

Crossmodal shaping of pain: a multisensory approach to nociception

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Noxious stimuli in our environment are often accompanied by input from other sensory modalities that can affect the processing of these stimuli and the perception of pain. Stimuli from these other modalities may distract us from pain and reduce its perceived strength. Alternatively, they can enhance the saliency of the painful input, leading to an increased pain experience. We discuss factors that influence the crossmodal shaping of pain and highlight the important role of innocuous stimuli in peripersonal space. We propose that frequency-specific modulations in local oscillatory power and in long-range functional connectivity may serve as neural mechanisms underlying the crossmodal shaping of pain. Finally, we provide an outlook on future directions and clinical implications of this promising research field.

Pain, attention, and crossmodal processes

A key function of pain is to protect our body from potential harm and to facilitate the preparation of a defense response [1]. Noxious stimuli can automatically capture our attention and it is likely that the salience network, which includes the anterior cingulate cortex (ACC) and the operculoinular cortex, plays a major role therein [2–4]. Furthermore, top-down attention toward noxious stimuli enhances the perception and facilitates the processing of pain [5–9]. Thus, shifts in attention following or preceding noxious stimuli may be important for the rapid preparation of a defense response (see [Glossary](#)).

Crossmodal processes, which are also known to interact with attention [10], are another important factor that can bias the processing of pain stimuli. Several recent studies suggested that crossmodal processes shape the perception of pain. For instance, an electroencephalography (EEG) study showed that a spatiotemporally aligned, task-irrelevant visual stimulus enhances the perception and processing of concurrent pain [11]. Crossmodal processes can also have diminishing effects on pain. For example, listening to preferred music [12], viewing pleasant pictures [13], or viewing their own body [14] reduces pain perception. These

studies suggest that crossmodal processes can indeed modulate the perception of pain.

In this review we examine in detail several factors that influence the crossmodal shaping of pain and highlight the important role of innocuous stimuli in peripersonal space. Particular emphasis is placed on studies investigating the role of neural oscillations, as reflected in pain-related changes in gamma-band, beta-band, alpha-band, and delta-band activity (GBA, BBA, ABA, and DBA) ([Box 1](#)). Neural oscillations and their dynamic coupling generally seem to play an important role in multisensory processing [15–20]. Recent studies suggest that neural oscillations may also be involved in the crossmodal shaping of pain [11,12,21,22]. The interesting topic of how, in particular, tactile stimuli affect pain has been covered in an excellent recent review [23] and is therefore only briefly discussed here. In the reviewed studies, different dimensions of pain have been assessed ([Box 2](#)). Rather than considering these separately, we use the term ‘pain perception’ when

Glossary

Crossmodal: this term is normally used to refer to situations in which the presentation of a stimulus in one sensory modality is shown to influence the perception, behavioral responses, or neural processing of a stimulus presented in another sensory modality [77].

Defense response: mobilization and protection of the body accomplished by attentional modifications such as alerting the organism and orienting it toward the threatening event while prioritizing relevant sensory input.

Frequency bands: stimulus-induced and ongoing intrinsic oscillations are usually categorized into five frequency bands: delta (2–3 Hz); theta (4–7 Hz); alpha (8–12 Hz); beta (13–30 Hz); and gamma (>30 Hz).

Functional connectivity: quantifies the correlation between the activity of two neuronal populations. Such correlations are assumed to indicate a functional relation or the exchange of information between the recorded populations.

Noxious stimulus: a stimulus that is damaging or threatens damage to normal tissues (IASP Taxonomy, <http://www.iasp-pain.org>).

Oscillations: rhythmic activity of neurons or neuronal populations. This rhythmic activity is often band limited and characterized by dominant frequencies. Oscillations can be quantified using spectral analysis.

Oscillatory power: a measure for the strength of an oscillatory signal. Power scales with the square of the signal amplitude.

Peripersonal space: the spatial region surrounding the body that a person regards as theirs psychologically. Unpleasant stimuli that enter the peripersonal space usually evoke a defense response.

Phase coherence: quantifies the consistency of the relative phase between two simultaneously recorded signals that have the same frequency.

Stimulus saliency: the ability of a stimulus to capture attention in a bottom-up fashion. A stimulus has a high saliency when it contrasts with its surrounding stimuli. Salient stimuli activate a circumscribed set of cortical regions, the so-called salience network.

Valence: characterizes a stimulus as pleasant (positive valence) or unpleasant (negative valence) in the context of affect and emotion.

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Box 1. Oscillatory power as a neural signature of pain

There is ample evidence for an involvement of neural oscillations in the processing of noxious stimuli, such as electrical [6], temperature [49], and laser [45–48]. Noxious laser stimuli, which have been frequently used to investigate the neural mechanisms underlying pain, modulate the power of oscillatory activity in different frequency bands and at different latencies (Figure 1). These different frequency bands have been associated with specific cognitive and sensorimotor functions [55,70,78]. In acute pain, a consistent finding is a positive correlation between the magnitude of GBA in the somatosensory cortex and pain perception [6,12,45,46]. Moreover, there is evidence that GBA reflects the sensorimotor transformation of pain, implicating a behavioral relevance for the initiation of a defense response [79]. However, GBA has also been linked to shifts in attention [80,81]. A recent EEG study in which trains of consecutive laser stimuli were presented at constant interstimulus intervals has addressed this question [46]. Repetition of sensory stimuli reduces saliency and, thus, repeatedly presented pain stimuli are less prone to capture attention or enhance arousal. The study showed that repeated stimulus presentation reduced laser-evoked potentials whereas pain ratings and GBA remained constant. Importantly, for all stimulus

