COMMENTARY

Unconscious and conscious mediation of analgesia and hyperalgesia

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Although a number of studies have shown that behavioral responses can occur without awareness of stimulus cues that evoke them, a study by Jensen et al. (1) in PNAS shows that increases (hyperalgesia) and decreases (analgesia) in pain can be classically conditioned without awareness of conditioning cues during both acquisition and test phases of a conditioning paradigm. These results suggest that nonconscious stimuli have salient effects on human brain function and complex dimensions of experience, such as pain. Because pain, analgesia, and hyperalgesia represent higher-order cognitive functions, their modulation without conscious awareness suggests that low levels of the brain's hierarchical organization are susceptible to learning that affects higher cognitive functions (e.g., pain). These findings, along with supportive past results (2–4), may have deep implications for subliminal influences on many forms of experience and behavior.

Because pain has long been known to be a powerful motivation for several behaviors—such as escape, self-protection, and aggression—one implication of this study is that well-organized adaptive behaviors associated with responses to pain are at least partially shaped by numerous unperceived environmental cues. This type of influence is likely to have advantages in contexts wherein an organism has to make adaptive responses in threatening or appetitive circumstances, and quickly initiates behaviors that avoid threat or provide pleasure. This kind of rapid regulatory mechanism contrasts with decisions that require conscious deliberation and longer-term plans for behavioral responses.

Despite differences between conscious and unconscious initiation of pain behavior, unconscious mediation of analgesia and hyperalgesia may well use some of the same general neural substrates of endogenous pain modulation that have been characterized for over 50 y (5). Early studies of this system emphasized structures in the lower brainstem, including the periaqueductal gray that projects to the rostroventral medulla. The latter in turn projects to the spinal cord dorsal horn (5), wherein pain-related signals are reduced or amplified. Then it became known that a core periaqueductal gray-rostrovental medulla-dorsal horn system has a bidirectional control over pain and ascending pathways that relay pain-related signals (5). For example, "off cells" of the rostroventral medulla inhibit and "on cells" facilitate neurotransmission in dorsal horn neurons involved in pain. This bidirectional control of pain is reflected behaviorally and is likely to provide some of the substrates of such phenomena as placebo analgesia and nocebo hyperalgesia, as well as subliminal effects observed in the study by Jensen et al. (1). With the advent of several neuroimaging methods, this core neural network has shown to be accessed by cortical structures. These include areas involved in emotions (e.g., rostral anterior cingulate cortex, amygdala, and orbitofrontal cortex), working memory and expectation (e.g., dorsolateral prefrontal cortex, hippocampus), and reward (e.g., nucleus accumbens, ventral striatum, orbitofrontal cortex) (5, 6).

Jensen et al. suggest that there exists a hierarchical activation of neural pathways for nonconscious and consciously conditioned analgesia and hyperalgesia.

Using functional MRI (fMRI) and conditioning methods similar to those used in the report under discussion (1), in another study Jensen et al. (3) investigated the neural structures involved in nonconscious activation of analgesic and hyperalgesic responses. Nonconscious compared with conscious production of conditioned placebo analgesia was accompanied by increased activation of the orbitofrontal cortex, a structure involved in emotions and reward processing. During nonconscious nocebo, there was increased activation of the thalamus, amygdala, and hippocampus. Given their roles in emotions, memory, reward processing, and their functional connections to brainstem structures involved in pain modulation, nonconscious conditioning of analgesia and hyperalgesia are likely to share neural mechanisms also engaged by more conscious forms of pain modulation. The latter are linked to expectations, emotions, and reward. Jensen et al. (1–3) suggest that there exists a hierarchical activation of neural pathways for nonconscious and consciously conditioned analgesia and hyperalgesia. Apparently, brainstem and cortical activations can modulate pain with or without neural activity sufficient to evoke conscious awareness of relevant environmental cues.

Consciously Evoked Placebo and Nocebo Effects

It is also important to recognize that placebo and nocebo effects on pain can occur consciously and without conditioning (7–10). Consciously evoked pain modulation is known to occur as a result of verbal suggestions (7–10), as well as physical simulations of active treatments (4). Do their psychological and neural mechanisms use brain areas that can also be activated without awareness of conditioning cues, such as those activated in Jensen et al.'s (1–3) studies? Verbally mediated analgesia and hyperalgesia entail conscious dimensions, such as expected pain reduction, desire for pain relief, and emotional feelings about prospects of pain increase or decrease (8). Some of these studies show that changes in pain are preceded by reduced ratings of expected pain in instances wherein analgesia is produced. However, expectation does not seem to act alone but is combined with other conscious parameters.

