The Neural and Psychological Constituents of Placebo and Distraction

Jason Buhle

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ABSTRACT

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Jason Buhle

Both placebo and distraction have long been used clinically to relieve pain. The present series of experiments examined the neural and cognitive processes that constitute these two psychological forms of analgesia. Study 1 provides evidence that overlapping cognitive resources are involved in both pain and executive attention and working memory. Study 2 provides evidence that these same executive attention and working memory resources are not involved in placebo analgesia, and that placebo analgesia and distraction provide separate routes to pain relief. Study 3 suggests that while distraction-based analgesia reduces the neural signature of pain, expectancy-driven placebo analgesia may not.

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Full references for studies comprising this dissertation:

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Study 3: Buhle, J., Stevens, B.L., Stevens, C., Williamson, C.M., Wager, T.D. Different effects of distraction and placebo on the neural expression of pain, (In prep).

Chapter 1: Introduction

What is pain?

The International Association for the Study of Pain (IASP) defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Merskey & Bogduk, 1994). While this definition encompasses chronic, neuropathic and psychogenic pain, the present discussion will focus on acute, induced pain, as this type of pain is most relevant to the research presented in this dissertation.

The IASP definition highlights the dual sensory and emotional nature of pain. Early philosophers including Aristotle and Plato did not classify pain as a distinct sensation, but rather saw pain as an emotional state accompanying the experience of strong sensations such as light, pressure or temperature (Dallenbach, 1939; Perl, 2007). This view was further elaborated by Erasmus Darwin in 1794 (Darwin, 2005), and led to the intensive theory of William Erb, who argued in 1874 that pain could be generated by any sufficiently intense sensory stimulus (Dallenbach, 1939; Erb, 1874; Perl, 2007). In contrast, specificity theory argued that pain was a unique sensation relying on mechanisms distinct from those of other sensations like heat and touch (Dallenbach, 1939; Perl, 2007). First put forth by Avicenna in the 11th century (Avicenna & Gruner, 1930), this view was elaborated on by Descartes in the 17th century (Benini & DeLeo, 1999).

While physiological and psychophysical evidence for both intensive and specificity theory were reported throughout the 19th century, by the early 20th century most scientists had come to support specificity theory (Perl, 2007). However, specificity of pain as a sensation did not necessarily mean that pain could not have an emotional component.

Livingston argued in 1943 that fear and other-pain related emotions could produce descending excitation of pain-specific transmission fibers, resulting in positive feedback loops (Livingston, 1943). In 1968, Melzack and Casey put forth their influential three dimension theory of pain, which characterized pain as a combination of "sensory-discriminative", "affective-motivational", and "cognitive-evaluative" dimensions (Melzack & Casey, 1968). Critically, the authors argued that pain was not simply a function of the intensity of the input stimulus, but also could be modulated by cognitive and affective factors. They noted that some cognitive factors, such as the excitement experienced in games or war, might modulate both affective-motivational and sensory-discriminative dimensions, while others, such as hypnosis or placebo, might exclusively impact the affective-motivational dimension. In conclusion, they urged clinicians and researchers to develop treatments for pain that relied on these affective-motivational and cognitive-evaluative factors in addition to physiological treatments of incoming painful sensation.

As is apparent in the IASP definition of pain, current thinking sees pain as a uniquely fused perceptual and emotional experience. Interestingly, current thinking also seems to favor a hybrid of the earlier intensity and specificity theories. While there is incontrovertible evidence for the existence of pain-specific nociceptors, there is also now strong evidence that parallel and convergent activity from other sensory modalities also plays a role in pain processing (Craig, 2003; Perl, 2007). In the following section, I will briefly discuss what is currently known about the functional neuroanatomy of pain, including a review of the ascending nociceptive pathways that travel from the periphery through the spinal cord and into the brainstem, and the network of brain regions that translate these nociceptive inputs into the perceptual and emotional experience of pain.

Functional neuroanatomy of nociception and pain

The term *nociception* is used to describe the neural process of encoding noxious stimuli (Merskey & Bogduk, 1994). It is distinct from *pain*, which implies conscious experience, as indicated in IASP definition above. The distinction between nociception and pain is somewhat akin to the distinction between sensation and perception that has been made in other domains, such as vision. Just as the physiological division between sensation and perception is not completely clear, neither is it clear exactly where in the ascending pain pathway nociception becomes pain. While pain and nociception typically co-occur, it is clear from these definitions that this need not always be so—nociception can occur without pain, and pain can occur without nociception. In the following discussion, I describe a typical sequence of events that might follow the application of a thermal, peripheral, nociceptive stimulation that is experienced as painful, as this is case that is most germane to the present research.

First, the hot probe will activate nerve endings in the skin called nociceptors (Snider & McMahon, 1998). Normally-functioning nociceptors only respond when a certain threshold is passed. For most of the body, the cell bodies of nociceptors are located in the dorsal root ganglia, with only cell bodies of face nociceptors located instead in the trigeminal ganglia. Specific nociceptive transducers in the nerve ending determine whether it is capable of responding to a given stimulus. For example, the response to nociceptive heat is mediated in part by TRPV1 and TRPV2, proteins which respond to temperatures higher than about 43 °C and 52 °C, respectively, as well as capsaicin, the chemical in hot peppers, and low pH (Tominaga et al., 1998). Nociceptive information is conveyed by both

myelinated nerves, such as Aδ fibers, and unmyelinated nerves, such as C fibers. The relatively fast transduction afforded by myelinated Aδ fibers leads to the sharp, initial part of the pain response, known as first pain, which typically drives the immediate impulse to pull away from an unexpectedly encountered burning stimulus. In contrast, slowly conducting C fibers are responsible for the dull, sustained burning sensation known as second pain (Craig, 2003).

Both Aδ and C fibers cross the midline and enter the dorsal horn of the spinal cord. Typically Aδ fibers synapse in laminae I and V, while C fibers synapse in lamina II. Most nociceptive nerves then project up the spinal tract via the anterolateral system. The anterolateral system consists of three main pathways: the lateral spinothalamic tract, which projects to the thalamus; the spinoreticular tract, which projects to the reticular formation of the midbrain; and the spinomesencephalic tract, which projects to the dorsal midbrain (Tracey & Mantyh, 2007). Recent evidence also suggests that at least some ascending spinal neurons also project directly to the amygdala and hypothalamus (Willis & Westlund, 1997).

Most nociceptive signals that reach the cortex do so via either the medial or lateral thalamus. The lateral thalamic projection involves relays in multiple nuclei of the ventral posterior region, including the ventral posterior lateral (VPL) and ventral posterior inferior (VPI) nuclei. Both nuclei contain somatotopically organized cells. VPL projects to the primary somatosensory cortex (SI), which is believed to be involved in spatial discrimination of pain perception, while VPI neurons are believed to project to secondary somatosensory cortex (SII), which is believed to be involved in affective components of pain (Willis & Westlund, 1997). In contrast, other projections target the intralaminar nuclei

of the medial thalamus. These neurons typically have been shown to have large, bilateral receptive fields, suggesting they are not important in spatial discrimination. However, they do discriminate between different levels of noxious heat. Historically, the medial thalamic pain relays have been thought to be primarily involved in motivational or affective responses to pain, but these findings suggest they may also play a role in the discrimination of intensity (Bushnell & Duncan, 1989). Some evidence also suggests that a somatotopically organized group of nociceptive cells project from the posterior portion of the ventral medial nucleus to the insula (Craig, Bushnell, Zhang, & Blomqvist, 1994), but the existence of this pathway remains under debate (Graziano & Jones, 2004).

Although early researchers denied a role for the cerebral cortex in pain processing (Penfield & Boldrey, 1937; Penfield & Faulk, 1955), neuroimaging has identified a network of cortical and subcortical areas active during pain processing. Sometimes referred as the "neuromatrix" or "pain matrix" (Melzack, 1999), this network is widely thought to mirror the segregation of pain processing assumed for the thalamus, with a lateral component preferentially involved in sensory-discriminatory pain processes, and a medial component preferentially involved in affective, evaluative, and cognitive pain processes (Tracey & Mantyh, 2007). A number of meta-analyses of pain neuroimaging results have been conducted (Apkarian, Bushnell, Treede, & Zubieta, 2005; Farrell, Laird, & Egan, 2005; Friebel, Eickhoff, & Lotze, 2011; Peyron, Laurent, & Garcia-Larrea, 2000; Salimi-Khorshidi, Smith, Keltner, Wager, & Nichols, 2009) and although the results differ somewhat across these analyses, the most reliably reported regions include SII, dorsal anterior cingulate cortex (ACC), insula, and thalamus.

Although these neuroimaging results clearly demonstrate cortical involvement in pain processing, neuroimaging results are inherently correlational, and thus they do not demonstrate that any of these regions are necessary or causal in the experience of pain. In that sense, they do not contradict Penfield's early findings that stimulation of no cortical area reliably produced pain (Penfield & Boldrey, 1937; Penfield & Faulk, 1955). Modern electrical stimulation studies have largely replicated Penfield's findings. For example, although painful stimulation elicits responses in neurons the human ACC, an area commonly seen in fMRI studies of pain, electrical stimulation of these same pain-responsive neurons does not lead to the experience of pain (Hutchison, Davis, Lozano, Tasker, & Dostrovsky, 1999). However, using techniques that were not available to Penfield, a number of studies have reported that pain is induced by about 10% of the time following stimulation of deep areas of the parietal operculum and insula, indicating that these regions are causally involved in pain processing (Afif, Hoffmann, Minotti, Benabid, & Kahane, 2008; Mazzola, Isnard, & Mauguiere, 2006; Mazzola, Isnard, Peyron, & Mauguiere, 2011; Ostrowsky et al., 2002).

Distraction

Distraction can be defined as the removal of attention from a particular mental representation and onto the source of the distraction. While distraction is often involuntary and unwanted, for example when a nearby conversation among colleagues draws one's attention away from one's work, it can also be intentional and desirable. For example, one might play a game on one's phone to distract oneself from anxiety-producing thoughts while waiting for tests results at the doctor's office.

Both medical professionals and lay people commonly use distraction to reduce pain. In fact, people prefer distraction to other coping strategies (McCaul & Haugtvedt, 1982; Wack & Turk, 1984), even when alternative strategies prove to be more effective (Ahles, Blanchard, & Leventhal, 1983). This widespread belief in its efficacy has led to extensive clinical and experimental research on distraction as a method of pain control (see Chapter 2, Introduction, for a general discussion of previous research, and Table 2.1 for a summary of results in experimental, human studies published from 2000 to 2009).

Why would distraction reduce pain? As I will discuss in greater detail below (see Chapter 2, Introduction), a limited-resources logic suggests that if pain is reduced by distraction, pain perception must involve effortful, non-automatic processes. This claim is consistent with previous theories, which have argued for the importance of cognition in mediating pain experiences (McCaul & Malott, 1984). It is important to note that while distraction-induced analgesia suggests that some pain processes relies on attention, it does not necessarily suggest that all pain processes are dependent on attention. For example, it might be the case that excess attentional resources allow one to think about pain, and thereby augment it. If so, removing these extra attentional resources might thus stop one from increasing one's pain, but not reduce pain past a certain point.

In recent years, several neuroimaging studies have examined the functional neuroanatomy of distraction-based analgesia (Bantick et al., 2002; Brooks, Nurmikko, Bimson, Singh, & Roberts, 2002; Frankenstein, Richter, McIntyre, & Remy, 2001; H. G. Hoffman, Richards, et al., 2004; Petrovic, Petersson, Ghatan, Stone-Elander, & Ingvar, 2000; Peyron et al., 1999; Ploner, Lee, Wiech, Bingel, & Tracey, 2011; Remy, Frankenstein, Mincic, Tomanek, & Stroman, 2003; Tracey et al., 2002; Valet et al., 2004). Taken together, these

studies indicate that distraction reduces activity in numerous pain processing regions, including medial thalamus (Bantick et al., 2002; H. G. Hoffman et al., 2011; Remy et al., 2003), anterior insula (Bantick et al., 2002; Brooks et al., 2002; H. G. Hoffman et al., 2011; Remy et al., 2003), and ACC (Bantick et al., 2002; Frankenstein et al., 2001; H. G. Hoffman, Richards, et al., 2004; Remy et al., 2003). More limited evidence suggests that distraction may reduce pain-related activity in SI and SII (H. G. Hoffman, Richards, et al., 2004; Petrovic et al., 2000).

An important question in this literature is whether these reductions in self-reported pain and activity in pain-processing regions occur as a result of general or specific mechanisms. For example, a general mechanism possibility is that, as a result of the resource-demanding task, otherwise available resources are tied up, and unavailable for competing nociceptive processes. In this scenario, the reduction of activity in pain processing areas is an indirect result of the activity supporting the distracting task. This activity could be observed with a contrast such as Distraction+Pain >No Distraction+Pain, but similar activity would be expected from a task-related contrast that did not involve pain, such as Distracting Task > No Task. Alternatively, specific source regions might come online when one performs a distracting task while experiencing pain that directly inhibit activity in pain-processing regions (Wiech, Ploner, & Tracey, 2008). If so, these specific processes would be observed by an interaction, for example of conditions such as Task (with levels of Task and No Task, or High Load Task and Low Load Task) and Pain (with levels of Pain and No Pain, or Painful Heat and Warmth).

Several studies have found evidence of such “direct source” activity in midbrain periaqueductal gray (PAG; Remy et al., 2003; Tracey et al., 2002; Valet et al., 2004),

although at least one study found distraction-related decreases in PAG, an incompatible result (Petrovic et al., 2000). Other identified direct source regions include orbital frontal cortex (OFC; Bantick et al., 2002; Petrovic et al., 2000; Valet et al., 2004), perigenual ACC (Bantick et al., 2002; Valet et al., 2004), rostral prefrontal cortex (Remy et al., 2003), and dorsocaudal ACC (Remy et al., 2003). Several theories have suggested distraction-based analgesia may rely at least in part on descending nociceptive inhibition acting at the level of the spinal cord (Bingel & Tracey, 2008; Tracey & Mantyh, 2007; Wiech et al., 2008). One possibility is that these frontal cortical regions might directly invoke a PAG-mediated descending modulatory influence in order to protect task-related processing. One piece of evidence in support of this theory is that attending to a painful stimulus increases nociceptive responses in dorsal horn neurons in monkeys (Bushnell, Duncan, Dubner, & He, 1984), and the nociceptive spinal flexion reflex in humans (Ruscheweyh, Kreusch, Albers, Sommer, & Marziniak, 2011), suggesting the involvement of descending nociceptive facilitation with attention. Two studies have also found distraction-related reductions in the nociceptive spinal flexion reflex in humans (Ruscheweyh et al., 2011; Willer, Boureau, & Albe-Fessard, 1979), though just as many have failed to detect a reduction, even though lower pain ratings indicated effective analgesia (Dowman, 2001; Terkelsen, Andersen, Molgaard, Hansen, & Jensen, 2004). The degree of distraction and the specific strategy used both seem to play a role in whether the spinal reflex is reduced (Ruscheweyh et al., 2011). Future work should seek to clarify the role of these parameters, and also to use hemodynamic imaging of the spinal cord, as has been done in placebo analgesia (Eippert, Bingel, et al., 2009).

Placebo

What is the placebo effect?

A placebo treatment is one that is known to have no direct physical or pharmacological benefit for a given condition, such as a sugar pill given to a child to cure a stomachache. A placebo response occurs when conscious expectancies or conditioning invoked by the placebo treatment recruit endogenous physiological processes that reduce symptomatology. For example, the child likely believes in the power of medicines, and may have had previous pain-relieving experiences with pills. The reduction of symptomology itself—in this case, the alleviation of the stomachache—is described as the placebo effect (Atlas, Wager, Dahl, & Smith, 2009).

Placebos appear to have been widely used and generally endorsed in medicine through the first half of the 20th century. However, they were generally thought to provide comfort to the patient, rather than to directly alleviate the medical condition under treatment (de Craen, Kaptchuk, Tijssen, & Kleijnen, 1999). Henry Beecher challenged this view in 1955 in his seminal article, "The Powerful Placebo", which examined a range of published clinical trials and found surprisingly large effects of placebo treatments (Beecher, 1955).

Although this article opened the door for serious scientific study of placebo, its conclusions were largely unfounded. In clinical trials, the goal is typically to test the efficacy of an intervention by seeing whether it can outperform a placebo control condition. Placebo control conditions in clinical trials are designed to mimic the experimental condition in every way, save for the specific, active component of the treatment. Despite their name, they are designed to control not just for placebo effects, but also for any other

effect or artifact that affect outcome of interest, including Hawthorne effects, spontaneous improvements, participant sampling bias, regression to the mean, and response bias. Hawthorne effects describe changes that occur simply as a result of being studied (Roethlisberger & Dickson, 1939). Spontaneous improvements might occur in any disease with a non-constant natural history. Regression to the mean describes the increased likelihood that a second sample mean will be closer to the population mean than the first sample mean if the first sample mean is far from the population mean. Participant sampling bias may increase the likelihood of observing spontaneous improvements, as patients might be more likely to enter a clinical trial when their symptoms are severe, leaving greater room for improvement due to natural symptom fluctuation and regression to the mean. Since placebo control conditions in clinical trials are designed to include all these potential influences, the clinical improvements that Beecher characterized as placebo effects could just as easily be attributed to any of them instead.

To make a claim that clinical improvements are placebo effects, it is necessary to have a comparison condition that can control for these potential confounds and artifacts. Typically, experiments designed to study placebo itself accomplish this with a no treatment condition or an active control intervention that is explicitly not portrayed as treatment. For example, Hawthorne effects should be equal among the active control and placebo groups, so that the difference between the two should provide a pure measure of placebo. However, of the 15 studies included in Beecher's original article, only two included no-treatment control groups. In these two studies, the improvement in the placebo conditions was no greater than that in the no treatment control groups (de Craen, Kaptchuk, et al., 1999). Thus, it seems that data used by this article to convince the scientific community

that placebos might have powerful effects could have more easily been used to downplay the power of placebos.

Nonetheless, in the years since, many studies have found placebo treatments lead to greater symptom improvements than no-treatment controls. However, the comparison of placebo and no-treatment conditions is still susceptible to decision-related confounds, including response bias, demand characteristics and criterion shifts. These confounds involve changes in a measured dependent variable that do not reflect an actual change in the underlying construct of interest. Rather, they involve changes in the how the participant reports her experience. Thus, they typically only affect subjective measures, such as self-reported pain or depressive symptoms. Response bias occurs when a participant shifts her response in a way she believes will please the experimenter. For example, in the context of placebo analgesia treatment, asking a participant how much relief she felt, rather than whether she felt any relief at all, could unintentionally signal the hypothesis of the experiment to participant, potentially encouraging a more positive response. The overlapping concept of demand characteristics describes cases when participants form a belief, possibly unconscious, about the purpose of the experiment, and shift their responses to either confirm or disconfirm that hypothesis (Orne, 1962). Given that the purpose of a placebo manipulation is to instill in the participant the belief that the placebo intervention will relieve his symptoms and the control procedure will not, a placebo study is defined by unequal expectations and beliefs between the experimental conditions. Thus, the problems of response bias and demand characteristics cannot be resolved through a comparison condition.

Beginning in the 1960s, Crawford Clark attempted to resolve this problem by using Signal Detection Theory (SDT), a statistical framework which seeks to disambiguate signal sensitivity and bias (Tanner & Swets, 1954), to analyze pain ratings in the context of placebo analgesia. Clark hypothesized that placebo interventions might not reduce actual pain experience, but instead simply change the criterion used by the participant when describing its intensity. In a series of studies, Clark found that SDT measures of pain sensitivity did not change as a result of placebo (Clark, 1969), suggestion (Clark & Goodman, 1974), or acupuncture (Clark & Yang, 1974), but measures of bias did, which he took as support of his hypothesis. In fact, these studies simply show that placebo treatments do not impair the ability of participants to accurately discriminate stimulus intensity. It is entirely conceivable that an individual might experience reduced pain without any loss in ability to discriminate signal intensity. Thus, these results are compatible with Clark's hypothesis, but they do not disprove the competing hypothesis that placebo treatment produces analgesia.

Given that response bias, demand characteristics and criterion shifts generally only affect self-report or other kinds of behavioral data that can be volitionally controlled, evidence for placebo effects free from these confounds can be found in studies which use dependent variables that are not subject to volitional control. For many medical conditions, objective measures are of primary interest. For example, in the treatment of throat cancer, while subjective measures of well-being are certainly important, the primary outcome measure is typically tumor growth. In contrast, other medical conditions, such as pain and depression, are defined by their subjective experience. In such cases, objective changes, such as reduced neural activity in brain regions associated with pain processing or negative

mood, are of minimal clinical value in the absence of changes self-report. Nonetheless, even when subjective measures are of primary clinical importance, objective measures provide crucial confirmation that placebo effects are not simply the result of decision-related confounds.

