

ATTENTIONAL MODULATION AND PLASTICITY IN THE HUMAN SENSORY SYSTEM

Ph.D. dissertation

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*Chapter One***INTRODUCTION****1. Motivations**

The perception and neural processing of a stimulus are influenced by the actual task to be solved, i.e. according to the given context. Sensory processing (including visual, tactile and pain processing) can be modulated by experience through neural plasticity and the related perceptual learning, but also by actual motivations through selective attention. Despite the fact that the research of pain perception, perceptual learning and of attentional mechanisms have been among the top research fields of cognitive neuroscience (Engel et al. 2001; Gilbert et al. 2001; Kanwisher and Wojciulik 2000, Wiech et al. 2008), very little is known about the interaction of these functions. This was the main reason for my choice to try to investigate these interactions.

It was long held that the topography of sensory areas was modifiable only during critical periods of development and could be considered “hard-wired” thereafter (Hubel and Wiesel 1970). It is a fact that the plasticity of the human brain greatly decreases after approximately 6–10 years (at least for early sensory cortices) however in the later half of the 20th century, more evidence began to mount to demonstrate that the central nervous system does indeed adapt and is mutable even in adulthood; this broad idea is commonly termed neural plasticity. Neural plasticity refers to modulations and its different types and levels, which induce different extents of change in the neural system.

The dissertation – in line with the three theses – presents three studies. The experiments were carried out with various aims but it is common to all three that they represent examples of different aspects of neural plasticity. The first thesis focuses on the topic of the interaction of attention, pain and –as a third factor- sensitization (few-hour modulation). The second thesis looks into the role of attention in relation to perceptual learning (as a result of one-week learning). The third thesis examines the spatio-temporal dynamics of the peri-personal spatial representation in relation to long term plasticity (when someone becomes an expert in a given field within a few years).

In the first experiment I aimed at investigating how distraction of attention from the noxious stimuli affects the perceived pain intensity in secondary hyperalgesia. Importantly, in this experiment I directly compared the attentional modulation of pain

intensity reports during capsaicin-induced secondary hyperalgesia to that in the case of capsaicin-untreated, control condition.

In the second thesis, I review a study where I tested the hypothesis that perceptual learning involves learning to suppress distracting task-irrelevant stimuli. Moreover, parts of the EEG experiments in that study were to test whether attention-based learning influences perceptual sensitivity for the visual features present during training via modulating the sensory gain for the different features at the early stages of visual cortical processing and/or by biasing the decision processes at the higher processing stages.

In the experiment described in the third thesis, I examined whether the multisensory spatial information concerning sensory events are coded in a similar manner throughout peripersonal space or might there instead be a difference between front and rear space (i.e. the space behind our backs), as a result of the existence of a detailed visual representations of the former but only occasional and very limited visual representation of the later. To address this question, I compared the effect of crossing the hands on tactile temporal resolution when the hands were placed in front of participants versus when they were placed behind their backs. I compared two groups of participants, non-musicians as well as professional piano players, in order to uncover how extensive practice in playing piano – leading to altered tactile perception in pianists – will affect tactile temporal resolution performance in front and rear space in the latter group.

I believe that my results contribute to the better understanding of the human sensory system especially in relation to the attentional mechanisms and different aspects of plasticity.

This knowledge may also contribute to the diagnosis, monitoring and/or treatment strategies for adult patients with certain pathologic conditions within the sensory/attentional system, like amblyopia, dyslexia, ADHD, chronic pain etc.

2. General background

2.1. Plasticity

The central nervous system has a wide array of functions: receiving sensory input, coordinating motor plans and generating consciousness and higher thought. A fundamental property of the brain is plasticity, the ability of the nervous system to rearrange its anatomical and functional connectivity and properties in response to

environmental input involving functional, structural and physiological changes or in other words, the ability to change in response to experience and use. Plasticity allows the brain to learn and remember patterns in the sensory world, to refine movements, to predict or filter relevant information etc. Even basic sensory perception is influenced by prior sensory experience, attention and learning (Gilbert 1998; Dan and Poo 2006; Han et al. 2007).

To date the strongest evidence for learning/ training induced structural reorganisation in the adult brain comes from primate and non-primate animal studies (Dale et al. 1999; Dancause et al. 2006; Trachtenberg et al. 2002). During the last decade, a steadily growing number of studies in primate and non-primate animals confirmed the notion that experience, attention and learning new skills can cause functional and structural reorganisation of the brain (Johansson et al. 2004).

At the cellular level, enrichment results in hippocampal cell proliferation, angiogenesis and microglia activation (Gage 2002). These effects are mediated through increased expression of brain-derived neurotrophic factor, nerve growth factor as well as through NMDA (N-methyl daspartate) and AMPA modulation (Ickes et al. 2000).

Learning-induced structural changes can also affect the anatomical connectivity in the adult brain. A vast amount of cross-sectional morphometric studies have demonstrated neuroanatomic correlates of learning and experience in different cognitive domains. For example musical proficiency has been associated with volume enlargement of motor and tactile (C. Gaser, G. Schlaug 2003) areas and their anatomical connections (Bengtsson et al.; Gaser et al. 2003). Plasticity is expressed by structural changes in macroscopic axonal projections including thalamocortical and horizontal, cross-columnar axons and, to a lesser extent, dendrites (Fox and Wong 2005, Broser et al. 2007). These large-scale structural changes typically lag physiologically measured plasticity by several days or weeks (Trachtenberg and Stryker 2001). In contrast, very rapid structural changes (hours to days) occur continuously at the level of spines and synapses.

In sensory areas of neocortex, two basic paradigms have been used to study plasticity. First, in experience-dependent map plasticity, the statistical pattern of sensory experience over several days alters topographic sensory maps in primary sensory cortex, in both animals and humans (Hubel and Wiesel 1998; Blake et al. 2002; Rauschecker 2002). Second, in sensory perceptual learning, training on sensory perception or discrimination tasks causes gradual improvement in sensory ability associated with changes in neuronal receptive fields and/or maps in cortical sensory areas (Gilbert 1998).

Sensory map plasticity and sensory perceptual learning are not unitary processes, but involve multiple discrete functional components. Many of these components occur with strong similarity across cortical areas, suggesting common underlying mechanisms. Map plasticity in juveniles occurs rapidly in response to passive sensory experience, such plasticity is slower and more limited in adults, except when stimuli are actively attended and behaviorally relevant (e.g. during a perceptual learning task) or explicitly paired with positive or negative reinforcement or neuromodulation (Gilbert 1998; Dan and Poo 2006).

Training can increase neural responses to reinforced stimuli, shift tuning curves toward (or away from) trained stimuli, or sharpen tuning curves to improve discrimination between stimuli. These changes in neural tuning are generally modest and do not cause large-scale changes in map topography, except with very extensive training (Blake et al. 2002; Karmarkar and Dan 2006). Common functional components of plasticity in the primate sensory areas are the potentiation of responses to active inputs during normal sensory use, and in response to temporal correlation between inputs and another potentiation of responses paired with reinforcement in adults. These components are both consistent with Hebbian strengthening of active inputs but differ in dependence on attention or reward.

2.2. Perceptual learning

Neural plasticity provides the background to perceptual learning (PL). PL is defined as a relatively persistent improvement in the ability to detect or discriminate sensory stimuli as a result of experience. More precisely, those learning processes and the acquisition of those visual skills are understood as perceptual learning, for which the neural bases are to be sought in the process of information processing or in its alternation (2002; Fahle 2002; Hochstein and Ahissar 2002).

Relatively long time and practice are needed for perceptual learning. The acquired skills are stored for a long time, even for years and can be recalled. Perceptual learning is surprisingly selective to the practiced stimulus, the circumstances of the training (including elemental characteristics, such as orientation and position in visual space and the learnt task). All these characteristics almost necessarily lead to the conclusion that plasticity underlying perceptual learning must involve quite early perceptual and neural processes. For example, the first electrophysiological experiments investigating the

neural bases of perceptual learning of the somatosensory system, demonstrated significant neural reorganization in areas of the early sensory cortex, matching the skin area used in the task (Blake and Merzenich 2002). The representation of the given skin area, just as the amplitude of the neural response evoked by the stimulation, significantly increased and the learning induced change could also be demonstrated in the selectivity and the reliability of the cells' responses. However, more recent electrophysiological research into visual perceptual learning provided considerably different results (Christ et al. 2001; Gilbert et al. 2001). They have found a decrease in the amplitude of the responses of neuron populations responsible for the processing of the learnt stimulus and they have not found any important change in the cells' selectivity or receptive field characteristics. In contrast, neural context-effects (including attentional modulation), coming from outside of the neurons' receptive field, significantly changed as a result of learning. Considering all these, we can state that perceptual learning should be under top-down control.

In order to absolutely optimize detection and discrimination of stimuli, it is essential to optimize the signal-to-noise ratio at as early level as possible. This can be achieved by optimizing the tuning of neurons at early stages of cortical processing to the task at hand under top-down control (Herzog & Fahle 1998). This hypothesis of „early selection“ by optimally tuned cortical filters is fully compatible with the richness of feedback connections in the brain. For example, the lateral geniculate nucleus (LGN) receives more feedback fibres from the cortex than it sends feed-forward ones towards the cortex. Early perceptual learning in its simplest form would involve one-dimensional categories, while late PL would also involve multidimensional categories. Processes involving mainly relatively late cortical areas in the temporal and parietal cortex may be called cognitive, or late PL, while those modifying processing mostly in the primer sensory cortex may better be classified as „top-down adaptations“, or early PL. These adaptive and learning processes, working mostly subconsciously, are permanently updating the signals received from different sense organs, such as the eyes, the ears, the skin and proprioceptors in the body, in order to realign the coordinated systems of different sense modalities, making sure we feel our hand to be where we see it and to see an object to be where we hear it.

2.3. Attention

Attention is crucial for perceptual learning. Within any environment one key aspect to sensory processing is our capability to distinguish between different sources of sensory information as well as any changes within these sources of sensory information. In order to achieve this, the difference in the amplitude between that which is relevant (signal) and that which is irrelevant (noise) must be sufficient in order to detect the relevant stimulus. Whether this difference is between two sources within one modality or two sources from different modalities it appears that we have the ability to alter the signal to noise ratio of various sensory events that we are processing, a mechanism commonly referred to as “attention”.

Early behavioral investigations of attention focused upon perceptual overload tasks. These tasks were largely driven by the increasing complexity of work environments and demonstrated the fundamental problem: as processing demands increased task performance decreased. It was accepted that attention must be the mechanism by which the most relevant aspects of a task were selected at the expense of less relevant aspects due to limitations imposed by processing ability.

Over the years the mechanism of attention has taken many forms. The earliest debates of attention centered upon the loci at which a filter served to select relevant information. It was not until the 1960's that the principles of facilitation and suppression were included in the debate. This resulted in a shift of thought from attention being a filter that blocked irrelevant information to a mechanism by which the irrelevant information is suppressed (Treisman 1960). Through the early nineties advances in various imaging techniques led to the evolution of attention research from primarily behavioral to physiologically based responses associated with information processing. It has been demonstrated since the early nineties that attention to a stimulus feature results in an increase in neural activity compared to when that stimulus is irrelevant and not being attended (Corbetta et al. 1990). These changes in neural activity were suggested to reflect an enhancement of relevant sensory information whereby the relevant information receives a competitive advantage through a higher signal to noise ratio (Hillyard et al. 1998). Moreover, attention today is most commonly regarded as a cognitive construct for dealing with the limited processing capacity of the brain (Pashler 1998). The so-called “biased competition” model has become one of the most commonly accepted and

experimentally confirmed neural models of visual attention (Desimone és Duncan, 1995). The most important statements of the model have been summarized in the points below:

- During the processing of the picture projected on the retina, the different stimuli of the picture are in competition;
- The competition begins at that level of processing, where the stimuli corresponding to the different objects are processed by the same neurons, i.e. the cells' receptive field is sufficiently large for encompassing several objects
- The role of attention is to influence the competition between the stimuli, ensuring that the stimulus in the centre of attention comes out as winner;
- Attentional modulation affects the processing of all properties of the observed object.

According to the "biased competition" model, the level of attentional selection is dependent on the physical distance between the object in the centre of attention and the surrounding irrelevant objects.

The pain experience also depends upon the focus of attention (Corbetta et al. 2002). Psychophysical studies indicate that attention can modulate sensory aspect of pain, possibly mediated by a modulation of the spatial integration of pain. Functional imaging studies showed that distraction from pain reduces pain-related activations in most brain areas that are related to sensory, cognitive aspects of pain. Attentional modulation does not only result in altered local activation but also affects the functional integration of activation. Attentional modulations of pain are supposed to share the general mechanisms and substrates of attentional modulations of sensory processing. However, the exceptionally close interaction between attention and pain seems to involve pain specific features that are not necessarily known from other modalities (Bantick et al. 2002; Tracey et al. 2002). Attention might modulate pain perception at least partially via a pain-specific opiate-sensitive descending modulatory pathway that regulates nociceptive processing largely at the level of the spinal cord dorsal-horn. This pain modulatory system might complement, interact and overlap with a more general system of attentional control, which has been well characterized in other modalities. Functionally, both networks might enable behavioral flexibility, which is limited by the involuntary attentional demands of pain (Tracey et al. 2007; Hadjupavlou et al. 2006).

Chapter Two

ATTENTIONAL MODULATION OF PERCEIVED PAIN INTENSITY IN CAPSAICIN-INDUCED SECONDARY HYPERALGESIA

First thesis:

I. I have shown that perceived pain intensity in secondary hyperalgesia is decreased when attention is distracted away from the painful stimulus with a concurrent visual task. Furthermore, it was found that the magnitude of attentional modulation in secondary hyperalgesia is very similar to that in capsaicin untreated, control condition. Interestingly, however, capsaicin treatment induced increase in perceived pain intensity did not affect the performance of the visual discrimination task. Finding no interaction between capsaicin treatment and attentional modulation suggest that capsaicin-induced secondary hyperalgesia and attention might affect mechanical pain via independent mechanisms.

1. Introduction

Capsaicin-induced hyperalgesia is a widely used experimental model of neuropathic pain (Treede et al. 1992b; Koltzenburg et al. 1994; Treede and Magerl 2000; Simone et al. 1989; Maihofner et al. 2004; Baumgartner et al. 2002; Klein et al. 2005). It involves topical application of capsaicin, a vanilloid receptor agonist, which elicits ongoing discharge in C-nociceptors and induces an area of hyperalgesia (Torebjork et al. 1992; Schmidt et al. 1995; Ziegler et al. 1999; Klede et al. 2003). Hyperalgesia occurs both at the site of application (primary hyperalgesia) and in the surrounding, untreated area (secondary hyperalgesia). Hypersensitivity towards heat stimuli, i.e. thermal hyperalgesia, is a key feature of primary hyperalgesia, whereas secondary hyperalgesia is characterized by hypersensitivity towards mechanical (e.g. pinprick) stimulation (Raja et al. 1984; Ali et al. 1996).

Several lines of clinical evidence suggest that attentional mechanisms may be involved in the pathogenesis of some chronic clinical pain states and that attention demanding activities reduce pain in chronically afflicted patients (Levine et al. 1982; Vlaeyen and Linton 2000; Rode et al. 2001). Previous research also showed that in case of acute, phasic pain decreased attention to noxious stimuli raises the pain threshold (McCaul et al. 1984; Miron et al. 1989; Eccleston et al. 1999), whereas perceived pain intensity is increased when a subject's attention is directed to painful stimuli (Bushnell et al. 1985). However, little is known about the influence of attention on subjective pain intensity ratings in capsaicin-induced hyperalgesia. The only study, which investigated the effect of attentional load on pain processing in the capsaicin-induced primary, heat hyperalgesia model (Wiech et al. 2005) found that subjective pain ratings as well as neural responses in the pain-related brain regions are reduced in the high attentional load conditions, when attention is distracted from the noxious stimulus with a highly attention demanding visual task. Surprisingly, however, attentional modulation of perceived pain intensity in capsaicin-induced secondary hyperalgesia has not been investigated before.

Yet, the identification of cognitive factors may have therapeutic consequences: (e.g. medical, surgical, cognitive or behaviour-therapy rehabilitation (Lesko & Atkinson, 2001). Furthermore, the more accurate exploration of the peripheral/central mechanisms of the sensation of chronic pain may contribute to the development of hyperalgesia and allodynia models as well as to the elaboration of an fMRI biomarker for reliable measurement of pain intensity and patient specific target identification for the pain killers (see further in Chapter six).

In the present study we aimed at investigating how distraction of attention from the noxious stimuli affects the perceived pain intensity in secondary hyperalgesia. Importantly, in our experiments we directly compared the attentional modulation of pain intensity reports during capsaicin-induced secondary hyperalgesia to that in the case of capsaicin-untreated, control condition. In each experimental condition, subjects received a pinprick stimulus and were required to rate the perceived pain intensity on a visual analog rating scale (VAS). Concurrently with the pinprick stimulus faces were displayed in rapid serial visual presentation (RSVP) and subjects either had to ignore the faces and attend to the pinprick stimulus selectively or had to perform a concurrent face orientation discrimination task. The randomly designed visual task could be of high or low attentional demand and in the beginning of each trial a cue indicated whether subjects should perform: 1. the pain intensity rating while ignoring the visual stimuli; 2. pain

rating and a difficult face discrimination task simultaneously; 3. pain rating and an easy face discrimination task simultaneously (Figure.1.1).

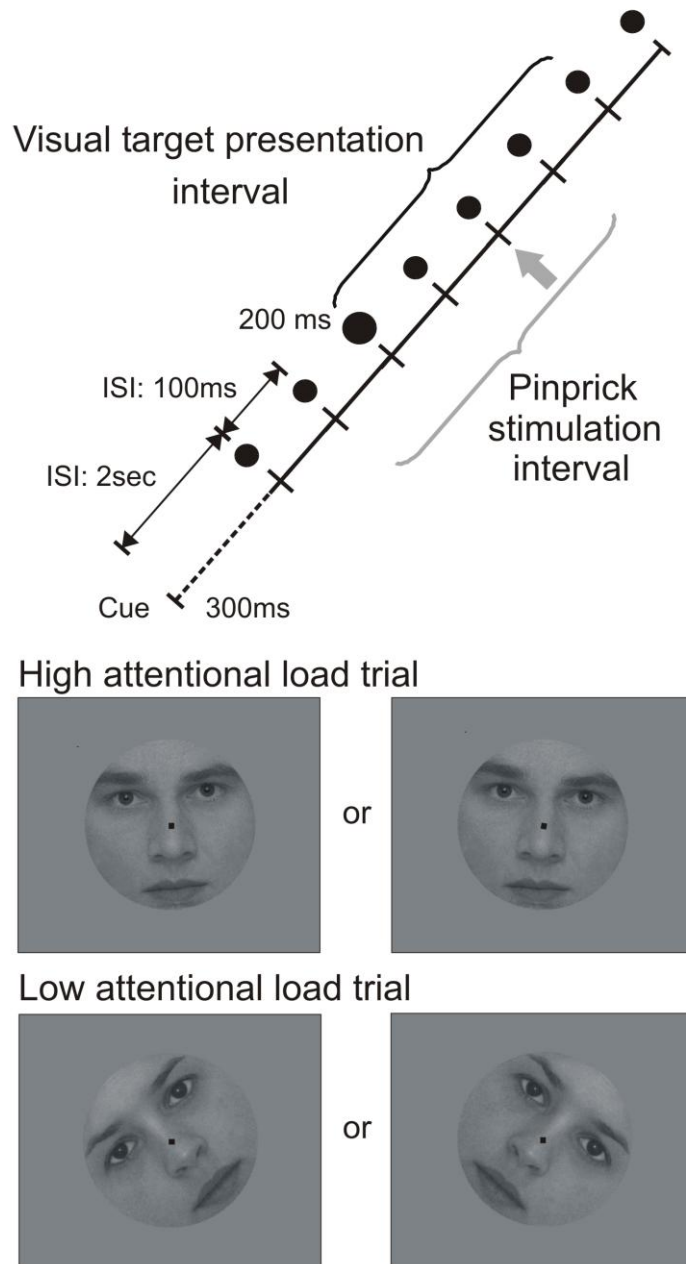


Figure.1.1 Schematic representation of the experimental conditions (randomized design).

2. Methods

2.1. Subjects

Sixteen healthy right handed naive subjects 19-25 years of age (5 females; mean age 22,9 years) participated in the experiment. All had normal or corrected to normal visual acuity and reported no history of neurological or psychiatric problems. Subjects gave informed

consent to participate in the study, which was approved by the local ethics committee of Semmelweis University. All experiments were performed by the same examiner.

2.2. The heat/capsaicin model

To induce secondary hyperalgesia in healthy people, we used the heat/capsaicin sensitization model (Petersen and Rowbotham 2002; Zambreau et al. 2005). A premarked 9cm² (3*3cm) square area on the medial side of the right lower leg (musculus gastrocnemius caput) was heated with a 45C° flask lasting 5min. Thermal stimulation was followed immediately by topical application of 0.075% capsaicin cream (Zostrix, Rodlen Laboratories, Inc., Vernon Hills, IL) and was covered by parafilm for 45min (Moulton et al. 2007). Capsaicin treated and untreated sessions were applied in a balanced order among subjects and they were at least 24h apart from each other.

2.3. Visual stimuli

Stimuli were programmed in MATLAB 7.1. (MathWorks, Inc., Sherborn, MA) using the Cogent 2000 Software Toolbox (Cogent, www.vislab.ucl.ac.uk/Cogent/) and were presented on generic PCs. Visual stimuli consisted of grayscale front view pictures of four male and four female faces with neutral expression on a uniform gray background. Faces were cropped and covered with a circular mask (Kovács et al. 2005, 2006). Face stimuli (7°deg in diameter) were presented centrally (with a viewing distance of 50 cm) on a 19" LCD monitor (screen-refresh rate of 60 Hz). Each trial consisted seven upright distractor faces and one target face, which was rotated clockwise or counter-clockwise. Within the same block there were trials where target faces were rotated by 2°-3° (high attentional load trials) or by 45° (low attentional load trials) in randomized order.

2.4. Mechanical stimuli

Two different forces of TOUCH TEST TM von-Frey sensory filaments (180g/0,98mm and 300g/1,09mm, low and intermediate pain intensity stimulation, respectively) were used to deliver pinprick stimuli within the delineated contact area (Petersen and Rowbotham 2002; Treede et al. 2002) in randomized order. Contact time was ~1s and all stimuli were applied with a ~7s ISI. In each trial an audio cue presented over headphones informed the experimenter about when and which of the two pin-prick stimuli should be applied. The pinprick stimulations were invisible for the subjects. Both,

in the capsaicin-treated and untreated sessions a 2 cm wide skin surface area, surrounding the marked 3*3cm square area (where capsaicin treatment was applied in the capsaicin-treated session) was stimulated.

