Subarea-specific Suppressive Interaction in the BOLD Responses to Simultaneous Finger Stimulation in Human Primary Somatosensory Cortex: Evidence for Increasing Rostral-to-caudal Convergence

In the primary somatosensory cortex (SI) of non-human primates, receptive field properties have been shown to differ between its subareas with increasing convergence in areas 1 and 2 as compared with area 3b. In this study, we searched for a similar functional organization of human SI. We performed fMRI in healthy subjects during separate or simultaneous electrical stimulation of the second and third finger of the right hand. Activation patterns in response to stimulation of single fingers reflected the somatotopical arrangement within the hand area of SI. Somatotopy was more clear-cut in area 3b as compared with areas 1 and 2. The response to simultaneous stimulation was considerably smaller than the summed responses to separate stimulation of each finger alone, pointing to a suppressive interaction effect. A region-of-interest analysis in the representational areas of the second and third finger revealed subarea-specific differential suppressive interaction with an increase along the rostro-caudal axis (areas 3b, 1 and 2: 26, 32.7 and 42.2%, respectively). These findings on differences in the topographic as well as functional organization between subareas of SI support the notion of increasing convergence and integration from area 3b to areas 1 and 2 in human subjects.

Keywords: electrical stimulation, fMRI, SI, somatotopy, suppressive interaction

Introduction

The primary somatosensory cortex (SI) of primates constitutes the main projection area of somatosensory afferents and comprises four different cytoarchitectonical subdivisions (areas 3a, 3b, 1 and 2) oriented along the rostro-caudal axis of the postcentral gyrus (Brodman, 1909; Vogt and Vogt, 1919). Each area contains a representational map of the contralateral body surface (Merzenich et al., 1978; Kaas et al., 1979; Nelson et al., 1980; Pons et al., 1985). However, convergence of afferents from adjacent body areas seems to differ between subdivisions of SI. Whereas neurons in area 3b have receptive fields restricted to single fingers or even parts of single fingers, neurons in the more caudally located areas 1 and 2 have increasingly larger receptive fields (Iwamura et al., 1980, 1983a,b, 1993; Iwamura, 1998).

Evidence has been given that processing of simultaneous multi-site stimulation differs from single-site stimulation, i.e. the responses of two simultaneously applied stimuli do not add up linearly, pointing to an underlying suppressive interaction process. Such effects have been observed in SI in animal studies, e.g. by intracortical recordings of excitatory postsynaptic potentials in response to stimulation of different forelimb nerves in the cat (Macgillis et al., 1983), and in the rat during simultaneous whisker and forelimb stimulation using optical intrinsic signal imaging (Blood and Toga, 1998). For humans, interaction has been found to already emerge at the subcortical level, but it occurs predominantly in SI (Hsieh et al., 1995). In early cortical somatosensory-evoked potential (SEP) components, the responses to simultaneous stimulation of two fingers of the same hand are considerably smaller than the summed responses to separate finger stimulation (Gandevia et al., 1983; Hsieh et al., 1995). Comparable results have been obtained employing magnetoencephalography (MEG) (Biermann et al., 1998; Ishibashi et al., 2000; Hoechstetter et al., 2001). In SEP recordings, interaction was reported for components presumably generated in area 3b as well as in area 1, whereas in somatosensory-evoked fields (SEFs) interaction was demonstrated mainly for area 3b, since this method is essentially sensitive to tangentially orientated sources. Though both techniques allow for a more direct measurement of neuronal activity at high temporal resolution, the accuracy of assigning the contributions of the different subareas of SI to the measured signals is limited. In comparison, functional magnetic resonance imaging (fMRI) offers the complementary advantage of obtaining temporally integrated responses that can be allocated to the anatomical structures of the postcentral gyrus with larger accuracy.

fMRI is capable of resolving the somatotopic representations in different subdivisions in human SI when fingers are stimulated separately (Gelnar et al., 1998; Kurth et al., 1998; Maldjian et al., 1999; Francis et al., 2000; Kurth et al., 2000; Ruben et al., 2001; Deuchert et al., 2002). In the current study we applied event-related fMRI at high spatial resolution during separate as well as simultaneous electrical stimulation of two adjacent fingers to address the following questions:

Which subdivisions within SI exhibit interaction?
Are there quantitative differences in interaction between the subdivisions of SI?