Many studies have found placebo effects on objective measures, including bronchial hyperreactivity (Kemeny et al., 2007; but see also Wechsler et al., 2011), opioid and dopamine receptor availability (de la Fuente-Fernandez et al., 2002; Wager, Scott, & Zubieta, 2007), duodenal ulcer healing (de Craen, Moerman, et al., 1999), and hemodynamic response (Wager et al., 2004). However, a series of influential meta-analyses of clinical trials by Hróbjartsson and Gøtzsche found no evidence for placebo effects in studies in which objective dependent variables were used (Hrobjartsson & Gotzsche, 2001, 2004a, 2004b, 2010). Notably, these meta-analyses did find placebo effects in trials using subjective outcome measures, such as pain report, leading the authors to conclude that reported placebo effects likely reflected only decision-related reporting biases. There are several possible reasons for this discrepancy between individual placebo studies and clinical trial meta-analyses. One possibility is that the positive findings of the placebo studies simply reflect chance compounded by publishing bias. This explanation is supported by analyses conducted by Hróbjartsson and Gøtzsche showing that, across studies, placebo effects diminished as sample size increased (Hrobjartsson & Gotzsche, 2004a). However, as the number of publications demonstrating placebo effects with objective dependent variables steadily rises, this explanation seems increasingly insufficient.

Alternatively, this discrepancy may reflect variability across medical conditions in susceptibility to placebo treatment. It may be the case that only a subset of maladies respond to placebos, and it is this subset that is addressed in placebo studies (Kirsch & Scoboria, 2001; Oh, 1994; Papakostas & Daras, 2001). In a follow-up re-analysis of the of the data used in Hróbjartsson and Gøtzsche (2001), studies were categorized by whether they were likely amenable to psychological factors (Wampold, Minami, Tierney, Baskin, & Bhati, 2005). Thus, insomnia, pain and depression were considered likely to be influenced to psychological factors, while anemia and bacterial infection were considered unlikely. In this analysis, studies of conditions deemed likely to be influenced by psychological factors showed robust placebo effects, while those deemed unlikely showed no effects. Although it seems that this distinction may have been confounded by the nature of the dependent variables, in that those studies with conditions deemed likely to be influenced by psychological factors also seem more likely to have used self-report measures, this possibility was discounted by a separate analysis that found no difference between subjective and objectively measured placebo conditions. Similarly, a separate meta-analysis of clinical trials found that "physical" dependent variables, such as blood pressure and expiratory volume, were responsive to placebo treatments, whereas "biochemical" dependent variables, such as cholesterol and cortisol, were not (Meissner, Distel, & Mitzdorf, 2007). In a follow-up analysis, these categories were validated on the dataset used by Hróbjartsson and Gøtzsche (2004a, 2004b). Clearly, an important future direction for placebo research is to delineate the conditions and physiological processes that are amenable to placebo interventions.

Finally, the discrepancy between the findings of placebo-specific studies and clinical trial meta-analyses may reflect relative differences in placebo-induced expectancies. There are several reasons to believe that placebo effects should be stronger in studies specifically designed to study placebo. In clinical trials participants are typically told from the outset that that may receive a placebo treatment, raising the possibility in the minds of the participants that they will not veridical treatment. Presumably, awareness of this possibility would decrease the expectation of relief, and reduce the placebo effect. In keeping with this hypothesis, Hróbjartsson and Gøtzsche (2010) found larger placebo effect sizes in studies in which participants were falsely informed that the placebo was a veridical treatment. In contrast, in studies designed to study the placebo researchers typically strive to convince the participant she is receiving a veridical and powerful treatment. Placebo studies may even include manipulation trials designed to associate the placebo treatment experience of relief. For example, in the context of a heat pain study, a topical analgesic might replace the placebo cream at first, or the applied temperatures might be covertly lowered. Manipulations such as these might strengthen expectations or even lead to unconscious conditioning in a placebo study, but would be expressly prohibited in a standard clinical trial. As such, it is not surprising that several meta-analyses have found larger placebo responses in studies specifically designed to study placebo then in clinical trials (Hrobjartsson & Gotzsche, 2010; Vase, Riley, & Price, 2002). Of course, such findings may reflect publication biases. On the one hand, clinical trials are most likely to be published if they find small placebo effects, as the relative advantage of active treatment is likely to be greater, while on the other hand studies designed to examine placebo effects would likely only be published if placebo effects were found.

Nonetheless, taken together, these factors lend validity to the ever-growing number of studies reporting placebo effects in objective dependent variables, and suggest that placebo effects found using subjective measures are not simply the product of confounds such as response bias, demand characteristics and criterion shifts.

Who responds to placebo treatments, and when?

We have already noted several factors that likely determine whether placebo effects occur. Perhaps the most important is whether the condition under treatment is even amenable to placebo. Most theories of placebo predict that only a subset of possible medical conditions could potentially be improved by a placebo intervention (Kirsch & Scoboria, 2001). Specifically, pain, many psychiatric illnesses, disorders of the autonomic nervous system, and immunobiochemical conditions are considered to have the potential to be placebo-responsive, whereas hyperacute illnesses like heart failure, chronic degenerative diseases, and unremitting diseases, such hereditary syndromes, are unlikely to have to potential to respond to placebo (Meissner, 2011; Meissner & Ziep, 2011; Oh, 1994; Papakostas & Daras, 2001; Wampold et al., 2005).

Research has identified a number of other situational factors that also influence the likelihood or magnitude of placebo effects. In general, factors that increase the expectation of treatment efficacy appear to increase placebo effects. Perhaps the most straightforward way doctors communicate treatment efficacy is by talking to patients. One experiment found that a strongly-worded statement of an inert pill's efficacy lead to greater pain relief than a weak message, which in turn lead to greater relief than no message at all (Gryll & Katahn, 1978). In placebo research, it is common to introduce the placebo intervention

with manipulation trials in which an active treatment surreptitiously and temporarily substitutes for the placebo treatment. Alternatively, experimenters might lower the stimulation level for the initial trials. In either case, the manipulation is designed so that participants come to associate the placebo intervention with reduced symptomology. In at least some cases, this association might constitute conditioned learning, and subsequent placebo effects might reflect unconscious conditioned responses (Amanzio & Benedetti, 1999; Benedetti, Amanzio, Baldi, Casadio, & Maggi, 1999). However, most of the time these manipulations likely simply provide experiences of efficacy that serve to strengthen the expectation of future relief, rather than fostering conditioned learning *per se* (Price et al., 1999).

The appearance and nature of the placebo delivery may also influence expectation. Several meta-analyses have found larger effects when more invasive procedures were used, such as sham acupuncture (Hrobjartsson & Gotzsche, 2010; Linde, Niemann, & Meissner, 2010). Similarly, treatment quantity has also been found to influence placebo magnitude. In one study, the level of activity participants reported after ingesting what they believed to be either a stimulant or a sedative scaled with whether they were given one or two pills (Blackwell, Bloomfield, & Buncher, 1972). More recently, a meta-analysis found that four placebo treatments per day more effectively healed duodenal ulcers than did two treatments per day (de Craen, Moerman, et al., 1999).

Disease-specific treatment knowledge may also play a role in shaping placebo expectations. If one knows one's illness is incurable, or that the intervention being described is medically implausible, one probably would not expect much from any new treatment, placebo or not (Cho, Hotopf, & Wessely, 2005). In support of this notion, one

meta-analysis found a positive correlation between the effects of placebo and active treatments across clinical trials (Moerman, 2000), suggesting a tight link between disease-related knowledge, expectations, and placebo effects. More broadly, numerous studies have shown that how effective one expects a purported treatment will be predicts individual differences in the magnitude of placebo response (De Pascalis, Chiaradia, & Carotenuto, 2002; Hyland & Whalley, 2008; Hyland, Whalley, & Geraghty, 2007; Price et al., 1999; Vase, Robinson, Verne, & Price, 2003; Whalley, Hyland, & Kirsch, 2008). In one study, expectation was manipulated by varying the magnitude of the reduction of painful heat during a conditioning phase (Price et al., 1999). The degree of reduction predicted both the post-conditioning expectation of relief and the subsequent placebo effect.

Context-specific individual differences in expectations may predict placebo responses, but what about enduring differences in personality? Such information could be useful in design clinical trials, as placebo responders could be potentially withheld from the sample or controlled for statistically, and it could be clinically useful, in that doctors seeking to use placebo treatments could target those most likely to respond. Many early studies trumpeted links found between personality and placebo responsivity, but these results often failed to replicate, and enthusiasm for such research waned (G. A. Hoffman, Harrington, & Fields, 2005; Kaptchuk et al., 2008; Shapiro & Shapiro, 1997; Turner, Deyo, Loeser, Von Korff, & Fordyce, 1994).

There are several possible explanations for this surprising lack of success. One possibility is there simply might not be any particular personality that is responsive to placebo. Alternatively, early placebo researchers might not have looked at the right personality characteristics. Motivated by this possibility, recent years have witnessed a

wave of new studies reporting links between placebo and personality characteristics, including suggestibility (De Pascalis et al., 2002; Morton, El-Deredy, Watson, & Jones, 2010), optimism (Geers, Kosbab, Helfer, Weiland, & Wellman, 2007; Geers, Wellman, Fowler, Helfer, & France, 2010; Morton, Watson, El-Deredy, & Jones, 2009), trait anxiety (Morton et al., 2009), behavioral drive (Schweinhardt, Seminowicz, Jaeger, Duncan, & Bushnell, 2009), fun seeking (Schweinhardt et al., 2009), and novelty-seeking (Schweinhardt et al., 2009), as well as other individual differences, such as motivation (Geers, Weiland, Kosbab, Landry, & Helfer, 2005) desire for relief (Vase et al., 2003). As of yet, none of these findings have shown robust replication, across multiple groups and paradigms, so more time will be needed to see whether this new wave of claimed personality-placebo links will revise the dominant current opinion that no specific placebo personality type exists.

Another possibility is that the question itself is flawed. Asking what personality factors predict placebo presumes that placebo-responsiveness is a stable and consistent trait within an individual. While a given placebo response appears to be relatively stable across multiple administrations (Morton et al., 2009; Whalley et al., 2008), several studies challenge the notion of a general placebo response tendency. In one early study, placebo response magnitude was found to be uncorrelated in a group of women exposed to three different types of pain (Liberman, 1964). In a more recent study, simply changing the brand name of the purported analgesic cream led to uncorrelated placebo responses (Whalley et al., 2008).

One possibility is that certain personality characteristics may predict placebo effects, but only in specific contexts. Using the terminology of pioneering personality

researcher Walter Mischel, placebo responding may be a function of Person x Situation interactions (Mischel, 2004). At least some studies have found convincing evidence that such interactions may exist. For example, in one study, trait spirituality predicted placebo response to a spiritually-characterized "flower essence" placebo treatment, but not when the same treatment was characterized as non-spiritual (Hyland & Whalley, 2008). In another study, trait spirituality predicted placebo response to the flower essence treatment, but not to "gratitude therapy" for sleep problems (Hyland et al., 2007). However, trait gratitude did predict the response to gratitude therapy. Taken together, these results suggest that studies designed to detect Person x Situation interactions may provide a powerful resolution to some of the confusion that has plagued efforts to understand who responds to placebo treatments. However, the intra-individual variability in placebo response that has been seen as a function of subtle changes of context (Liberman, 1964; Whalley et al., 2008) suggests that such work will remain challenging. An important direction for future research will thus also be to more thoroughly explore the intra-individual variability of placebo responses across diverse placebo contexts.

Functional neuroanatomy of placebo analgesia

The following section focuses on the physiology of placebo analgesia, as it the most well-studied placebo domain and the most germane to the present research. In recent years, numerous PET and fMRI studies have examined the functional neuroanatomy of placebo analgesia (Bingel, Lorenz, Schoell, Weiller, & Buchel, 2006; Craggs, Price, Perlstein, Verne, & Robinson, 2008; Craggs, Price, Verne, Perlstein, & Robinson, 2007; Eippert, Bingel, et al., 2009; Eippert, Finsterbusch, Bingel, & Buchel, 2009; Harris et al., 2009; Kong et al.,

2006; Kong et al., 2009; Lieberman et al., 2004; Lu et al., 2010; Petrovic et al., 2010; Price, Craggs, Verne, Perlstein, & Robinson, 2007; Scott et al., 2008; Wager, Atlas, Leotti, & Rilling, 2011; Wager et al., 2004; Wager et al., 2007; Watson et al., 2009; Zubieta et al., 2005). Before reviewing the findings of this growing literature, it is important to consider the different roles that we can broadly assign to brain regions identified through different types of contrasts. A primary distinction can be made between target and source regions. Target regions are those in which pain-related activity is reduced. Target activity would be observed with a contrast such as Control>Placebo. Source regions are those in which activity increases during placebo. These are regions that might be important for initiating and maintaining the placebo response. Source activity would be observed with a contrast such Placebo>Control. It is also important to distinguish activity according to when it occurs. Activity can be measured during the stimulus period or during a pre-stimulus, anticipation period (Wager et al., 2011; Wager et al., 2004; Watson et al., 2009). Several studies have also broken up long pain periods, for example looking separately at early and late pain activity (Eippert, Bingel, et al., 2009; Wager et al., 2004).

Looking across these studies, consistent source activity is seen in a number of frontal cortical regions, including bilateral dorsolateral prefrontal cortex (DLPFC), anterior PFC, OFC, and pregenual ACC (Wager & Fields, In press). While the exact roles of these regions in the placebo response is not known, one possibility is that they act as a circuit which generates and maintains expectations that lead to altered pain appraisals. This would be consistent with the established role of DLPFC in manipulating information in working memory (Smith & Jonides, 1999), and the OFC in generating and updating reward value and hedonic processes, and pregenual ACC in regulating emotional responses (Egner,

Etkin, Gale, & Hirsch, 2008; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Sarinopoulos et al., 2010). Reliable activity increases have also been observed in PAG (Wager & Fields, In press). PAG is a critical relay in a descending pathway which interacts with ascending pathways to up- and down-regulate nociceptive processing (Heinricher, Tavares, Leith, & Lumb, 2009; Tracey & Mantyh, 2007). It may be that altered appraisals or expectations in frontal cortical regions directly invoke this PAG-mediated descending modulatory influence.

Neural target regions that have been consistently reported include established pain-processing regions, such as rostral dorsal anterior cingulate cortex, SII and SI, medial thalamus and anterior insula (Wager & Fields, In press). A central question in placebo analgesia research has been the level at which nociceptive processing is affected. One possibility is that placebo analgesia exclusively involves modulation of brain regions that are primarily involved in post-nociceptive aspects of pain, such as affect. This hypothesis seems to fit well with two aspects of the neuroimaging literature. First, the target regions that are most consistently observed appear to be the ACC and anterior insula, regions that are typically believed to be involved primarily in post-nociceptive aspects of pain. Second, several studies have found effects on pain-processing regions primarily during the latter portion of the pain stimulus, or even subsequent to it (Eippert, Bingel, et al., 2009; Wager et al., 2004). In contrast to the hypothesis that placebo analgesia is accomplished primarily by modulation of post-nociceptive pain processing regions, the gate-control theory posits brainstem-mediated regulation of ascending nociceptive processing in the brainstem and spinal cord (Melzack & Wall, 1965). Several findings provide support for the gate-control theory in placebo. One is the reliable activation of PAG in placebo, consistent with the

implementation of a descending modulatory influence, as described above. In perhaps the most striking support of gate-control theory, one recent study reported placebo-induced decreases of nociceptive activity in the spinal card (Eippert, Finsterbusch, et al., 2009). Importantly, the gate-control theory would imply reduction of post-nocicpetive pain-processing activity as well. Thus, reduced activity in target regions in no way contradicts the gate-control theory. Taken together, these results suggest placebo analgesia arises at least in part from descending-inhibition of early pain-processing regions, but there may also be other effects that act on more-central, post-nocicpetive pain regions.

Overview of the present research

The present series of experiments examined the neural and cognitive processes that constitute distraction and placebo analgesia. Study 1 used the limited resources logic that when tradeoffs are observed between two concurrently performed tasks, it may be inferred that the tasks overlap in the mental resources they engage (Norman & Bobrow, 1975). Results suggest that overlapping cognitive resources are involved in both pain and executive attention and working memory. Extending this limited resources logic, study 2 provides evidence that these same executive attention and working memory resources are not involved in placebo analgesia, and that placebo analgesia and distraction provide separate routes to pain relief. Study 3 tested whether distraction and placebo analgesia reduce expression of a whole-brain, pain-predictive activity pattern. We found that while both distraction and placebo reduced pain reports, only distraction led to a widespread reduction of the neural signature of pain.

Chapter 2: Performance-dependent Inhibition of Pain by a Working Memory Task

Abstract

It is widely assumed that distraction reduces pain. Similarly, it is assumed that pain distracts from concurrent, unrelated cognitive processing, reducing performance on difficult tasks. Taken together, these assumptions suggest pain processing and cognitive function engage an overlapping set of domain-general, capacity-limited mental resources. However, experimental tests of this proposal have yielded mixed results, leading to alternative proposals that challenge the common model of a bidirectional relationship between concurrent pain and task performance. We tested these contrasting positions using a novel concurrent pain and executive working memory paradigm. Both task difficulty and nociceptive stimulus intensity were individually calibrated for each participant. Participants reported less pain during the working memory task than a visually matched control condition. Conversely, increasing levels of heat incrementally reduced task performance. Path analyses showed that variations in pain completely mediated this effect, and that even within a given heat level, trial-by-trial fluctuations in pain predicted decrements in performance. In sum, these findings argue that overlapping cognitive resources play a role in both pain processing and executive working memory. Future studies could use this paradigm to understand more precisely which components of executive function or other cognitive resources contribute to the experience of pain.

Introduction

It is commonly assumed that distraction reduces pain. Also common is the assumption that pain captures attention, reducing performance on difficult mental tasks (Eccleston & Crombez, 1999). Taken together, these assumptions imply a tradeoff between the experience of pain and goal-directed task performance (Legrain et al., 2009). When tradeoffs are observed between two concurrently performed tasks, it may be inferred that the tasks overlap in the mental resources they engage, and that the processing capacity of these resources is limited (Norman & Bobrow, 1975). Applying this logic to the tradeoff between performance and pain suggests the same executive resources that are believed to support goal-directed mental functioning may also play a role in the experience of pain.

Extensive research has tested the common wisdom assumption that pain engages domain-general cognitive resources in non-human animals (Boyette-Davis, Thompson, & Fuchs, 2008; Bushnell et al., 1984; Casey & Morrow, 1983; Dubner, Hoffman, & Hayes, 1981; Hayes, Dubner, & Hoffman, 1981; D. S. Hoffman, Dubner, Hayes, & Medlin, 1981), chronic pain patients (Dick, Eccleston, & Crombez, 2002; Dick & Rashiq, 2007; Glass & Park, 2001; Harman & Ruyak, 2005; Oosterman, de Vries, Dijkerman, de Haan, & Scherder, 2008; Park, Glass, Minear, & Crofford, 2001; Scherder et al., 2008; Tassain et al., 2003; Veldhuijzen, van Wijck, et al., 2006), and healthy volunteers exposed to transient noxious stimuli (Bantick et al., 2002; Bingel, Rose, Glascher, & Buchel, 2007; Brooks et al., 2002; Coen et al., 2008; Crombez, Eccleston, Van den Broeck, Van Houdenhove, & Goubert, 2002; Dick et al., 2003; Dowman, 2004; Frankenstein et al., 2001; H. G. Hoffman, Richards, et al., 2004; H. G. Hoffman, Sharar, et al., 2004; Houlihan et al., 2004; Kobor, Gal, & Vidnyanszky, 2009; Lautenbacher, Prager, & Rollman, 2007; Petrovic et al., 2000; Pud & Sapir, 2006; Raudenbush, Koon, Cessna, & McCombs, 2009; Remy et al., 2003; Roelofs, Peters, van der

Zijden, & Vlaeyen, 2004; Schlereth, Baumgartner, Magerl, Stoeter, & Treede, 2003; Seminowicz & Davis, 2007a, 2007b; Seminowicz, Mikulis, & Davis, 2004; Terkelsen et al., 2004; Valet et al., 2004; Van Damme, Crombez, Eccleston, & Goubert, 2004; Veldhuijzen, Kenemans, de Bruin, Olivier, & Volkerts, 2006; Wiech et al., 2005; Yamasaki, Kakigi, Watanabe, & Hoshiyama, 2000). We can distinguish these studies according to the explicit hypothesis tested (Fig. 2.1):

I. Pain ratings or other indices of pain experience are reduced by unrelated, concurrent, cognitive demand;

II. Cognitive performance is reduced by concurrent pain.

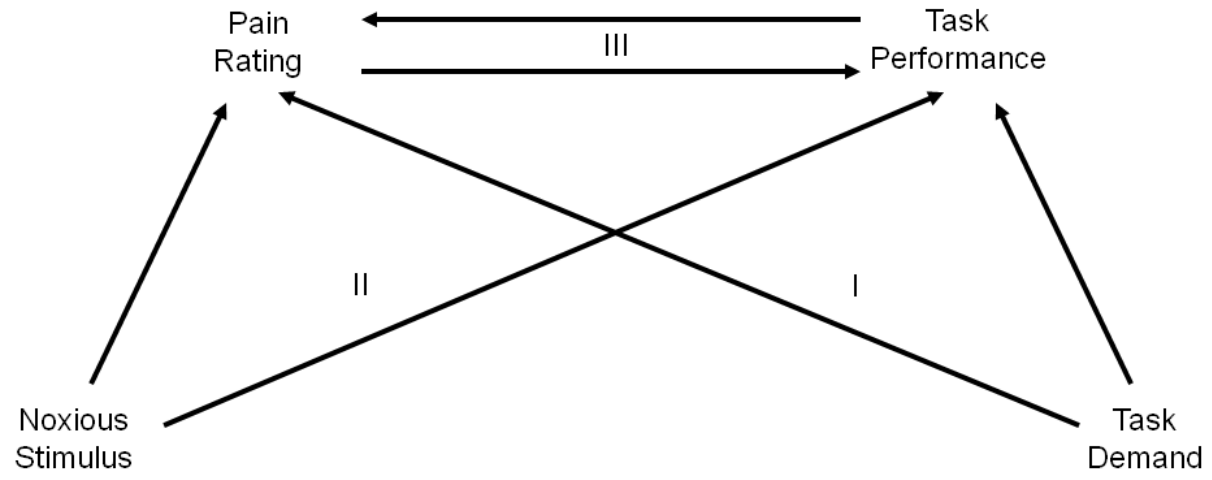


Fig. 2.1. Conceptual model of the relationship between pain and performance. Three general hypotheses can be tested to evaluate this model: I. Pain ratings or other indices of pain experience are reduced by unrelated, concurrent, cognitive demand; II. Cognitive performance is reduced by concurrent pain; III. A negative relationship exists between trial-by-trial fluctuations of performance and pain, even within a given heat level.

