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Mislocalization of near-threshold tactile stimuli in humans: a central or peripheral phenomenon?

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Abstract

Principles of brain function can be disclosed by studying their limits during performance. Tactile stimuli with near-threshold intensities have been used to assess features of somatosensory processing. When stimulating fingers of one hand using near-threshold intensities, localization errors are observed that deviate significantly from responses obtained by guessing – incorrectly located stimuli are attributed more often to fingers neighbouring the stimulated one than to more distant fingers. Two hypotheses to explain the findings are proposed. The 'central hypothesis' posits that the degree of overlap of cortical tactile representations depends on stimulus intensity, with representations less separated for near-threshold stimuli than for suprathreshold stimuli. The 'peripheral hypothesis' assumes that systematic mislocalizations are due to activation of different sets of skin receptors with specific thresholds. The present experiments were designed to decide between the two hypotheses. Taking advantage of the frequency tuning of somatosensory receptors, their contribution to systematic misclocalizations was studied. In the first experiment, mislocalization profiles were investigated using vibratory stimuli with frequencies of 10, 20 and 100 Hz. Unambiguous mislocalization effects were only obtained for the 10-Hz stimulation, precluding the involvement of Pacinian corpuscles in systematic mislocalization. In the second experiment, Pacinian corpuscles were functionally eliminated by applying a constant 100-Hz vibratory masking stimulus together with near-threshold pulses. Despite masking, systematic mislocation patterns were observed rendering the involvement of Pacinian corpuscles unlikely. The results of both experiments are in favor of the 'central hypothesis' assuming that the extent of overlap in somatosensory representations is modulated by stimulus intensity.

Introduction

Patients suffering from diseases affecting the somatosensory system commit mislocalization errors during tactile stimulation by localizing tactile stimuli to a body part other than the stimulated location. For example, finger agnosia is a neurological disorder in which the patients' ability to correctly localize unseen touch of fingers is impaired (Gerstmann, 1924; Rusconi *et al.*, 2005). Mislocalization errors are not completely random, but rather show some somatotopic pattern, as errors primarily involve central fingers of the stimulated hand. It thus appears as if these patients systematically mislocate touch to neighbouring fingers rather than having a more general problem with verbal and semantic knowledge about finger identity and order (Tucha *et al.*, 1997). The disability supports the notion that somatotopic representations along the tactile pathway may be confused. Interestingly, characteristic patterns of mislocalization of touch have also been described in hand-amputated patients. In some of these patients, weak touch applied to regions of the face induced specific phantom sensations at (non-existing) fingers of the amputated hand (Ramachandran *et al.*, 1992, 1995; Knecht *et al.*, 1995; Birbaumer *et al.*, 1997; Borsook *et al.*, 1998). It was speculated that these mislocalization patterns were the consequence of a modified functional organization of primary somatosensory cortex (SI) or of cortical areas more upstream in the afferent pathway. In summary, evidence from finger agnosia and hand amputations points to an altered organization of finger representation in primary somatosensory cortex and/or parietal cortical regions as the origin for characteristic mislocalizations errors.

In healthy subjects, systematic mislocalization errors can be induced by tactile stimuli with intensities close to the localization threshold. Similarly to patients suffering from different diseases mentioned above, healthy subjects mislocalize near-threshold stimuli to the finger neighbouring the one actually stimulated (Braun *et al.*, 2000, 2005b; Schweizer *et al.*, 2000, 2001). These findings imply that even on trials where subjects mislocalized the stimulus they had access to some

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information about its location, albeit with a lower spatial resolution. The phenomenon has been referred to as systematic mislocalization of tactile stimuli (Schweizer *et al.*, 2000, 2001).

So far, the underlying neuronal mechanisms of systematic mislocalization in healthy subjects is not clear. Based on the findings in patients, it seems that systematic mislocalization in healthy subjects is also the consequence of blurred somatotopic representations of near-threshold stimuli in these cortical areas. This explanation is referred to as the 'central hypothesis'. However, before this explanation can be accepted, an alternative explanation based on sensitivity of skin receptors has to be ruled out. As such, the alternative 'peripheral hypothesis' has been derived from electrophysiological and psychophysical experiments on frequency tuning and spatiotemporal summation of peripheral skin receptors, as well as their effects on perception (Bolanowski *et al.*, 1988; Gescheider *et al.*, 2001, 2002, 2004). These studies identified four psychophysical channels of touch, each of which is based on a different skin receptor with different sensitivities for different stimulation frequencies. The P-channel, related to Pacinian corpuscles, is characterized by a low spatial resolution and high sensitivity for vibratory stimuli with frequencies > 100 Hz. In contrast, two out of the three non-Pacinian (NP) channels (NPI and NPIII in Table 4) are more sensitive at lower frequencies and have better spatial resolution. The third NP channel is also sensitive in the frequency range > 100 Hz but with a lower sensitivity than the P-channel (NPII in Table 4).

The 'peripheral hypothesis' for tactile mislocalization posits that near-threshold tactile stimuli, in contrast to suprathreshold stimuli, selectively activate low-threshold P-channels with a coarse spatial resolution and a frequency tuning most sensitive for frequencies between 250 and 300 Hz. According to this view, spatial resolution as well as the frequency sensitivity of the somatosensory system should vary dependent on stimulus intensity. While stimuli at higher intensities would be processed by NP-channels at high spatial resolution, near-threshold stimuli activating exclusively the P-channel would only be processed at low spatial resolution and thus generate systematic mislocalization.

The present experiments were designed to adjudicate between the 'peripheral' and 'central hypotheses'. Involvement of the P-channel in the processing of near- and above-threshold stimuli was examined by exploiting its characteristic spatial resolution and frequency tuning. If the 'peripheral hypothesis', tuning of P-channel receptors, were true, mislocalization effects should be observable for stimulation frequencies > 100 Hz. On the other hand, masking the P-channels with a persisting strong sinusoidal stimulus > 100 Hz should abolish the systematic mislocalization of near-threshold stimuli. The two experiments presented here tested both predictions and found strong evidence against the 'peripheral hypothesis'.

