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PhD thesis

The somatotopic representation of nociceptive stimuli in perceptual space

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2007

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Foreword

The studies included in this thesis were conducted in the course of a cooperation between the universities of Mannheim and Aalborg. After a visit to the Otto Selz Institute lab in Mannheim in 2003, Lars Arendt-Nielsen suggested that our—at this time only roughly sketched—experiment addressing the saltation phenomenon in the nociceptive domain could be run with the superior laser set-up at his lab. This changed the then-existing plans for my PhD thesis completely (certainly for good, as I admit in retrospect). In 2003 and 2004 I payed several visits to Aalborg to prepare and run the experiments and came back to Mannheim with huge stacks of psychophysical data. Analysis and publication proved to be more time-consuming than expected, as we soon found out that simple standard statistics were only partly helpful in highlighting the most interesting details of the results. At last, this volume presents the outcome of these efforts.

In addition, the approaches detailed in this volume will be continued in a larger framework. Just recently, the international, interdisciplinary research network SOMAPS ('Multilevel systems analysis and modeling of Somatosensory, Memory, and Affective maPs of body and objects in multidimensional Subjective space'), funded by the European Union, has started its work.

Many people were involved in the success of these studies, but some deserve special citation:

Annette M. Stolle helped develop the direct localisation procedure and experimental design, which were both based on her own excellent studies on tactile localisation.

Carsten D. Mørch and *Rodney J. Wilkins* supported me in adminstrative and technical issues and were particularly involved in setting up the laser.

I appreciate *Dieter Kleinböhl*'s methodological advice and recommondations. In addition, I have to thank him for partly taking over a lot of our common administrative work which provided me with the time to finish this thesis at last.

Without the good cooperation between the Otto Selz Institute in Mannheim and the Centre for Sensory-Motor Interaction in Aalborg, the whole project would not have been possible. *Lars Arendt-Nielsen* and *Rupert Hölzl* provided me with the necessary funds, gave important feedback on design, analysis, and publication issues, and exercised patience while I was struggling with my paperwork.

I also have to thank *Herta Flor*, *Jan R. Buitenweg*, and *Lotte N. S. Andreasen Struijk* for acting as opponents in my PhD defence. Their questions during the defence gave me further food for thought, and their comments on the preliminary version of this thesis certainly helped to improve it.

Mannheim, November 2008

Summaries

Summary

The three studies contained in this PhD project implement the first steps in a framework for measuring, depicting, and analysing *perceptual maps* for laser-induced heat/pain stimuli delivered to the body surface. Such quantitative descriptions of stimulus positions as individually perceived provide *independent psychophysical measures* of the central somatotopic representation of the body. Their applications include the refinement and interpretation of neuroimaging approaches to somatotopy as well as the diagnostics of plasticity in the body image accompanying pain and other syndromes.

In study 1, heat/pain stimuli were presented to predefined positions on the dorsal forearm and participants were instructed to point at the perceived positions with a 3D digitiser. The results indicated that in general the somatotopic order of selective heat/pain stimuli can be reported accurately, but some individuals exhibited particular systematic distortions in their ratings. Study 2 repeated the same paradigm with the the same sample, this time after experimental modulation of the nociceptive processing characteristics through topical application of capsaicin. Besides an expected decrease in accuracy, the topographic order and the metric relations of the individual somatotopic representations were well preserved after capsaicin, but in most participants the range of the average perceived positions was 'compressed' to a smaller range. Using the same technique for reporting perceived positions, study 3 demonstrated the existence of the *saltation* phenomenon in the heat/pain domain. Saltation consists of a systematic perceived displacement of a target stimulus towards a following reference stimulus at a distant position which increases with shorter delays in terms of activation-dependent plasticity. Our results indicate spatio-temporal interaction in the processing of heat/pain location information similar to the mechanoceptive modality.

Taken together, these studies (1) introduced a psychophysical approach to the measurement of subjective localisation on the body surface and (2) demonstrated the existence of a modality-specific somatopic representation of heat/pain stimuli which is subject to alterations induced by modulation and activation-dependent plasticity. These results have implications for a wide area of applications ranging from diagnostic procedures to the validation of neurofunctional data.

Sammenfatning
De tre studier, der er indeholdt i dette Ph.D.-projekt, implementerer de første trin i et metodeapparat til måling, afbildning og analyse af *perceptionskort* til laser fremkaldt varme/smerte stimulationer påført på kroppens overflade. Sådanne kvantitative beskrivelser af stimulationspositioner, som opfattes individuelt, giver *uafhængige psyko-fysiske målinger* af kroppens centrale somatotopiske repræsentation. Deres anvendelse inkluderer videreudvikling og fortolkning af neuroimaginære tilgange til somatotopi og ligeledes også diagnosticering af plasticitet i det kropsbillede, der ledsager smerter og andre syndromer.

I studie 1 blev varme/smerte stimulationer påført på prædefinerede positioner på den dorsale underarm, og deltagerne blev instrueret i at udpeget den opfattede position med en 3D digitiser. Resultaterne indikerede, at generelt kan den somatotopiske organisation af varme/smerte stimulationer rapporteres nøjagtigt, men visse personer udviste særlige systematiske forvridninger i deres bedømmelser. Studie 2 gentog det samme paradigme med det samme eksempel, denne gang efter eksperimental modulering af de nociceptive behandlingskarakteristika gennem topisk påføring af capsaicin. Ud over det forventede fald i nøjagtighed blev den topografiske organisation og de individuelle somato-topiske afbildningers metriske relationer velbevaret efter capsaicin, men hos de fleste deltagere blev spændvidden af de gennemsnitlige positioner "komprimeret" til en smallere spændvidde. Ved hjælp af samme teknik blev eksistensen af *saltations*-fænomenet i varme/smerte domænet påvist i studie 3. Saltation består af en systematisk opfattet forskydning af mål stimulus hen imod den følgende reference stimulus på en fjerntliggende position, som stiger med kortere forsinkelse hvad angår aktiveringsafhængigt plasticitet. Vore resultater indikerer spatio-temporal interaktion i behandlingen af varme/smerte lokationsinformation i lighed med den mekanoceptive modalitet.

