

Neural circuitry underlying pain modulation: expectation, hypnosis, placebo

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The ability to predict the likelihood of an aversive event is an important adaptive capacity. Certainty and uncertainty regarding pain cause different adaptive behavior, emotional states, attentional focus, and perceptual changes. Recent functional neuroimaging studies indicate that certain and uncertain expectation are mediated by different neural pathways—the former having been associated with activity in the rostral anterior cingulate cortex and posterior cerebellum, the latter with activation changes in the ventromedial prefrontal cortex, mid-cingulate cortex and hippocampus. Expectation plays an important role not only in its modulation of acute and chronic pain, but also in other disorders which are characterized by certain expectation (specific phobias) or uncertain expectation (generalized anxiety disorder) of aversive events.

Millions of people worldwide suffer from chronic pain and pharmaceutical expenditure for its treatment is enormous, but treatment efficacy remains low for many chronic pain states. Patients with chronic pain frequently report that they suffer more from the cognitive and emotional consequences of chronic pain than from the pain itself [1], and pain, in turn, is subject to considerable modulation by these processes [2]. Current treatments do not target these interactions, but with the advent of functional neuroimaging, their neural basis can now be studied.

One important cognitive factor is expectation regarding pain. Although the ability to predict the likelihood of pain or other unpleasant events by learning from prior experience is an important adaptive behavior in healthy organisms [3], it can cause disabling fear and avoidance in patients with chronic pain [1]. Functional neuroimaging studies of pain expectation have now provided important information regarding the underlying neural circuitry. The present article argues that the variability between results found in these studies reveals the effect of a biologically important mediating variable: the degree of certainty associated with an expectation. Behavioral studies have shown that different degrees of certainty are associated with different emotional, physiological and behavioral consequences [4].

Subjective certainty that a particular aversive event is impending ('certain expectation') is associated with the emotional state of fear. Fear mobilizes the organism to take action (fight or flight), or, if these options are not available, to minimize the impact of the aversive event (e.g. by cognitive distraction) [5,6]. Furthermore, fear has an impact on pain perception: numerous studies in experimental animals (and some in humans) have shown that fear leads to decreased pain sensitivity or hypoalgesia [7].

In contrast, uncertainty about the nature of the impending event ('uncertain expectation'), has very different consequences. It is associated with the emotional state of anxiety (rather than fear) which is characterized by risk assessment behavior or behavioral inhibition, and by increased somatic and environmental attention (rather than by distraction as in the case of fear) [5,6]. Compared with fear, anxiety has the opposite effect on pain perception: it has been shown to lead to increased pain sensitivity or hyperalgesia [7,8].

In the following, we identify brain areas involved in certain expectation/fear and uncertain expectation/anxiety, respectively (see also Table 1), and to derive a possible explanation for the involvement of these brain regions in pain modulation by hypnosis and placebo.

Fear and certain expectation of pain

The functional neuroanatomy of certain expectation of aversive stimulation has been examined in experiments by Buchel [9], Chua [10], Ploghaus [11], and their colleagues. In these experiments, visual signals served as reliable

Table 1. Imaging expectation of aversive events^a

	Certain expectation	Uncertain expectation	
		Outcome type	Intensity
vmPFC	–	↑	↓
RACC	↑	–	–
MCC	–	↑	↓
SI	–	↑	↓
AINS	↑	–	–
pCEREB	↑	–	–

^aThe effect of certain expectation and two types of uncertain expectation of an aversive event on activation change in the ventromedial prefrontal cortex (vmPFC), rostral anterior cingulate cortex (rACC), mid-cingulate cortex (mCC), primary somatosensory cortex (SI), anterior insula (aINS) and posterior cerebellum (pCEREB). ↑ signifies increased activity, ↓ signifies decreased activity.

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predictors of the type of impending stimulation, thereby allowing subjects to learn by experience to anticipate the characteristics of the stimulation.