Experiment 1

Subjects and methods

Fifteen subjects (eight male) aged between 20 and 30 years (mean ± SD, 24.1 ± 2.0) participated in the experiment. All subjects were right-handed according to the Edinburgh Inventory with individual scores ranging from 0.578 to 1. Positive values that can be maximally as high as 2 indicate right-handedness and negative values with a minimum of −2 left handedness (Oldfield, 1971). All subjects declared that they were not aware of any neurological or psychiatric disease. Participants gave informed consent prior to inclusion in the study. The study followed the rules of the Declaration of Helsinki and was approved by the local ethical committee of the University Hospital of Tübingen, Germany. Subjects received 20 € for participating in both experiments.

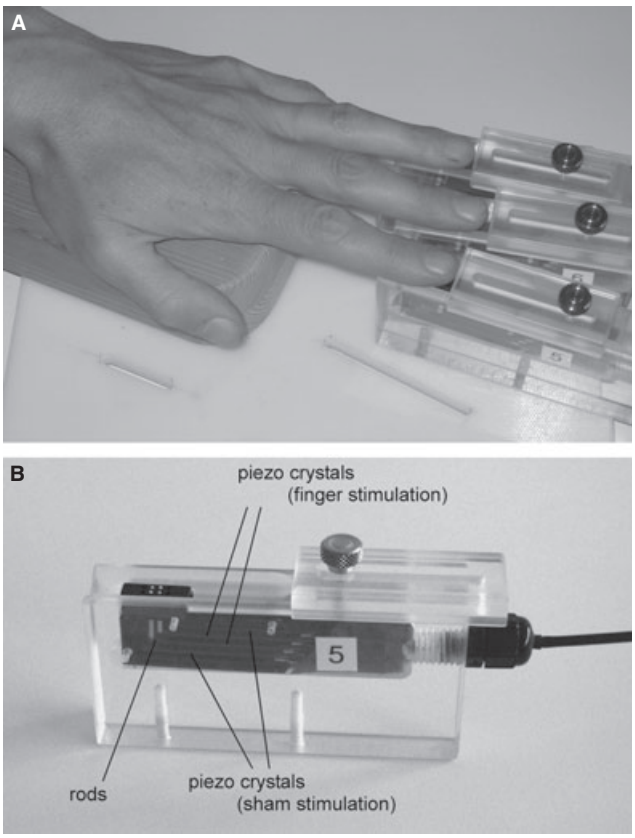

FIG. 1. Tactile stimulation. (A) Subject's left index, middle and ring finger were placed on the stimulation modules and fixed with Velcro strips. (B) A stimulation module housed eight piezo crystals that could be activated individually. Four of the eight piezo crystals could protrude and retract a small rod that caused an indentation of the skin. The stimulator allowed for vibratory and pulse stimulation or a combination of the two. The remaining four piezo crystals were not connected to rods and were activated for sham stimulation.

During the experiment, tactile stimulation was applied to the index (D2), middle (D3) and ring (D4) finger of the subject's left hand using a piezoelectric stimulator (Fig. 1A). To achieve a relaxed and comfortable hand posture, the palm of the left hand was supported. The stimulator consisted of three modules each stimulating one finger tip. Only one finger was stimulated in a trial. Individual modules were adjusted to the finger tips and fixed with adhesive tape. Each module consisted of eight piezo crystals that were computer-controlled. Four of the eight piezo crystals moved small plastic rods (0.9 mm diameter) in a graded manner (resolution 5 μm) causing a peak skin indentation of 1.2 mm. The amplitude was set via 8-bit digital-to-analog (DA) converters. Due to the inertia of the mechanics and due to individual differences in the elasticity of the subjects' skins, the actual indentation of the skin surface cannot easily be provided in the current setup. Accordingly stimulation intensities are presented in DA units. The other four crystals were not connected to rods and allowed for sham stimulation. The four moveable rods were arranged in a 2 × 2 matrix with 2.5 mm spacing between rods. They fully covered the finger tip. All four rods were activated simultaneously and provided a sinusoidal vibratory stimulus of 200 ms duration. The phase of the sine function controlling the rods was chosen such that at stimulus onset the rods started from the most retracted position,

ensuring smooth stimulation onset. The frequency of the vibration was either 10, 20 or 100 Hz. For 10-Hz stimulation, rods complete two sine cycles. For 20 and 100 Hz they completed four and twenty cycles, respectively.

In order to mask any acoustic cue originating from the activated stimulator modules the four crystals in each module not connected to the rods served as sham stimuli. They were operated at the same frequency as the crystals that stimulated the skin. The whole hand was covered with a blanket to maintain the temperature of the hand, and to dampen any possible acoustic noise originating from the piezo stimulator. Remaining acoustic emissions of the stimulator were masked by continuous white noise applied through ear phones. The loudness of the white noise sound was adjusted individually until no auditory percept of the emissions of the tactile stimulator was reported by the subject.

In each trial, one of the three fingers was stimulated 1.5 s after the presentation of a visual warning stimulus on the computer screen in front of the subject. Subjects were prompted 300 ms after stimulation to indicate stimulus location using button presses. They indicated the finger at which they had perceived the stimulus by pressing one of three buttons using their right hand. Each button was assigned to one of the three fingers of the left hand. To minimize subjects' response bias towards a single finger, the assignment of buttons to the fingers varied randomly from trial to trial. The actual assignment in each trial was indicated by three rectangles (labeled with the initials of each finger) that were displayed on a screen in front of the subject just before the response was requested. Subjects were instructed to respond in each trial. If they did not feel anything they were encouraged to guess. If subjects did not respond within 3 s the trial was terminated and repeated later.