repetitions the amplitude of GBA correlated significantly with pain perception. Another response pattern following noxious stimulation is a suppression of BBA in the sensorimotor cortex [21,82]. Because BBA also plays a role in motor processing, one possible interpretation is that the pain-related suppression of BBA in the sensorimotor cortex reflects the preparation of a defense response [83]. The observation that painful stimulation increases beta-band coherence between motor cortex and peripheral muscles supports this view [84]. In the primary somatosensory cortex, pain-related suppression in BBA is usually accompanied by suppression in ABA [82]. Moreover, pain-related suppression in ABA has been related to increased excitability of the sensorimotor system [47,85]. For example, pain-related ABA suppression correlates positively with electromagnetic responses over the primary somatosensory cortex to a non-painful electrical stimulus [47]. A fourth response pattern following noxious stimulation is an increase in DBA. Studies investigating the sources of pain-related DBA suggested an involvement of the sensorimotor cortex and the medial cingulate cortex [6,12]. Together, these studies strongly suggest that neural oscillations play a role in the processing of noxious stimuli.

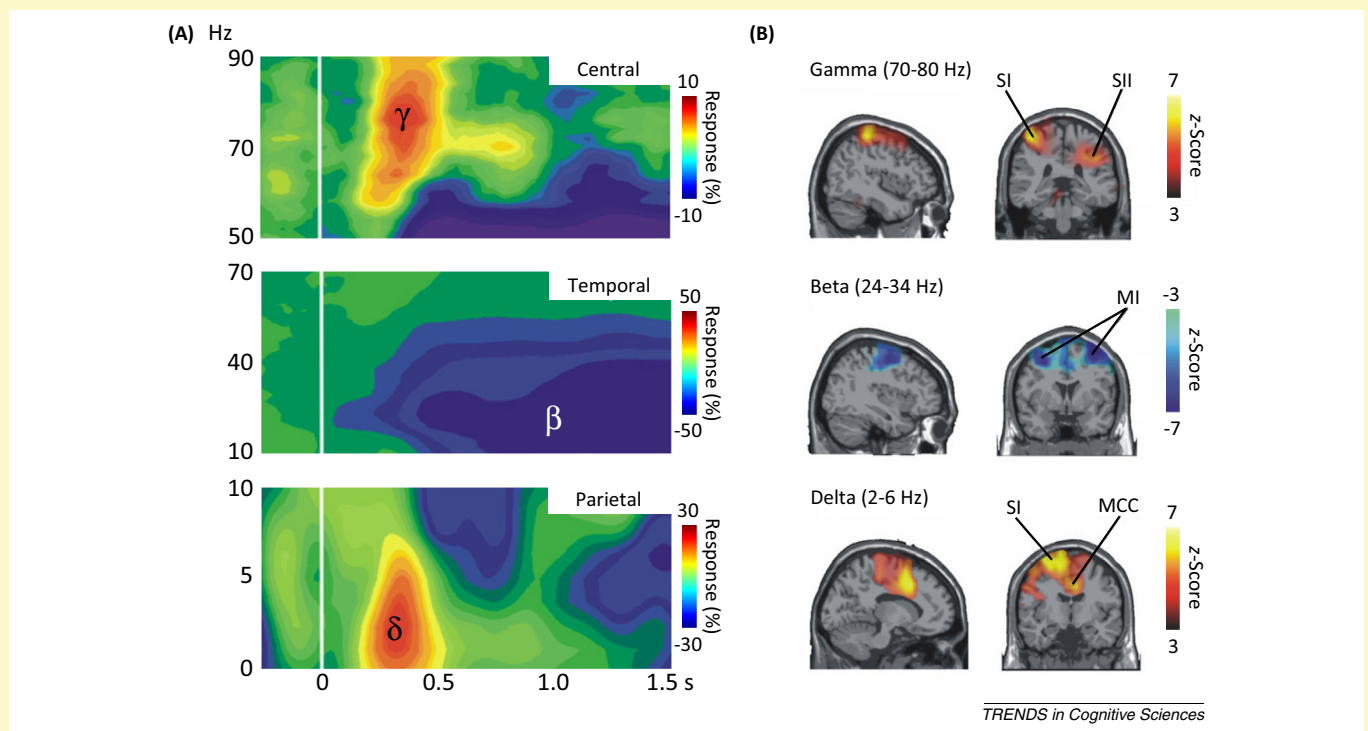


Figure 1. Pain-related modulations in the power of oscillatory activity measured by magnetoencephalography (MEG). (A) Following a painful laser stimulus, enhanced delta-band activity (DBA) (bottom panel) and gamma-band activity (GBA) (top panel) are observed. The third response component is longer-latency suppression of beta-band activity (BBA) (middle panel). (B) The sources of GBA can be localized in the somatosensory cortices (SI, SII; top panel). The suppression of BBA is found in the motor cortex (MI; middle panel) and the increase in DBA is observed in the somatosensory and medial cingulate cortex (MCC). Adapted, with permission, from [12]. The figure has been reproduced with permission of the International Association for the Study of Pain. The figure may not be reproduced for any other purpose without permission.

describing study results regarding the subjective experience of pain.

Factors influencing the crossmodal shaping of pain *Stimulus intensity, temporal synchrony, and spatial alignment*

Studies using innocuous stimuli showed that multisensory interactions are most likely when the constituent inputs are spatially and temporally aligned and when they elicit weak neural responses by themselves [24,25]. The latter observation has been termed the ‘principle of inverse

effectiveness’. Thus far, only a few studies have investigated whether such known principles of multisensory integration apply to the crossmodal shaping of pain. Given that stimuli that elicit strong neural responses, such as noxious stimuli, are usually less susceptible to crossmodal modulations, it seems conceivable that the crossmodal shaping of pain may not strictly follow the principles of multisensory integration.