In the experiment by Chua *et al.* [10] electric shocks were administered to subjects in the context of a red signal, but not in the context of a blue signal. No shocks were given during the red signal while a scan was performed, so scanning could have become a safety signal. Using PET, the authors found increased activation during the red relative to the blue signal in the rostral anterior cingulate cortex (rACC) and in the insula, and the magnitude of the activation was positively correlated with self-rated fear. Using fMRI, Buchel and colleagues [9] demonstrated activity in rACC during visual stimuli predicting unpleasant loud noise.

Ploghaus *et al.* [11] presented subjects with painfully hot as well as innocuous warm stimulation. Color cues signaled in advance the type of impending stimulation (color–temperature associations were randomized across subjects). Steady anticipation throughout the signal presentation was achieved by randomizing signal–temperature intervals, and color cues were the only reliable predictors due to randomization of trial order and inter-trial intervals. As subjects learned to anticipate the type of impending stimulation, fMRI responses increased in rACC, anterior insula and posterior cerebellum to the colored light signaling pain, but not to the color signaling warm stimulation. A direct comparison of painful heat and certain expectation of painful heat (Ref. [11], Note 13) revealed close but separate activation sites: painful heat activated the mid-cingulate, mid-insula and anterior cerebellum around the vermis.

Taken together, the studies by Buchel, Chua, and Ploghaus suggest that rACC, anterior insula and posterior cerebellum play an important role during certain expectation of unpleasant events. In the next section, we derive a more specific hypothesis by taking into account conditioning studies in animals, and studies of human brain activity during pain modulation by hypnosis and placebo, which also induce certain expectation.

Certain expectation in hypnotic and placebo effects

Research in experimental animals has firmly established that light or tone stimuli reliably predicting specific noxious stimulation acquire the ability to decrease pain sensitivity [12,13,14,15]. This effect is mediated by fear [16], which triggers descending opioidergic and nonopioidergic analgesic systems [17]. Similar effects of certain expectation of pain have been demonstrated in humans: it has been shown in experimental [4], as well as clinical settings [18], that pain sensitivity is decreased in subjects who obtained reliable information about the characteristics of impending noxious stimulation.

What predictions about brain activity during certain expectation of pain can be derived from these observations? Increased activity should be found in brain areas controlling descending analgesic systems, but not in brain areas receiving ascending nociceptive input. Ploghaus and colleagues [11] found significantly increased activation during certain expectation of pain in rACC, anterior insula and posterior cerebellum, but not in adjacent areas that

responded to pain (mid-cingulate, mid-insula and cerebellar vermis). Hence, the function of rACC, anterior insula, or posterior cerebellum might be to mediate the influence of certain expectation on the perception of pain and other aversive events.

Studies examining brain activity during pain modulation by hypnosis and placebo confirm this hypothesis, but also increase its scope. Using hypnotic suggestions, Rainville and colleagues [19] induced powerful expectations of increased as well as decreased unpleasantness of experimental painful stimulation. They found significantly increased activity in rACC during both conditions compared with a hypnosis control condition. Petrovic and colleagues [20] used a placebo treatment to induce expectations of decreased pain, and found an activation pattern that closely resembles the activation pattern during pain anticipation shown by Ploghaus *et al.* [11]: placebo-induced expectation of decreased pain activated rACC and posterior cerebellum, whereas pain itself activated the mid-cingulate and the anterior cerebellum around the vermis.

Importantly, during hypnosis and placebo, expectation continues throughout noxious stimulation and dominates the perception of pain. Thus, these studies provide us with two important additional insights. One, rACC and posterior cerebellum are active when expectation governs behavior, irrespective of whether this is *before* or *during* an actual aversive event. Two, rACC and posterior cerebellum are active irrespective of whether expectation *increases* or *decreases* perception of the aversive event. Thus, we propose that activity in these areas indicates a perceptual bias in favor of the certain expectation and against potentially conflicting nociceptive input.