To find out which type of receptor is mainly involved in the systematic mislocalization phenomenon, the differential sensitivity of skin receptors to different stimulation frequencies was exploited in the first experiment. During each trial, a vibratory pulse of either 10, 20 or 100 Hz lasting for 200 ms was presented to one of the three fingers. Stimulus frequency and location (stimulated finger) was randomized throughout the experiment. Using an adaptive staircase method, the intensity of the tactile stimuli was continuously adapted to the localization threshold for each finger and stimulus frequency ('individual threshold intensity'). This adaptive procedure was used throughout each experimental session. This resulted in a total of nine individual threshold intensities – three stimulated fingers × three stimulation frequencies. In the case of correct stimulus localization, stimulus intensity was decreased in the next trial of the same frequency–finger combination. Intensity was increased for a certain frequency–finger combination in the case of the stimulus not being localized correctly. In order to infer the subject's response bias, additional catch trials were interspersed. In these trials stimuli of zero intensity, i.e. without any rod protrusion, were applied together with the sham stimulation. Three separate response profiles for guessing were acquired, one for each stimulation frequency. The response profile obtained from catch trials, reflecting subjects' guessing behavior, served as a control condition to which mislocalization profiles were compared.

The experiment was terminated whenever one of the following conditions was met: (i) for each stimulation frequency and for stimulation of each finger there were at least 20 mislocalizations and 40 correct localizations (for catch trials each finger should be named 30 times, 10 for each frequency); (ii) after the application of 1200 trials; or (iii) after 45 min of total stimulation time. In order to obtain enough responses in all stimulation and response categories, the probability of conditions for which responses were lacking was increased towards the end of the experiment. However, the probability for any one of the twelve stimulation conditions never exceeded 25 %. In two subjects the experiment was stopped after reaching the time limit of 45 min. As these subjects had on average only 42 and 77 total mislocalizations per frequency condition, they were excluded from further analysis. The remaining group had on average (mean ± SD) 120.8 ± 13.3 mislocalizations per frequency.

Data analysis

For data analysis, only catch trials and trials with incorrect localizations were included. For each stimulation frequency $f(q) = \{10, 20, 100\,\mathrm{Hz}\}$, and for each stimulated finger j, the number of mislocalizations N^q_{ijk} to the non-stimulated fingers $k \neq j$ was determined for each subject i. From these responses, mislocalization profiles depending on the neighbourhood relationship between the stimulated and the named finger were derived. In order to compare mislocalization profiles, unequal numbers of mislocalizations for the different fingers and for the frequencies applied were corrected. Accordingly, numbers of mislocalizations were normalized such that the total number of mislocalizations obtained for each stimulated finger at each stimulation frequency was identical for each individual subject (Schweizer *et al.*, 2001; Braun *et al.*, 2005a). The normalization procedure (explained in detail in appendix 1 and Table 1) yielded corrected numbers of mislocalization v^q_{ir}, with $r = 1$ referring to the first and $r = 2$ to the second neighbour.

As in our previous studies (Schweizer *et al.*, 2001; Braun *et al.*, 2005a,b) mislocalization profiles to near-threshold stimulation were compared with a profile that was based on subjects' response biases. The response bias was estimated from responses to catch trials with zero intensity stimulation when subjects reported perceived stimulus locations without being stimulated. With N^c_{ik} being the number of subject i naming the k^{th} finger during catch trials (zero-intensity

TABLE 1. Example of the normalization of mislocalizations in one subject for experiment 1: (a) raw mislocalizations; and (b) normalized mislocalizations

N^q_{ijk} Subject i Stimulation				Response k			
				1	2	3	
q		j		D2	D3	D4	Total
(a) Raw							
1	10 Hz	1	D2	–	19	16	35
		2	D3	14	–	15	29
		3	D4	20	17	–	37
2	20 Hz	1	D2	–	16	15	31
		2	D3	19	–	17	36
		3	D4	24	14	–	38
3	100 Hz	1	D2	–	18	23	41
		2	D3	18	–	19	37
		3	D4	16	19	–	35
Total				319			
(b) Normalized							
1	10 Hz	1	D2	–	19.2	16.2	35.4
		2	D3	17.1	–	18.3	35.4
		3	D4	19.2	16.2	–	35.4
2	20 Hz	1	D2	–	18.3	17.1	35.4
		2	D3	18.7	–	16.7	35.4
		3	D4	22.4	13.0	–	35.4
3	100 Hz	1	D2	–	16.6	18.8	35.4
		2	D3	17.1	–	18.3	35.4
		3	D4	18.3	17.1	–	35.4
Total							319

stimulation), the number of randomly named first and second neighbour is

$$M_{ir}^{c} = \begin{cases} N_{i1}^{c} + 2N_{i2}^{c} + N_{i3}^{c}\,, & \text{for } r = 1 \\ N_{i1}^{c} + N_{i3}^{c}\,, & \text{for } r = 2 \end{cases}. \quad (1)$$

Normalizing the number of responses based on catch trials (zero intensity stimulation) with $\bar{N}_i$ being the average number of mislocalizations across fingers and stimulation frequencies for one subject, yields the following distribution for guessed responses.

$$\tilde{v}_{ir}^{c} = M_{ir}^{c} \frac{\bar{N}_i}{\sum_{r=1}^{2} M_{ir}^{c}}. \quad (2)$$

For the statistical comparison a *G*-test was applied, after summing mislocalization profiles v_{ir}^{q} and control profiles $\tilde{v}_{ir}^{c}$ across subjects *i*. The *G*-test has been proposed by Sokal & Rohlf (1994) as a conservative chi-square-test.

To compare the individual threshold intensities for near-threshold stimulation the rod protrusion was inferred indirectly from the control voltage of the stimulator. A two-way ANOVA with repeated measurement factors Finger (levels: D2, D3 and D4) and Stimulation Frequency (levels: 10, 20 and 100 Hz) was applied to test for significant differences.

Results

Across all subjects ($N = 13$) and stimulation frequencies there were 4713 mislocalizations. The individual threshold intensities in DA units for near-threshold stimulation are summarized in Table 2. Comparing the individual threshold intensities there was no significant effect for Stimulation Frequency ($F_{2,12} = 0.448$, $P = 0.64$). Significant differences in individual threshold intensities were only found for the stimulation of the different fingers ($F_{2,12} = 7.75$, $P = 0.003$), with the lowest intensity of the middle finger (mean ± SEM; D2, 135.4 ± 9.3 μm; D3, 98.6 ± 10.3 μm; D4, 150.5 ± 8.0 μm).