Using stimuli of different intensities, a recent EEG study examined the crossmodal influence of spatiotemporally aligned visual stimuli on the perception and proces-

Box 2. Dimensions of pain

Pain is a multifaceted experience comprising at least two components [86–88]: (i) a sensory–discriminative component that reflects intensity and spatiotemporal aspects; and (ii) an affective–motivational component that encodes the disturbing character of pain and relates to emotion, arousal, and defense behavior. This unpleasant experiential quality is immanent to pain. The two components of pain perception seem to be processed in partially distinct networks [87,89,90]. The sensory–discriminative component has been related to activity in the primary somatosensory cortex [91], whereas the affective–motivational component has been attributed to regions of the salience network, including the ACC and the insular cortex [90]. Interestingly, responses of the autonomic nervous system have primarily been related to the affective–motivational pain component [38,88]. Experimental manipulations can differentially affect the two components of pain [34,38,39]. For instance, attention seems to primarily affect the sensory–discriminative component, whereas emotional processes mainly influence the affective–motivational component [34,92]. Behaviorally, these two main components of pain perception can be monitored by subjective ratings of stimulus intensity and stimulus unpleasantness, respectively. However, subjective ratings of these two dimensions are often highly correlated and therefore it has been discussed whether they represent separate components of pain [93,94]. Yet the findings that these components are differentially modulated by experimental manipulations [11,33,38,89,92] suggest that they reflect, at least in part, distinct aspects of the experience and processing of pain.

sing of pain [11]. To examine multisensory interactions in the local power of oscillatory activity, a nonlinear analysis approach was used [26]. The crossmodal influence of visual stimuli on pain perception and pain-related neural oscillations was stronger when pain stimuli were low compared with when they were high in intensity. The behavioral effect was paralleled by a similar effect on BBA, which had a topography indicating involvement of the sensorimotor cortex (Figure 1A). Thus, this study suggests that the crossmodal shaping of pain follows the principle of inverse effectiveness. Using magnetoencephalography (MEG), Inui *et al.* [27] investigated the effect of temporal alignment between vibrotactile and electrical pain stimuli on pain perception and pain-induced event-related responses. The study showed reduced pain perception and modulations of pain-induced event-related responses when vibrotactile stimuli and pain stimuli were presented simultaneously or when pain stimuli preceded vibrotactile stimuli by up to 40 ms. Notably, the study also demonstrated that the latency difference of event-related responses for these different stimuli had the same magnitude; that is, the response latencies were about 40 ms shorter for vibrotactile compared with noxious stimuli. Hence, this study suggests that the crossmodal shaping of pain is robust when vibrotactile and noxious inputs reach the cortex at about the same time. However, due to the close association between the cortical networks involved in the processing of these inputs, the crossmodal shaping of pain through tactile stimuli may be a special case [23]. The question whether differences in response latencies also play a role in the modulation of pain by other sensory modalities remains to be addressed.

Another factor that could influence the crossmodal shaping of pain is spatial alignment. Van Ryckeghem *et al.* [28] examined pain perception and response speed to painful stimuli when visual stimuli that were spatially aligned or nonaligned with a pain stimulus were presented

at a short negative time lag. The study revealed higher pain perception and shorter response times for spatially aligned compared with spatially nonaligned visual–pain stimuli. Taken together, the studies reviewed above suggest that the crossmodal shaping of pain follows the known principles of multisensory integration.

Stimulus valence

The valence of stimuli surrounding us strongly modulates the efficiency and depth of sensory processing. Therefore, it is likely that the valence of other sensory stimuli influences their impact on pain perception. Studies investigating the effect of pictures with emotional content on pain perception showed pain-reducing effects for pleasant and -enhancing effects for unpleasant pictures [29,30]. A MEG study investigated the impact of facial expressions with neutral, positive (happy), and negative (angry and fearful) valence on the perception and processing of pain [21]. Independent of their valence, faces with emotional expressions compared with faces with neutral expression led to increased pain processing, as reflected by stronger modulation of BBA in the sensorimotor cortex (Figure 1B). Interestingly, happy facial expressions also led to enhanced pain perception, which seems to contradict findings of pain-relieving effects for pictures with positive emotional content. The authors [21] suggested that a happy face that is presented in combination with a pain stimulus may be interpreted as negative; for example, as if this person might be laughing about the observer.

Valence-specific modulations of pain are also found for emotional stimuli of other sensory modalities, such as audition [12,31,32] and olfaction [33,34]. A recent MEG study investigated the perception and processing of pain in the context of pleasant and unpleasant music [12]. The study showed enhanced pain perception and stronger GBA in the somatosensory cortex when participants were listening to unpleasant compared with pleasant music. A functional MRI (fMRI) study showed that smelling unpleasant compared with pleasant odors is associated with enhanced pain perception and stronger hemodynamic responses in a network comprising the ACC, the medial thalamus, and the somatosensory cortex [34]. Taken together, these findings suggest that the valence of stimuli shapes the perception and processing of pain in a similar manner across modalities. Stimuli that are perceived as pleasant usually diminish the intensity of pain perception and reduce pain-related neural processing. Conversely, stimuli that are perceived as unpleasant enhance the perception and processing of pain. In conclusion, we propose that the strength and direction of the crossmodal influences on pain by other inputs depend on the valence of stimuli and follow integration principles that are of general relevance in multisensory perception.

