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Marion Höfle[1] · M. Hauck[2] · A.K. Engel[1] · D. Senkowski[1]
[1] Department of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf, Hamburg
[2] Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg

Pain processing in multisensory environments

Introduction

Imagine yourself cutting peppers. While you watch the pepper getting smaller, your mind might wander and the knife accidentally carves the skin of your finger and you feel a sharp pain. Painful events in real-world situations do not occur in isolation but often comprise input from additional sensory modalities, i.e., the visual percept of the knife penetrating the finger. The successful integration and recall of painful stimuli in combination with highly informative input of other sensory modalities is often crucial for our wellbeing and survival. It enables us to detect and correctly respond to potentially harmful stimuli. To understand pain processing in naturalistic multisensory environments, it is therefore important to study how sensory inputs of other modalities influence the processing of pain.

It is well known that different environmental and cognitive factors can modulate activity in the so-called *pain matrix*, i.e., the network of brain regions involved in pain processing [28]. Moreover, there is elaborate knowledge of the neurophysiological mechanisms underlying pain processing, as well as of the *principle mechanisms* of multisensory integration of non-painful information (◘ **Box 1**). Surprisingly, however, only few studies have systematically addressed how stimuli from other sensory modalities affect nociceptive processing. Thus, it is not known whether such influences may follow the general principles of multisensory integration.

In this article, we will first introduce the different dimensions of pain and describe factors that have been shown to modulate pain perception and pain processing. Then, we provide an overview of recent studies focusing on cross-sensory influences between visual and pain stimuli. These studies support the notion that visual inputs can strongly affect the processing of painful stimuli. Finally, we give an outlook for future research on pain processing in multisensory environments.

Dimensions of pain perception

The application of different pain models (◘ **Box 2**) revealed that pain is a complex experience that can be described along two major dimensions, which themselves comprise different components. On the one hand, there is the *sensory-discriminative* dimension of pain, which comprises quality, intensity, and spatio-temporal aspects of the nociceptive sensation. For instance, in the finger-cutting example described above, the intensity of the pain sensation may crucially depend on the force and the edge of the knife and the pain can be well localized to the respective fin-

Box 1: Principles governing multisensory processing

Studies using non-painful stimuli showed that a large number of multisensory processes follow specific principles that predict the strength of multisensory interactions. The principles, which have been originally derived from studies on single neuron activity in the superior colliculus (SC) of cats [27], but which can be also applied to multisensory processing in humans describe the impact of: (1) the relative temporal alignment of sensory inputs, (2) the spatial configuration of stimuli, and (3) the intensity of sensory inputs on multisensory integrative processing.

A first principle of multisensory processing considers the *relative timing* of sensory inputs. Studies on the effects of timing on multisensory interactions in the SC show that there is a relatively flexible time interval of 100–200 ms in which sensory inputs delivered to one modality can influence responses to stimuli delivered to another modality. Stimuli that are presented in close temporal synchrony are more likely to be integrated than inputs that are presented with a large temporal asynchrony. A second principle deals with the influence of the *spatial configuration* of sensory inputs. Enhanced responses in SC [18] are observed for multisensory stimuli with combinations of inputs that originate from the same location in space compared to combinations of inputs that originate from different locations in space. A third principle covers the effects of *stimulus intensities* on multisensory processes. This principle, which is frequently labeled "principle of inverse effectiveness", describes the observation that the strength of a multisensory integration effect is in many cases inversely related to the magnitude of the response to the combined unimodal inputs. Thus, the combination of stimuli that by themselves elicit weak responses often leads to stronger multisensory interactions than the combination of inputs that by themselves elicits strong responses. Together, these principles provide an important framework to inform and drive current research on multisensory processing.

Box 2: Human experimental pain models

There are different methods to induce pain under controlled settings. The most frequently used pain models in electrophysiological studies are laser and electric stimulation (for a review see [5, 26]). Laser stimulation consists of a brief radiant heat pulse delivered by a laser beam, typically applied to the dorsum of the hand. Electric stimulation is either applied via a surface electrode at the wrist or via a thin electrode that is fed through a small hole in the epidermal skin of a fingertip. Usually, the individual pain threshold is determined beforehand and for the experimental procedure, stimuli comprising 1.5- to 2-fold individual pain threshold intensity are used. On the perceptual level these stimuli are comparable to a weak pinprick or pulling a single hair follicle.

ger. On the other hand, the *affective-motivational* dimension of pain comprises unpleasantness and disturbing character as well as distress caused by the pain sensation [17, 21]. Interestingly, the unpleasantness and disturbing character of the pain sensation can vary depending on contextual factors (e.g., if friends are around) and prior learning experience (e.g., if one already knows how to cope with the respective painful situation). Thus, different aspects of painful events can have different impacts on the two main dimensions of pain.