The frequencies for naming the different fingers for zero intensity stimulation (catch trials) were compared to a distribution with equal frequencies in order to estimate response biases for each finger. Results show that subjects named the middIe finger more often than the index or ring finger (D2, 376; D3, 568; D4, 383; $G_2 = 51.6$, $P < 0.001$). No deviation from an equal distribution was found if only frequencies for naming index and ring finger were compared ($G_1 = 0.065$, $P = 0.80$).

When mislocalizations were analyzed according to their neighbourhood relation with respect to the stimulated finger, a significant difference was found between the mislocalization and the control profile ($G_1 = 9.62$, $P = 0.0019$) for 10-Hz stimulation. There were significantly more mislocalizations to the first neighbour ($v_1^{10\,\mathrm{Hz}} = 1193.0$) than expected by guessing ($\tilde{v}_1^{c} = 1138.8$;Fig. 2). Accordingly, the number of mislocalizations to the second neighbour was lower for the experimental condition ($v_1^{10\,\mathrm{Hz}} = 378.0$) than expected from guessing ($\tilde{v}_2^{c} = 432.2$). Stimulating with 20 Hz, no significant difference between the mislocalization profile (first neighbour, $v_1^{20\,\mathrm{Hz}} = 1135.7$; second neighbour, $v_2^{20\,\mathrm{Hz}} = 435.3$) and what was expected from catch trials was obtained ($G_1 = 0.03$, $P = 0.86$). Comparing the mislocalization profile for 100-Hz stimulation with the control profile, there were significantly less mislocalizations to the first neighbour ($v_1^{100\,\mathrm{Hz}} = 1087.5$) than would have been expected from the zero-intensity stimulation ($G_1 = 8.21$, $P = 0.004$). Consequently, there were more mislocalizations to the second neighbour than expected ($v_2^{100\,\mathrm{Hz}} = 483.5$).

TABLE 2. Mean stimulation intensities in units of the analog-to-digital converter

	Finger		
Frequency	D2	D3	D4
10 Hz	55.5 ± 5.0	51.5 ± 5.7	65.6 ± 2.3
20 Hz	59.6 ± 4.6	52.3 ± 5.8	68.2 ± 1.9
100 Hz	67.8 ± 1.0	48.4 ± 5.8	58.8 ± 5.5

AD units: 0, rods are completely retracted; 255, rods are maximally protracted.

Discussion

The purpose of experiment 1 was to determine whether previously described effects of systematic mislocalization of near-threshold tactile stimuli reflect characteristics of central or peripheral processing of somatosensory input. The 'central hypothesis' assumes that weak tactile stimuli create a blurred representation in SI. In contrast, the 'peripheral hypothesis' suggests that the afferent input in near-threshold stimulation as compared to suprathreshold stimuli is exclusively mediated by Pacinian corpuscles constituting the P-channel. Strong somatosensory input activates a variety of receptors that differ with respect to threshold, spatial resolution and frequency tuning. In the case of activating multiple channels simultaneously, it is assumed that the spatial resolution is defined by the most sensitive channel and therefore the channel with the highest resolution will dominate the processing of spatial information. In contrast, near-threshold pulse-like stimuli activate only low-threshold Pacinian corpuscles with a coarse spatial resolution corresponding to a broad and defocused cortical representation that responds optimally to stimulus frequencies between 250 and 300 Hz.

Our results confirmed previous observations of systematic mislocalizations of near-threshold stimuli for the 10-Hz stimulation. The number of mislocalizations exceeded the number that would have been obtained by guessing, even after controlling for subjects' response biases. However, no systematic mislocalization was found for 20-Hz stimulation (Fig. 2B). For the 100-Hz stimulation a systematic mislocalization profile was observed, with more mislocalizations to the second than the first neighbouring finger. This finding is in contradiction to typical results of mislocalization experiments.

Central and peripheral hypothesis

The current findings provide some support for the 'central hypothesis' in explaining somatosensory mislocalization errors. If the 'peripheral hypothesis' were true, the application of 100-Hz vibratory stimuli should have produced more mislocalizations to the first neighbour than stimulating with lower frequencies, because 100-Hz stimuli mainly activate Pacinian corpuscles with very low spatial resolution. However, this was not demonstrated in the current experiment. As the 'central hypothesis' does not make any predictions about the frequency dependency of the extent of tactile mislocalization, the failure to support the 'peripheral hypothesis' may be interpreted as support for the 'central hypothesis'.

Frequency dependency of near-threshold intensities

Despite the clear outcome of the experiment, a more detailed look at the data raises some questions. It might be argued that if our

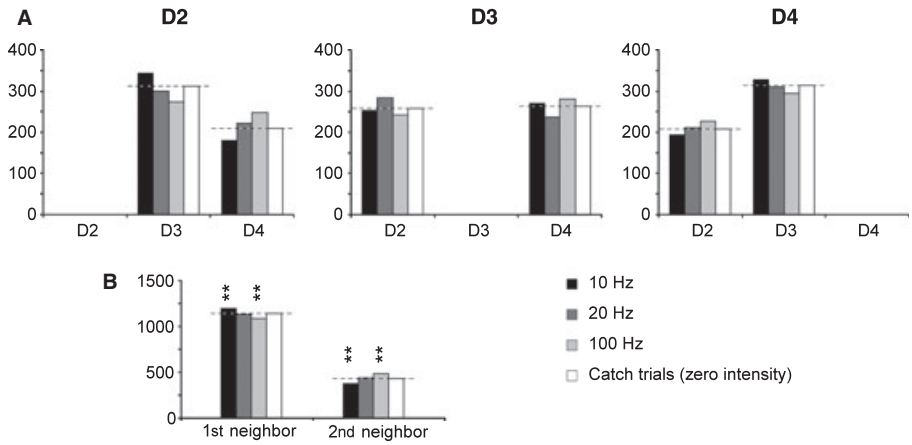

FIG. 2. Mislocalization profile for experiment 1. (A) Graphs correspond to the mislocalization profiles obtained for stimulation of the index finger (D2), the middle finger (D3) and the ring finger (D4). As only localization errors are presented, the number of trials in which the stimulus was correctly localized is not presented. Numbers of mislocalizations were normalized such that the total number of stimulations provided to each finger at each stimulation frequency was identical. The number of mislocalizations in the control condition is the number of mislocalization that was obtained when subjects' response bias while guessing was taken into account. (B) The total number of mislocalizations to the first and the second neighbour with respect to the stimulated fingers are presented. The number of mislocalization for 10 Hz was significantly higher than would be expected from guessing (zero intensity stimulation – dashed line); $^{**}P < 0.01$.