Impact of stimuli in peripersonal space on pain

Sensory stimuli in close proximity to one's body may signify potential threat and imminent pain. To prepare a defense response, they must be analyzed rapidly with regard to their threat value and potential harm for the body [35]. Therefore, the influence of innocuous stimuli in peripersonal space on pain may be particularly strong. Virtual

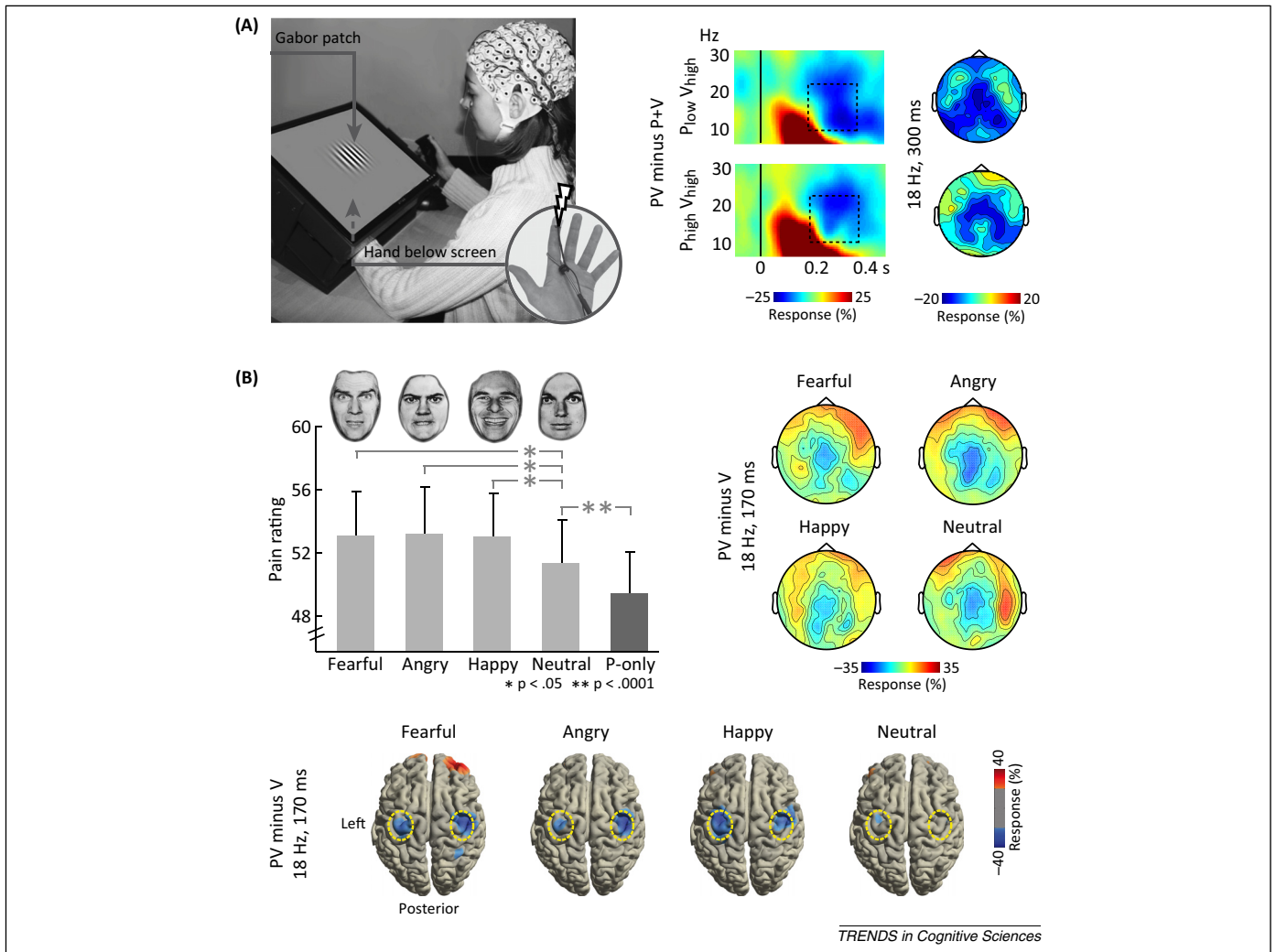


Figure 1. Crossmodal effects of visual stimulus intensity and emotional facial expressions on pain. **(A)** Influence of visual input on pain stimuli of different intensities on pain perception and pain-related oscillations in the electroencephalogram. Painful electrical stimuli (P) of different intensities (P_{low} , P_{high}) were presented simultaneously and spatially aligned with Gabor patches (V) of different contrast levels (V_{low} , V_{high}) (left panel; only V_{high} is shown). The effect of visual stimulation was stronger for low-compared with high-intensity pain stimuli, as reflected by enhanced modulation of subjective pain ratings (not illustrated) and enhanced suppression of pain-related beta-band activity (BBA) power (right panel). Adapted from [11]. **(B)** Influence of emotional facial expressions on pain perception and pain-related oscillations in the magnetoencephalogram. Painful electrical stimuli were presented simultaneously with facial expressions of different valence. Electrical stimuli were perceived as more painful when combined with faces compared with pain stimulation alone. In augmenting pain rating, emotional faces were more effective than faces with a neutral expression (upper left panel). The pain-related modulation of BBA power at sensors located over the contralateral sensorimotor cortex was stronger for faces with emotional expressions compared with neutral faces (upper right panel). Source localization revealed that the increase in pain ratings was paralleled by a stronger pain-related modulation of BBA in the sensorimotor cortex (lower panel). Adapted from [21].

reality setups inducing the embodiment of artificial limbs (Box 3) are effective tools to study the crossmodal shaping of pain in peripersonal space [14,22,36–41]. A recent study demonstrated that viewing a needle pricking a hand that is perceived as one's own compared with viewing a Q-tip that touches the hand enhances pain perception and anticipatory pupil dilation responses (Figure 2A) [38]. A follow-up EEG study showed that this effect is reflected by a stronger anticipatory suppression of ABA in the needle compared with the Q-tip condition [39]. Threat-related processes induced by viewing a needle approaching one's body reflecting expectation of pain are likely to have contributed to this effect [42]. Thus, visual input in peripersonal space modulates neural processes involved in predicting pain.