Sammenlagt introducerer disse studier (1) en psykofysisk tilgang til måling af subjektiv lokalisering på kroppens overflade og (2) påviste eksistensen af en modalitets-specifik somatopisk repræsentation af varme/smerte stimuli, der er genstand for ændringer fremkaldt af modulering og aktiveringsafhængig plasticitet. Disse resultater har implikationer for et stort område af applikationer rækkende fra diagnostiske procedurer til validering af neurofunktionelle data.

Introduction

The perception of our own body is subject to changes depending on situation and previous experience. These changes go along with functional and even structural reorganisations of the neural substrate of sensation and perception (for a review see Elbert and Rockstroh, 2004). Distortions in the perception of one own's body have been repeatedly reported for some acute and a number of chronic pain conditions, in particular phantom pain (Flor et al., 1998; Ramachandran and Blakeslee, 1998), but direct experimental analyses of the perceptual changes involved are still scarce (see below). In addition, many studies rely heavily on changes in correlated cerebral activation to assess related neuroplastic changes in central representation. However, the relation between cerebral topography and the topology and metrics of the *perceptual space* itself is not clear (see below, p. 11ff.).

Experiments with healthy participants have shown that the perceived size of body parts increases in response to acute innocuous or painful stimulation and under local anaesthesia (Gandevia and Phegan, 1999), suggesting that such paradigms could provide suitable markers of body image distortions in pathological pain states as well. In one of the rare systematic clinical studies addressing this issue, Moseley (2005) presented patients with complex regional pain syndrome (CRPS1) a set of one correct and six manipulated (expanded and compressed) photographs of their hand and instructed them to choose the picture they thought was accurate. 63% of the CRPS1 patients chose an expanded picture, while this was only the case in 17% of the control patients. Moseley's work highlights the possibility to derive systematic *measures* of the changes in body perception experienced by pain patients, instead of settling with clinical phenomenology, which is of limited use in regard to an integrated analysis with other dimensions.

Moseley's approach was targeted on the demonstration of the altered body perception in a clinical group, and it serves this purpose well. If however one is interested in the characteristics of these alterations themselves, one has to think of an approach which allows a description of the body surface as it is individually perceived. The most intuitive way to achieve this aim is to deliver stimuli to the body surface and to record where the participant under study has *perceived* these stimuli. If this procedure is repeated at varying positions, a *perceptual map* will result which provides a parametric description of the somatotopic representation of the body surface in subjective phenomenal space.

Such maps are capable of integrating *multiple* dimensions, which may be used to represent separate somatosensory modalities, e.g., touch and pain, in independent but directly comparable maps. This concept is not restricted to spatial dimensions. In fact, the power to further add a *temporal* dimension is a crucial feature, as perception is inherently *dynamic*. Last not least, these maps provide access to different ontological levels of perception than the mere assessment of the underlying neural processes and are as such complementary to neuroimaging approaches to somatosensation. They may be directly and quantitatively related to brain activation maps in order to promote further insights in the relation between perception and its underlying neural basis.

Aims

The studies presented in this volume are first steps towards a conceptual framework for measuring perceptual maps in humans. A distinctive feature of these studies is that they all use heat stimuli which selectively activate nociceptive pathways. On the one hand, this reflects the outstanding importance of this 'special flavour' of somatosensation concerning future clinical applications. On the other hand, this choice already demonstrates that our approach can be applied to a more 'complicated' modality than mechanoception.

An overview of the studies and their respective main focus is given in Figure 1. In particular, the following specific aims were addressed:

Implementation of a psychophysical procedure for the assessment of perceived positions on the body surface

One of the basic aims of all studies was to provide starting points for a methodological framework for measuring perceptual maps. We implemented and applied a technique for measuring the perceived positions of heat/pain stimuli on the skin by direct localisation with a 3D digitiser, derived from an earlier approach to tactile localisation (Stolle, 2004). Study 1 demonstrates the practicality of this approach, which is used in all studies.

Development of an appropriate graphical representation for the depiction of perceptual maps

In order to depict the individual relations between the physical stimulus positions on the body surface and the according perceived positions, we developed a unique graphical representation. The resulting 'localisation profiles' were introduced in study 1 and applied again in an expanded form in study 2.

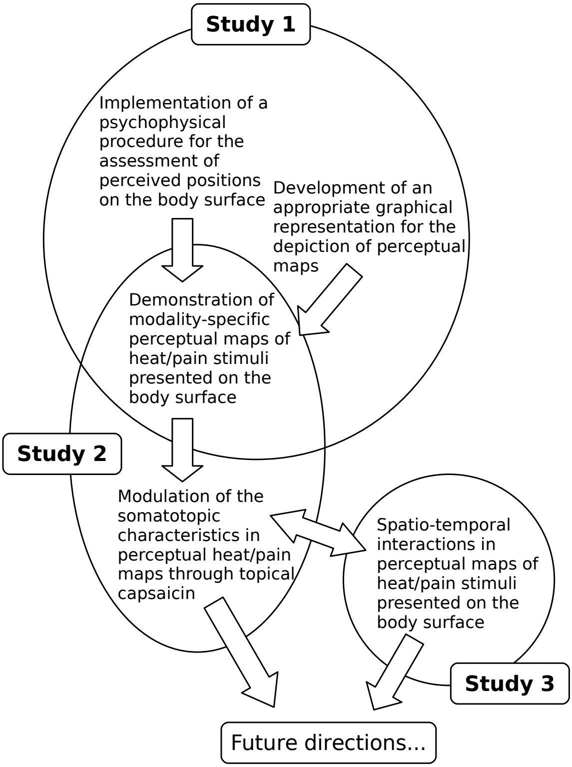

Figure 1: Overview of the studies and their respective aims. See text for details.

Modulation of the somatotopic characteristics in perceptual heat/pain maps through topical capsaicin

As discussed above, alterations of the 'body image' in chronic pain are frequently reported but seldom experimentally validated. Perceptual maps could in principle be used to track changes in the perceptual representation of the body and/or to compare them to norm values. In order to test the diagnostic capabilities of our approach, study 2 used the same experimental protocol as study 1 in the same sample of healthy participants, this time, however, after modulating their body perception with topical capsaicin as a model for alterations in the peripheral nociceptive signal.

