the two ERP responses for separate stimulation of the fingers. Interaction ratios were calculated with the following equation (adapted from Hsieh et al. 1995):

$$IR = -\log_2\left(\frac{SIM}{S1 + S2}\right) \quad (1)$$

in which IR is the interaction ratio, SIM represents the response amplitude for simultaneous stimulation, and S1 and S2 are the response amplitudes for separate stimulation. In this way six interaction ratios were calculated (see Table 1). If the interaction ratio is equal to zero, the amplitude of the simultaneous stimulation is a simple linear addition of amplitudes in the two individual stimulations. If the interaction ratio is positive, there is an attenuation of the amplitude. Likewise, if the interaction ratio is negative, simultaneous stimulation causes facilitation.

ERP

For the ERP analysis epochs from 300ms before to 600 ms after the start of the stimulation were used. The data in these epochs were analyzed using a few extra preprocessing steps. Epochs containing artifacts, such as eye blinks, were rejected from further analysis if the standard deviation (SD) of a frontal electrode (Fpz) was 1.7 times larger within a sliding window of 250 ms than the average SD of the whole epoch.

Furthermore, the EEG was filtered with a band-pass filter of 2-45 Hz. The ERPs in the time interval from -150 to 200 ms relative to onset of the stimulus were base-lined with the average amplitude over the 150 ms preceding the stimulus. This results in a vector S_i per condition for channel i , with $1 \leq i \leq N$, in which N is the total number of channels. The components S_{ij} correspond to the j time samples of the ERP signal with $1 \leq j \leq M$ in which M corresponds to the length of the ERP signal. A template ERP response was calculated based on the average response over all subjects. This template was then windowed around the start of the first clearly visible positive and the end of the subsequent negative peak with a smooth cosine window, to focus on the transient response only. To find the transient response with a high signal-to-noise ratio, the windowed template was then used to create a normalized spatial filter per subject and stimulation condition, which was then applied to the averaged ERP per subject and condition with the following equation

$$F = \frac{XT}{\|XT\|} \quad (2)$$

in which X is a matrix with in each row the pre-processed, base-lined, and averaged ERP response S_i of channel i . T is a vector with the windowed template (in time), $\|XT\|$ is the Euclidean norm of XT , and F is the spatial filter. On the base-lined ERP response this spatial filter is then applied by multiplication ($X_F = F^T X$) resulting in one temporal response for each subject and condition (X_F). From the spatially filtered response the amplitude of P60 was determined. The peak amplitude of this P60 response was used to calculate the interaction ratio of the transient ERP response.

SSSEP

For the SSSEP analysis the epoch of interest started 500 ms after onset of the stimulation and lasted to the end of the stimulation period. This insured that no ERPs evoked by the start of a stimulus contaminated the steady state data. Per subject a spatial filter (G) was calculated. G was defined as the eigen vector of the covariance matrix WW^T with the largest eigen value. Here W is a vector with the power of the mean EEG response over all conditions band-passed at the control stimulus frequency (18 Hz). The largest component was selected because this component explains most of the variance in the data. The EEG time-series averaged over trials per subject and condition (Y) was then multiplied with this spatial filter ($Y_G = G^T Y$). On these spatially filtered EEG signals (Y_G), the frequency spectrum was calculated for each condition, with a Fast Fourier Transform (FFT). The interaction ratio was calculated on the sum of the amplitudes in the three frequency bins of interest (18, 22 and 26 Hz).

Statistical analysis

To test for significant interactions ($IR > 0$) and differences between finger combination (adjacent vs distant) and frequencies of stimulation (SAME vs DIFF-22 and SAME vs DIFF-26), a within subject randomization test was used (Maris et al. 2007).

RESULTS

ERP

Figure 3a shows a superposition of the ERP responses (the vectors S_i) for all subjects averaged over stimulation conditions. A clear positive peak with a latency of about 60 ms and a negative peak near 90 ms after stimulus onset are visible. This negative peak was not consistently present in all subjects and all stimulation conditions. Therefore, the interaction ratio was based only on the peak amplitudes of the P60 response. Figure 3b shows the windowed template ERP (T) created from the grand average ERP data, which was used to build the spatial filter (filter F in equation 2).