The anatomical structures underlying the dimensions of pain processing in humans have primarily been examined in studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). A large number of fMRI and PET studies showed that the two dimensions of pain are linked to processing in different anatomical structures of the pain matrix (for a review see [22]). The sensory-discriminative dimension of pain has often been associated with processing in primary and secondary somatosensory cortices (SI and SII, respectively), whereas the affective-motivational dimension has frequently been linked to processing in anterior cingulate cortex (ACC), insular cortex (IC), and prefrontal cortex [22]. Hypnotic suggestions have been used in PET studies to demonstrate that the sensory-discriminative and affective-motivational dimensions of pain can be separately targeted by experimental manipulations [14, 23]. Hypnotic suggestions aiming at the sensory-discriminative dimension resulted in changes in SI, while suggestions aiming at the affective-motivational dimension selectively changed the perceived unpleasantness, which was reflected by enhanced ACC activity for suggestions that increased perceived unpleasantness compared to suggestions that decreased the perceived unpleasantness. These studies show that the dimensions of pain can be separately targeted by experimental manipulations and that functional neuroimaging studies provide an excellent tool for the study of the anatomical structures of pain processing and pain modulations.

The temporal dynamics of pain processing have been examined in electroencephalography (EEG) and magnetoencephalography (MEG) studies, which allow the non-invasive measurement of neuronal activity with a high temporal resolution. Pain-evoked potentials or fields in the EEG and MEG, respectively, which can be measured by the repeated presentation of identical pain stimuli and subsequent averaging of response signals across trials, typically occur between 100 and 350 ms after the onset of painful events [4, 11]. Short latency deflections (<200 ms) in the evoked potentials or fields are thought to reflect parallel activity in primary and secondary somatosensory areas, whereas longer latency deflections (around 200–350 ms) seem to primarily reflect pain processing in IC and ACC [11]. In addition, oscillatory responses have more recently been shown to reflect the modulation of pain within the pain matrix [13, 12]. In particular, oscillatory responses in the gamma band (activity >30 Hz) seem to be a neuronal marker for pain processing. Generally, sensory-discriminative aspects of pain processing often seem to be reflected in earlier neural response components, whereas affective-dimensional aspects of pain perception have frequently been related to longer latency components. Thus, EEG and MEG make it possible to distinguish the different stages of pain processing and are therefore powerful techniques to study the temporal dynamics underlying pain processing.

A variety of cognitive factors, such as mood and attention, can modulate the perceived intensity and unpleasantness of pain sensation [30]. Several studies demonstrated the modulatory influence of emotional states on pain (for a review see [30, 33]). Emotional pictures depicting scenes or faces are commonly used for mood induction during pain processing (e.g., [15, 16]). Moreover, odors [30, 31], emotional statements [34], and hypnotic suggestions [14, 23] are capable of inducing different emotional states during pain processing. Most of the studies found that positive mood tends to reduce the perception of painful events and that negative mood tends to enhance pain perception [33]. Another factor that can modulate pain processing is attentional distraction. Painful events are perceived as less intense when individuals are distracted from the event (for a review see [30]). Thus, attentional and affective factors have a strong influence on pain perception. Given that inputs from other sensory modalities often enhance attention to the sensory aspect of the painful input and that in particular the visual perception of painful events can evoke negative affective states, it is likely that contextually relevant inputs from other sensory modalities affect pain processing.

Pain processing in the context of visual input

To date, much of the research on pain processing in multisensory environments focuses on the effects of observed pain in others. These studies consistently showed activations within the pain matrix that were elicited by mere observation of painful events in others. For instance, Cheng et al. [8] presented their participants with static pictures depicting body parts in painful and non-painful situations (e.g., a picture of a saw cutting a finger versus a picture of a saw cutting the branch of a tree). Synchronously, non-painful electric stimuli were applied to the left median nerve of participants' wrist. Using MEG, the authors found suppression in low frequency-band activity (~10 Hz) in primary somatosensory areas that was stronger when participants watched pictures depicting painful compared to non-painful situations synchronous to the non-painful electric stimulus. This shows that the mere observation of painful events modulates sensory processing in somatosensory areas.