Research in which healthy humans are exposed to transient pain balances the experimental control afforded by animal studies and the applicability and specificity

possible in research with chronic pain patients (Table 1). Looking at these studies in total, the results are surprising. While many found that participants reported less pain when task demand was greater (Bantick et al., 2002; Bingel et al., 2007; Coen et al., 2008; Dowman, 2004; Frankenstein et al., 2001; H. G. Hoffman, Richards, et al., 2004; H. G. Hoffman, Sharar, et al., 2004; Kobor et al., 2009; Lautenbacher et al., 2007; Petrovic et al., 2000; Pud & Sapir, 2006; Raudenbush et al., 2009; Remy et al., 2003; Schlereth et al., 2003; Seminowicz & Davis, 2007b; Terkelsen et al., 2004; Valet et al., 2004; Veldhuijzen, Kenemans, et al., 2006; Yamasaki et al., 2000), a large number found no effect of increased task demand (Houlihan et al., 2004; Pud & Sapir, 2006; Roelofs et al., 2004; Seminowicz & Davis, 2007a, 2007b; Van Damme et al., 2004). Furthermore, only a few studies have reported a decline in cognitive performance as a function of pain (Bingel et al., 2007; Crombez et al., 2002; Houlihan et al., 2004), while most have found no effect (Coen et al., 2008; Dick et al., 2006; Dick et al., 2003; Houlihan et al., 2004; Kobor et al., 2009; Petrovic et al., 2000; Pud & Sapir, 2006; Seminowicz & Davis, 2007a, 2007b; Seminowicz et al., 2004; Veldhuijzen, Kenemans, et al., 2006; Wiech et al., 2005). This paucity of supportive findings has given rise to alternative proposals that task demand does not reduce concurrent pain (Leventhal, 1992; McCaul, Monson, & Maki, 1992), that pain does not reduce concurrent performance (Veldhuijzen, Kenemans, et al., 2006), and that pain and goal-directed cognitive performance can occur simultaneously without meaningful interaction (Seminowicz & Davis, 2007a, 2007b). All of these proposals challenge the common model of a bidirectional relationship between pain and goal-directed cognitive performance.

Alternatively, conceptual and methodological factors may account for the lack of support for the shared resources model found in the current literature (Devine & Spanos,

1990; Eccleston, 1995a). To discriminate among these competing models, we designed a paradigm to examine the relationship between pain and performance that accounted for several potentially confounding factors. Previous studies of the relationship between pain and cognitive demand have restricted their hypotheses to the level of experimental condition. However, the shared processes model would further predict a negative relationship between trial-by-trial fluctuations of performance and pain, even within a given heat level (pathway III in Fig. 2.1). A second goal of the current research was to test this prediction using a multilevel mediation framework. These analyses allowed us to further ask whether pain is a mediator of the heat level-performance relationship, which would suggest that conscious access to pain processing is an indicator of resource utilization.

Table 2.1. Summary of literature since 2000 examining the relationship between experimentally-induced pain and concurrent, unrelated task demand in healthy adults.

Study	Number of participants	Pain Induction Method	Cognitive Task	Did Noxious Stimulation Disrupt Performance?[1]	Did Task Demand Reduce Pain?[1]	Did Worse Performance Correspond to Greater Pain?[1,2]
Bantick et al., 2002 [1]	8	Heat	Counting Stroop	NR	Yes	NR
Bingel et al., 2007 [2]	16	Laser	N-Back	Yes	Yes	NR
Brooks et al., 2002 [6]	11,18[3]	Pressure	Global Motion Discrimination	NR	NR	NR
Buhle & Wager (present study)	24	Heat	3-back	Yes	Yes	Yes
Coen et al., 2008 [12]	12	Esophageal Pressure	1-back	No	Yes	NR
Crombez et al., 2002 [14]	67	Electrical Nerve Stimulation	Tone Discrminiation	Yes	NA	NA
Dick et al., 2006 [16]	16	Pressure	Auditory Oddball	No	NA	NA
			Compatability	No	NA	NA
Dowman, 2004 [20]	28	Electrical Nerve Stimulation	Subtraction	NA	Yes	NA
Frankenstein et al., 2001 [27]	10	Cold Pressor	Word Generation	NA	Yes	NA
Hoffman et al., 2004 [33]	8	Heat	Virtual Reality Game	NA	Yes	NA
Hoffman et al., 2004 [34]	39	Heat	Virtual Reality Game	NA	Yes	NA
Houlihan et al., 2004 [35]	20	Cold Pressor	Sternberg	Mixed	No	NR
Kobor et al., 2009 [39]	16	Capsaicin and Pinprick	Mental Rotation	No	Yes	NR
Lautenbacher et al., 2007 [40]	20	Heat and Electrical	Counting	NR	Yes	NR
Petrovic et al., 2000 [54]	7	Cold Pressor	Maze	No	Yes	NR
Pud & Sapir, 2006 [56]	60	Heat	Auditory Discrimination	No	Mixed	NR
Raudenbush et al., 2009 (exp 1) [57]	30	Cold Pressor	Video Games[4]	NA	Yes[5]	NA
Raudenbush et al., 2009 (exp 2) [57]	27	Cold Pressor	Video Games[4]	NA	Yes[5]	NA
Remy et al., 2003 [58]	12	Heat	Word Generation	NA	Yes	NA
Roelofs et al., 2004 [59]	60	Cold Pressor	Tone Discrimination	NA	No	NA
Schlereth et al., 2003 [62]	10	Laser	Subtraction	NA	Yes	NR
Seminowicz & Davis et al., 2007 [63]	23	Electrical Nerve Stimulation	Multi-Source Interference	No	No	NR
Seminowicz & Davis et al., 2007 [64]	13[5]	Electrical Nerve Stimulation	Counting Stroop	No	Yes	NR
			Emotional Distraction Stroop	No	No	NR
Seminowicz et al., 2004 [65]	16	Electrical Nerve Stimulation	Counting Stroop	No	NA	NA
			Emotional Distraction Stroop	No	NA	NA
Terkelsen et al., 2004 [70]	26	Electrical Nerve Stimulation	Addition	NA	Yes	NA
Valet et al., 2004 [71]	7	Heat	Stroop	NR	Yes	NA
Van Damme et al., 2004 [72]	99	Cold Pressor	Tone Detection	NA	No	NA
Veldhuijzen et al., 2006 (exp 1) [74]	16	Cold Pressor	Visual Search (1)	No	NA	NA
Veldhuijzen et al., 2006 (exp 2) [74]	12	Cold Pressor	Visual Search (2)	No	Yes	NR

Wiech et al., 2005 (behavioral) [78]	11	Capsaicin and Heat	Rapid Serial Visual Processing	NR	Yes	NR
Wiech et al., 2005 (fMRI) [78]	15	Capsaicin and Heat	Rapid Serial Visual Processing	No	NA	NA
Yamasaki et al., 2000 [79]	11	Electrical	Addition	NR	Yes	NR
			Memorization	NR	Yes	NR

1 "NA" indicates “Not applicable”, meaning the necessary conditions were not included in the experimental design. “NR” indicates "Not reported", meaning the necessary conditions were included in the experimental design, but the relevant analysis was not presented. 2. Within level of nociceptive input or task demand. 3. The effect of noxious stimulation on performance could be assessed for only 11 of the 18 participants, while the effect of task demand on pain could be assessed for entire sample. 4. Although several video game conditions were used, it is not clear that pain ratings were reduced in all conditions. 5. Personal communication with David Seminowicz, August 6, 2009.

Table 2.1. Summary of literature since 2000 examining the relationship between experimentally-induced pain and concurrent, unrelated task demand in healthy adults.

Method

Design. We designed a novel paradigm combining three levels of transient thermal pain with a 3-back executive working memory task. We chose the n-back paradigm (Kirchner, 1958) because of the high demand it places on central executive resources (Kane & Engle, 2002; Smith & Jonides, 1999). To ensure the 3-back was sufficiently challenging for each participant, we calibrated difficulty prior to the main experiment by adaptively adjusting the interval between probes. The allocation of executive resources in a given task reflects both task difficulty and contextual factors such as motivation (Legrain et al., 2009; Leotti & Wager, in press.). To increase motivation, participants were told that they could earn bonus money for good 3-back performance.

We compared pain in this demanding executive working memory condition to pain in the context of passively viewing a continuous letter mask, a baseline condition requiring minimal executive processes. In order to assure sufficiently high nociceptive input, we calibrated heat levels for each participant prior to the main task. We excluded participants who during this calibration procedure did not give pain ratings that corresponded reliably

with temperature or for whom we could not safely induce a high level of pain. For those individuals who remained in the study heat stimulation was only applied to the three most reliable skin sites out of eight initially tested. These procedures helped to substantially reduce within-participant variation. Finally, to obtain sensitive pain and performance measurements during the main experiment, participants rated each stimulus immediately after it occurred on a continuous rating scale, and 3-back responses were considered within a signal detection framework (Tanner & Swets, 1954; J. Zhang & S.T. Mueller, 2005).

All procedures were approved by the Columbia University Morningside Institutional Review Board.

Participants. Thirty participants began the experiment but five completed the calibration procedure with results that prohibited their continuation in the experiment: two participants were insufficiently sensitive to the maximum permitted temperature (48 °C), while 3 participants were insufficiently reliable in their ratings across sites (R2 less than .5, as described below). One additional participant began the main experimental task but could not complete it on account of intolerable pain. Twenty-four right-handed volunteers (mean age: 25.0 years, range: 18.2 years to 43.5 years; 15 female) completed the experiment in its entirety and were included in analyses. All participants had normal or corrected-to-normal vision and were free of neurological and psychiatric illness. Compensation was given at a rate of $12 per hour. Participants were told they could earn up to $10 in bonus compensation for fast and accurate performance to enhance motivation, but in fact this additional $10 was given to everyone, regardless of performance. Most

participants completed the entire experimental session in 2 hours to 2.5 hours, resulting in total payment of $34 to $40.

3-Back Task. At the beginning of each trial, an on-screen message stated whether the current trial would require performance of the 3-back task or passive viewing of the serial letter mask. In the 3-back task, participants indicated whether each letter presented in a pseudorandom sequence was the same or different from the letter exactly three positions prior. The letters were presented centrally for 840 ms, subtending approximately 0.7° visual angle vertically and 0.4° visual angle horizontally. Subsequent to the first three letters of a sequence, approximately 30% of letters were targets. Immediately after each probe letter a serial letter mask began. As described in greater detail below, for each participant a calibration procedure was conducted prior to the main experiment to determine a unique mask duration (mean: 698 ms, range: 104 ms to 1404 ms). Each letter in the serial letter mask was displayed for 26 ms. Participants pressed the "1" and "2" keys of the numeric keypad on a standard keyboard to indicate responses of "same" or "not the same". Responses could be made any time during the presentation of the letter or the subsequent mask. The mapping of the keys was randomized across participants.

Rating Scale. During both the nociceptive calibration procedure and the main task (described in greater detail below), ratings were made on a visual analogue scale anchored with numbers from 0 to 8 and the following verbal descriptors: 0 was ''no sensation''; 1 was ''non-painful warmth''; 2 was ''just painful''; 5 was "moderate pain"; 8 was ''the maximum level of pain you are willing to experience here today". Although pain intensity

and unpleasantness can be dissociated with specific instructions (for example, (Gracely, Dubner, & McGrath, 1979)), they are often highly correlated under normative conditions (Chapman et al., 2001). This scale was designed to integrate the two in a single intuitive rating. Although 8 was the largest number depicted on the scale, if the pain induced by a stimulation was greater than the maximum a participant was willing to tolerate in the experimental session, he or she was asked to rate the pain with a number reflecting how much greater the pain was than a level 8, up to a maximum of 10.

Procedure. The experimental session consisted of three distinct parts: nociceptive calibration, task difficulty calibration, and the main experimental task.

Nociceptive Calibration. Nociceptive calibration involved 24 trials in which participants rated the pain induced by thermal stimulation (10 °C/s ramp up, 7 s at target temperature, 10 °C/s ramp down) applied using a 16 mm TSA-II Neurosensory Analyzer (Medoc Ltd., Chapel Hill, NC). Ratings were given verbally, and participants were told they were free to give non-integer ratings. Trials proceeded in a fixed order through 8 different candidate skin sites on the participants left forearm. On each trial after the initial three stimulations, an adaptive procedure was used to predict temperatures corresponding to pain ratings of 2, 5, and 8 (henceforth referred to as low, medium, and high). First, a linear regression model was fit with Temperature as the independent variable and Pain as the dependent variable. On the basis of this regression, trials were identified for which the absolute value of the residual was greater than the median of the absolute values of the residuals of all trials. A second regression was then performed in which Pain values for

these trials were replaced with predicted values from the first regression. The low, medium, and high heat level temperatures predicted by this second model were used to determine the temperature applied on the subsequent trial. A fixed, counterbalanced order, chosen to minimize predictive power, ensured one application each of a predicted low, medium and high temperature at each of the eight locations. Thus, the order of low, medium, and high trials was always the same, but the actual temperatures applied varied across trials and participants. If the predicted temperature for the heat level to be applied on a given trial was greater than the maximum permitted temperature of 48 °C, 48 °C was used instead. Participants were not told how the temperatures were determined or what they were. Following completion of the calibration trials, participants were excluded from further participation if the ratings they provided did not reliably correspond to the applied temperatures (R^2 less than .5) or if the maximum permitted temperature of 48 °C did not induce sufficient pain (estimated pain rating less than 6.5).

For 6 out of the 24 participants included in this analysis, the temperature estimated to correspond to a pain rating of 8 was greater than the maximum permitted temperature of 48 °C (max = 50.5 °C, mean = 49.1 °C, SD = .8 °C). For these participants, 48 °C was used as their final high heat level temperature in place of their estimated level 8. For all participants, the final heat level temperatures determined at the end of the calibration procedure were used for the duration of the experimental session (low: mean = 41.4, SD = 2.0; medium: mean = 44.5, SD = 1.4; high: mean = 47.4, SD = .9).

Task difficulty calibration. The second part of the experimental session was intended to familiarize participants with the 3-back task and to calibrate its difficulty.

Following written and verbal instruction, participants practiced the task in a short block of trials. Accuracy was indicated with a positive or negative sound immediately after each response. Participants were required to repeat this practice block if low performance suggested a lack of understanding, and were allowed to choose to repeat the practice block as many times as they wished. The calibration block consisted of 160 letter stimuli. Initial mask duration was 1000 ms. Prior to letter stimulus number 26, target sensitivity over the previous 15 stimuli was assessed with the nonparametric signal detection measure A (J. Zhang & S.T. Mueller, 2005), which provides a measure of performance accuracy independent of response bias (the tendency to report "yes" or "no" systematically). If sensitivity was higher than the targeted level of A = .75, mask duration was reduced by 200 ms * (A-.75) * 4, while sensitivity equal or lower than A = .75 lead to an increase of 200 ms * (A-.75) * -4/3. Additional adjustments were made every 15 stimuli until all 160 stimuli were complete, yielding ten adjustments for each participant.

Main task: Pain judgment and 3-back dual task. The third part of the experimental session consisted of 36 trials lasting about 50 s each (Fig. 2.2). Before each trial, the experimenter placed the thermode on one of the 3 skin sites identified as reliable during the nociceptive calibration. When ready, the participant pressed a key to begin the trial. An on-screen message indicated whether the current trial would require performance of the 3-back task (Working Memory Load trial) or passive viewing of the serial letter mask (No Load trial). On Working Memory Load trials, participants were cued to perform the 3-back task for the next 39 s of the trial. On No Load trials, they were cued to maintain fixation on a continuous serial letter mask for the 39 s trial. Each participant performed 18

trials of each type over the course of the experiment; the assignment of task condition on each trial was randomized. On both Working Memory Load and No Load trials, after 13 s a tone indicated to the participant that noxious heat would be delivered. Heat onset began after a 26 s delay. The heat lasted for approximately 13 s, (2.1 s ramp up, 8.8 s target temperature, 2.1 s ramp down). Ramp rates ranged from 4.2 °C/s to 10 °C/s, depending on the target temperature. Unbeknownst to participants, only the temperatures determined at the end of the nociceptive calibration to correspond to the low, medium, and high heat levels were applied during the main task. In total, each participant performed 6 Working Memory Load and 6 No Load trials at each of the 3 heat levels.

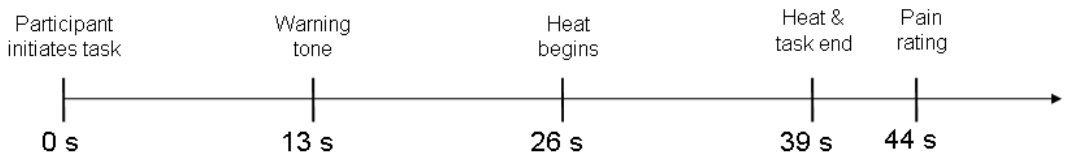


Fig. 2.2. Timeline of single trial.

After 39 s, the temperature returned to baseline. On Working Memory Load trials the 3-back task ended at this point. For both Working Memory Load and No Load trials, the remaining portion of the trial was identical. After an additional 5 s of the serial letter mask, an onscreen rating bar appeared, along with the cue "how painful?" Participants were instructed to use the mouse to rate the pain they experienced during the heat stimulus by clicking anywhere on the rating bar that appeared on the screen, using the same anchors and following the same instructions as during the nociceptive calibration. After the rating was made following each trial, the experimenter then moved the thermode to the next skin site, after which the participant could begin the next trial whenever she was ready. To ensure the ratings given during the main experimental session were consistent with those

given during the calibration procedure, participants were given an opportunity to practice using the onscreen rating bar with feedback in a training procedure prior to the main experimental task.

Unique letter and trial sequences were created for every participant and every trial with scripts written in MATLAB (version 7.5.0.342). Pseudorandom sequences were determined using the Mersenne Twister number generation algorithm (Matsumoto & Nishimura, 1998), with constraints to avoid long strings of identical letters and trial types.

Mediation Analyses. A mediation framework was used to assess the hypothesis that trial-by-trial fluctuations in pain would negatively correlate with task performance. A test for mediation indicates whether a covariance between two variables (X and Y) can be explained by a third variable (M). A significant mediator is one whose inclusion as an intermediate variable in a path model of the effects of X on Y significantly affects the slope of the X – Y relationship; that is, the difference (c - c') is statistically significant. More formally, the mediation test can be captured in a system of three equations:

$$Y = cX + e'_Y$$

$$M = aX + e_M$$

$$Y = bM + c'X + e'_Y$$

where Y, X, and M are n (Participant) by t (Trials) data vectors containing the outcome (either Y_1, Performance, or Y_2, Pain), the predictor ($X_{1,2}$, Heat Level), and data from a candidate mediating variable (either M_1, Pain, or M_2, Performance). e_Y, e_M, and e'_Y vectors denote residual error for the outcome and mediator controlling for x and the outcome controlling for x and m, respectively. The a path is the estimated linear change in M per X

(the slope of the Heat Level-Performance or Heat Level-Pain relationship). The *b* path is the slope of the mediator-outcome relationship controlling for *x* (Pain-Performance, or Performance-Pain, controlling for Heat Level). The *c* and *c'* paths are as described above. Statistical tests on *a* and *b* path coefficients assess the significance of each relationship. In addition, a statistical test of (*c* – *c'*) can be performed by testing the significance of the product of the path coefficients *ab*. We tested the significance of *ab* using the accelerated, bias-corrected bootstrap test (Efron & Tibshirani, 1993) with 10,000 bootstrap samples to test each of the *a*, *b*, and *ab* path coefficients . Since the hypotheses contained explicit predictions of the direction of the relationships between variables (all negative except for the relationship between Heat Level and Pain), all tests were one-tailed.