Spatio-temporal interactions in perceptual maps of heat/pain stimuli presented on the body surface

Study 3 combined two aims in one experiment: Firstly, we wanted to demonstrate the saltation phenomenon in the thermal-nociceptive domain in order to underline its importance as an indicator of fundamental spatio-temporal processes common to most if not all sensory modalities. The second goal was to introduce saltation as a marker for activation-dependent plasticity in the pain-specific spatial perception of the body surface, applicable as a diagnostic tool similar to activation-dependent characteristics in pain intensity perception (cf., Kleinböhl et al., 1999).

The results of the presented three studies provide many links to future developments (see p. 27f.) and have already fostered the establishment of an interdisciplinary research network funded by the European Union (see p. 1).

Prerequisite considerations for the assessment of perceptual heat/pain maps

The somatosensory aspects of nociception and thermoception

Somatosensation encompasses mechanoception, proprioception, thermoception, and nociception (Gardner et al., 2000). The latter two possess certain features which set them somewhat apart from the former two: Nociception and thermoception not only serve somatosensory purposes, but also play a major part in a framework of *interoception* 'in the sense of the physiological condition of the entire body' (Craig, 2002).

Nociception denotes the detection and processing of events which—at least potentially—cause harm to the biological system and is seen as the neural basis for the subjective sensation of pain (Basbaum and Jessell, 2000). However, the activation of peripheral nociceptive fibres is neither mandatory nor sufficient for the experience of pain. On the one hand, nociceptors may respond to innocuous temperatures as low as 40 °C (Torebjörk et al., 1984; Treede et al., 1998), well within the range of thermoceptors, leading to paradoxical non-painful 'pre-pain' sensations (Pertovaara et al., 1988). On the other hand, there is a wide range of clinical syndromes in which peripheral factors alone cannot explain the pain sensation or can be excluded altogether.

A yet unsolved question concerns the relative contribution of thermoception to the pain sensation, as '[p]ain and temperature sensibilities are closely coupled structurally at all levels of the central nervous system' (Craig, 1996, p. 31). The response ranges of thermoceptors and nociceptors overlap considerably, so it must be assumed that at stimulus intensities around the individual pain threshold both receptor types are active. Even if their relative contribution to the subjective sensation of heat pain is assumed to be relatively stable in a single organism, inter-individual differences may be large. At the spinal level multi-modal integration plays an important role in pain processing, e.g., in the wide dynamic range neurons, which also receive input from mechanoceptive fibres. Based on individual experiences, the processing characteristics at such relatively basal stages may already differ considerably between organisms. The situation becomes even more complex at higher stages: The subjective experience of pain depends on a range of factors, entering the equation in a specific organism with an individual set of weights. Consequently, even if the response characteristics of peripheral neurons are known, their specific effect on the overall experience in a given individual is difficult to predict.

These examples underline the ambiguity of 'nociception' already at the sensory level, without even taking into account the vast amount of motivational and cognitive influences. In this paper, a pragmatic view of nociception as class of neuronal processes contributing to the sensation of pain will be used, not denying the possible input of non-nociceptive structures, already at the level of peripheral receptors.

The ability to localise nociceptive stimuli

The most important requirement for the assessment of perceptual heat/pain maps is the ability of humans to accurately localise such stimuli. Measuring the spatial accuracy of somatosensory perceptions in regard to their physical position has a long tradition. However, researchers mostly limited themselves to the investigation of touch, while thermal and nociceptive stimuli received little interest. This may relate to the fact that in everyday speech the term 'pain' is much more associated with its *motivational-affective* than with its *sensory-discriminative* component (cf., Melzack and Casey, 1968 for definitions of these terms). Some years ago, Moore and Schady (1995) stated that '[t]he generally held view is that painful stimuli are poorly localised', and it has changed little since. This is astonishing, as a small but consistent body of research exists which refutes this view. As early as 1934, (Zigler et al., 1934) had reported findings indicating that

> stimulations of pain are localised with a slightly greater degree of accuracy than stimulations of pressure. Stimulations of pressure-pain complex are localised, in general, with a degree of accuracy slightly greater than for either of the simple qualities of pain or pressure. (Zigler et al., 1934, p. 58)

In these early studies, usually small needles or thorns were used to elicit pain. However, as long as a stimulus requires direct contact to the skin, concomitant activation of mechanoceptive pathways can never be ruled out completely. Consequently, the problem of separating 'touch' and 'pain' components led to controversial findings (e.g., Mayer, 1925, 1927; Zigler et al., 1934; Ponzo, 1911; von Skramlik, 1925, 1927).

It took several decades until the introduction of lasers in experimental pain research (Arendt-Nielsen and Chen, 2003; Bromm and Treede, 1984; Mor and Carmon, 1975) improved the situation by allowing touchless well-localised painful stimulation. Physiological studies clearly indicate that laser stimuli activate nociceptive Aδ and C fibres (Bromm and Treede, 1984) which are responsible for the 'first' and 'second' pain sensations (Gardner et al., 2000). Still, to date only a very small number of pain localisation experiments using laser stimuli have been published. Two particular studies are especially noteworthy, as they demonstrated convincingly that laser-elicited nociceptive stimuli can be localised almost as accurately as tactile stimuli:

Moore and Schady (1995) compared tactile and nociceptive localisation accuracy on the dorsum of the hand, forearm, and the dorsum of the foot. Generally, tactile stimuli (70 mN von Frey hair) yielded the smallest localisation errors, followed by 'sharp pricking' (i.e. 'first') pain (100 ms CO_2 laser pulses of 1 W, beam diameter 4.4 mm) and 'hot burning' (i.e. 'second') pain (300 ms CO_2 laser pulses of 1 W, beam diameter 1.5 mm). A significantly better accuracy for the first pain localisations was only found on the dorsum of the hand. Most important for the comparison with our own studies, on the forearm the mean localisation errors for tactile stimuli were 20.6 mm (SEM 7.5, range 3–50), while for 'first' and 'second' pain values of 21.5 mm (SEM 7.9, range 0–50) and 22.0 mm (SEM 8.8, range 3–90) were reported, respectively. These results show that there is virtually no difference between tactile and presumably AMH-fibre-related 'first' pain localisation accuracy, and even 'second pain' C-fibre-related localisation is only set apart by the higher variability of the ratings, not the average accuracy.