Other studies used video clips depicting body parts like a hand or a foot receiving either painful or non-painful stimuli to examine the influence of visual events on processing within the pain matrix. An early study on this topic was conducted by Avenanti et al. [1], who used single-pulse transcranial magnetic stimulation (TMS) over the primary motor cortex to investigate whether the observation of painful and non-painful events might change corticospinal excitability. Single-pulse TMS over primary motor cortex produces activity in the respective muscle, referred to as motor-evoked potential (MEP) that can be recorded by electromyography (EMG). Several previous studies using TMS found that processing of painful stimuli can inhibit motor cortex activity (e.g., [10]). Avenanti and colleagues compared the MEP for two different hand muscles while participants watched video clips containing either a painful event (a needle penetrating a human hand) or a non-painful event (a Q-tip touching the hand). Importantly, only one of the recorded muscles was congruent with the location where stimuli were applied in the videos. The authors found reduced MEPs when participants watched clips in which the hand was penetrated by a needle compared to when they watched clips in which a Q-tip touched the hand. Strikingly, this effect was observed only for the muscle that was congruent with the location where the needle penetrated the skin in the clips. This suggests a specific modulation of corticospinal excitability by visually observed pain. The authors conclude that the empathy with the pain of a conspecific and the anticipation of painful events that might be applied to oneself both modulate not only higher-order pain processing networks, but also sensorimotor structures of the pain matrix.

A more recent MEG study further investigated the effect of observing painful events on neuronal processing within the pain matrix [2]. The authors addressed the interplay of somatosensory and motor areas during the presentation of needle-penetrating-hand clips. The main focus in this study was on functional coupling between primary sensory and motor cortex through neural coherence in the gamma band. Participants either watched a static hand, a Q-tip stimulation of a hand, or were presented with needle-penetrating-hand clips. Interestingly, while the amplitude of gamma responses was not affected by the experimental manipulations, an enhanced coherence in the gamma band between somatosensory and motor areas was found during the presentation of pain-suggestive video compared to the control stimuli. The authors suggest that the modulation of neuronal synchrony in the gamma band may reflect a specific role of combined activity of somatosensory and motor cortices in observing painful stimulation in others.

The studies described above show that observation of painful stimuli in others can result in neuronal changes within the pain matrix. An interesting question arising from this is whether the observed changes can actually affect processing of simultaneously presented painful inputs. Valeriani and colleagues [29] addressed this question by presenting video clips of a hand being stimulated by a needle or a Q-tip, amongst others, while applying painful laser inputs to the matching hand of their participants (▣ **Fig. 1a**). The participants' task was to imagine that the observed hand belonged to them and to rate the perceived intensity and the unpleasantness of each painful stimulus, while laser evoked potentials (LEP) were recorded in the EEG. The authors found that early deflections of the LEP, which presumably reflect the sensory-discriminative dimension of pain, were reduced in amplitude when participants simultaneously watched needle-penetrating-hand clips compared to when they were simultaneously presented with Q-tip-touching-hand clips (▣ **Fig. 1b**). However, no effects of visual stimulation on pain intensity and unpleasantness ratings were observed. This suggests that observing painful stimulation in others modulates electrophysiological brain responses to pain stimuli. Apparently, the authors did not precisely synchronize the timing of the visually observed painful event (i.e., the mo-

Abstract

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Abstract

"Don't look and it won't hurt" is common advice heard before receiving an injection, but is there any truth in this statement? Pain processing can be separated into two major components: a sensory-discriminative component, which reflects the location and intensity of a painful event, and an affective-motivational component that reflects the unpleasantness of pain. The differentiation between these components and the effects of additional sensory inputs on them becomes apparent if you watch a needle penetrating your skin: On the one hand, it may be somewhat reassuring to know precisely when and where to expect the pinprick, on the other hand, you eye-witness damage inflicted on your body, which can increase personal distress. Here we review recent studies, which demonstrate that a host of variables such as onset timing, spatial alignment, semantic meaning, and attention differentially affect how visual inputs influence pain processing. These studies also indicate that there is some truth in the opening statement.

Keywords
Pain · Multisensory integration · Cross-modal · Emotion · EEG · MEG

ment when the needle hit the hand) and the actual nociceptive stimulus applied to the subject's skin. Since temporal synchrony plays a crucial role for the integration of sensory information across modalities (◘ **Box 1**) this may account for the lack of behavioral effects in this study.