By contrast, uncertain expectation has very different cognitive and behavioral consequences (see Introduction) and would not be expected to cause such a bias. In the following section we show that uncertain expectation is also associated with a different functional neuroanatomy.

Anxiety and uncertain expectation

Starting with pioneering work by Reiman *et al.* [21], several studies on uncertain expectation of pain have been performed. Two different forms of uncertainty have been examined: uncertainty about outcome type (painful or innocuous), and uncertainty about pain intensity. We will start our discussion with two studies from the former category.

Uncertainty about outcome type

Using fMRI, Porro and colleagues [22], studied brain activation after a tactile warning signal to the foot that might be followed either by a painful ascorbic acid injection into the same foot or by innocuous touching of the same skin area with a needle. The authors found that the warning signal increased activity in the foot representation of primary somatosensory cortex (SI) as well as in ventromedial prefrontal cortex (vmPFC) and mid-cingulate cortex. As these activation changes might be due to the tactile nature of the warning signal rather than due to uncertain expectation, a second experiment included a control group where the tactile stimulation ‘warned’ of no further stimulation. This experiment replicated the

activation pattern in SI, but no activation changes in the cingulate cortex were reported.

Hsieh and colleagues [23] obtained similar results using PET. Subjects in this study received either a painful ethanol or an innocuous saline injection, 10s (ethanol) or 20s (saline) after the start of each 100s PET scan. Subjects were instructed that the first two injections ('saline control') would not be painful, but some of the later injections (either ethanol or saline) would be. The authors found higher activation in mid-cingulate and vmPFC during saline compared with saline control scans. This could reflect up to 20s of uncertain expectation of pain, but also up to 90s of relief of not having received the painful ethanol injection. However, the studies by Porro *et al.* and Hsieh *et al.* share similar activation patterns but not similar design limitations, therefore we can conclude that uncertain expectation of outcome type is associated with activation in the vmPFC, mid-cingulate, and SI.

Using a gambling task that also provided uncertainty about outcome type (reward or punishment), Bechara and colleagues [24] demonstrated that patients with vmPFC lesions failed to show autonomic arousal (as measured by skin conductance) during high uncertainty or risk. In healthy volunteers, autonomic arousal is the first indicator of behavioral inhibition and improved task-related risk management [25]. The vmPFC activation in the present context could therefore also mediate an autonomic 'alert' signal triggering reassessment of behavioral strategy. As will be discussed below, vmPFC might receive the signal from the hippocampal formation [26].

Mid-cingulate cortex, the other activation site identified by Hsieh and Porro, is the second most frequently reported activation site in pain neuroimaging after the insular cortex [27]. These two brain areas are also implicated in increased somatosensitivity resulting from uncertain expectation of outcome type [28], a process that probably also accounts for the mid-cingulate activity found by Hsieh and Porro. The neural basis of anxiety-induced hyperalgesia will be discussed in more detail below.

Uncertainty about pain intensity

A different activation pattern emerges when subjects are certain that impending stimulation will be painful, but uncertain as to how painful. The experimental paradigm by Reiman *et al.* [21] used three PET scans per subject. Subjects were informed that they would receive no pain during the first and last scan, but would receive a painful electric shock sometime during the second scan, and that this shock would be more painful the longer the delay between the start of the scan and delivery of the shock. In fact, the shock was only delivered after the scan. Using this paradigm, Simpson *et al.* [29] showed that uncertain expectation of pain intensity was associated with decreased activation in vmPFC, and that the extent of this deactivation was inversely related to the anxiety about the likelihood of impending pain: the more anxious the subject, the less deactivation in vmPFC.

Drevets *et al.* [30] and Hsieh *et al.* [23] used the same paradigm except that they repeated the scan involving threat of shock multiple times within each subject, which could have turned scanning into a safety signal by allowing

subjects to learn that no shocks are delivered during scans. Drevets *et al.* found that uncertain expectation of pain intensity was associated with decreased activation in SI, which was positively related to anxiety about the likelihood of impending pain: the more anxious the subject, the more deactivation in SI. Hsieh *et al.* found decreased activation in the vmPFC, consistent with Simpson *et al.* [29], as well as in mid-cingulate cortex.