Schlereth and colleagues (2001) used another approach to assess spatial discrimination thresholds for heat pain (3 ms thulium laser pulses, beam diameter 5 mm), mechanically-induced pain (200 µm probe) and innocuous touch (1.1 mm von Frey probe): With a two-alternative forced-choice paradigm they assessed on which of two parallel lines marked with a felt-pen on the dorsum of the hand a stimulus was perceived. This procedure resulted in mean discrimination thresholds of 9.0 mm for touch, 8.6 mm for heat pain, and 5.1 mm for pin-prick pain. Considering the methodological differences, these results compare fairly well to those reported by Moore and Schady (1995). Of special interest in regard to the issue of somatotopic representations (see below) is their observation that discrimination thresholds in radial-ulnar direction were generally smaller than in proximal-distal direction.

Taken together, these reports demonstrate that the accuracy of Aδ-related 'first' pain localisation is comparable to tactile localisation. Even more surprising is the fact that the localisation of C-fibre-related 'second' pain is only marginally worse, which had already been observed earlier by Koltzenburg and colleagues (1993) using a thermode in combination with a differential A-fibre nerve block.

Cerebral somatotopic representations of nociceptive stimuli

The concept of the 'lateral pain system' as described by Treede et al. (1999) explicitly includes the postcentral gyrus, which serves as a plausible cortical correlate of the somatotopic representation of thermal and nociceptive stimuli. Especially the fact that this location would allow direct references to the mechanoceptive body map supports this idea. In all cited studies, as well as in our own, participants were directly or indirectly asked to rate positions in relation to the percept of their body surface. In other words, the heat/pain-specific representation had to be referenced to an integrated multisensory body map.

The high localisation accuracy for nociceptive stimuli provokes questions on how these perceptions are encoded in the nervous system. The fact that selective activation of thermal and nociceptive pathways does not impair the localisation accuracy indicates that there has to be some somatotopic representation which is independent of the 'classic' mechanoceptive homunculus but allows a comparable accuracy. Most importantly, however, this representation can be consciously accessed and is subject to focused attention.

Neurofunctional evidence supports this idea. Nociception-related activations ascribed to the postcentral gyrus have been demonstrated (Andersson et al., 1997; Tarkka and Treede, 1993), which presumably do not stem from the mechanoceptive SI 'proper' (area 3b), but rather from the neighbouring area 3a (Ohara et al., 2004). Nonetheless, such postcentral nociception-related activations are only found inconsistently with EEG, PET and fMRI methods (Derbyshire, 2000; Garcia-Larrea et al., 2003). This partial failure may relate to three main reasons.

1. Neurofunctional methods have certain spatial and/or temporal limits, which only allow the detection of comparably large and/or prolonged activations. As a side effect, the processing characteristics of smaller, deeper, and less structured areas are generally less well understood than those of cortical areas.

2. The impressive evidence on the tight somatotopic organisation of the primary somatosensory and visual cortices has led to a bias in looking for somatotopic

representations as two-dimensional maps. However, somatotopy on the perceptual level need not necessarily be implemented in terms of spatial neighbourhood of neural activations.

3. There may be several different somatotopic representations of the body, not only modality- but also task-specific. Consequently, brain activation maps must be seen as indicators of *functional* representations, which can be subject to change depending on task and situation.

Based on these considerations, it is conceivable that the functional role of SI lies in the 'active' localisation of nociceptive stimuli in reference to the body. For tasks not addressing this function, however, activation of SI may not even be necessary or at least become less consistent. This would be an explanation for the controversial findings on SI activation in neurofunctional studies, as they usually did not include specific tasks. One study by Bentley and colleagues (2004) is a rare exception, as they reported a laser-evoked potential component specific to a pain localisation task. Unfortunately, its topography was consistent not only with a possible generator in SI, *but also* in the insula or SII, thus not settling the case. The presumed integration site of the 'body image', the insula, is indeed another possible candidate for a uni- and/or multi-modal somatotopic representation of heat/pain sensations, however, probably having a different functional focus (cf., Craig, 2002).

Spatio-temporal dynamics in somatotopic representations

Woolf and Salter (2000) suggested three stages of plasticity in pain intensity perception, activation-dependent plasticity, modulation and modification. This concept explicitly addresses interactions between the three stages, meaning that short-term processes may induce lasting changes in medium- and long-term processes and vice versa.

The *wind-up* phenomenon is as a good example for these interactions: The term wind-up denotes the reversible sensitisation achieved within seconds by temporal summation of single pain stimuli at rates faster than 0.3 Hz, supposed to be caused by activation-dependent neuronal plasticity in spinal dorsal horn neurons (Mendell, 1966). While not playing a direct role in the development of chronic pain, as was assumed in earlier times, it has been demonstrated that the psychophysical characteristics of this phenomenon are altered by medium- and long-term modulation and modification, thus serving as a diagnostic indicator for clinical pain (Kleinböhl et al., 1999).

Wolf and Salter's concept has to date mainly been applied to the plasticity of intensity perception. However, as argued above (p. 5), there is evidence that alterations in the *spatial* perception of one own's body are an important component in pain disorders (and many other syndromes as well). Such phenomena also represent acquired changes resulting from patterns of sensory information, thus it seems plausible that the proposed three stages may be transferred to the plasticity of body perception, although the underlying neural processes may be different.

In this sense, the category of *activation-dependent plasticity* clearly applies to a wide range of phenomena usually termed perceptual *illusions*, referring to distortions of the mental compared to the physical stimulus patterns related to their spatio-temporal characteristics. A prominent example is the *phi* phenomenon, in which the perception of motion is produced by a succession of still images presented in a certain frequency (Wertheimer, 1912).

Being one of the rare illusions originally discovered in somatosensation rather than in auditory or visual perception, the *saltation* phenomenon (Geldard and Sherrick, 1972) consists of systematic distortions in the spatial perception of spatio-temporal stimulus patterns presented to the skin: the perceived displacement of a *saltatory* stimulus towards a following reference stimulus at a distant location increases with shorter delays, eventually leading to the spatial 'coincidence' of the two stimuli. The phenomenon is restricted to a certain distance between the presented stimuli, the so-called 'saltatory area'. Saltation was first demonstrated in the tactile modality (Geldard and Sherrick, 1972), but it exists also in the visual and auditory systems (Lockhead et al., 1980; Shore et al., 1998) and seems to represent a common property of sensory networks in the CNS.