Material and Methods

Subjects

Twelve healthy volunteers (eight male; mean age 26.7 years, range 23-31 years; 11 right-handed, one left-handed) without any history of neurological or psychiatric disease participated in this study. The study was approved by the local ethics committee and written consent was obtained from each subject prior to investigation.

Stimulus Application

Somatosensory stimulation consisted of innocuous electrical stimuli generated by two constant-current stimulator devices (Digitimer Limited, Welwyn Garden City, Hertfordshire, UK). The following stimulation conditions were applied: separate stimulation of the second finger, separate stimulation of the third finger, and simultaneous stimulation of the second and the third finger of the right hand (Fig. 1A).
Stimuli and additional null events were presented in a randomised order with a range of ISIs varying from 3 to 9 s at 1 s steps (mean ISI of 6 s). The sensory as well as the third finger at an uncorrected threshold were 7.0 ± 0.2 mA (mean ± SD) for the second finger and 1.6 ± 0.2 mA for the third finger; pain thresholds were 7.0 ± 2.3 and 6.6 ± 2.4 mA, respectively. In order to avoid potential saturation of the blood oxygenation level-dependent (BOLD) response due to high stimulus intensities, applied current amplitudes were individually adjusted according to the following formula: perception threshold for second finger + perception threshold for third finger + 0.5 mA. From this base intensity, the intensity delivered to the finger associated with the stronger percept was successively lowered until it was equal to that of the other finger. The resulting stimulus intensities applied during fMRI were 3.9 ± 0.4 mA for the second finger and 3.6 ± 0.3 mA for the third finger, and were considerably lower than the respective pain thresholds.

fMRI Setup

Imaging was performed on a 1.5 T scanner (Magneton Vision, Siemens, Erlangen, Germany) using a surface coil (CP Flex large). The surface coil was centred over the left parietal cortex approximately at the C3 position according to the extended 10/20 EEG system. The subject’s head was immobilized by means of fixation tapes to minimize movement-related artefacts. For functional measurements, blood oxygenation level-dependent (BOLD) response in the hand area of SI (FOV = 256 mm, matrix = 128 × 128, voxel size = 2 × 2 × 3 mm, gap 1 mm). For all subjects, three successive runs in an event-related design were performed (Burock et al., 1998; Dale, 1999). Within a single run of 250 images, each stimulation condition was applied 28 times with an equal number of null events in a randomized order, with interstimulus intervals (ISIs) uniformly distributed in the range of 3-9 s at 1 s steps (mean ISI = 6 s); thus, repetitive stimulation was unlikely to generate a potential decrease in stimulus responses (adaptation). For anatomical co-registration, an MPRAGE (magnetization prepared rapid gradient echo) sequence (TI = 9.7 ms, TR = 4 ms, flip angle = 12°, voxel size = 1 × 1 × 1 mm) covering the whole brain was used to acquire a high resolution T1-weighted dataset.

Data Analysis

Imaging data were analysed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). The initial five volumes of each run were discarded from further analysis due to T1 saturation effects. Functional volumes were realigned to the first volume of the respective subject, slice-time corrected, normalized into MNI (Montreal Neurological Institute) space (resolution of 2 × 2 × 2 mm), spatially smoothed (Gaussian Kernel, full width at half maximum = 6 × 4 × 8 mm), and voxel time-series were high- and low-pass filtered.

For analysis of fMRI time series by multiple regression analysis we applied the well-established linear model approach (Friston et al., 1995). Evidence for the validity of this linear approach for human SI has been given experimentally (Arthurs et al., 2000; Backes et al., 2000). Time series time points were modelled using event-related regressors for each condition and convolved with the hemodynamic response function. Three regressors were defined (Fig. 1B): the regressor d2 contained all events when the second finger was stimulated, i.e. separate as well as simultaneous stimulation; the regressor d3 was defined correspondingly. Because we hypothesised that simultaneous stimulation of d2 and d3 would give a smaller response (i.e. parameter estimate) than predicted by adding up the responses to the stimuli when applied separately, we included an interaction term as the third regressor that was created by multiplying the regressors of d2 and d3.