2.5. Procedure

Each subject performed two sessions (5 blocks in each): one that was preceded by heat/capsaicin treatment of the skin (secondary hyperalgesia) and another without treatment (control). In each block 3 different trials were presented in randomized order (48 trials altogether). In the beginning of each trial a cue (a letter displayed for 300 ms) indicated whether subjects should perform: 1. the pain intensity rating while ignoring the visual stimuli; 2. pain rating and a difficult face discrimination task simultaneously (high attentional load trials); 3. pain rating and an easy face discrimination task simultaneously (low attentional load trials) (Fig. 1.1). The cue was followed (with a 2 sec delay) by the stream of eight face stimuli. Each face stimulus was presented for 200ms with 100ms ISI. The visual target appeared randomly in either of the 3rd-7th position of the RSVP series. On each trial, the auditory cue signaling the initiation of the pinprick stimulus was presented simultaneously with the onset of one of the face stimuli at positions 2nd-5th, in a randomized order. In the high and low attentional load trials subjects first responded to the visual task, indicating whether the target face was rotated clockwise or counter-clockwise by pressing the left or right computer mouse button, respectively. Following the response to the visual task, subjects rated the perceived pain intensity evoked by the pinprick stimulation on a graphical continuous visual analog scale (VAS) displayed on the screen. The 10cm sliding scale was labeled with words: „no pain“ and „highest tolerable pain (Quevedo et al. 2007). Out of the subjects“ view the analog scale was converted to discrete digital values and normalized to 0–1 range. Subjects were instructed to start pain rating when a response cue appears on the screen (a gray circle, displayed 1200 ms after the offset of the last face stimulus for 200ms). A scroll bar had to be adjusted between two end points of subjective pain intensity by moving a pc-mouse.

2.6. Statistical analysis

We used Matlab 7.1. (MathWorks, Inc., Sherborn, MA) and Statistica 8. (StatSoft Inc.) for the statistical analyses. For across subject analysis data were analyzed by repeated measures analysis of variance (ANOVA). For the analysis of face orientation

discrimination performance two within-subject factors were defined: TREATMENT (capsaicin treated and untreated) and LOAD (low attentional load, high attentional load). For the analysis of the pain intensity ratings we defined 3 within-subject factors: TREATMENT (capsaicin treated or untreated); LOAD (single task-pain only, low attentional load or high attentional load conditions); and STRENGTH of the pinprick stimuli (low or intermediate).

3. Results

Subjects' face orientation discrimination performance was close to 100% correct in the low attentional load condition and it was strongly reduced in the high attentional load condition (Figure.1.2), indicating that the task was much easier and required less attentional resources in the low than in the high attentional load conditions. ANOVA revealed a significant main effect of LOAD, $F(1,15)= 423,503$, $p < 0,001$), whereas the main effect of capsaicin treatment was not significant (TREATMENT, $F(1,15)= 0,852$, $p= 0,371$). It was also found that face orientation discrimination performance was not affected by the capsaicin treatment, since subjects' performance was very similar in the secondary hyperalgesia and in the control, capsaicin untreated conditions (as shown by the lack of significant interaction between TREATMENT x LOAD $F(1,15)= 0,98$, $p= 0,336$). Accordingly, post-hoc analysis showed no significant difference between the performance in the capsaicin treated and untreated conditions ($F(1,15)= 0,05$, $p= 0,827$ and $F(1,15)= 0,942$, $p= 0,347$ for LOAD), providing further support for the lack of modulation of face orientation discrimination performance by the capsaicin treatment. Thus, these results suggest that attention was distracted away from the pinprick stimulus by the visual task to a similar extent in the capsaicin treated and untreated conditions and thus the difference in pain intensity ratings between these two conditions cannot be explained by difference in the attentional load.

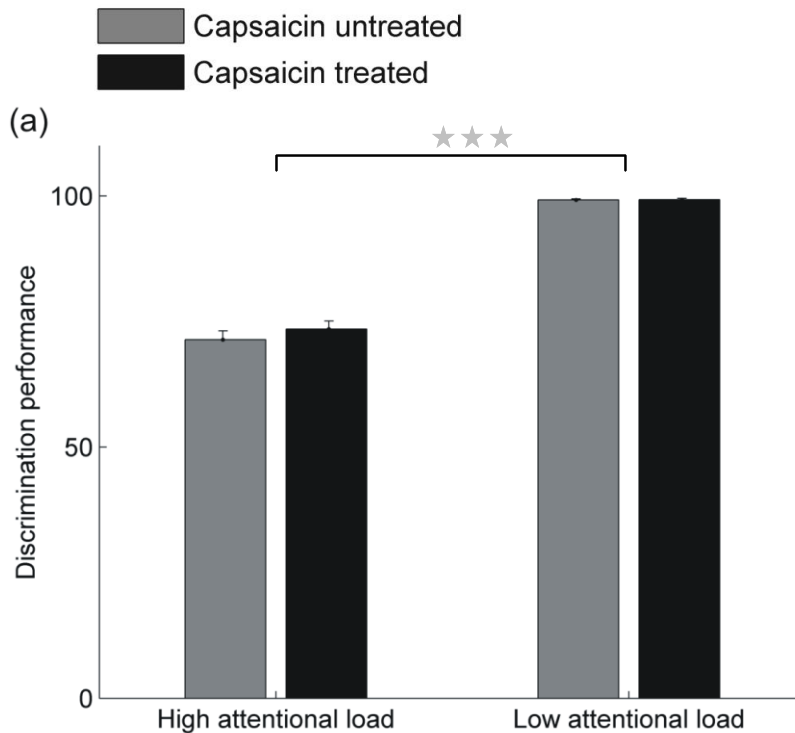


Figure.1.2 Face orientation discrimination performance in capsaicin untreated and capsaicin treated conditions. Data are shown for the low and the high attentional load conditions

Subjects' pain intensity ratings were strongly modulated by capsaicin treatment (Figure1.3; Figure.1.4), which is supported by the results of ANOVA, showing a significant main effect of capsaicin treatment (TREATMENT, $F(1,15)= 15.95$, $p= 0.001$). Subjects gave significantly greater pain intensity ratings after capsaicin treatment than without treatment in all experimental conditions (Post hoc analysis, $p < 0.05$ for all conditions), except in the case of low pinprick stimulation under dual task low attentional load condition, where the trend was similar but the difference between capsaicin treated and untreated condition did not reach the significance level ($F(1,15)= 3,163$, $p= 0,09$). Furthermore, it was found that subjects' pain intensity ratings were also strongly modulated by LOAD (Figure1.3; Figure.1.4), which is supported by the results of ANOVA, showing a significant main effect of attentional load (LOAD, $F(2,30)= 10.93$, $p= 0.0002$).

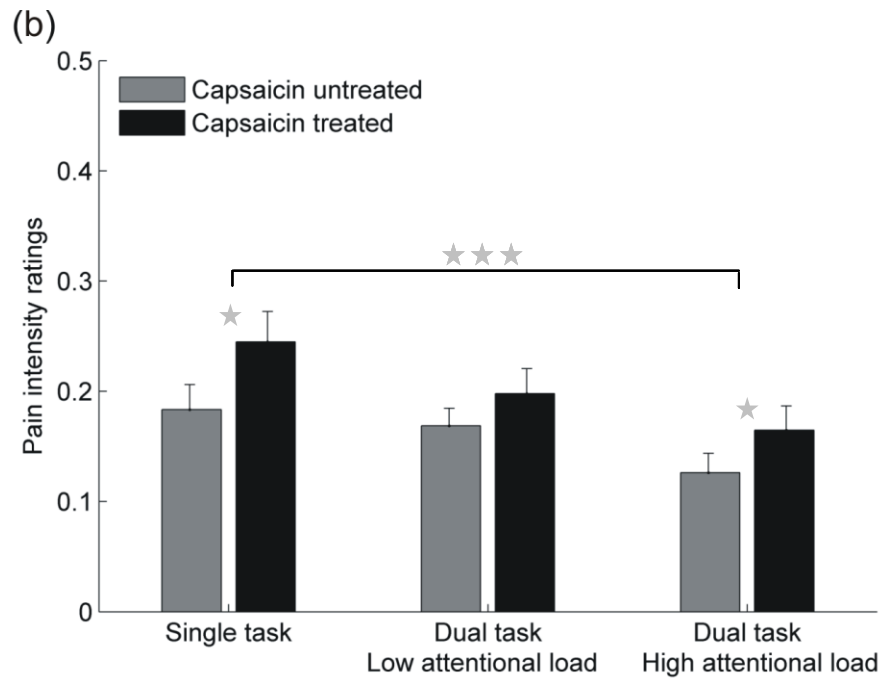


Figure 1.3 Attentional modulation of pain intensity ratings in the capsaicin untreated and capsaicin treated conditions in case of low (180g) pinprick stimuli

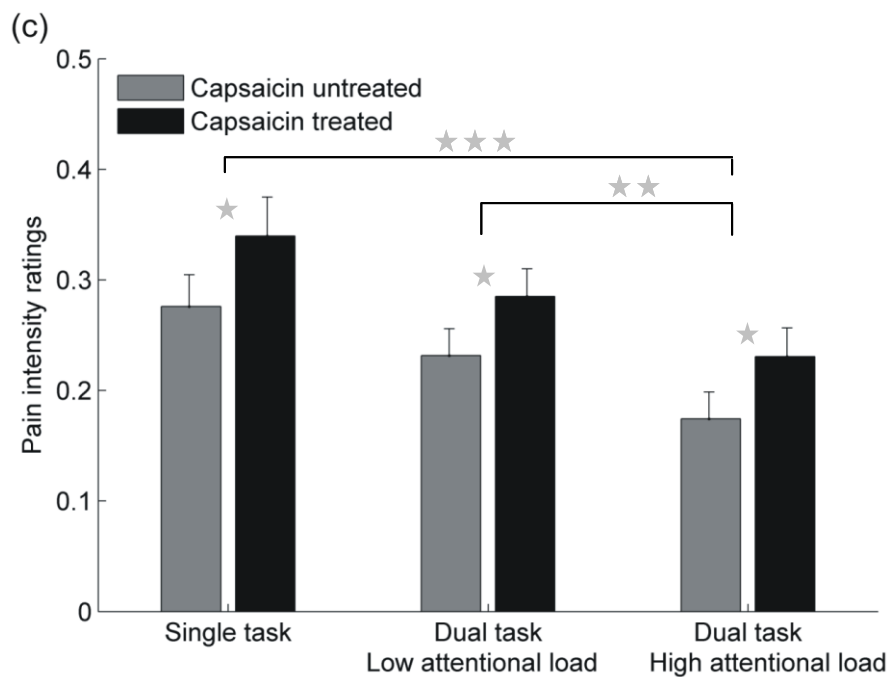


Figure 1.4 Attentional modulation of pain intensity ratings in the capsaicin untreated and capsaicin treated conditions in case of intermediate (300g) pinprick stimuli

The perceived pain intensity was significantly lower in dual task high attentional load trials than in the single task trials (Post hoc analysis, for all conditions $p < 0.001$) as well as than in the dual task low attentional load trials (Post hoc analysis, for all conditions $p < 0.003$, except in the case of low pinprick stimulation with capsaicin

treatment, where it was marginally significant $F(1,15)=4,13, p=0,06$). Most importantly, however, ANOVA revealed no significant interaction between TREATMENT x LOAD ($F(2,30)=1,97, p=0,157$), suggesting that the magnitude of modulation of subjective pain intensity ratings by attention was similar in the secondary hyperalgesia and in the capsaicin-untreated condition. Furthermore, although there was a significant main effect of the strength of pinprick stimulation (STRENGTH, $F(1,15)=30,00, p<0,0001$); the effect of capsaicin treatment and attentional modulation was similar in the case of low and intermediate pinprick stimulation, as it is indicated by the lack of significant interaction between STRENGTH x TREATMENT ($F(1,15)=2,09, p=0,169$) and between STRENGTH x LOAD ($F(2,30)=1,11, p=0,343$).

4. Discussion

Consistent with earlier findings showing that attention modulates pain perception, we found that distracting attention away from the pinprick stimulus with a demanding visual task strongly reduced subjective pain ratings in the capsaicin untreated condition. Furthermore, the results of the present study provide the first evidence that attention affects pain intensity ratings also during secondary hyperalgesia. Importantly, the magnitude of the attentional modulation during secondary hyperalgesia was similar to that found in conditions without capsaicin treatment. Interestingly, however, capsaicin treatment induced increase in perceived pain intensity did not affect the performance in the visual face orientation discrimination task. These results are in line with previous findings (Apkarian et al. 2004; Patil et al. 1995; Houlihan et al. 2004; Veldhuijzen et al. 2006), showing that painful stimulation has no or very little effect on the performance in a concurrent cognitive task.

Previous research showed that distracting attention away from the thermal stimuli with a visual task – similar to that used in the present study - leads to reduced perceived pain intensity in primary hyperalgesia only in case of high pain intensity but not in case of low pain intensity stimulation (Wiech et al. 2005). In the present study, however, we found that perceived mechanical pain intensity in secondary hyperalgesia is modulated by attention both at low and intermediate pain intensity stimulation but in the case of the former just a marginally significant value was detected. A possible explanation for the trend of somewhat reduced modulatory effect of capsaicin treatment and attention in the case of low pinprick stimulation under dual task low attentional load condition is that the

visual face orientation discrimination task was very easy in the low attentional load conditions (performance was close to 100% correct) and thus resulted in less controlled allocation of the attentional resources in these conditions. Therefore, it is possible that in the dual task low attentional load trials subjects developed different strategies for the allocation of residual attentional resources in case of capsaicin treated and untreated, control conditions. Earlier results showed that in capsaicin untreated condition attention can affect the perceived pain intensity at low and intermediate intensity of pain stimulation (Veldhuijzen et al. 2006; Del Percio et al. 2006), which is in agreement with the results of the present study. Further research is required to uncover why Wiech et al. (2005) failed to show attentional effect on pain perception at low pain intensity stimulation in primary hyperalgesia.

Previous research suggested that hyper attention might be an important component of chronic pain, because abnormal anticipatory attentional processes towards painful sensations are involved in the maintenance of chronic pain (Al-Obaidi et al. 2000; Pfingsten et al. 2001). Therefore, one might expect that distracting attention from the painful stimuli should result in stronger modulation of the perceived pain intensity in the capsaicin-induced secondary hyperalgesia (an experimental model of chronic pain: Treede et al. 1992b; Treede and Magerl 2000; Klein et al. 2005) than in the capsaicin-untreated conditions. However, our results showed that the magnitude of attentional modulation of perceived pain intensity in the capsaicin treated and untreated conditions are very similar, suggesting that the mechanisms underlying modulation of the perceived mechanical pain intensity by capsaicin-induced secondary hyperalgesia and attention are independent. The results of functional magnetic resonance imaging (fMRI) studies investigating the neural processes of secondary hyperalgesia might help to reconcile the apparent conflict between these findings and the proposed role of attention in chronic pain. It was found that secondary hyperalgesia is associated with the activation of an extensive network of brain areas, involving the brainstem, thalamus, primary and secondary somatosensory cortices, insula, cingulate cortex and the prefrontal cortex (Zambreanu et al, 2005; Maihöfner and Handwerker, 2005; Lee et al, 2008). However, a recent study showed that it is the brainstem which is primarily responsible for the maintenance of central sensitization underlying secondary hyperalgesia, whereas activation of the cortical areas might be associated with the perceptual and cognitive aspects of hyperalgesia (Lee et al, 2008). If so, one might assume that the capsaicin sensitization protocol used in the present study - which includes a short, 45 min

sensitization period immediately followed by the testing procedure- results in secondary hyperalgesia that is based primarily on the brainstem mediated central sensitization mechanisms and involve very little or no modulation of anticipatory attentional processes. This could explain why in the present study distraction of attention from the painful stimulus resulted in similar attentional modulation of perceived pain intensity in secondary hyperalgesia and control, capsaicin untreated condition.

*Chapter Three***PSYCHOPHYSICAL AND ELECTROPHYSIOLOGICAL
CORRELATES OF LEARNING-INDUCED MODULATION OF
VISUAL MOTION PROCESSING IN HUMANS****Second thesis:**

II.1 *The results of my study propose that in cases when there is direct interference between task-relevant and task-irrelevant information that requires strong attentional suppression, training will actually produce decreased sensitivity for the task-irrelevant information.*

II.2 *I found that the strength of a coherent motion signal modulates the ERP waveforms in an early (300ms) and a late (500ms) time-window. The early component is most pronounced over the occipitotemporal cortex and may reflect the process of primary visual cortical extraction, the late component is focused over the parietal cortex and can be associated with higher level decision making mechanisms. I demonstrated training related modulation of the ERP in both the early and late time-windows suggesting that learning affects via modulating the sensory gain for the different features at the early stages as well as the integration and evaluation of motion information at decisional stages in the parietal cortex.*

1. Introduction

Developing perceptual expertise is essential in many situations, from an air traffic controller monitoring complex video displays to a radiologist searching for a tumor on an x-ray. With practice, these complex tasks become much easier, a phenomenon referred to as perceptual learning. Visual attention plays an important role in perceptual learning (Christ et al, 2001; Gilbert et al, 2001; Fahle 2002; Hochstein and Ahissar, 2002). It has been demonstrated that as a result of learning, performance improves only for stimuli in the centre of attention (Fahle 2002; Hochstein and Ahissar, 2002) but does not change for stimuli also present but ignored. Thus, the mere presence of the stimulus in the course of practising does not result in learning. Previous research in humans has focused on the

role of training in increasing neural sensitivity for task-relevant visual information; such plasticity in early sensory cortices is thought to support improved perceptual abilities (Dolan et al. 1997; Vaina et al. 1998; Gauthier et al. 1999; Schiltz et al. 1999; Schwartz et al. 2002; Furmanski et al. 2004; Kourtzi et al. 2005; Sigman et al. 2005; Op de Beeck et al. 2006; Mukai et al. 2007). However, in most complex natural scenes, an ideal observer should also attenuate task-irrelevant sensory information that interferes with the processing of task-relevant information (Ghose 2004; Vidnyánszky & Sohn 2005). The implementation of this optimal strategy is supported by the observation that training leads to much stronger learning effects when the task-relevant information is displayed in a noisy, distractor rich environment compared to when no distractors are present (Doshier & Lu 1998, 1999; Gold et al. 1999; Li et al. 2004; Lu & Doshier 2004) (for a review see Fine & Jacobs 2002). However, previous studies have not examined how training influences the neural representation of task-irrelevant information to facilitate learning.

Previous behavioral research addressing the effect of perceptual learning on the processing of task-irrelevant information showed that pairing a very weak task-irrelevant motion stimulus with a task-relevant stimulus during training actually increased perceptual sensitivity for the task-irrelevant stimulus (Watanabe et al. 2001; Watanabe et al. 2002; Seitz & Watanabe 2003). Based on this result, they proposed that perceptual learning involves a diffuse reinforcement signal that improves information processing for all stimuli presented concurrently with the task-relevant information during training, even if the stimulus is a task-irrelevant distractor (Seitz & Watanabe 2003, 2005). However, in contrast to the weak task-irrelevant stimuli used by Watanabe and coworkers (2001; 2002; 2003), real world perception more often involves suppressing highly salient and spatially intermingled distractors. Accordingly, recent psychophysical studies suggest that salient stimulus features are suppressed when they are present as task-irrelevant distractors during the training phase of a perceptual learning task (Vidnyánszky & Sohn 2005; Paffen et al. 2008). These findings are also in line with the results of a previous neurophysiological study showing that neural responses to irrelevant masking patterns are suppressed in the monkey inferior temporal cortex as a result of training to recognize backward-masked objects (Op de Beeck et al. 2007).

In the behavioral experiments of the present study we tested the hypothesis that perceptual learning involves learning to suppress distracting task-irrelevant stimuli

Most of the relevant studies use bidirectional transparent motion display as stimuli to investigate object-based attentional selection on perceptual learning. It is important to note that this allowed us to examine overlapping and structurally same stimuli which cause massive distractor effect and drastically increase the extent of competition between the task-relevant and task-irrelevant directions because these use the same neural processing mechanisms.

Also an important unresolved question concerns the temporal dynamics of these attention-based learning effects on the neural responses to attended and neglected visual features. Computational models (Smith and Ratcliff, 2004; Beck et al., 2008) and experimental studies (for reviews, Glimcher 2003; Gold and Shadlen 2007; Heekeren et al. 2008) suggest that the neural events underlying detection or discrimination of visual stimuli consist two stages: a first stage where the low-level sensory properties of stimuli are computed in the early visual cortical areas, followed by a second stage in which this sensory evidence is accumulated and integrated so that a perceptual decision can be formed (this evidence accumulation is thought to occur primarily in downstream feature-specific visual cortical areas and the parietal and frontal cortex).

Single-unit and neuroimaging studies have shown that stimulus-induced activity in V1 is modulated by attention. An object-based modulation of neuron firing rate has been described in motion processing areas MT/MST of a macaque monkey using a selective attention task with transparent surfaces. Several recent neurophysiological studies have shown that directing attention to a stimulus over the receptive field of a cortical visual neuron is usually accompanied by an attention-dependent increase of the firing rate. That is, the neuron fires more spikes in response to the attended object than to the non-attended object (Luck et al. 1997; Reynolds et al. 2006). Moreover, relevant electrophysiological studies (Skrandies and Fahle 1994; Skrandies et al. 1996, 2001; Pourtois et al., 2008; Shoji and Skrandies, 2006; Händel et al. 2007; Aspell et al. 2005) investigating the timecourse of learning effects in the trained task condition revealed perceptual learning effects on the processing of task-relevant information starting early, from ~100 ms after stimulus onset. Previous studies also showed lateralization effect of the learning-induced modulation of the first motion coherence-related ERP peak. Right hemisphere dominance was detected in visual motion processing (Aspell et al. 2005; Kubová et al. 1990). Based on these results it was suggested that perceptual learning might modulate the earliest cortical stages of visual information processing.

On the other hand, recent monkey neurophysiological (Law and Gold 2008) and modelling results (Law and Gold 2009), suggest that perceptual learning in a motion direction discrimination task primarily affects the later, decision-related processes and in particular the readout of the directional information by the lateral intraparietal (LIP) neurons. Furthermore, in recent EEG studies examining the neural mechanisms of object discrimination in humans, a late stage of recurrent processing has been observed (the marker for this is an ERP component that starts between 300-400 ms after stimulus onset) during the accumulation of sensory evidence about object-related processing under degraded viewing conditions (Philiastides and Sajda 2006; Philiastides et al. 2006; Murray et al. 2006; Fahrenfort et al. 2008).

Based on these results we hypothesized that attention-based learning might affect both, the visual cortical extraction and the parietal integration of the visual feature information that was present during training. More exactly, we predicted that as a result of attention-based learning neural responses to the visual information that was task-irrelevant during training will be reduced as compared to the responses to the task-relevant information both, at the stage of early visual cortical processing as well as at the later stage of decision-related processing.

