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Mechanisms of placebo analgesia: A dual-process model informed by insights from cross-species comparisons

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Abstract

Placebo treatments are pharmacologically inert, but are known to alleviate symptoms across a variety of clinical conditions. Associative learning and cognitive expectations both play important roles in placebo responses, however we are just beginning to understand how interactions between these processes lead to powerful effects. Here, we review the psychological principles underlying placebo effects and our current understanding of their brain bases, focusing on studies demonstrating both the importance of cognitive expectations and those that demonstrate expectancy-independent associative learning. To account for both forms of placebo analgesia, we propose a dual-process model in which flexible, contextually driven cognitive schemas and attributions guide associative learning processes that produce stable, long-term placebo effects. According to this model, the placebo-induction paradigms with the most powerful effects are those that combine reinforcement (e.g., the experience of reduced pain after placebo treatment) with suggestions and context cues that disambiguate learning by attributing perceived benefit to the placebo. Using this model as a conceptual scaffold, we review and compare neurobiological systems identified in both human studies of placebo analgesia and behavioral pain modulation in rodents. We identify substantial overlap between the circuits involved in human placebo analgesia and those that mediate multiple forms of context-based modulation of pain behavior in rodents, including forebrain-brainstem pathways and opioid and cannabinoid systems in particular. This overlap suggests that placebo effects are part of a set of adaptive mechanisms for shaping nociceptive signaling based on its information value and anticipated optimal response in a given behavioral context.

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1. Introduction

Drug treatments can reduce negative symptoms associated with a wide array of clinical disorders. However, *placebo* treatments—which have no direct pharmacological effect—can also alleviate symptoms across a wide array of disorders. These include, but are not limited to, chronic pain (Kaptchuk *et al.*, 2010; Kaptchuk *et al.*, 2008; Vase *et al.*, 2002), depression (Fields *et al.*, 1991; Franklin, 1989; Kirsch *et al.*, 2008; Leuchter *et al.*, 2014), Parkinson's disease (Benedetti *et al.*, 2016; de la Fuente-Fernández *et al.*, 2001; Lidstone *et al.*, 2010; Pollo *et al.*, 2002), and asthma (Kemeny *et al.*, 2007; Luparello *et al.*, 1968).

A growing literature focuses on the brain and psychological mechanisms underlying placebo effects (Benedetti, 2014; Buchel *et al.*, 2014; Finniss *et al.*, 2010; Geuter *et al.*, 2017b; Wager and Atlas, 2015). Placebos mitigate disease signs or symptoms by virtue of a patient's perceptions and beliefs about the treatment and its context. The mechanisms of placebo effects are likely not specific to placebos alone, and also contribute to symptom relief following standard drug treatment (Atlas *et al.*, 2012; Bingel *et al.*, 2011; Colloca *et al.*, 2004; Schenk *et al.*, 2014). Thus, standard 'open-label' drug treatment can be thought of as working in two ways: via specific drug actions, on one hand, and treatment context effects on the other. In some cases, the effect of treatment context may be as great or greater than the simple drug effect (Khan *et al.*, 2012; Kirsch and Sapirstein, 1998; Tuttle *et al.*, 2015). Placebo studies isolate those context effects, and so provide a way of studying the mechanisms of endogenous self-regulation and healing.

Understanding the psychological and brain mechanisms underlying placebo effects is thus important for understanding all kinds of treatments, and is the focus of this review. In particular, we focus here on inferring mechanisms of placebo analgesia, the best-studied area in placebo research, by comparing findings from human neuroimaging with those of invasive studies in non-human animal models. A large literature on the mechanisms of analgesia in animal models, particularly rodents, reveal much about the neural pathways and neuropharmacology of pain control that is likely conserved in humans and provides a neurobiological substrate for human placebo effects.

In this review, we first briefly explore differences between placebo and drug effects, establishing definitions and clarifying the different levels at which placebos can operate. Then, we present evidence supporting the standard "expectation model" of placebo analgesia, which focuses on patients' cognitive beliefs, as well as evidence that is incompatible with this explanation. We propose a dual-process model of placebo analgesia to account for both cognitively mediated (i.e., expectation-dependent) and cognition-independent placebo effects.

Using the dual-process model as a framework, we draw connections between psychological processes and neural mechanisms underlying placebo analgesia, focusing on both neuroanatomical and neurochemical systems. While the neurobiological systems underlying expectation-dependent placebo analgesia have been outlined across many studies (Bingel *et al.*, 2006; Eippert *et al.*, 2009a; Petrovic *et al.*, 2002; Wager *et al.*, 2004; Wager *et al.*, 2007; Zubieta *et al.*, 2005), few studies have directly examined the systems underlying

expectation-independent analgesia (Benedetti *et al.*, 2011). We will review neurobiological studies of conditioned analgesia in rodents to infer which mechanisms may underlie expectation-independent analgesia in humans. To conclude, we explore potential implications of this model, discussing how it could generalize to placebo effects outside of pain and how the processes identified in the model could impact clinical treatment outcomes.

2. Psychological principles underlying placebo effects

2.1 Placebo and drug effects

When comparing placebos and drugs, *drug effects* refer to symptom changes directly caused by pharmacological properties of a drug. Similarly, *placebo effects* describe symptom improvement caused by a placebo treatment, although the placebo itself is inert. Placebo effects are directly caused by the participant or patient undergoing a treatment procedure, and cannot be explained by regression to the mean or other statistical artifacts (Wager and Fields, 2013). By contrast, the term *placebo response*, as used in clinical trials, typically refers to overall improvement after placebo treatment, without attempting to estimate the causal effects of the treatment. Many placebo-controlled clinical studies examine drug effects, and include placebo conditions in order to estimate drug effects over and above a placebo response. However, these paradigms do not isolate placebo effects; for that, it is necessary to compare the placebo group to a natural history group that receives no treatment, to account for regression to the mean and other biases (Kirsch, 2003).

Standard clinical treatments are usually delivered ‘open-label,’ with the patient’s knowledge that they are receiving the treatment. Thus, their therapeutic benefits are caused jointly by a person’s response to the specific treatment (e.g., a drug) and their response to the act of treatment and related context effects (Bialosky *et al.*, 2011; Kemeny *et al.*, 2007; Kirsch and Sapirstein, 1998; Meissner *et al.*, 2011). Thus, symptom improvement resulting from treatment across a variety of disorders is partly attributable to placebo effects. Varying changes to the environmental context can enhance or diminish the level of symptom relief following these treatments.

As placebo effects are an inescapable part of open drug administration, they are an important component of the treatment process that can be deliberately manipulated to achieve desired effects. Rather than simply being used as a control for drug effects, placebo effects should be emphasized as useful enhancements to standard treatment regimens. For example, ethical manipulations of the context surrounding drug treatment could enhance symptom relief without explicitly giving the patients a placebo. Even when using open administration of placebos instead of drugs (Kaptchuk *et al.*, 2010), educating patients about placebos and how they work can enhance treatment efficacy when compared to non-informed patients (Kisaalita *et al.*, 2014). Understanding how and why placebo effects occur could allow clinicians and researchers to capitalize on these effects to improve patient response to treatment across a wide array of disorders and symptomologies.

2.2 The adaptive value of placebo and related context effects

The context surrounding a treatment is rich, and includes a variety of factors that can influence placebo effects. Some examples of these factors includes expectations for symptom relief (Kirsch *et al.*, 2014; Kotsis *et al.*, 2012; Price *et al.*, 1999), physician communication (Dutt-Gupta *et al.*, 2007; Kaptchuk *et al.*, 2008), hidden versus open administration of a treatment (Atlas *et al.*, 2012; Bingel *et al.*, 2011; Colloca *et al.*, 2004), and prior experience with both specific treatments (Colloca *et al.*, 2010; Schafer *et al.*, 2015; Voudouris *et al.*, 1990) and treatments as a whole (Leuchter *et al.*, 2014). Collectively, these and other contextual factors comprise the 'active' ingredients that elicit placebo effects. Any manipulation of these factors, whether purposeful or accidental, could affect therapeutic outcomes.

In order to successfully harness these contextual factors in clinical treatment, we must understand why, how, and under what conditions they operate. What are the internal mechanisms that drive placebo effects, and what is their purpose? The central nervous system, from the spinal cord and retina to the prefrontal cortex, is adapted to make accurate inferences about which behaviors are optimal in a given environment. Part of this adaptation is the use of contextual information to constrain perception, which confers potential advantages to both speed and accuracy in noisy sensory environments. For example, ganglion cells in the retina do not simply respond to stimulation; they anticipate the position of a moving stimulus (Berry *et al.*, 1999) which permits the perception of moving objects. Similar predictive behavior is observed in neuronal activation across multiple brain regions, and theories of 'predictive coding' suggest that it represents a general principle nervous system function (Barrett and Simmons, 2015; Buchel *et al.*, 2014; Friston, 2005; Geuter *et al.*, 2017a; Muckli *et al.*, 2015; Summerfield and de Lange, 2014).

Consistent with the notion of predictive coding, the behavioral response to potentially threatening stimuli can vary based on the surrounding environmental context. The threat value associated with the jagged, white outlines of a dog's teeth or an indistinct shadow lurking outside your home lies not in the percept itself, but in its projected effects. The anticipated threat of a territorial dog defending its home is markedly different from a dog getting its teeth cleaned, and a shadow is much less eerie if one is expecting company. The appropriate behavioral response in these and other cases depends on the context of an event, and each affords different responses depending on the particulars of the scenario. It is plausible then, that placebo effects are specific instantiations of adaptation processes that prepare organisms to respond to anticipated stimuli and events based on contextual cues (Buchel *et al.*, 2014; Eikelboom and Stewart, 1982).

2.3 Pain as a target system for studying placebo effects

Pain provides critical information that is used to identify appropriate behavioral responses in the environment. In most cases, pain is adaptive, as it encourages rest, helps to prevent further injury, and increases the survival rate of injured animals in life-threatening situations (Crook *et al.*, 2014). However, pain experience is not a veridical representation of tissue damage, or even a direct mapping of ascending nociceptive input to the brain (Baliki and Apkarian, 2015; Buchel *et al.*, 2014; Melzack and Katz, 2013). Rather, pain is a fluid

representation of the body that, like other adaptive responses, is shaped by anticipated outcomes based on contextual information (Geuter *et al.*, 2017a). This context can include external environmental factors (Lester and Fanselow, 1985; Walf and Frye, 2003), internal state (Foo and Mason, 2011; Onen *et al.*, 2001; Tomim *et al.*, 2015), and cognitively directed goals (Buhle *et al.*, 2012; Ford *et al.*, 2015; Sprenger *et al.*, 2012). The flexibility of the relationship between pain experience and body state means that it can be adaptively modulated up or down to provide the appropriate amount of information for an organism to balance pursuit of current motivational goals with the potential worsening of an injury (Fields, 2004, 2006).

Pain serves as a good model for studying placebo effects for several reasons. First, the neural systems that modulate and induce pain experience are well-defined (Millan, 2002; Ossipov *et al.*, 2010), and activation of these pain control mechanisms are often implicated in placebo analgesia and other forms of behaviorally induced pain relief (Butler and Finn, 2009; Eippert *et al.*, 2009a; Geuter *et al.*, 2013; Wager *et al.*, 2004). Furthermore, placebo effects on pain have been studied extensively within both healthy and clinical populations (Pollo *et al.*, 2001; Vase *et al.*, 2011; Vase *et al.*, 2002), with significant overlap between the biological systems underlying these effects. Thus, models of placebo analgesia in healthy populations are likely to apply to pain management within clinical populations. Finally, numerous studies have explored the neurobiological mechanisms underlying other forms of pain modulation in rodents, including fear-conditioned analgesia (Butler and Finn, 2009; Fanselow and Baackes, 1982), social threat (Rodgers and Hendrie, 1983; Rodgers and Randall, 1986), predator odor effects (Kavaliers *et al.*, 1997; Vendruscolo *et al.*, 2006; Walf and Frye, 2003), and distraction (Ford *et al.*, 2015). There is extensive overlap between the neurobiological mechanisms related to pain relief under these non-placebo manipulations and the systems modulated by placebo administration (De Felice *et al.*, 2011; Heinricher *et al.*, 2009; Meng *et al.*, 1998). Examining how these regions interact during induced analgesia in rodents may provide insight into how placebo effects work in humans.

2.4 Placebo effects are not simple response biases

One explanation of placebo analgesia is that it represents a reporting bias rather than true reductions in pain experience (Allan and Siegel, 2002). If placebo effects are limited to decisions about how to report pain, then they are not relevant for ‘organic’ disease, and their mechanisms cannot be harnessed in therapeutic treatments. This view has been used to argue that significant placebo effects in chronic pain are not meaningful (Hróbjartsson and Gøtzsche, 2001), and that pain patients who respond to placebo sympathetic blockade must not be experiencing genuine pain (Ochoa, 1997).

While placebo treatments are almost certain to influence decision processes, their effects are not limited to subjective reports. Placebos can influence health-relevant physiological outcomes that cannot be ascribed to decision biases, including autonomic (Geuter *et al.*, 2013; Jepma and Wager, 2015; Koban and Wager, 2016; Nakamura *et al.*, 2012), endocrine (Meissner, 2009, 2011), and immune effects (Albring *et al.*, 2014; Vits *et al.*, 2011). Placebo treatment can influence pupillary, electrodermal, and cardiovascular responses to painful events (Nakamura *et al.*, 2012), in a manner that is also influenced by subject expectations

(Geuter *et al.*, 2013). Placebo treatment reduces pain-related activity in the spinal cord (Eippert *et al.*, 2009b), while a "nocebo" treatment—where subjects believe a treatment will enhance their pain—increases pain-related spinal activity (Geuter and Buchel, 2013; Tinnermann *et al.*, 2017). Additionally, many placebo effects on pain are reversed by systemic administration of naloxone, an opioid antagonist (Amanzio and Benedetti, 1999; Eippert *et al.*, 2009a; Levine *et al.*, 1978). This indicates that at least some forms of placebo analgesia are directly mediated by the release of endogenous opioids, and thus are not reducible to changes in response bias.