Geldard and Sherrick (1983) argued that the neural basis of saltation lies in the cortex, with the saltatory area being directly related to the size of cortical receptive fields. They based their conclusion on several observations which disqualified a more peripheral origin, among them the possibility to perceive the illusionary stimulus in anaesthetised skin areas or the blind spot of the retina (cf., Lockhead et al., 1980) as well as their failure to observe saltation across the body mid-line. Acting on these assumptions, Wiemer et al. (2000) proposed a neural network model designed to explain the saltation phenomenon as the perceptual correlate of the dynamic behaviour of sensory maps in the brain. Although some details of these positions may be subject to criticism, the idea of altered activation patterns in the cortex as a correlate of saltation has been supported by a recent neuroimaging study: Blankenburg and co-workers (2006) demonstrated that activation in the primary somatosensory cortex was indeed related to the perceived 'illusionary' position of saltatory stimuli.

These results demonstrate the dynamic, i. e., spatio-temporal nature of the representation of the body surface in perception. Thus, the psychophysical characteristics of saltation and related phenomena may provide the adequate quantitative correlate in subjective space of the dynamics of uni- and multi-sensory brain maps in cerebral space. From this perspective, experimental saltation paradigms appear to be an ideal probe into the computational bases of our body image.

Main results

A method for measuring perceived positions on the body surface

In all three studies, stimulus locations were arranged in an array on the dorsal forearm. The participants were instructed to mark the perceived location of CO_2 laser pulses directly after presentation by pointing at them with the 3D digitiser and pressing a button. In our experiments the participants were only asked to rate the perceived position along the distal-proximal dimension without touching the skin. This procedure provided us with individual one-dimensional indicators of the subjective somatotopic representation of the presented stimuli.

All experiments followed a common approach: Instead of the accuracy of single pulse localisations we examined the perceptual pattern resulting from a larger number of stimuli applied at numerous different locations on the skin. The method of pointing at the perceived positions with a 3D digitiser provided a comparably intuitive way of reporting the perceived positions and could be operated easily by the participants.

We developed a method of depicting these results in the form of *localisation profiles* which allow to visualise the relations between the two levels of *physical stimulus positions* on the body surface and the *perceived positions* as reported by the participants (study 1, figure 2). These graphs also allow a direct comparison *between* individuals. Taken together, this approach provides a straightforward psychophysical description of the somatotopy of heat and pain stimuli.

Study 1: Individual perceptual maps of heat/pain stimuli

The most surprising result in study 1 was the inter-individual variability, not in terms of localisation accuracy, but rather concerning the localisation 'style', e.g., manifesting in the ratings as systematic attractions towards or repulsions from certain positions, or overall compression or distension of the range of perceived positions in relation to the actual stimulus pattern (study 1, figure 2).

For each individual participant, the relation between the physical positions and the perceived positions could be described quite well with linear regressions yielding high amounts of explained variance. The many 'distortions' visible in the localisation profiles led us to believe that in principle non-linear regressions

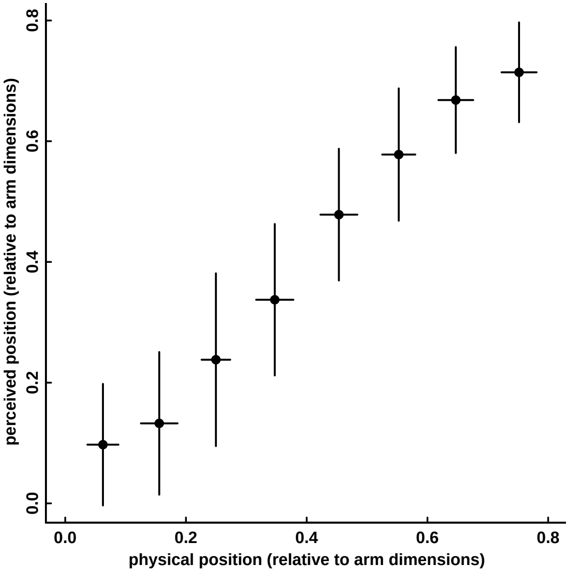

Figure 2: Mean perceived positions in study 1, aggregated over intervals of one tenth of the armlength, in relation to the according physical positions. Horizontal and vertical bars indicate standard deviations of physical stimulus positions and perceived positions within these intervals.

should be more appropriate in describing the relation. However, our approach of fitting exponential and logistic regressions to the data proved to be unsatisfactory: While in some individuals the more complex models indeed increased the amount of variance explained, this was not consistently the case. A refined conceptual framework is needed for future studies in order to generate and test hypotheses specifically aimed at these individual parameters.

Figure 2 shows a descriptive attempt for a concise visual description of the relation between physical and perceptual space for the whole group, which we developed after the publication of the original article and which has also been adopted for study 2. While not allowing any statistical inferences, the figure summarises the main results of study 1:

1. Averaged over the entire sample, the perceived positions match the physical positions very well, as can be seen by the close proximity of the mean positions to the gradient of absolute correspondence.

2. The large standard deviations show that the amount of unsystematic ‘noise’ in the group data is relatively high, which is both due to the inherently limited measurement accuracy of the pointing procedure as well as the remarkable individual differences.

3. The ‘s-shaped’ curving of the relation between physical and perceived positions which was more pronounced in some and less pronounces in other individual graphs is preserved after averaging. This *may* be seen as an indicator for its general relevance, but more studies, which explicitly address this effect, are needed for a fair evaluation.

Study 2: Modulation of perceptual heat/pain maps

As expected, we found an unspecific decrease in localisation accuracy after the topical application of capsaicin. The topographic order and the metric relations of the individual somatotopic representations were well preserved after capsaicin, to the effect that the personal localisation ‘style’ was maintained in the individual profiles. However, in 9 out of 11 participants, the range of the average perceived positions was reduced, that is, the somatotopic map was ‘compressed’ to a smaller range. This effect can be observed quite well in the individual localisation profiles (study 2, figure 2), but also in the group graph contrasting the average results before and after capsaicin (study 2, figure 3).

The observations from study 1 showed that in some paticipants non-linear terms increased the fit of our regressions and that non-linear influences were still prominent in the averaged group graph. Based on the reports indicating that ongoing nociceptive input alters the perceived size of body parts (Gandevia and Phegan, 1999; Moseley, 2005), we expected that after capsaicin application the deviations from linearity would increase further. This was not generally the case. Figure 3, which was not included in the original manuscript, shows individually fitted regressions with non-linear terms. Only in 5 out of 11 participants did exponential and/or logistic regression terms increase the fit slightly (additional 1–3 %) compared to linear terms. This mixed result is contrasted by the strong non-linear influences visible in the averaged group graph (study 2, figure 3A): Not only is the ‘s-shaped’ curving from study 1 preserved, it is even more pronounced.