To test this prediction, we measured ERP responses to motion directions that were present as task-relevant or task-irrelevant features during training. Subjects were trained on a speed discrimination task, which required them to attend to one of the components of a bidirectional transparent motion display (i.e. task-relevant direction) and ignore the other component (task-irrelevant direction) throughout several practice sessions (see Fig.2.1A). The two components of the transparent motion display were moving in orthogonal directions and thus perceptually were segmented into two transparent surfaces sliding over each other. This allowed object-based selection of the task-relevant motion direction during the training trials (Valdes-Sosa et al., 1998; Sohn et al. 2004). To examine the effect of training on the processing of task-relevant and task-irrelevant motion directions, ERP responses to the two motion directions were measured before and after training while subjects performed a motion direction discrimination task. We varied the strength of the task-relevant and task-irrelevant motion signal during the test sessions by modulating the number of dots moving coherently in a given trial. This allowed us to measure motion coherence-dependent modulation of the ERP responses, i.e. the sensitivity of the ERP responses to the strength of coherent motion signal. This is important because previous monkey electrophysiological studies have shown that motion

coherence modulates neural responses both in the motion sensitive visual cortical area MT (Newsome et al., 1989; Britten et al. 1992, 1996) as well as in the LIP (Shadlen et al. 1996; Shadlen and Newsome 2001; Gold and Shadlen 2000), which is involved in the accumulation and integration of the sensory evidence for decision making. Furthermore, in agreement with the monkey electrophysiological results, recent MEG studies revealed strong motion coherence-dependent modulation of neural responses starting from about 200 ms after the onset of the coherent motion stimuli and the results of the source localization analysis suggested that the primary source of this modulation might be localized in the human area MT+ (Händel et al. 2007; Aspell et al. 2005). Importantly, in the Händel et al. (2007) study, motion coherence-dependent modulation was also present in a later time window (between 400 - 700 ms), however, the source of this late modulation was not reported. Taken together, these results suggest that motion coherence-dependent modulation of the neural responses might be a good marker of the neural sensitivity for the motion directional signal both at the early stage of visual cortical processing as well as at the later decision-related parietal processing stages.

Accordingly, in the current study we quantified the magnitude of the motion strength dependent ERP modulations and used this measure to investigate the effects of training on responses to task-relevant and task-irrelevant motion directions both before and after training.

2. Materials and Methods

2.1. Subjects

Fourteen subjects (6 females; age range 22–25 years) participated in the main experiment and nine subjects (3 females, age range 22-30) took part in the control experiment. All had normal or corrected to normal visual acuity and reported no history of neurological problems. Subjects gave informed consent to participate in the study, which was approved by the local ethics committee of Semmelweis University.

2.2. Stimuli and apparatus

Stimuli were programmed in MATLAB 7.1. (MathWorks, Inc., Sherborn, MA) using the Cogent 2000 Software Toolbox (Cogent, www.vislab.ucl.ac.uk/Cogent/) and

were presented on generic PCs. All visual stimuli were rendered in white on a black background. The luminance of the background and the moving dots was <2 cd/m² and 32.2 cd/m², respectively. In all experiments subjects were instructed to maintain gaze on a central fixation square subtending 0.25 deg visual angle present for the entire duration of each experiment. In all experiments, moving dots (N=200) were presented within a 20 deg (diameter) circular field centered on the fixation square, with a 1.6 deg (diameter) circular blank region around the fixation point. Dots subtended 0.15 deg in diameter, and had a limited lifetime of seven frames. Behavioral responses were collected by means of mouse button presses.

During the psychophysical and ERP experiments visual stimuli were presented at 75Hz on a 21" Syncmaster 1100mb CRT monitor (Samsung Electronics, Seoul, Korea); the monitor was the only light source in the room. Eye movements were recorded in these sessions using an iView XTM HI-Speed eye tracker (Sensomotoric Instruments, Berlin, Germany) at a sampling rate of 240Hz. The eye tracker also served as a head rest that fixed the viewing distance at 50 cm.

2.3. General procedure

The experiment protocol consisted of a training phase and two testing phases, one before and another after training (see Fig. 2.1 B). The testing phases consisted a psychophysical testing session to estimate motion coherence detection thresholds, an ERP session, and an fMRI scanning session. Training phase comprised six one-hour sessions of psychophysical testing during which subjects performed the speed discrimination task.

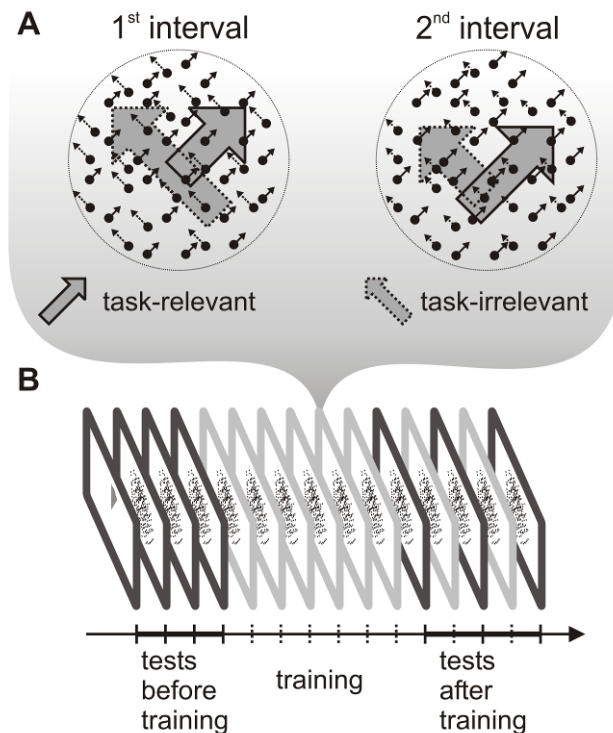


Figure 2.1 Schematic representation of the stimuli during training and the experimental procedure. (A) Transparent random dot motion display used during the training sessions. One of the motion directions was task-relevant and the other direction was task-irrelevant throughout training. The different length of the arrows indicate that dot speed was different in the two intervals both, in the case of task-relevant and task-irrelevant direction. (B) The experimental protocol consisted of a training phase and two testing phases, one before and another after training. During training (six one-hour sessions), subjects performed a speed discrimination task. Before and after training, the test phase included an ERP recording session.

The post-training testing sessions were separated by two „top-up“ learning sessions to ensure that learning effects were maintained. Each testing session was performed on a different day and their order was randomized across subjects. Psychophysical testing and training sessions lasted for 1 hour, while ERP and fMRI experiments lasted for 1.5 hours.

2.3.1. Training

In the training sessions subjects performed a 2-interval forced choice speed discrimination tasks. In each trial the two 500 ms stimulus presentation intervals were separated by a 200 ms inter-stimulus interval. There was a inter-trial interval (jittered between 300-500 ms) between the subject's response button press and the beginning of the next trial. Each stimulus interval contained two populations of spatially superimposed dots moving in a direction either $+45^\circ$ or -45° tilted from the upward direction (Fig. 2.1

A). Subjects were instructed to attend to dots moving in one of the directions (task-relevant direction) while simultaneously ignoring dots that moved in the orthogonal direction (task-irrelevant direction). They were asked to indicate which of the two intervals contained faster motion in the task-relevant direction. The speed of the task-relevant direction was fixed for one of the two intervals (at 6 deg/s), while that of the other interval was varied using a QUEST adaptive staircase procedure (Watson and Pelli, 1983) arriving at a value providing 75% correct performance. The speed of the task-irrelevant motion direction was also changing across the two stimulus intervals: it jittered between 6 and 7 deg/s. Every training session consisted of 8 experimental blocks of 80 trials each. Task-relevant and irrelevant directions were randomized across subjects, but kept constant across training sessions.

2.3.2. Testing motion coherence detection threshold

We measured motion coherence thresholds within the same block for three different motion directions: for the two directions present during training ($\pm 45^\circ$ from the upward direction) and for a third, control direction (180° , downward direction). A single trial consisted of two 250 ms stimulus presentation intervals, separated by a 250 ms ISI. There was a inter-trial interval (jittered between 300-500 ms) between the subject's response button press and the beginning of the next trial. Motion coherence for each direction was varied independently by using the QUEST adaptive staircase procedures to converge at 75% correct performance in 60 steps. Two staircases (one starting at 0% and the other starting at 100% coherence) were randomly interleaved within an experimental block for each motion direction. Data were analyzed with repeated measures ANOVA with factors of test session (before training, after training), and task relevance (task-relevant, task-irrelevant).

2.3.3. Main EEG experiment

During EEG recordings motion discrimination thresholds were measured using the method of constant stimuli in a 2-alternative forced choice procedure. Motion directions ($+45^\circ$ or -45°) were displayed at six different coherence levels (5, 10, 15, 20, 30, and 45%). The six different coherence levels for both motion directions were presented randomly within a single block, resulting in 12 different trial types. Each EEG

experimental session contained 5 blocks and each block contained 40 repetitions for each trial type (for a total of 2400 trials per session). The subject's task was to report whether they perceived coherent motion in the +45° or -45° directions. All subjects gave responses with their right hand. They were required to press the left mouse button to indicate that coherent motion was perceived in the -45° (northwest) direction and press the right mouse button for +45° (northeast) direction. Stimuli were displayed for 250 ms. Between the manual response and the subsequent stimulus there was a short delay, jittered between 200-300 ms. Reaction times were measured starting from the stimulus onset.

2.3.4. Control experiment

The stimuli and the procedure were the same as those used in the main EEG experiment except that only two motion coherence levels (10% and 45%) were used and in each trial all the dots appearing on the screen were colored either red or green in an unpredictable way. In separate blocks subjects either performed a motion direction discrimination task, just as in the main experiment or a color discrimination task, i.e. the subject's task was to report whether the color of the dots was red or green. The control EEG experimental session contained 3 blocks of 40 trials for both motion and color discrimination tasks conditions.

2.4. EEG data acquisition

EEG data were acquired using a BrainAmp MR EEG system (Brain Products GmbH) from 60 (Ag/AgCl) scalp electrodes mounted in an EasyCap (EasyCap GmbH, Herrsching-Breitbrunn, Germany, extended 10–20 System). Horizontal and vertical EOGs were monitored using four electrodes placed on the outer canthi of the eyes and in the inferior and superior areas of the left orbit. All channels were referenced to linked earlobes with input impedance of ≤ 5 k Ω and a forehead electrode was used as ground. Data were sampled at 1000 Hz with an analog band-pass filter of 0.016–250 Hz and were digitally band-pass filtered and rereferenced to average reference for the subsequent analysis (butterworth zero phase; high cutoff: 30 Hz, 12dB/oct; low cutoff: 0.1 Hz, 12dB/oct attenuation and 50Hz notch filter). Trials containing blinks, movements, A/D saturation or EEG baseline drift were rejected on the basis of [+100 μ V -100 μ V]

rejection criterion and visual inspection of each recording by semi-automatic artifact detection.

2.5. EEG data analysis

For each subject, averaged epochs ranging from -100 to 600 ms relative to the onset of the stimuli and containing no EEG artefacts were computed for each combination of motion direction, motion coherence and training session separately and baseline corrected using the 100 ms prestimulus time window.

To quantify the strength of the motion coherence-dependent modulation of ERP responses the area under the average ERP curve was calculated in successive 10 ms time-bins for each of the six different motion coherence levels. Linear regression was used separately for each time-bin to estimate the beta value (slope) of the best fitting line that relates the area under the curve to motion coherence level. The beta value indicates the degree to which motion coherence modulated the ERP responses, with a slope of zero indicating no effect. We constructed scalp maps of beta values to visualize their spatial distribution. All scalp maps were plotted by commercially available EEG software BESA 5.2 (MEGIS Software GmbH) that uses spline interpolation designed for irregularly spaced data points.

2.6. Eye movement data analysis

During the ERP recordings, we tracked the eye position of four randomly selected subjects while they performed the motion discrimination task before training, and of eleven randomly selected subjects after training. We calculated the mean eye position using an interactive computer program. Artifacts like drifts or blinks were identified by visual analysis and removed. Trials were binned based on motion direction and we calculated the mean eye position (x and y values) for the period when the motion stimulus was present on each trial. We compared these values between the different conditions using Student's t -test. Moreover, we performed an additional analysis of the EOG data obtained during the experiment. The goal was to test whether there are any differences in the EOG signals between the case of task-relevant and task-irrelevant motion directions after training. We reasoned that if our analysis reveals that EOG signals are similar in the case of the two motion directions than these results would

provide further evidence against an unlikely explanation of our main results (i.e. differential neural responses to the task-relevant and task-irrelevant motion directions after training) based on eye movements.

Bipolar EOG signals were derived by computing the difference between the voltages at electrodes placed to the outer canthi of the eyes [horizontal EOG (HEOG)] and above and below the left orbit [vertical EOG (VEOG)]. The averaged EEG epochs (we obtained for the different conditions and subjects in the main analysis) were quantified for the bipolar EOG channels (as in Khoe et al. 2005).

3. Results

3.1. Behavioral results during training

During training, observers were presented with two fields of spatially superimposed moving dots (Fig. 2.1 A); they had to discriminate the speed of dots moving in one direction while simultaneously ignoring dots that moved in an orthogonal direction (i.e. a task-irrelevant distractor). As shown in Figure 2.2, speed discrimination thresholds gradually improved as a result of training. Comparison of the performance during the first 6 blocks of training (speed discrimination threshold: 0.58 deg/s) with the performance during the last six blocks of training (speed discrimination threshold: 0.49 deg/s) revealed a significant learning effect ($t(9)=4.48$; $p<0.002$). These data demonstrate that the training sessions were sufficient to improve the efficiency of processing basic visual attributes such as stimulus speed.

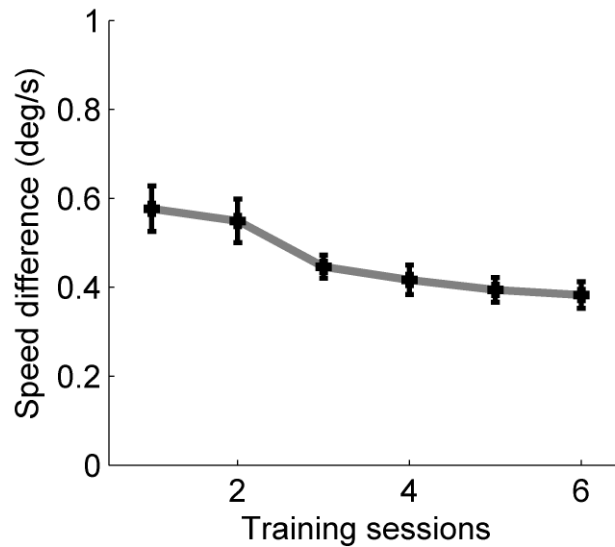


Figure 2.2 Motion speed discrimination performance during training. Speed discrimination thresholds gradually improved as a result of training. Error bars indicate the SEM.

3.2. Effect of training on motion detection thresholds

We next investigated how training on a speed discrimination task affects perceptual sensitivity to different motion directions by measuring motion detection thresholds for three different directions before and after training (i.e. the motion coherence required for threshold performance). The three tested directions included the two directions that were present during training ($+45^\circ$ and -45°) as well as a control direction that was equidistant from them (180° , downward). The results revealed that training had a strong effect on the observers' performance (Fig 2.3.). A repeated measures analysis of variance (ANOVA) showed no significant main effect of test session (before and after training, $F(1,9) = 1.21$, $p=0.3$); however, there was a significant main effect of task relevance (task-relevant and task-irrelevant, $F(1,9) = 30.7$, $p<0.001$) and a significant interaction between these variables ($F(1,9) = 58.2$, $p<0.001$). Before training (Fig. 2.3, left side), there was no difference in motion detection thresholds for the two directions that were present during training ($t(9)=0.04$, $p=0.966$); however, both of these directions had higher thresholds than the control direction.

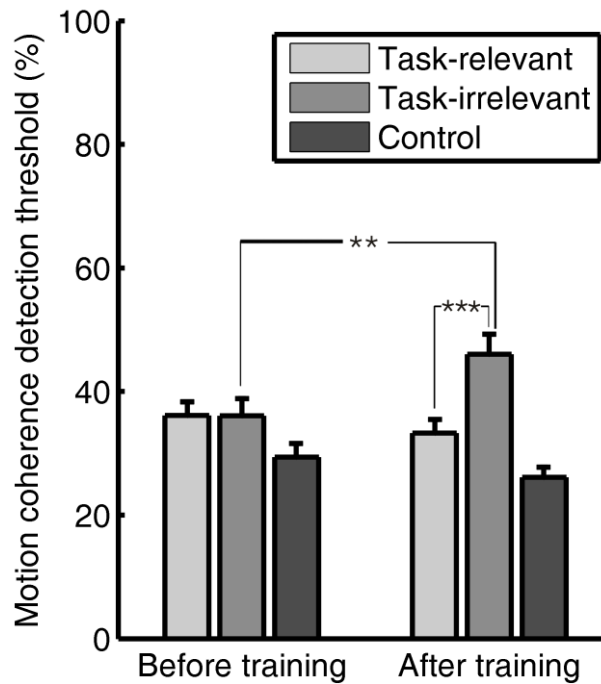


Figure 2.3 Perceptual sensitivity for the different motion directions. Before training, there was no difference between the motion coherence detection thresholds for the directions that were task-relevant and task-irrelevant during training as well as for a control direction. After training, sensitivity for the direction that was task-irrelevant during training was strongly reduced. Error bars indicate the SEM.

The increased sensitivity for the control direction might be explained by the fact that it was a cardinal direction (downward), for which transparent motion detection has been shown to be better than for non-cardinal motion directions (Greenwood & Edwards 2007). However, the motion coherence threshold for the task-relevant direction was significantly lower than the threshold for the task-irrelevant direction (Fig. 2.3, right side) after training ($t(9)=-8.33$, $p<0.0001$). Furthermore, a comparison of the motion coherence thresholds before and after training reveals that thresholds for the task-relevant direction decreased non-significantly ($t(9)=0.89$, $p=0.396$) whereas thresholds for the irrelevant direction significantly increased ($t(9)=-8.33$, $p<0.001$). The threshold for the control direction also underwent a non-significant decrease ($t(9)=1.13$, $p=0.289$), further supporting the observation that training decreased sensitivity to motion in a direction that was continuously present as a task-irrelevant distractor during training. Importantly, in our motion coherence detection experiment the three motion directions were presented randomly within a block and observers were required to indicate which of the two temporal intervals contained coherent motion. Thus, our design ensured that a possible learning-induced bias to choose the task-relevant rather than the task-irrelevant direction

in case of uncertainty can be excluded as an explanation of the results of our motion coherence detection experiment.

For all experimental conditions subjects were instructed to maintain eye-gaze on the small fixation point at the center of the display. However, to verify that subjects were able to maintain fixation and that there was no differential pattern of fixations for different motion directions, we tracked the eye position of subjects while they were performing the motion coherence detection task. We did so for five randomly chosen subjects in the sessions before and after the training period. Trials were binned based on motion direction and we calculated the mean eye position (x and y values) for the period when the motion stimulus was present on each trial. We found no significant differences in the mean eye position for the 3 different motion directions (main effect of direction: before training $F(2,8)=1.83$ $p=0.221$; after training $F(2,8)=0.506$ $p=0.621$) indicating that there was no systematic bias in eye position induced by the direction of the motion stimulus (Fig. 2.4.).

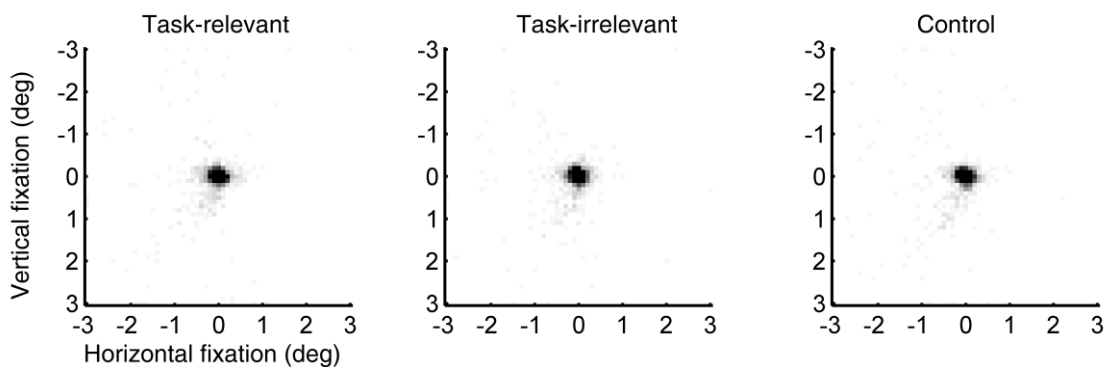


Figure 2.4 Representative fixation patterns of one of the subjects during the motion coherence detection threshold measurements after training in the case of the three different motion directions. There was no difference between the fixation patterns for different motion directions.

Furthermore, additional analysis using ANOVA showed that there were no significant differences between the three motion directions in the saccadic frequency (main effect of direction before training $F(2,8)= 1.628$ $p=0.255$ and after training $F(2,8)= 1.613$ $p=0.259$) and in the cumulative saccadic amplitude (main effect of direction before training $F(2,8)= 0.301$ $p=0.748$ and after training $F(2,8)=0.676$ $p=0.535$).

3.3. Behavioral results during the ERP recording

The behavioral results obtained during the ERP recording sessions before training revealed no difference in the subjects' motion direction discrimination performance between the task-relevant and the task-irrelevant directions (Fig. 2.5A). On the other hand, after training observers more often reported seeing the task-relevant than the task-irrelevant direction (Fig 2.5A).

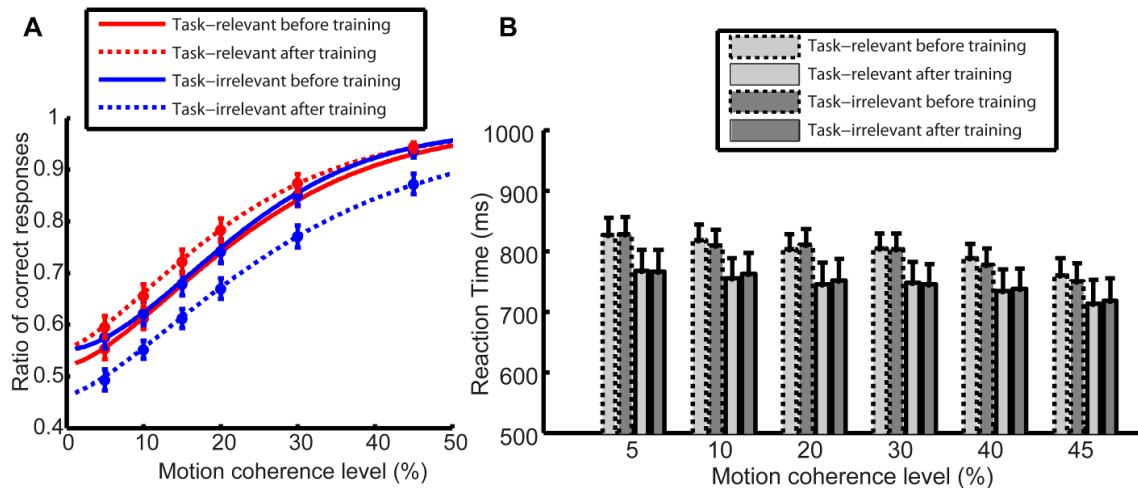


Figure 2.5 (A) Motion direction discrimination performance during the ERP recording sessions. Before training, (solid line), there was no difference between the performance in the case of task-relevant (red) and task-irrelevant (blue) directions. After training (dashed line), subjects more often reported seeing the task-relevant than the task-irrelevant direction. Data were modeled by Weibull psychometric functions. (B) Reaction times in the motion direction discrimination task. Learning led to overall reduction of reaction times after training (bars with solid outlines). There was no difference in subjects' reaction times between task-relevant (light shaded bars) and task-irrelevant direction (dark shaded bars) neither before nor after training. Error bars indicate the SEM.