assumptions were true and Pacinian corpuscles have the lowest threshold, a lower stimulation intensity threshold for the 100-Hz than for the 10- and 20-Hz stimuli should be expected. However, no significant difference in individual threshold intensity was found between 10, 20 and 100 Hz stimulation. Based on this finding it might be questioned whether in the 100-Hz stimulation Pacinian corpuscles were indeed stimulated. In the current procedure, using a staircase method, the stimulation intensity was driven not towards the detection threshold but towards the localization threshold. While the detection threshold is lowest for the P-channel because of its high sensitivity, its localization threshold would be expected to be high due to the large receptive fields of Pacinian corpuscles. To conclude, the lack of any frequency dependency of near-threshold intensities does not exclude an involvement of Pacinian corpuscles in the processing of 100-Hz vibratory stimuli.

Due to the constant stimulus duration across stimuli, the number of sinusoidal cycles differed for the different frequencies. The 10-Hz stimulation comprised two cycles and the 20- and 100-Hz stimulation involved 4 and 20 cycles, respectively. As there is evidence that the adaptation of the various somatosensory channels behaves differently depending on the stimulation frequency (Hollins *et al.*, 1990; Simons *et al.*, 2005), it might well be that the increased number of cycles for the 100-Hz stimulation causes stronger adaptation and thus an increase in individual threshold intensity. Currently, a detailed understanding of the impact of cycle number and stimulus duration on the adaptation and sensitization of tactile input, that might fully explain the present results, is still lacking.

Frequency dependency of the mislocalization profile

The mislocalization profile for 10-Hz stimulation, presumably activating the NPI and NPIII channels, which are subtypes of the NP system, is in accordance with the profile obtained for near-threshold pulses. This was not the case with 100-Hz vibrations activating the P-channel, which surprisingly yielded an inverted profile, i.e. a decreased number of mislocalizations for the first neighbour to the stimulated finger as compared to what would be expected from guessing.

Unfortunately our knowledge about the specific characteristics of the NP- and P-channel system is incomplete and only a few features with respect to stimulus discrimination and adaptation have been studied systematically (Hollins *et al.*, 1990; Tommerdahl *et al.*, 2005). According to the high spatial resolution of the NP- as compared to the P-channel, cerebral representations are smaller for the NP- than for the P-channel.

Assuming the 'central hypothesis' to be true, it might be speculated that leakage of activation for near-threshold stimuli, presumably causing mislocalization effects, might even extend to the second neighbour of the stimulated finger for P-channels rather than just the first, like for NP-channels.

No significant effect was found for 20-Hz stimulation. If the frequency dependency of the mislocalzation profile is regarded as a continuum, with the profile obtained for 10 Hz on the one end and the one obtained for 100 Hz on the other end, the effects for 20-Hz stimulation should be in between.

Effects of response bias

The current experiment was designed to compare mislocalization profiles for near-threshold stimulation with a profile that would be obtained if subjects were just guessing. In order to minimize any response bias, a variable assignment of the response buttons to the different fingers was chosen requiring the subjects to map the perceived stimulus location to the response buttons in every trial differently. It was expected that in the case of uncertainty about the stimulus location subjects might tend to always respond with the same finger without any engagement in the task. In the case of a fixed button–finger assignment, such a behavior would be reflected in a systematic finger-naming bias. We selected this procedure because in a variable assignment a stereotyped button press response will generate a profile in which mislocalizations are equally distributed to all fingers.

Interestingly, subjects still showed a strong response bias towards the middle finger, reflecting a preference for deliberately naming the middle finger. This response behavior might reflect a response tendency towards the center of the hand, avoiding naming of more extreme locations. The central response tendency, which can explain the current finding, is a commonly observed phenomenon when subjects have to judge features of stimuli with respect to a set of parameters (Hollingworth, 1910; Huttenlocher *et al.*, 1991).

The response bias towards the middle finger may also account for the lower thresholds found for D3 stimulation. The intensity at

individual fingers was chosen according to subjects' finger naming. If subjects have an increased tendency to name the middle finger they are more often correct in the case of D3 stimulation but less often in the case of D2 and D4 stimulation. Therefore the stimulation intensity of the localization threshold will decrease for D3 and increase for D2 or D4.

It might be argued that a variable button-finger assignment is cognitively more demanding than having a fixed relation and might therefore represent an additional source for mislocalizations. As the number of mislocalizations due to the variable finger-button assignment affects all fingers equally, this type of error is regarded as being less critical than a stereotyped response pattern in the case of a fixed finger–button relationship. In order to minimize the effect of a systematic bias we chose the variable finger-button assignment.

In order to substantiate our interpretation that the 'peripheral hypothesis' cannot account for patterns of tactile mislocalizations, a second experiment was conducted in which any presumptive contribution of Pacinian corpuscles to the occurrence of the systematic tactile mislocalization phenomenon was functionally eliminated by predominantly masking the P-channel.

Experiment 2

Subjects and methods

All subjects of the first experiment also participated in the second study. The second experiment was identical to the first one with respect to the procedure and the task. In order to eliminate the contribution of the Pacinian corpuscles to the systematic mislocalization of near-threshold stimuli, the left index, middle and ring finger were continuously stimulated with a 100-Hz vibratory stimulus throughout the second experiment. The amplitude of the vibratory stimulation was 80 % of the maximal amplitude of the stimulator, presumably masking the high sensitivity of Pacinian receptors (Gescheider *et al.*, 2004). Superimposed on the vibratory stimuli a rectangular pulse of 50 ms duration was presented to one finger per trial. As in the first experiment, subjects had to localize the pulse at one of the three possible fingers and respond with a button press. As before, the assignments of buttons to fingers were shuffled randomly in each trial. Stimulation intensity of the pulse was adapted according to the subject's response. The amplitude of the rectangular pulse was maximally 20 % of the total amplitude range of the rods, which corresponds to a protraction of 240 μm. All other procedures were identical to those in experiment 1.