It seems plausible that subjects devote more processing capacity to analyzing the likelihood of strong than mild pain. In the Reiman task, the subjective certainty of strong pain increases throughout the PET scan. One might expect, therefore, both the neural substrates of certain and of uncertain expectation of stimulus type to be engaged, the latter decreasingly, the former increasingly, in the course of the scan. Anxiety, as measured by Simpson and colleagues, can be thought of as a marker of the contribution of uncertain expectation of stimulus type (painful/innocuous) to the activation image – that is, more or less activation in the case of vmPFC. Under the assumption that the deactivating influence of certain expectation on vmPFC exceeds the activating influence of uncertain expectation of stimulus type, the activation pattern observed by Simpson *et al.* [29] would be expected: the more anxious the subject, the less deactivation in vmPFC. However, data pertinent to the assumption have not yet been reported.

Anxiety-induced hyperalgesia

Uncertain expectation and anxiety have been shown to increase pain sensitivity. Ploghaus *et al.* [8] performed an fMRI study to examine the functional neuroanatomy underlying this process. In the study, pain stimuli of different intensities were preceded by visual signals. One visual signal, which reliably predicted pain of moderate intensity, came to evoke low anxiety about the impending pain. Another visual signal was followed by the same, moderate-intensity stimulation on most of the trials, but occasionally by discriminably stronger noxious stimuli, and came to evoke higher anxiety.

We found that physically identical noxious stimulation was perceived as more painful in the context of higher anxiety. This anxiety-induced hyperalgesia was associated with activation in the entorhinal area of the hippocampal formation, and correlated activity in the ACC and insula. This is consistent with the Gray–McNaughton theory [31], which proposes that the hippocampal formation responds to aversive events whenever they form part of a behavioral conflict (e.g. during uncertain expectation). It resolves the conflict by sending amplification signals to the neural representation of the aversive event, thereby biasing the organism toward a behavior that is adaptive to the worst possible outcome. According to the theory, this process is accompanied by anxiety.

Conclusion

Cognitive and emotional processes interact with pain perception, and the neural circuitry underlying this interaction provides an untapped opportunity for targeting acute and chronic pain states. In the last decade, functional neuroimaging of pain has provided us with a

sound understanding as to which brain areas are activated by acute painful stimulation. However, research on the neural pathways underlying pain modulation by cognitive, emotional, pharmaceutical and other factors, is only just beginning.

One important cognitive factor interacting with pain is expectation. The present article argues that the behavioral effects and the neural basis of expectation depend on the level of certainty. Certain expectation is associated with activity in the rostral anterior cingulate cortex and in the posterior cerebellum, whereas uncertain expectation activates the ventromedial prefrontal cortex, mid-cingulate cortex and hippocampus. Our analysis illustrates that apparent variability between results in functional neuroimaging is often caused by seemingly subtle differences in experimental design, in the present case different levels of certainty. These differences can cause different behavioral consequences and therefore different activation patterns.

Expectation is a multidimensional construct and is associated with multiple brain activation sites. An important future direction is to achieve a closer mapping between the psychological components (cognition, emotion, autonomic responses, motor responses and others) of expectation on the one hand, and brain activation sites or functional connectivity on the other hand. Recent studies on the expectation of appetitive events [32], and of monetary gain and loss [33], provide exemplary examples of this research direction.

The ability to predict biologically relevant events is essential for survival, but is also a critical factor in common disease states (e.g. chronic pain and anxiety disorders). A better understanding of the neural processes underlying different forms of expectation is of great interest from a basic science perspective, but will also help to develop novel therapeutic strategies.

Acknowledgements

This work was supported by a grant from NIH to DB (NIDA DA 13650).

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