Placebo response: theory, mechanisms and teleological roots.

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Abstract: Why pain can be relieved with placebos is heavily debated. The term 'placebo response', implies that the placebo treatment induces pain relief which is imprecise because it is the mental cueing to the context of treatment and not the placebo itself that can reduce pain. This essay reverts to fundamentals of perception that have been used to explain how context generates predictions that can in turn effect the process of processing, organizing and interpreting of sensory inputs received from the periphery. We reinterpret placebo response as a neurobiological phenomenon that occurs through the process of reward and aversive learning. The brain uses learnt information to generate predictions. The perceptual processes adjust the experience of pain to fit with the predictions generated from prior information. Placebo response is thus understandably a result of the expectations and mental states that result from engaging in the process of treatment. These processes have teleological roots in ancient medicine and are the context that produces these responses is transforming with the evolution of modern medicine. Thus, when placebo response is observed, the potent agent that induces pain reduction is not the placebo itself, but the mental cueing to the context of taking treatment.

Placebo response is an intriguing but frequently misunderstood phenomenon. Despite a large number of convergent studies, the debate continues on validity of placebo response as clinically useful[1]. That pain is reduced in response to placebos is a phenomenon widely witnessed and systematically recorded in clinical trials. Experimental and clinical studies have delved into this phenomenon to demonstrate that the body generates physiological responses that aid the process of treatment [2]. A major barrier for applying this knowledge into clinical strategies is the ambiguity around the term placebo response. In this chapter, first the issues with the term placebo response will be discussed to make the assertion that veridical improvements that occur independent of drug action are formed by the contextual factors through a mental cueing process. Acknowledging this fact allows for a better conceptual and utilitarian model for understanding the physiological capacity that aids the therapeutic process. In addition, teleological role of mental cueing will be explained to postulate how we may have developed this response through persistence of cultures from antiquity. The significance of underlying brain mechanisms will be discussed with an emphasis on predictive processes and reward based learning that shape the mental cueing response.

Does the brain respond to placebos or to mental cues? Through the numerous studies on placebo mechanisms, it has been established that placebos can in fact trigger physiological changes in brain processes to alter pain[3]. We associate the term placebo with the mental image of a dummy pill, and have been made to think that objects or procedures that is framed as an effective pain treatments can produce affects comparable to actual pain relievers. The word 'placebo' means 'to please' and has roots in earlier era of medicine when fake medicines were used as a tool to patronize and deceive the patient with the intent to make them think that they were being cared for. The term placebo originates from *placebo effect* where the latter pertains to responses seen in the placebo arm of a Randomised Controlled trial (RCT). The canonical assumption for using RCTs is that unlike real medicines, placebos lack potency and hence serves as a control for non-drug related factors. For practical purposes, the factors to be controlled are non-specific and represent a list of irrelevant effects such as spontaneous fluctuations in pain, regression to mean, statistical artifacts, or anomalous psychosomatic responses[1,4]. Unlike real medicines, it should be clearly acknowledged that a placebo by itself lacks any potency or ability to alter mental or physiological processes. Beecher's assertion that people respond to placebo's in a non-trivial manner created interest in the possibility that placebos have an impact on medical symptoms and the response was referred to as placebo response [5,6].

Placebos have been most thoroughly scrutinized in the context of randomized double-blind placebo controlled clinical trials have been repeatedly shown to reduce pain by 30-50%; this represents pain relief

quantitatively similar to opioids and NSAIDS[1,4,7,8]. Nevertheless, despite of the fact that placebos lack potency of an actual drug or treatment, the indubitable evidence for strong improvements in pain in the placebo arm suggests that there is a measurable and significant effect. A large body of psychophysical and neuroimaging studies have modelled the mechanisms that induce placebo response. Extensive scientific understanding of the validity of placebo response has been established and an essential link has been drawn between placebo response and learning systems of the brain.[9-14] However, the value of administering placebos, the longevity of responses and their clinical significance are useful questions that have still not been fully resolved.