The studies presented so far focused on the impact of observing pain in others on processing within the pain matrix. A limitation of these studies was that the visually perceived painful events were spatially misaligned with the location of the painful stimuli applied to the participant's own hands. However, multisensory interactions are known to be more robust when the different inputs originate from the same location in space (see ◘ **Box 1**). In a recent study, Longo et al. [19] studied pain processing in an experimental setup in which visual and somatosensory inputs were more carefully matched in terms of latency and location. The authors used laser stimulation for pain induction and measured subjective pain intensity and unpleasantness ratings while recording the LEP in the EEG. When participants received painful laser stimuli, a red laser spot was simultaneously presented at the same location on the hand and at the same time at which a painful laser pulse was applied. In the control condition, participants' hands were hidden behind a cardboard baffle and participants were instructed to look at an object (i.e., a book) that was placed in front of the baffle and at which a similar red dot was projected by means of a laser pointer (◘ **Fig. 2a**). In comparison to the control condition, watching the hand with the red laser spot significantly reduced pain intensity and pain unpleasantness ratings (◘ **Fig. 2b**). This attenuation effect was reflected in reduced long latency LEP components, which are thought to be related to the affective-motivational dimension of pain processing (◘ **Fig. 2c**). This finding is of particular note when interpreting it in the context of the results by Valeriani et al. [29]. While Longo et al. [19] observed modulations of longer latency LEPs when a simple visual input is presented signaling the occurrence of the painful event, Valeriani et al. found effects of spatially non-aligned visual contextual

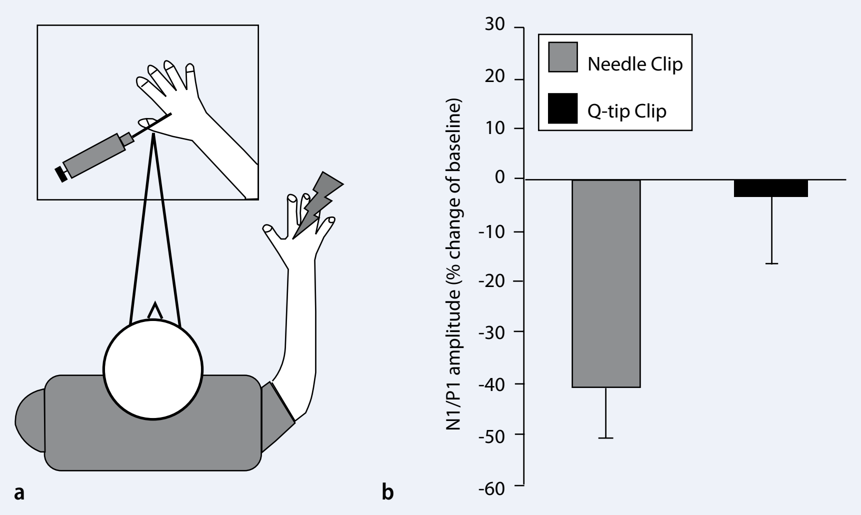

Fig. 1 ▲ Seeing a needle-penetrating-hand clip reduces early LEP components. **a** The experimental setup. Participants sat in front of a screen on which different video clips were presented (needle-penetrating-hand and Q-tip-touching-hand clips, among others). While participants were watching the video clips, painful laser pulses were delivered to the dorsum of their right hand. **b** Normalized amplitude of early deflections in the LEP. The amplitude was significantly lower when participants watched needle-penetrating-hand clips compared to Q-tip-touching-hand clips. (Redrawn from [29])