ANOVA revealed that the main effect of test session showed marginal significance (before and after training, $F(1,13)=4.26$, $p=0.059$); however, there was a significant main effect of task relevance (task-relevant and task-irrelevant, $F(1,13)=4.91$, $p=0.045$); and a significant interaction between these variables ($F(1,13)=16.6$, $p<0.002$). Importantly, even though learning led to an overall reduction of reaction times after training, there was no difference in subjects' reaction times between task-relevant and task-irrelevant direction either before or after training (Fig. 2.5B). ANOVA showed no significant main effect of test session (before and after training, $F(1,13)=2.345$, $p=0.149$); no significant main effect of task relevance (task-relevant and task-irrelevant, $F(1,13)=0.035$, $p=0.855$);

and no significant interaction between these variables ($F(1,13)=2.352$, $p<0.149$). Taken together, the behavioral results obtained during the ERP sessions are in agreement with the results of the motion coherence detection threshold measurements obtained in the current experiment and presented in the part of the fMRI experiment (Gál et al. 2009). In this previous report we showed that learning resulted in decreased coherence detection thresholds for the task-relevant motion direction as well as increased detection thresholds for motion in a direction that was continuously present as a task-irrelevant distractor during training.

3.4. Effect of training on the ERP responses

We next examined how training influences the sensitivity of ERP responses to coherent motion signals for task-relevant and task-irrelevant motion directions. Average ERPs were computed at each of six different motion coherence levels from the data obtained before and after training. Over occipito-temporal electrodes, ERP responses were modulated by motion strength both before and after training (as illustrated in Fig. 2.6A-D for electrode PO8) in a time interval peaking approximately 330 ms after stimulus onset: ERPs were more negative as the motion coherence increased. On the other hand, over the parietal electrodes, ERP responses were modulated by motion strength both before and after training (as illustrated in Fig. 2.6E-H for electrode Pz) in a time interval peaking approximately 500 ms after stimulus onset: ERPs were more positive as the motion coherence increased.

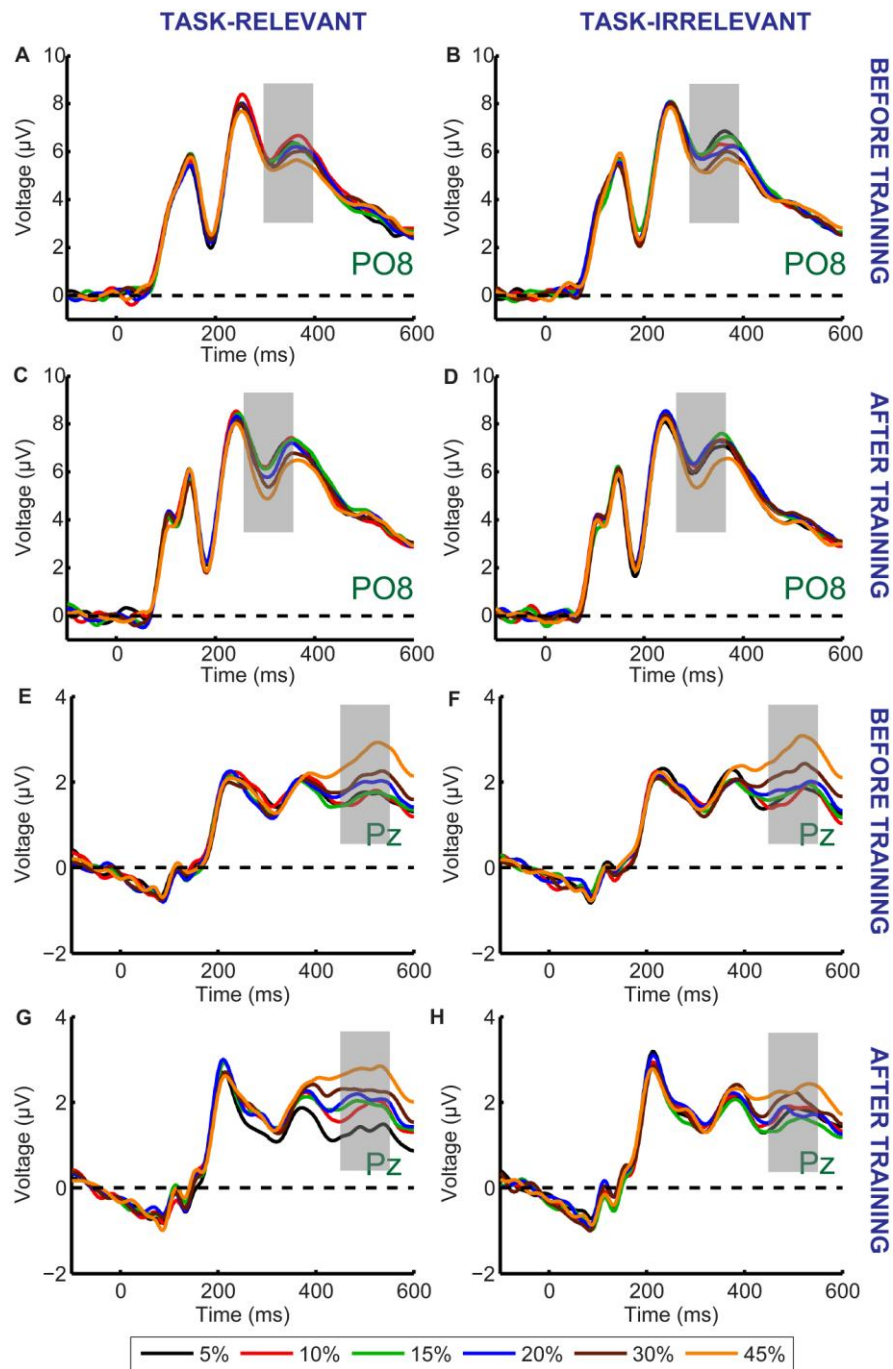


Figure 2.6 Grand average ERP responses shown for the PO8 (A-D) and Pz (E-H) electrodes. There was no difference between the ERP responses to the task-relevant (A,E) and task-irrelevant (B,F) directions before training. After training, the magnitude of motion signal strength dependent modulation of the ERP responses in the 300 -550 ms time interval is reduced in the case of task-irrelevant direction (D,H) compared to that in the case of task relevant direction (C,G). Different colors represent different motion coherence levels. Grey shaded bars indicate the time-windows where motion signal strength dependent modulations are most pronounced.

Next, we quantified the magnitude of the motion strength dependent ERP modulations and used this measure to investigate the effect of training on responses to task-relevant and task-irrelevant motion directions. We constructed scalp maps of beta values to visualize their spatial distribution; Figure 2.7 illustrates the distribution of beta values related to task-relevant motion before training (the scalp map was similar to the map obtained in response to task-irrelevant motion). The two peaks of motion coherence-dependent modulation of ERP responses that were observed in the average ERP waveform can clearly be identified by examining the beta value maps. The first peak is at 330 ms, it is bilateral, and is most pronounced over the lateral occipito-temporal cortex. The second peak is around 500 ms and is strongest over the parietal cortex.

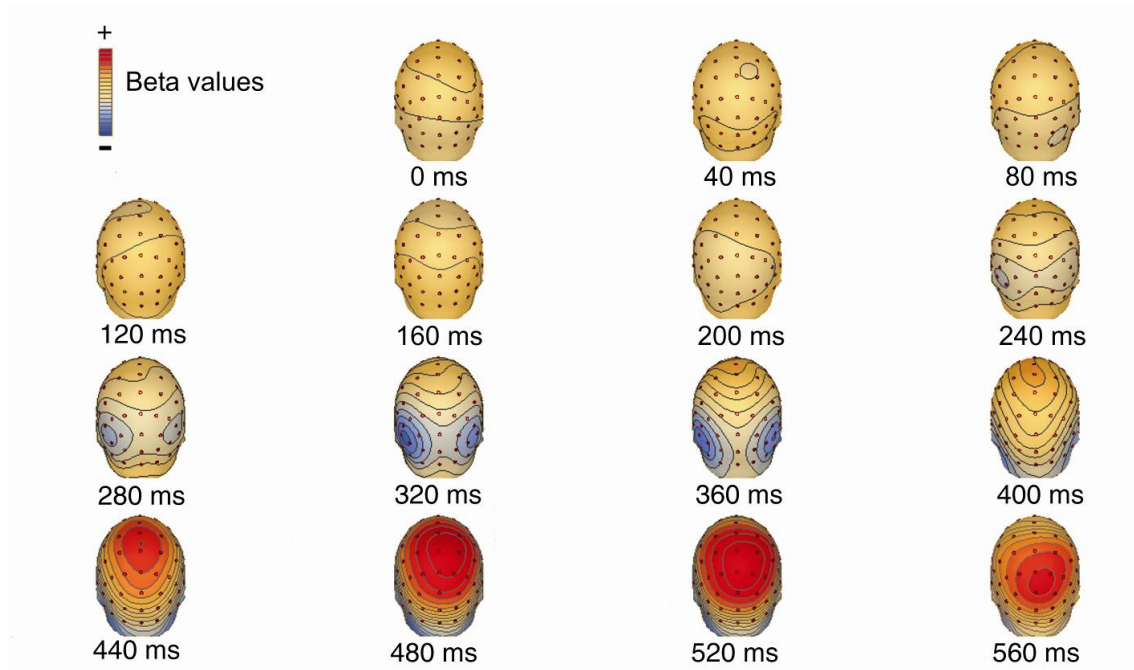
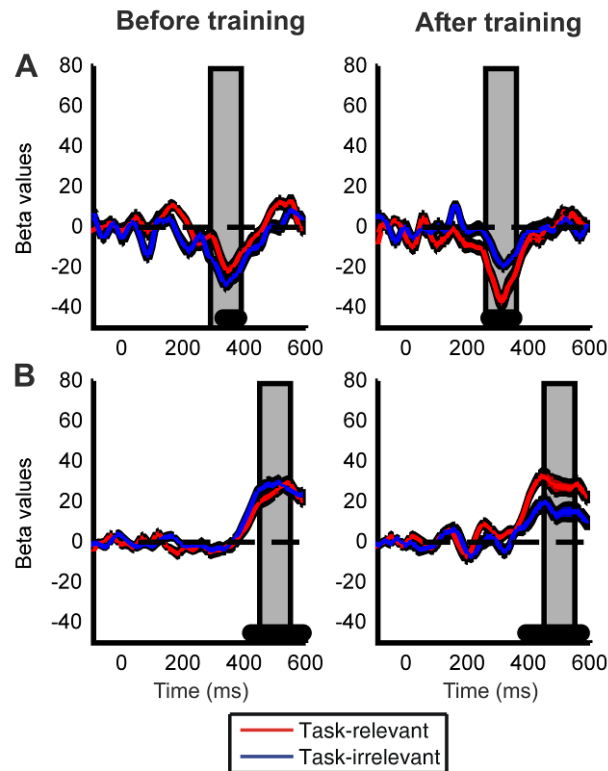


Figure 2.7 Spatial distribution of motion strength dependent modulation of the ERP responses: scalp maps of beta values related to task-relevant motion before training (the scalp map was similar to the map obtained in response to task-irrelevant motion.). The temporal evolution of the distribution shows an early (320-360ms) bilateral occipital and a late(480-520ms) parietal peak.

Next, we examined the influence of training by computing motion strength dependent modulations within a cluster of occipito-temporal (O1, O2, PO3, PO4, PO7, PO8, P7, P8) and a cluster of parietal (Pz, P1, P2, P3, P4) electrodes. These two clusters of electrodes were selected because in the data obtained before training they showed the largest beta values during the early and late peaks of the motion strength dependent

modulation, respectively (collapsed across task-relevant and task-irrelevant directions). There were two significant peaks of motion strength dependent modulation observed one at 330 ms after stimulus onset in the occipito-temporal electrodes (Fig. 2.8A) and the other significant peak at 500 ms after stimulus onset (Fig. 2.8B) in the parietal electrodes.



*Figure 2.8 Learning effects on the motion strength dependent modulation of the ERP responses. Time courses of the beta values for the task-relevant (red) and the task-irrelevant (blue) direction are shown; computed within a cluster of occipito-temporal (A) and parietal (B) electrodes. Black filled dots at the bottom of the figure indicate the intervals where beta values averaged across the two conditions are significantly different from zero (Student *t*-tests, corrected for multiple comparison, FDR=0.05). Data from the time interval indicated by the vertical gray shaded bars placed at the peaks of the beta values were used for ANOVA. Red and blue shaded bands around the time courses indicate the SEM.*

To further investigate the effect of training on ERP responses, we performed a repeated measures ANOVA on the beta values averaged across 100 ms time windows centered on the significant peaks (as shown in Fig. 2.8A-B). Although there was a clear trend of higher beta values in the occipito-temporal electrodes (Fig. 2.8A) after but not before training, ANOVA revealed a marginally significant interaction between test session and task relevance ($F(1,13)=4.651$, $p=0.052$). However, a closer examination of

the data revealed that the modest size of this interaction might be due to the fact that learning effects on the occipito-temporal electrodes were lateralized to the right hemisphere (interaction between test session and task relevance for the right hemisphere: $F(1,13)=6.894$, $p=0.021$; and for left hemisphere $F(1,13)=1.037$, $p=0.326$). Importantly, training also had a strong effect on the late parietal motion coherence-related peak of the ERP responses (Fig. 2.8B): beta values associated with the task-irrelevant direction were significantly reduced compared to the task-relevant direction after training but not before training (significant interaction between test session and task relevance: $F(1,13)=6.465$, $p=0.0245$ for parietal electrodes).

The behavioural findings showing no difference in the subjects' reaction times between the task-relevant and task-irrelevant directions after (as well as before) training speak against a possible explanation of the learning effects found on the ERP responses based on training induced differential modulation of motor responses to the two motion direction. Nevertheless, to further investigate this possibility we tested the relationship between the motion coherence dependent modulation of the ERP responses and subjects' RTs. Similarly to the calculation of the motion coherence-dependent modulation of the ERP responses, for each subject, direction and test session we calculated beta values based on the average RTS obtained in the case of the six different motion coherence levels. Our analysis revealed no correlation between the motion coherence dependent modulation of the ERP responses and RTs: $r(12)<0.3$ and $p>0.3$ in all cases (both test sessions, directions and hemispheres, tested separately).

To verify that subjects were able to maintain fixation during the ERP recordings, we tracked the eye position of four randomly selected subjects while they performed the motion discrimination task before training, and of eleven randomly selected subjects after training. We found no significant difference in the mean eye position for the 2 different motion directions (paired t test, before training: $t(3)=-0.299$ $p=0.784$ for x coordinates and $t(3)=-0.438$ $p=0.691$ for y coordinates; after training: $t(10)=-0.347$ $p=0.735$ for x coordinates and $t(10)=0.294$ $p=0.774$ for y coordinates) indicating that there was no systematic bias in eye position induced by the direction of the motion stimulus. Moreover, repeated measures of ANOVA were calculated over the average amplitudes within the same time-windows that were selected in the main analysis (early 260-360ms and late 450-550ms). ANOVA revealed no significant difference between the two motion directions: $p>0.29$ and $F<1.19$ for either of the EOG channels and time-windows.

3.5. Control experiment

A control experiment was performed to determine if attending to the motion directional signal and performing the motion discrimination task is required to evoke the observed motion coherence-related ERP peaks. The stimuli were the same as those used in the main experiment except that only two motion coherence levels (10% and 45%) were used and in each trial all the dots were colored either red or green in an unpredictable way. In separate blocks subjects either performed a motion direction discrimination task, just as in the main experiment or a color discrimination task (red vs. green). Behavioral results showed that in the motion direction discrimination task, but not in the color discrimination task subjects' performance was significantly better at the higher than at the lower motion coherence level (at 10% motion coherence: 60.44%; at 45% motion coherence: 94.29%; main effect of motion coherence levels: $F(1,8)=301.993$, $p=0.0001$), whereas performance in the color discrimination task was similar at the two different motion coherence levels (at 10% motion coherence: 98.27% and at 45% motion coherence: 97.66%; $F(1,8)=2.47$, $p=0.154$).

In the case of direction discrimination task ERP responses to the low and high motion coherence stimuli differed in two time intervals, which closely corresponded to the two peaks of motion coherence-related modulation of the ERP responses observed in the main experiment (Fig 2.9). On the other hand, in the case of color discrimination task, ERP responses differed between the low and high motion coherence stimuli only in a temporal interval corresponding to the first coherence-related peak found in the motion direction discrimination task both in the main and in the control experiment (Fig 2.9). Accordingly, ANOVA revealed no significant difference in modulation of the first motion coherence-related ERP peak between the direction and color discrimination conditions (occipital-temporal electrodes interaction between direction and color discrimination: $F(1,8)=0.732$, $p=0.417$). However, there was a significant difference in modulation of the late motion coherence-related ERP peak between the direction and color discrimination condition (parietal electrodes: $F(1,8)=6.3$ $p=0.036$). Post hoc analysis showed that ERP responses to the high and low motion coherence stimuli in the time interval corresponding to the late coherence-related ERP peak differed during the motion direction discrimination task ($F(1,8)=14.569$ $p=0.005$) but not during the color discrimination condition task ($F(1,8)=0.054$ $p=0.823$).

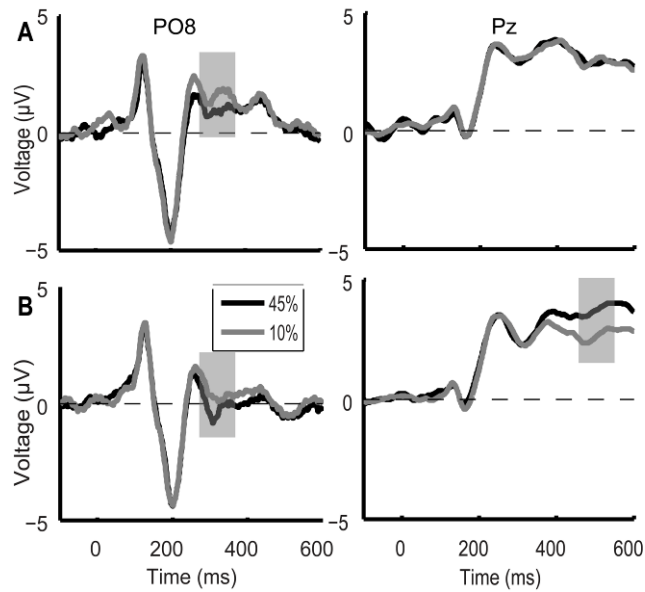


Figure 2.9 Control experiment Grand average ERP waveforms during the color discrimination task (A) and the motion direction discrimination task (B) shown for the PO8 and Pz electrodes. In the case of color discrimination task (A), ERP responses differed between the 10% (grey line) and 45% (black line) motion coherence stimuli only in an early temporal interval (330 ms after stimulus onset, grey shaded bar). During the direction discrimination task (B) ERP responses to the low and high motion coherence stimuli differed in two time intervals (indicated by grey shaded bars) which closely corresponded to the two peaks of motion coherence-related modulation of the ERP responses observed in the main experiment.

4. Discussion

Our findings provide evidence that learning results in increased detection thresholds for task-irrelevant features. This learning-induced sensitivity decrease was specific for the feature that served as a distractor during training since the detection threshold for a control direction that was not present during training slightly decreased (rather than increased) after training. The observation of a small non-significant increase in sensitivity to task-relevant motion in the present task is consistent with previous reports showing improved perceptual performance for visual features that were task relevant during training (Ramachandran & Braddick 1973; Fiorentini & Berardi 1980; Ball & Sekuler 1982; Karni & Sagi 1991) (for review see Fahle & Poggio 2002). On the other hand, recent studies also suggest that learning results in increased sensitivity for subthreshold task-irrelevant visual features presented concurrently with the task-relevant information during training (Watanabe et al. 2001; Watanabe et al. 2002; Seitz & Watanabe 2003) whereas suprathreshold task-irrelevant features are not affected by

training (Tsushima et al. 2008). These findings apparently conflict with our observation of reduced sensitivity for task-irrelevant information. However, several key differences between the studies might explain this discrepancy. First, the task-irrelevant stimulus used by Watanabe and coworkers (2001, 2002, 2003) was spatially separated from the task-relevant stimulus during training. Secondly, the target and distractor stimuli were very different - alphanumeric characters and moving dots respectively - suggesting that task-relevant and task-irrelevant stimuli were processed by at least partially distinct regions of the visual cortex: one region specialized for processing shape/letter information and the other for processing visual motion. Due to distinctiveness of the relevant and irrelevant stimuli, it seems likely that the irrelevant stimulus did not strongly interact or interfere with target processing. In the present study, however, task-relevant and task-irrelevant stimuli were spatially overlapping and structurally similar (i.e. both were moving dot patterns). Therefore, the stimuli were likely competing for access to the same neural processing mechanisms, which would be expected to drastically increase the extent of competition. We therefore posit that the learning-induced suppression of distractors – as opposed to enhancement as reported by Watanabe et al. (2001)– may only be observed when the task-irrelevant information strongly interferes with the processing of task-relevant information and thus must be suppressed by attention during training.

The possibility that the strength of distractor suppression during training might affect learning has also been invoked (Tsushima et al. 2008) to explain why learning leads to increased sensitivity for subthreshold but not for suprathreshold task-irrelevant information. For example, attentional suppression of task-irrelevant information is less pronounced when the distractor is a very weak, subthreshold signal as compared to when it is suprathreshold (Tsushima et al. 2006). Thus, learning may result in increased sensitivity for subthreshold distractors but not for suprathreshold distractors because only the later must be suppressed during training (and this suppression should attenuate any positive consequences of learning, Tsushima et al. 2008). The results of the present study take this logic one step further and show that in cases when there is direct interference between task-relevant and task-irrelevant information that requires strong attentional suppression, training will actually produce decreased sensitivity for the task-irrelevant information.