2.5 Expectations as a driver of placebo analgesia

This section will first present and summarize evidence that supports the expectation model of placebo analgesia, focusing on how many manipulations used to induce placebo analgesia also enhance expectations for pain relief. Afterward, we review studies that counter this theoretical understanding and require analgesic processes that operate independent of explicit, reportable expectations for pain relief. The discrepancy between these two sets of results sets the stage for our proposed dual-process model of placebo analgesia.

Placebo analgesia is typically induced in the laboratory using two different manipulations. The first is an *expectation manipulation*, where subjects are encouraged to believe in the effectiveness of a treatment. The other is a *conditioning manipulation*, where a placebo treatment is paired with surreptitious reductions in pain intensity (Voudouris *et al.*, 1985). Some theories of placebo analgesia suggest that conditioning and expectation manipulations induce placebo analgesia via a final common pathway that critically depends on expectation for pain relief (Kirsch *et al.*, 2014; Meissner *et al.*, 2011; Stewart-Williams and Podd, 2004). This is supported by the finding that conditioning manipulations fail to induce placebo analgesia when expectations are lowered (Montgomery and Kirsch, 1997). This conceptualization will be referred to as the *expectation model* of placebo analgesia.

2.5.1 Evidence supporting the expectation model of placebo analgesia—

Expectation for pain relief following treatment is often measured by self-report, and is associated with subsequent placebo analgesia across multiple studies (de Jong *et al.*, 1996; Kirsch *et al.*, 2014; Price *et al.*, 1999; Watson *et al.*, 2006). Procedures that diminish expectations for pain relief from a placebo also reduce pain relief following treatment with that placebo (Montgomery and Kirsch, 1997; Price *et al.*, 2008). Expectation manipulations performed without a conditioning manipulation can be used to induce placebo analgesia (Geers *et al.*, 2010; Pollo *et al.*, 2001), and this is particularly effective among subjects who score higher on specific personality traits such as openness (Yu *et al.*, 2014), dispositional optimism (Geers *et al.*, 2010; Morton *et al.*, 2009) or ego resiliency and other factors related to agreeableness (Pecina *et al.*, 2013).

If expectations for pain relief are reduced, either through explicit information or the omission of instructions regarding associations with pain relief, subsequent analgesia is reduced. When using a conditioning manipulation to associate a cue with pain relief, subjects who are explicitly informed that the cues are associated with different stimulation intensities report greater cue-dependent differences in pain levels at test (Carlino *et al.*, 2015). Even when subjects are told the placebo will reduce their pain, revealing that the

intensity of the painful stimulus is reduced following placebo administration can prevent the attribution of pain relief to the placebo. In this case, subjects have lower expectations for pain relief, and fail to report reductions in pain for a placebo treatment during test (Montgomery and Kirsch, 1997; Watson *et al.*, 2006).

When combined, conditioning and expectation manipulations induce stronger analgesia as compared to expectation manipulations alone (Carlino *et al.*, 2015; Vase *et al.*, 2002). However, this combination also generates greater expectations for pain relief (Colloca *et al.*, 2008; Colloca *et al.*, 2009; Kirsch *et al.*, 2014; Klinger *et al.*, 2007; Voudouris *et al.*, 1990). While including a conditioning manipulation enhances analgesia, this effect could be fully mediated by an expectation-dependent process. Prior to conditioning, an initial pairing of a placebo with very painful stimulation reduces the magnitude of a subsequent analgesic response (Colloca and Benedetti, 2006; Kessner *et al.*, 2013). The pairing of high pain with a placebo treatment is likely to reduce expectations for pain relief, which inhibits the subsequent acquisition of a placebo response. Even after a conditioning manipulation, verbal suggestions of hyperalgesia can attenuate an analgesic response and sometimes abolish it entirely (Benedetti *et al.*, 2003; Goffaux *et al.*, 2007).

Expectations are important for modulating pain experience other ways beyond standard placebo paradigms. In one study, conditioned cues (shapes) were paired with visual representations of stimulus intensity (pictures of thermometers) rather than actual changes in pain experience (Jepma and Wager, 2015). In this ‘symbolic conditioning’ paradigm, participants learned associations between visual cues and pain intensity without experiencing any actual physical pain—thus, in the absence of any primary reinforcement. In a later test phase, participants reported more pain at equivalent stimulation intensities for cues that were previously paired with higher symbolic representations of temperature. Furthermore, these changes in pain experience were mediated by changes in expected pain. In another example, visual cues that ostensibly signaled *other participants*’ experiences of pain were presented immediately before participants experienced painful stimuli (Koban and Wager, 2016). High- and low-pain cues were presented, but they were never systematically reinforced, meaning that equal numbers of high-pain, medium-pain, and low-pain stimuli were delivered following each cue type. Nonetheless, pain and pain-related autonomic responses were strongly influenced by the false social information. This paradigm influences pain-related brain responses as well (Yoshida *et al.*, 2013). Critically, the pain associations in both of these examples were generated via changes in expectations and did not rely on conditioned associations with physical experience, highlighting the importance of expectations in the modulation of pain. They parallel learning procedures used mainly in animal models, such as sensory preconditioning, that also suggest that the information value of cues is a critical ingredient of conditioning in animal models (Rescorla, 1988; Schoenbaum *et al.*, 2009).

In clinical populations, expectation manipulations are particularly effective at reducing pain associated with Irritable Bowel Syndrome (IBS) (Vase *et al.*, 2003). Among these patients, placebo treatment can be as effective as treatment with lidocaine, a topical analgesic, and can remain effective for extended periods of time (Vase *et al.*, 2005). Verbal reassurances that the placebo is effective at reducing pain can dramatically reduce pain intensity in IBS

(Craggs *et al.*, 2014; Price *et al.*, 2007). Furthermore, encouraging patients to believe in the effectiveness of the placebo can elicit pain relief in 'open-label' treatments where patients are informed that the treatment is chemically inert (Kam-Hansen *et al.*, 2014; Kaptchuk *et al.*, 2010).

Despite the strong association between expectations and pain relief, expectation manipulations sometimes fail to reliably induce analgesia (Colloca *et al.*, 2008; Colloca *et al.*, 2009; de Jong *et al.*, 1996; Reicherts *et al.*, 2016; Voudouris *et al.*, 1990). One potential explanation for these results is that the expectation manipulation failed to produce sufficiently strong expectations for pain relief. The increased effectiveness of expectation manipulations on optimists and individuals high on openness (Geers *et al.*, 2010; Morton *et al.*, 2009; Yu *et al.*, 2014), agreeableness (Pecina *et al.*, 2013), and suggestibility (De Pascalis *et al.*, 2001) may simply be because those subjects are predisposed towards belief in the treatment and less likely to require confirming evidence as compared to their more pessimistic counterparts. Alternatively, greater expectation-induced analgesic effects within subjects high on ego resiliency may instead reflect that expectation manipulations tend to fail in those who are more susceptible to stress, effectively blocking any placebo response from being induced by the manipulation (Pecina *et al.*, 2013). Either of these cases may explain the increased difficulty in reliably inducing placebo analgesia in healthy populations without a conditioning manipulation, as the effectiveness of an expectation manipulation alone may partially depend on the specific distribution of personality traits within a given sample.

2.5.2 Expectation-independent processes in placebo analgesia—While conditioning procedures enhance both expectations and subsequent pain relief, placebo effects induced via conditioning do not always act via expectation-mediated processes. Informing subjects that the intensity of a painful stimulus is reduced during placebo conditioning trials prevents acquisition of a placebo response (Montgomery and Kirsch, 1997), however this effect is weakened if conditioning and testing sessions are performed on different days. Under these procedures, placebo analgesia induced by standard expectation and conditioning manipulations in one group was not significantly different from a second group who were informed about the temperature manipulation during conditioning (de Jong *et al.*, 1996). This finding suggests that when conditioning occurs across multiple days, memory consolidation processes may make placebo effects expectation-independent.

When subjects complete a single session of conditioning, the subsequent analgesia is correlated with expectations and can be attenuated or abolished by reducing expectations for pain relief (Benedetti *et al.*, 2003; Schafer *et al.*, 2015). However, this manipulation fails to abolish placebo analgesia if subjects have participated in multiple conditioning sessions. Increasing the number of conditioning sessions can lead to stronger analgesia without enhancing expectations (Colloca *et al.*, 2010; Schafer *et al.*, 2015). Furthermore, in one recent study (Schafer *et al.*, 2015), subjects who completed four sessions of conditioning across multiple days continued to experience placebo analgesia after a subsequent reversal of expectations, despite a nearly complete lack of expectations for analgesia after the reversal. This provides evidence that placebo analgesia is not always dependent on reportable beliefs and expectations.

In addition to variations in the common paradigms used to induce placebo analgesia, other manipulations can also induce expectation-independent analgesic effects. Following repeated sessions of pharmacological conditioning, where pain is reduced via active medication and the drug is replaced by a placebo during the test phase, the placebo effect is fully dependent on expectations if an opiate is used, but only partially dependent when conditioned with ketorolac, a non-steroidal anti-inflammatory drug (NSAID) (Amanzio and Benedetti, 1999). Furthermore, analgesic responses can be induced without manipulating conscious expectations at all. After pairing a set of face images with either high or low pain, subliminal presentation of those faces modulates subsequent pain responses up or down accordingly (Jensen *et al.*, 2012). Even when faces are displayed subliminally during the conditioning phase, subliminal presentation of conditioned face cues at test continues to modulate pain response (Jensen *et al.*, 2015). Together, these results show that analgesia induced across a variety of different paradigms cannot be explained using the standard expectation model.

Expectation-independent analgesic effects cannot be explained by relying on a single expectation-dependent process to induce pain relief. Instead, at least two learning processes underlie placebo analgesia: one that can flexibly adjust the placebo response following changes in expectations and beliefs about the treatment, and another that influences the placebo response based on evidence slowly accumulated over multiple pairings of the treatment context with pain relief. Together, these processes can explain and account for discrepancies in placebo effects reported in the literature. The following section will explore this dual-process model of placebo analgesia, using it to explain findings that cannot be interpreted within the standard expectation model of placebo analgesia.

3. A dual-process model of placebo analgesia

In our proposed dual-process model of placebo analgesia, the response to contextual information is acquired through two different process categories (Table 1). These categories are analogous to the two systems described in psychological theories of reasoning (termed ‘System 1’ and ‘System 2’) that are used to capture differences in the way we reason, learn, and respond to stimuli in our environment (Kahneman and Frederick, 2002; Stanovich and West, 2000). In general, ‘System 1’ processes are more automatic and ingrained, requiring little to no conscious effort to activate. In contrast, ‘System 2’ includes reasoning and decision making processes that rely on conscious awareness and effortful cognition. These two reasoning processes operate simultaneously to enable one to navigate through the environment. Note that these systems parallel ideas from reinforcement learning theory, which distinguishes between model-free and model-based learning (Dayan and Berridge, 2014).

The dual-process model of placebo analgesia is comprised of a dynamic and an accumulative process. The *dynamic process* is comparable to ‘System 2’ reasoning processes and its function is largely analogous to the expectation model of placebo analgesia. This process acts by generating a mental schema within which to understand the surrounding context. In this instance, a schema is a mental pattern used to represent the situation as a whole that can be used to guide behavioral outcomes (DiMaggio, 1997; Wager

and Atlas, 2015). This schema is flexible and can be rapidly changed after learning new information, which in turn affects the intensity of the placebo effect. The *accumulative process* relates to the 'System 1' form of reasoning and involves the slow accumulative of information over time to form pre-cognitive associations that do not require conscious thought to activate. Within this process, specific contextual elements are associated with experienced outcomes—e.g., via conditioning procedures—which after learning trigger adaptive associative responses. For example, changes in pain experience can be initially paired with visual cues. Afterward, subliminal presentation of those cues can increase or decrease pain experience without influencing conscious awareness (Jensen *et al.*, 2015; Jensen *et al.*, 2012). Placebo effects that arise from an accumulative learning process are not dependent upon reportable beliefs and expectations, but rather on the strength of conditioned associations.

Under the dynamic learning process, new information is evaluated purposefully and rapidly, leading to placebo effects that can be reversed with new information. This form of learning has the advantage of being able to encode a single experience into a mental schema, and use that schema to extrapolate to non-experienced potential outcomes. This form of learning is amodal, in that information acquired in one sensory modality (e.g. verbal suggestions of pain relief absent painful stimulation) can directly influence response in another (e.g. pain response). This is in contrast to a conditioning procedure where a treatment context must be first paired with changes in pain before subsequent presentations of that context can induce pain relief.

Many manipulations used to induce placebo analgesia focus on enhancing expectations for pain relief, and thus rely primarily on this dynamic learning process to induce effects. Both expectation and conditioning manipulations can be used to strengthen a mental schema of pain relief, and the subsequent analgesia is generally correlated with reported expectations for pain relief regardless of the manipulation used (de Jong *et al.*, 1996; Jepma and Wager, 2015; Koban and Wager, 2016; Montgomery and Kirsch, 1997). Verbal and other manipulations of expectations (e.g. physician cues, professional environment) can enhance the 'pain relief schema' associated with the placebo and lead to greater placebo effects. Similarly, experience with a placebo treatment reducing pain during a conditioning manipulation can reinforce the expectation that a treatment will elicit pain relief. A recent study demonstrated the importance of mental schemas in relationship to placebo treatments. Locher *et al.* (2017) tested two groups with open-label placebos. Both groups were told that they received a placebo, but the second group was also told that the placebo could still reduce their pain via endogenous mechanisms. Interestingly, placebo analgesia was only evident in the second group, highlighting the role of activated mental schemas.