The general perception of placebo response is still clouded by obscurity. In the clinical realm, placebo response can be misunderstood as pertaining to the use of sham medicines and as a result, the potential clinical value of placebo response is often unclear and doubtful[15,16]. The social and ethical ambiguities associated with the process of deception used in placebo is also problematic[17]. Here we contend that the responses observed with placebos are induced through physiological mechanisms and do not represent a response to placebo *per se*. The imprecise nomenclature is an important barrier for clinical conceptualization. As explained below, the clinical improvements are not owed to the placebo but to the mental cueing process that occurs through engaging with the context of the treatment process. Hence the response is ubiquitous and embedded in all treatment processes and hence should not be referred to commonly as placebo response. Despite its complexity, the motivation to understand how context and mental cueing contributes to treatment response is an important line of investigation with potential rewards and benefits for patients and healthcare.

Mental cueing response: We now know that mental state such as expectations, attention and arousal are significantly altered based on the context of undergoing treatment[18-20]. Aligning expectations and prior states with treatment goals plays a significant role in triggering changes in the neurobiological apparatus leading to changes in neurotransmitters and altering brain responses and connectivity [13,21-24]. This process can be referred to as the mental cueing effect and the responses generated to as mental cueing response.

Mental cueing is useful as a term since it implies that the agency for inducing changes lies with the brain's ability to adjust perception based on changes in context. This is necessary because dummy medicines or sham devices are by definition inactive and hence ascribing a response to them is imprecise. The term placebo response is conflicted since the large observed in the placebo arm can be confused to mean that the placebo can cause a response. On the contrary, responses generated on starting a new treatment are not specific to the tool used for administering a sham or actual drug[25]. The device or tool itself is a small

contributor relative to other factors such as prior knowledge, expectation and social effects[26,27]. The term mental cueing response thus more accurately suggests that the response occurs to a mental cueing to the context of initiating a treatment.

This distinction is important because if we consider that mental cueing is a significant phenomenon then we can begin to perceive its role in day to day clinical practice. Viewed from this vantage point, it becomes possible to acknowledge that drug activity is not the only necessary element for generating therapeutic responses. In other words, the responses normally attributed to analgesics are in reality a combination of pharmacological action of the drug and the mental cueing effect to varying degrees [28,29]. Moreover, the mental cueing occurs not just during treatments with pills, but during any type of treatment, be it behavioral therapy such as CBT (cognitive behavioral therapy), surgery or alternative therapy[30,31].

Another important dimension to mental cueing is the nocebo response[32]. The tendency of some individuals to show worsening of symptoms after taking a drug is another layer of important evidence that mental cueing determines treatment success. The role of negative expectations and conditioning is well demonstrated and nontrivial. From a clinical perspective, it has been extensively noted that a negative context during the process of treatment can have a deleterious effect on the treatment outcomes by not only blocking the effect of the treatment, but may also worsen the symptoms. From a scientific and knowledge perspective, the possibility of negative mental cueing is in fact a demonstration of our physiological capacity for intrinsic adjustments in the disease process based on context.

The factors that initiate mental cueing can be external or internal. The rituals that occur daily in an outpatient clinic are demonstrative evidence of *external* mental cueing. The doctor's bed side manner, the formalisms such as lab coats and scrubs, implicit or explicit verbal or facial suggestions made by clinicians about the effectiveness of the prescribed drug and encountering people who offer positive feedback verbally or implicitly are some examples of factors that are inherently positive external cues[8,33]. The concept of 'therapeutic encounter' points at the implicit therapeutic relationship is established between the clinicians and patients which in a positive situation asserts a level of confidence and reduces anxiety to trigger physiological healing processes.