Results

To test the hypothesis that task demand would reduce pain, we analyzed the data in a linear mixed effects model with Participant as a random-effects predictor, Task Demand (Working Memory Load or No Load) as a fixed-effects predictor, Heat Level as a continuous, fixed-effects predictor (low, medium, high), and Pain as the dependent variable (Fig. 2.3). A main effect of Heat Level indicated that higher levels of heat led to greater Pain, $F(1, 768) = 281.82$, $MSE = 2934.89$, $p < .001$, while a main effect of Task Demand indicated that greater demand led to lower Pain, $F(1, 768) = 48.3$, $MSE = 166.73$, $p < .001$. A main effect of Participant indicated that average Pain was different across individuals, $F(23, 768) = 3.07$, $MSE = 10.61$, $p < .005$. An interaction of Heat Level and Task Demand indicated that greater Task Demand reduced Pain by different amounts depending on the level of heat, $F(1, 768) = 12.64$, $MSE = 17.45$, $p < .005$. Post-hoc comparisons using Tukey's honestly significant difference procedure confirmed that task demand reduced pain ratings at each

Heat Level ($p < .05$, corrected). A Participant x Task Demand interaction indicated that the magnitude of task-induced reduction in Pain varied across individuals, $F(23, 768) = 3.45$, $MSE = 3.45$, $p < .05$, and a Participant x Heat Level interaction indicated additional individual variability in the amount of Pain reported across the three levels of heat, $F(23, 768) = 10.41$, $MSE = 7.54$, $p < .001$.

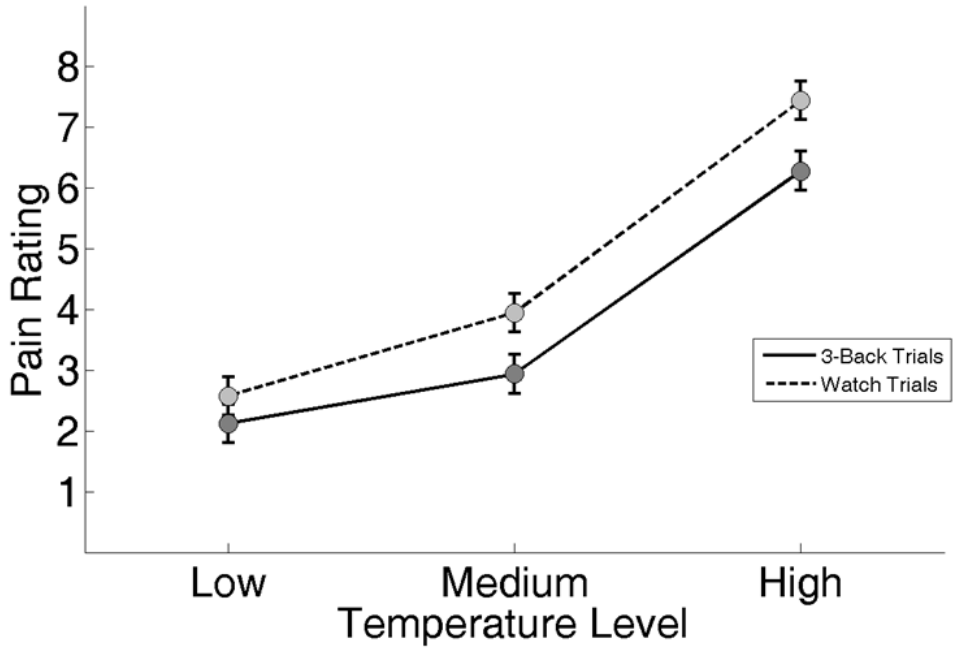


Fig. 2.3. The effect of task demand on pain. Error bars reflect within-subject standard error computed using pooled variance from the Participant x Performance and Participant x Performance x Heat Level interactions [47].

A second mixed effects model tested the hypothesis that higher heat levels would reduce task performance (Figs. 2.4 and 2.5). Heat Level was entered as a continuous, fixed-effects predictor and Participant was entered as a random-effects predictor. The dependent measure was Performance, assessed with the nonparametric measure of target sensitivity A. Only Working Memory Load trials were included in this analysis, as no performance data were available for the No Load trials. A main effect of Heat Level indicated that higher levels of heat led to lower Performance, $F(1, 378) = 9.24$, $MSE = .130$, $p < .01$, while a main

effect of Participant indicated that Performance varied across individuals, $F(23, 378) = 5.51$, $MSE = .157$, $p < .001$. Post-hoc comparisons using Tukey's honestly significant difference procedure indicated worse Performance at the high versus low level of heat, but no difference between the medium level of heat and the other two ($p < .05$, corrected).

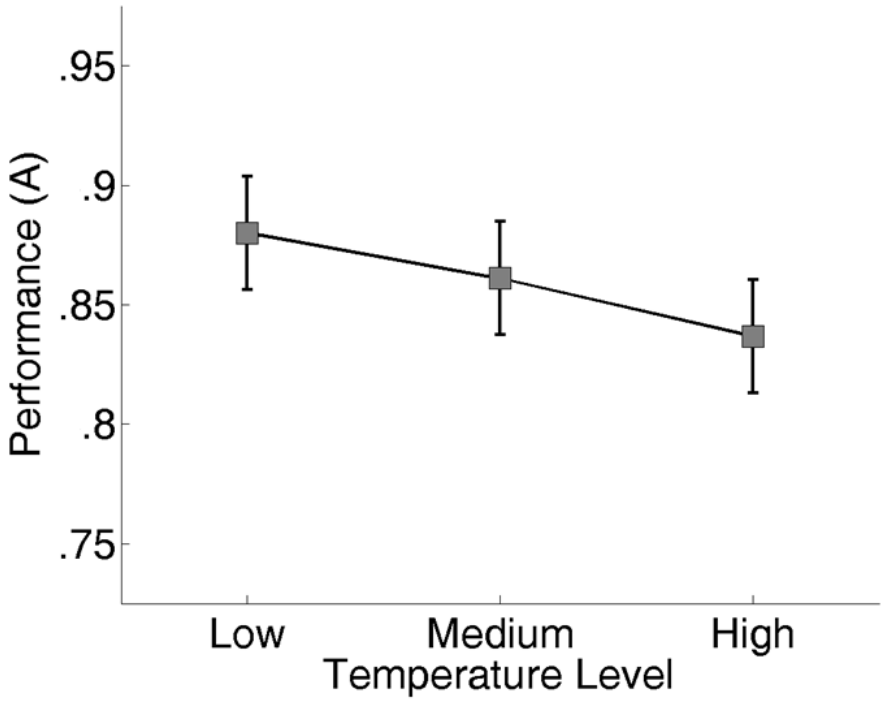


Fig. 2.4. The effect of heat level on performance. Error bars reflect within-subject standard error of the Participant x Heat Level interaction. The mean within-subject standard deviations of A were .14, .14, and .16 for low, medium, and high levels of heat, respectively.

In order to test the relationships among heat level, pain, and task performance, we conducted two multilevel mediation analyses. The results of these are summarized in Figure 2.6. The first analysis assessed the hypothesis that trial-by-trial fluctuations in pain mediated the relationship between heat level and performance. We found that Pain fully mediated the relationship between Heat Level and Performance (ab= -.03, Z = -3.91, $p <$ .001). In addition to the significant mediation (ab) effect, there was a significant, positive effect of Heat Level on Pain (a = 2.07, Z = 4.22, $p < .001$), and a negative effect of Pain on

Performance, controlling for Heat Level (b = -.02, Z = -3.52, p < .001). Although there was a strong positive relationship between Heat Level and Performance (c = -.02, Z = -3.35, p < .001), after controlling for Pain, this relationship was no longer significant (c' = .02, *ns*), indicating that Pain was a complete mediator.

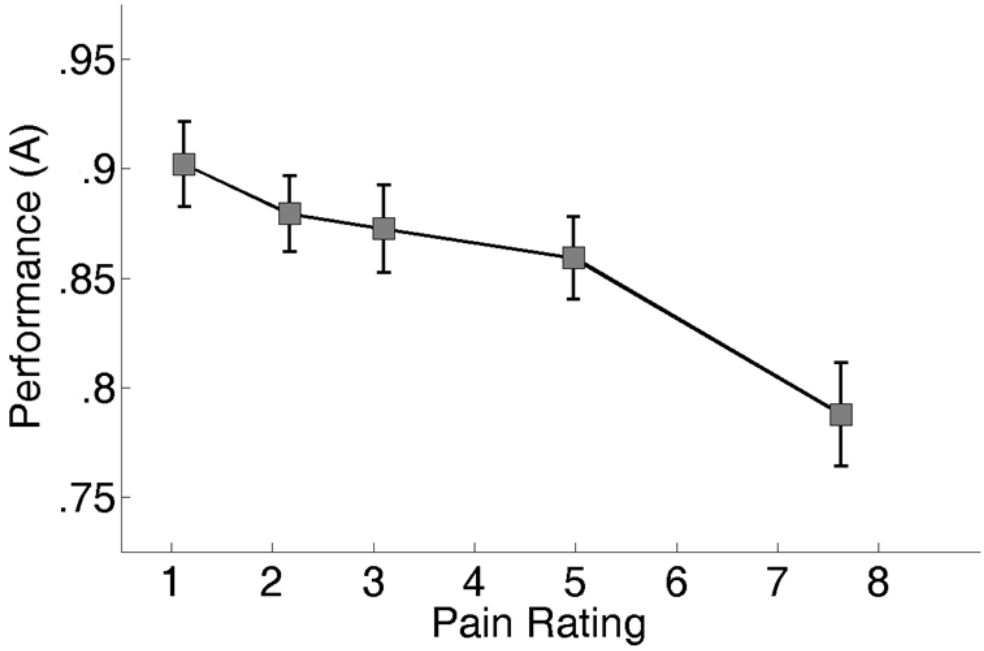


Fig. 2.5. The relationship between pain and performance. For visualization, performance data were binned into quintiles based on pain ratings.

A second mediation analysis assessed the complementary hypothesis that trial-by-trial fluctuations in performance mediated the relationship between heat level and pain. We found that Performance partially mediated the relationship between Heat Level and Pain (ab = .01, Z = 1.77, p < .05). In addition to the significant mediation (ab) effect, there was a significant, negative effect of Heat Level on Performance (a = -.02, Z = -3.36, p < .001), and a negative effect of Performance on Pain, controlling for Heat Level (b = -2.16, Z = -3.61 p < .001). After controlling for Performance, a direct relationship remained between Heat Level and Pain (c = 2.07, Z = 4.20, p < .001; c' = 2.04, Z = 4.13, p < .001).

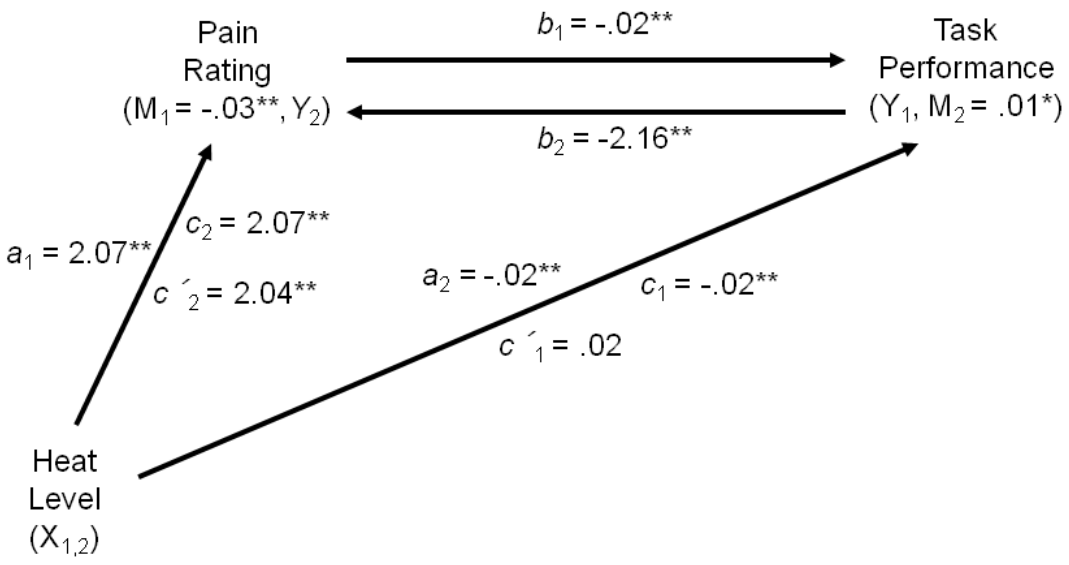


Fig. 2.6. Summary of mediation results for Working Memory Load trials. A first mediation analysis assessed whether Pain (M1) mediated the relationship between Heat level (X1) and Performance (Y1): a1: the relationship between Heat Level and Pain; b1: : the relationship between Pain and Performance, controlling for Heat Level; c_1: the observed relationship between Heat level and Performance; c'_1: the relationship between Heat Level and Performance, controlling for a_1 and b_1. A second mediation analysis assessed whether trial-by-trial fluctuations in Performance (M_2) mediated the relationship between Heat Level (X_2) and Pain (Y_2): a_2: the relationship between Heat Level and Performance; b_2: the relationship between Performance and Pain, controlling for Heat Level; c_2: the observed relationship between Heat Level and Pain; c'_2: the relationship between Heat Level and Pain, controlling for a_2 and b_2. * p< .05. **p< .001.

Discussion

Previous research has typically assumed a bidirectional relationship between pain and task performance (Legrain et al., 2009), implying both engage an overlapping set of domain-general, capacity-limited cognitive resources. Yet experimental evidence has been equivocal, leading to alternative proposals (Leventhal, 1992; McCaul et al., 1992; Seminowicz & Davis, 2007a, 2007b; Veldhuijzen, Kenemans, et al., 2006). We sought to distinguish between these competing views using a novel paradigm designed to place continuous demand on executive processes and sensitive, trial-level analyses. Participants reported less pain during a difficult 3-back working memory task than a visually matched control condition. Conversely, increasing levels of heat incrementally reduced task

performance, and trial-by-trial pain reports predicted performance within a given heat level. Using a mediation framework, we found that accounting for these trial-by-trial pain reports fully explained the relationship between heat and performance. In a separate mediation analysis, we also found that trial-by-trial performance in the task partially explained pain reports. Taken together, these findings suggest that the processes that contribute positively to both pain and executive working memory performance share capacity-limited resources (Legrain et al., 2009). Furthermore, resource allocation varies from one process to the other over time, so that observed variation in each predicts effects on the other. That is, better performance on a given trial predicts lower pain, and higher pain predicts worse performance. Though our mediation analyses are consistent with the notion that each causally influences the other, follow-up experiments that independently manipulate both pain and task performance experimentally are needed to solidify causal inferences.

A shared resources model of pain and cognitive performance is consistent with several neuroimaging meta-analyses that found reliable pain-related activity in lateral and anterior PFC (Peyron et al., 2000; Salimi-Khorshidi et al., 2009). These regions have been strongly implicated in diverse executive processes (Wager & Smith, 2003), and activity in them has been shown to increase parametrically with demand in an number of executive tasks (Braver et al., 1997; Cohen et al., 1997; Durston et al., 2003; Jonides et al., 1997; Szameitat, Schubert, Muller, & Von Cramon, 2002; Veltman, Rombouts, & Dolan, 2003). However, the few previous studies that have directly examined the effects on PFC activity of incremental changes in pain have found activation with painful stimulation, but not incremental changes of activity that tracked increases in stimulus intensity or reported

pain (Bornhovd et al., 2002; Buchel et al., 2002). One possible explanation for this difference is that PFC activity may not provide a sensitive index of resource limitation across levels of pain. For example, PFC may be activated under both weak and strong noxious stimulation, but for different reasons. At low levels of stimulation, PFC might be recruited to reappraise pain or allocate attention elsewhere, consistent with previous studies that suggest a pain-regulatory role (Lorenz, Minoshima, & Casey, 2003; Valet et al., 2004; S. Zhang, J. S. Tang, B. Yuan, & H. Jia, 1997; Zhang, Tang, Yuan, & Jia, 1998; Y. Q. Zhang, J. S. Tang, B. Yuan, & H. Jia, 1997). Conversely, at high levels of stimulation, greater PFC activity might reflect increased generation of pain-related cognitions or allocation of attention towards pain. This account predicts that the PFC-pain relationship may be moderated by the intensity of noxious stimulation: it should be negatively correlated with pain at low stimulus intensity and positively correlated with pain at high stimulus intensity. Other explanations that need to be tested are also possible, including: (a) BOLD activity may show a ceiling effect, because PFC is strongly engaged by even weak noxious stimuli; (b) as pain increases, individuals may shift toward alternate coping strategies that do not recruit lateral PFC; and (c), PFC may be recruited to resolve ambiguity and enhance discrimination under weak stimulation, but to regulate pain during intense stimulation. Interestingly, these latter two alternatives imply moderation effects opposite to our initial explanation above, yielding divergent empirical predictions.

The affirmative findings of the present research again raise the question of why some studies have observed interference between pain and cognitive performance while others did not (Table 2.1). Comparing these studies suggests several technical and conceptual factors may be critical to observing this relationship, including the type and

intensity of task demand and the degree of temporal overlap between task and pain processing (see also discussions in (Eccleston, 1995a; Seminowicz & Davis, 2007b)). Specifically, we posit that the task must substantially and continuously demand executive resources. While we did not test this hypothesis in the current research, several aspects of the experimental design reflect this assumption. First, we chose a task that places heavy demands on executive working memory and that has been well characterized both theoretically and neurally. N-back performance requires both the continuous updating of representations in working memory and response selection (Wager & Smith, 2003). An earlier study similarly found that concurrent n-back performance reduced pain (Bingel et al., 2007). However, consistent with the view that executive demand is critical for a task to interfere with pain processing, another study that used the Sternberg task, a working memory task that places relatively little demand on executive function, found no reduction in pain during task performance (Houlihan et al., 2004). Interference tasks and other Stroop-like tasks also engage executive processes (Miyake et al., 2000), but current results from interference tasks are mixed: pain reduction was reported with a standard Stroop task (Valet et al., 2004) and with numeric Stroop task variants (Bantick et al., 2002; Seminowicz & Davis, 2007b), but not when the challenging Multisource Interference Task was used (Seminowicz & Davis, 2007a). Several other studies found a task-related reduction in pain using paradigms that are less well characterized in the literature, including maze performance (Petrovic et al., 2000), visual search (Veldhuijzen, Kenemans, et al., 2006), arithmetic (Dowman, 2004; Schlereth et al., 2003; Terkelsen et al., 2004; Yamasaki et al., 2000), word generation (Frankenstein et al., 2001; Remy et al., 2003), video and virtual reality games (H. G. Hoffman, Richards, et al., 2004; H. G. Hoffman, Sharar,

et al., 2004; Raudenbush et al., 2009), mental rotation (Kobor et al., 2009), detection and discrimination (Brooks et al., 2002; Crombez et al., 2002; Pud & Sapir, 2006; Roelofs et al., 2004; Van Damme et al., 2004), and rapid serial visual presentation tasks (Wiech et al., 2005). Because it is less clear which component processes these tasks require, at present these findings cannot be used assess the hypothesis that executive demand is critical. Furthermore, tasks which should place minimal demand on executive resources have yielded mixed results: while an emotional distraction counting Stroop task variant (Buhle, Wager, & Smith, in press.) had no effect on pain (Seminowicz & Davis, 2007b), a simple 1-back task successfully reduced pain (Coen et al., 2008). Future research will need to explicitly compare different types of demand within a single experiment in order to provide a rigorous test of the role of executive demand in pain reduction.

A second choice was to calibrate task difficulty. Our goal was twofold. First, we sought to ensure the task would yield a measure sufficiently sensitive to detect a deleterious influence of pain on performance for each participant. If the task is not sufficiently demanding, then painful stimulation may only transiently and subtly interrupt task performance. Modest decrements in performance will only be detectable if participants are performing near capacity and performance measures are sensitive. Second, we sought to ensure that successful performance of the task would require a profound commitment of executive resources (Eccleston, 1995a). Even tasks that engage executive function may not interfere with pain if they do not place a heavy demand on information processing.