The effect of personality on verbal induction of placebo analgesia can also be understood within the dual-process model. Optimistic and open individuals may simply be more inclined to believe assurances that a treatment will reduce their pain, and consequently are more likely to generate a mental schema where a placebo leads to pain relief (Geers *et al.*, 2010; Morton *et al.*, 2009; Yu *et al.*, 2014). In contrast, more pessimistic individuals may require evidence that the treatment works before they will create a similar schema (Pecina *et*

al., 2013; Watson *et al.*, 2006). However, the dynamic process alone cannot account for instances when placebo analgesia occurs in the absence of participant expectations.

Under an accumulative learning process, associations between contextual elements in the environment, subsequent actions, and expected outcomes are learned slowly over time. As the association between the placebo and pain relief becomes stronger, preparatory responses become more 'stamped in' and are less flexible compared to responses dependent on mental schemas. Furthermore, the accumulative responses are specific to a given treatment context, and may not generalize to novel treatments. However, placebo responses learned this way have the benefit of creating a rapid response to a treatment cue without the need for explicit cognitive control, and this response can occur much more rapidly than the more flexible responses governed by mental schemas (Kahneman and Frederick, 2002).

The combination of these two processes can be used to explain inconsistencies among the results of various placebo studies. Verbal manipulations of expectations induce placebo effects via a dynamic process without engaging the slower accumulative learning process. In contrast, conditioning procedures that pair a placebo with experienced pain relief induce placebo effects via both dynamic and accumulative learning processes by simultaneously enhancing expectations and creating a low-level association between the placebo and pain relief. Furthermore, the separate action of the accumulative process explains why conditioning over longer periods of time can lead to stronger placebo effects without measurable increases in expected analgesia that are only reduced, rather than eliminated, by a reversal of expectations (Colloca *et al.*, 2010; Schafer *et al.*, 2015).

The function of these two processes on placebo analgesia is at least partially additive, as it is possible to separate the effects of these processes via experimental manipulation. For example, following two sessions of conditioning with a NSAID, subjects report analgesia in response to a placebo administered within the same context. This occurs even when subjects are told that the placebo is not an analgesic but is instead an antibiotic with no effect on pain (Amanzio and Benedetti, 1999). This placebo response is reduced, though still significant, compared to the response of subjects who believe the placebo to be an active analgesic, consistent with additive effects of dynamic and accumulative responses.

In another study, subjects experienced either one or four sessions of conditioning, and placebo analgesia was assessed both before and after they were made aware that the placebo did not possess any pharmacologically active ingredients. After this information was revealed, reported expectations for pain relief were no different between the two conditioning groups. However, only those subjects who had received multiple sessions of conditioning continued to experience pain relief despite being aware that the treatment was an inert placebo (Schafer *et al.*, 2015). As in the pharmacological conditioning study, analgesia within this group was diminished following the reversal of expectations, but remained significant. The subjects in this "long" conditioning group were the only ones who gained sufficient experience with the treatment context to engage the accumulative process to induce placebo analgesia, and thus were the only group to continue to report pain relief following a reversal of expectations.

Both of these cases demonstrate placebo effects that are partially dependent on both expectations and previous experiences. This demonstrates the behavioral separability and additive effects of dynamic and accumulative processes on placebo analgesia. However, the extent to which these processes are subsumed by different neural mechanisms is unknown. Both processes likely influence analgesia by attenuating ascending pain signals at the level of the spinal cord (Basbaum and Fields, 1984; Goffaux *et al.*, 2007; Hohmann and Suplita, 2006; Lichtman and Fanselow, 1991; Matre *et al.*, 2006), but it is unclear at which level these processes diverge. The following section will aim to address this by reviewing how neuroanatomical and neurochemical systems involved in endogenous pain control could separately influence placebo analgesia mediated by these different processes.

4. Neurobiological Mechanisms of Placebo Analgesia

While behavioral manipulations can reveal how dynamic and accumulative processes can separately contribute to placebo analgesia, it is unknown how these processes separately map onto neurobiological systems. The brain is well suited to make predictions and adapt to changes in the environment using both accumulative and dynamic processes (Buchel *et al.*, 2014; Friston, 2005), and placebo effects represent one aspect of this adaptability. Though a number of studies and reviews have clarified the neurobiological systems involved in placebo analgesia (Benedetti and Amanzio, 2013; Geuter *et al.*, 2017b; Wager and Atlas, 2015; Wager and Fields, 2013), it is unclear which mechanisms, if any, are specific to dynamic or accumulative processes, and which are shared between the two.

Although previous work has found that accumulative and dynamic processes can be partially separated at a behavioral and pharmacological level (Amanzio and Benedetti, 1999; de Jong *et al.*, 1996; Schafer *et al.*, 2015), to date no neuroimaging study has been performed that can assess the similarities and differences in the neural mechanisms that underlie placebo analgesia learned through these different processes. To address this gap, we first review different neuroanatomical and neurochemical systems involved in endogenous pain control. We then examine how activity within these systems changes during placebo analgesia in humans. To assess how separate neurobiological mechanisms may govern the dynamic and accumulative processes involved in pain control, we compare systems activated during placebo analgesia in humans to those involved in studies of conditioned pain relief in rodents. Using this comparison, we infer distinctions between neural systems that elicit either dynamic or accumulative placebo analgesia, and generate a full dual-process model that explains placebo effects at both a neurobiological and psychological level.

4.1 The architecture of pain control

Modulation of nociceptive signals occurs at multiple stages along pain processing pathways. For example, pain modulation can be achieved by a reduction of receptor potentials in the periphery (Janson and Stein, 2003; Labuz *et al.*, 2007; Obara *et al.*, 2004; Richardson *et al.*, 1998), within the spinal cord (Eippert *et al.*, 2009b; Goffaux *et al.*, 2007; Matre *et al.*, 2006; Sprenger *et al.*, 2012), or in cortical regions that evaluate the meaning and context surrounding nociceptive signals (Krummenacher *et al.*, 2010). Today, several descending pain-modulating networks have been identified. These networks involve multiple pathways

and neurochemical systems, including opioids, cannabinoids, serotonin, dopamine, norepinephrine, oxytocin, cholecystokinin, galanin, and NK-1 (Altier and Stewart, 1999; Millan, 2002; Ossipov *et al.*, 2010; Watkins and Mayer, 1982). Much of the work identifying these pathways has been accomplished in rodent research, but similar systems have been identified in humans (Eippert *et al.*, 2009a; Matre *et al.*, 2006; Vogt *et al.*, 1995; Yelle *et al.*, 2009; Zubieta *et al.*, 2005).

The *descending pain modulation system* includes the periaqueductal gray (PAG), rostral ventromedial medulla (RVM), and projections to the spinal cord (SC) (Basbaum and Fields, 1984; Heinricher and Fields, 2013; Heinricher *et al.*, 2009; McNally, 1999). The descending pain modulation system receives direct and indirect input from multiple cortical and subcortical brain regions, including the dorsolateral prefrontal cortex (dlPFC), ventromedial prefrontal cortex (vmPFC), rostral anterior cingulate cortex (rACC), anterior insula (aIns), amygdala, nucleus accumbens (NAc), and hypothalamus (Millan, 2002). Direct electrical stimulation of PAG elicits strong analgesia (Fardin *et al.*, 1984; Reynolds, 1969); however PAG neurons themselves do not directly synapse onto nociceptive neurons in the spinal cord. Instead, PAG neurons affect neurotransmission in the dorsal horn via projections to both the RVM and the dorsolateral pontine tegmentum (Benarroch, 2008; Moreau and Fields, 1986; Roychowdhury and Fields, 1996). The RVM constitutes a major target of PAG projections, and RVM efferents contact nociceptive neurons in laminae I, II and V of the dorsal horn where they can either inhibit or facilitate nociceptive signals (Antal *et al.*, 1996; Fields, 2004; Fields *et al.*, 1995; Finnegan *et al.*, 2004; Vanegas *et al.*, 1984).

Within the PAG, GABAergic interneurons synapse onto output neurons that project to other neuroanatomical structures (Park *et al.*, 2010). Opioids and cannabinoids inhibit these GABAergic interneurons (Chieng and Christie, 1994; Chiou and Huang, 1999; Vaughan and Christie, 1997), resulting in a net activation of the PAG output neurons via disinhibition (Drew *et al.*, 2009; Park *et al.*, 2010). Injection of opioids or μ-opioid agonists into PAG induces analgesia (Lewis and Gebhart, 1977; Sharpe *et al.*, 1974) (Table 2), whereas opioid-antagonists in the PAG can attenuate the analgesic effects of systemic morphine (Heinricher and Fields, 2013). In addition to opioidergic actions in the PAG, the cannabinoidergic CB-1 receptor is densely expressed in the PAG (Tsou *et al.*, 1998) and CB-1 activation within the dorsolateral PAG also elicits analgesia (Martin *et al.*, 1999; Walker *et al.*, 1999) (Table 3).

There is some evidence that anatomical regions involved in opioid and cannabinoid dependent analgesia in the PAG may be partially distinct. For example, electrical stimulation of dorsal PAG elicits strong analgesia which can be attenuated by cannabinoid antagonists, whereas ventral PAG stimulation elicits opioid-dependent analgesia (Cannon et al., 1982; Walker et al., 1999). There is a large proportion of opioid-sensitive GABAergic interneurons in the ventrolateral PAG (Chiou and Huang, 1999; Park *et al.*, 2010), and injection of morphine into ventral PAG is more effective at eliciting analgesia than injections into dorsal PAG (Sharpe *et al.*, 1974). This spatial distinction can also be found in studies of conditioned analgesia in rodents, where analgesia can be attenuated by injections of cannabinoid antagonists in dorsolateral PAG (Hohmann *et al.*, 2005; Olango *et al.*, 2012) or opioid antagonists in ventrolateral PAG (Helmstetter and Landeira-Fernandez, 1990).

Projections from the PAG activate descending neurons governing pain response in the RVM (Behbehani and Fields, 1979; Drew *et al.*, 2009; Lau and Vaughan, 2014; Morgan *et al.*, 2008). Within the RVM, 'OFF' cells pause in firing immediately following a painful stimulus, and activation of these cells inhibits ascending pain signals at the dorsal spinal cord (Fields, 2004; Fields *et al.*, 1995). As in the PAG, projection neurons in the RVM are modulated by both cannabinoid and opioid release through similar disinhibition processes (Drew *et al.*, 2009; Katona *et al.*, 2001; Lau and Vaughan, 2014; Millan, 2002; Pan *et al.*, 1990; Vaughan *et al.*, 2000). Injections of cannabinoid (Martin *et al.*, 1999; Martin *et al.*, 1998; Meng and Johansen, 2004; Meng *et al.*, 1998) or opioid (Heinricher *et al.*, 1994) agonists into the RVM is sufficient to induce analgesia. In addition to generating analgesia, inactivating the RVM through either lesions or reversible chemical processes can prevent various forms of analgesia. These include systemic administration of either morphine (Azami *et al.*, 1982; Young *et al.*, 1984) or cannabinoid (Meng *et al.*, 1998) agonists, microinjections of morphine into the PAG (Young *et al.*, 1984), and microinjections of opioid agonists into the amygdala (Helmstetter *et al.*, 1998). These studies demonstrate that RVM function is central to descending pain control, and is a common point of integration for antinociceptive pathways in an opioid- and cannabinoid-dependent manner.

Placebo analgesia has been associated with the action of endogenous opioids and cannabinoids (Amanzio and Benedetti, 1999; Benedetti *et al.*, 2011; Eippert *et al.*, 2009a; Levine *et al.*, 1978), and both neurochemical systems play a large role on pain modulation within the PAG-RVM-SC system (Basbaum and Fields, 1984; Drew *et al.*, 2009; Hohmann and Suplita, 2006; Park *et al.*, 2010). Moreover, placebo effects have been associated with changes in both the primary descending pain control network and a variety of higher-order input systems. The next few sections will review how these systems are activated during placebo treatment, before exploring the function of these systems during conditioned analgesia in rodents.

4.2. Neuroanatomical systems underlying placebo analgesia

Human neuroimaging studies have identified placebo induced activations and deactivations within the PAG-RVM-SC system (Eippert *et al.*, 2009a; Eippert *et al.*, 2009b; Wager *et al.*, 2004) as well as in cortical input areas to this pain modulatory network. Many forebrain regions show increased activity during placebo analgesia and are thought to inhibit pain processing. These regions include dlPFC (Eippert *et al.*, 2009a; Lui *et al.*, 2010), rACC (Bingel *et al.*, 2006; Eippert *et al.*, 2009a; Kong *et al.*, 2006; Petrovic *et al.*, 2002; Wager *et al.*, 2004), vmPFC (Petrovic *et al.*, 2002), medial orbitofrontal cortex (mOFC), and NAc (Lee *et al.*, 2012). In contrast, activity within regions that are activated during painful stimulation is reduced following placebo treatment (Bingel *et al.*, 2006). These regions include aIns (Eippert *et al.*, 2009a; Lee *et al.*, 2012; Lu *et al.*, 2010; Wager *et al.*, 2004), thalamus (Elsenbruch *et al.*, 2012; Wager *et al.*, 2004), dorsal anterior cingulate cortex (dACC) (Eippert *et al.*, 2009a; Lee *et al.*, 2012; Lu *et al.*, 2010; Wager *et al.*, 2004), amygdala (Eippert *et al.*, 2009a), and somatosensory cortex (Lu *et al.*, 2010) (Figure 1A).

Reductions in pain following placebo treatment are often correlated with changes in brain activation within pain-responsive regions. Greater pain relief is associated with reduction in

pain-related activity within insular cortex, thalamus, dACC, and somatosensotry cortex (Geuter *et al.*, 2013; Lu *et al.*, 2010; Wager *et al.*, 2004). Similarly, stronger pain relief is associated with greater increases in activity within rACC (Bingel *et al.*, 2006; Ellingsen *et al.*, 2013; Geuter *et al.*, 2013; Kong *et al.*, 2006), vmPFC (Kong *et al.*, 2006; Wager *et al.*, 2004), and dlPFC (Geuter *et al.*, 2013; Lui *et al.*, 2010; Wager *et al.*, 2004). Activation of dlPFC in particular is required to induce placebo analgesia, as inhibition of this region via transcranial magnetic stimulation is sufficient to abolish a conditioned placebo response (Krummenacher *et al.*, 2010).