Another set of factors are *internal* and related to the individual. Seeking or receiving medical attention, participating in the therapeutic encounter and undergoing treatment is inherently a substrate for triggering helpful physiological processes by reconfiguring the mind to prerequisite mental states. Thus, the agency lies not only with the treatments but with the patient as well. Therapy benefits from an internal locus of

control and self efficacy[34]. Entering the treatment process requires a shift in motivational state and expectancy towards getting better. Thus, seeking or eliciting help is a type of reward seeking behavior which needs a baseline intent for improvement. This assumption also implies that therapeutic process is not passive and that it requires mental and neurobiological engagement on the patient's behalf[35]. Inferences are generated and continually checked and updated based on new information that can have a major effect on expectations[10,36]. Inferences and conditioned responses are also updated based on positive and negative outcomes thus also contributing to an update in expectations.

Psychological factors such as anxiety and cognitive control and personality are factors that can interfere with and preclude the ability to generate the required intent and positive motivational state[37]. Another important determining factor is prior experience with a particular medical system which can be affected due to medical history replete with treatment failures[38]. For instance, sufferers of chronic condition may be disenfranchised from modern medicine and may turn towards alternative treatments as a recourse. An extreme recourse resulting from disenchantment from medical system coupled with a desire for relief can lead to eliciting and abusing prescribed or illegal pain killers such as opioids. The worst-case outcomes from these situations are addictions and overdose and a maladaptive mental cueing is potentially a major cause behind treatment failures and soliciting higher doses, multiple treatments and non-standard drugs. Chronic pain sufferers that are referred to tertiary pain clinics after failure of standard pain treatments benefit from undergoing comprehensive treatment approaches such as behavioral therapy and movement based treatments perhaps because they have not built negative expectations towards alternative approaches.

A complimentary aspect to actual experience is prior knowledge[10,39]. Clinical information on drugs and diagnosis is now widely accessible on the internet and can play a major role in generating expectations. Patients have easy access to knowledge on disease and treatments which they can access on their own through media such as electronic information, news and books[40,41]. Another resource for setting prior expectations is through social exchange like conversation, and also through social observation of other people engaging and showing overt signs of improvement[12,42]. This aspect is in particular bound to vary between individuals since it is derived from our sociocultural world view and is subject to be different between ethnic groups and geographic distances.

Although there are many sources for positive mental cueing, and regardless of if a single type of cue is of specific importance or has the strongest role in triggering treatment response, how these factors will affect an individual will vary between individuals and will be contingent on patient history[38], prior experiences[39], emotional states[20], personality traits [20], and brain connectivity [14,43].

Teleological reasons for mental cueing: Mental cueing that occurs during treatment and the responses generated by this phenomenon has deep teleological origins and are shaped by evolution of cultures. The cultural traditions of different ethnic and geographic groups may be distinct but the common aspect is the adaptation of the mind to derive meaning from symbols and icons. Therapy and treatment has taken on different types of symbolism that signify a force to ward off evil and initiate healing. Hence, mental cueing has an inherent adaptive value.

The use of iconic symbols and our neurobiological capacity to induce relief from such symbolism has deep roots in ancient culture[44,45]. Regardless of the type of treatment, the element of symbol-rich rituals was a key part of healing diseases. Ailments were considered as associated with bad spirits and the medicines and rituals were considered to be laden with magical properties. In addition to the symbolism in artifacts, the healer or shaman was positioned as the learned man with secret knowledge that he used for curing diseases. Symbolism, story-telling, and mythological references are used in many types of old healing traditions and such elements can have a stronger impact at many levels of information processing in the brain, including those levels that are not directly accessed during conscious processing.

It has been posited that we encounter symbolic external cues during the treatment process and the symbolism varies between cultures and ages, but these symbols are unified in that they signify relief or improvement in the medical condition[46]. The image of a nurse wearing a uniform or the doctor in a white coat are iconic symbols that are loaded with implicit meaning of relief from disease and resource for overcoming physical ailments. As such, the symbolic meaning is much greater than mere expectancy cues, and in many situations, the mental cueing is stronger than a mere expectation and the intensity of this effect is based on stronger priors represented by beliefs and faith. Expectations, especially those that are inferred on the short term are subject to re-evaluation, but some expectations, inferences and beliefs are based on long term learning. These beliefs normally go unquestioned because for practical purposes, our reality is immersed in the milieu of conceptual knowledge of how things occur. This knowledge is reinforced into common belies through our shared societal constructs and interpersonal subjectivity.