A session in experiment 2 was terminated when: (i) for each finger there were at least 20 mislocalizations and 40 correct localizations (with respect to catch trials each finger had to be named at least 10 times); (ii) after application of 600 trials; or (iii) after 20 min of total stimulation time. As in the first experiment, the probability of stimulation conditions underrepresented early in the current session were presented more often towards the end of the session. However, the probability for one out of the four stimulation conditions never exceeded 50%.

Data analysis

Localization errors were analyzed in the same way as in experiment 1, except that in the second experiment there was only one type of stimulus applied to the three fingers. Following the normalization procedure the number of mislocalizations v_{ir} to the r^{th} neighbour of the stimulated finger was computed for subject i (see appendix 2 and Table 3), and finally summed across participants. One subject showing only 115 mislocalizations in total was excluded because of the low number of usable trials. On average there were (mean ± SD) 166.64 ± 14.09 mislocalizations per subject.

TABLE 3. Example for the normalization of mislocalizations in one subject for experiment 2: (a) raw mislocalizations, (b) normalized mislocalizations

		Response k			
		1	2	3	
N_{ijk} Subject i Stimulation j		D2	D3	D4	Total
(a) Raw					
1	D2	–	45	20	65
2	D3	25	–	24	49
3	D4	22	35	–	57
Total					171
(b) Normalized					
1	D2	–	39.5	17.5	57
2	D3	29.1	–	27.9	57
3	D4	22.0	35.0		57
Total					171

The statistical comparison of the distribution of mislocalizations to the first and second neighbour, with a distribution derived from the response behaviour for catch trials (Eqn 9 in appendix 2), was made using a G-test (Sokal & Rohlf, 1994).

Results

Across subjects there were a total number of 2333 mislocalizations (Fig. 3A). Comparing the observed mislocalization with the ones expected based on catch trials yielded a significant effect ($G_1 = 13.61$, $P = 0.00022$). There were more mislocalizations to the first neighbour ($v_1 = 1789.7$) than expected ($\tilde{v}_1^c = 1712$). In contrast, the number of mislocalizations to the second neighbour ($v_2 = 543.3$) was less than expected ($\tilde{v}_2^c = 621$; Fig. 3B).

Discussion

Assuming that the continuous vibratory stimulation at a frequency of 100 Hz had effectively masked the P-channel system (Hamer *et al.*, 1983), the results of the second experiment indicate that systematic mislocalization profiles could be shown even if Pacinian corpuscles were functionally eliminated. Therefore, as in experiment 1, our findings indicate that the systematic mislocalization obtained for near-threshold stimuli is not likely to be mediated by Pacinian corpuscles. Thus, one might conclude that results are strongly in opposition to the 'peripheral model' and support the 'central hypothesis'.

This argument depends critically on the masking properties of the continuous 100-Hz stimulation. Studies which investigated the perception of sequentially applied stimuli provided evidence that the first stimulus does not necessarily cause impaired stimulus detection or stimulus discrimination. Indeed, sensitization and improvement in perceptual performance have been reported (Tommerdahl *et al.*, 2005; Tannan *et al.*, 2007). However, unlike these studies, the ongoing 100-Hz stimulation and the short pulse were not separated in time, but rather overlapped completely in our experiment. Following Fourier's theorem, a rectangular tactile pulse can be regarded as the weighted sum of vibratory oscillations in a broad frequency band. Due to the frequency-specific processing of sensory input in different channels of the somatosensory system, higher frequency components of the pulse will be processed together with the ongoing 100-Hz stimulation in the

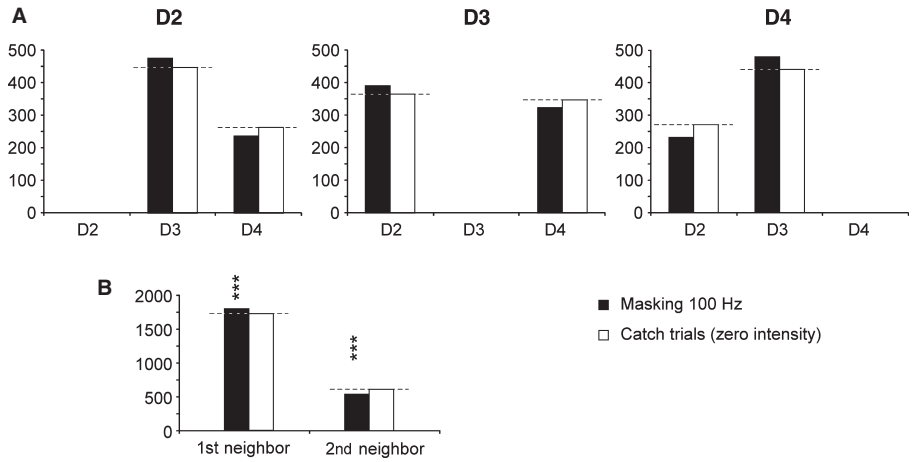

FIG. 3. Mislocalization profile for near-threshold tactile pulses while masking Pacinian corpuscles with a continuous 100-Hz vibratory stimulus in experiment 2. (A) Graphs correspond to the mislocalization profiles for the stimulation of the index finger (D2), the middle finger (D3) and the ring finger (D4). As only localization errors are presented, the average number of trials that had been localized to non-stimulated fingers is presented. Numbers of mislocalizations were normalized such that the total number of stimulations provided to each finger was identical. The number of mislocalizations in the control condition is the number of mislocalization that was obtained by guessing, taking the subjects' response bias into account. (B) The total number of mislocalizations to the first and the second neighbour with respect to the stimulated finger are presented. Despite masking, a significant deviation of the mislocalization profile obtained by guessing (zero intensity stimulation; dashed line) could be shown; $***P < 0.001$.