Although many questions are left open for further investigations, this study clearly demonstrated that the perceptual maps as derived from subjective report can be altered substantially already in a time frame of several minutes by modulation of nociceptive pathways. The changes induced by topical capsaicin follow a common pattern, namely a general decrease in accuracy and detection rate accompanied by a systematic distortion of the map metrics in terms of a compression of the perceived area. This success in tracking medium-term plasticity (‘modulation’) gives rise to the hope that the very same technique is capable of assessing chronic changes and may be developed into a diagnostic tool for alterations in body perception accompanying pain and other syndromes.

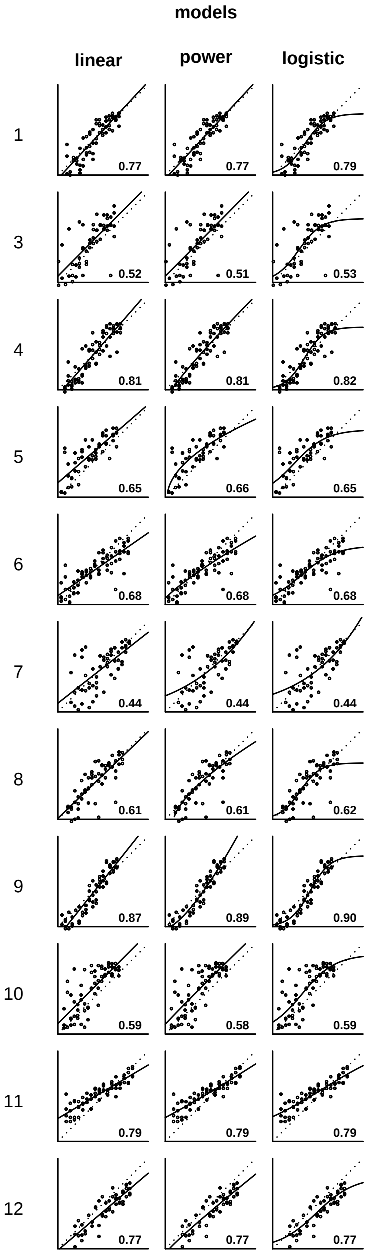

Figure 3: Scatter plots of the relations between physical (abscissa) and perceived positions (ordinate) after the topical application of capsaicin, separate for each individual participant. Overlaid are the graphs of the three estimated regressions (linear, exponential, and logistic) and corresponding adj. R^2 values. Coordinates are normalised to the subjects' individual forearm length. The dotted bisecting line represents the (theoretical) gradient of absolute correspondence between physical and perceived locations, values above showing proximal and values below denoting distal mislocalisations.

Study 3: Dynamics of perceptual heat/pain maps

In this study, we demonstrated the saltation phenomenon in the processing of heat and pain stimuli without tactile co-activations (study 3, figure 2). The resulting psychophysical characteristics were in line with those found in the classic tactile studies (e. g., Geldard and Sherrick, 1972; Cholewiak and Collins, 2000), and compared particularly well to more recent results from our group in which a very similar experimental set-up was used (Stolle, 2004). This is another demonstration of the similarity between the perceptual somatotopic representation of heat/pain and tactile stimuli, even in terms of being subject to the very same spatio-temporal interactions.

In addition to the predicted effect of the inter-stimulus interval, another factor had an unexpectedly high influence on the amount of mislocalisation of the saltatory stimulus: In order to reduce the amount of laser pulses directed at the same spot on the skin, we had to systematically move the stimulus pattern along a predefined array. The results showed that the more proximal the stimuli were presented, the smaller was the distance between the perceived positions of the 'reference' stimuli, and the higher was the amount of relative mislocalisation of the saltatory stimulus (study 3, figures 3 and 4). However, no comparable data from the tactile domain are available to determine whether this effect is also present in a purely mechanoceptive protocol (see Discussion, p. 21ff.).

Our second aim in this study was to introduce saltation as a marker for activation-dependent plasticity in the pain-specific spatial perception of the body surface. The results indicate that in principle the applied technique is sensitive enough to measure the stimulus-response characteristics of the spatio-temporal interactions underlying the saltation phenomenon. With an adequate control of the distal-proximal differences in future implementations it will be possible to assess individual saltation profiles as indicators of the perceptual metrics. These profiles may serve as psychophysically well-defined markers for modulations and modifications in the body image. If only the suggestions concerning the cerebral basis of the saltation phenomenon (Geldard and Sherrick, 1983; Wiemer et al., 2000) are roughly appropriate, functional changes in the body representation will lead to detectable deviations in the mislocalised saltatory position. As a related effect, changes in the size of cortical receptive fields are expected to affect the size of the saltatory area. A diagnostic procedure based on our method will be applicable to a wide range of syndromes including changes in the body image, not restricted to pain. Especially the availability of comparable techniques in the mechanoceptive *and* thermo-/nociceptive modalities opens new perspectives to a multi-modal assessment of body perception.

Discussion

Many details of the above results require further consideration. Our use of a direct localisation approach is second to none in this respect, as it forms the base of all our results. The objections expressed by Schlereth and colleagues (2001) regarding the accuracy of pointing methods clearly apply: Our method has some pitfalls, both concerning reliability and validity of the measurement. The former relates to unsystematic errors (e. g., the unavoidable shaking of the hand while pressing the response button) which can in principle be counteracted by averaging. More important is the latter issue, as it concerns the question of which mental processes are actually being measured with this technique. Obviously, besides the 'simple' detection of the stimuli, the participants' responses are also dependent on attentional, cognitive-evaluative, and motor processes. In short, the currently used direct localisation method needs further refinement. However, as already mentioned above (p. 15), our technique does not first and foremost strive for high accuracy in single position ratings but rather for ratings of a high number of positions covering larger skin areas. At present, it is not clear how this project could be tackled efficiently with a methodologically superior forced-choice approach. In addition, it is likely that direct pointing and forced-choice methods not only differ in terms of accuracy but also in respect to the mental reference frames being employed due to the different tasks, and direct pointing has a much higher face validity for localisation than the cognitive decision between two predetermined positions. Consequently, we see our method as complementary to alternative-choice approaches, although the need for its methodological refinement is acknowledged.