Recently, Martini *et al.* [37] investigated the effect of skin color on pain (Figure 2B). In this experiment, the temperature of a thermal heat stimulus was increased while participants were watching an avatar's wrist perceived as their

own that concurrently changed its color toward red, green, or blue. Participants stopped the stimulation as soon as the thermal heat stimulus was felt as painful. The participants' pain perception was enhanced when the avatar's wrist became red compared with when it turned blue. Interestingly, the authors did not observe enhanced pain perception when a gray spot next to the participant's wrist turned red. This shows that the effect of color change is confined to the embodied limb and suggests that the meaning attributed to a sensory cue affects the crossmodal shaping of pain.

Support for this assumption comes from a series of studies that used the mirror-box technique [43] to examine the influence of viewing one's body on pain [14,22,40,41]. These studies demonstrated that viewing one's own body has a diminishing effect on pain perception. An fMRI study revealed that the pain-reducing effect of viewing one's own body is associated with reduced hemodynamic responses in somatosensory areas, the insular cortex, the ACC, and

Box 3. Embodiment of artificial limbs in virtual reality setups

In appropriate experimental settings, artificial limbs can be perceived as if they belong to one's own body; that is, they can become integrated into the body schema. A prominent protocol to create the illusion of embodiment of artificial limbs is the 'rubber-hand illusion' [95]. In the rubber-hand illusion, participants do not see their own hand but a rubber hand with the same posture and at the same location where they would expect their own hand. When artificial and real hands are synchronously stroked with a brush, most participants get the impression of feeling the touch at the viewed hand. Often, participants perceive the viewed hand as belonging to their own body. The rubber-hand illusion can be induced only when the observed and the felt touch happen synchronously [95]. Interestingly, the rubber-hand illusion can also be induced when pain stimuli instead of tactile stimuli are applied [77]. In recent years there have been several modifications of the classical rubber-hand paradigm. For instance, studies have used virtual hands presented on a screen [38,39] or a head-mounted display [37]. These setups allow well-controlled presentation of innocuous and noxious stimuli. Besides the rubber-hand illusion, the 'mirror-box' paradigm has been used to manipulate perception of the body [14,40]. In the mirror-box paradigm, the participant's hand is hidden behind a mirror and thus, participants do not directly look at the respective hand but see the reflection of the opposed hand in the mirror superposing the actual hand at the viewed location (Figure 2C in the main text). In this setup, participants get the impression of looking at their hidden hand. Using the mirror-box paradigm it is possible to manipulate what participants see in the mirror; for instance, an object or the hand of the experimenter [14]. Both the rubber-hand and the mirror-box paradigms are well suited for studying the crossmodal shaping of pain.

more posterior brain areas that have been related to visual body representation [41]. Furthermore, a recent EEG study demonstrated that the pain-relieving effect of viewing one's own body is reflected by an enhancement of pain-related BBA (Figure 2B) [22]. Taken together, these studies indicate that visual stimuli in peripersonal space are particularly prone to modulating the perception and processing of pain. Whether this is also the case for inputs from other sensory modalities, such as auditory stimuli, remains to be investigated.

Neural mechanisms underlying the crossmodal shaping of pain

The last decade has seen an increasing number of studies highlighting the role of neural oscillations in pain perception [6,44–51]. Most of these studies showed pain-related changes of local oscillatory power (Box 1). However, there is some evidence that phase coherence of oscillatory signals is also relevant for the functional interaction of pain-related brain regions [6,44,50,52,53]. For instance, an electrocorticography study investigated functional connectivity, as reflected in phase coherence, between the somatosensory, medial frontal, and insular cortex during the processing of attended and unattended noxious stimuli [50]. In the attended compared with the unattended condition, an increase in beta-band and alpha-band connectivity was found in this network. An additional analysis of directed connectivity in the alpha band showed an influence of the primary somatosensory cortex on the other network regions, particularly in the attention condition [52]. Using MEG, another study found enhanced interhemispheric connectivity in the gamma band between sensors over

the left and right sensorimotor cortex for attended compared with unattended noxious stimuli [6]. We would like to emphasize that the study of functional connectivity in EEG and MEG data requires great caution. Factors like the signal-to-noise ratio, power of oscillatory signals, and volume conduction can strongly influence the results and must be thoroughly considered [54,55]. Taken together, the studies suggest that local oscillatory signals and their interaction across regions are important for pain perception and that attention can modulate both local power and functional connectivity.