The topic of how treatment outcomes are influenced by unconscious mechanisms is explored in psychology, psychoanalysis and neuroscience but very little is known about how these mechanisms are connected to the deeper aspects of symbolism and faith. The belief in alternative medicine and knowledge ascribed to these traditions, as long as it is accepted as veridical by the subject can hold significant sway on inferential activity at the mental level. Thus, the persistence of faith based healing methods and some forms of alternative treatments is perhaps an indicator of their ability for mental cueing, albeit in some but not all people. This could explain why alternative treatments such as acupuncture, homeopathy and reiki hold a surprising significance with a large number of people and are widely popular[47]. Regardless of whether the explanation of mechanisms behind them don't match with modern science, their efficacy can be meaningful in a significant number of people and the outcomes may not be a direct result of the purported mechanisms but due to their potency in mentally cueing the suggestible individual. This suggestibility is rooted in culture. Old traditions and historical roots are entrenched in the local social milieu and can be effective at least in part because of the strong psychological impact they can have on a person who is interested more in relief and less in critiquing the source of treatment. These treatments serve as potent mental cues for initiating endogenous relief but the outcome albeit will be heavily contingent upon the credulity of the cues, the cultural and social belief systems and impressionability and suggestibility of the subject.

Our scientific knowledge of *disease* ontology and medicinal cures is relatively recent compared to the older culture of shamans and ritualistic healing. Instead of being sourced from superstition and faith, the cures are in general derived from physical causes and evidence collected from the scientific method. The dialectical suppositions that are assumed during the scientific process are constantly revised and renewed through the fast pace of technological and scientific progress. Our assumptions and inferences about the medical system ought not to be based on faith, and should instead be based on belief in the scientific process. This assumption derives from the fact that modern medicine should not be seen as a faith-based and more as a direct derivative of the scientific process. This especially holds credence for how we view pharmacological treatments that have succeeded the gold standard RCT challenge. The medical experts are not faith based healers, but are individuals trained in specialized scientific knowledge of practical and fact-based cures and are less rich in the social, interactive and symbolic aspects. This cut and dry method of administering cures is relatively new in relation ancient healing cultures and hence, how we mentally cue patients in modern medicine is shaping up in new unknown dimensions across the world.

Interestingly, this dichotomy can be cosmetic since many so-called evidence-based treatments were introduced into medicine through a heuristic process and have not undergone gold standard clinical trials. Like classical alternative therapies, modern medicine is also laden with covert symbolism. That being said, icons in modern medicine follow certain common archetypes that are controlled to fall within that expected from a science-oriented and practical medical environment. Even the items used to furnish and decorate an office are standardized to be reasonably consistent and can serve as mental cues useful for generating conditioned responses. However, the effects of the relatively sparse symbolism inherent in modern medicine contrasts sharply to the older mythically rich, stimulating and interactive rituals of our past. The acceptance and belief systems in older systems used strong psychologically potent symbolism. Current symbols are relatively vacuous and responses to these types of cues are more associative and conditioned rather than hermeneutic. Taken together, there is a common historical theme that is delimited from the type of therapy and involves expectations and inferences that are derived from belief and faith in the medical tradition or system.

In contrast to modern medicine, many alternative therapies such acupuncture and yoga have a strong symbolism, ritualistic and interactive dimension[48]. This can create a real dichotomy in the types of mental cues transmitted and how these cues are interpreted will depend on the patient's biases or beliefs regarding science-based vs. tradition based therapies. Whether alternative treatments are effective independent of mental cueing effect, or if the mental cueing effect of alternative therapies is stronger than allopathic methods, is a debate beyond the scope of this discussion. But, the marked placebo responses observed in RCTs are a strong indicator that even a psychologically sparse and less interactive methods of therapy such as those used during clinical trials do have strong mental cueing impact. It can also be assumed that any differences in the mental cueing outcomes of these two types of medical approaches to medicine may be linked with the type of therapy to a lesser extent and more closely to the individual's characteristics such as past inferences on alternative therapy and openness to alternatives.