TABLE 4. Characteristics of somatosensory input channels

	Channel			
	P	NPI	NPII	NPIII
Receptors	Pacinian Corpuscles	Meissner Bodies	Ruffini Organs	Merkel Cells
Skin layer	Deep	Superficial	Deep	Superficial
Adaptation	Fast (FAII)	Fast (FAI)	Slow (SAII)	Slow (SAI)
Frequency tuning	250–300 Hz	25–40 Hz	150–400 Hz	0.4–1.0 Hz
Threshold intensity	Low	Medium	Medium	High
Spatial resolution	Low	High	Low	High
Spatial summation	Yes	No	No	No

P-channel. It is evident that high-frequency components of the pulse stimulus are only detected if they exceed the activation of the background stimulation. As the frequency tuning of the P-channel is rather coarse (Gescheider *et al.*, 2001), it has to be assumed that the pulse and the 100-Hz stimuli interfere over a rather broad frequency range. On the other hand, low frequency components of the pulse stimulus in the range approximately 10–20 Hz will be less affected by the background stimulation. In conclusion, there are good reasons to assume that the continuous 100-Hz stimulation strongly suppresses the processing of higher frequency components and only marginally the processing of lower frequency components.

General discussion

By definition, near-threshold tactile stimuli are localized only partially correctly. Interestingly, the wrongly located stimuli are not randomly assigned to non-stimulated body parts but are preferentially assigned to sites in the vicinity of the stimulated skin location. More distant sites are less frequently indicated. In principle, these findings can be explained by the 'central hypothesis' which assumes that the systematic mislocalization phenomenon is caused by an intensity-dependent focus of cerebral representations of the body surface. This neural activity is characterized by spreading representations for near-threshold intensities, and small and sharp representations for above-threshold intensities.

Evidence for this hypothesis is provided by experimental findings showing overlapping representations of skin regions on various levels of the somatosensory system, such as primary and secondary somatosensory cortex (Biermann *et al.*, 1998; Churchill *et al.*, 1998; Gelnar *et al.*, 1998; Disbrow *et al.*, 2000). However, according to neurophysiological studies, overlapping representations in area 3b are few (Manger *et al.*, 1997; Iwamura, 1998) and rather small (Krubitzer *et al.*, 2004). In contrast, the amount of spatial integration increases towards posterior somatosensory regions, in particular in areas 1 and 2 (Iwamura *et al.*, 1980). Accordingly, systematic mislocalization should emerge on these latter levels than in area 3b. As, however, previous studies have almost exclusively used above-threshold stimulation for the study of functional representations of the body, it might well be that the degree of overlap in primary somatosensory regions is augmented for near-threshold stimulation.

The 'central hypothesis' postulates that strong suprathreshold stimuli activate disjunctive representational zones and that stimulation close to the detection threshold activates representations that cover extended skin regions. Evidence has been found in animal studies suggesting that lateral inhibition is a candidate neural mechanism that might be involved in this process (Gardner & Costanzo, 1980; Chen *et al.*, 2003; Simons *et al.*, 2005; Friedman *et al.*, 2008). Intensive stimuli create strong activation in the center of stimulus representations and concurrently strong inhibition in its surround, which creates a sharp representation with little overlap of neighbouring representations. In contrast to above-threshold stimulation, near-threshold stimulation causes low activation in the centre of the representation and low inhibition of the surround, implying weaker yet broader activation. Experimental evidence for the existence of this type of lateral inhibition arises from studies in animals (Moore & Nelson, 1998; Sripati *et al.*, 2006) and humans (Biermann *et al.*, 1998; Simões *et al.*, 2001). Thus, for strong tactile stimuli the proposed circuitry serves the enhancement of the contrast of tactile input. In monkeys an increase in surround inhibition has been shown from the periphery to area 3b and 1 (Sripati *et al.*, 2006). The increased sensitivity resulting from integrating input from a larger sensory epithelium, and the

enhancement of contrast by lateral inhibition, appears to be a ubiquitous mechanism in the nervous system that can also be found in other sensory systems such as vision. In vision, lateral inhibition has been demonstrated to play a role both on a retinal (McCourt, 1990; Balboa & Grzywacz, 2000) and on a cortical level (Eysel *et al.*, 1988). Accordingly, it renders the 'central hypothesis' very attractive as an explanation for systematic mislocalizations for near-threshold tactile stimulation.

Additional support for the 'central hypothesis' emerges from findings in cortical reorganization. Lateral inhibition and disinhibition have also been shown to be involved in functional reorganization of sensory cortex (Dykes *et al.*, 1984; Garraghty *et al.*, 1991; Chowdhury & Rasmusson, 2002; Benali *et al.*, 2008). It has been shown that the organization of sensory cortex is not strictly fixed, and the extent of representation zones can be altered by lesions (Yu *et al.*, 2010), changes in the sensory input stream (Merzenich *et al.*, 1984; Knecht *et al.*, 1995) or by training sensory capabilities (Jenkins *et al.*, 1990; Elbert *et al.*, 1995). A greater number of mislocalization errors have been found in blind Braille readers, in whom primary somatosensory cortex representations are purportedly reorganized due to the intensive and simultaneous use of the three central fingers for reading. In these patients impaired localization performance was positively correlated with deviations of finger representation in SI from the homuncular organization observed in sighted controls (Sterr *et al.*, 1998a,b, 2003). This finding led to the conclusion that during permanent concurrent employment, the three reading fingers provide a broader 'field of view', albeit at the expense of good localization accuracy for near-threshold stimuli.