Figure 4 shows a representative example of such a spatial filter for stimulation of the index finger at 18 Hz. The weights of the spatial filter resemble the activation pattern of the P60 response. In this case an ipsilateral fronto-central and a contralateral central-parietal activation area can be seen. However, the distribution of the weights of these spatial filters differed depending on the finger that was stimulated. Such differences in distribution for stimulation of different fingers were found in all subjects. Therefore these individual spatial filters for each stimulation condition were used for further analysis.

Figure 5 shows the grand average of the spatial filtered ERP response (X_F) for the combinations of adjacent (Fig. 5a) and distant finger (Fig. 5b) stimulation by 18 Hz. In general, simultaneous stimulation results in a smaller P60 response than the sum of the individual stimulations. The peak P60 response was used to calculate the IR per interaction combination and these were then used to for statistical analysis. Figure 6 shows these IRs. The dark bars indicate data for the adjacent finger combination and the light bars indicate the data for distant finger combination. Bars are grouped by stimulation frequencies. All interaction combinations show a suppressive interaction effect (i.e. $IR > 0$, $p < 0.05$).

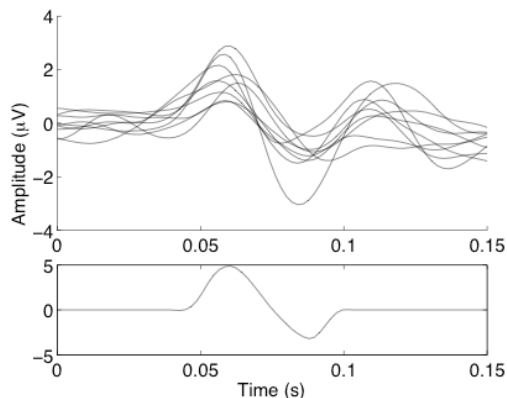


Figure 3. a) Superposition of ERP response (S_i) for all subjects obtained by averaging over all stimulation conditions for electrode CP5. A P60 and N90 response can be seen. b) Windowed temporal template ERP. This template was correlated with the EEG data to create a spatial filter for the 64 electrode EEG data.

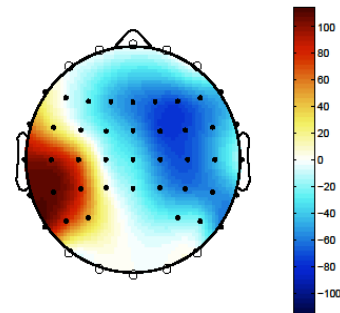


Figure 4. Example of a spatial filter for subject HG in arbitrary units. This figure shows the topography of the filter for the 18 Hz index finger stimulation, resembling the activation pattern of the P60 response. Black dots indicate the electrodes used for analysis. To reduce extrapolation in the plotting, electrodes on the edge of the head plot (circles) are included with zero weights.

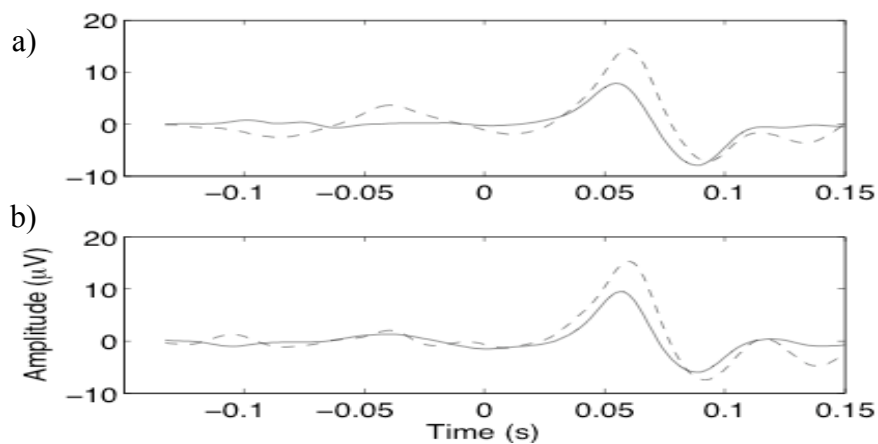


Figure 5. Grand average of the spatial filtered ERP for the adjacent (a) and distant (b) finger combination stimulated with the reference frequency. The plots show the ERP responses to the simultaneous stimulation of both fingers (solid line) and the sum of both single stimulations (dashed line).