A third choice we made was to motivate participants with a monetary reward for good performance. Our intention was to ensure the greatest possible dedication of

resources to the task. Unmotivated participants might perform at a lower level sufficiently below their ability, leaving idle resources available for concomitant pain processing (Legrain et al., 2009). However, given the possibility that reward processing may interact with pain (Leknes & Tracey, 2008), future research should confirm that motivated performance of a demanding task can reduce pain regardless of reward context.

Even if pain and task processing engage overlapping executive resources, if this engagement does not overlap in time, participants would be able to switch attention back and forth between pain and cognitive demand, allowing both to be fully processed (Eccleston, 1995b; Veldhuijzen, 2006; Veldhuijzen, Kenemans, et al., 2006). Thus, a fourth choice we made was to combine continuous thermal pain with a speeded n-back task that placed relatively continuous demand on executive working memory. In contrast, when Seminowicz and Davis (Seminowicz & Davis, 2007a) combined relatively continuous electrical pain with the relatively brief and interspersed processing demands of the Multisource Interference Task, no reductions in pain or performance were observed.

Future studies could directly test the hypotheses we offered to explain the inconsistent previous findings. For example, the criticality of executive demand could be examined by directly comparing the pain reduction incurred by executive working memory tasks such as the n-back with working memory tasks which only involve storage, such as the Sternberg task (for more on this distinction, see (Wager & Smith, 2003)). Future research could also examine whether different types of executive function, such as perceptual attention demand and executive working memory, influence pain differently (Lavie, 2005). A third important goal for future research would be to clarify the role of pain duration. We hypothesize that brief shock or contact heat will cause intermittent and minor

disruption of task performance on response selection, such as a Stroop task, but more profound disruption of tasks that require temporal continuity, such as a difficult n-back. Furthermore, brief noxious stimuli with rapid onsets may capture attention even in the context of a challenging cognitive task.

In sum, these findings support the view that subjective pain and executive working memory performance engage overlapping, capacity-limited cognitive resources. Furthermore, reciprocal variation in pain and performance within a given heat level suggests these limited resources are dynamically allocated between the two processes. Future studies could use the paradigm and analyses we present here to more precisely identify which cognitive resources participate in pain processing and to illuminate the specific roles they play.

Chapter 3: Placebo and Distraction: Two Distinct Routes to Pain Relief

Abstract

An explosion of recent research has studied whether placebo treatments influence health-related outcomes and their biological markers, but almost no research has examined the psychological processes required for placebo effects to occur. This study tested whether placebo and cognitive distraction reduce pain through shared or independent processes. We crossed an executive working memory task with placebo treatment and tested their joint effects on thermal pain perception. A Task x Placebo interaction would provide evidence for shared mechanisms, whereas additive effects would imply separate mechanisms. Participants (n=33) reported less pain in both Task and Placebo conditions, but the reductions were additive, indicating that the executive demands of the task did not interfere with placebo analgesia. Furthermore, placebo analgesia did not impair task performance. Together, these data suggest that placebo analgesia does not depend on active redirection of attention, and that expectancy and distraction can be combined to maximize pain relief.

Introduction

Placebo effects have long been both a nuisance to clinical researchers and a therapeutic adjuvant to medical practitioners, and they are thought to affect diverse treatment outcomes (Finniss, Kaptchuk, Miller, & Benedetti, 2010). Placebo effects have been most commonly documented in pain (Vase, Petersen, Riley, & Price, 2009), and placebo analgesia has been demonstrated in both laboratory and clinical contexts

(Hrobjartsson & Gotzsche, 2004a). While earlier theories often assumed placebo effects simply reflected response bias on the part of participants (Clark, 1969), neuroimaging studies have demonstrated that placebo analgesia involves modulation of pain-related responses in the brain (Petrovic, Kalso, Petersson, & Ingvar, 2002; Price et al., 2007; for review, see Wager & Fields, In press; Wager et al., 2004; Wager et al., 2007) and spinal cord (Eippert, Finsterbusch, et al., 2009).

While much research has focused on whether placebo effects exist, there is almost no research on the constituent psychological processes that are required for placebo analgesia. In particular, although most current theories emphasize the role of expectations (Stewart-Williams & Podd, 2004), it is unclear how expectations relate to other cognitive processes such as attention, and what conditions are required for their creation and maintenance. One possibility is that reduced expectations of pain might lead one to redirect attention away from pain, which is known to have analgesic effects (Buhle & Wager, 2010; Legrain et al., 2009; Valet et al., 2004). If so, expectations might be thought of as a form of cognitive control, and executive processes that control attention might be necessary for expectations to influence pain. In support of this view, a number of neuroimaging studies have reported placebo- and expectancy-related activity in the dorsolateral prefrontal cortex (Atlas, Bolger, Lindquist, & Wager, 2010; Eippert, Bingel, et al., 2009; Kong et al., 2006; Pariente, White, Frackowiak, & Lewith, 2005; Wager et al., 2004; Wager et al., 2007; Zubieta et al., 2005), an area known to be involved in executive working memory (Smith & Jonides, 1999). Furthermore, fronto-parietal activity predicts the magnitude of placebo analgesia (Wager et al., 2011), and measures of frontal activity have been shown to be

correlated with both placebo analgesia and tasks requiring executive control (Benedetti et al., 2006).

However, this support is indirect, as the prefrontal cortex is involved in a number of cognitive and emotion-related processes not specifically related to control of executive attention and working memory. Alternatively, expectations may exert their influences primarily though non-cognitive state changes. For example, believing one has been given an analgesic may reduce anxiety (Evans, 1985), known to enhance pain (Weisenberg, Aviram, Wolf, & Raphaeli, 1984), or such beliefs may engage descending anti-nociceptive systems that release pain-reducing neurotransmitters such as endogenous opioids (Amanzio & Benedetti, 1999; Wager et al., 2007) without mediation by cognitive processes.

To directly test whether executive resources mediate placebo analgesia, we designed a novel paradigm combining thermal pain, performance of a difficult working memory task, and placebo drug treatment. In previous work, we confirmed that performing a task that places demands on multiple aspects of executive attention and working memory (the N-back; Kane & Engle, 2002; Kirchner, 1958; Smith & Jonides, 1999) substantially reduces pain (Buhle & Wager, 2010). Here, we tested whether this cognitive demand interferes with analgesia produced by a placebo treatment or whether the two manipulations have independent analgesic effects. When interference is observed between two concurrently performed tasks, it may be inferred that those tasks overlap in the mental resources they engage, and that the processing capacity of these resources is limited (Norman & Bobrow, 1975). We applied this limited resources logic to the relationship between attention-driven analgesia caused by the task and expectation-driven analgesia caused by the placebo. If the executive attention and working memory processes engaged

by the task also support placebo analgesia, then we would expect concurrent performance of the task would inhibit placebo analgesia, resulting in an under-additive interaction of placebo and task on pain ratings. Alternatively, if placebo analgesia does not involve these executive processes, than the effects of task and placebo should be additive, implying independent mechanisms.

Method

Participants. Thirty-three right-handed volunteers (mean age: 27.2 years, range: 18 years to 55 years; 19 female) completed the experiment. Participants were compensated at a rate of $12 per hour, with performance bonuses up to $10 in Session One and $20 in Sessions Two and Three. All gave informed consent in accordance with the Columbia University Institutional Review Board.

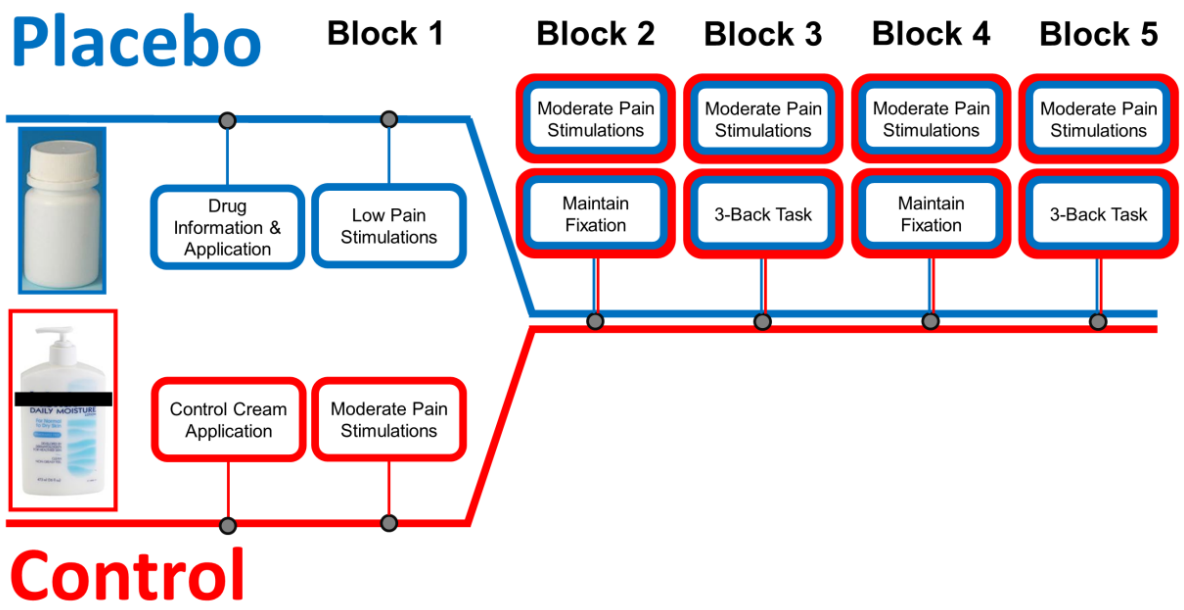
Procedure. Each participant completed three experimental sessions on separate days. In Session One, participants completed 3-back task and thermal calibration procedures similar to those reported previously (Buhle & Wager, 2010). The 3-back calibration consisted of single block of 16 trials, matched in duration (20.16 s) to those used in Sessions Two and Three. Performance was assessed in a signal detection framework, using *A*, a non-parametric measure of target sensitivity (Jun Zhang & Shane T. Mueller, 2005). The duration of individual letters in a given trial was reduced if participants demonstrated good performance on the previous two trials ($A \geq .95$). The final letter duration achieved in the calibration procedure was then used for the remainder of the experiment.

Thermal pain was delivered using a 16 mm TSA-II NeuroSensory Analyzer (Medoc Ltd., Israel). The calibration procedure consisted of 24 trials, matched in duration (20.16 s, including 4 s ramp up and 2 s ramp down) to those used in Sessions Two and Three. Ratings were made on a 100 unit visual analog scale (VAS) with anchors of "No pain" and "Worst imaginable pain" (Price, McGrath, Rafii, & Buckingham, 1983). Trials proceeded in a fixed order through 8 skin sites on the left volar forearm. On each trial after the initial three, an adaptive procedure was used to predict temperatures corresponding to pain ratings of 10, 50, and 90 (henceforth referred to as low, moderate, and high). A linear regression model was fit with Temperature as the independent variable and pain as the dependent variable. Temperatures whose predicted values corresponded to low, moderate, and high pain in were used to determine the temperature applied on the subsequent trial. A fixed, counterbalanced order, chosen to maximize predictive power and avoid confounds between temperature and time, ensured one application of each of the three levels at each of the eight locations. Thus, trial order was always the same, but the temperatures applied varied across trials and participants. The final temperature levels derived from this procedure were then used for the remainder for of the experiment (for those completing the study, low: mean=41.5 °C, SD=1.83 °C; moderate: mean=44.9 °C, SD=1.99 °C) Participants were not permitted to advance to Sessions Two and Three if they demonstrated an inconsistent relationship between temperature and pain ($r^2<.7$; n=13), if they could not perform the task (n=2), or if their calibrated moderate temperature was higher than 50 °C; (for safety reasons; n=1).

Sessions Two and Three consisted of counterbalanced placebo and control sessions (Fig. 3.1A). In both sessions, an emollient cream was applied to the skin. In placebo

sessions, participants were told this cream contained a powerful analgesic, while in control sessions, participants were told it was a non-analgesic control cream. In each session, participants then rated pain in 5 blocks of 16 thermal stimuli (Fig 3.1B). In control sessions, only moderate pain stimuli were administered. In placebo sessions, low pain stimuli were covertly administered in the first block, in order to strengthen the expectation of analgesia. The remaining 4 blocks featured moderate stimuli, identical to those applied during the control session. In both sessions, during blocks 2 and 4 participants were told to fixate on a centrally located cross during stimulation. During blocks 3 and 5, participants performed the 3-back task for the duration of stimulation. We chose to compare pain during the 3-back task to pain during fixation rather than cognitive task with lower executive demand, such as a 2-back, in order to maximize our power to detect attention effects and to provide the best estimate of the total effect of distraction for comparison with the placebo effect.

A.



B.

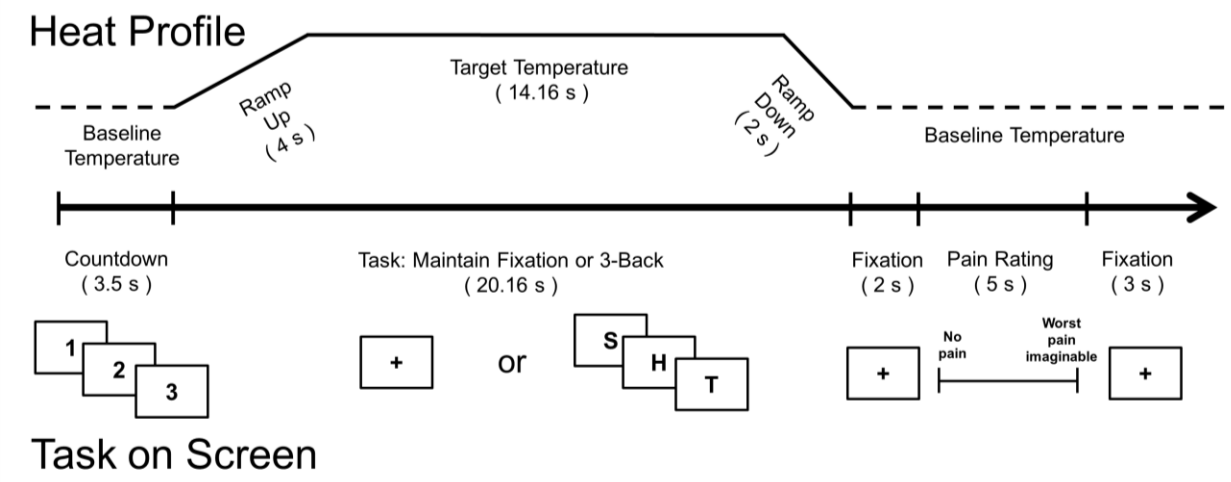


Fig. 3.1. Experimental Design**. A.** Sessions Two and Three. Placebo and Control session order was counterbalanced between participants. Blocks 2-5 were identical in both conditions. **B.** Pain trial timeline. Each block included 16 pain trials.

At the end of Session Three, participants were asked to rate the effectiveness of the analgesic, (1="not at all effective"; 10="extremely effective"). Participants were then asked how much they would pay to use the cream in a hypothetical fourth session identical to Sessions Two and Three.

Analyses. In all analyses, session order was used as a between-subjects predictor. Only data from the experimental blocks (blocks 2-5) were used.

A first set of analyses used general linear models (GLMs) to test for effects of Task (3-back vs. fixation) and Placebo (placebo vs. control cream) on pain. Model 1A was a mixed-effects GLM that included within-subjects effects of Placebo, Task, Placebo *x* Task, and mean-centered trial number and mean-centered trial number squared to model habituation/sensitization. Participant was modeled as a random effect. To account for variability in mean pain reports and scale use across participants, we first normalized trial-by-trial ratings within-participant by converting them to z-scores. We calculated Cohen's *d* to estimate the effect sizes of the main effects and interaction. Because conventional statistics cannot provide evidence about the likelihood of the null hypotheses, we used Gallistel's Bayesian procedure on condition averages to estimate the odds in favor of accepting the null hypothesis that there was no interaction of Task and Placebo (Gallistel, 2009). Models 1B through 1D were repeated-measures ANOVAs using condition averages. In model 1B, we used the normalized trial-by-trial ratings. In model 1C, to provide an alternate method to account for between-participant variability, we used non-normalized pain ratings as the outcome variable and each participant's average pain rating as a between-subjects covariate. To account for the possibility that results might be influenced

by non-linear habituation effects across blocks, resulting in higher pain ratings in block 2 (the first experimental no task block) than in blocks 3-5 (the second experimental no task block and both task blocks), models 1D and 1E repeated the analyses of 1B and 1C with data from block 2 removed.

Models 2 and 3 concerned the relationship between Placebo, Pain, and task performance. As during the calibration procedure, task performance was assessed using *A*. Only data from blocks in which participants performed the task (blocks 3 and 5) were used in these analyses. Model 2 tested whether performance differed as a function of Placebo (placebo vs. control runs) using a mixed-effects GLM. As before, we examined the strength of evidence for vs. against effects of placebo on task performance using Gallistel's Bayesian procedure (Gallistel, 2009). Model 3 sought to confirm that Pain predicted performance on a trial-by-trial basis. First, we normalized pain ratings made by each participant in these two blocks by converting them to z-scores. Next, Pain was used as a continuous, within-subjects predictor in a mixed-effects GLM, with Participant as a random effect, Placebo, mean-centered trial number and mean-centered trial number squared as within-subjects covariates of no interest, and performance as the outcome variable.

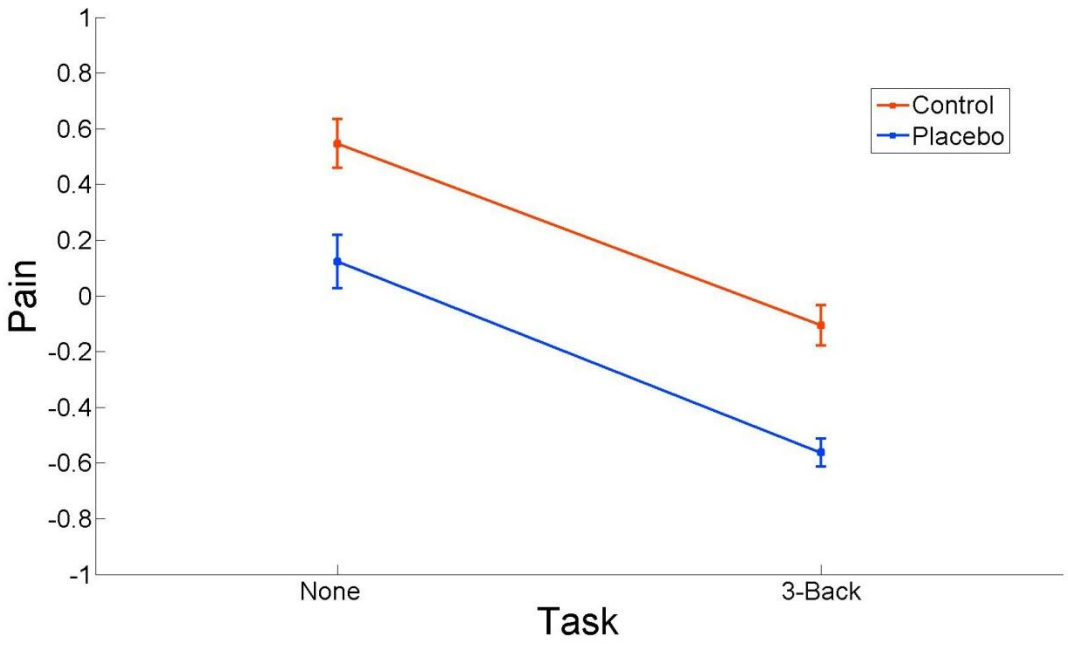
Results

Participants on average rated the effectiveness of the placebo as 6.6 (SD = 1.9) on the 10 point scale, and said they would pay $16.69 (SD = $9.23) to use it again.

Results from Model 1A confirmed both a main effect of Task, indicating that performing the task reduced pain, $t(31) = 9.82$, $p < .001$, $d = 1.71$, and a main effect of Placebo, $t(31) = 4.10$, $p < .001$, $d = .71$, indicating that the placebo treatment also reduced

pain. There was no Task x Placebo interaction, indicating that the strength of the placebo analgesia was unaffected by the concomitant working memory load, $t(31) = -.33$, $p = .746$, $d = -.06$ (Fig. 3.2A). Gallistel's Bayesian procedure estimated the odds in favor of the null hypothesis that the effects of Task and Placebo were additive to be 6.44 to 1, evidence deemed "substantial" in this framework (Gallistel, 2009). Models 1B, 1C, 1D and 1E yielded qualitatively identical findings, confirming that these results were not dependent on the scaling of pain reports or driven by habituation.

A.