Although the laser stimuli were invisible and no other visual cues were present, the influence of visual factors should not be underestimated. Most likely, the participants based their ratings not only on the somatosensory input, but related this information to the visual representation of their arm. This uncontrolled factor may indeed have led to diverse effects, including mislocalisations toward or away from specific visual anchors, e. g., the wrist. Another intervening factor was our particular method of reporting the perceived positions, that is, pointing at them. This included movements, which needed to act on a 'motor map' of the area under examination. Consequently, the depicted profiles are in fact the integrated result of multiple processing stages, which include the detection of the stimuli, referencing them to a representation of the body surface, cognitive decisions on where to report the perceived positions, implementation of the related motor responses, and finally the pointing behaviour itself. These stages and their mutual interactions cannot be disentangled with our set-up. But, and this is crucial as a starting point for further investigations, the implemented experimental procedure for the first time allows a parametric description of the behavioural outcome *at all*. Only having profound measures of these maps in the first place allows to pose detailed questions on how they are composed.

The question of how to combine the individual perceptual data to a group graph depicting the relation between physical and perceived positions implies a large range of methodological considerations. The core of this issue is how to average the data across subjects in a manner which accounts for the different sources of variance. The approach of plotting the normalised data in a scatter plot and fitting a regression curve seems not appropriate for two main reasons: (1) participants detected varying amounts of stimuli and would enter the calculation with different weights, and (2) the normalised stimulus positions have individually varying offsets and ranges, which means that at the most extreme distal and proximal positions only a subset of the sample enters the calculation. The descriptive solution we arrived at is shown in Figure 2 (p. 16) as well as in Figure 3A of study 2.

Especially the latter provokes further discussion, as the increased deviation from linearity, which is visible on the group level, contrasts with the failure to find an advantage of non-linear terms in fitting the data on the individual level. The reasons for these somewhat contradictory findings may be manifold. The most important factor is probably the decrease in detection rate and accuracy after capsaicin application: The regression estimates are based on a smaller amount of *and* less accurate data, generally decreasing the fit and especially counteracting the plan to demonstrate the advantage of more complex regression terms in the single participant. The purely descriptive, but intuitively convincing, effect visible in the group graph defines the mission for future studies, that is, to strive for an implementation, which provides adequate data for solving the question of whether linear or more complex regressions are adequate descriptions of the relations between physical and perceptual space.

The already mentioned studies by Gandevia and Phegan (1999) and Moseley (2005) reported an *increase* in the perceived size of a limb resulting from ongoing nociceptive input. At first this seems to contradict our finding of a *compressed* representation of the stimulus positions in the reported perceived positions. However, there may be a simple solution to this conflict: It is possible that our intervention led to a subjectively perceived distension of the forearm, while the reference frame for the perceived stimulus position remained constant, or at least was not affected

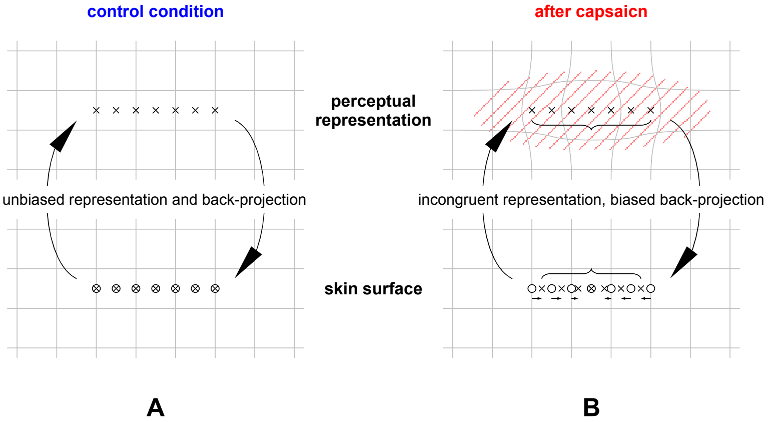

Figure 4: A possible explanation for the 'compression' of the average perceived positions to a smaller range after capsaicin. **A:** Under normal conditions, physical stimulus positions (circles) are referenced to an undistorted perceptual representation of the body surface. Leaving aside any additional individual factors which may additionally affect this representation, participants are generally able to yield good matches between physical and perceived positions if thy are asked to indicate the latter by back-projecting them to the skin surface. **B:** If the neural processes which underlie the representations of the body surface and the perceived positions, respectively, are differentially affected by capsaicin, their relation to each other may be distorted. Based on the current state of knowledge capsaicin most likely leads to an enlargement of the according portion of the perceptual 'body map' in comparison to the surrounding areas. The 'stimulus map' however may not or at least to a lesser degree be affected by capsaicin. As a result, the back-projection of the perceived positions to the body surface which affords an integration of these two maps may lead to an apparent compression. See text for more details.

in the same manner. In other words, the dimensions of the sensitized skin area as a part of the representation of one own's body may indeed have appeared larger. But this may not have applied to the perceptual map of the external stimuli, which nonetheless had to be referenced to the body surface. Figure 4 demonstrates how this situation could lead to an effective compression of the perceived positions. The validity of this idea has to be assessed in future studies.

Study 3 addresses a fundamental issue, which, in fact, was the starting point for this series of studies. Perception is a *dynamic process*, and as such not the spatial, but rather the *spatio-temporal* parameters of a stimulus determine its spatial representation. Along with the phi and tau illusion, the saltation phenomenon is a fine example for what happens when integration mechanisms are led to their temporal