There was a trend for larger interaction for the adjacent finger combination than for the distant finger combination, in both the SAME (5 out of 9 subject) and DIFF-22 (6 out of 9 subjects) frequency combination. These differences, however, were not significant ($p=0.06$ and $p=0.13$ for the SAME and DIFF-22 respectively). No differences between stimulation frequency combinations (SAME vs DIFF-22 and SAME vs DIFF-26) within the adjacent finger combination (dark bars) were found. In the distant finger combination, the IR for the

DIFF-26 frequency combination is larger than for the SAME frequency combination. This difference, however, was not significant ($p=0.053$).

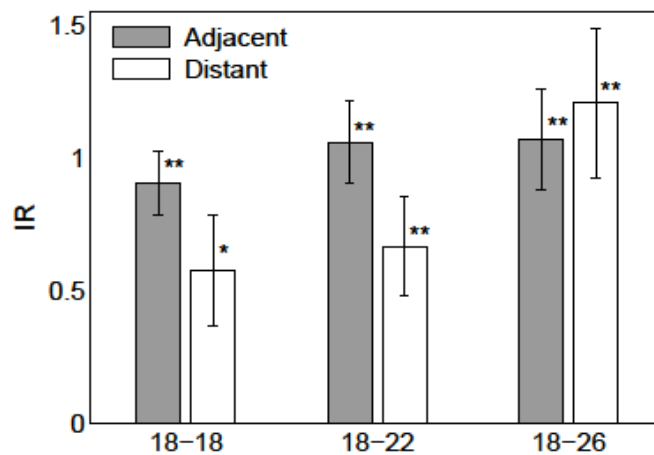


Figure 6. Interaction ratios calculated for the ERP responses to onset of stimulation. Bars are grouped by the three stimulation frequency combinations (SAME, DIFF-22 and DIFF-26). Dark bars represent the adjacent conditions and white bars the distant conditions. Asterisks indicate significant suppressive interaction ($IR > 0$), * $p < 0.05$, ** $p < 0.01$.

SSSEP

Figure 7 shows the filter weights of the spatial filter (G), indicating that the SSSEP is most pronounced at two activation sites; a fronto-central and a central-parietal electrode group. A typical temporal response of the spatially filtered data (Y_G) is shown in Figure 8. This figure shows a clear SSSEP during the stimulation period, which is much larger than during the rest period. Just after the start of the stimulation, the SSSEP builds up and decreases back to baseline level after the end of the stimulation.

The amplitude spectrum of the spatially filtered EEG response to the individual IF18, MF22 and the simultaneous IF18&MF22 is shown in Figure 9 for subject LR. The peaks in the SSSEP frequency spectrum correspond to the stimulation frequencies at 18 and 22 Hz. This figure shows that the amplitude of the signal at the stimulation frequencies is smaller for the combined stimulation condition than for linear summation of individual stimulation responses. The decreased response to the combined stimulation is reflected in the interaction ratio, which was used for statistical analysis and is shown for all interaction combinations in Figure 10. Interaction ratios for all stimulation combinations were larger than zero, indicating a suppressive interaction ($p < 0.05$).

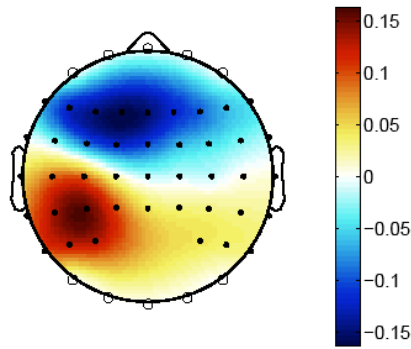


Figure 7. Filter weights in arbitrary units of the SSSEP spatial filter (G) averaged over subjects, showing a fronto-central and central-parietal activation area. Black dots indicate the electrodes used for analysis. To reduce extrapolation in the plotting, electrodes on the edge of the head plot (circles) are included with zero weights.