The pain-modulatory function of many of these brain regions operates via direct and indirect connections to the PAG (Millan, 2002). White matter connectivity between PAG and both rACC and dlPFC is correlated with individual variation in placebo analgesia (Stein *et al.*, 2012), and functional coupling between dlPFC and PAG predicts future placebo analgesia (Sevel *et al.*, 2015b). Furthermore, functional connectivity between the PAG and each of rACC (Bingel *et al.*, 2006; Eippert *et al.*, 2009a; Petrovic *et al.*, 2002; Valet *et al.*, 2004), dlPFC (Wager *et al.*, 2004), and vmPFC (Wager *et al.*, 2004) is enhanced during behaviorally induced analgesia, though in some cases the connectivity between dlPFC and PAG is actually reduced (Sevel *et al.*, 2015a).

In particular, rACC plays a strong modulatory role during placebo analgesia. Functional connectivity between rACC and a brainstem region containing RVM increases during placebo treatment (Petrovic *et al.*, 2002). Furthermore, greater rACC-PAG coupling predicted greater RVM activity (Eippert *et al.*, 2009a) and reduced activation of somatosensory cortex (Ellingsen *et al.*, 2013) during placebo analgesia. Rostral ACC serves as a general hub for top-down pain control, and functional coupling of rACC with other pain-responsive regions including vmPFC, amygdala, and NAc is increased following placebo treatment (Bingel *et al.*, 2006; Ellingsen *et al.*, 2013). These functional pathways are mirrored in recent work demonstrating PFC-induced analgesia can be attenuated by inactivation of NAc (Lee *et al.*, 2015).

Placebo-related changes in brain activation are often correlated with expectations, such that greater expectations for pain relief are associated with greater activation within rACC (Geuter *et al.*, 2013) and reduced activation within thalamus (Craggs *et al.*, 2014; Geuter *et al.*, 2013), insula (Geuter *et al.*, 2013; Schmid *et al.*, 2013), amygdala (Schmid *et al.*, 2013), dACC (Craggs *et al.*, 2014) and somatosensory cortex (Schmid *et al.*, 2013) during placebo treatment. These expectation-related changes are not specific to placebos alone. Greater expectation for analgesia from opioid treatment leads to diminished insula and thalamus and increased dlPFC, rACC, vmPFC activation (Bingel *et al.*, 2011). Furthermore, open vs. hidden administration of an analgesic is correlated with reduced activity in aIns, secondary somatosensory cortex (S2), thalamus, dACC, and amygdala and increased activation within dlPFC and vmPFC (Atlas *et al.*, 2012; Schenk *et al.*, 2014). Inducing expectations for hyperalgesia attenuates pain relief from these analgesics and leads to increased activation of the thalamus, dACC and aIns (Bingel *et al.*, 2011), further highlighting the importance of expectation in determining analgesic response.

The regions identified above all play a role in eliciting pain relief following placebo treatment. However, it is unclear whether the neuroanatomical systems identified here play a role in placebo analgesia in general, or whether they are specifically involved in either dynamic or accumulative processes. Each of these studies used either a verbal manipulation of expectations or a combination of an expectation manipulation with a brief conditioning manipulation to generate placebo analgesia. This form of placebo analgesia has been shown to rely strongly on expectations and is reversible by verbal information (Benedetti *et al.*, 2003; Montgomery and Kirsch, 1997). Thus, it is difficult to use these studies to dissociate between brain regions specifically involved with the different learning processes. The neurobiological mechanisms identified in these studies primarily inform about dynamic and general mechanisms underlying placebo analgesia, and do not address separable accumulative mechanisms.

4.3 Neurochemical systems underlying placebo analgesia

In humans, manipulating expectation for pain relief has a strong effect on how well placebo and drug treatments modulate pain experience (Atlas *et al.*, 2012; Bingel *et al.*, 2011; Montgomery and Kirsch, 1997; Price *et al.*, 2008), and the strength of these changes is often correlated with opioid activity in the brain (Pecina *et al.*, 2014b; Scott *et al.*, 2008). Given these results, it is plausible that the net effect of expectations on placebo analgesia is mediated at the neurobiological level by endogenous opioid release (Pecina and Zubieta, 2014; Zubieta *et al.*, 2005). It is thus reasonable to assert that when placebo analgesia is governed by mental schemas, it is also mediated by endogenous opioid release. However, it is less clear whether the release of opioids, cannabinoids, or some combination of the two generates placebo analgesia via an accumulative learning process. For example, opioid activity in ACC is correlated with error signals analogous to accumulative learning rather than to explicit expectations (Pecina *et al.*, 2014b).

While expectation-independent placebo analgesia has been shown to be mediated by endogenous cannabinoid release in specific cases (Benedetti *et al.*, 2011), it is unknown whether cannabinoid release is a simple conditioned response to the analgesics used during conditioning in this instance, or instead represents a critical mechanism of expectation-independent placebo analgesia in general.

Opioids play a major role in placebo analgesia. Placebo related changes in activation within vmPFC, dlPFC, rACC, dACC, PAG, thalamus, hypothalamus, and RVM are all reversible by the μ-opioid antagonist naloxone, as is the rACC-PAG coupling and subsequent enhancement of RVM activity following placebo treatment (Eippert *et al.*, 2009a). Changes in endogenous opioid activity are also associated with placebo analgesia. Placebo treatment elicits increased μ-opioid activity in the rACC (Petrovic *et al.*, 2002; Wager *et al.*, 2007; Zubieta *et al.*, 2005), and there is a positive correlation between dlPFC μ-opioid activity and expectations for reduced pain (Pecina *et al.*, 2014b; Zubieta *et al.*, 2005). The strength of placebo analgesia is associated with enhanced μ-opioid activity within rACC, vmPFC, insula, amygdala, NAc and PAG (Pecina *et al.*, 2013; Petrovic *et al.*, 2002; Scott *et al.*, 2008; Wager *et al.*, 2007) (Table 4). Furthermore, stronger expectations for pain relief are

associated with greater release of opioids as well as greater placebo analgesia (Scott *et al.*, 2008).

Conditioning with an opiate analgesic such as morphine induces placebo analgesia that is dependent on expectations and blocked by opioid antagonists. However, conditioning with a NSAID such as ketorolac elicits opioid-independent analgesia that is only partially mediated by expectations (Amanzio and Benedetti, 1999). When ketorolac conditioning is used, the expectation-dependent component of the analgesic response is still opioid-dependent and reversible by naloxone. However the expectation-independent component is specifically mediated by cannabinoid release and blocked by the CB-1 receptor antagonist rimonabant (Benedetti *et al.*, 2011). Given the link between expectation-independent analgesia and cannabinoid release in this case, it is possible that endogenous cannabinoid release underlies expectation-independent placebo effects identified in other paradigms (Jensen *et al.*, 2015; Jensen *et al.*, 2012; Schafer *et al.*, 2015).

Placebo analgesia is related to reductions in brain activity within regions associated with pain experience, however the connection between the release of opioids and cannabinoids to different components of placebo analgesia remains unclear. Previous studies have consistently found analgesia to be correlated with opioid release (Pecina *et al.*, 2013; Pecina and Zubieta, 2014; Wager *et al.*, 2007), however each of these studies used procedures that induce expectation-dependent placebo analgesia. While opioid release is related to expectation-mediated placebo analgesia that is rapidly learned and schema-dependent, the relationship between opioid release and expectation-independent placebo analgesia is unclear. To date, no study has systematically compared the differences in neural mechanisms underlying expectation-dependent and expectation-independent placebo analgesia. In the following section, we examine the neural mechanisms underlying context dependent analgesia within other paradigms to infer whether separate mechanisms may underlie these different types of placebo analgesia.

4.4. Neural mechanisms underlying conditioned analgesia in rodents

Neurobiological studies within rodents have explored both opioid and non-opioid mechanisms governing pain (Butler *et al.*, 2012; Helmstetter and Fanselow, 1987; Helmstetter and Landeira-Fernandez, 1990; Helmstetter *et al.*, 1998; Hohmann *et al.*, 2005; Martin *et al.*, 1998; Olango *et al.*, 2012) (Figure 1B), and demonstrated how different manipulations of context learning can elicit one or both of these modulatory processes (Lichtman and Fanselow, 1991). It is possible that differences in neurochemical mechanisms governing analgesia under different behavioral paradigms in rodents similarly explain the variation in expectation dependence within placebo analgesia. To explore this idea, we review contextual learning processes and neural structures involved in conditioned analgesia within rodents and infer how these systems may be separately activated during expectation-dependent and expectation-independent placebo analgesia.

Placebo analgesia-like responses can be conditioned in rodents using morphine (Guo *et al.*, 2011; Miller *et al.*, 1990; Valone *et al.*, 1998) and other opioid agonists (Bryant *et al.*, 2009), though conditioned analgesia effects can be inconsistent across studies (McNabb *et al.*, 2014; Nolan *et al.*, 2012). Similar to examples in humans, opiate conditioning in rodents

elicits placebo analgesia-like reductions in pain that can be reversed by opioid antagonists (Guo *et al.*, 2010; Zhang *et al.*, 2013). Moreover, conditioning with NSAIDs (e.g., aspirin) induces opioid-independent placebo analgesia (Guo *et al.*, 2010). However, it is unknown whether this analgesia is mediated by endogenous cannabinoids as it is in humans (Benedetti *et al.*, 2011).

Stress-induced analgesia (SIA) refers to analgesia expressed following a stressful experience. As a paradigm, SIA experiments in rodents are far more numerous when compared to the pharmacologically conditioned analgesia studies described above, and the neurobiological mechanisms needed to induce these analgesic responses are better identified. Various stressors can be used to induce SIA, including restraint stress, swim stress, conditioned fear, and mild shock (Butler and Finn, 2009). Among these varied manipulations, conditioned fear is unique in that, rather than testing pain response immediately following the offset of a painful stimulus or stressor, a threatening context previously associated with pain is used to induce analgesia. When conditioned fear is used as the stressor, the resulting analgesia is often termed fear-conditioned analgesia (FCA). A common method for inducing FCA involves first placing rats in a novel context and administering uncontrollable painful stimuli such as foot shocks. When later returned to the shock context and subjected to a novel painful stimulus (often a formalin injection), fear conditioned rats exhibit diminished recuperative pain-related behaviors (e.g. raising paw, licking paw) compared to non-conditioned controls (Hayes *et al.*, 1978; Helmstetter and Fanselow, 1987; Watkins *et al.*, 1982). This behavior is related to anticipated threat, as it can be extinguished by additional presentations of the threat context without a corresponding shock prior to testing (Fanselow, 1984).

SIA and FCA are not specific to rodents, as humans can also demonstrate analgesic responses to stress (Willer *et al.*, 1981). In an exemplary study of FCA in humans, an experimental group was conditioned to a visual CS with loud white noise plus a mental arithmetic task over several days. During the subsequent test phase, this group showed increased pain thresholds and tolerance when compared to a control group. The final tests were conducted in a different room than the conditioning, so that potential confounds due to environmental context were mitigated. In this case, the CS alone was sufficient to induce analgesia for the experimental group (Flor and Grüsser, 1999). This form of conditioned analgesia can also be evoked by auditory stimuli (Flor *et al.*, 2002) or faces (Williams and Rhudy, 2007). While the specific anatomical structures underlying FCA in humans are unknown, these effects do rely on opioidergic neurotransmission (Flor *et al.*, 2002; Willer *et al.*, 1981).

Within rodents, FCA is mediated by both opioid (Table 5) and cannabinoid (Table 6) release, as it can be attenuated by central injections of either opioid (Butler *et al.*, 2008; Fanselow *et al.*, 1989; Helmstetter and Fanselow, 1987) or cannabinoid (Finn *et al.*, 2004) antagonists. However, enhancement of standard FCA by cannabinoid agonists (Butler *et al.*, 2012) is completely blocked by injection of an opioid antagonist (Butler *et al.*, 2008), implying that opioid activity can “gate” cannabinoid-mediated analgesia. However, this gating effect may specifically apply to changes in FCA behavior, as injection of an opioid antagonist fails to reduce analgesia following treatment with a cannabinoid agonist (Meng *et al.*, 1998).

The neural structures most commonly investigated within FCA are the amygdala, PAG and RVM (Helmstetter and Tershner, 1994; Helmstetter *et al.*, 1998). The amygdala coordinates behavioral responses to painful stimuli (Herry *et al.*, 2007), and projections from amygdala to PAG are directly involved in descending pain control (Davis, 1994; Helmstetter *et al.*, 1998; Hopkins and Holstege, 1978; Oka *et al.*, 2008). Like many prefrontal regions involved in pain modulation, opioid release in the amygdala is associated with pain relief (Finnegan *et al.*, 2005; Helmstetter *et al.*, 1998). In contrast to these cortical regions, however, the amygdala can also induce pain relief in a cannabinoid dependent manner. Direct injections of CB-1 agonists into cingulate cortex fail to elicit analgesic responses, while microinjections of cannabinoid agonists into the amygdala induce analgesia (Martin *et al.*, 1999). There is a large concentration of cannabinoid receptors within basolateral amygdala (BLA), and activation of these receptors presynaptically modulates GABAergic neurons that may be involved in descending pain control (Katona *et al.*, 2001).