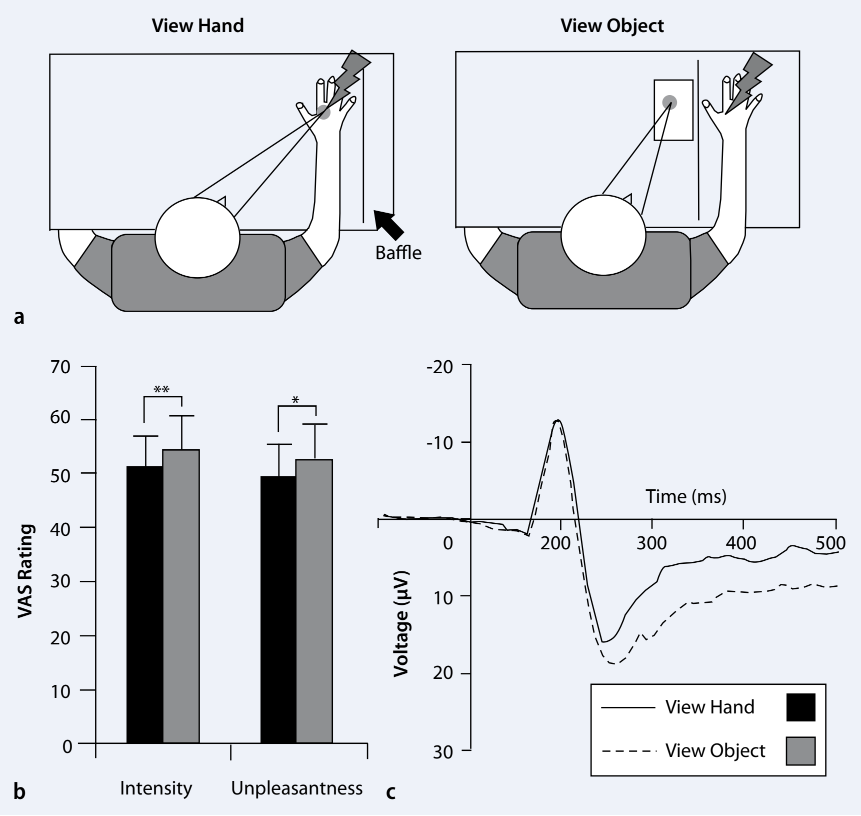

Fig. 2 ▲ Seeing the hand modulates late LEP components and pain ratings. **a** The experimental setup. Participants received painful laser pulses and looked at a red laser dot that was either projected directly onto their hand (*left*) or onto an object while their hand was hidden behind a cardboard baffle (*right*). **b** Visual analogue scale (*VAS*) ratings of subjective pain intensity and unpleasantness. The painful laser stimulation was perceived as less intense and unpleasant when participants saw their hand compared to when they saw an object. **c** Grand mean LEPs. Seeing the hand significantly reduced long latency LEP deflections compared to seeing an object. (Reprinted from [19])

inputs already at early stages of pain processing.

We have recently conducted an experiment using similar video materials that may shed new light on this issue (Höfle et al. unpublished). We applied painful intracutaneous electric stimuli to participants' fingers at exactly the moment when the video clip showed a needle penetrating the finger. Moreover, the video clips in our experiment were spatially aligned with the actual stimulation sites (i.e., the screen on which the clips were presented was located directly above the participants' hands). Using this more realistic setup, we observed that the presentation of the needle clips led to enhanced pain unpleasantness ratings compared to control conditions. Interestingly, these findings are in sharp contrast to the results by Longo et al. [19] who found that the observation of a red laser dot signaling the pain event led to lower pain ratings. Since both studies differ in several aspects, the divergent results have to be interpreted with care. The static visual cue used by Longo and colleagues might be perceived as less threatening as a moving needle and may also provide a much less 'naturalistic' cue for a painful event. Our results indicate that the semantic contents of visual contextual stimuli may play a crucial role for the modulatory effects of these stimuli on pain processing.

Summary and outlook

The findings reviewed above clearly demonstrate that visual contexts can influence the processing of pain. A major challenge that arises when studying pain processing consists in creating an experimental protocol that mimics pain in naturalistic real-life situations. In recent years, an increasing number of studies have focused on the question of how visual inputs influence the processing of pain, but only few of these studies have tried to mimic a 'truly' naturalistic setting (see [19] for an exception). Therefore, one needs to be cautious when interpreting the results of these studies with regard to pain processing in real-life multisensory environments.

That said, the studies summarized in this article provide first compelling evidence that sensory information from other modalities, especially visual input, can bias the processing and perception of painful events. Moreover, these studies show that a variety of factors, including spatial congruency, temporal synchrony and semantic contents, influence how sensory information arriving through other channels affects the processing of nociceptive signals. Interestingly, these factors also crucially affect the multisensory processing of non-painful inputs. Therefore, they need to be considered in future studies on multisensory influences on pain processing.