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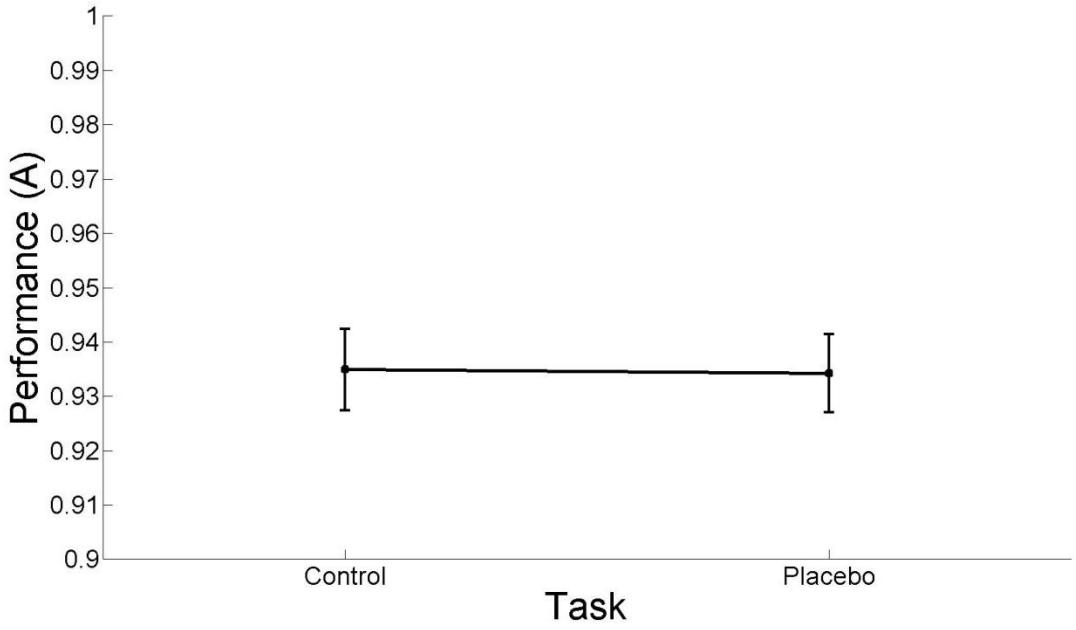

Fig. 3.2. Pain and performance. **A.** Both Placebo and Task reduced pain, but there was no interaction. Pain ratings were normalized within participants for all experimental blocks (blocks 2-5). **B.** Working memory task performance was identical in the Placebo and Control conditions. In both plots, error bars reflect between-subjects standard error.

Results from Model 2 showed no effect of Placebo on task performance $t(31) = -.48$, $p = .63$, $d = -.08$ (Fig. 3.2B). Thus, while placebo analgesia was effective in relieving pain, it did not improve task performance. Gallistel's Bayesian procedure estimated the odds in favor of the null hypothesis that the effects of Task and Placebo were additive to be 7.97 to 1, also deemed "substantial" (Gallistel, 2009). Results from Model 3 showed a significant effect of trial-to-trial pain reports on task performance, with higher pain reports predicting lower performance, $t(31) = -2.42$, $p < .05$, $d = -.43$.

Discussion

Recent theories of placebo analgesia have posited a role for executive processes in the transformation of expectations into pain relief (Benedetti, 2010; Benedetti et al., 2006;

Krummenacher, Candia, Folkers, Schedlowski, & Schonbachler, 2010; Wager et al., 2004). However, these theories have largely relied on indirect, neural evidence of DLPFC involvement. To test this hypothesis directly, we used a dual task design that independently manipulated executive demand and placebo processing. If placebo analgesia requires executive attention and working memory, then the performance of a secondary task that places high demands on these limited resources should inhibit placebo analgesia. We found that both placebo treatment and executive demand reduced pain substantially, but their effects were nearly perfectly additive, and Bayesian odds substantially favored the null hypothesis of no interference. Furthermore, placebo analgesia had no effect on working memory performance, in spite of the fact that performance was sensitive to trial-by-trial fluctuations in pain. Taken together, these data suggest that placebo analgesia does not require executive attention or working memory during pain processing. It is therefore unlikely that placebo-related expectations cause relief by altering cognitive processes related to the perception and online interpretation of the nociceptive stimuli, for example by leading one to redirect attention away from pain (Buhle & Wager, 2010).

At first blush, these findings might appear to contradict those of Benedetti and colleagues (2006), who found that placebo analgesia was reduced in patients with Alzheimer's disease. In that study, the degree of reduction in placebo analgesia was largest for those with reduced performance on a frontal lobe task battery and reduced functional connectivity between prefrontal and posterior brain sites. Given the profound impairments in executive function and frontal atrophy in Alzheimer's patients, Benedetti and colleagues' findings imply that executive function is involved at some point in the placebo process. However, it is also possible that impairments in other processes besides executive

attention or working memory, such as long-term memory, might be responsible for the failure to recall context information and generate appropriate expectations. Given the present results, one plausible explanation is that executive function is important for understanding context and constructing meaning during placebo administration (including the treatment and delivery of care-related context cues; (Benedetti, 2002; Moerman, 2002)), but neither executive attention nor working memory is not critical for actively maintaining placebo responses once the context has been established.

Other evidence for the role of executive function in placebo analgesia has been suggestive, but still indirect, demonstrating the involvement during placebo of neural regions believed to support executive function (Eippert, Bingel, et al., 2009; Kong et al., 2006; Krummenacher et al., 2010; Pariente et al., 2005; Wager et al., 2004; Wager et al., 2007; Zubieta et al., 2005). Our results suggest that the involvement of the frontal cortex does not imply the engagement of executive attention and working memory in this case. The DLPFC is a broad, heterogeneous area containing neurons that subserve a number of different functions. The DLPFC-dependent processes that support placebo analgesia may be different from the DLPFC-dependent processes that support working memory. In a recent analysis of individual differences in placebo analgesia, for example, Wager and colleagues (2011) found that DLPFC and superior parietal activity strongly predicted the magnitude of placebo analgesia. While the regions involved at first glance appeared to be similar to those involved in executive working memory, the placebo-predictive regions did not overlap with those derived in a meta-analysis of working memory. Furthermore, a formal test of whether placebo analgesia could be predicted by areas involved in working memory vs.

those involved in emotional appraisal, including regions in DLPFC in both cases, showed that only the appraisal-related regions predicted the magnitude of placebo effects.

The same ambiguity complicates interpretation of a recent study that found rTMS to DLPFC eliminated placebo analgesia (Krummenacher et al., 2010). While their findings, like the fMRI studies, implicate DLPFC in placebo analgesia, the study did not test whether the TMS stimulation influenced cognitive performance as well. In a commentary on the work, Benedetti (2010) noted that the use of a standard reference system in that study rather than individual functional localization of DLPFC also raised the possibility that the effect could be due to suppression of adjacent tissue, rather than DLPFC itself. Future TMS studies could reduce this ambiguity by demonstrating a selective deficit of executive function at the stimulated regions.

However, while such a demonstration would resolve the ambiguity of localization, it would not resolve the question of functional specificity. Swaths of cortex as large as those impacted by TMS, or resolved by current neuroimaging techniques, likely support a great diversity of functions (Wager, Lindquist, Nichols, Kober, & Van Snellenberg, 2009). Thus, the possibility remains that DLPFC is important for placebo analgesia in ways unrelated to cognitive control. In fact, extensive evidence suggests that DLPFC regions are also involved in the descending opioidergic system mediating placebo analgesia (Eippert, Bingel, et al., 2009; Wager et al., 2007; Zubieta et al., 2005), which may be relatively independent of executive control. The lateral and medial prefrontal cortices project directly to the brainstem periaqueductal gray (PAG), a major site of opioid production that modulates descending analgesia in the spinal cord, and stimulation of the lateral prefrontal cortex in rats evokes analgesia that is reversed by blocking opioids in the PAG (Y. Q. Zhang et al.,

1997). Thus, the frontal cortex might play a role in affective appraisal and direct regulation of brainstem systems that is conceptually and functionally distinct from its role in cognitive control. The present findings bear on this hypothesis, because they suggest that placebo expectancy-based analgesia, believed to rely on this system, is independent of cognitive processes that underlie distraction-based analgesia. This dissociation provides a step forward towards establishing the existence of multiple, independent systems for the regulation of pain.

Given that trial-by-trial pain reports predicted task performance, both in these data and in previous work (Buhle & Wager, 2010), it is noteworthy that there was no significant effect of placebo on performance. Two uninteresting reasons for this finding could be a) lack of power and b) insensitivity of performance scores to resource demands, e.g., due to floor or ceiling effects (Norman & Bobrow, 1975). Four pieces of evidence argue against these alternatives. First, the effect size was very small and opposite the predicted direction, Second, Bayesian odds substantially favored the null hypothesis that placebo does not affect performance. Third, performance was calibrated to be well below ceiling, and fourth, there existed a negative relationship between pain and performance on a trial-by-trial basis, demonstrating sensitivity. Thus, these two explanations are less likely than a theoretically interesting alternative: That placebo and executive working memory distraction may influence different aspects of pain. This interpretation is in line with the main findings of the study showing separable effects of placebo and 3-back demand, and further suggests that placebo may influence affective aspects of pain that are separable from those driven by cognitive elaboration. In addition, it suggests that pain-related

cognitive impairment is an interesting functional outcome measure in its own right, which may not be affected by the same treatments that influence pain report.

In addition to helping illuminate the mechanisms that underlie placebo analgesia, the results of the present study may also have important clinical implications. If placebo and distraction do not rely on overlapping resources, then each provides a separate route to pain relief. Combining them may be an efficient way for physicians to maximize analgesia without the use of drugs. To further explore this possibility, future work should test the same interaction using neural correlates of pain as outcomes. Such work would be important not only for confirming the additive effects on pain reported here, but could also reveal important distinctions in how placebos (and related expectancy-based interventions) and distraction impact pain. For example, they may exert their influence on discrete pain processing stages, on distinct anatomical systems as discussed above, or on distinct neurochemical systems. An intriguing possibility is that expectancy effects are mediated mainly by medial prefrontal-striatal-brainstem systems, with strong involvement of the opioid system and only a peripheral role for frontal and parietal cortices (Atlas et al., 2010; Wager et al., 2007; Zubieta et al., 2005), whereas the effects of cognitive distraction are mediated mainly by direct frontal cortical-somatosensory interactions, without engagement of brainstem pain-control systems.

The present results also raise the possibility that placebo treatments may work in patients with impaired executive function. We suggested above that the disrupted placebo response observed in Alzheimer's patients (Benedetti et al., 2006) might reflect the importance of executive function or mnemonic processes at the time of placebo induction. In some cases, it might be possible to strengthen the induction procedures and thereby

counteract the effect of weakened executive function, or to use conditioning-based methods that may not require executive function (Atlas et al., 2010; Colloca et al., 2008; Stewart-Williams & Podd, 2004). In other cases, life experiences prior to the development of the deficit may provide the needed therapeutic expectation, obviating the need for a specific induction procedure (Colloca & Benedetti, 2006). Future research examining the placebo response in different patient groups and different treatment contexts will be critical to unravel this important clinical issue.

Finally, it is important to note there exist several alternative explanations for the results of the current study. Executive function encompasses a complex set of cognitive processes. It remains possible that placebo analgesia does involve executive processes other than those required for 3-back task performance. While the present results cannot exclude this possibility, we selected the 3-back task because it is complex and places a relatively continuous demand on an array of executive functions that load on general fluid intelligence, including working memory maintenance in the face of distraction, updating, attention shifting and task switching, scheduling of sequences of cognitive operations, and monitoring of working memory control (Kane & Engle, 2002; Smith & Jonides, 1999). The involvement of multiple executive working memory components is thought to underlie findings that training on the N-back task improves general fluid intelligence as assessed by Raven's Advanced Progressive Matrices test (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008). Another possible alternative explanation is that placebo analgesia involves the same executive processes as the 3-back task, but in the present experiment the combined requirements of the placebo and task did not exceed available executive resources. However, this alternative is unlikely because task difficulty was titrated for each

participant, pushing performance well below ceiling. In addition, the task had a strong impact on pain, even relative to other published distraction tasks (see Buhle & Wager, 2010), suggesting that demand on executive attention and working memory was high and continuous during task performance.

In sum, the present data suggest that placebo analgesia does not require executive attention or working memory during the processing of painful stimuli, and that distraction and placebo provide two separate routes to pain relief. Previous data suggesting the involvement of DLFPC likely reflect the involvement either of adjacent regions or non-executive functions subserved by the DLPFC. If executive function does play a role in placebo analgesia, it is probably limited to the development of appropriate expectations, rather than the ongoing, active redirection of attention or reappraisal of painful events.

Chapter 4: Distraction but not placebo reduces neural signature of pain

Abstract

Distraction and placebo analgesia are two effective psychological manipulations for alleviating pain. Recently, we showed that distraction and placebo do not appear to rely on overlapping cognitive resources, and thus they can be combined to maximize pain relief (Buhle, Stevens, Friedman, & Wager, in press). In the present study, we crossed an executive working memory task with an expectancy-based placebo treatment in two separate fMRI sessions in order to directly compare the neural effects of each method of pain relief (n=21). Both distraction and placebo significantly reduced behavioral pain reports. Because pain processing involves a complex network of brain regions, we tested for neural reductions in two independently-derived, whole-brain, pain-predictive pattern maps. The first pattern was generated using machine learning analyses on heat pain data from participants run previously in our lab (Wager, Atlas, Lindquist, & Kross, Submitted). The second pattern was generated using 'reverse-inference' meta-analysis on 224 pain imaging studies (neurosynth.org; Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). Pattern-expression analysis with both maps yielded nearly identical results: While distraction reduced the neural signature of pain in nearly all participants (95% and 90%, respectively, $P < .001$ in both), placebo reductions were not different from chance (38% and 48% of participants). These results call into question whether expectancy-driven placebo effects exert widespread effects on pain processing, and provide a way to distinguish different brain effects of different types of pain modulatory techniques in a principled, a priori fashion.

Introduction

Clinicians have long used distraction and placebo as treatments for pain. For example, a pediatrician may give a child a shot while telling an engrossing story, and internists commonly prescribe antibiotics for viral colds against which they are impotent. Despite the profound growth in medical technology in recent decades, these psychological manipulations have not disappeared from clinical settings. In fact, virtual reality video systems intended to distract patients from ongoing pain have become increasingly common in burn units (H. G. Hoffman et al., 2011), and more than 40% of clinicians believe placebos have therapeutic effects (Raz et al., 2011).

Much laboratory research on distraction and placebo has used pain as a model system, both because the physiology of pain is relatively well-understood, and because pain can be reliably and transiently induced in healthy participants. Experimental studies have established that both distraction and placebo effectively reduce pain reports (Buhle & Wager, 2010; Vase et al., 2009). Recently, we showed that distraction and placebo do not appear to rely on overlapping cognitive resources, and thus they can be combined to maximize pain relief (Buhle et al., in press). However, there has long been debate as to whether changes in pain reports reflect online changes in the internal experience of pain, or other factors, such as response biases (Clark, 1969; Clark & Goodman, 1974; Hrobjartsson & Gotzsche, 2003, 2006).

The advent of neuroimaging promises a possible resolution to this debate. Reductions in pain-processing regions as a function of psychological manipulation would provide strong confirmation that reduced pain reports reflect veridical changes in pain

experience. In the case of distraction, a number of studies have done just that, showing reduction in numerous pain processing regions, including medial thalamus (Bantick et al., 2002; H. G. Hoffman et al., 2011; Remy et al., 2003), anterior insula (Bantick et al., 2002; Brooks et al., 2002; H. G. Hoffman et al., 2011; Remy et al., 2003), and ACC (Bantick et al., 2002; Frankenstein et al., 2001; H. G. Hoffman, Richards, et al., 2004; Remy et al., 2003). More limited evidence suggests that distraction may reduce pain-related activity in SI and SII (H. G. Hoffman, Richards, et al., 2004; Petrovic et al., 2000). Similarly, neuroimaging studies of placebo have consistently reported reduced activity in established pain-processing regions (Lieberman et al., 2004; Lu et al., 2010; Price et al., 2007; Wager et al., 2011; Wager et al., 2004). One recent summary identified areas in which at least three studies reported at least one coordinate. This analysis found replicated decrease in established pain-processing regions such as rostral dorsal anterior cingulate cortex, SII and SI, medial thalamus and anterior insula (Wager & Fields, In press). A recent meta-analysis found reliable decreases in some overlapping pain-processing regions, including the rostral cingulate, thalamus, and anterior and posterior insula, as well as other potential pain-processing regions, including the mid-cingulate and the basal ganglia (Amanzio, Benedetti, Porro, Palermo, & Cauda, in press).

Although this growing body of work suggests that distraction and placebo may indeed dampen activity in pain processing regions, caution is still warranted. To date, all studies claiming decreases have done so on the basis of activation peaks in putative pain processing regions. However, pain is a complex experience involving many brain regions, and it may involve both increases and decreases in regional activity. Furthermore, nearly all cortical regions involved in pain processing are likely also involved in other processes.

Thus, it is unclear if the scattered peaks reported previously reflect widespread neural reductions in pain processing, reductions in a limited number of pain processing areas, reductions in non-pain related processes, or even chance findings and publication bias.

In the present study, we crossed an executive working memory task with an expectancy-based placebo treatment in two separate fMRI sessions in order to obtain measures of both distraction and placebo analgesia within the same participants. Next, we calculated summary measures of neural activity in each condition using pain-predictive pattern maps derived from independent samples. Our results provide the first tests of whether distraction and placebo lead to overall reductions in the neural signature of pain.

Method

Participants. Thirty-one right-handed volunteers (mean age: 27.8 years, range: 18 years to 45 years; 14 female) completed the experiment. However, scanner errors rendered imaging data unusable for 10 participants. Additionally, behavioral data was lost for 9 participants, including 6 of the participants with usable imaging data. To maximize sample size, behavioral analyzes were conducted on all 22 participants with behavioral data (mean age: 27.5 years, range: 18 years to 45 years; 9 female), and imaging analyses were completed on 21 participants (mean age: 27.9 years, range: 18 years to 45 years; 10 female). Participants were compensated at a rate of $12 per hour, with performance bonuses up to $10 in Session One and $20 in Sessions Two and Three. All gave informed consent in accordance with the Columbia University Institutional Review Board.

Procedure. Each participant completed three experimental sessions on separate days. In Session One, participants completed 3-back task and thermal calibration procedures similar to those reported previously (Buhle & Wager, 2010). The 3-back calibration consisted of a single block of 16 trials, matched in duration (20.16 s) to those used in Sessions Two and Three. Performance was assessed in a signal detection framework, using A, a non-parametric measure of target sensitivity (Jun Zhang & Shane T. Mueller, 2005). The duration of individual letters in a given trial was reduced if participants demonstrated good performance on the previous two trials (A≥.95). The final letter duration achieved in the calibration procedure was then used for the remainder of the experiment.

Thermal pain was delivered using a 16 mm TSA-II NeuroSensory Analyzer (Medoc Ltd., Israel). The calibration procedure consisted of 24 trials, matched in duration (20.16 s, including 4 s ramp up and 2 s ramp down) to those used in Sessions Two and Three. Ratings were made on a 100 unit visual analog scale (VAS) with anchors of "No pain" and "Worst tolerable pain" (Price et al., 1983). We explained that a rating of 100 should be comparable to coffee cup so hot that, if it were any hotter, he or she would no longer be able to hold it. Trials proceeded in a fixed order through 4 skin sites on the left volar forearm. Six temperatures (44.5 °C, 45.3 °C, 46.1 °C, 46.9 °C, 47.7 °C, 48.5 °C) were used. A fixed, counterbalanced order, chosen to maximize predictive power and avoid confounds between temperature and time, ensured one application of each of the six levels at each of the four locations. Thus, trial order and temperature levels used in the calibration were the same for all participants. Following the calibration procedure, a linear regression model was fit with Temperature as the independent variable and pain as the dependent variable.

Temperatures whose predicted values corresponded to 10 and 50 (henceforth referred to as low and moderate pain were then used for the remainder for of the experiment (for those completing the study, low: mean=45.5 °C, SD=.7 °C; moderate: mean=47.1 °C, SD=.8 °C) Participants were not permitted to advance to Sessions Two and Three if they demonstrated an inconsistent relationship between temperature and pain (r^2<.5; n=12), if they could not perform the task (n=7), or if their calibrated moderate temperature was above our safety cut-off (>50 °C; n=5).

Following the thermal and task calibration procedures, participants underwent a placebo induction procedure similar to those we have used previously (Buhle et al., in press). First, participants rated a single moderate stimulation on each of the four volar forearm locations. Next, the experimenter applied to the skin an emollient cream, which participants were told contained a powerful analgesic. Following cream application, participants were asked to wait ten minutes for the cream to take effect. After the wait, participants rated a single low stimulation on each of the four volar forearm locations. Importantly, participants were told that these stimulations were at the same temperature as those they experienced before the cream was applied.