Our ERP results revealed that training on a task which requires object-based attentional selection of one of the two competing, spatially superimposed motion stimuli

will lead to strong modulation of the neural responses to these motion directions when measured in a training-unrelated motion direction discrimination task. Motion direction that was task-relevant during training evoked significantly stronger modulation of the earliest motion coherence-related peak of the ERP responses over the right hemisphere peaking around 330 ms as compared to the motion direction that was present as a distractor during practice. The latency of the first motion coherence-related peak found in the present study is in agreement with the results of previous studies showing that motion coherence-related modulation of the neural responses starts more than 200 ms after stimulus onset (Händel et al. 2007; Aspell et al. 2005). Lateralization of the learning-induced modulation of the first motion coherence-related ERP peak to the right hemisphere appears to be in line with the results of previous studies showing right hemisphere dominance in visual motion processing (Aspell et al. 2005; Kubová et al. 1990).

Our control experiment showed that this first peak of motion coherence-related modulation in the conditions where subjects perform a task in which motion information is task-irrelevant (color discrimination task) is very similar to that found in the condition where the motion signal is attended (direction discrimination task). This suggests that the first motion coherence-related peak reflects the initial, feed-forward stage of representing the coherent motion signal in visual cortex. The fact that the learning effects related to this early motion-related ERP peak was most pronounced over the occipital cortex is in agreement with previous electrophysiological and neuroimaging studies suggesting that perceptual learning effects act on early visual cortical stages of information processing (Skrandies et al. 1996; Dolan et al. 1997; Pourtois et al. 2008; Vaina et al. 1998; Gauthier et al. 1999; Schiltz et al. 1999; Schwartz et al. 2002; Furmanski et al. 2004; Kourtzi et al. 2005; Sigman et al. 2005; Shoji and Skrandies 2006; Skrandies and Fahle 1994). Our ERP results are also in agreement with the effects of learning on fMRI responses associated with task-relevant and task-irrelevant motion directions (Gál et al. 2009). It was found that, after training, task-irrelevant motion direction evoked weaker fMRI responses than the task-relevant direction in early visual cortical areas, including the human area MT+, where neural responses are sensitive to motion coherence and are associated with the perceived strength of the global coherent motion signal (for review see Serences and Boynton 2007).

Learning also had a strong effect on the late motion strength-dependent peak of the ERP responses. Our control experiment revealed that the late motion coherence-

related modulation of the ERP responses was present only in the motion discrimination but not in the color discrimination task. This suggests that the late peak of motion coherence-dependent modulation might reflect decision processes related to the motion direction discrimination task. This interpretation is also supported by our results showing that the late ERP response peaked over the parietal cortex. For example, Shadlen and coworkers (2001) have shown that oculomotor circuits in parietal cortex are involved in accumulating and integrating sensory evidence about different motion directions during decision making (e.g. Shadlen and Newsome 2001; reviewed by Gold and Shadlen 2007). In agreement with this, recently it was also reported that in humans different regions of the posterior parietal cortex are involved in accumulation of sensory evidence for perceptual decisions depending on whether subjects were required to respond by eye movements or by hand-pointing (Tosoni et al. 2008). Furthermore, the results of recent studies that examine the neural mechanisms of object discrimination in humans provide additional support for the notion that the late peak of motion coherence-dependent modulation reported here might be related to perceptual decision making. For example, a late stage of recurrent processing has been observed during the accumulation of sensory evidence about object-related processing under degraded viewing conditions consists (Philiastides and Sajda 2006; Philiastides et al. 2006; Murray et al. 2006; Fahrenfort et al. 2008). Importantly, the marker for this late processing stage is an ERP component that starts between 300-400 ms after stimulus onset (Philiastides and Sajda 2006; Philiastides et al. 2006; Murray et al. 2006). Although the onset of the late motion strength dependent ERP modulation that we observed in the present study starts approximately 100 ms after the late component observed during visual object processing (Philiastides and Sajda 2006; Philiastides et al. 2006; Murray et al. 2006), we suggest that both modulations might reflect similar neural mechanisms. The differential onset times might be due to the fact that the motion stimuli we used were made up of limited lifetime dots and embedded in distracting noise; this noise likely delayed the formation of a decision about the direction of the global motion signal. If we posit that the motion coherence-dependent modulation in our study started around 250 ms – which is in agreement with earlier findings (Aspell et al. 2005) – the delay between our early and late time window of motion coherence-dependent modulation (which started between 400-500 ms) corresponds well to that found in the case of object processing: 150-200 ms (Carmel and Carrasco 2008; Philiastides and Sajda 2006; Philiastides et al. 2006; Murray et al. 2006; Fahrenfort et al. 2008).

In conjunction with these previous reports, the present demonstration of a significant training-related modulation of the late peak of motion coherence-dependent modulation of ERP responses suggests that learning affects the integration and evaluation of motion information at decisional stages in the parietal cortex. This conclusion appears to be in agreement with recent monkey neurophysiological (Law and Gold 2008) and modeling results (Law and Gold 2009), suggesting the perceptual learning in a motion discrimination task requiring an eye movement response primarily affects the decision processes and in particular the readout of the directional information by the lateral intraparietal neurons. Based on previous results demonstrating human posterior parietal cortex is involved in accumulating sensory evidence in a task requiring manual responses, it is reasonable to suppose that the modulation of the late peak of motion coherence-dependent modulation of ERP responses we observe in the current study reflects the influence of learning on the parietal decision processes involved in performing the motion discrimination task.

From a broader perspective, our results are also in agreement with the growing body of psychophysical, neuroimaging and modeling results suggesting a close relationship between perceptual learning and attention (Ahissar and Hochstein 1993, 1997; Li et al. 2004, 2009; Lu et al. 2006; Gál et al. 2009; Gutnisky et al. 2009; Mukai et al. 2007; Xiao et al. 2008; Vidnyánszky and Sohn 2005; Petrov et al. 2006; Law and Gold 2008, 2009; Paffen et al. 2008); for review see: Tsushima and Watanabe 2009). It was proposed that visual perceptual learning affects visual attentional selection mechanisms leading to more efficient processing of the task-relevant as well as more efficient suppression and exclusion of the task-irrelevant visual information as a result of training. The possibility that plasticity of attentional selection might be involved in the learning effects found in the current study are supported by previous results showing that attention can modulate processing of motion information in the visual cortical areas, including the human area MT+ (Valdes-Sosa et al. 1998; O'Craven et al. 1999; Corbetta and Shulman 2002; Pessoa et al. 2003; Händel et al. 2008). Furthermore, it is also known that the parietal cortex plays a critical role in attentional functions (Serences and Yantis 2006) and thus learning-induced changes in the parietal responses to motion information might reflect modulation of the attentional selection processes involved in decision making as a result of training. In fact, in the previous study investigating the effect of perceptual learning on visual motion direction discrimination (Law and Gold 2008) one possible explanation for the observed modulation of motion-driven responses of neurons

in area LIP by perceptual learning was based on improved attention to appropriate features of the motion representation used to form the decision.

*Chapter Four***SPATIOTEMPORAL REPRESENTATION OF VIBROTACTILE STIMULI****Third thesis:**

I found that the spatiotemporal representation of non-visual stimuli in front versus rear space (in the human body-based coordinate system) is different. My experiments show that crossing the hands behind the back leads to a much smaller impairment in tactile temporal resolution as compared to when the hands are crossed in front. My investigation have also revealed that even though extensive training in pianists resulted in significantly improved temporal resolution overall, it did not eliminate the difference between the temporal discrimination ability in front and rear space, demonstrating that the superior tactile temporal resolution I found in the space behind people's backs cannot simply be explained by incidental differences in tactile experience with crossed-hands at the rear versus in the front. These results suggest that the difference in the spatiotemporal representation of non-visual stimuli in front versus rear space originates in the differences in the availability of visual input.

1. Introduction

Our brains typically localize sensory events – including touches and sounds – according to an externally defined coordinate system, which is dominated by vision (Botvinick, Cohen 1998; Ehrsson, Spence, Passingham 2004; Graziano 1999; Kitazawa 2002; Pavani et al. 2000). The remapping of tactile stimuli from body-centered coordinates—in which they are coded initially—into external coordinates is fast and relatively effortless when the body is in its “typical” posture (i.e., with the left hand on the left of the body and vice versa for the right hand) (e.g., see Amlot, Walker 2006; Groh, Sparks 1996). However, when more unusual body postures are adopted, such as crossing the hands, remapping takes more time and can result in substantial deficits in the perception of tactile stimuli, at least under conditions of bimanual and/or bimodal stimulation. For example, several studies have highlighted impaired temporal order

judgment (TOJ) performance regarding which of two tactile stimuli – delivered in rapid succession, one to either hand – was presented first when the hands are crossed as compared to when they are uncrossed (Shore et al. 2002; Yamamoto, Kitazawa 2001). A similar deficit has been observed when the fingers of the two hands are interleaved (Zampini et al 2005).

Recently, Röder et al. (2004) reported that congenitally blind individuals do not show any such impairment in tactile TOJs as a result of crossing their hands, thus raising the following intriguing question: would crossing the hands behind the back – i.e., in a region of space where we normally have no, or very limited, visual input – result in a similar amelioration of the crossed-hands tactile TOJ deficit in normal sighted individuals? Put another way, is the multisensory spatial information concerning sensory events coded in a similar manner throughout peripersonal space (Rizzolatti et al. 1997) or might there instead be a difference between front and rear space (i.e., the space behind our backs), as a result of the existence of a detailed visual representations of the former but only occasional and very limited visual representation of the later (Bryant et al. 1992; Farne, Ladavas 2002; Franklin, Tversky 1990; Graziano et al. 2000; James (p. 275); Kitagawa et al. 2005)?

People who lost their sight during their life (i.e. not congenitally blinds) the crossing of the hands decreases the performance in the same way as in the case of normal sighted people. As the case of non-congenitally blind people demonstrates, the multisensory representation system of peripersonal space finishes during early development. Therefore the question arises as to whether the encoding and weighting of different modalities can be influenced by intensive practice in the later stages of development as well. Professional piano playing requires extensive and long-term training of finger movement, auditory and visual perception and the spatial tactile acuity in professional pianists is significantly higher compared with a non-musician control group. Thus, the examination of this group could provide the possibility for the comparison of neural processes of sensory coding, which preserves its plasticity in adulthood and which can not be changed through learning in adulthood. In this way, pianists are also a useful group for studying the neural mechanisms of long-term training and neural plasticity (Münste et al., 2002).

The cortical reorganization of the representation has altered in the pianists. Representation of the fingers is more pronounced in pianists who had begun their musical training at an early age. Previous studies found increased grey matter volume in

pianist in a motor network that included the left and right primary sensorimotor regions, the left basal ganglia, anterior parietal lobe and the bilateral cerebellum, as well as the left posterior perisylvian region (Gaser et al. 2001). Reduced asymmetry scores were found in some areas. For example, a greater intrasulcal length on both sides was found, but more so on the right, non-dominant hemisphere. Piano playing requires precise coordination of bimanual movements. Pianists who began their musical training before the age of seven have a larger anterior midsagittal corpus callosum than controls or musicians who started training later (Schlaug et al. 1995). A bilateral transcranial magnetic stimulation (TMS) study revealed decreased interhemispheric inhibition (Ridding et al. 2000). Together, the findings indicate that professional piano players have anatomical and functional differences in several brain areas that are involved in motor, auditory and visual processing.

I compared the effect of crossing the hands (POSTURE) on tactile TOJ performance when the hands were placed in front of participants versus when they were placed behind their backs (SPACE). I tested two groups of participants, non-musicians as well as professional piano players (GROUP), in order to uncover how extensive practice in playing piano – leading to altered tactile perception in pianists (Hatta, Ejiri 1989; Ragert et al. 2004) – will affect TOJ performance in front and rear space in the latter group.

2. Methods

2.1. Stimuli and Procedure

Eighteen non-musicians (mean age, 22 years; range, 19–39 years, 3 left handed) with normal or corrected-to normal vision and 15 pianists, 9 students at the Liszt F. Academy of Music as well as 6 recent graduates (mean age, 23 years; range, 18–26 years; 9 females, 2 left-handed) took part in the experiments. The pianists began piano playing at an average age of 8 years, and practiced for an average of 3 h per day. The experiment was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. All participants gave their informed consent.

Participants (with their eyes closed) were presented with pairs of suprathreshold vibrotactile stimuli (30 ms duration), one to the second finger of either hand, and were required to make unspeeded TOJs regarding which finger was stimulated first. We used

bone-conducting hearing aids (Oticon) as vibrotactile stimulators (Figure.3.1) (Shore et al. 2002).

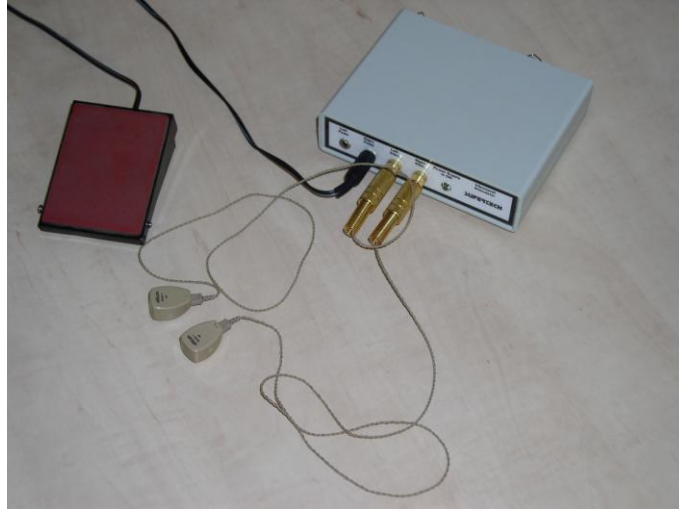


Figure.3.1 Vibrotactile stimulators and footpedal as response button.

Participants responded by pressing the left footpedal if their left hand appeared to have been stimulated first and the right footpedal if their right hand appeared to have been stimulated first. A small block of foam was placed between the participant's arms in the crossed-hands posture in order to reduce any contact between them. The right arm was always crossed over the top of the left arm. The spatial separation between the vibrotactile stimulators (placed 20 cm in front or behind the back of the participants and 15 cm to either side of the midline) was kept constant throughout the experiment. We performed a pilot study to determine whether tactile temporal resolution differs when the task is performed with palms facing downward as compared to when they face upward. Since, the pilot experiments revealed that TOJs did not differ in the two conditions, in the main experiments – both in the uncrossed and crossed-hand conditions – the task was performed with the palms facing downward when the hands were placed in the front and with palms facing upward when hands were placed at the rear, i.e., with palm orientation that was more convenient and closer to a „natural“ posture (Figure.3.2). White noise was presented through headphones to mask any sounds made by the operation of the tactile stimulators.

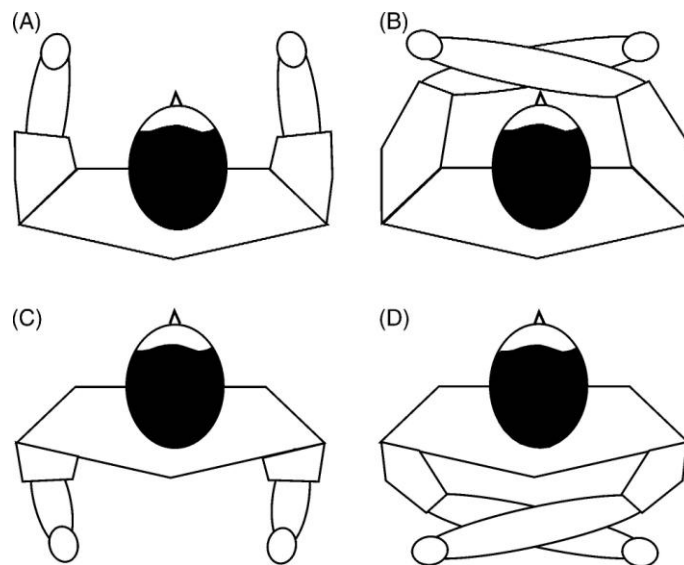


Figure.3.2 Schematic illustration of hand postures (uncrossed and crossed) when they were placed in the front (A, B) and at the rear space (C, D).

There were 10 possible stimulus onset asynchronies (SOAs) between the stimuli (in the uncrossed condition: -200 , -90 , -55 , -30 , -15 , 15 , 30 , 55 , 90 , or 200 ms and in the crossed condition: -300 , -180 , -110 , -60 , -15 , 15 , 60 , 110 , 180 , or 300 ms; where negative values indicate that the left hand was stimulated first) presented according to the method of constant stimuli. At the beginning of the experiment, observers completed 4 blocks of 30 practice trials. The practice blocks were followed by 8 blocks of 200 experimental trials, with the posture (uncrossed versus crossed) and the space (front versus rear) alternated between successive blocks of trials, and the order of presentation counterbalanced across observers.

2.2. Statistical analysis

The mean percentages of right first responses were calculated for SOA through, POSTURE, SPACE and GROUP. The data were modelled by a Weibull psychometric function, using the *psignifit* toolbox (ver. 2.5.6) for Matlab (<http://bootstrap-software.org/psignifit/>). We calculated just noticeable differences (JNDs; the smallest interval needed to indicate temporal order reliably) by subtracting the SOA needed to achieve 75% performance from that needed to achieve 25% performance and dividing by two (Shore et al. 2002).

3. Results

In accordance with previous results (Shore et al. 2002; Yamamoto, Kitazawa 2001) – based on their TOJ performance with crossed-hands at short intervals – participants (both non-musicians and pianists) fell into two groups: (1) veridical-TOJ group, including those who reported the veridical temporal order (10 out of 18 non-musicians; and 8 out of 15 pianists) and (2) reversed-TOJ group, including those who reliably reported a reversed subjective temporal order at shorter SOAs (<300 ms). Given that it is still unclear what causes this reversal of TOJ performance in certain individuals we focused our analyses on the data from the veridical-TOJ group (Figure.3.3 nonmusicians: A and B; pianists: C and D). Data from the reversed-TOJ group, who showed the same pattern of results (Figure.3.4 nonmusicians: A and B; pianists: C and D).

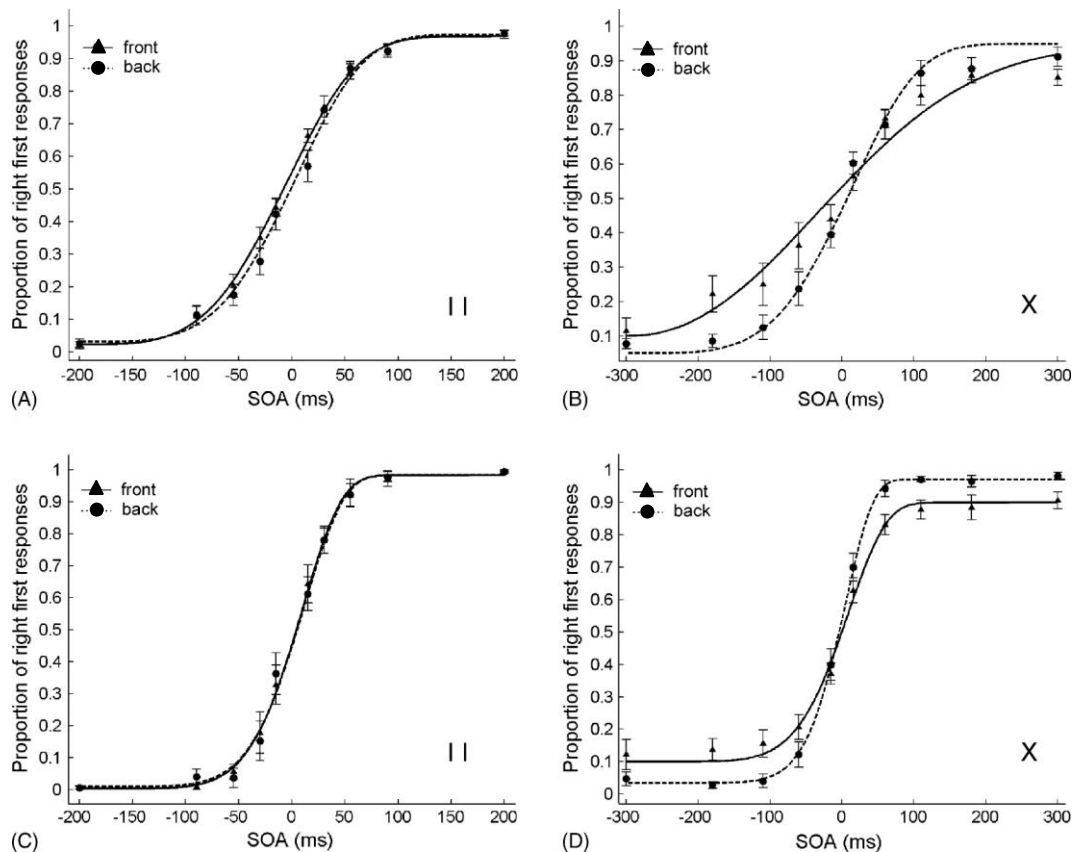


Figure.3.3 Proportion of right hand first responses of the veridical-TOJ group. Weibull fits to the mean proportions of right hand first responses across individual observers are presented for the non-musicians (A—uncrossed posture; B—crossed posture) and pianists (C—uncrossed posture; D—crossed posture), both when the hands were placed in front and rear space. Error bars represent the between observer S.E.M.

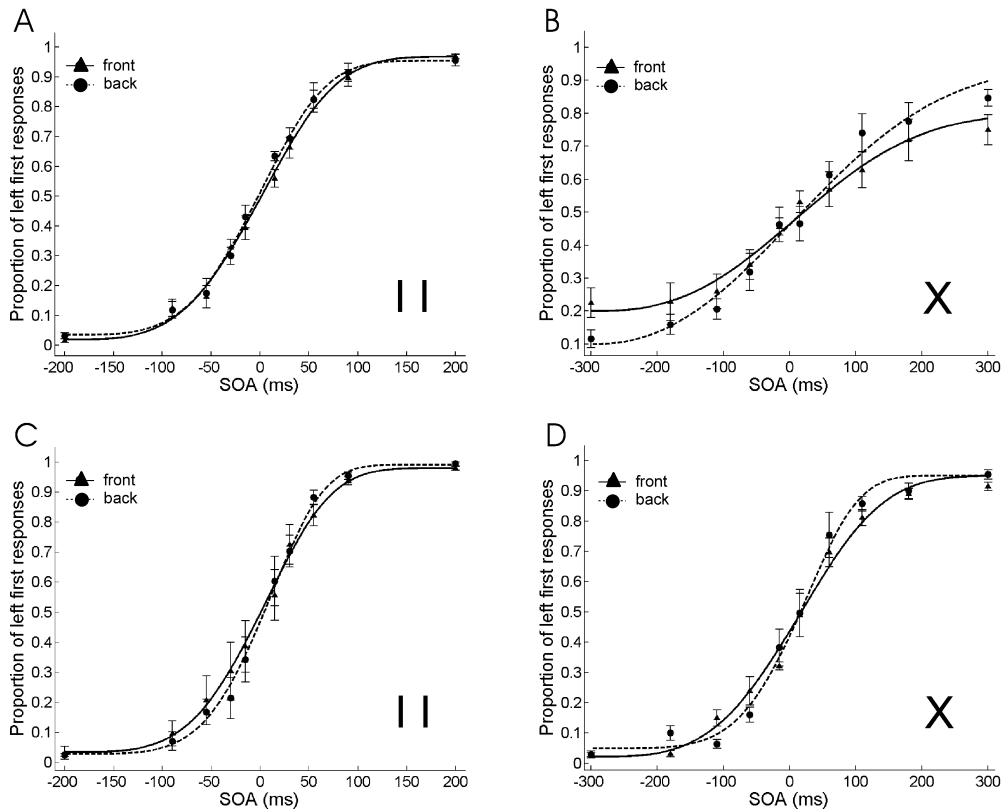


Figure.3.4 Proportion of right hand first responses of the reversal-TOJ group. Weibull fits to the mean proportions of right hand first responses across individual observers are presented for the non-musicians (A—uncrossed posture; B—crossed posture) and pianists (C—uncrossed posture; D—crossed posture), both when the hands were placed in front and rear space. Error bars represent the between observer S.E.M.