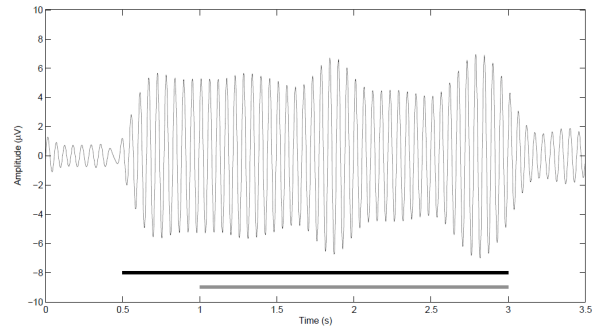


Figure 8. Example spatial filtered EEG data (Y_G , see methods) filtered (around 18 Hz for the IF18MF18 stimulation condition of subject 6. The black line indicates the stimulation period, the grey line the SSSEP analysis epoch. In the rest period there is a baseline level of 18 Hz activity, due to normal EEG activity. During stimulation a clear increase in this 18 Hz activity can be seen, giving rise to the SSSEP.

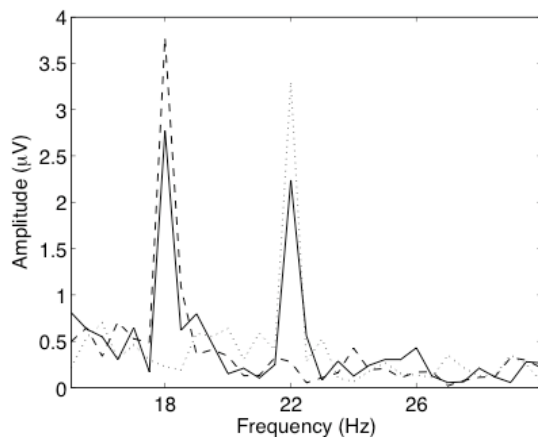


Figure 9. Amplitude spectra of the steady-state response (Y_G) of the index finger stimulation (18 Hz, dashed line) middle finger stimulation (22 Hz, dotted line) and the simultaneous stimulation (solid line) for an example subject (LR).

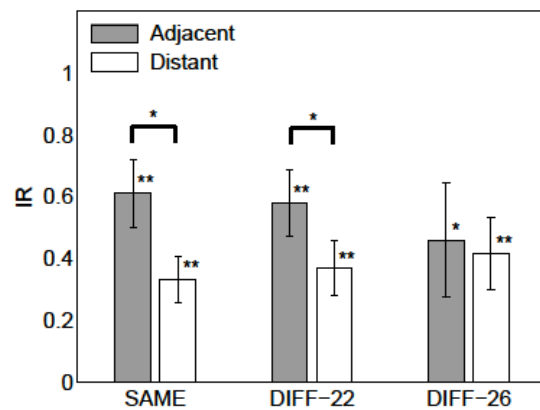


Figure 10. SSSEP Interaction ratios during the steady-state stimulation periods. Bars are grouped by the three stimulation frequency combinations (SAME, DIFF-22 and DIFF-26). Dark bars indicate the adjacent conditions and white bars indicate the distant conditions. Asterisks indicate significant suppressive interactions ($IR > 0$), brackets indicate significant differences between adjacent and distant conditions * $p < 0.05$, ** $p < 0.01$.

An effect of spatial proximity was also found in the SSSEP interaction ratios. For the SAME and DIFF-22 stimulation conditions the mean interaction ratio for the adjacent finger combination was significantly larger than for the distant combination, (8/9 subjects and 9/9 subjects respectively; $p < 0.05$). The difference between the interaction ratios for the adjacent and distant finger combination for the DIDFF-26 stimulation frequency was not significant. As in the ERP interaction ratios, the interaction ratios of the SSSEP responses did not significantly differ for different stimulation frequency combinations (SAME vs DIFF-22 and SAME vs DIFF-26), neither for the adjacent nor for the distant finger combination.