$$d2d3 = d2 + d3$$

Negative parameter estimates for this regressor indicate that the effect of simultaneous stimulation is smaller than the sum of the separate stimulations, positive parameter estimates indicate a stronger effect. The negative contrast (‘suppressive interaction’, 0 0 – 1) thus yields voxels with suppressive interaction and the positive contrast (‘facilitation’, 0 0 1) shows where facilitation is present. The response to simultaneous stimulation (d2d3) is given by adding the parameter estimate of the third regressor to the sum of parameter estimates for d2 and d3:

$$d2d3 = d2 + d3 + response\_interaction\_term$$ (1)

For statistical inference, a fixed effects analysis was performed on the subjects exhibiting significant activation of SI (P < 10^-3) for the regressor d2 and d3 in single subject analysis (n = 10).

To test for subtle interaction effects within subregions of SI which might not have been detectable in the voxelwise analysis described above, we performed an additional region-of-interest (ROI) analysis. A ROI for SI was defined as the merged representation sites of the second and the third finger at an uncorrected P < 10^-3 obtained from the group analysis. Interaction ratios (IRs) were then determined from the parameter estimates for each voxel within this ROI in analogy to previous reports (Hsieh et al., 1995) using the following formula:

$$IR = \frac{(response\_d2 + response\_d3) - (response\_d2d3)}{(response\_d2 + response\_d3)}$$ (2)

Inserting equation (1) into (2) gives:

$$IR = -\frac{(response\_interaction\_term)}{(response\_d2 + response\_d3)}$$ (3)

To quantify differential interaction between subareas of SI, this ROI was further subdivided. However, cytoarchitectonically defined subareas and interareal borders cannot be identified precisely based on anatomical landmarks alone due to high interindividual variability (Geyer et al., 1999). For this reason, the subareas within this SI-ROI were specified in line with criteria used consistently in numerous recent imaging studies (Lin et al., 1996; Burton et al., 1997; Gelnar et al., 1998; Servos et al., 1998; Francis et al., 2000; Moore et al., 2000; Krause et al., 2001; Deuchert et al., 2002; Blankenburg et al., 2003) for an operational definition. Accordingly, the posterior wall of the central sulcus and the adjacent anterior lip of the postcentral gyrus comprises area 3b, the crest of the postcentral gyrus area 1, and the anterior wall of the postcentral sulcus area 2. Anatomical parcellation (see also Fig. 4B) was performed on an average T1-weighted image obtained from all single subject T1 images. Due to the inevitable blurring of anatomical structures in the average brain, for visualization purposes group analysis data arc finally presented on an individual brain that matched the pericentral region of the average brain best; the superposition of data on
the average T1-weighted brain is additionally given in the Supplementary Material. The resulting IRs were then averaged across all voxels for each operationally defined subarea separately, and t-statistics were used to compare the mean IRs between subareas (post-hoc Bonferroni corrected).

To account for a potential influence of interindividual variability regarding the location of interareal borders (Geyer et al., 1999) on the resulting interaction ratios, we shifted the respective operationally defined borders in an additional analysis. The border between area 3b and area 1 was shifted in the rostral as well as the caudal direction by 50% of the activation volume of area 3b. Accordingly, the border between area 1 and area 2 was shifted by 50% of the activation volume of area 2 in the rostral as well as caudal direction. Then again, IRs were calculated for the resulting subareas as described above.

**Results**

In the group analysis, electrical stimulation of the second and the third finger led to statistically highly significant increases in fMRI signal intensity within the hand area of the postcentral gyrus. These activations comprised multiple foci across the postcentral gyrus which were located within the posterior wall of the central sulcus, within the crown of the postcentral gyrus, and within the anterior wall of the postcentral sulcus, presumably corresponding to area 3b, area 1 and area 2, respectively. No significant activation was seen in the fundus of the central sulcus in projection to presumptive area 3a.