At an initial stage of reorganization and during short-term plasticity, changes in the organization of primary somatosensory cortex have been revealed to be related to disinhibition of cortical interneurons in SI (Dykes *et al.*, 1984; Benali *et al.*, 2008). Based on studies showing mislocalization effects as a consequence of cortical reorganization, it is reasonable to assume that plasticity-induced disinhibition and decrease in lateral inhibition for near-threshold stimulation share a general neuronal mechanism. During both the plastic changes of cortical organization and the processing of weak stimuli, disinhibition of lateral cortical connections in sensory cortex increases the amount of sensory input to a certain representation zone. This mechanism presumably enables the processing of weak sensory input. However, disinhibition related to cortical reorganization, as well as to near-threshold stimulation, will occur at the expense of spatial localization accuracy, which is captured by assessment of systematic mislocalization profiles.

Although the results of the present study do not support the 'peripheral hypothesis' there are good reasons to consider a peripheral mechanism for the explanation of the characteristic mislocalization profiles found for near-threshold stimulation.

Psychophysical studies of somatosensory processing have identified four psychophysical channels, each of which is based on a different skin receptor. Accordingly, tactile processing and the contribution to the tactile percept differ characteristically between the four channels (Johansson & Vallbo, 1979). The P-channel receives its input from Pacinian corpuscles while the so-called non-Pacinian (NP-) channels are associated with rapidly adapting Meissner bodies (NPI), slowly adapting Ruffini organs (NPII) and Merkel cells (NPIII) (Bolanowski *et al.*, 1988; Gescheider *et al.*, 2001, 2002, 2004). NPI and NPIII channels, associated with receptors in the superficial skin, are characterized by a high spatial resolution and sensitivity for low frequencies of approximately 30 Hz. The receptors located in deeper layers of the skin, Ruffini organs and Pacinian corpuscles, show a high sensitivity for higher frequencies of approximately 200–300 Hz. In contrast to NP-channels, the P-channel processes tactile signals at a low spatial resolution. For intensity processing the order is reversed, with P-channel being highly sensitive, followed by NPI/NPII channels, and the NPIII channels showing the highest threshold (see Table 4) (Johansson & Vallbo, 1979; Gescheider *et al.*, 2002, 2004).

The activation of different receptor types for the processing of weak and strong stimuli seems also to be a general feature that is not specific to the somatosensory system. Analogous mechanisms can be found in vision. In the retina there are two types of receptors: rods and cones. Low-intensity visual stimuli can only activate low-threshold rods that relate to black-and-white vision and that are characterized by low spatial acuity. High-intensity visual stimuli also activate cones that allow for high-acuity colour vision. Input from either rods or cones dominates visual stimulus perception depending on light intensity.

In the present study, the frequency tuning of the different somatosensory input channels was used to test whether the 'peripheral hypothesis' can be supported. As discussed above, our results are incompatible with the 'peripheral hypothesis'. However, from the present study it remains unclear at which level of central processing the mislocalization phenomenon occurs. According to studies in patients suffering from finger agnosia, higher level somatosensory areas in parietal cortex seem to be involved (Roeltgen *et al.*, 1993; Roux *et al.*, 2003). However, from studies in amputees, the lateral part of ventroposterior thalamus (Rasmusson, 1996; Jones, 2000; Jain *et al.*, 2008), as well as primary (Merzenich *et al.*, 1984; Knecht *et al.*, 1995; Jones, 2000; Jain *et al.*, 2008) and secondary (Grüsser *et al.*, 2004) somatosensory cortex or parietal cortex are potential brain regions where stimulus intensity-dependent overlap of body representation might take place. Physiological experiments in animals and imaging studies in humans may help to identify the neural substrate of systematic mislocalizations in the future.

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Abbreviations

D2, index finger; D3, middle finger; D4, ring finger; DA, digital-to-analog; NP, non-Pacinian; P, Pacinian; SI, primary somatosensory cortex.

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Appendix 1 – Normalization procedure for experiment 1

To obtain subjects' mislocalization profiles the number of subject's i total mislocalizations for a certain stimulation frequency f_q and for the stimulation of the j^{th} finger

$$N_{ij}^{q} = \sum_{k \neq j} N_{ijk}^{q} \tag{3}$$

was determined. In addition, average numbers of mislocalizations across all stimulation frequencies and stimulated fingers were calculated:

$$\overline{N_i} = \frac{1}{QJ} \sum_{q=1}^{Q} \sum_{j=1}^{J} \sum_{k \neq j} N_{ijk}^{q}. \tag{4}$$

$Q = 3$ and $J = 3$ corresponded to the total number of frequencies studied and to the total number of stimulated fingers. By normalizing the number of mislocalizations according to

$$n_{ijk}^{q} = N_{ijk}^{q} \frac{\overline{N_i}}{N_{ij}^{q}}, \tag{5}$$

the sum of mislocalizations for a certain stimulation frequency and for the stimulation of a certain finger was set to a subject's average value $\overline{N_i}$.

In the final step, the number of mislocalizations to the first $(r = |k - j| = 1)$ and the second $(r = |k - j| = 2)$ neighbour with respect to the stimulated finger was computed (see Table 1 for an example of the normalization procedure).

$$v_{ir}^{q} = \sum_{k,j} n_{ijk}^{q}\ , \quad \text{for } r = |k - j|. \tag{6}$$

Appendix 2 – Normalization procedure for experiment 2

The normalization of number of mislocalization errors N_{ijk} to finger j after stimulation of finger k for subject i was based on the average number of mislocalizations across the stimulated fingers:

$$\overline{N_i} = \frac{1}{J} \sum_{j=1}^{J} N_{ij}, \text{ with } N_{ij} = \sum_{k \neq j} N_{ijk}. \tag{7}$$

J corresponds to the number of fingers stimulated. By normalizing the number of mislocalizations according to

$$n_{ijk} = N_{ijk} \frac{\overline{N_i}}{N_{ij}}, \tag{8}$$

the sum of mislocalizations for the stimulation of a certain finger was set to the average value $\overline{N_i}$.

Again, the number of mislocalizations to the first $(r = |k - j| = 1)$ and the second $(r = |k - j| = 2)$ neighbour with respect to the stimulated finger was computed (see Table 3 for an example of the normalization procedure)

$$v_{ir} = \sum_{k,j} n_{ijk}\ , \quad \text{for } r = |k - j| \tag{9}$$

and summed across participants.