Likewise, the crossmodal processing of innocuous stimuli involves modulations of both local oscillatory power [20,56] and long-range functional connectivity [19,57–59]. This raises the question of whether similar mechanisms mediate the crossmodal shaping of pain. As discussed above, the available data suggest that the crossmodal modulation of pain perception is associated with local power changes in various frequency bands [11,12,21,22]. Given its importance for pain processing and for multisensory integration, it is tempting to hypothesize that long-range coupling of oscillatory signals may also be important for the crossmodal shaping of pain. Currently, however, there is a lack of studies examining this possibility directly. Figure 3 illustrates an example for a hypothetical network scenario involving modulations of both local oscillations and long-range neural connectivity. In cases where processing of pain stimuli is facilitated by visual input, we hypothesize that pain-related regions and structures of the top-down attention network are recruited in an anticipatory manner due to crossmodal long-range interactions with visual cortex. Compared with the processing of unisensory pain, which primarily occurs in a bottom-up manner, this may then lead to enhanced local oscillatory activity as well as to increased functional connectivity within pain-related regions.

Such scenarios are likely to involve both the frontoparietal attention [60] and the salience [3] network (Figure 3). Intracranial recordings in humans showed that pain-related responses in the sensorimotor cortex occur at latencies similar to those of responses in the operculoinsular [61] and cingulate [62] cortex, which are key structures of the salience network. Numerous studies have shown activity in the salience network after noxious stimulus presentation [2,4,63–65]. Interestingly, the salience network is also involved in the detection of salient stimuli across sensory modalities [3,66,67]. Due to its multisensory function, it seems likely that the crossmodal shaping of pain involves neural processing in the salience network. The salience network is closely linked to the frontoparietal attention network [60]. Support for an involvement of the frontoparietal attention network in the crossmodal shaping of pain comes from a recent fMRI study, which showed that pain-related modulations of hemodynamic responses by affective pictures involve interactions between the insular cortex and other cortical structures, including the frontoparietal attention network [68]. Another fMRI study demonstrated that higher-order frontal structures and the ventral striatum mediate predictive cue effects in the salience network and in the thalamus relating to pain perception [69]. Furthermore, oscillatory activity, especially in the gamma band, is