In all subareas, activations in response to stimulation of the second and third finger showed considerable overlap. In area 3b, the respective activation maxima exhibited the known somatotopical arrangement with the third finger representation at a more superior, posterior and medial location as compared with the second finger; the Euclidian distance between both representation maxima was 10.8 mm. The somatotopic arrangement of activation foci within area 3b is illustrated in Figure 2. In contrast to area 3b, locations of finger representations in areas 1 and 2 shared similar coordinates, resulting in smaller Euclidian distances of 3.5 mm in both area 1 and area 2.

The T-map for the contrast ‘suppressive interaction’ thresholded at $P < 10^{-5}$ (uncorrected for multiple comparisons) revealed an activation cluster on the crest of the postcentral gyrus, presumably corresponding to area 1 (Fig. 5). At a lower threshold of $P < 10^{-3}$ activated voxels could also be specified corresponding to area 2; however, no significant activation was seen within the anterior wall of the central sulcus (area 3b). By the contrast ‘facilitation’ no significant voxels could be specified in SI ($P < 10^{-5}$).

In a different approach, suppressive interaction was determined and quantified by a ROI-analysis based on the merged representations of the second and the third finger in SI, as shown in the interaction ratio map (Fig. 4). With this approach, suppressive interaction can be seen to be prevalent also within area 3b. Furthermore, IRs can be seen to gradually increase along the rostral-to-caudal axis, i.e. from area 3b to areas 1 and 2.

Within this ROI, no voxels with negative IRs were obtained, indicating that there were no voxels exhibiting facilitation.

Suppressive interaction was assessed by two different approaches: on the basis of the interaction contrast, interaction was determined in terms of significance. By this analysis, suppressive interaction was detected in area 1, at a lower threshold also in projection to area 2. However, since responses to finger stimulation can differ between subareas of SI, it is necessary to relate the absolute amount of interaction to the sum of single finger responses in order to obtain a relative measure for the degree of interaction as expressed in the IR (see Materials and Methods) that is independent from the level of significance. As a result, while the interaction contrast specified area 1 as the site with the largest absolute interaction, the interaction ratio was maximal within area 2. The IR map demonstrated that interaction was also prevalent within area 3b. Consequently, subarea-related mean IRs could be determined for the operationally defined areas: 26% for area 3b, 32.7% for area 1 and 42.2% for area 2. A crucial issue concerning our main finding of subarea-specific different interaction ratios might be the anatomical parcellation of SI into different subareas. As stated in Material and Methods, a parcellation based on macroanatomical landmarks alone cannot be clear-cut due to high intersubject variability (Geyer et al., 1999), although it has been commonly used in numerous recent imaging studies by similar criteria as in the current study (Lin et al., 1996; Burton et al., 1997; Gelnar et al., 1998; Servos et al., 1998; Francis et al., 2000; Moore et al., 2000; Krause et al., 2001; Deuchert et al., 2002; Blankenburg et al., 2003). In that way, since a definite parcellation is only possible in a cytoarchitectonic study, our parcellation represents an operational definition of subareas. Nevertheless, significant differences in IRs are still observable when the borders between areas 3b and 1 and between areas 1 and 2 were shifted towards the rostral as well as caudal direction. This approach yielded a very similar pattern of significantly different interaction ratios, increasing from area 3b to areas 1 and 2. It thus principally confirms that the IRs obtained for the

**Discussion**

In the present study, we show a substantial suppressive interaction in BOLD responses within human primary somatosensory cortex: the response to simultaneous stimulation was considerably smaller than the sum of the responses to separate stimulation of the second and the third finger. The main finding is that this suppressive interaction was subarea-specific and increased along the rostro-caudal axis from area 3b to areas 1 and 2.

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operationally defined subareas are not due to an erroneous random choice of borders between subareas and strongly supports our finding of an increase in interaction ratios in the rostral-to-caudal direction.