DISCUSSION

In the present study we have investigated the interaction effect on ERP's and SSSEP's for combined tactile stimulation of adjacent and distant fingers at different stimulation frequencies. Both in the ERPs and SSSEP's, an interaction was found for all stimulation conditions indicating that the response to simultaneous tactile stimulation is significantly less than the linear summation of the responses to separate stimulation. A significantly larger interaction was found for adjacent stimulation relative to distant stimulation for the SSSEP's, in the SAME and DIFF-22 frequency combination. Variations in stimulation frequency (SAME and DIFF conditions) did not result in significantly different interaction ratios for the ERP's and SSSEP's.

The average weights of the spatial filter for the steady state responses indicate which electrodes have high amplitude signals at the stimulation frequency. The topography of these filter weights corresponds well with the topography of SSSEP responses reported in previous studies. For example, Giabbiconi et al. (2004) found greatest SSSEP amplitudes at frontal and fronto-central electrodes. Moreover, Pollok et al. (2002) reported that the SSSEP responses in MEG could be explained by a single dipole in S1. This observation, together with the very similar interaction results for the ERP and SSSEP responses provides strong evidence that similar neuronal structures underlie the interaction effects.

The aim of this experiment was to use stimulation at different frequencies to distinguish between the effects of occlusion and lateral inhibition. The idea was that if occlusion was the underlying mechanism for the interaction, a stronger interaction would be observed for simultaneous stimulation of two fingers at the same frequency compared to stimulation at different frequencies. This differs from the effects that would be predicted if lateral inhibition would be responsible for the interaction effect. As mentioned before, lateral inhibition has a

much longer timeframe of 150 ms (Forss et al. 1995). For the optimal SSSEP stimulation frequencies the time between subsequent tactile stimuli is within this period. In this experiment, this time was between 38 ms (corresponding to 26 Hz stimulation) and 56 ms (corresponding to 18 Hz stimulation). Therefore, lateral inhibition predicts an attenuation for simultaneous stimulation for all frequencies in this range, independent of whether the stimulation frequencies are the same or different. Our results show an interaction effect for all stimulus conditions and all stimulation frequencies. Furthermore, no significant stronger interaction was found when stimulating with the same frequency compared to stimulating with different frequencies. These results provide support of lateral inhibition as the main mechanism for the interaction effect.

Interaction of somatosensory impulses has been found at different levels of the somatosensory pathway, from brainstem to cortex (Costa et al. 2008, Hsieh et al. 1995). The recovery time of these interaction effects differs between subcortical and cortical responses. The interaction effects in the thalamus have a recovery time of about 40 ms, which implies that ISIs longer than 40 ms will not evoke interaction effects (Costa et al. 2008). These results are compatible with the notion that active lateral inhibitory processes rather than occlusion effects underlie the thalamic interaction effects. In somatosensory cortex the recovery of early cortical responses, such as the N20 component, however, continues after 50 ms (Costa et al. 2008) and can be as large as 120 to 150 ms (Huttunen et al. 1992, Wikstrom et al. 1996). Quite surprisingly, later components like the P60 are attenuated for ISI's as large as one second (Wikstrom et al. 1996). All these results are in favour of the hypothesis that long lasting inhibitory processes, such as lateral inhibition, are the cause of these interaction effects.

A comparable interaction effect with continuous frequency stimulation has been described in cats using optical imaging (Tommerdahl et al. 1999). In that study the effect of combined flutter (up to 50 Hz) and vibration (50 Hz and higher) stimulus was investigated. They found that the increase in absorbance in S1 that is found with pure flutter stimulation was less when a combination stimulus of flutter and vibration was applied. The authors concluded that vibration stimulation has a powerful inhibitory action on S1. Our results show, however, that this inhibitory action is not restricted to vibration stimulation; simultaneous flutter stimulation has a similar effect.