Crossing the hands led to a significant decrement in performance at the SPACE in the non-musicians (see Figure.3.5; chart 3.1; the main effect of POSTURE: $F(1,9)=21.3$, $p < 0.001$). Importantly, there was also a significant main effect of SPACE; ($F(1,9)=8.4$, $p < 0.02$), as well as a significant interaction between SPACE x POSTURE; $F(1,9)=5.6$, $p < 0.05$, attributable to the reduced decrement in performance observed when the hands were crossed behind the back as compared to when they were crossed in the front.

We also tested whether professional piano players (i.e., individuals who had had extensive practice of bimanual tactile perception in the front) showed a similar pattern of results. In general, the piano players exhibited better temporal resolution than the non-musicians in all conditions (see Figure.3.5; chart 3.1); ($F(1,16)=9.1$, $p < 0.008$). Just as for the non-musicians, there were significant main effects of POSTURE ($F(1,3)=9.2$, $p < 0.02$) and SPACE ($F(1,7)=10.2$, $p < 0.02$), as well as a significant interaction between SPACE x POSTURE ($F(1,7)=8.9$, $p < 0.02$). Importantly, the trained pianists showed no

significant POSTURE deficit when their hands were crossed behind their backs (post hoc analyses: $p = 0.712$).

	Control	Pianist
POSTURE	$F(1,9)=21.3, p < 0.001$	$F(1,3)=9.2, p < 0.02$
SPACE	$F(1,9)=8.4, p < 0.02$	$F(1,7)=10.2, p < 0.02$
POSTURE x SPACE	$F(1,9)=5.6, p < 0.05$	$F(1,7)=8.9, p < 0.02$

Chart 3.1 Summary of the statistical analysis.

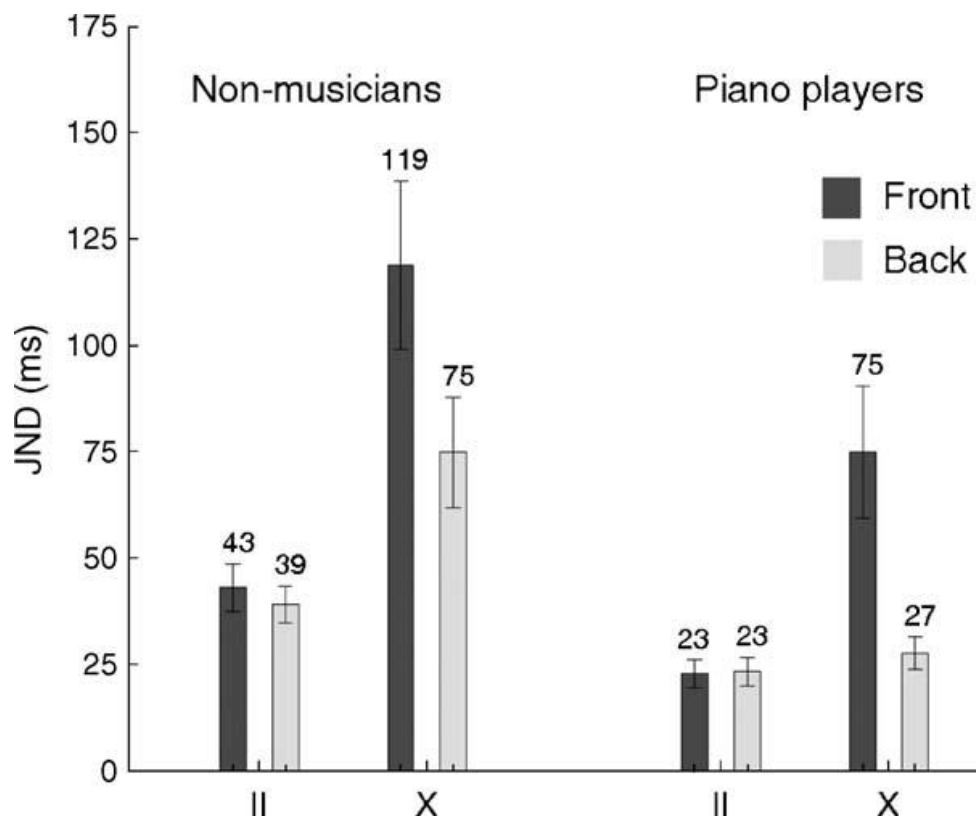


Figure 3.5 TOJ performance of the veridical group. Average JNDs (calculated by subtracting the SOA needed to achieve 75% performance from that needed to achieve 25% performance and dividing by two) are shown for the non-musicians and pianists for all four conditions tested (II = uncrossed posture; and X = crossed posture). JNDs were determined independently for all participants based on the slope of the Weibull functions that were fitted to the individual data obtained in the four conditions (see Fig. 3.3 for the Weibull fit to participants' mean performance). Error bars represent the between observer S.E.M.

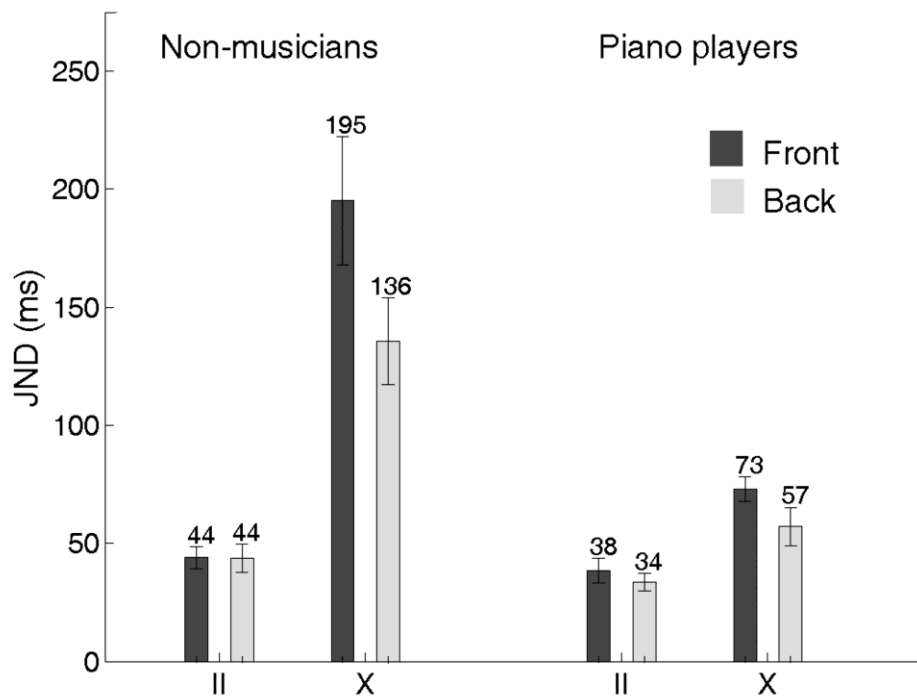


Figure 3.6 TOJ performance of the reversal group. Average JNDs (calculated by subtracting the SOA needed to achieve 75% performance from that needed to achieve 25% performance and dividing by two) are shown for the non-musicians and pianists for all four conditions tested (II = uncrossed posture; and X = crossed posture). JNDs were determined independently for all participants based on the slope of the Weibull functions that were fitted to the individual data obtained in the four conditions (see Fig. 3.4 for the Weibull fit to participants' mean performance). Error bars represent the between observer S.E.M.

When their hands were uncrossed, TOJ performance was similar at the SPACE, in both non-musicians (post hoc analyses: $p = 0.082$) and pianists (post hoc analyses: $p = 0.971$), suggesting that simply placing the hands behind the back did not influence TOJ performance deleteriously.

The results of this study show that crossing the hands behind the back leads to a much smaller impairment in tactile TOJs as compared to when the hands are crossed in front. Our results also show that even though extensive training in pianists resulted in significantly improved temporal resolution overall, it did not eliminate the difference between the efficiency of TOJs in front and rear space, suggesting that the superior tactile temporal resolution we found in the space behind peoples' backs cannot simply be explained by incidental differences in tactile experience with crossed-hands at the rear versus in the front.

4. Discussion

The finding that TOJ performance in the crossed-hands posture was significantly better in the space behind participants – i.e., in the region where people have very limited access to visual information – than in the space in front of participants – a region of space that tends to be dominated by visual inputs – are in line with recent results showing that congenitally blind individuals do not show any such impairment in tactile TOJs as a result of crossing their hands (Röder et al. 2004). The results of electrophysiological studies in macaques (see refs. (Graziano et al. 2004; Stein et al. 2004) for recent reviews) as well as neuropsychological and brain imaging studies in humans (see ref. Ladavas and Farne 2004) converge on the view that a distributed neural network – involving the superior colliculus, putamen, parietal and premotor cortical areas – is responsible for the multisensory representation of peripersonal space surrounding the hand. In these brain regions, many neurons are multimodal, responding to tactile, visual, and sometimes even to auditory stimuli.

It has also been shown that in the frontal, visible part of peripersonal space tactile stimuli are typically localized according to an externally defined coordinate system, which is predominantly determined by visual inputs. In sighted individuals, crossed-hand effects are believed to reflect the longer time that may be required for the remapping of tactile stimuli into an externally defined reference frame when the external and body-centered coordinates conflict (Kitazawa 2002). In congenitally blind individuals, however, crossing the hands has no effect on tactile temporal resolution (Röder et al. 2004), suggesting that, due to the lack of any visual reference frames: (1) remapping of tactile stimuli from body-centered into externally defined coordinates is independent of hand posture; or (2) localization of tactile stimuli in space and time can take place more directly, based on the body-centered coordinates. Further studies are required to uncover exactly why crossed-hands effects are absent in congenitally blind individuals. However, it is reasonable to suppose that the underlying mechanisms are common with those leading to reduced crossed-hands effect in the space behind us – where little or no visual information is available – as found in the present study.

Such a conclusion is also supported by our findings that in non-musicians, even when the hands are uncrossed, tactile temporal resolution tends to be better in rear space than that in the front (N.B.: this difference did not quite reach statistical significance). This is because it was also shown earlier that tactile temporal resolution in congenitally

blind individuals is better than in the sighted controls both in the case of uncrossed and crossed-hand postures. If it is the lack of a visual reference frame in the representation of peripersonal space that leads to improved tactile temporal resolution in both congenitally blind individuals as well as at the rear space of sighted individuals. The spatiotemporal representation of tactile stimuli in space behind the backs of sighted individuals – especially in those who are trained in tasks requiring fine spatiotemporal analyses of tactile information – might be used as a normal model for the spatial representation of tactile information in congenitally blind individuals.

Our results also have important implications with respect the learning processes leading to professional piano playing. Musician's brains constitute a useful model for studying neuroplasticity evoked by extensive long-term training (Münste et al. 2002; Pantev et al. 2003; Schlaug 2001). Recently, it has been shown that there are structural differences in the gray matter (Gaser and Schlaug 2003) as well as in the white matter (Bengtsson et al. 2005) between professional piano players and non-musicians. Interestingly, it has also been shown that extensive practice in playing the piano leads not only to improved motor skills but also to higher spatial tactile resolution in pianists as compared to non-musicians (Ragert et al. 2004). Here, we show for the first time that the temporal resolution of tactile stimuli is also significantly higher in professional piano players than in non-musicians. Thus, our results are in agreement with Ragert et al.'s (2004) suggestion that extensive piano practice has a broad effect on somatosensory information processing and sensory perception, even beyond training-specific constraints.

*Chapter Five***CONCLUSIONS**

The results of the first experiment provide evidence that attention affects the perceived pain intensity of pinprick stimulation in capsaicin-induced secondary hyperalgesia and that the magnitude of attentional modulation is similar to that found in the capsaicin untreated, control conditions. These findings imply that controlling attentional load should enhance the reliability of pain intensity measurements in the model capsaicin-induced secondary hyperalgesia.

Nearly a decade of neuroimaging research has revealed that supraspinal activity is increased during mechanical hyperalgesia that is experimentally induced sensitization by capsaicin in healthy volunteers (Zambreanu et al. 2005). Increased activity is found in the brainstem, the thalamus, cerebellum, primary and secondary somatosensory cortices, insula and cingulate cortex. A recent study showed that it is the brainstem which is primarily responsible for the maintenance of central sensitization underlying secondary hyperalgesia, whereas activation of the cortical areas might be associated with the perceptual and cognitive aspects of hyperalgesia (Lee et al. 2008). However, my results suggest that the *short, 45 min sensitization period* is restricted primarily to the brainstem mediated central sensitization mechanisms and involves very little or no modulation of anticipatory attentional processes.

The attention-based perceptual learning -discussed in the second thesis- leads to reduced neural sensitivity for visual motion directions that were neglected compared to those that were attended during training by modulating the efficacy of visual cortical extraction of the coherent motion signal as well as the accumulation and readout of motion directional information by parietal decision processes.

My results (in agreement with the previous studies) emphasize the role of attention in -a couple of days long- *perceptual learning* (Tsushima and Watanabe 2009). The parietal cortex plays a critical role in attentional functions and thus learning-induced changes in the parietal responses to motion information might reflect modulation of the attentional selection processes involved in decision making as a result of training.

The last thesis showed that crossing the hands behind the back leads to a much smaller impairment in tactile temporal resolution as compared to when the hands are

crossed in front and the tactile temporal order judgments were much better in the musicians overall than in control. Importantly, the trained pianists showed no significant posture deficit when their hands were crossed behind their backs. My results showing the difference between the multisensory representation of the peripersonal space in the front and the rear space, can provide an opportunity for the comparison of the neural processes of sensory coding, which preserves its plasticity in adulthood and of the neural processes of sensory coding, which can not be modified in adulthood. This experimental set up also involving professional pianists constitutes a useful model for studying neuroplasticity evoked by extensive *long-term training*.

In recent years a number of promising methods have emerged for the development of a biomarker or for the improvement or correction of abnormally developing, injured sensory functions through practising specific perceptual tasks. Knowledge gained through my research may contribute to the refining of these methods, or may be starting points for developing new procedures as well.

*Chapter Six***A POSSIBLE APPLICATION****HYPERALGESIA AND ALLODYNIA MODELS IN HEALTHY VOLUNTEERS AS WELL AS DEVELOPMENT OF BEHAVIORAL AND fMRI BIOMARKERS FOR RELIABLE MEASUREMENT OF PAIN INTENSITY****1. Introduction**

BIOMARKER: a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic response to a therapeutic intervention (Lesko & Atkinson 2001). Medical imaging is creating a field that sheds new light on disease progression by enabling the precise measurement of small changes in structure and function over time. fMRI and Pharmacological fMRI (phMRI) aims at measuring the direct modulation of regional brain activity by different stimuli or/ and drugs that act within the central nervous system (CNS) or the indirect modulation of regional brain activity. fMRI is a noninvasive technique, which permits detailed longitudinal examination of healthy volunteers as well as patients.

The pharmacological fMRI biomarkers: identify/validate new drug targets and can predict the reaction (even individual) to drugs. fMRI biomarker can be regarded as the specific indicator of change in brain activity as induced by/in response to drug therapy (e.g. analgesia).

Pain is a highly subjective and complex experience: „an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.“ (Merksey and Bogduk 1994). The perception of pain is a rather complex neuronal process. Many parts of the brain are active during pain perception (anterior cingulate cortex, insular cortex, somatosensory cortex, amygdala, thalamus etc.). While the management and treatment of acute pain is reasonably good, the needs of chronic pain sufferers are largely unmet. Relatively few investigations focused on the neural correlates of neuropathic pain so far. The findings concerning the balance between peripheral versus central influences are contraversial.

As the sensation of pain is multifactorial, with many subjective, individual components, it is difficult to objectify it. The identification – with application of fMRI method - of the peripheral/central sources of sensation of pain or that of pathological (as opposed to the emotional or cognitive) factors has therapeutic consequences (e.g. medical, surgical, cognitive behaviour therapy or physical rehabilitation). The advantage of pain biomarkers over the verbal reports is that they can be much more sensitive to drug-induced change in pain intensity, because they promise the direct read out of pain sensation. It is possible that there are etiology-specific biomarkers, which allow the localization of the source of pain: central sensitization, attentional factors, etc. The fMRI signal may be changed in response to drugs that have an affect on the cerebral blood flow, on the cerebral blood volume, and on the oxygen metabolism of the brain.

In this on-going study, our goal is to develop a hyperalgesia and allodynia model in healthy volunteers as well as an fMRI biomarker for reliable measurement of pain intensity. In order to achieve this, we developed/ tested experimental set-ups for mechanical noxious stimulation, elaborated subjective pain rating protocols, designed fMRI protocols for measuring pain-related brain activations.

2. Methods

2.1. Methods of psychophysical experiments

2.1.1. Participants and Stimuli

Subjects: 24 healthy subjects participated in this experiment (fourteen male, mean age: 22,3 ranging from 18 to 37 years). All of them reported no history of neurological or psychiatric problems. Subjects gave informed consent to participate in the study, which was approved by the local ethics committee of Semmelweis University. In the psychophysics experiments, we used manual TOUCH TEST™ von-Frey sensory filaments (forces: 8g, 10g, 15g, 26g, 60g, 100g, 180g, 300g). However for the MR experiments, we developed and tested a PC-MR-compatible mechanical stimulus presentation equipment (forces: min. 100mN and max. 1,1 N), (Fig. 6.1).



Figure 6.1 PC-MR-compatible mechanical stimulus presentation equipment in the 3 Tesla Philips Achieva scanner (Philips, Best, The Netherlands) room

2.1.2. Heat-capsaicin model

To induce secondary hyperalgesia in healthy people, we used the heat/capsaicin sensitization model (Petersen and Rowbotham 2002; Zambreau et al. 2005). A 9 cm² (3*3 cm) premarked square area on the medial side of the right lower leg (musculus gastrocnemius caput) was heated with a 45C° flask lasting 5min (Fig. 6.2.). Thermal stimulation was followed immediately by topical application of 0.075% capsaicin cream (Zostrix, Rodlen Laboratories, Inc., Vernon Hills, IL) and was covered with parafilm for 45min (Moulton et al. 2007).

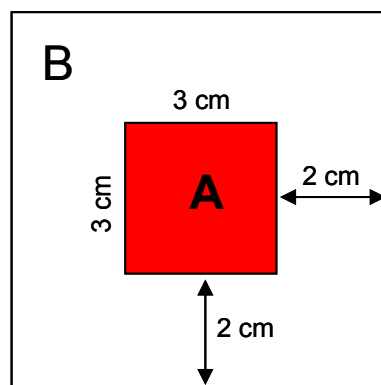


Figure 6.2 Heat/capsaicin treated area A and Areas of punctate stimulation (A or B),

2.1.3. Procedure

The peripheral sensitization refers to sensitization at the peripheral level (i.e. peripheral nervous system) while central sensitization refers to sensitization at the central level, (i.e. spine, back horn and supraspinal areas). In the case of the peripheral sensitization, we stimulated the skin area treated with capsaicin A, while, in the case of central sensitization, we stimulated the skin area right outside the treated area B (Fig. 6.2, Chart 6.1). Capsaicin treated and untreated (control) sessions were applied in a balanced order among subjects and they were at least 24h apart from each other.

Conditions	Capsaicin treatment	Treated area	Stimulation	Model of sensitization
1	Yes/ Hyperalgesia	A	A	Peripheral sensitization
2	No/ Control	-	A	Control
3	Yes/ Hyperalgesia	A	B	Central sensitization
4	No/ Control	-	B	Control

Chart 6.1 Two kind of sensitization model: peripheral sensitization (1), central sensitization(2) and them controls (2,4)

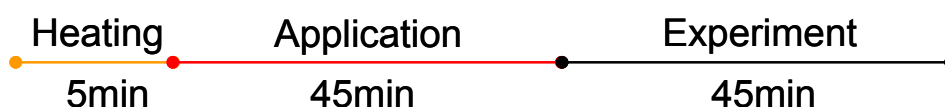


Figure 6.3 Procedure of treatment-session.

We conducted and compared three psychophysical experiments. In one of them we applied central sensitization model and in other two experiments we performed peripheral model. In one of the latter we stimulated simultaneously the untreated and treated leg and in the other one we stimulated the right leg in a separate session (Fig. 6.3). We measured subjective pain perception in two ways. In one case with scaling method, where subjects answered with the movement of a pc-mouse which tuned a scroll bar between the two end points (not painful - very painful) of subjective pain intensity. In

the other case, we used the categorization method, where subjects answered with the aid of left (not painful) and right (painful) pc-mouse button. The stimulations were randomized. We used Matlab 7.1. (MathWorks, Inc., Sherborn, MA) for both the stimulus presentation and the statistical analysis.

2.1.4. Statistical analysis

We calculated grand average, standard error and sensitization index (R capsaicin treatment - R control)/(R capsaicin treatment + R control).

2.2. Methods of fMRI experiments

2.2.1. Mechanical stimuli

fMRI protocols: fMRI methods developed for measuring and evaluating mechanical stimulation induced brain activation Unlike with psychophysics experiments, stimulation was made using an MR-compatible, controllable mechanical stimulator, which was developed and tested by us. Four stimuli of different intensity (min. 100mN and max. 1,1 N) were selected for mechanical stimulation in the fMRI experiment. The stimuli were provided above the medial head of musculus gastrocnemius at the locations and under the conditions discussed in details under the psychophysics experiments section.