But regardless of the type of treatment, the above discussion underscores the fact that the more invasive, social, ritualistic, theatrical but convincing the treatment process, the stronger the mental cueing effect and stronger will be the treatment response. The veridical aspects of an effective treatment will also play a role in establishing the treatment outcome and the repeated success of a treatment will enhance the mental cueing effect. In this way, the active treatment and the mental cueing are integrally linked.

Mental cueing responses result from predictive processes generated by reward and aversive learning:

Placebos demonstrably shifts mental states, altering the patterns of brain activity and changes expectations that are conducive for generating strong therapeutic responses to both active and inactive pain analgesics[3,6]. Conversely, an inability to build positive expectations or appropriate mental states (i.e., the right 'mind set') before starting treatment negatively affects treatment outcomes[14,43,49]. This is particularly true for analgesics because pain is a highly subjective percept and particularly malleable to context [22]. In general, placebo response demonstrates our neurobiological capacity to translate mental cues, prior experience, and our conceptual beliefs in treatments into pain relief. These elements also direct treatment efficacy. The ability to generate prerequisite mental states from mental cues combined with conceptual inferences not only facilitate the treatment process, but a lack of these elements can also reduce and sometimes even completely block the efficacy of a drug. The impact of this phenomenon on pain responses is non-trivial and the level to which this mental-cueing effect can alter pain responses is putatively a demonstration of embedded evolutionary psychology and the neurobiological wiring of our expectation, inference and learning systems in the brain.

Role of predictive processing in mental cueing effects: Complex and interlinked factors determine whether mental cues will be effective in triggering the prerequisite activity in neurobiological systems to induce positive responses. The factors can be external and internal and the juncture where these two classes of factors juxtapose is the nervous system. External cues received by the brain are processed within the context of prior mental state [10]. The concept of prior states and predictive processing is a useful model for understanding the placebo phenomenon. Perceptual processes are guided by prior information that creates thoughts and mental states that contain predictions, inferences and beliefs about future events [11,50-54]. Our brain uses predictions because they confer the ability to expect contingencies, anticipate what is ahead, and prepare for events. The concept of priors can be illustrated from relevant examples from semiotics and language studies, which describe that the brain uses cues and context as symbols to interpret new information based on prior knowledge in a goal directed manner[55,56]. Hence, expectations reflect the capacity to which learning and past experience have prepared the brain to interpret and understand how a stimulus should be perceived based on context and adaptive needs. A similar phenomenon underlies placebo response where the process of receiving treatment is inherently linked with positive or negative expectations. The strong inferential link between seeing a doctor and relief from ailment is implied by social observation and confirmed through experience. Hence the fact that we see systematic changes in pain to placebos in experiments and in clinical trials is not entirely surprising.

Expectations, prior knowledge, conditioning, motivation, and a healthy emotional state are the main ingredients mobilized by mental cues during the treatment process [22,57]. From a neuroscientific perspective, the external cues induce expectations, orienting responses and increase arousal (alerting response) that can act as top-down factors. These prior states act as top-down signals for shaping and modulating pain perception. All of these contexts require mental cueing to elicit prior mental states that can then alter the perceived amount of pain.

Prior information that alters pain perception, referred to as top-down information, can take on many forms. It can be an explicit expectation that is conscious thought (inner talk), or it can be unconscious reflexive conditioned response. The intensity of pain is demonstrably a malleable and compliant perceptual system [47,58,59] which is controlled by top-down expectations i.e. we feel less pain when we expect less pain. Since the discovery of opioid systems in the brain, it has been known that the brain can adaptively adjust the intensity of pain based on the context and survival needs of an animal. This adjustment, or 'modulation', of pain intensity by the brain has been observed systematically by testing effects of attention, expectation, conditioned pain modulation, and placebo responses[27,52,60,61]. Distraction from a consciously attended pain stimulus, such as diverting attention away from the injection site during vaccination, has been quantified to reduce perceived pain intensity. The intensity of pain has been shown to be malleable and compliant to top-down expectations, i.e., we feel less pain when we expect less pain. Taken together, there is indubitable evidence that context can alter the perceptual reality of pain.