Amygdala activation is required for inducing fear conditioned analgesia in rodents (Helmstetter, 1992; Helmstetter and Bellgowan, 1993) in an opioid (Butler *et al.*, 2008) and cannabinoid (Connell *et al.*, 2006) dependent manner. Specifically, FCA is mediated by increased cannabinoid activity (Rea *et al.*, 2013) and decreased concentration of GABA (Rea *et al.*, 2009) within BLA, consistent with both the high concentration of CB-1 receptors (Katona *et al.*, 2001) and the inhibition of GABAergic neurons by cannabinoids. However, other researchers have reported that cannabinoid antagonists within BLA have no effect on FCA per se, but rather work in the short term to briefly attenuate expression of pain independent of fear conditioning (Roche *et al.*, 2007). While the specific role of endogenous cannabinoids within the amygdala in FCA is unclear, the amygdala is an important hub for generating FCA (Helmstetter, 1992; Helmstetter and Bellgowan, 1993) and relays signals to the PAG that serve to initiate descending pain control mechanisms (Finnegan *et al.*, 2005; Millan, 2002).

Within the brainstem, lesions of the RVM, dorsolateral PAG (dlPAG) or ventral/ventrolateral PAG (vPAG) can reduce FCA (Helmstetter and Tershner, 1994; Kinscheck *et al.*, 1984; Watkins *et al.*, 1983). Though all of these structures play a role in FCA, the neurochemical systems involved vary by region. Within the dlPAG, a pain modulatory response depends on endogenous cannabinoid, but not opioid, activity. FCA is unaffected by application of an opioid antagonist within dlPAG (Bellgowan and Helmstetter, 1998), but is attenuated by cannabinoid antagonists within the same region (Olango *et al.*, 2012). Cannabinoid function within dlPAG is important within other pain modalities as well, as SIA induced from foot shocks is attenuated by cannabinoid antagonists and enhanced by cannabinoid agonists in dlPAG (Hohmann *et al.*, 2005).

This dissociation between cannabinoid and opioid dependence is not as distinct within vPAG and RVM, however. Analgesia is influenced by opioid activity within these regions, as injection of opioid antagonists into either vPAG (Bellgowan and Helmstetter, 1998; Helmstetter and Landeira-Fernandez, 1990) or RVM (Foo and Helmstetter, 1999) attenuate FCA. The effect of cannabinoids within these regions is less clear, as no study has examined how local inhibition of cannabinoid function within vPAG or RVM affects FCA. However, cannabinoids in these regions do have an effect on endogenous pain modulation. Local

injection of a cannabinoid agonist into RVM induces pain relief (Martin *et al.*, 1999; Martin *et al.*, 1998; Meng and Johansen, 2004), and systemic administration of a cannabinoid antagonist reduces the expression of pain-related genes in the RVM during FCA (Olango *et al.*, 2014). Similarly, injections of cannabinoid agonists into vPAG enhances footshock-induced SIA (Hohmann *et al.*, 2005), while intra-vPAG injections of cannabinoid antagonists attenuate restraint-induced SIA (Lee *et al.*, 2016).

The neurochemical systems underlying FCA are not static, and can change with different behavioral manipulations. When animals are conditioned to a single extra session following criterion for fear conditioning, FCA can be blocked by naloxone and is thus opioid-dependent. However, if animals experience multiple conditioning sessions following criterion, FCA is no longer opioid-mediated and is not attenuated by naloxone administration (Lichtman and Fanselow, 1991). This has direct parallels to the shift of placebo analgesia from an expectation-dependent to expectation-independent state following multiple conditioning sessions (Schafer *et al.*, 2015).

In summary, FCA is mediated by opioid and cannabinoid activity within the amygdala, RVM, and PAG. Expectation-dependent placebo analgesia has been shown to be dependent on opioid release in many cases, and conditioning with non-opioid analgesics induces expectation-independent analgesia that is mediated by cannabinoid release. However, these rodent studies demonstrate that with extended training, a conditioned analgesic response shifts from an opioid to a non-opioid system. It is possible, therefore, that when subjects in a placebo conditioning paradigm experience multiple conditioning sessions, the resultant placebo analgesia shifts from a largely opioid-mediated process that flexibly depends on expectations to incorporate a greater proportion of non-opioid elements via a slower accumulative process that function independent of expectations. Furthermore, given the importance of cannabinoid release in FCA (Butler *et al.*, 2012; Olango *et al.*, 2012) and previous associations of cannabinoid activity with some forms of expectation independent placebo analgesia (Benedetti *et al.*, 2011), it is possible that non-opioid placebo analgesia following multiple conditioning sessions may specifically be mediated by cannabinoid release.

5. A dual process model of placebo analgesia

Placebo effects can be conceptualized as a learned adaptive response to contextual cues that prepares an organism to appropriately respond to external events. We argue that placebo analgesia is best understood as arising from two learning processes that are instantiated within separate, but connected, neurobiological systems. The first of these learning processes supports the acquisition of a placebo response by using information about the environment to update a mental schema of the placebo context. Expectations for pain relief operationalize the strength of this schema and are correlated with the magnitude of placebo analgesia. The activation of this schema depends on activity within frontal areas (Schuck *et al.*, 2016), such as rACC and dlPFC, and culminates with inhibition of ascending pain signals in the spinal cord via disinhibition of projection neurons in PAG and RVM. This schema-dependent analgesia depends critically on the release of endogenous opioids.

The second learning system is activated by repeated pairing of a placebo with reduced pain resulting in the formation of pre-cognitive associations that can induce pain relief without relying on mental schemas (Jocham *et al.*, 2016). We hypothesize that this analgesia is independent of prefrontal control, and instead utilizes connections between the basic associative learning systems (including the amygdala) and the PAG-RVM-SC system. These pre-cognitive associations can be used to induce analgesia dependent on either opioid or cannabinoid responses.

An interesting example of crosstalk between the two processes is the mitigation of morphine-conditioned opioid release by changes in the underlying schema—for example by informing subjects that they are not receiving an analgesic (Amanzio and Benedetti, 1999). One explanation for this phenomenon could be that opioid-dependent analgesia is always influenced by dynamic learning processes—even when enhanced via accumulative learning. Alternatively, it is also possible that conditioning with morphine induces a potential un-blinding effect during test, as participants may perceive different side effects following morphine vs. saline injection. Interestingly, when placebo conditioning was done via a non-opioid drug in this study, naloxone only partially blocked placebo analgesia (Amanzio and Benedetti, 1999). This suggests that the effect of mental schemas on analgesia learned via accumulative learning processes depends on the specific neurochemical system used to attenuate pain.

During fear conditioning in rodents, a single extra conditioning session following criterion for FCA elicits opioid-mediated analgesia, whereas adding further conditioning sessions renders FCA opioid-independent (Lichtman and Fanselow, 1991). In humans, a single session of conditioning tends to elicit placebo responses that are mediated by expectations (Montgomery and Kirsch, 1997), but multiple conditioning sessions can be used to generate placebo effects that are independent of expectations (Schafer *et al.*, 2015). Given a) the involvement of cannabinoids in conditioned analgesia within rodents (Connell *et al.*, 2006; Finn *et al.*, 2004) and b) the importance of cannabinoids in conditioned expectation-independent analgesia within humans (Benedetti *et al.*, 2011), it is reasonable to hypothesize that expectation-independent placebo analgesia is generally mediated by cannabinoid release. We would thus predict that placebo analgesia conditioned on masked, subliminal cues (Jensen *et al.*, 2012) depends on the release of endogenous cannabinoids, rather than opioids.

The circumstances under which analgesia is mediated by opioidergic and cannabinoidergic mechanisms suggest the following explanatory hypotheses of conditioned analgesia: When conditioned analgesia is mediated by schema-dependent processes, it incorporates activity within a wide array of brain regions, including both cognitive and associative forebrain areas such as dlPFC, rACC, and NAc. Activation within these regions then activates descending pain control mechanisms within the PAG and RVM in an opioidergic manner (Figure 2). In contrast, when conditioned analgesia is independent of expectations, analgesia is mediated by a conditioned release of endogenous cannabinoids and relies on an intact pathway from amygdala to PAG and RVM to activate descending pain control.

5.1 Relationship between learning processes and modulatory mechanisms

Placebo effects are generated via changes within endogenous modulatory mechanisms. Critically, one can infer how learned contextual information affects those mechanisms by examining how different learning processes induce the related placebo effects. In cases where a placebo effect is independent of either dynamic or accumulative learning processes, the corresponding placebo mechanisms are *also* independent of those processes. This means that the reason placebo effects such as conditioned immunosuppression or growth hormone release are not mediated by expectations (Albring *et al.*, 2012; Benedetti *et al.*, 2003) is simply because the underlying mechanisms themselves are not affected by changes in mental schemas. The following sections will detail how the different learning processes that induce placebo analgesia can inform about the separability of the underlying neurobiological mechanisms for both placebo analgesia and endogenous pain modulation as a whole.

5.1.1. Neurochemical specificity of learning process in analgesia—As we have argued above, evidence suggests that the mechanisms associated with expectation-based and associative learning processes are partially distinct in placebo analgesia. However, this need not be the case across all classes of placebo effects, or all forms of pain modulation. For example, while placebo analgesia can be induced via both conditioning and expectation manipulations, conditioning does not seem induce appreciably greater hyperalgesia over and above manipulations of expectations (Colloca *et al.*, 2008). This suggests that the neurobiological processes leading to hyperalgesia depend on mental schemas and may not be as affected by slowly learned pre-cognitive associations.

One explanation for this effect could be that the potential cost of an action determines the balance between these two processes. For example, there is a high cost to missing cues that predict enhanced pain, as such errors could result in significant injury or even death. In this case, a flexible learning system that can rapidly adapt to changes in the surrounding context is given preference over a slower accumulative process in order to minimize future harm experienced. This does not mean that associative processes cannot pair associations between cues and enhanced pain (Jensen *et al.*, 2015), merely that these changes are more susceptible to changes in a mental schema as compared to conditioned analgesic associations.

The dual-process model hypothesizes that expectation-independent placebo analgesia is induced via pre-cognitive associations learned over time, and is mediated by the release of endogenous cannabinoids. The use of multiple conditioning sessions to shift placebo analgesia from an expectation and opioid dependent form to a partially expectation-independent form (Schafer *et al.*, 2015) does so by recruiting cannabinoidergic modulatory processes (Benedetti *et al.*, 2011). Studies of FCA in rats support this idea by demonstrating that multiple conditioning sessions can be used to elicit a non-opioid form of placebo analgesia, leaving open the possibility of mediation by endogenous cannabinoids (Lichtman and Fanselow, 1991).

This hypothesis raises some important questions. First, which neural regions would be involved in this cannabinoid release and how would they work to activate the descending pain control mechanisms that lead to placebo analgesia? Based on parallels drawn from FCA, the amygdala, PAG and RVM would be critical to this type of placebo analgesia

(Helmstetter and Tershner, 1994; Kinscheck *et al.*, 1984). Interestingly, a recent study in humans demonstrated that the amygdala supports non-contingent learning, in which humans associate stimuli with outcomes based on statistical patterns without being aware of those associations (Jocham *et al.*, 2016). Activating this form of learning should require a procedure where pain relief is paired with a treatment context across multiple trials.

While a pain relief schema is not necessary to express expectation-independent analgesia, it is unclear whether such a schema is necessary during acquisition. Even if the conditioned analgesia is dependent on cannabinoid release, cannabinoid function in turn may depend on endogenous opioids. Studies in rodents find that increases in FCA from cannabinoid agonists can be completely abolished using opioid antagonists (Butler *et al.*, 2008). This suggests that under certain circumstances opioid function is required to enable cannabinoid-induced analgesia, similar to a case where lack of a pain relief schema could suppress accumulative learning of an association between placebo treatment and pain relief. This view is supported by the observation that informing participants about reduced stimulation intensities during placebo conditioning prevents subsequent placebo analgesia—impairing the accumulative process while the dynamic process is set to a “no-analgesia” schema (Montgomery and Kirsch, 1997). Another study that induced placebo analgesia through a positive interpretation of the pain (Benedetti *et al.*, 2013) reported that both cannabinoidergic and opioidergic antagonists blocked parts of the placebo analgesia. This observation and the fact that the combination of both antagonists completely abolished placebo analgesia, suggests parallel and independent neurochemical mechanisms are involved in some forms of placebo analgesia.

Even when associations are learned independent of the opioid system, a pain relief schema may still be necessary to condition associations between a placebo and pain relief. For example, both NSAID conditioning and subliminal conditioning can induce expectation-independent analgesia and should primarily rely on accumulative (and largely cannabinoidergic) processes to induce analgesia. If opioid activity is needed to “gate” the accumulative response in both of these cases, it is possible that an injection of naloxone or another opioid antagonist during conditioning could impair subsequent analgesia in both of these cases. From a psychological perspective, this would imply that explicit changes in the mental schemas prior to conditioning could also inhibit learning.

5.1.2. Context effects on learning and modulatory processes engaged—A major difference between FCA and placebo analgesia is that FCA occurs in response to a negatively valenced context associated with pain, whereas placebo analgesia is induced following a positively valenced context associated with pain relief. Fear conditioned analgesia can be interpreted as an adaptive response to prepare the organism to function under a threatening circumstance. This is completely at odds with the response to a placebo. In the case of placebo analgesia, an organism associates a context with pain relief, and then experiences relief, perhaps because of threat reduction or enhancement of a positive affective state or reward expectation (Scott *et al.*, 2007).

In addition to FCA, conditioning with other forms of stress can be used to induce hyperalgesia rather than analgesia. For example, presentation of flavored water that has been

previously associated with stomach pain leads to hyperalgesia (Wiertelak *et al.*, 1994), as opposed to FCA induced by associating a novel context with footshocks (Hayes *et al.*, 1978). Hence, the direction of pain modulation is susceptible to context valence – as in the differences between FCA and placebo analgesia – and also differences among the particular contexts paired with a given stimulus. Within placebo analgesia, disconfirming information that suggests a placebo does not induce pain relief, for example by initially pairing a placebo with high pain, prevents acquisition of an analgesia response (Colloca and Benedetti, 2006).