In various animal studies, a sublinear summation during simultaneous multi-site stimulation in comparison with separate stimulation has been described by different methods: electrophysiologically, for instance, in whisker barrel cortex in terms of spiking activity and in cat’s SI on the basis of intracellularly recorded postsynaptic potentials (Macgillis et al., 1983; Mirabella et al., 2001), as well as in vascular/metabolic responses using optical intrinsic-signal imaging in rats and monkey’s area 3b

(Blood and Toga, 1998; Chen et al., 2003). Moreover, our findings on interaction in SI are in general agreement with studies in humans assessing far field potentials recorded from the scalp, i.e. SEPs. An earlier study reported interaction ratios of up to 50% in responses evoked by separate and simultaneous stimulation of the second and the third finger, although no separation of certain components of the SEPs was performed (Gandevia et al., 1983).

In the study by Hsich et al. (1995), evoked potentials in response to stimulation of the second and the third finger were obtained intraoperatively, and an interaction ratio of 27.0% was determined for the N20 component and of 35.9% for the P25 component of the SEP. The N20 is presumably generated in

Figure 2. T-maps for the group for d2 and d3 superimposed on T1-weighted images of an individual subject. Representation sites based on the most significant voxels differ from each other within the posterior wall of the central sulcus, presumably corresponding to area 3b (asterisk), exhibiting a somatotopical arrangement with the representation site of d3 at a more medial, posterior and superior position. In comparison, the more caudally located representation sites, presumably corresponding to areas 1 and 2 (circle), showed considerable overlap for d2 and d3. For delineation of overlapping voxels, the third column shows the superposition of the maps of d2 and d3 (d2, green; d3, magenta; overlap, white).
area 3b, whereas area 1 is regarded as a likely generator of the P25 (Allison et al., 1989, 1991). These interaction ratios are strikingly similar to those obtained in the current study, although the responses obtained in BOLD-signal fMRI represent temporally integrated signals that cannot be directly compared with specific components of the SEP or SEF. Comparable results of interaction in early SEF components have also been obtained in recent studies investigating the responses to simultaneous multi-site mechanical stimulation on the same finger (Hoechstetter et al., 2001) or electrical stimulation of adjacent finger pairs (Biermann et al., 1998; Ishibashi et al., 2000). However, due to methodological constraints of MEG in detecting radially oriented sources, these results were mainly assigned to area 3b. Our results strongly suggest that the interactions observed within human SI in the electrophysiological signals are paralleled by corresponding changes in the BOLD responses.

In principle, interaction can be physiologically explained by nonlinear signal integration in interconnected target principal neurons or by inhibition of principal neurons due to coactivation of surrounding inhibitory interneurons. Recording of excitatory postsynaptic potentials of cortical neurons in SI of cats revealed that both mechanisms are involved in processing of simultaneous multi-site mechanical stimulation on the same finger (Hoechstetter et al., 2001) or electrical stimulation of adjacent finger pairs (Biermann et al., 1998; Ishibashi et al., 2000). However, due to methodological constraints of MEG in detecting radially oriented sources, these results were mainly assigned to area 3b. Our results strongly suggest that the interactions observed within human SI in the electrophysiological signals are paralleled by corresponding changes in the BOLD responses.

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similar to that described in non-human primates. Microelectrode recordings in non-human primates have shown that the majority of neurons in area 3b have receptive fields comprising a single finger or even parts of a single finger, whereas in areas 1 and 2 a continuous increase in the number of neurons with receptive fields covering multiple fingers was measured; as a consequence, the representations of fingers were found to be rather overlapping within areas 1 and 2 (Iwamura et al., 1980, 1983a, b, 1993).

Facilitation effects have been described in an SEP study using near-threshold intensities (Gandevia et al., 1983). In our study we used intermediate stimulus intensities in order to avoid a possible saturation of the hemodynamic response, which, however, might have been too high to mediate any facilitory effects.

In summary, this study provides evidence for interaction in the BOLD responses due to simultaneous stimulation of two adjacent fingers within primary somatosensory cortex of humans. Interaction was more pronounced within areas 1 and 2 as compared with area 3b. In parallel, the somatotopical arrangement was less clear-cut within areas 1 and 2 as compared with area 3b. This is in line with evidence for a rostro-to-caudal increase in convergence within SI and concepts suggesting a hierarchical processing with 3b as the primary projection area of somatosensory information ('SI-proper') whereas in the more caudal parts of SI information is increasingly integrated (Kaas, 1983; Iwamura et al., 1993; Iwamura, 1998).

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

Notes
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