In this regard, a promising setup may be the use of an illusionary phenomenon called the *rubber hand illusion*. In the standard protocol of experiments on the rubber hand illusion, participants do not see their own hand but a rubber hand with the same posture as their actual hand [3]. When artificial and virtual hands are synchronously stroked with a brush, most participants get the impression of feeling the touch in the viewed and not in their own hand. Participants even tend to mislocate their own hand towards the rubber hand when asked to define its position. Interestingly, a recent behavioral study indicated that the rubber hand illusion works also for painful stimulation [7]. The neural mechanisms underlying this rubber hand illusion effect on pain processing are thus far not understood.

A neural mechanism that may be crucial for the influence of other sensory inputs on pain processing could be coherent oscillatory activity, in particular in the gamma band. Oscillatory activity is abundant in the nervous system and is crucially involved in a broad range of processes, including feature integration, attention, sensorimotor integration, memory formation and even awareness [6, 9, 25]. Recently, synchronous oscillatory activity has also been linked to pain processing [13] and multisensory integration [24]. Thus, this mechanism may also be important for multisensory interactions contributing to pain perception. First evidence supporting this assumption derives from the study by Betti et al. [2], who reported enhanced functional coupling between primary sensory and motor cortex through neural coherence in the gamma band when participants are presented with needle-penetrating-hand clips. Thus, we suggest that the examination of oscillatory activity is a promising research target for future studies on pain processing in multisensory environments.

In summary, the data available show that sensory inputs from other modalities can affect the processing of pain. A variety of factors, including the timing and spatial alignment of stimuli as well as semantic contextual information, seem to influence how sensory inputs, in particular visual ones, interact with pain processing. Interestingly, these factors have also been linked to multisensory processing of non-painful information, indicating that cross-sensory processing of pain may follow similar integration patterns as the integration of non-painful inputs. Taken together, we believe that the study of pain processing in multisensory settings will improve our understanding of how painful stimuli are integrated in sensory information processing, and thus that it will improve our understanding of pain processing and pain modulation in real-life situations.

Corresponding address

Dipl.-Psych. Marion Höfle
Department of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf
Martinistr. 52, 20246 Hamburg
m.hoefle@uke.uni-hamburg.de

Marion Höfle: Born 1980 in Friedrichshafen. 2002–2008 Studied psychology in Würzburg and Amsterdam. Doctoral student since late 2008 at the University Medical Center Hamburg-Eppendorf on the DFG project "Multisensory processing of pain stimuli" (SE 1859/1–1).

M. Hauck
Department of Neurology, University Medical Center Hamburg-Eppendorf
Martinistr. 52, 20246 Hamburg
please@delete.de

Michael Hauck: Born 1975 in Oldenburg. 1996–2003 Studied medicine in Hamburg. 2000–2001 Research assistant at the University of Michigan. 2003 PhD at the Department of Neurophysiology of the University Medical Center Hamburg-Eppendorf (UKE). 2005–2008 Research assistant and 2007–2008 Magnetoencephalography research group leader at the Department of Neurophysiology of the UKE. Specialist medical training in neurology since 2008 at the UKE Hamburg.

A.K. Engel
Department of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf
Martinistr. 52, 20246 Hamburg
please@delete.de

Andreas K. Engel: Born 1961 in Villingen. 1979–1986 Studied medicine at the universities of Saarbrücken and Munich. 1983–1987 Doctoral thesis at the Max-Planck Institute of Psychiatry in Munich. 1987–1990 studied philosophy at the University of Frankfurt. 1987–1995 Postdoc and 1996–2000 head of research group and Heisenberg fellow at the Department of Neurophysiology at the Max-Planck Institute for Brain Research in Frankfurt. 1995 Postdoctoral studies in physiology. 2000–2002 Head of Cellular Neurobiology Group at the Jülich Research Center. 2002 Specialist medical training in physiology. Professor of physiology and Director of the Department of Neurophysiology and Pathophysiology at the University Medical Center Hamburg-Eppendorf.

D. Senkowski
Department of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf
Martinistr. 52, 20246 Hamburg
please@delete.de

Daniel Senkowski: Born 1974 in Hannover. 1995–2000 Studied psychology at the University of Trier and Freie Universität Berlin. 2001–2004 Doctoral student at the Max-Planck Institute for Human Cognitive and Brain Sciences. 2002–2003 Guest researcher at Duke University, North Carolina. 2004–2006 Postdoctoral researcher at the Nathan S. Kline Institute, New York. 2005–2006 Adjunct Professorship at the Department of Psychology at the City College of New York. Since 2006 Research assistant and EEG research group leader at the Department of Neurophysiology and Pathophysiology at the University Medical Center Hamburg-Eppendorf.

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