The exact reasons for why positively and negatively valenced contexts can lead to either analgesia or hyperalgesia remains an open question. One explanation may involve associations with the contexts themselves. For example, placebo effects are typically induced in comforting, familiar settings where subjects have at least some knowledge about what they are participating in, whereas FCA in rodents is induced within completely novel environments associated with uncertainty. A recent study in humans reported that uncertainty about the upcoming stimulus also enhances pain (Yoshida *et al.*, 2013) and this uncertainty effect can interact with stimulus intensity (Jensen and Yaksh, 1986). An important contextual difference between FCA and placebo analgesia might be uncertainty about what to expect in this environment as uncertainty *per se* is aversive and associated with anxiety behavior as well as amygdala activation (Herry *et al.*, 2007).

Another potential difference between these two paradigms are the actual stimuli associated with pain. Within FCA, pain is associated with a general environmental context, while in placebo analgesia, pain relief is associated with a specific treatment ritual (pill, injection, etc.) within an environmental context (social cues, setting, location, etc.). It is possible that this difference between conditioning the environmental context and the treatment ritual could underlie whether pain or pain relief could be used to elicit analgesia. Understanding why associations with both aversive and appetitive stimuli can be used to induce analgesic effects, and how those associations can sometimes reverse, could further enhance pain treatment outcomes in clinical settings.

5.2 Predictions of a dual-process model

One goal of the dual-process model is to account for differences in how expectation-dependent and expectation-independent placebo analgesia is formed across different paradigms. This framework was then extended to neurobiological systems to suggest how these two processes could operate in the brain. However, this model can also be used to explain individual differences in the systems underlying placebo analgesia, as well as make novel predictions about how pre-cognitive associations can be manipulated to change analgesic experience.

5.2.1. Individual differences in processes mirrored in neurochemical system—

Personality traits such as openness and optimism have been shown to affect whether placebo analgesia can be induced in subjects using verbal manipulation of expectations alone (De Pascalis *et al.*, 2002; Morton *et al.*, 2009; Pecina *et al.*, 2013). When interpreted within the dual-process framework, it is possible that “optimists” may simply have an easier time of forming, and believing in, a mental schema where the placebo elicits pain relief. Furthermore, it is possible that these differences are more accurately captured by individual

differences in opioidergic and cannabinoidergic tone within the descending pain control system (King *et al.*, 2013; Pecina *et al.*, 2013).

These two neurochemical systems may combine differently within individual subjects based on idiosyncratic experiences and personal genetics. In one study, subjects who were told that a painful stimulus would strengthen their muscles demonstrated greater pain tolerance than controls. This tolerance was attenuated by either opioid or cannabinoid antagonists (naloxone and rimonabant, respectively) and fully blocked by a combination of the two (Benedetti *et al.*, 2013). Critically, there was a strong negative correlation between the effectiveness of naloxone and rimonabant on attenuating pain tolerance, such that the stronger effect one antagonist had, the weaker effect the other had. While this suggests that these two systems may combine semi-independently to induce analgesia (Cichewicz and McCarthy, 2003; Wilson-Poe *et al.*, 2013), the individual experiences and traits that lead to the preference of one system over the other remains unclear.

Another study found that a certain genotype in humans is associated with a less active form of FAAH, an enzyme in the body that metabolizes endogenous cannabinoids (Pecina *et al.*, 2014a). Individuals with this genotype maintain higher levels of endogenous cannabinoids, and also show enhanced opioid release during placebo analgesia compared to individuals without this genotype. It is possible that these variations underlie individual differences in how placebo analgesia is induced in humans. Identifying whether personality traits, genotype, or opioidergic and cannabinoidergic tone affect different processes that in turn elicit placebo analgesia, is an important future goal and could explain why certain procedures are effective at inducing placebo effects in some individuals, but not others.

In addition to personality traits, person-by-situation interactions can explain additional variance in placebo responses (Atlas and Wager, 2012). Some people may be more susceptible to certain treatments compared to others (Geuter *et al.*, 2013; Whalley *et al.*, 2008) based on their neurochemical dispositions. Such interactions will make it harder to identify consistent placebo responders, which may be one of the reasons for the failure of so-called wash-in periods aiming at removing placebo responders from clinical trials.

5.2.2. Susceptibility of pre-cognitive associations to other conditioning manipulations—The dynamic learning process relies on the formation of a mental schema, and thus cannot generate expectation-independent analgesia. It is telling then, that all forms of expectation-independent placebo analgesia induced in the laboratory to date include some form of conditioning manipulation that could induce placebo effects via an accumulative learning process (Amanzio and Benedetti, 1999; de Jong *et al.*, 1996; Jensen *et al.*, 2012; Schafer *et al.*, 2015). Although this mixture of processes may impede the isolation and study of relevant sub-processes, we can still make some predictions about the processes involved. If this accumulative process is comparable to the process by which conditioned and unconditioned stimuli are paired in classical conditioning, it is reasonable to hypothesize that many of the properties examined in studies of associative learning would also apply to these placebo effects. Thus, the dual-process model makes the prediction that expectation-independent analgesia should be extinguishable, be subject to spontaneous recovery, and be modality specific, such that responses conditioned to one form of treatment (e.g. oral

ingestion of a placebo) fail to generalize to another (e.g. intravenous injection) (Delamater and Westbrook, 2014; Maren *et al.*, 2013).

Following acquisition, there are several possibilities for how subsequent presentations of the placebo could affect extinction of the placebo response. For example, if pain relief is always experienced after placebo treatment, the placebo effect could be self-reinforcing as the association between the placebo and reduced pain is never broken (Vase *et al.*, 2005; Watson *et al.*, 2006). In the case of partial reinforcement, where the placebo mitigates but does not consistently reduce pain, repeated presentations lead to a slower extinction of placebo response than full reinforcement during acquisition (Au Yeung *et al.*, 2014). Even if cases where placebos are fully self-reinforcing, however, placebo responses should still be extinguishable by surreptitious *increases* of pain intensity following placebo treatment.

While the accumulative and dynamic processes can separately induce analgesic responses, these two processes may interact when forming associative pairs. In this case, the time course for extinction of a placebo response would be influenced by subject expectations, such that lower expectations for pain relief would lead to more rapid extinction and vice versa. This would be consistent with models of conditioning where pairings are not simply low-level associations but instead incorporate value judgments and motivational state (Fanselow, 1984; Gallistel *et al.*, 2004; Rescorla and Wagner, 1972). An activated schema could suppress prediction errors, which would otherwise drive the extinction as suggested by a recent study (Schenk *et al.*, 2017).

5.3. Caveats to the dual-process model

There are several caveats and particulars about the dual-process model that must be clearly enumerated before concluding. It is important to note that PAG, RVM, and associated structures are not the only systems involved in contextual changes in pain experience. Rather, the purpose of this review is to clarify how the PAG, RVM, and related systems elicit context-dependent analgesia. Separate pathways for pain modulation that do not involve opioids, cannabinoids, PAG or RVM exist and these systems may also play a role in placebo and other forms of conditioned analgesia (Maire *et al.*, 2016; Wager *et al.*, 2011).

While the dual-process model predicts that schema-dependent analgesia is independent of cannabinoid release, that does not imply that this analgesia always depends on opioid function. For example, expectation-mediated analgesia in IBS is not always mediated by opioids (Vase *et al.*, 2005), from which we can infer that the effect of mental schemas on pain experience cannot be purely governed by opioid function. While this review has focused primarily on the function of opioids and cannabinoids, other systems exist that can be used to modulate pain (e.g., dopaminergic and serotonergic systems), and these systems may underlie analgesia described in the study by Vase and colleagues (2005).

Some readers may note that the hippocampus, a critical neuroanatomical structure in the formation and retrieval of memories, has been excluded from discussion of learned placebo responses. The hippocampus plays a major role in regulating context dependent effects in a wide variety of situations (Maren *et al.*, 2013). However, this review is primarily focused on how placebo effects induce analgesia so discussion of the importance of the hippocampus to

context representation has been omitted. Several studies have found that hippocampus is needed to induce fear conditioned analgesia (Ford *et al.*, 2011), and other conditioned associations (Kim and Fanselow, 1992; Selden *et al.*, 1991), as well as nocebo hyperalgesia (Bingel *et al.*, 2011; Dickenson *et al.*, 1979; Kong *et al.*, 2008; cf. Tinnermann *et al.*, 2017). Thus, context associations mediated by hippocampal activation may also play a critical role in both associative and schema-dependent placebo effects, though it is not specific to conditioned analgesia in particular and instead plays a more general role in facilitating associative pairings.

6. Summary

The ubiquity of placebo effects across multiple illnesses and disorders represents an opportunity to enhance the effectiveness of drug treatments through relatively simple psychological manipulations with little to no adverse side effects. Placebo effects occur across such a wide variety of disorders and paradigms that the existence of separate and specific processes for each instance seems unlikely. Understanding how underlying neurobiological mechanisms and psychological processes induce placebo effects, and why some people respond to placebos and other do not, can help clinicians capitalize on these effects to enhance symptom relief from prescribed treatments without incurring additional costs and side effects.

Abbreviations

ACC	anterior cingulate cortex
aIns	anterior insula
Amy	amygdala
BLA	basolateral amygdala
CeA	central amygdala
dACC	dorsal anterior cingulate cortex
dlPAG	dorsolateral periaqueductal gray
dlPFC	dorsolateral prefrontal cortex
DRN	dorsal raphe nucelus
FCA	fear-conditioned analgesia
Hy	hypothalamus
IBS	Irritable Bowel Syndrome
IL	infralimbic cortex
mOFC	medial orbitofrontal cortex
NAc	nucleus accumbens

NRM	nucleus raphe magnus
NSAID	non-steroidal anti-inflammatory drug
PAG	periaqueductal gray
PFC	prefrontal cortex
PL	prelimbic cortex
rACC	rostral anterior cingulate cortex
RVM	rostral ventromedial medulla
S2	secondary somatosensory cortex
SC	spinal cord
SIA	stress-induced analgesia
Thal	thalamus
vHipp	ventral hippocampus
vlPAG	ventrolateral periaqueductal gray
vPAG	ventral periaqueductal gray
vmPFC	ventromedial prefrontal cortex
VTA	ventral tegmental area.

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Highlights

- We propose a dual-process model of placebo analgesia, in which strong placebo responses are created by appropriate flexible conceptual beliefs, reinforced by affective experiences (reward and punishment).
- Cognitive schemas, mental representations of the self in context, are critical for many forms of placebo analgesia.
- An extensive review of animal studies on behavioral analgesia is used to inform a neural systems implementation of the model
- The model predicts that opioidergic neurotransmission underlies expectation-dependent placebo analgesia and cannabinoidergic neurotransmissions supports expectation-independent placebo analgesia.

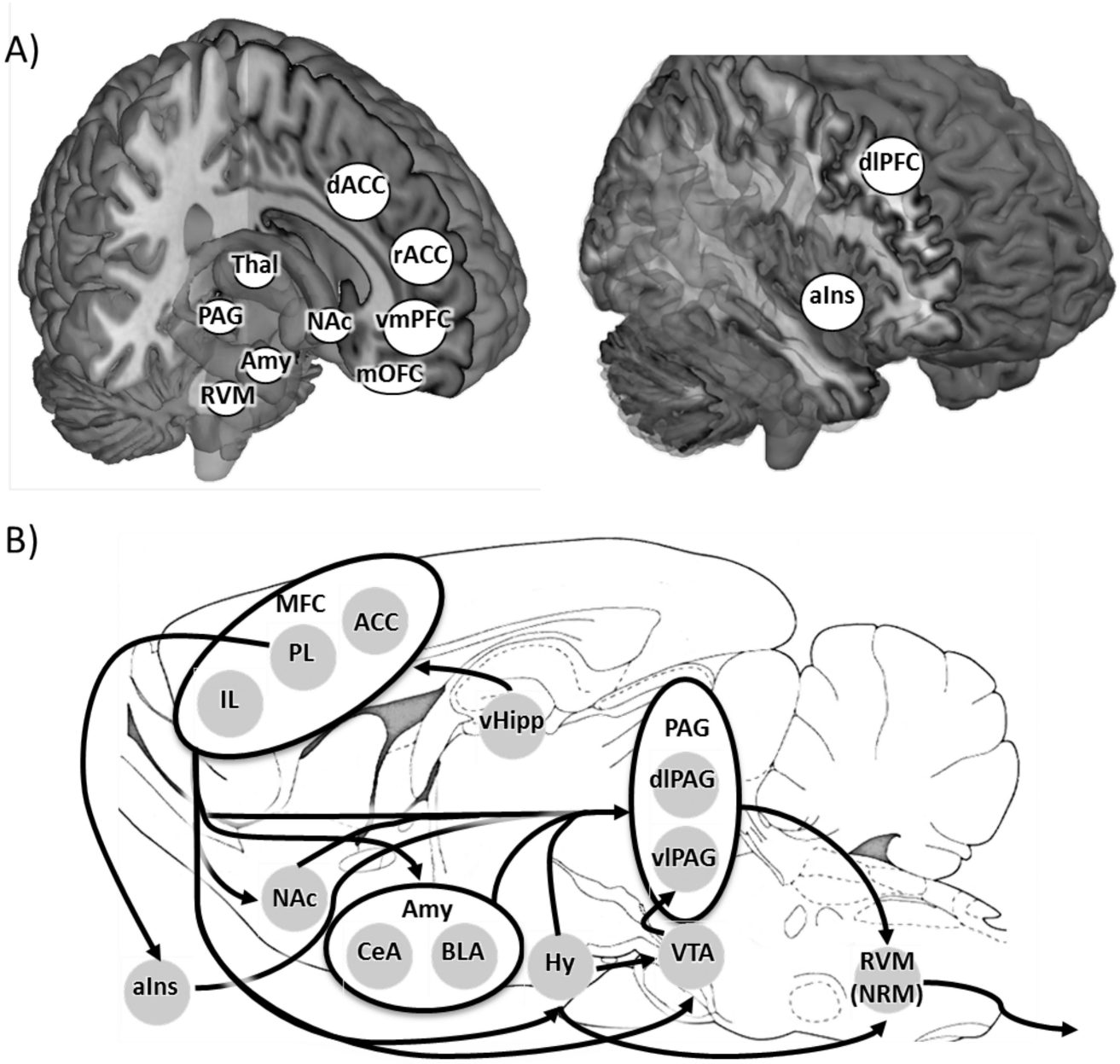

Figure 1. Endogenous pain network in the human and rat

A) In humans, pain-induced activity in PAG, RVM, and other pain-related brain areas is affected by placebo administration. Placebo administration reduces activity in regions associated with pain experience such as aIns, dACC, Thal, and Amy. In contrast, activity in regions thought to be involved in pain modulation such as dlPFC, rACC, vmPFC, mOFC, and NAc increases with placebo treatment. B) This figure shows a selection of projections descending from MFC to regions involved in pain nociception and regulation in the rat. Black arrows represent connections between brain regions that were identified via either anterograde or retrograde labeling. These connections do not represent an exhaustive list. Of the pathways shown, only a few have been explicitly tested and shown to be relevant to endogenous modulation of pain experience.