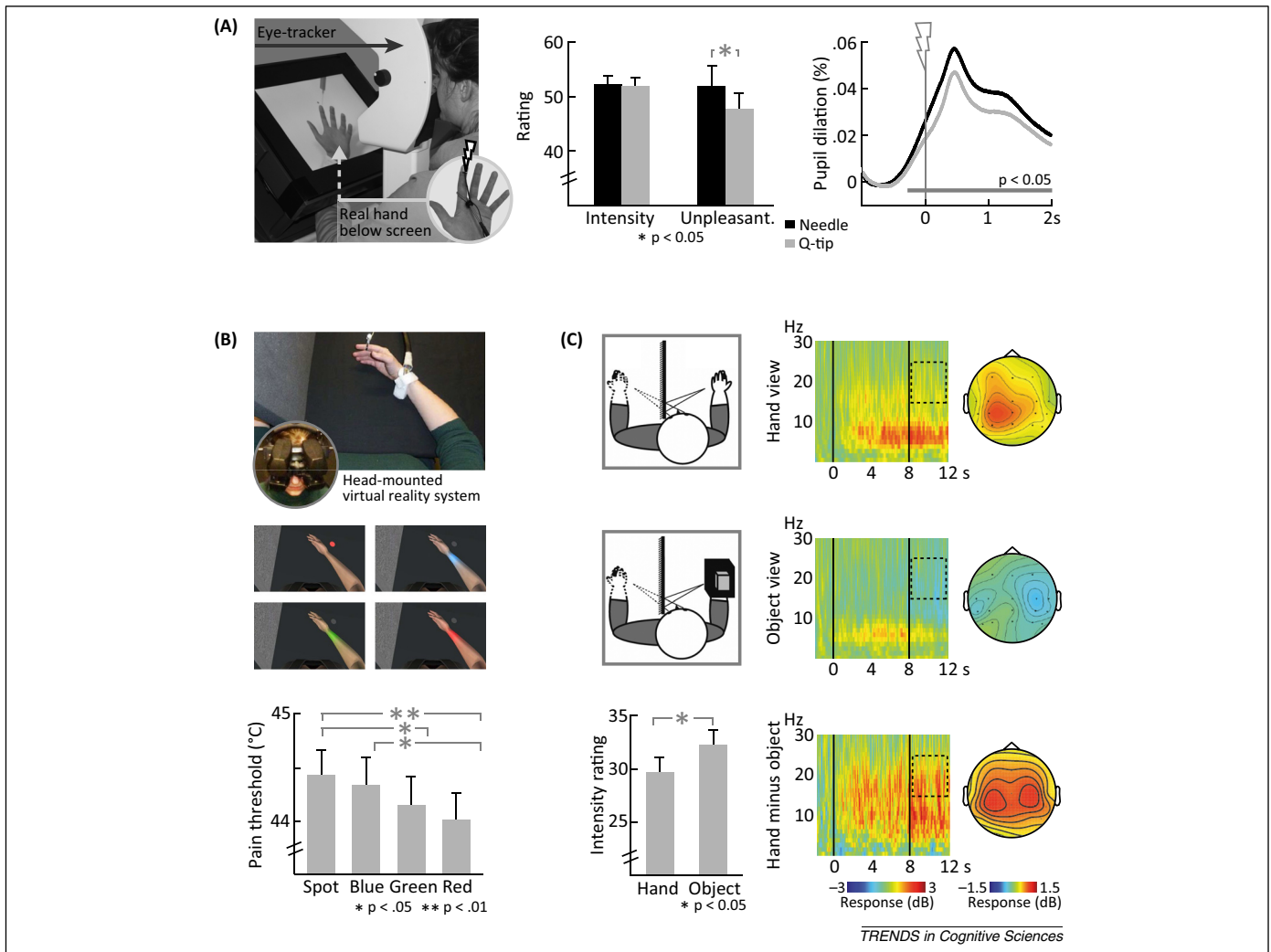


Figure 2. Studies using virtual reality setups with artificial limbs. **(A)** Influence of viewing a needle pricking a hand that is perceived as one's own on pain perception and pupil dilation responses. Participants were presented with video clips depicting a needle prick or a Q-tip touch while receiving spatiotemporally aligned painful or non-painful electrical stimuli (left panel). Pain unpleasantness ratings were enhanced when a needle prick compared with a Q-tip touch was presented (middle panel). This effect was paralleled by an enhanced pupil dilation response (right panel). Adapted from [38]. The figure has been reproduced with permission of the International Association for the Study of Pain. The figure may not be reproduced for any other purpose without permission. **(B)** Influence of skin color on pain perception. Participants wore a head-mounted virtual reality system that showed an avatar arm at the same location as their real arm. Thermal heat stimuli were presented to the real arm while there was either a grey dot next to the avatar arm that turned red or a color change of the skin toward blue, green, or red. The study revealed an enhancement in pain perception, as reflected in reduced pain thresholds, when the skin turned red. Adapted from [37]. **(C)** Diminishing effect of viewing one's own hand on pain perception and pain-related oscillations on electroencephalography (EEG) using the mirror-box paradigm (Box 3). The participant's left hand received painful thermal stimulation while the participant viewed the reflection of their right hand with a fake thermode or a box superposing their stimulated left hand. Viewing the hand compared with viewing a box reduced pain perception, which was paralleled by enhanced power of pain-related beta-band activity (BBA) over the sensorimotor cortex (right panel). Adapted from [22].

likely to reflect attentional processing in the frontoparietal attention network [70]. Taking these studies together, we propose that functional connectivity between pain-related regions and modulation of local oscillatory power are crucial neural mechanisms underlying the crossmodal shaping of pain.

Concluding remarks and outlook

The studies reviewed above show that innocuous stimuli can modulate the processing and perception of pain. Different factors, such as temporal and spatial alignment, stimulus intensity, and valence, have an impact on how other sensory stimuli shape pain perception. In this context, sensory stimuli in peripersonal space seem to be of particular relevance. At the neural level, oscillatory signals may be crucial for the crossmodal shaping of pain. In agreement with the hypothesis that much, if not all, of

the neocortex is multisensory [71], we propose that innocuous stimuli can shape pain-related neural responses essentially at all processing stages.

Thus far, the data available suggest that the crossmodal shaping of pain follows, at least to a large extent, the general principles of multisensory integration. Moreover, the studies reviewed above indicate that comparable mechanisms, such as changes in unspecific arousal and modulations in spatial or feature-based attention, which have previously been related to the crossmodal processing of innocuous sensory stimuli, are also involved in the crossmodal shaping of pain. This raises the interesting question of whether there are qualitative differences between the crossmodal shaping of pain and the crossmodal processing of innocuous stimuli. Because a main function of acute pain is to protect the body's integrity and to prevent future tissue injuries, it is likely that crossmodal shaping of pain