Interaction of the P60 component in the ERP has most often been investigated by simultaneous transient stimulation on multiple sites (Gandevia et al. 1983, Hsieh et al. 1995, Ishibashi et al. 2000, Simoes et al. 2001). This is comparable with our SAME frequency

interaction combinations. However, the results for the interaction ratio for simultaneous stimulation in the literature are contradictory. Some studies have shown a significant interaction effect and an effect of spatial proximity (Hoechstetter et al. 2001, Ishibashi et al. 2000). As far as one can judge the degree of interaction was comparable with the interaction found in the current study. On the other hand, Tanosaki et al. (2002) did not find a significant interaction on the P60 component. However, this study is less comparable to our study, because two modalities (electrical and tactile stimulation) were used in the former. With respect to the effect of adjacent versus distant stimulation of fingers, we did find a (non significant) trend in that the interaction effect tended to be smaller for distant finger stimulation. This trend may reflect a true effect in agreement with the results of Hoechstetter et al. (2001) and Ishibashi et al. (2000).

The current findings show that the interaction effect of simultaneous stimulation of two fingers in transient ERP responses can also be observed in the steady-state signal. Furthermore, in some frequency combination conditions a difference was found between stimulating an adjacent or distant finger simultaneously in both the ERPs and SSSEPs. The interaction was stronger in the adjacent compared to the distant stimulation combination, which is in agreement with previous findings (Biermann et al. 1998, Hsieh et al. 1995, Ishibashi et al. 2000, Tanosaki et al. 2002). This spatial proximity effect in the ERP and SSSEP is probably caused by the adjacent finger representations in SI. In area 3b the receptive fields are somatotopically organized in the order of the fingers and there is only a small overlap (Hsieh et al. 1995, Ishibashi et al. 2000). Hence, lateral inhibition and convergence could cause a stronger interference effect in adjacent fingers compared to distant fingers. In other sensory areas there is more overlap and the finger representations are not in the same order. This may explain why the effect of distance between stimulation sites is only observed in SI, and not in SII (Hsieh et al. 1995, Ishibashi et al. 2000).

The mechanisms, by which occlusion and lateral inhibition are hypothesized to cause interaction effects, depend on the assumption that the output of neurons in S1 is coupled to the input from afferents. Evidence in favor of this assumption is provided by research on the coding of stimulation frequency in SI, which is the major source of the SSSEP. Mountcastle et al. (1990, 1969) showed in primates that not the mean firing rate, but rather the periodicity of the spikes discriminates between frequencies. This means that while the number of spikes stays the same for different stimulation frequencies, the temporal order of the spikes is indeed coupled to the vibration cycle of the tactile stimulus. This effect is also known as entrainment (Whitsel et al. 2001).

The brain receives a massive amount of sensory information from the whole body. For normal CNS function it is important that relevant sensory information is selected from multiple concurrent sources. The interaction effects described in this paper most likely have a role in this perceptual filtering (Costa et al. 2008) which can serve as protection of pre-attentive stimulus processing (Graham 1992). Another functional role of interaction between simultaneous stimuli could be facilitation of sensory integration. Hamada and Suzuki (2003) showed that interaction effects are modified by an open or closed hand posture. In early responses stronger interactions were found in the closed hand position compared to the open hand position. This modification corresponds to the sensory integration that is necessary for the different functional roles of these hand postures. A closed hand posture is used for picking up small objects for which a high spatial precision is necessary. The stronger lateral inhibition seen by the higher interaction ratios could facilitate this. More generally, the role of lateral inhibition may be linked to a facilitation of independent finger movement (Zatsiorsky et al. 2008).

In conclusion, the current results show that interaction effects between responses of simultaneous stimulation occur in SSSEP as well as in ERP responses. The interaction for both responses is influenced in a similar way by different stimulation sites and frequencies. This suggests that similar processes are responsible for these effects. More importantly, we have shown in SSSEP responses, that inhibitory processes are the most likely cause for the interaction effects.

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