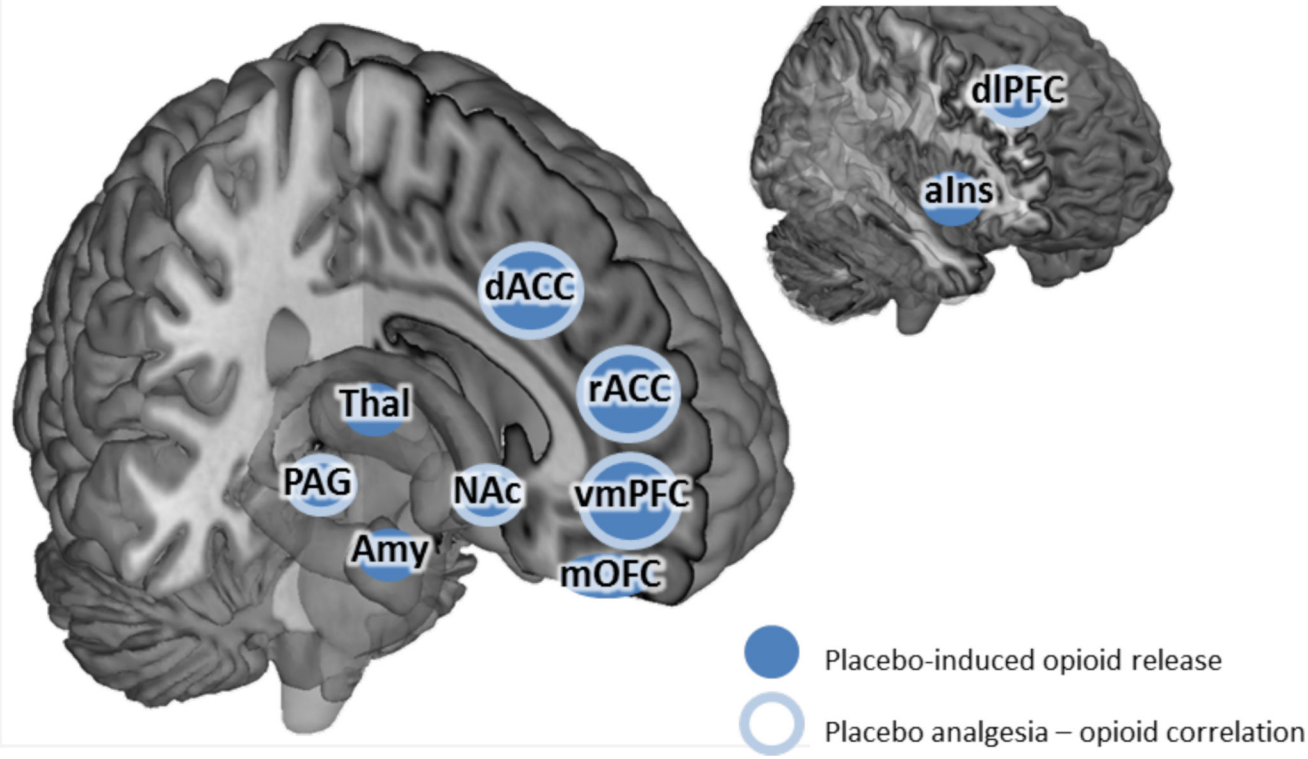

Figure 2. Endogenous opioids and placebo analgesia in humans

Placebo treatment is associated with enhanced opioid activity within dlPFC, aIns, dACC, rACC, vmPFC, mOFC, thalamus, NAc, amygdala, and PAG (dark blue fill). Opioid activity within PAG, NAc, rACC, vmPFC, and dlPFC is correlated with placebo analgesia (light blue outline).

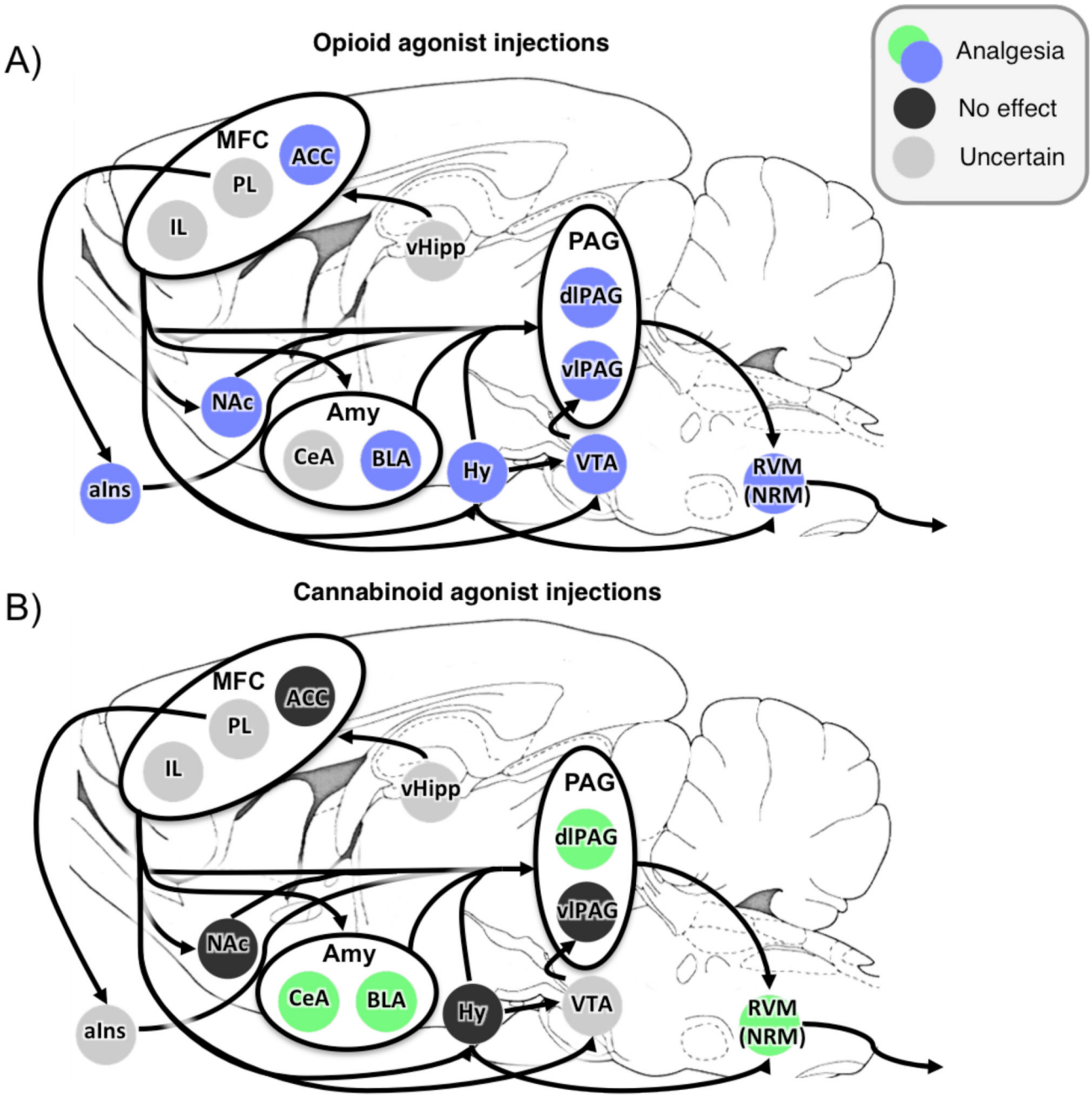

Figure 3. Drug injection effects on pain

A) Blue circles represent sites where local injection of opioid agonists reduces pain in rodents in at least one study, as measured by either reduction in pain-related behaviors or enhanced latency to escape from a painful stimulus. Gray circles represent regions that are involved in pain modulation where we failed to find studies testing the effect of local microinjections of opioid agonists on analgesia. B) Green circles represent sites where local injection of cannabinoid agonists reduces pain in rodents in at least one study, as measured by either reduction in pain-related behaviors or enhanced latency to escape from a painful stimulus. Gray circles represent regions that are involved in pain modulation where we failed

to find studies testing the effect of local microinjections of cannabinoid agonists on analgesia. Black circles indicate that every reviewed study found no effect of local injection of cannabinoid agonists within this region on analgesia.

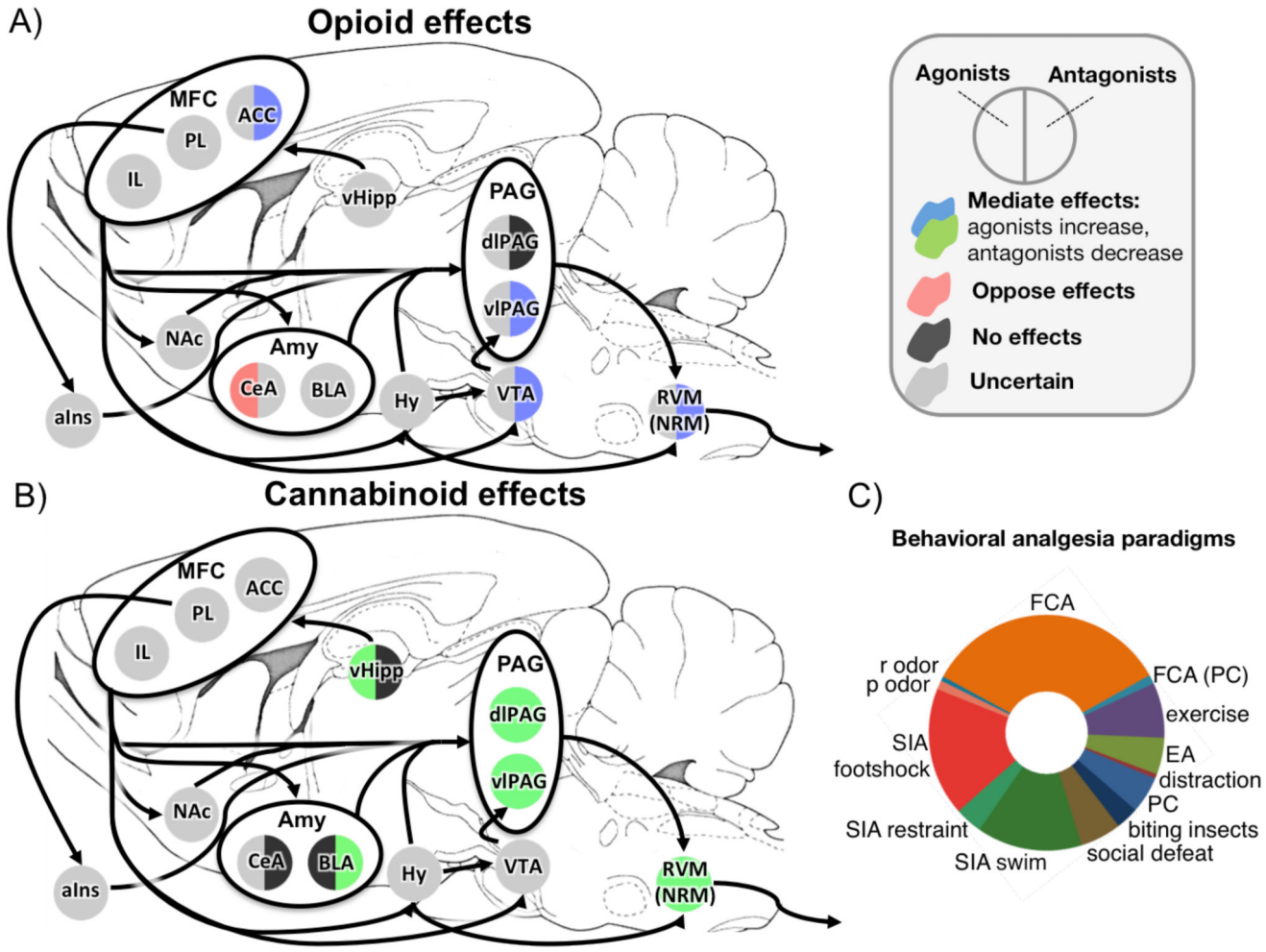

Figure 4. Drug effects on behaviorally mediated analgesia

A) Local injection of opioid antagonists within ACC, vlPAG, and RVM reduce behavioral analgesia. In contrast, microinjections of opioid agonists into CeA reduce behavioral analgesia and microinjections of opioid antagonists in dlPAG have no effect on behavioral analgesia. Other regions involved in opioidergic pain control that have not been demonstrated to be involved in behavioral analgesia include aIns, NAc, BLA, Hy, and VTA. B) Local injection of cannabinoid antagonists within BLA, PAG, and RVM reduce behavioral analgesia. Similarly, microinjections of cannabinoid agonists within PAG, RVM, and vHipp enhance behavioral analgesia. Interestingly, while CeA injections of cannabinoid agonists are sufficient to induce analgesia, cannabinoid antagonists in CeA fail to reduce behavioral analgesia.