Neurobiological circuitry for adjusting pain based on prior predictions: The ability to adjust pain based on context is linked directly with how pain pathways are organized in the nervous system. At a physiological level, the fact that "top down" factors modulate pain was demonstrated by Sherrington who showed that reflex withdrawal from painful stimuli is more pronounced when the animal's brain is transected from the body[62]. It was later shown in a series of studies, that analgesia could be produced by electrically stimulating areas such as the periaqueductal gray area (PAG) in the mid brain and in the reticular formation (RVM) in the pons[63]. Subsequent studies identified circuits that bidirectionally connect the PAG, RVM, and sensory relays to processing units of the spinal dorsal horn including lamina 1 and lamina 5[64-67]. These pathways were named the descending pain modulation systems. Moreover, connections of the PAG and RVM were also mapped to connect with subcortical structures in the brain, such as the amygdala and hypothalamus[68,69], and to cortical structures such as the anterior cingulate, and to orbital and lateral parts

of the prefrontal cortex[70-72]. The sub-cortical structures, especially those in the brain stem that are known for their role in pain processing and modulation, are bi-directionally connected to the spinal dorsal horn. In this way, the cortical and sub-cortical systems can exert their influence on nociceptive signals at early or at later stages of neural processing. These hierarchically organized interconnected structures can thus process and adjust nociceptive signals to generate adaptive responses to pain at the motor, autonomic and behavioral level. The activity in these pathways were shown to be fine-tuned by multiple neurotransmitters such as opioids, norepinephrine, dopamine and serotonin. Although the exact processes behind pain modulation are unclear, there is sufficient data demonstrating bidirectional circuits and pathways that connect higher order regions in the cerebral cortex that process contextual sensory information received from different modalities, to sub-cortical brain structures that process memory, associations, salience, reward and value. Animal electrophysiology and neuroimaging with fMRI have mapped activity in several structures such as the anterior cingulate, orbitofrontal cortex, insula, PAG/RVM lateral prefrontal cortex as important regions for pain modulation[6,22,60].

Several studies have shown that positive expectations for pain relief result in greater benefit from analgesic medication [6]. Expectation is relatively well studied in the field of perception and as a concept, it permits deductive inquiries for understanding mechanisms of mental cueing at the psychophysical and neural level.

In experimental studies, we can quantify the extent to which expectations modify pain perception, and the change in pain reported is referred to as pain modulation. Expectations are generated in these studies by presenting cues as a context. The cues can be symbols, words or images of other people, or verbal suggestions, and are presented paired with a painful stimulus. Cues contain the prior information on the nature or intensity of the pain stimulus and are useful for building expectations towards incoming stimuli. Another technique for testing expectation induced pain modulation is to use cues for building expectations towards a treatment and quantifying pain reports after treatment with and without the expectation inducing cues. When expectations are built towards treatment, the models are called placebo analgesia models[73]. Other models build expectations directly towards pain and are called expectancy models[53,54,74].

These types of models demonstrate show that expectations can significantly modulate pain, and the expectations can be induced to be positive or negative to either reduce or enhance pain thus mimicking placebo or nocebo responses respectively. But the size of the effect is often small and quickly extinguished. A relatively stronger and longer lasting effect of expectation on pain is observed when the expectations induced by the cues are validated with physical conditioning[11,75]. For instance, in one type of model, after

giving expectancy cues and the placebo treatment, expectations are validated by applying conditioning stimuli where the pain evoking stimulus is surreptitiously reduced in intensity and the weaker stimuli are inferred as a treatment effect[14]. The conditioning stimulus is repeated to validate and reinforce the expectation. As a result of this process, when the expectation is tested, the stimulus is perceived as less painful when the stimulus intensity is increased.