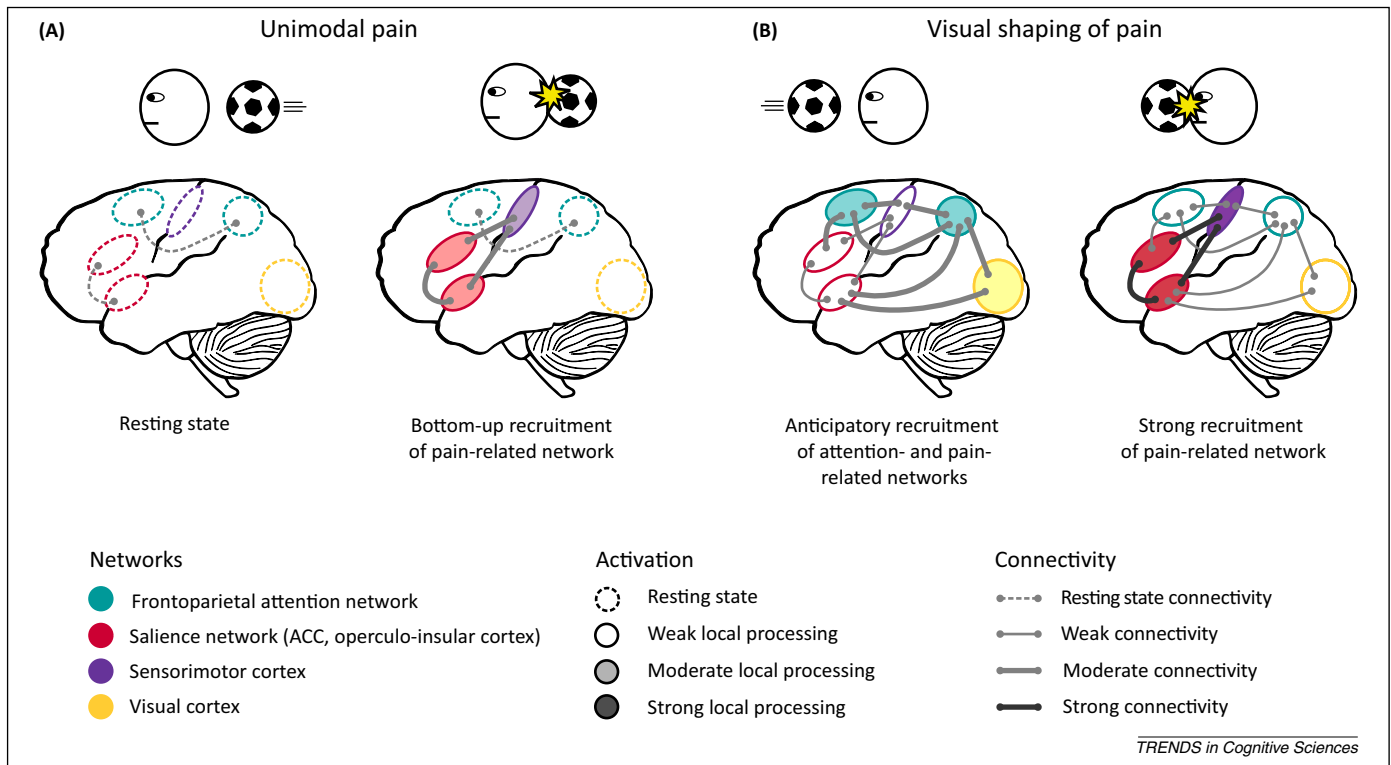


Figure 3. Example network scenario for the visual modulation of pain processing. **(A)** For unisensory pain we expect bottom-up recruitment of pain-related regions (i.e., sensorimotor cortex and regions of the saliency network). This recruitment may be reflected in moderate changes of local oscillatory power. Moreover, we predict that the bottom-up recruitment results in moderately increased connectivity between the sensorimotor cortex and the saliency network. The thin broken lines in the left panel indicate resting-state connectivity within the attention and the saliency network. **(B)** When a visual input predicts pain, we expect that the interplay between bottom-up and top-down processes via visual areas and the attention network, respectively, leads to anticipatory recruitment of pain-related regions. These anticipatory interactions may then lead to enhanced activation and enhanced connectivity between the sensorimotor cortex and the saliency network following the painful stimulus. Thus, in this scenario the crossmodal shaping of pain is reflected in stronger local processing within and enhanced functional coupling between pain-related regions compared with the unisensory processing of pain. Not illustrated is possible direct coupling between visual areas and the sensorimotor cortex. Moreover, connectivity between the visual cortex, attention network, and saliency network is illustrated for only one area per network.

in many cases involves modulation of motor-related processes that serve to prepare and execute a defense response. Whether this modulation occurs primarily during anticipatory stages (i.e., in expectancy of pain when processing threatening input from other sensory modalities) or during the concurrent processing of pain stimuli remains to be elucidated.

Most of the studies reviewed above focused on the processing of acute pain. This raises the question of how treatment programs for clinical pain could benefit from a better understanding of the crossmodal shaping of pain (Box 4). One approach that has been applied successfully for the treatment of clinical pain, including complex regional pain syndrome [72] and phantom limb pain [73], is mirror therapy. One cause of phantom limb pain may be a conflict between the proprioceptive representation of the amputated limb and visual feedback [74]. This assumption is in line with the finding that resolving this conflict by illusions of movement of the amputated limb during mirror therapy can alleviate phantom limb pain [73]. However, mirror therapy is not effective in all amputees. Recently, Schmalzl *et al.* [75] applied a novel approach that combines the mirror illusion with the rubber-hand illusion in amputees for which mirror therapy did not work. The study revealed a reduction of phantom pain that in most participants lasted minutes to hours. This suggests that the type of multisensory stimulation that most effectively reduces phantom pain can vary

across subgroups of patients. Thus, a better understanding of how crossmodal stimuli shape phantom pain may be helpful for the individual selection of multisensory stimulation protocols in amputees.

Box 4. Outstanding questions

- Are the two main components of pain differently modulated by the crossmodal shaping of pain?
- How does functional connectivity between regions of the saliency network relate to pain perception?
- Is there a role for cross-frequency interactions in the crossmodal shaping of pain?
- Differences in response latencies have been shown to play a role in the crossmodal shaping of pain through vibrotactile stimuli. Is there a critical time window for the crossmodal shaping of pain through other sensory modalities?
- Visual stimuli in peripersonal space play an important role in the crossmodal shaping of pain. Is this also relevant for input from other sensory modalities, such as auditory stimuli?
- Threatening visual stimuli in peripersonal space modulate neural processes related to anticipation of pain. Does this anticipatory modulation influence the perception and processing of pain itself and how does it relate to motor responses?
- Besides modulations of anticipatory processes involved in the preparation and execution of a defense response, are there other aspects in which the crossmodal shaping of pain differs from the crossmodal processing of non-painful stimuli?
- How can multisensory stimulation protocols be optimized to improve clinical treatment of pain?

An interesting recent finding is that visual distortion of body size modulates pain perception [40]. Using a virtual reality system including real-time videos that capture the hand from the same position as if viewed directly, Preston and Newport [76] showed that, in patients with osteoarthritis, stretching or shrinking the painful body part temporarily reduces pain. Multisensory virtual reality setups may be also incorporated in counter-conditioning programs for blood-injection-injury phobia. In this regard, setups like the one introduced by Höfle *et al.* [38,39] may be promising (Figure 2A). If needle prick clips were repeatedly paired with spatially and temporally aligned non-painful somatosensory stimuli, one might expect a learning-induced reduction of fear in subjects suffering from such phobias. Thus, multisensory stimulation protocols with virtual limbs (Box 3) may represent a promising approach that might be useful in clinical treatment programs for pain. A particular challenge lies in the development of multisensory stimulation protocols that result in longer-lasting ameliorating effects on pain. Taken together, research on the crossmodal shaping of pain has clinical implications and provides interesting new insights into the relevance and mechanisms of multisensory processing.

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