Finally, participants performed one practice block of the task similar to those used in Sessions Two and Three. The block consisted of 9 trials, each lasting 20.16 s (Fig. 4.1). Each of three trials types (Watch, Left-Right, and 3-Back) appeared three times in pseudorandom, counterbalanced order. On Watch trials, participants were told to simply maintain fixation on a centrally-presented crosshair. On Left-Right trials, participants were asked to press the left mouse button when an “L” appeared and the right button when an “R” appeared. On 3-Back trials, participants were asked to press one button whenever a

letter shown was the same as the letter presented three prior, and the other button when the letter was not the same. The letter duration achieved in the calibration procedure was used for both Left-Right and 3-Back trials. Furthermore, the sequence of each trial of one type was tethered to the sequence of a trial of the other type, such that correct responding would entail an identical sequence of button presses. Temperatures were also applied for the duration of each trial. To maintain the placebo rouse, low temperatures were used throughout the block. Participants rated the temperatures following each trial.

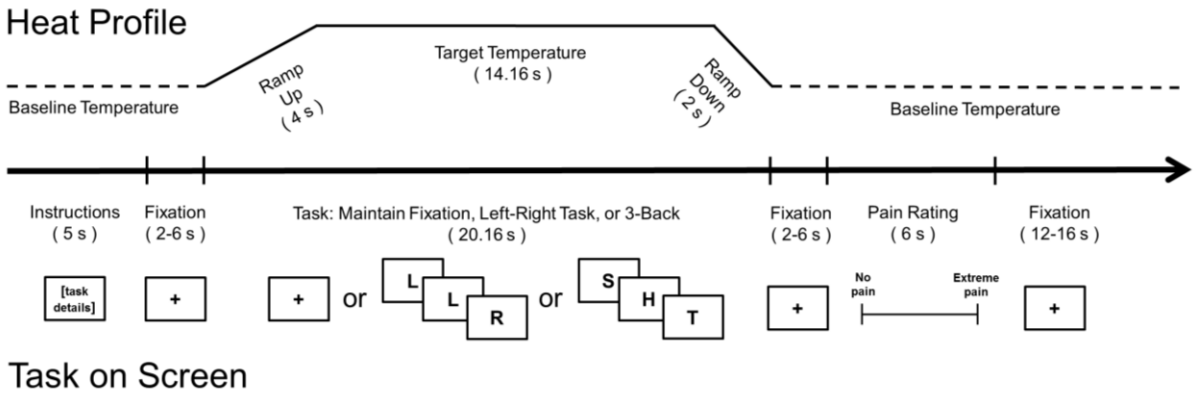

Fig. 4.1. Experimental design for Sessions Two and Three. Placebo and Control session order was counterbalanced between participants. Blocks 2-5 were identical in both conditions.

Sessions Two and Three consisted of counterbalanced placebo and control sessions. After practicing the task, subjects were placed in a 3-Tesla Phillips scanner. In both sessions, the same emollient cream used during Session One was then applied to the skin. While in placebo sessions participants were told this cream contained the analgesic used previously, in control sessions participants were told it was a non-analgesic control cream. Following cream application, two five minute resting-state functional scans were acquired. Participants then performed 6 blocks of the task. In control sessions, only moderate pain

stimuli were administered. In placebo sessions, low pain stimuli were covertly administered during the first block, in order to strengthen the expectation of analgesia. The remaining 5 blocks featured moderate stimuli, identical to those applied during the control session. All blocks contained three trials of each type (Watch, Left-Right, and 3-Back) in pseudorandom, counterbalanced order. For a given participant, the same trial order was used in both the placebo and control sessions. In addition, the same order of correct and incorrect responses was maintained across the two sessions, though the actual letters used varied.

At the end of Session Three, participants were asked to rate the effectiveness of the analgesic, (1="not at all effective"; 10="extremely effective"). Participants were then asked how much they would pay to use the cream in a hypothetical fourth session identical to Sessions Two and Three.

Functional MRI Acquisition and Preprocessing. Whole-brain functional data were acquired in 42 axial slices (3 × 3 × 3 mm voxels) with a T2*-weighted gradient echo sequence (repetition time (TR) = 2,000 ms, echo time (TE) = 20 ms, flip angle = 72, field of view (FOV) = 22.4 cm). Structural data were acquired with an MP-RAGE SENSE sequence (1 × 1 × 1 mm, flip angle = 8, FOV = 25.6 cm x 20 cm).

Functional scans were preprocessed with SPM5, using slice-time correction, motion correction, spatial normalization to the MNI space, and spatial smoothing using an 8-mm full-width at half-maximum Gaussian kernel. To perform spatial normalization, we: 1. Coregistered the two structural images and computed a mean structural image; 2. Coregistered the functional images from the two sessions and computed a mean functional

image; 3. Coregistered the mean structural and functional images; 4. Normalized the mean structural image to the SPM template using the "unified segmentation" algorithm; 5. Applied the normalization parameters to the functional images, and sampling the resulting images at 3 × 3 × 3-mm resolution.

Analyses. In all analyses, Session Order (placebo or control first) was used as a between-subjects predictor, and Participant was modeled as a random effect. Only data from the experimental blocks (blocks 2-6) were used. Since we had directional hypotheses based on prior results, all tests were one-tailed.

Behavioral data were analyzed with a mixed-effects GLM that included within-subjects effects of Placebo, Task, Placebo *x* Task.

For the imaging data, subject-level statistical analyses were conducted using the general linear model framework implemented in SPM8. Boxcar regressors, convolved with the canonical hemodynamic response function, modeled as epochs the three trial types, the trial instructions, and the rating periods. Voxel-wise statistical parametric maps summarizing differences between trial types were calculated for each participant participant and then entered into robust-regression, random-effects group analyses. Group analysis maps and tables were generated by identifying clusters consisting of at least 5 voxels, each with $p<.001$. For the maps, contiguous voxels with $p<.05$ were then added to these clusters to aid with visualization.

For the pattern-expression analysis, we used three independently-derived, whole-brain pattern maps. The first pattern map was generated using machine learning analyses on heat pain data from participants run previously in our lab (Fig. 4.2A; Wager et al.,

Submitted). The second map was generated using 'reverse-inference' meta-analysis on 224 pain imaging studies (neurosynth.org; Yarkoni et al., 2011). The two pain-predictive maps were somewhat correlated (r=.29). The third map was also generated using 'reverse-inference' meta-analysis, but on 363 working memory imaging studies. The working memory map showed small, negative correlations with each pain map (r=-.19 and -.06, respectively). For each map, pattern-expression was calculated as the cross-product of the weights in the mask and the condition beta maps for each participant ($PExp = Xw$, where w is mask weights and X is a matrix with voxel-wise beta weights, organized with images in rows and voxels in columns). We then performed repeated-measures ANOVAs on these pattern-expression values, with Placebo, Task, and Placebo *x* Task, as fixed-effects predictors.

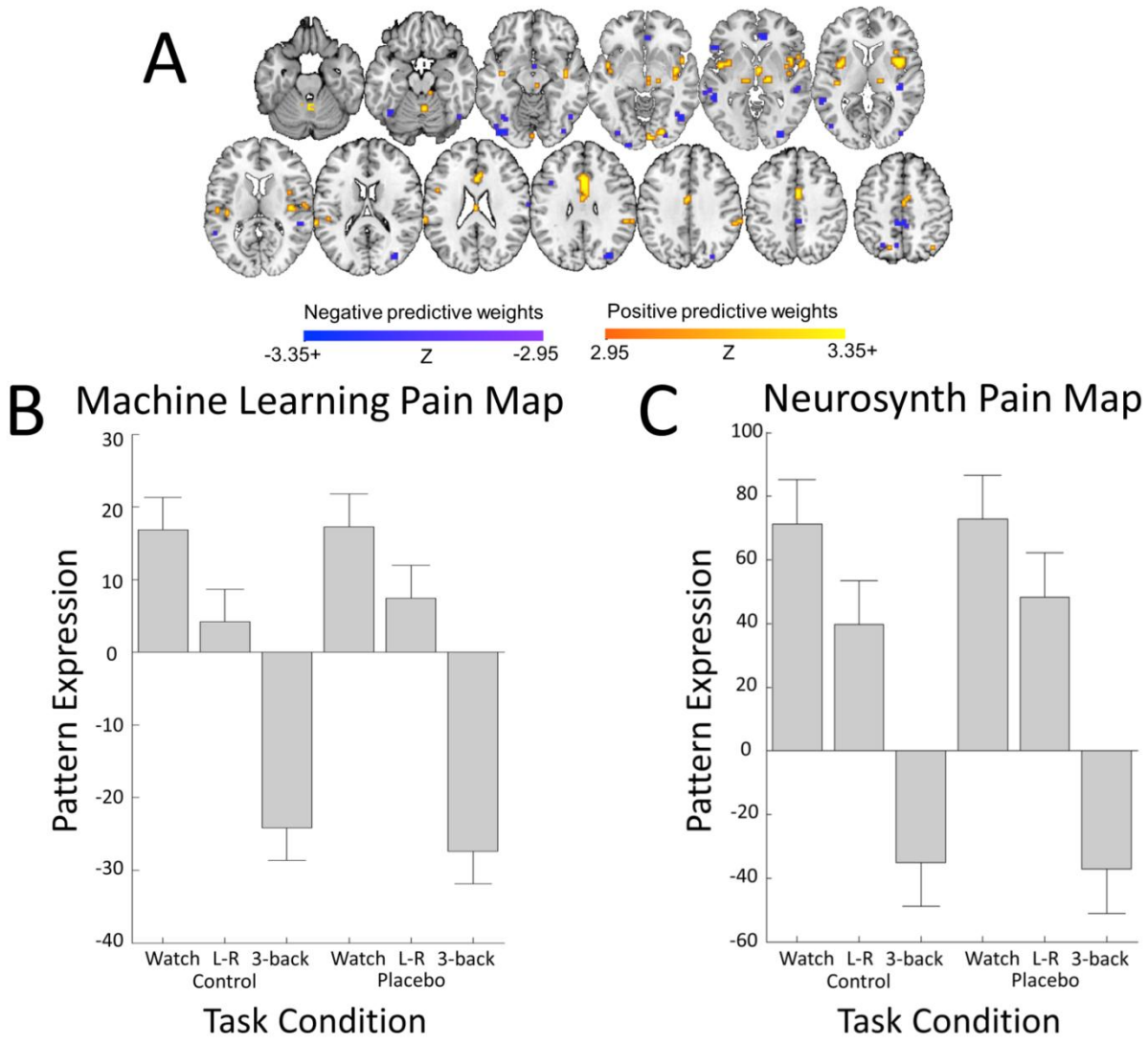

Fig. 4.2. Neural signature of pain. **A. T**hresholded machine learning pattern map. **B.** Machine learning pain pattern expression as a function of Task and Placebo. **C.** Neurosynth pain pattern expression as a function of Task and Placebo. In both pattern expression analyses, Task reduced the neural signature of pain, but Placebo did not. Only data from the experimental blocks (2-6) were included, and error bars reflect between-subjects standard error.

Results

Participants on average rated the effectiveness of the placebo as 6.5 (SD = 1.8) on the 10 point scale, and said they would pay $11.70 (SD = $6.40) to use it again.

The behavioral analysis confirmed both a main effect of Task, indicating that performing the task reduced pain, $t(20) = 6.02$, $p < .0001$, $d = 1.28$, and a main effect of Placebo, $t(20) = 1.73$, $p < .05$, $d = .37$, indicating that the placebo treatment also reduced pain. There was also a Task x Placebo interaction, $t(20) = 2.20$, $p < .05$, $d = .47$ (Fig. 4.3).

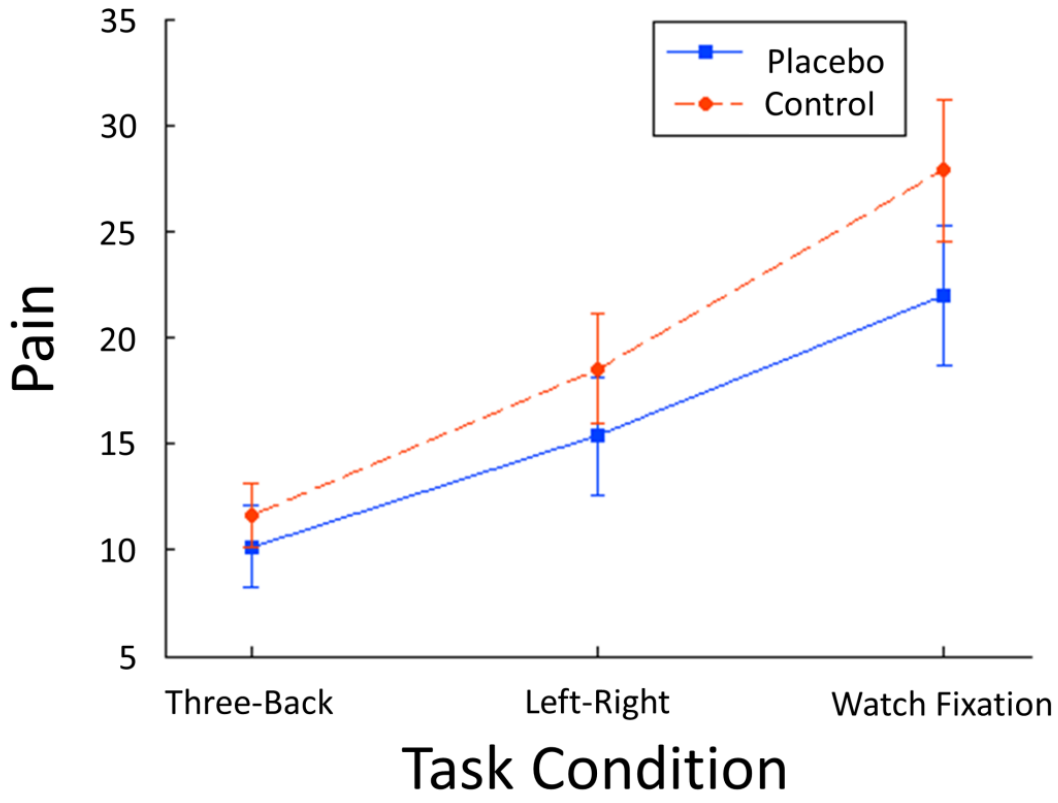

Fig. 4.3. Pain ratings as a function of Task and Placebo. Both Task and Placebo reduced pain. Only data from the experimental blocks (2-6) were included, and error bars reflect between-subjects standard error.

A voxel-wise group contrast of three-back trials greater than watch trials, collapsing across placebo conditions, revealed positive clusters in regions associated with executive attention and working memory, including DLPFC, dorsal ACC (dACC), dorsal anterior insula, premortor cortex, and parietal cortex, and negative clusters in regions associated with pain, including SII, rostral ACC (rACC), and middle and posterior insula (Fig. 4.4, Table

4.1). A group contrast of three-back trials greater than left-right trials, collapsing across placebo conditions, revealed a nearly identical pattern of increases in regions associated with executive working memory and attention, and decreases in regions associated with pain (Fig. 4.5, Table 4.2). A group contrast of control trials greater than placebo trials, collapsing across task types, revealed positive clusters in regions including anterior and posterior insula, left dorsal PFC, anterior PFC, and dorsomedial parietal cortex, and negative clusters in regions including parietal cortex, occipital cortex, and (Fig. 4.6, Table 4.3). A group contrast of control trials greater than placebo trials that included only the watch task trials revealed positive clusters in regions including dorsal anterior insula, precuneus, and parietal cortex, and negative clusters in regions including dorsomedial PFC (Fig. 4.7, Table 4.4).

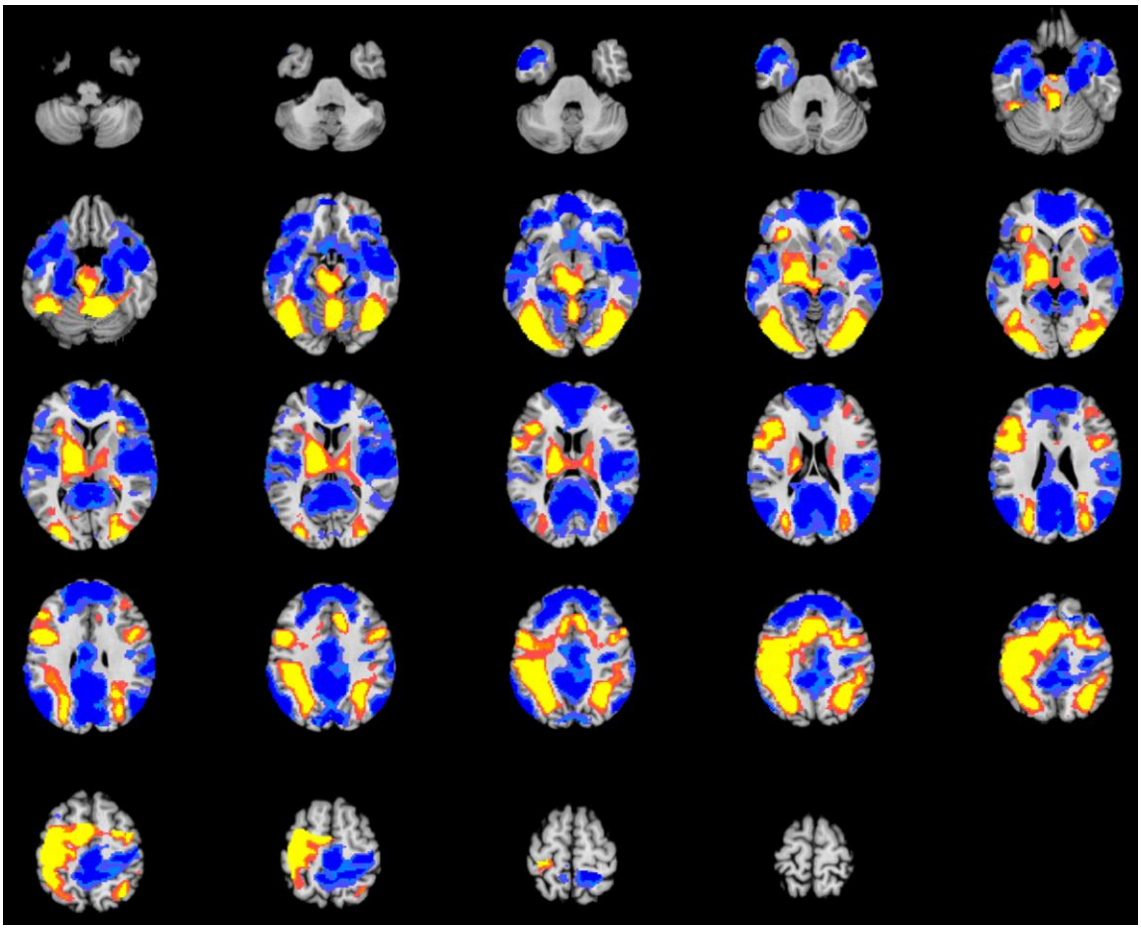

Fig. 4.4. Group contrast of three-back greater than watch trials, collapsing across placebo conditions.

Region	X	Y	Z	Size in Voxels	Size in mm^3	T-statistic
1	-6	-28	-6	3120	24960	22.93
2	-38	-74	-8	2268	18144	14.78
3	-2	-12	-24	12	96	5.04
4	30	-72	6	2988	23904	11.19
5	-30	24	0	152	1216	7.37
6	34	24	2	62	496	5.48
7	28	-34	4	20	160	4.55
8	14	-14	12	57	456	4.64
9	-28	-18	44	8524	68192	20.77
10	-44	6	-14	3325	26600	-18.47
11	14	-36	4	15061	120488	-16.96
12	44	38	-2	1003	8024	-8.41
13	-64	-36	-8	256	2048	-7.47
14	-2	50	20	7956	63648	-15.45
15	14	10	-10	9	72	-4.3
16	66	-38	-2	172	1376	-8.07
17	68	-24	-6	9	72	-5.19
18	36	6	10	64	512	-5.57
19	-52	-30	10	7	56	-4.39
20	-52	-62	30	1313	10504	-10.85
21	50	-64	26	1020	8160	-9.8
22	-16	-40	18	7	56	-4.56
23	36	-24	52	380	3040	-6.25

Table 4.1. Group contrast of three-back greater than watch trials, collapsing across placebo conditions. . Only clusters with at least 5 contiguous voxels at p<.001 were included.