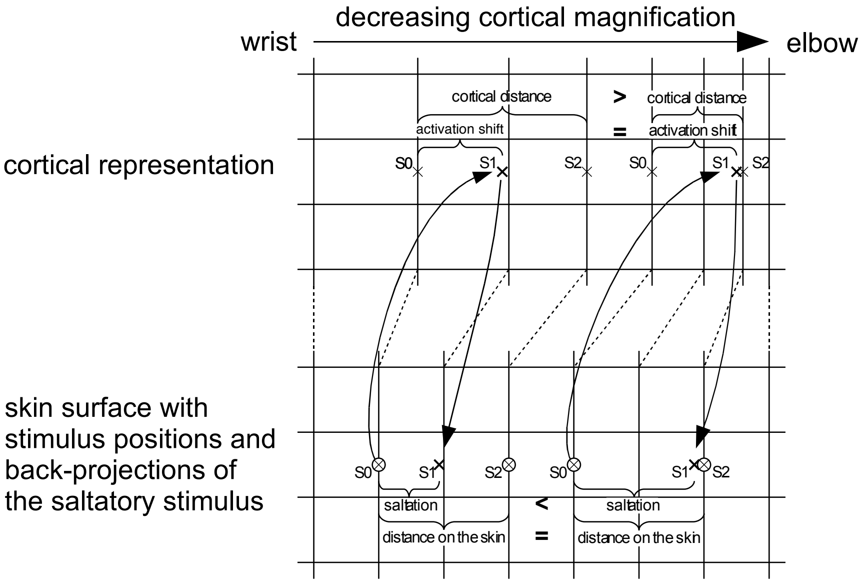

Figure 5: If saltation indeed relates to some sort of wave-like propagation of cortical activations as suggested by Wiemer *et al.* (2000), it is most likely that the absolute cortical distance between two activation peaks codetermines the the size of the saltatory mislocalisation. This demonstration shows the saltation effect for two areas on the skin surface with the same distance between the reference positions and at the same stimulus onset interval. Due to the latter, the absolute cortical activation shift would be expected to be roughly comparable, leading in turn to a higher amount of saltation in areas with smaller cortical magnification.

limits and thereby produce misperceptions. The complexities of such interactions can be illustrated with our observation that the more proximal the stimuli were presented, the smaller was the distance between the perceived positions of the 'reference' stimuli, and the higher was the amount of relative mislocalisation of the saltatory stimulus (study 3, figures 3 and 4). We interpreted this finding based on the well-known fact that the cortical magnification factor varies substantially between different areas of the body surface (Sur *et al.*, 1980). For the forearm it is commonly assumed that the cortical magnification factor decreases in proximal direction. Wiemer *et al.* (2000) suggested that the mislocalisation of the saltatory stimulus relates to the spatio-temporal features of the *cortical representations* of two stimuli. Consequently, a decreasing cortical magnification factor would implicate larger mislocalisations (see figure 5).

Unfortunately, the results from study 1 are only of limited value for clarification of this issue. The descriptive group data in figure 2 (p. 16) imply a slightly s-shaped slope in the relation between posiitions on the skin surface and the perceptual representation. Single positions are discriminated much better at the middle of the forearm than in more proximal or distal areas. One can speculate that better discrimination capabilities reflect smaller receptive field sizes, i.e., a higher cortical magnification factor. The decrease at the most proximal positions fits this view, as based on the classic Penfield homunculus one would indeed expect a distal-to-proximal decrease in cortical magnification factor. However, reduced discrimination at the most distal positions close to the wrist is clearly inconsistent with this interpretation. Considering the high resolution of the hand representation, one would rather expect increased discrimination in the wrist area in relation to the mid-forearm. There is only one observation which puts the latter result into perspective: The most distal category mean seems to be particularly affected by extremely proximal ratings of some single subjects (especially 3, 10, and 11), which questions the validity of this particular result and thereby reduces the inconsistency in regard to the model depicted in figure 5.

Of course, the methodological problems concerning interpretations of the group results already addressed above disqualify undue interpretations of these *post hoc* observations. Nonetheless, we are optimistic that the already available data form a solid basis for a systematic evaluation of the relation between body area and the amount of saltatory mislocalisation in future studies.

Conclusions and outlook

The main feature of the presented methodological approach is the acknowledgement of the phenomenal space of the body surface as a genuine ontological level, not to be identified with cortical activation patterns. This perspective fosters an empirical approach to how perceptual characteristics are rooted in neural processes. A promising pursuit of this question has to incorporate not only the spatial but also the temporal domain. Although brain activations may be spatially homomorph to perceptual patterns, this need not generally be the case. Given the obvious dynamic aspect of perception it is far more plausible to regard it as the result of spatio-temporal interactions in neural activation matrices. The saltation phenomenon is a fine example for this position and may serve particularly well as a probe into these mechanisms. Our results show that perceptual maps can deliver dimensional descriptions of the body surface as it is individually perceived, providing several advantages for the future assessment of body perception:

1. Their characteristics and transformations can be expressed in formal mathematical terms, allowing a refinement of hypotheses concerning the experimental investigation of body perception.
2. They provide psychophysical measures which can be directly related to brain activation maps, e.g., in order to predict activation patterns in the primary somatosensory cortex from perceptual characteristics and vice versa.
3. Separate dimensions may be integrated in one multi-dimensional map, which may be used to compare the representations of the various somatosensory modalities, e.g., touch and pain.
4. The inclusion of a *temporal* dimension allows the modelling of the inherent *dynamics* of perception.

The plans for further application and development of our approach are threefold: (1) More comprehensive localisation data has to be assessed for single subjects in order to derive appropriate parameters for their specification. (2) The systematic comparison of body perception measures from controls and clinical samples will shed further light on its diagnostic capabilities. (3) Neurofunctional studies will be implemented which will address the relation between neural and phenomenal space.

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Appendix: Papers

For copyright reasons, the original papers are not available in the electronic version.

Psychophysical 'perceptual maps' of heat and pain sensations by direct localization of CO_2 laser stimuli on the skin

Jörg Trojan, Dieter Kleinböhl, Annette M. Stolle, Ole K. Andersen, Rupert Hölzl, Lars Arendt-Nielsen

published in *Brain Research* 170 (2006), pp. 88–96

DOI: 10.1016/j.brainres.2006.08.065

Independent psychophysical measurement of experimental modulations in the somatotopy of cutaneous heat-pain stimuli

Jörg Trojan, Dieter Kleinböhl, Annette M. Stolle, Ole K. Andersen,
Rupert Hölzl, Lars Arendt-Nielsen

Accepted for publication in *Somatosensory & Motor Research*, August 2008

The saltation illusion demonstrates integrative processing of spatiotemporal information in thermocpetive and nociceptive networks

Jörg Trojan, Annette M. Stolle, Dieter Kleinböhl, Carsten D. Mørch, Lars Arendt-Nielsen, Rupert Hölzl

published in *Experimental Brain Research* 1120 (2006), pp. 106–113

DOI: 10.1007/s00221-005-0190-z