Note that in most studies, expectations are produced with explicit cues, and the physical reinforcement validates the explicit verbal suggestion[14,50]. On the other hand, some types of top-down effects on pain are encoded implicitly and the associations are not explicitly declared hence the expectations are formed but may or may are not be fully consciously known by the subject[12,22,75,76]. As is observed with procedural motor memories that are encoded at the sub-cortical level and occur outside of conscious perception, prior learning of associations of pain with other objects also contributes to top-down effects on pain. For instance, rats conditioned with morphine analgesia within a specific environmental context, show reduced pain response to saline injections administered within the same but not in a different environmental context[77-79]. These learning effects may be subliminally triggered through unconsciously perceived external cues as was observed recently in a few studies done in humans[12,80]. Illustrating this effect, a recent study presented cues that created expectations of less heat evoked pain which effectively reduce perceived pain; however, these positive cues were not presented alone but instead they were juxtaposed on an object that was subliminally perceivable in the background of the explicit cue[13]. These subliminal cues were effective for reducing perceived pain independently of the explicit cue albeit the effect was less pronounced relative to the explicit cues. Whether the participants created conscious and explicit expectations towards the background cues is unclear, but this underscores a putative top-down effect on pain that is offline or unconscious.

Based on vast evidence of procedural learning we know that prior experience and explicit/implicit learning results in adoption of procedures and responses in the form of habits. This offline processing of environmental and contextual information is useful for conserving brain resources and allows for complex mental functions such as learning and multitasking. As observed with habitual behaviors, offline associations control our behavior in the background: the expectations are not explicit and are instead more similar to unconscious motivations[77,78]. Although speculative, it is plausible that top-down expectation and beliefs guide our motivations for mental cueing and will adjust our pain responses to external and internal stimuli either with or without explicit expectations. Thus, pain modulation is another demonstration that

the brain extracts situationally relevant meaning, engenders conscious or implicit expectations to predict subsequent events from cues in the surrounding and also adapts the perceived sensation to fit with the prediction and the current motivational state of the organism.

Utility of studying mental cueing and potential for adapting this knowledge for improving clinical outcomes: It is recognized that endogenous pain relief systems such as opioid circuitry contribute to placebo response and several PET and fMRI have been consistently highlighting these brain circuits through consistent and reproducible findings [73]. But the role of this circuitry in treatment outcomes needs wider acknowledgement to be clinically useful. The new conceptual models for understanding these phenomenon and new imaging and analysis techniques are quickly revolutionizing our ability to understand the underlying brain mechanisms[11,36,81]. In coming years, these efforts we will be able to use brain and behavioral data to predict the individual's capacity for mental cueing. Blue-sky research goals to deploy and enhance these intrinsic responses are quickly surging[1,19,35]. The exact mechanisms that contribute to placebo response remain to be properly mapped out, but with these advances, the mechanisms are being elucidated rapidly. An important implication of these new approaches is the possibility that the mental cueing phenomenon will no longer be seen as non-specific cryptic response relevant to clinical trials and devoid of clinical value. Instead, the brain circuits and neurotransmitter systems behind these responses are compelling us to think of the significance of physiological systems as a powerful resource for generating therapeutic responses.

Conclusion: The context of receiving a pain treatment alters pain perception and this effect is widely known because it has been systematically witnessed and the mechanisms have been linked to learning, motivational circuitry and descending pain inhibition. The placebo response is an important indicator that analgesic responses to treatment are mediated by the active ingredient in part, and endogenous systems that reduce pain participate in shaping the extent to which a treatment will be effective in reducing pain.

Taken together, I have discussed that pain being a subjective and intransitive percept is particularly subject to reconfigurations of mental states during the process of eliciting and receiving treatment. As such, prior information in the form of inferences, beliefs, memories and conditioned responses are triggered by mental cues received during treatment and have an internal or external locus. These processes can occur on receiving placebos, but more importantly, they can also effect real treatments that have active effects. Thus by adopting a less restrictive terminology and thinking of this phenomenon as a mental cueing response

that effects all types of treatments, we can shift direction towards thinking about the bodies intrinsic mechanisms that contribute to treatment outcome.

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