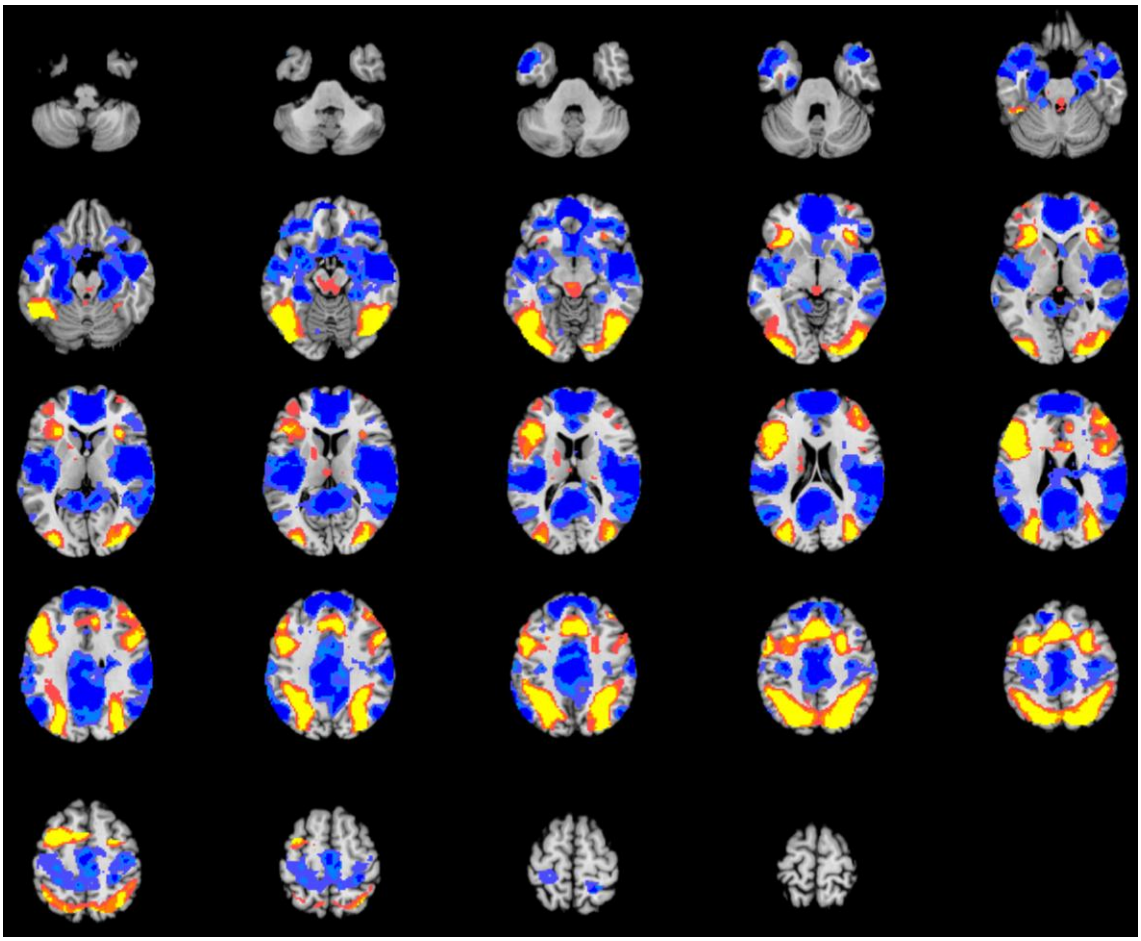

Fig. 4.5. Group contrast of three-back greater than left-right trials, collapsing across placebo conditions.

Region	X	Y	Z	Size in Voxels	Size in mm^3	T-statistic
1	-20	-68	26	7480	59840	14.07
2	-32	26	0	299	2392	9.21
3	34	26	0	119	952	5.27
4	30	-76	2	5	40	4.73
5	-28	12	42	3309	26472	11.44
6	44	38	26	120	960	5.58
7	2	10	24	30	240	6.46
8	50	10	32	204	1632	5.91
9	28	6	50	274	2192	10.73
10	-4	36	42	5	40	6.06
11	-44	-12	-4	4582	36656	-9.8
12	50	-18	4	7780	62240	-14.62
13	24	12	-18	5	40	-4.41
14	0	50	12	6282	50256	-13.84
15	42	34	-12	275	2200	-7.41
16	32	-36	-12	13	104	-5.14
17	-68	-38	-4	34	272	-5.27
18	-2	-38	30	5005	40040	-10.83
19	-50	-62	30	661	5288	-7.59
20	24	-16	28	50	400	-12.98
21	22	22	32	7	56	-7.53
22	-32	-20	46	52	416	-5.01
23	38	-16	50	84	672	-6.01
24	30	-36	58	45	360	-5.35
25	22	-48	66	8	64	-5.04

Table 4.2. Group contrast of three-back greater than left-right trials, collapsing across placebo conditions. . Only clusters with at least 5 contiguous voxels at p<.001 were included.

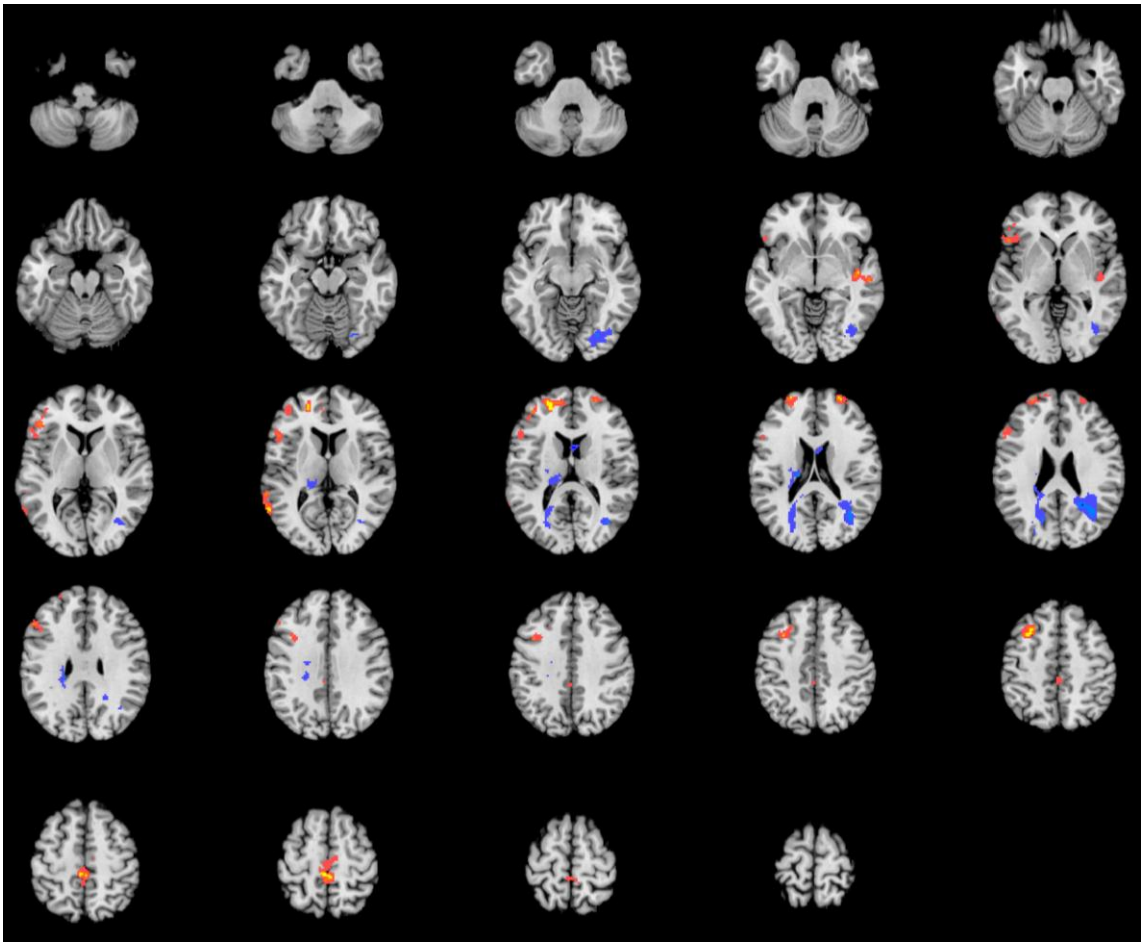

Fig. 4.6. Group contrast of control greater than placebo trials, collapsing across task types.

Region	X	Y	Z	Size in Voxels	Size in mm^3	T-statistic
1	46	-14	-2	5	40	4.12
2	-62	-56	10	5	40	4.54
3	-22	50	14	38	304	5.84
4	-52	22	12	6	48	5.05
5	26	60	20	5	40	4.26
6	-24	58	24	12	96	4.71
7	-30	16	50	20	160	4.8
8	-2	-34	60	28	224	7.17
9	4	6	18	5	40	-5.29
10	38	-62	22	7	56	-4.73
11	-18	-64	24	7	56	-5.4
12	28	-52	24	5	40	-4.07

Table 4.3. Group contrast of control greater than placebo trials, collapsing across task types. Only clusters with at least 5 contiguous voxels at p<.001 were included.

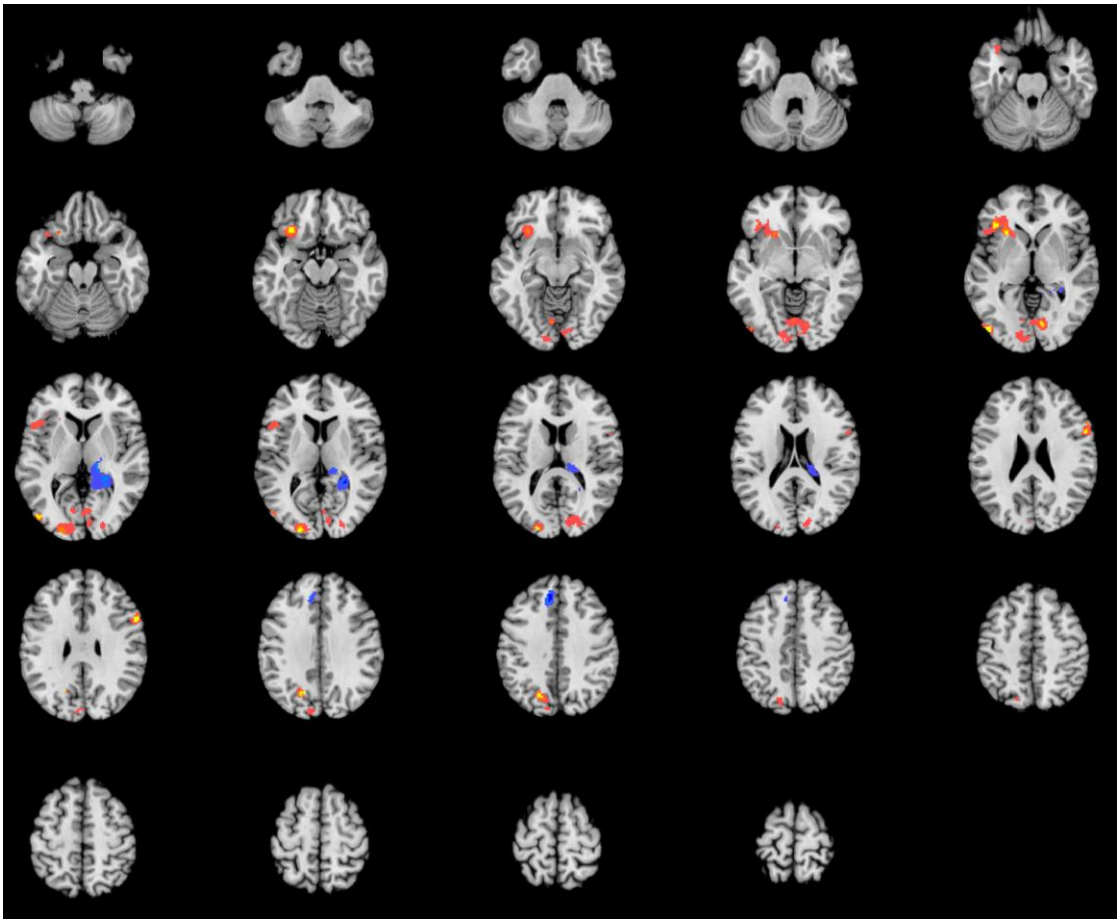

Fig. 4.7. Group contrast of control greater than placebo trials, watch trials only.

Region	X	Y	Z	Size in Voxels	Size in mm^3	T-statistic
1	-30	24	-14	20	160	5.8
2	-46	-82	2	37	296	8.59
3	12	-76	-2	9	72	4.33
4	-38	30	0	18	144	9.56
5	-26	22	0	5	40	6.23
6	-20	-94	12	19	152	5.62
7	58	12	28	22	176	6.26
8	-18	-68	38	25	200	8.26
9	26	-44	8	7	56	-4.61
10	-8	36	40	19	152	-5.86

Table 4.4. Group contrast of control greater than placebo trials, watch trials only. . Only clusters with at least 5 contiguous voxels at p<.001 were included.

The first pattern-expression analysis, using the machine learning pattern maps derived from a previous heat pain study in our lab, confirmed a main effect of Task, indicating that performing the task reduced pain expression, $F(2, 100) = 49.01$, $p < .001$, but found no main effect of Placebo, $F(1, 100) = .002$, $p = .962$, indicating that the placebo treatment had no effect on the expression of the neural pain pattern. The summary pattern expression values were higher in the watch condition than the three-back in 95% of participants, higher in the watch condition than the left-right condition in 71% of participants, and higher in the left-right condition than the three-back condition in 95% of participants. The summary pattern expression values were higher in control condition than the placebo in 52% of participants, close to chance. There was no Task x Placebo interaction, indicating that the strength of the distraction-induced analgesia was unaffected by the placebo manipulation, $F(2, 100) = .27$, $p = .77$ (Fig. 4.2B).

Nearly identical results were obtained using the second pattern map, generated from neurosynth.org, with a main effect of Task, $F(2, 100) = 32.79$, $p < .001$, but no main effect of Placebo, $F(1, 100) = .05$, $p = .816$, and no Task x Placebo interaction, $F(2, 100) = .08$, $p = .924$ (Fig. 4.2C). The summary pattern expression values were higher in the watch condition than the three-back in 90% of participants, higher in the watch condition than the left-right condition in 62% of participants, and higher in the left-right condition than the three-back condition in 90% of participants. The summary pattern expression values were higher in control condition than the placebo in 48% of participants, close to chance.

The third pattern-expression analysis, using the working memory pattern map generated from neurosynth.org, confirmed a main effect of Task, indicating that performing the task increased working memory expression, $F(2, 100) = 82.26$, $p < .001$, but found no main effect of Placebo, $F(1, 100) = .595$, $p = .442$, indicating that the placebo treatment had no effect on the expression of the working memory pattern. The summary pattern expression values were higher in the three-back condition than the watch condition in 100% of participants, and higher in the three-back condition than the left-right condition in 95% of participants, but higher in the left-right condition than the watch condition in only 48% of participants, close to chance. The summary pattern expression values were higher in placebo condition than the control in 43% of participants, also close to chance. There was no Task x Placebo interaction, indicating that the strength of the distraction-induced analgesia was unaffected by the placebo manipulation, $F(2, 100) = .27$, $p = .77$ (Fig. 4.2B).

Discussion

Although both distraction and placebo lowered pain ratings, only distraction reduced the neural signature of pain throughout the brain. We obtained nearly identical

results using two different pattern maps, generated using different methods and entirely different data sets.

The results are surprising, given that previous placebo research has found reliable activated reductions of activity in pain-processing regions. One possible explanation is that the lack of neural placebo effects in the present experiment reflects a critical design flaw of some kind. Given that we obtained clear reductions in pain processing as a function of distraction, such a flaw cannot be attributed to the stimulation paradigm, or the quality of the fMRI data. It might be the case that the placebo manipulation in this study was insufficient to produce strong effects. Consistent with this possibility, we did not see placebo-induced increases in PFC similar to those that have been reported previously (Wager & Fields, In press). We did see some placebo-induced reductions similar to those that have been previously in regions including the ACC and anterior insula, but only during the watch trials.

However, the design we used is very similar to one we have previously shown to produce placebo analgesia, and it is comparable to many others used commonly in the literature. Furthermore, the placebo effectively reduced pain reports, although the effect size was smaller in the present compared to the previous study (d = .37 and .71, respectively). It is also possible that the difference between our behavioral and neural results reflects the overlapping but not identical participants in each analysis. However, each analysis contained a similar number of participants (22 and 21 in the behavioral and imaging analyses, respectively), so different sample sizes probably did not drive the difference in results. At the very least, the present results show that is possible to obtain reduced placebo effects without a concomitant reduction in the neural signature of pain. Of

course, it is possible that the brain is a considerably less sensitive measure of placebo than self-report. If so, our study may have had sufficient power to detect a behavioral effect, but insufficient power to detect a neural effect. The best way to address this possibility will be for other groups to perform similar analyses on previously collected placebo data. This should be relatively easy to do, as one of the pattern maps we used is freely available online.

In the present study, we used an expectancy-based placebo manipulation. Although we did expose participants to trials with covertly lowered temperature, these trials were intended only to enhance the expectation, not to induce a true conditioned response. Future research should test whether conditioning-based placebo treatment reduces the neural expression of these pain-predictive patterns.

It is worth noting that in the present data we observed an interaction between Task and Placebo in the behavioral pain reports. This result appears to conflict with a previous study (n=33) in which we found no interaction between these factors. The paradigms were very similar in the two experiments, and the limited differences between the two paradigms, such as the present use of a fixed temperature calibration, the MRI context, or the addition of the left-right condition, seem unlikely to explain a change in the interaction. As can be seen in Fig. 4.3, the interaction was driven by under-additive differences in the three-back and left-right conditions. A pattern like this is often produced when participants cannot or will not rate stimuli below a certain level—a floor effect. Consistent with this possibility, 8 of the 22 participants in the behavioral analysis had average ratings below 3 on the 100 point scale in at least one condition. Furthermore, no floor effect would be expected in the pain pattern expression data, and in those analyses we observed no

interaction between Task and Placebo. For these reasons, we believe that the previously reported lack of interaction most likely reflects the true pattern of pain experience.

In sum, these results suggest that while distraction effectively dampens pain processing in the brain, expectancy-driven placebo effects may not exert widespread effects on pain processing. More generally, this approach provides a way to distinguish different brain effects of different types of pain modulatory techniques in a principled, a priori fashion. We hope our results will encourage other groups to perform similar analyses, both on novel and existing data, so that we may more clearly identify psychological and non-psychological manipulations that effectively reduce the neural signature of pain.

Chapter 5: General Discussion

The present series of experiments examined the neural and cognitive processes that constitute distraction and placebo analgesia. All three studies used the limited resources logic that when tradeoffs are observed between two concurrently performed tasks, it may be inferred that the tasks overlap in the mental resources they engage (Norman & Bobrow, 1975). Result from Study 1 suggested that overlapping cognitive resources are involved in both pain and executive attention and working memory. Study 2 provided evidence that these same executive attention and working memory resources are not involved in placebo analgesia, and that placebo analgesia and distraction constitute separate routes to pain relief. Study 3 tested whether distraction and placebo analgesia reduce expression of a whole-brain, pain-predictive activity pattern. We found that while both distraction and placebo reduced pain reports, only distraction led to a widespread reduction of the neural signature of pain.

A great deal of work remains to be done to understand the neural mechanisms underlying distraction-based analgesia. As reviewed in Chapter 1, converging evidence supports the hypothesis that when performing a demanding cognitive task concurrent with pain experience, frontal regions invoke PAG-mediated descending inhibition. Future work should seek additional support for this extraordinary hypothesis, by using brainstem-specific imaging techniques to confirm the involvement of other crucial brainstem regions in the descending pathway, such as the rostroventromedial medulla (RVM), as well as reduced activity in the spinal cord, as has been done recently in placebo analgesia (Eippert, Finsterbusch, et al., 2009). If distraction-based analgesia relies on similar descending

mechanisms as placebo analgesia, these mechanisms may also be opioid-mediated. Future work should examine whether the opioid antagonist naloxone disrupts the analgesic effect of distraction, as it does in placebo (Grevert, Albert, & Goldstein, 1983).

The pattern expression approach to assessing the neural signature of pain used in Study 3 offers an exciting new method for testing the effects of pain modulatory techniques. As can be seen in sections of the Introduction that discuss the neuroanatomy of distraction and placebo, many previous studies have reported reductions in pain processing areas. However, not all studies reported reductions, and among those that did report reductions, there were differences in the specific regions observed. The pain matrix is vast. Not only is it comprised of many regions, but some of these regions are quite large, leading to a difficult to quantify multiple comparisons problem. Thus, it is possible that chance alone is responsible for the presumed pain processing reductions that have been reported. To make matters worse, the borders cannot be perfectly delineated. It is likely that some of the activations believed to represent pain activity in fact reflect activity in adjacent, non-pain related areas. Finally, most pain processing regions are known to be involved in non-pain processes as well. Reduced processing observed in a limited set of pain regions might reflect a real reduction in pain processing, but it also might reflect a change in activity unrelated to pain.

The pattern expression approach at least partially overcomes these concerns by providing a summary value that reflects pain activity across the brain. To our knowledge, Study 3 represents the first use of such a technique in testing pain modulation approaches. As reported in Chapter 4, we found widespread reductions in the neural signature of pain as a function of distraction, but no differences as a function of placebo. It is quite possible

that our design lacked sufficient power to detect the influence of the placebo effect on the neural signature of pain. To answer this question, we hope to extend these analyses soon to other datasets that have been previously collected by our lab, and we hope other groups will perform similar analyses. If these results do in fact hold across multiple datasets, it may profoundly change our understanding of the placebo effect.

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