As an example, a series of similarly designed studies of placebo analgesia in IBS patients (7–9) contained groups of patients

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that were given a suggestion that "the agent you have just been given is known to powerfully reduce pain in some patients" and one of these studies compared a group of irritable bowel syndrome (IBS) patients that received the verbal suggestion and an inert agent with another group who only received an inert agent without the verbal suggestion (7). Although all other aspects of the placebo procedures were the same, IBS patients given the verbal suggestion had much larger placebo effects than patients not given the suggestion (7, 9). When both groups were compared in fMRI analyses of brain activity, only the group receiving the verbal suggestion showed large reductions in brain activity related to processing pain (7). IBS patients who received the verbal suggestion also had increases in neural activity in brain structures involved in endogenous analgesia, such as prefrontal cortical areas, rostral anterior cingulate, and right amygdala. These areas are also involved in the regulation of emotions and consciousness. For example, the amygdala has been implicated in both conscious and unconscious forms of emotional learning (11).

Other observations further suggest that placebo responses of IBS patients given a verbal suggestion for analgesia involve conscious mechanistic steps. First, ratings of desire for relief and expected pain predicted most of the variability in pain ratings in the placebo condition (8). Second, ratings of expected pain, desire for pain reduction, and experimentally evoked pain (from visceral distension) progressively decreased with each successive test stimulus used to measure the placebo analgesic response (7–9). This progressive increase in placebo responding has been explained by a somatic feedback mechanism in which patients' experiences of pain relief lead to still further reductions in pain during subsequent test stimuli (12). Finally, in one study of IBS patients that used fMRI, placebo responses were accompanied by increases in neural activity in brain structures involved in memory and verbal/semantic processing (7). These increases occurred at the onset of each test stimulus and were maintained over the 20-s period of the test stimulus. The increases did not occur in the IBS group not given the verbal suggestion. Taken together, these studies of IBS patients reflect the conscious cognitive nature of this form of analgesia (7–9). After all, the patients have to hear the verbal suggestion, understand its meanings, retain a working memory of it, and develop expectations and feelings about reduced pain (which they can rate on scales), unlike the mechanisms of subliminally conditioned changes in pain described by Jensen et al. (1). There is nothing subliminal about hearing a suggestion in a specific language, understanding its meaning, and developing expectations/feelings related to it. IBS patients given this verbal suggestion also had thoughts and emotions about receiving an effective treatment during the placebo condition (reported during a postsession interview) (8).

Meanings and Placebo/Nocebo Effects

Those forms of pain modulation that involve the meanings of receiving a therapy or medication (4, 13) and consequent expectations of changes in pain seem most relevant to placebo and nocebo responses that are induced by verbal suggestions (4, 8, 10). However, an abundance of subliminal environmental cues whose influence is shaped by past experience cannot be ignored. Previous effective treatments, and therefore conditioning, may facilitate meanings, expectations, and feelings about treatments even when the latter variables are likely to be the proximate causes of verbally mediated placebo/nocebo responses. Meanings and expectations require some degree of awareness in those contexts where patients actively interact with healthcare professionals or actively perceive a "treatment." As far as is known, subliminal conditioning alone doesn't include experiences about treatments and it is noteworthy that Jensen et al. (1) are careful not to claim to have directly studied placebo or nocebo responses. Nevertheless, subliminal conditioning and more conscious forms of placebo/nocebo phenomena may share some common psychological factors and neural mechanisms. Both forms of pain modulation use some common brain structures likely to be a part of a classic pain modulatory system (5), and Jensen et al. raise the possibility that subliminally conditioned analgesic and hyperalgesic responses are accompanied by consciously accessible expectancies (1). This raises an intriguing question: Do subliminal cues lead to expectations of changes in pain as well as changes in pain intensity itself despite absence of awareness of conditioning cues? If so, then expectation could still be a critical mediator of changes in pain even during unconscious conditioning. Participants may have expectations despite no awareness of the cues that lead to them. This possibility is at least consistent with a study in which classic conditioning resulted in analgesia, yet the effects were shown to be mediated by expectation (14). Subliminal conditioning and verbally mediated pain modulation may entail mechanisms that are more commonly shared than anyone has suspected. The mechanistic differences between the two forms of pain modulation are equally interesting.

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