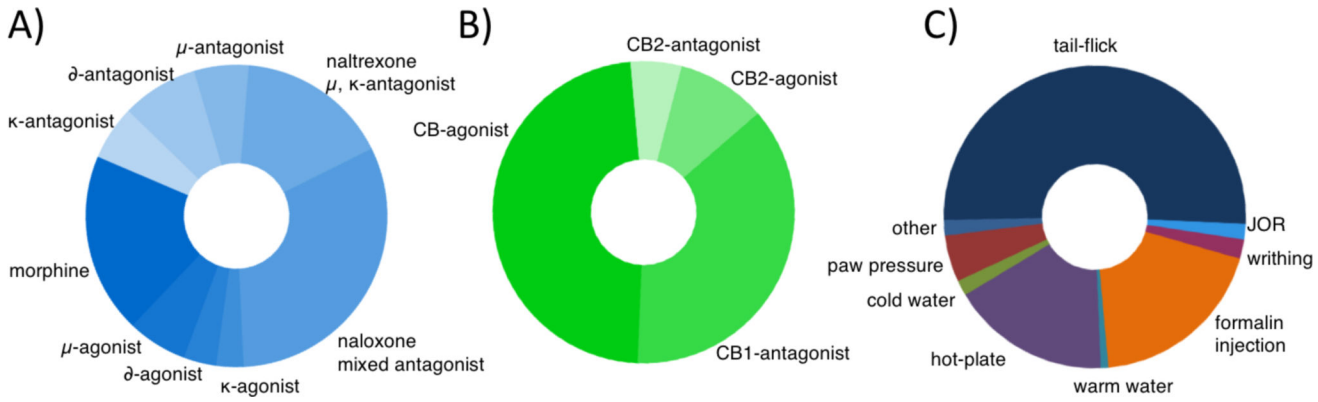

Figure 5. Distribution of drugs and pain measures across rodent studies

A) Opioid interventions of behavioral analgesia paradigms including direct injections into brain regions (total: 171). B) Cannabinoid interventions of behavioral analgesia paradigms including direct injections into brain regions (total: 73). C) This chart shows the relative distribution of pain measures across the reviewed studies of pain modulation in rodents (total: 241).

Table 1

Dual Learning Processes[1]

	Dynamic	Accumulative
Learning Speed	Fast	Slow
Modality Specific	No	Yes
Automatic	No	Yes
Flexible	Yes	No

[1]This table summarizes key differences between the dynamic and accumulative learning processes. Under the dynamic process, information is learned rapidly, and can generalize to other modalities. Activation of this process requires explicit awareness and is flexible, as it can be rapidly changed with new information. In comparison, learning under the accumulative processes is slower and may not generalize to situations that are too different from the learned context. However, placebo effects induced via this process do not require explicit cognitive control, nor are they be immediately affected by new information.

Table 2

Opioid agonists and analgesia[2]

Site	Type	Effect	References
Systemic	μ Agonist	Analgesia	(Fanselow *et al.*, 1989b)
	κ Agonist	Analgesia	(Fanselow *et al.*, 1989b; Helmstetter *et al.*, 1995)
	δ Agonist	Analgesia	(Fanselow *et al.*, 1989b; Helmstetter *et al.*, 1995)
	Agonist	Analgesia	(Azami *et al.*, 1982; Deakin and Dostrovsky, 1978; Dostrovsky and Deakin, 1977; Gilbert and Franklin, 2002; Hart *et al.*, 1983; Young *et al.*, 1984)
ACC	Agonist	Analgesia	(Pavlovic *et al.*, 1996)
aIns	Agonist	Analgesia	(Burkey *et al.*, 1996)
CeA	Agonist	Analgesia	(Pavlovic *et al.*, 1996)
NAc	δ Agonist	None	(Schmidt *et al.*, 2002)
	μ Agonist	None	(Schmidt *et al.*, 2002)
	δ + μ Agonist	Analgesia	(Schmidt *et al.*, 2002)
Hy	Agonist	Analgesia	(Fuchs and Melzack, 1995; Manning *et al.*, 1994)
VTA	Agonist	Analgesia	(Altier and Stewart, 1997, 1998; Franklin, 1989; Manning *et al.*, 1994)
dPAG	Agonist	Analgesia	(Jensen and Yaksh, 1986; Levy and Proudfit, 1979; Manning *et al.*, 1994; Miczek *et al.*, 1985; Pert and Walter, 1976)
vPAG/DRN	Agonist	Analgesia	(Jensen and Yaksh, 1986; Levy and Proudfit, 1979; Lewis and Gebhart, 1977; Manning *et al.*, 1994;Sharpe *et al.*, 1974; Young *et al.*, 1984)
RVM	μ Agonist	Analgesia	(Heinricher *et al.*, 1994)
	Agonist	Analgesia	(Dickenson *et al.*, 1979; Jensen and Yaksh, 1986; Levy and Proudfit, 1979)

[2]This table summarizes the effect of local and systemic injections of opioid agonists on pain.

Table 3

Cannabinoid agonists and analgesia[3]

Site	Type	Effect	References
Systemic	Agonist	Analgesia	(Martin *et al.*, 1999; Meng *et al.*, 1998)
	Antagonist	Hyperalgesia	(Meng *et al.*, 1998)
Cingulate	Agonist	None	(Martin *et al.*, 1999)
BLA	Agonist	Analgesia	(Martin *et al.*, 1999)
CeA	Agonist	Analgesia	(Martin *et al.*, 1999)
NAc	Agonist	None	(Martin *et al.*, 1999)
dlPAG	Agonist	Analgesia	(Martin *et al.*, 1999)
RVM	Agonist	Analgesia	(Martin *et al.*, 1999; Martin *et al.*, 1998; Meng and Johansen, 2004)
	Agonist	Analgesia	(Martin *et al.*, 1998)

[3]This table summarizes the effect of local and systemic injections of opioid agonists on pain.

Table 4

Opioid activity and placebo analgesia[4]

Brain Region	Contrast	References
dlPFC	Placebo	(Wager *et al.*, 2007; Zubieta *et al.*, 2005)
	Placebo Analgesia	(Wager *et al.*, 2007)
vmPFC	Placebo	(Pecina *et al.*, 2013; Scott *et al.*, 2008; Wager *et al.*, 2007)
rACC	Placebo	(Scott *et al.*, 2008; Wager *et al.*, 2007; Zubieta *et al.*, 2005)
	Placebo Analgesia	(Pecina *et al.*, 2013; Pecina *et al.*, 2014a)
dACC	Placebo	(Pecina *et al.*, 2013)
	Placebo Analgesia	(Pecina *et al.*, 2013; Pecina *et al.*, 2014a)
aIns	Placebo	(Pecina *et al.*, 2013; Scott *et al.*, 2008; Wager *et al.*, 2007; Zubieta *et al.*, 2005)
Amygdala	Placebo	(Pecina *et al.*, 2013; Scott *et al.*, 2008; Wager *et al.*, 2007)
NAc	Placebo	(Pecina *et al.*, 2013; Scott *et al.*, 2008; Zubieta *et al.*, 2005)
	Placebo Analgesia	(Scott *et al.*, 2008)
Thalamus	Placebo	(Wager *et al.*, 2007)
PAG	Placebo	(Pecina *et al.*, 2013; Scott *et al.*, 2008; Wager *et al.*, 2007)
	Placebo Analgesia	(Pecina *et al.*, 2013)

[4] This table summarizes studies that found enhanced opioid activity following placebo treatment, or found opioid activity to correlate with behavioral analgesia.

Table 5

Opioidergic modulation of behavioral analgesia[i]

Site	Type	Manipulation	Effect	References
Systemic	δ antagonist	FCA, SIA	Less analgesia	(Fanselow *et al.*, 1989a; Hart *et al.*, 1983)
	κ antagonist	FCA, SIA, Social Defeat, Biting Insects	Less analgesia, None	(Fanselow *et al.*, 1989b; Kavaliers *et al.*, 1998; McLaughlin *et al.*, 2006; McLaughlin *et al.*, 2003)
	μ antagonist	FCA	Less analgesia	(Fanselow *et al.*, 1989b)
	naloxone	FCA, SIA, Social Defeat, Morphine conditioning, Biting Insects, Predator Odor	Less analgesia, (None)	(Bodnar *et al.*, 1978; Bragin, 1986; Butler *et al.*, 2008; Colwell and Kavaliers, 1990; Fanselow, 1984; Galdino *et al.*, 2014b; Galdino *et al.*, 2010; Good and Westbrook, 1995; Guo *et al.*, 2010; Hart *et al.*, 1983, 1985; Hayes *et al.*, 1978; Helmstetter and Fanselow, 1987b; Kavaliers *et al.*, 1998; Kavaliers *et al.*, 1997; Kurrikoff *et al.*, 2008; Lee *et al.*, 2016; Lewis *et al.*, 1981; Lewis *et al.*, 1980; Marek *et al.*, 1992; Miczek *et al.*, 1982; Miller *et al.*, 1990; Przewlocka *et al.*, 1990; Rodgers and Hendrie, 1983; Rodgers and Randall, 1986; Teskey *et al.*, 1984; Watkins *et al.*, 1982; Zhang *et al.*, 2013)
	naltrexone	FCA, SIA, Social Defeat, Morphine conditioning, Odor of different shocked rat	Less analgesia, (None)	(Fanselow, 1985; Fanselow and Baackes, 1982; Girardot and Holloway, 1984, 1985; Grisel *et al.*, 1993; Helmstetter and Fanselow, 1987a, b; Kelly and Franklin, 1987; Lee *et al.*, 2016; Lichtman and Fanselow, 1991; Meagher *et al.*, 1989; Miczek *et al.*, 1982; Terman *et al.*, 1986)
rACC	δ antagonist	Morphine conditioning	None	(Zhang *et al.*, 2013)
	κ antagonist	Morphine conditioning	None	(Zhang *et al.*, 2013)
	μ antagonist	Morphine conditioning	Less analgesia	(Zhang *et al.*, 2013)
	naloxone	Morphine conditioning	Less analgesia	(Zhang *et al.*, 2013)
CeA	morphine	FCA	Less analgesia	(Good and Westbrook, 1995)
VTA	naltrexone	SIA	Less analgesia	(Altier and Stewart, 1996)
dlPAG	κ antagonist	FCA	None	(Bellgowan and Helmstetter, 1998)
	μ antagonist	FCA	None	(Bellgowan and Helmstetter, 1998)
	naltrexone	SIA	None	(Hohmann *et al.*, 2005)
vlPAG	κ antagonist	FCA	None	(Bellgowan and Helmstetter, 1998)
	μ antagonist	FCA	Less analgesia	(Bellgowan and Helmstetter, 1998)
	naltrexone	FCA	Less analgesia	(Helmstetter and Landeira-Fernandez, 1990)
RVM	κ agonist	FCA	Less analgesia	(Foo and Helmstetter, 2000a)
	δ antagonist	FCA	None	(Foo and Helmstetter, 1999)
	κ antagonist	FCA	None	(Foo and Helmstetter, 1999)
	μ antagonist	FCA	Less analgesia	(Foo and Helmstetter, 1999, 2000b)

[i]This table summarizes the effect of local and systemic injections of opioid agonists and antagonists on various types of behavioral analgesia.

Table 6

Cannabinoidergic modulation of behavioral analgesia[5]

Site	Type	Manipulation	Effect	References
Systemic	Agonist	FCA, Exercise, SIA	More analgesia	(Butler *et al.*, 2012; Butler *et al.*, 2008; Galdino *et al.*, 2014a; Galdino *et al.*, 2014b; Hohmann *et al.*, 2005; Suplita *et al.*, 2005)
	CB-1 Antagonist	FCA, SIA, Exercise, Distraction	Less analgesia	(Finn *et al.*, 2004; Ford *et al.*, 2015; Galdino *et al.*, 2014a; Galdino *et al.*, 2014b; Kurrikoff *et al.*, 2008; Lee *et al.*, 2016; Olango *et al.*, 2014; Rea *et al.*, 2013; Suplita *et al.*, 2005)
	CB-2 Antagonist	Exercise	Less analgesia	(Galdino *et al.*, 2014a; Galdino *et al.*, 2014b)
BLA	Agonist	SIA	None	(Connell *et al.*, 2006)
	CB-1 Antagonist	FCA, SIA	Less analgesia, None	(Connell *et al.*, 2006; Rea *et al.*, 2013; Roche *et al.*, 2010; Roche *et al.*, 2007)
CeA	CB-1 Antagonist	FCA, SIA	None	(Connell *et al.*, 2006; Rea *et al.*, 2013)
vHipp	Agonist	FCA	More analgesia	(Ford *et al.*, 2011)
	CB-1 Antagonist	FCA	None	(Ford *et al.*, 2011)
dlPAG	Agonist	SIA	More analgesia	(Hohmann *et al.*, 2005; Suplita *et al.*, 2005)
	CB-1 Antagonist	FCA, SIA	Less analgesia	(Hohmann *et al.*, 2005; Olango *et al.*, 2012; Suplita *et al.*, 2005)
	CB-2 Antagonist	SIA	None	(Hohmann *et al.*, 2005)
vlPAG	Agonist	SIA	More analgesia	(Hohmann *et al.*, 2005)
	CB-1 Antagonist	SIA	Less analgesia	(Lee *et al.*, 2016)
RVM	Agonist	SIA	More analgesia	(Suplita *et al.*, 2005)
	CB-1 Antagonist	SIA	Less analgesia	(Suplita *et al.*, 2005)

[5]This table summarizes the effect of local and systemic injections of cannabinoid agonists and antagonists on various types of behavioral analgesia.