2.2.2. Procedure

Each subject participated in four sessions in the MR in randomized order and the experiments were carried out according to the paradigm discussed above (see Chart. 6.1): fMRI experiments twice without treatment and twice following treatment with capsaicin. Functional experiments were started 45-50 minutes after the treatment with capsaicin. An fMRI experiment took approx. 50 minutes. Each experiment consisted of six measurement series: between series, the place of stimulation was slightly (few cms) changed within the pre-drawn boundaries. During the 412 second-long series, the stimulation with the four selected mechanical stimuli of different intensity was repeated according to a set pattern. The stimulator was operated by a serial port and through an optic converter from MATLAB environment. The exact stimulation-measurement patterns were determined using a widely used fMRI paradigm type, the so-called event

related design. The subjects answered after each stimulation by special MR-compatible response buttons whether they categorized the pinprick stimuli painful or non-painful.

13 subjects took part in the series of experiments, which can be characterized by event related design (ER): in this case the stimuli of different intensity followed each other randomly and with small intervals. At least four seconds passed in-between stimulations and all four types of stimuli were repeated 20 times within one series. In this set-up, a stimulation unit consisted of a stimulation and the subsequent stimulus-free period: 20 blind stimulation unit (i.e. four-second stimulus free period, at the beginning of which no stimulation occurred) were also inserted randomly among the 80 stimulation units.

fMRI data acquisition and analysis

MRI scanning was performed on a 3 Tesla Philips Achieva scanner (Philips, Best, The Netherlands) equipped with an eight-channel SENSE head coil. High resolution anatomical images were acquired in all of the imaging session using a T1 weighted 3D TFE sequence yielding images with a $1 \times 1 \times 1$ mm resolution. During the experimental session, T2*-weighted functional images were acquired using an echo planar imaging sequence, transverse slices were acquired (64×64 voxel image matrix, $.438 \times 3.438 \times 4$ mm resolution, TR=2000 ms, TE=30, flip angle=75° (Fig 6.4.). Data analysis was performed using BrainVoyager QX (v 1.74; Brain Innovation, Maastricht, The Netherlands) and custom built time series analysis routines written in Matlab (v 7.1; The Math Works, Natick, MA). The three anatomicals were homogeneity corrected, coregistered and then averaged to provide a better grey and white matter contrast (Fig 6.5.). Images were then normalized to Talairach coordinates and then segmented, and inflated to provide a 3D reconstruction of the grey and white matter boundary. This was followed by the timing correction of the measurements based on the time-markers, high cutoff filtering (temporal) and motion correction.

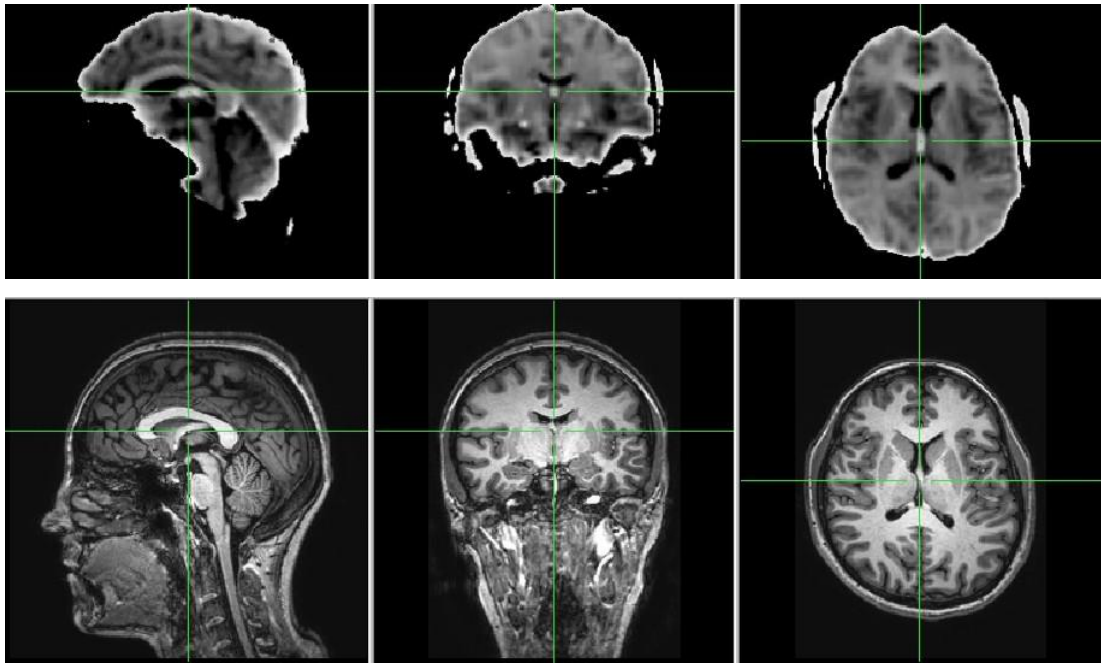


Figure 6.4 upper: $T2^*$ weighted functional images. Lower: $T1$ weighted anatomical images

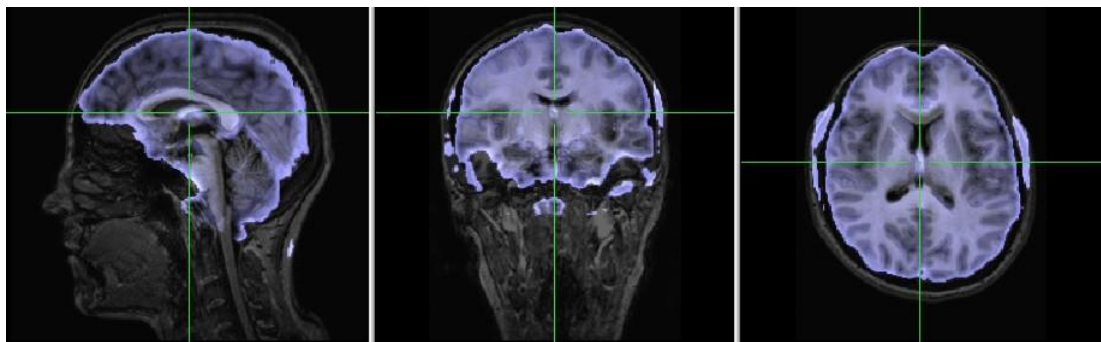


Figure 6.5 Co-registration

Using the general linear model module of BrainVoyager, we analyzed the data by voxels. The module carries out multi-variable linear regression, where each independent variable – predictors or regressors – represent one of the (four) stimulation intensities, the dependent variable is the BOLD signal, correlating to the brain activation, in the given voxel.

As a result of the statistical analysis, we obtain four weights (average BOLD response amplitude) for each voxel corresponding to each stimulation. Both individual and between-subjects statistics were calculated and represented the block and event related experimental data sorted separately. At places of statistically significant activation (modell fit) we also calculated the stimulation related averages and evaluated

them by stimulus separately. As a result of the statistical analysis, in each voxel, we obtained 24 (average BOLD response amplitude) weights corresponding to the experiment type (capsaicin treatment, peripheral or central sensitization), the individual stimuli, and the responses to them: four experiment conditions X 4 different stimulus intensity X 2 types of response. Between the weights and with the baseline (0 value weight) making post hoc contrasts, taking into account the fit errors. We obtain a statistical significance value for each voxel. These values are represented with colour-codes in the 3D anatomical images, and indirectly, these colourful 3D images provide information on the stimulation induced brain activation, more precisely the stimulus intensity, response and sensitisation dependant activation differences. Both individual and between-subjects statistics were calculated and depicted. At places, voxel groups of statistically significant activation (modell fit) we also calculated stimulation dependant BOLD responses (with the so-called deconvolution technic) and estimate separately by stimuli.

3. Results

In the first experiment we measured in separate sessions the modulation of peripheral sensitization on the right leg (Fig. 6.6 A,B).

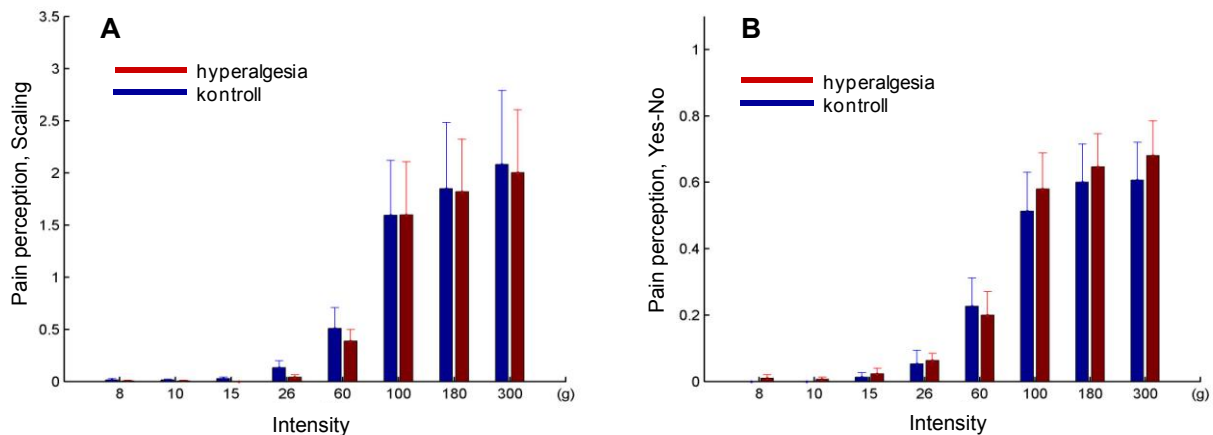


Figure 6.6 Peripheral sensitization on the right leg. Scaling (A) and Yes-No categorization (B)

Stimulation of the treated area did not result in a stronger perception of pain as compared to the stimulation of untreated area (control condition).

In the second experiment we measured in separate sessions the modulation of central sensitization on the right leg (Fig. 6.7 A,B). The stimulation resulted in a

significantly stronger perception of pain (hyperalgesia) as compared to the stimulation of the same surface without treatment (control condition).

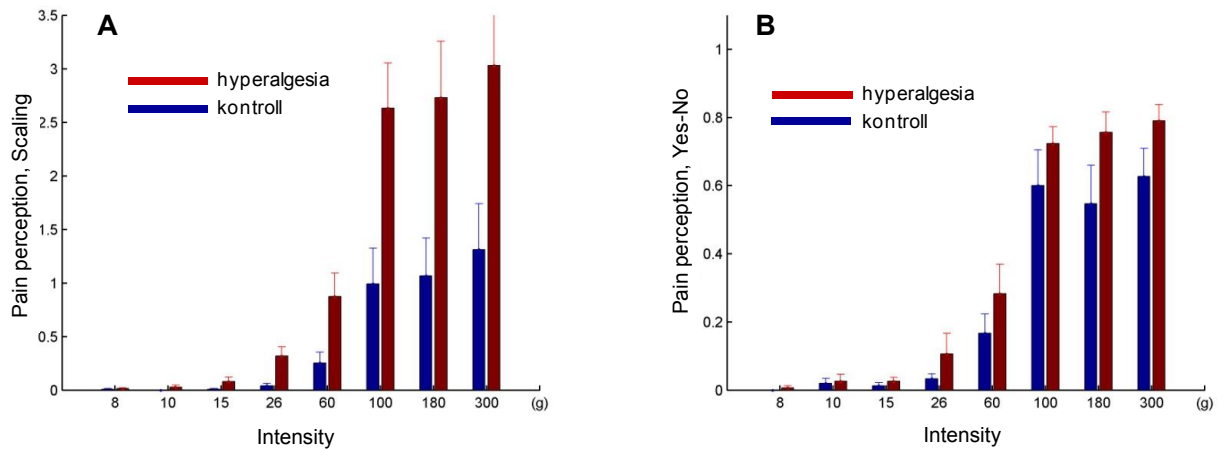


Figure 6.7 Central sensitization on the right leg. Scaling (A) and Yes-No categorization (B)

The effect of central sensitization was bigger in the scaling task rather than in categorization task.

In the third psychophysics experiment we measured simultaneously the peripheral sensitization on the left and right legs (Fig. 6.8 A,B). The simultaneous measurement of the two legs could have the advantage over sequential that the measurement data obtained for the right and left leg can be compared directly and the results are not disturbed by the subjects' different psychological, physiological status (e.g. emotional, drug effect, etc.). Simultaneous stimulation of the treated area on one leg and the same area on the other untreated leg resulted in a significantly stronger perception of pain (hyperalgesia) as compared to the control condition.

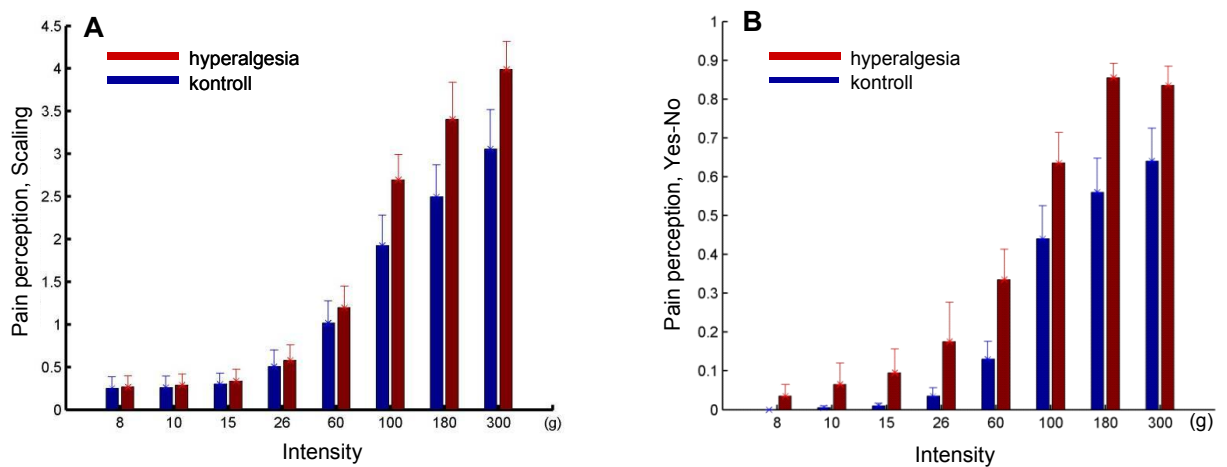


Figure 6.9 Peripheral sensitization on the left and the right legs simultaneously. Scaling (A) and Yes-No categorization (B)

Our findings were significant with stimulation of large intensity in both tasks (scaling and yes-no categorization) in the case of central sensitization method on the right leg (Fig. 6.9 A,B) and also in case of the peripheral sensitization method when simultaneously stimulating both legs (Fig. 6.10 A,B).

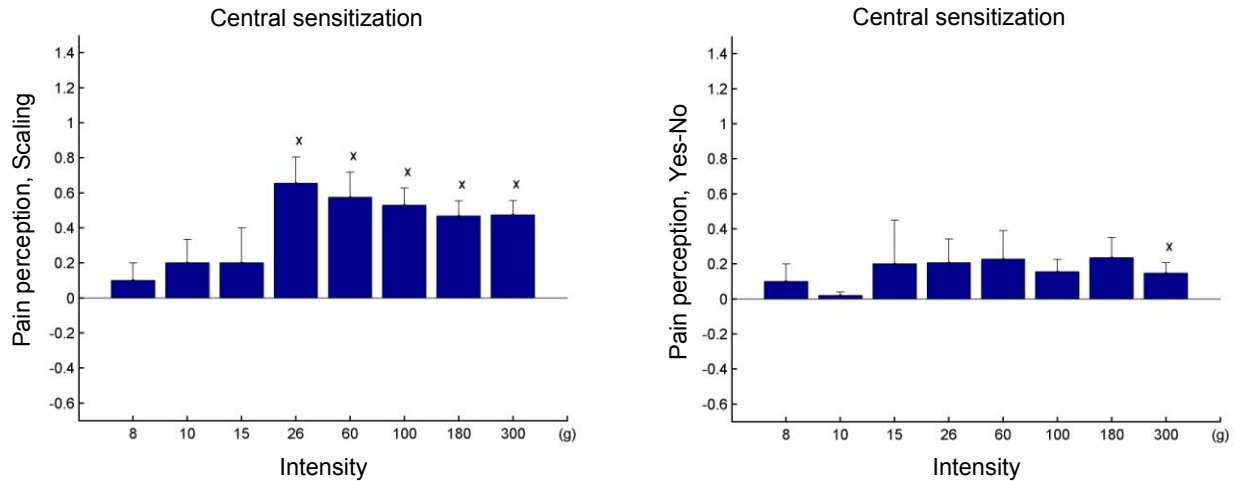


Figure 6.9 Sensitization index in the central sensitization, right leg stimulation

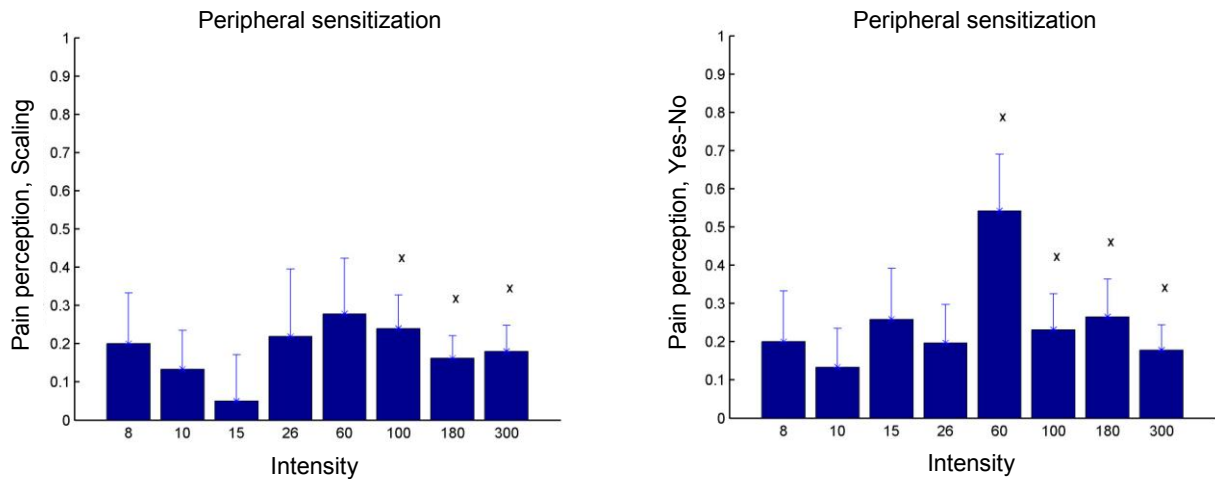


Figure 6.10 Sensitization index in the peripheral sensitization, simultaneously stimulation

Three psychophysics methods were developed and compared to measure hyperalgesia induced by capsaicin treatment. The central sensitization method results in hyperalgesia that can be demonstrated with both the scaling and the yes-no categorization tests. The sensitization index demonstrates that significant hyperalgesia arises primarily with stimulation of large intensity. Surprisingly when we applied, in separate sessions, the peripheral sensitization method, hyperalgesia was not observed.

However in the case when we measured simultaneously the peripheral sensitization effect we found robust hyperalgesia. The sensitization index demonstrates that significant hyperalgesia arises primarily from stimulation of large intensity.

In the fMRI experiments with the separation and distinct analysis of the BOLD responses received for the stimuli categorized as painful and as non-painful, we demonstrated that BOLD activations in several brain areas which play an important role in pain perception (Fig. 6.11), are significantly larger when stimulated by painful stimuli rather than non-painful stimuli but of same mechanical intensity (S2 – Fig 6.12; Insula – Fig 6.13; Cingular cortex – Fig 6.14).

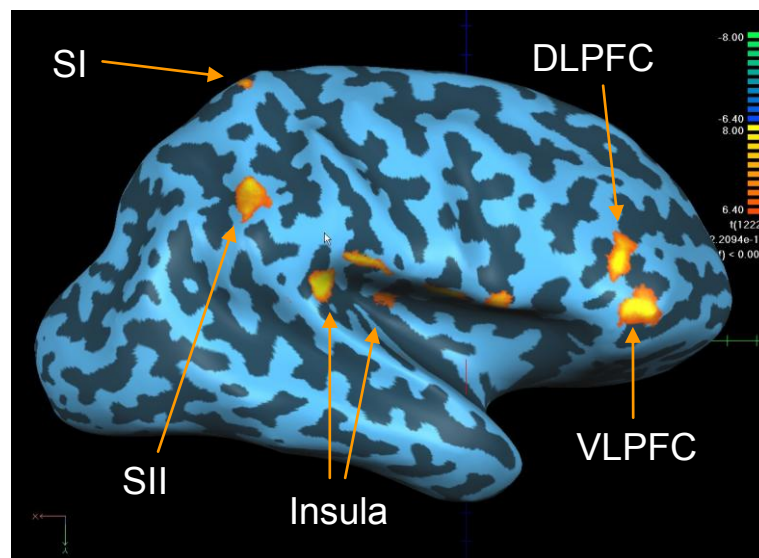


Figure 6.11 Pain-matrix (inflated right hemisphere, lateral side).

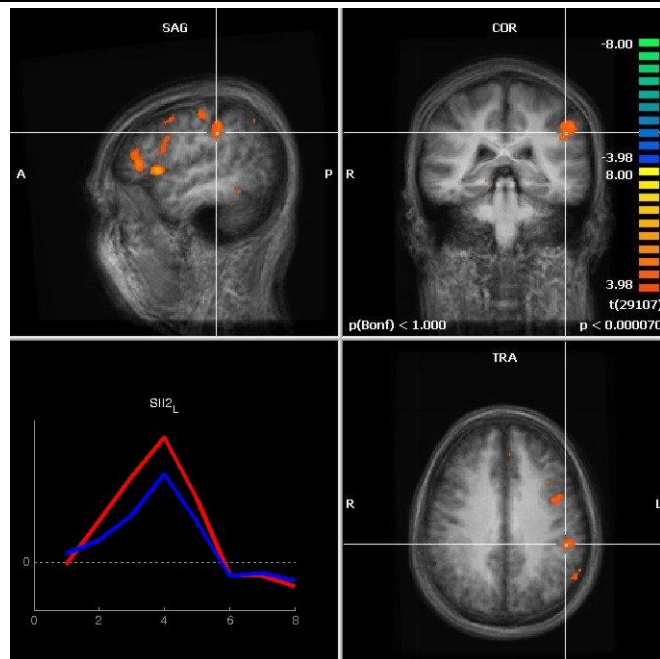


Figure 6.12 BOLD responses to stimulations categorized as painful and non-painful in the secondary somatosensory (S2) cortex in the case of accumulated data for all conditions. In the three sections, the intersection of the vertical and horizontal white lines indicates the S2 region, where from stimulation (Time=0) time related average activation was calculated: we depicted in the lower left graph the time course of the response to painful (red) and non-painful (blue) stimulation in function of time.

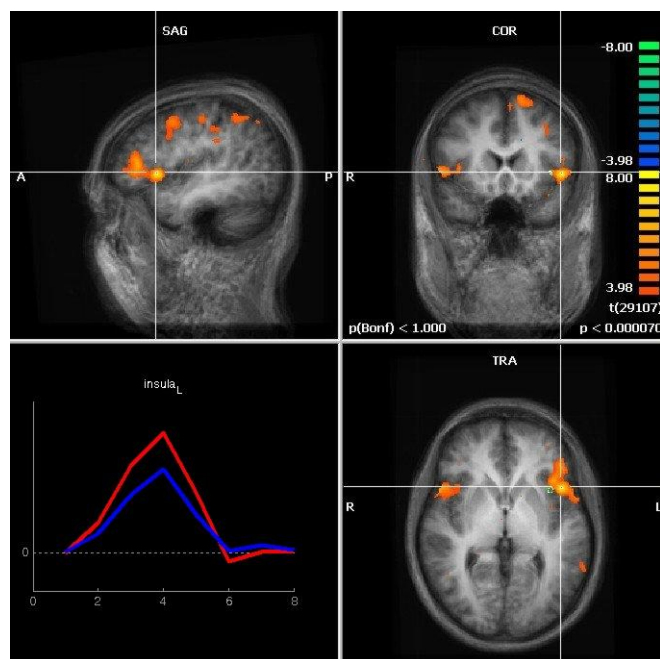


Figure 6.13 BOLD responses in insula when subjects categorized stimuli as painful and non-painful. In the three sections, the intersection of the vertical and horizontal white lines indicates the insula, where we calculated stimulation (Time=0) time related average activation. Left lower graph shows the the painful (red) and non-painful (blue) perceptions of stimuli in the function of time.

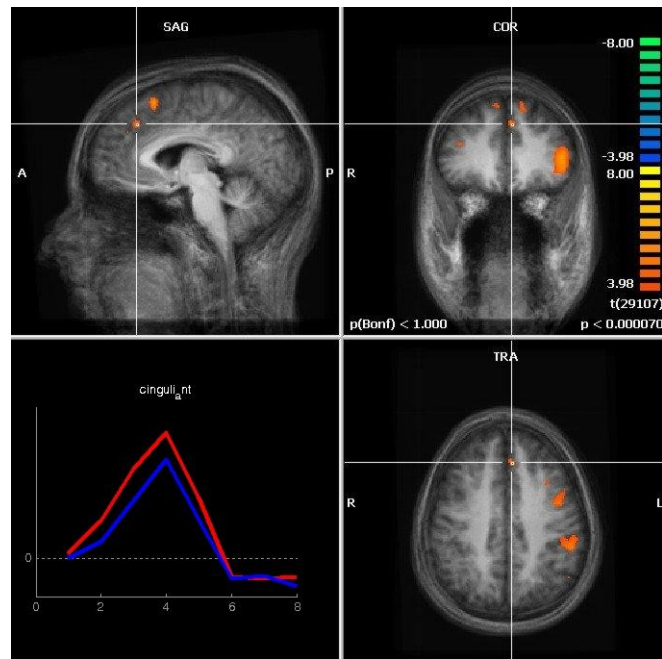


Figure 6.14 BOLD responses in the cingular cortex when subjects categorized stimuli as painful and non-painful. In the three sections, the intersection of the vertical and horizontal white lines indicates the cingular cortex. Left lower graph shows the painful (red) and non-painful (blue) perceptions of stimuli in the function of time.

If we only examine BOLD responses evoked by stimuli perceived as painful, we find that the intensity of responses on several cortical areas is proportional to the strength of mechanical stimulation and the resulting intensity of the subjective perception of pain (S2– Fig 6.15; Insula - Fig. 6.16).

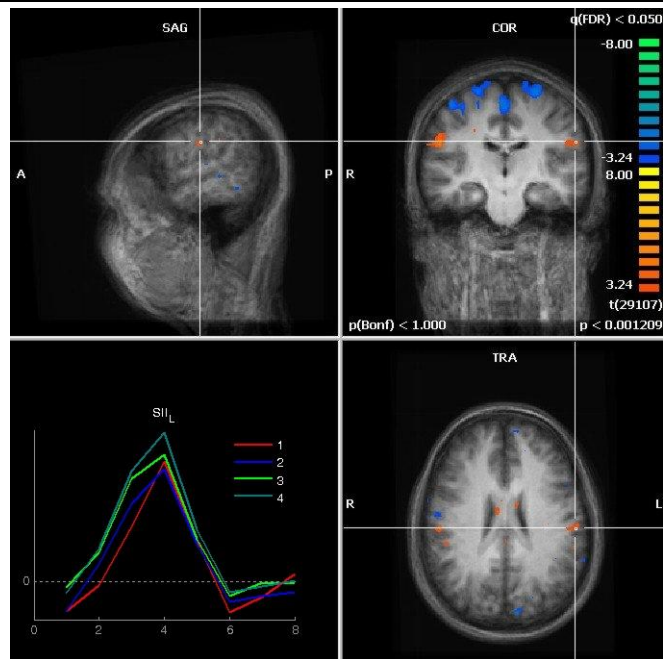


Figure 6.15. Changes in the activation of S2 area depending on intensity of stimuli. Left lower graph shows BOLD response evoked by different intensities of mechanical stimuli in function of time in the S2 cortex. Color bar means different forces of stimuli – from the most powerful (turquoise) to weakest (1-red).

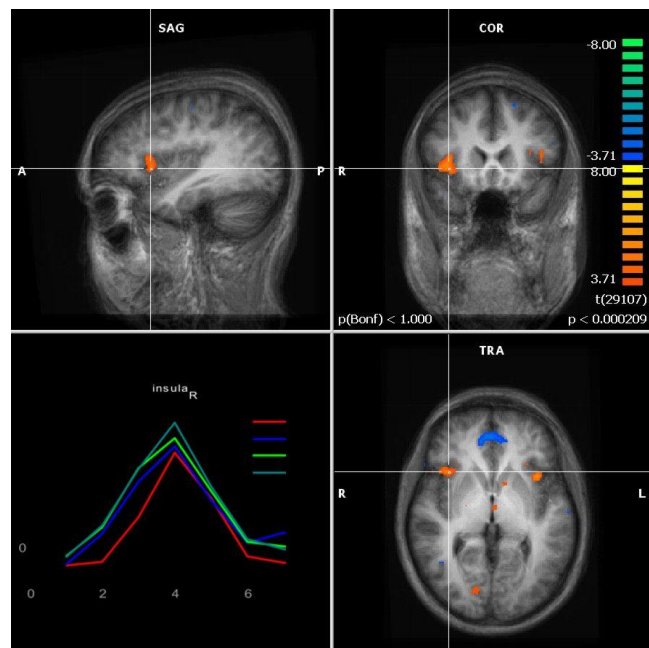


Figure 6.16 Changes of the activation of insula depending on intensity of stimuli. Left lower graph shows BOLD response evoked by four different intensities of mechanical stimuli in function of time in insula. Color bar means different intensities of stimuli – from the most powerful (turquoise) to weakest (red).

When separately investigating BOLD responses evoked by painful and non-painful stimuli in control and central sensitization conditions, we also found that the differences are significantly larger in the case of central sensitization (Fig. 6.17).

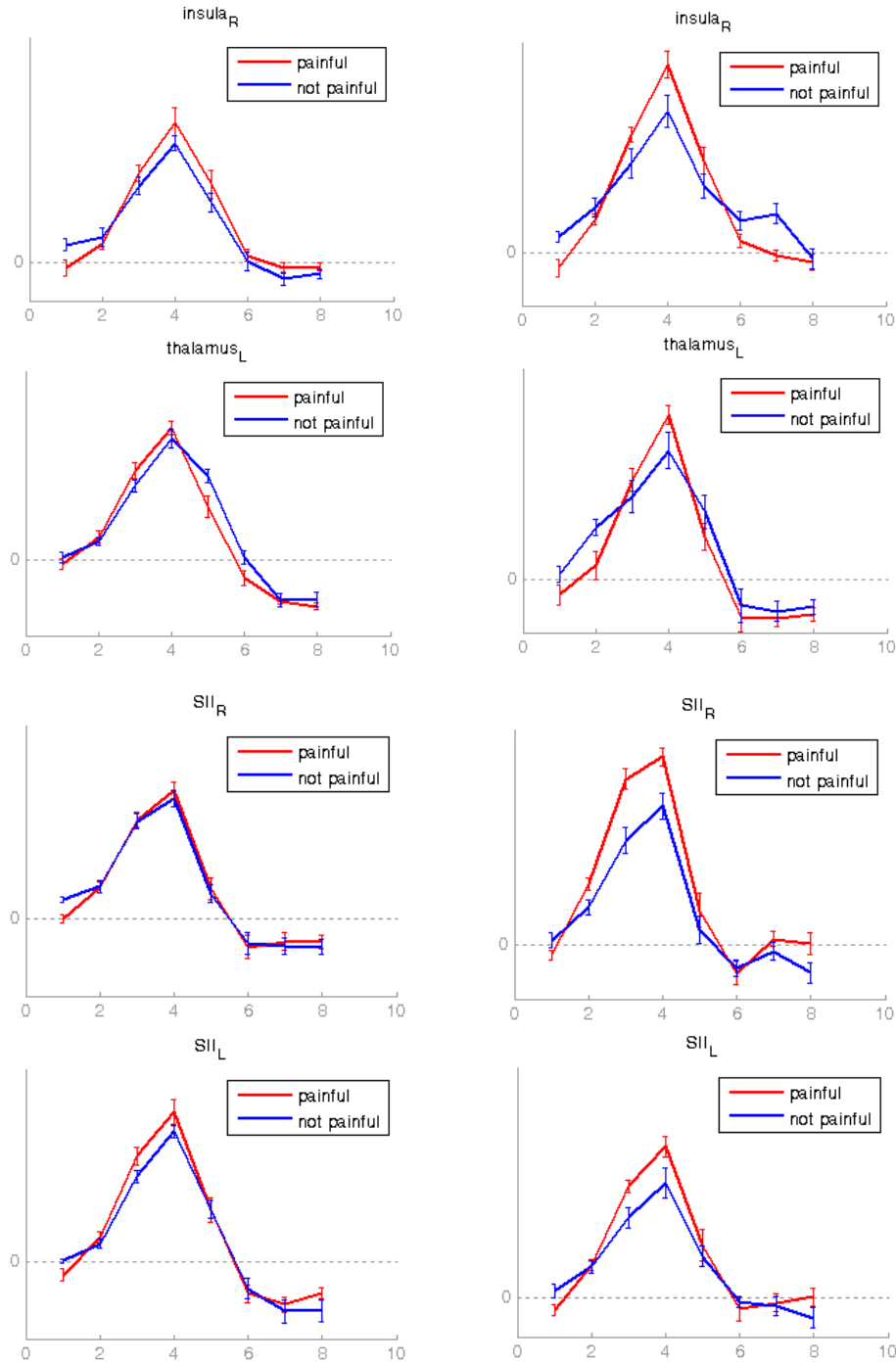


Figure 6.17 Effects of central sensitization: thalamus, insula anterior, S2 cortex (left, right) – BOLD responses in the different brain areas in the conditions of control (left column) and central sensitization (right column) when subjects categorized painful and non-painful stimuli

4. Conclusion

We developed and experimentally compared three psychophysics methods to accurately and reproducibly measure subjective perception of pain and hyperalgesia induced by capsaicin treatment. We demonstrated that using these methods subjective pain perception can be well characterized even in case of a small number of subjects (N~10). Our psychophysics experiments have shown that the exact temporal- and spatial parameters of stimulation greatly influence pain perception and the detection of hyperalgesia. We determined the optimal parameters for measuring secondary hyperalgesia evoked by capsaicin treatment – and in the background of which there is central sensitization.

Our fMRI experiments demonstrated that in accordance with relevant earlier publications, BOLD responses in certain brain areas reflect primarily the subjective pain perception and not the intensity of physical stimulation. Furthermore, our fMRI results have also demonstrated that several pain perception related brain areas (primarily in S2 and insula) stimuli of the same physical intensity result in bigger BOLD responses when the subjects perceive them as painful rather than as non-painful. The results of our psychophysics and fMRI experiments suggest that our behavioural biomarkers and our preliminary fMRI results could be applied to exactly and effectively measure subjective pain perception and changes in sensitivity to pain in both normal and pathologic (allodynia, hyperalgesia) circumstances.

*Chapter Seven***SUMMARY****1. Methods used in the experiments**

For my dissertation I worked with healthy normal subjects with the exception of the third study in which my participants were professional piano players. I used a wide array of experimental methods applicable in cognitive neuroscience research these included psychophysics, electrophysiology with classical ERP and several mathematical analytical approaches as well as functional magnetic resonance imaging (fMRI).

I used several tasks: perceived pain intensity rating on a visual analog rating scale (VAS); face orientation detection on rapid serial visual presentation (RSVP); 2-interval forced choice speed discrimination task (QUEST); motion coherence thresholds detection (QUEST); motion discrimination thresholds with constant stimuli in a 2-alternative forced choice procedure; color discrimination task; and pairs of suprathreshold vibrotactile stimuli-TOJs performance task.

I used bone-conducting hearing aids (Oticon) for the vibrotactile stimulation. To deliver mechanical and pain stimuli 1. TOUCH TEST™ von-Frey sensory filaments of different strengths and 2. a custom made PC controllable MR-compatible mechanical stimulator were used, which is being developed and tested by the members of MR Research Center (Szentágothai J. Knowledge Center - Semmelweis University, MR-RC and Neurobionics Research Group, Hungarian Academy of Sciences - Pázmány Péter Catholic University - Semmelweis University).

For the experimental presentation and for analyzing the data, I used MATLAB 7.1. (MathWorks, Inc., Sherborn, MA) with various toolboxes: Psychtoolbox 2.54 (Brainard 1997; Pelli 1997) psignifit toolbox (ver. 2.5.6) for Matlab (<http://bootstrap-software.org/psignifit/>); Cogent 2000 Software Toolbox (Cogent, www.vislab.ucl.ac.uk/Cogent/); Statistica 8 (StatSoft Inc.).

To track the eye position, I used an iView XTM HI-Speed eye tracker (Sensomotoric Instruments, Berlin, Germany). EEG data were acquired using a BrainAmp MR EEG system (Brain Products GmbH, Munich, Germany) from 60

(Ag/AgCl) scalp electrodes mounted in an EasyCap (Easycap GmbH, Herrsching-Breitbrunn, Germany, extended 10–20 System).

EEG pre-processing and pre-analyzing was implemented using BrainVision Analyzer (Brain Products GmbH) and for the source localization BESA 5.2, (MEGIS softwareGmbH, Germany) was used.

I performed fMRI data acquisition and analysis at the MR-RC on a 3 Tesla Philips Achieva scanner (Philips, Best, The Netherlands) equipped with an eight-channel SENSE head coil. Data analysis was performed using BrainVoyager QX (v 1.74; Brain Innovation, Maastricht, The Netherlands) and custom time series analysis routines written in Matlab.

1. New scientific results

Thesis I: Attentional modulation of perceived pain intensity in capsaicin-induced secondary hyperalgesia

Perceived pain intensity is modulated by attention. However, it was not known how pain intensity ratings are affected by attention in capsaicin-induced secondary hyperalgesia.

I.1. I have shown that perceived pain intensity in secondary hyperalgesia is decreased when attention is distracted away from the painful stimulus with a concurrent visual task. Furthermore, it was found that the magnitude of attentional modulation in secondary hyperalgesia is very similar to that in capsaicin untreated, control condition. Interestingly, however, capsaicin treatment induced increase in perceived pain intensity did not affect the performance of the visual discrimination task. Finding no interaction between capsaicin treatment and attentional modulation suggest that capsaicin-induced secondary hyperalgesia and attention might affect mechanical pain via independent mechanisms.

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Consistent with earlier findings showing that attention modulates pain perception, I found that distracting attention away from the pinprick stimulus with a demanding visual task strongly reduced subjective pain ratings in the capsaicin untreated condition. Furthermore, the results of the presented study have provided the first evidence that attention affects pain intensity ratings also during secondary hyperalgesia. The difference in pain intensity ratings between these two conditions cannot be explained by difference in the attentional load. Contradictory results can be found in earlier relevant publications but my results are in line with a recent study which showed that it is the brainstem which is primarily responsible for the maintenance of central sensitization underlying secondary hyperalgesia, whereas activation of the cortical areas might be associated with the perceptual and cognitive aspects of hyperalgesia (Lee et al 2008). Taking these into account, I assumed that the capsaicin sensitization protocol used in my study - which included a short, 45 min sensitization period immediately followed by the testing procedure- resulted in secondary hyperalgesia that is based primarily on the brainstem mediated central sensitization mechanisms and involve very little or no modulation of anticipatory attentional processes. This explains why in my study distraction of attention from the painful stimulus resulted in similar attentional modulation of perceived pain intensity in secondary hyperalgesia and control, capsaicin untreated condition.

Thesis II: Psychophysical and electrophysiological correlates of learning-induced modulation of visual motion processing in humans

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Gál, V., Kozák, L.R., **Kóbor, I.**, Bankó, É.M., Serences, J.T., and Vidnyánszky, Z. (2009). Learning to filter out visual distractors. *European Journal of Neuroscience*, 29(8):1723-1731.

When learning to master a visual task in a cluttered natural environment, it is important to optimize the processing of task-relevant information and to efficiently filter

out distractors. Previous studies have not examined how training influences the neural representation of task-irrelevant information to facilitate learning. Moreover, the mechanisms that suppress task-irrelevant information are not well understood. Additionally, the time course of these attention-based modulations of neural sensitivity for visual features has not been investigated before. Another important unresolved question concerns the temporal dynamics of these attention-based learning effects on the neural responses to attended and neglected visual features.

II.1. The results of my study propose that in cases when there is direct interference between task-relevant and task-irrelevant information that requires strong attentional suppression, training will actually produce decreased sensitivity for the task-irrelevant information.

The results revealed that training had a strong effect on the observers' performance. The motion coherence threshold for the task-relevant direction was significantly lower than the threshold for the task-irrelevant direction after training. Furthermore, a comparison of the motion coherence thresholds before and after training reveals that thresholds for the task-relevant direction decreased non-significantly whereas thresholds for the irrelevant direction significantly increased. The threshold for the control direction also underwent a non-significant decrease. Importantly, in this study, task-relevant and task-irrelevant stimuli were spatially overlapping and structurally similar. Therefore, the stimuli were likely competing for access to the same neural processing mechanisms, which would be expected to drastically increase the amount of competition.

II.2. I found that the strength of a coherent motion signal modulates the ERP waveforms in an early (300ms) and a late (500ms) time-window. The early component is most pronounced over the occipitotemporal cortex and may reflect the process of primary visual cortical extraction, the late component is focused over the parietal cortex and can be associated with higher level decision making mechanisms. I demonstrated training related modulation of the ERP in both the early and late time-windows suggesting that learning affects via modulating the sensory gain for the different features at the early

stages as well as the integration and evaluation of motion information at decisional stages in the parietal cortex.

The main goal of my EEG study was to test whether attention-based learning influences perceptual sensitivity for the visual features present during training via modulating the sensory gain for the different features at the early stages of visual cortical processing and/or by biasing the decision processes at the higher processing stages. My ERP results revealed that training on a task which requires object-based attentional selection of one of the two competing, spatially superimposed motion stimuli will lead to strong modulation of the neural responses to these motion directions when measured in a training-unrelated motion direction discrimination task. The first motion coherence-related peak reflects the initial, feed-forward stage of representing the coherent motion signal in visual cortex. The fact that the learning effects related to this early motion-related ERP peak was most pronounced over the occipital cortex is in agreement with previous electrophysiological and neuroimaging studies. Learning also had a strong effect on the late motion strength-dependent peak of the ERP responses. The late peak of motion coherence-dependent modulation might reflect decision processes related to the motion direction discrimination task. This interpretation is also supported by our results showing that the late ERP response peaked over the parietal cortex.

Thesis III: Spatiotemporal representation of vibrotactile stimuli

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Perceptual localization of tactile events are localized according to an externally-defined coordinate system, which is dominated by vision. The remapping of tactile stimuli from body-centred coordinates – in which they are coded initially – into external coordinates is fast and effortless when the body is in its “typical” posture but slow when more unusual body postures are adopted, such as crossing the hands. Moreover congenitally blind individuals do not show any such impairment in tactile Temporal Order Judgements (TOJ) as a result of crossing their hands. Thus the following intriguing

question arises: is the multisensory spatial information concerning sensory events coded in a similar manner throughout the peripersonal space or might there instead be a difference between front and rear space, as a result of the existence of detailed visual representations of the former but only occasional and very limited visual representation of the later?

III.1. I have demonstrated that the spatiotemporal representation of non-visual stimuli in front versus rear space (in the human body-based coordinate system) is different. My experiments show that crossing the hands behind the back leads to a much smaller impairment in tactile temporal resolution as compared to when the hands are crossed in front. My investigation have also revealed that even though extensive training in pianists resulted in significantly improved temporal resolution overall, it did not eliminate the difference between the temporal discrimination ability in front and rear space, demonstrating that the superior tactile temporal resolution I found in the space behind people's backs cannot simply be explained by incidental differences in tactile experience with crossed-hands at the rear versus in the front. These results suggest that the difference in the spatiotemporal representation of non-visual stimuli in front versus rear space originates in the differences in the availability of visual input.

I investigated differences in people's ability to reconstruct the appropriate spatiotemporal ordering of multiple tactile stimuli, when presented in frontal space (a region where visual inputs tend to dominate) versus in the space behind the back (a region of space that we rarely see) in professional piano players and in non-musicians. I found that the lack of a visual reference frame in the representation of peripersonal space that leads to improved tactile temporal resolution at the rear space of sighted individuals, so my results raise the following intriguing possibility: namely, that the spatiotemporal representation of tactile stimuli in the space behind the backs of sighted individuals – especially in those who are trained in tasks requiring fine spatiotemporal analyses of tactile information – are used as a normal model for the spatial representation of tactile information in congenitally blind individuals. The presented results also have important implications with respect to the learning processes leading

to professional piano playing. Interestingly, it has also been shown that extensive practice in playing the piano leads not only to improved motor skills but also to higher spatial tactile resolution in pianists as compared to non-musicians (Ragert P. et al. 2004). I showed for the first time that the temporal resolution of tactile stimuli is also significantly higher in professional piano players than in non-musicians. Thus, my results revealed that extensive piano practice has a broad effect on somatosensory information processing and sensory perception, even beyond training-specific constraints.

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THE AUTHOR'S PUBLICATIONS

Journal papers related to the thesis

- [1] **Kóbor, I.**, Füredi, L., Kovács, G., Spence, C., Vidnyánszky, Z. (2006). Back-to-front: Improved tactile discrimination performance in the space you cannot see *Neurosci. Lett.* 400(1-2):163-7.
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Conference papers related to the thesis

- [5] **Kóbor, I.**, Füredi, L., Kovács, Gy., Spence, C., Vidnyánszky, Z. (2006): Back-to-front: Improved tactile discrimination performance in the space you can't see Annual Meeting of the Hungarian Neuroscience Society.
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