The Dissociation of Valence and Intensity Using Alliesthesia and Thermal Stimulation

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ABSTRACT

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Psychological models have proposed that valence, how pleasant or unpleasant a stimulus is perceived, and intensity, the strength with which a stimulus is perceived, constitute two primary dimensions that describe affective experience. However, the inherent relationship between valence and intensity has limited imaging studies of these models and the neural substrates are poorly understood. For example, it is not known if the neural representations for each dimension are discrete or shared. To overcome these limitations, we applied properties of alliesthesia, the phenomenon where the valence of a stimulus is dependent upon the physiological state of the body, using thermal stimuli to the hand in combination with whole-body warming and cooling. In this way, we were able to manipulate the hedonic aspect of our thermal stimuli independent of their perceived intensity. Brain regions correlating with stimulus valence included the medial orbitofrontal cortex, subgenual anterior cingulate cortex and amygdala, whereas stimulus intensity was correlated with activity in the insula, thalamus and striatum, among others. Our results suggest segregated patterns of neural activity underlying perceptions of valence and intensity, consistent with dimensional models of emotion.

TABLE OF CONTENTS

FIGURES AND TABLES

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CHAPTER I

INTRODUCTION

Background on Emotion Research

Emotions influence nearly all aspects of perception and cognition, and appear to play a role in many motivating behaviors. Although many theories have been put forth, the fundamental neurobiological substrates of emotion remain poorly understood. The application of experimental techniques has only recently been applied to this once intractable problem, and affective neuroscience has employed many of these to begin building a neural basis of emotion.

The study of emotion began its migration from phenomenology to the laboratory bench as researchers realized that many basic human affective behaviors are mediated by brain structures shared with lower mammals. Early work evaluated animal behaviors following experimental lesions at various levels of the central nervous system. This demonstrated that emotional reactions could be elicited in dogs with lesions segregating the central and peripheral nervous systems (Sherrington, 1900), and also in decerebrate cats (Canon, 1927). Such findings violated the tenets of the dominant James-Lange theory of visceral triggering of emotion in the cortex (James, 1884). This seminal work located the source of emotion in the brain, not the body, and gave rise to a profusion of models to rival the James-Lange dogma.

Two influential attempts at describing the neural circuits subserving emotion were the Papez circuit (Papez, 1937) and the limbic system (MacLean, 1949). The Papez circuit placed the thalamus and hypothalamus at the core of a "feeling stream" of information, while the limbic system also focused on other areas such as medial temporal structures. The search for discrete functional units subserving emotion gained traction when Kluver and Bucy (Kluver and Bucy, 1939) identified the amygdala as a key

component of the fear response, leading to the start of anatomical specificity in emotional subtypes, particularly the division between positive and negative affect. With these early findings as motivation, fear became a center point of research because it was easily elicited with conditioning paradigms and was readily measured by behavioral responses such as freezing, startle, or avoidance (LeDoux, 2003). Throughout the latter half of the 20th century, improvements in lesion methods and advances in electrophysiological, biochemical and genetic techniques gave rise to an extensive effort to characterize the neurobiology of fear and other emotional responses. Where this work focused on elucidating the neural underpinnings of unconscious emotional processing, it largely avoided claims of affect or feeling (LeDoux, 2000) that have been the aim of many human studies.

The rise of neuroimaging has driven a large corpus of literature dedicated to the study of emotion in human subjects. Much of this effort has taken from findings in animals and sought to extend this work by probing questions that may only be asked in humans. For example, Whalen and coworkers presented subjects with masked fearful faces and showed that these were associated with activation in the amygdala even though subjects did not report seeing the fear stimulus (Whalen et al., 1998), a finding that is consistent with the proposal that the amygdala is involved in unconscious aspects of fearful responses (Halgren et al., 1994; Bechara et al., 1995). A comprehensive analysis of studies of emotion revealed functionally organized groups of brain regions that were widespread across the cortex and subcortex (Kober et al., 2008). This organization followed a pattern of multisensory association with traditional limbic regions such as the insula, amygdala and hippocampus, as well as other areas such as the orbitofrontal cortex

(OFC) and periacqueductal gray. The identification of this array of functional groupings involved in emotion generally, as opposed to specific emotional labels, should inform the way theoretical models of emotion are constructed. A brief introduction to two proposals that are pertinent to the study presented here is included below.

Basic Emotions

Drawing on findings from investigations in other animals, popular models of human emotion posit distinct basic units, such as fear, anger, or happiness. Basic emotion theorists claim that all affective experiences share a common denominator of at least one of these types, which in turn are represented by distinct patterns of neural activity. In this framework, anger and sadness, for example, cannot share all the same neural correlates if each is basic. Another component of these theories is that each emotion is associated with unique patterns of behavioral and physiological responses, such as facial expressions (Ekman et al., 1992), variations in the autonomic nervous system (Ekman et al., 1983; Boiten et al., 1994; Rainville et al., 2005; Critchley et al., 2009), and impulsive actions (Frijda, 2010) as illustrated by Barrett 2008 (Figure 1.1). Moreover, it is believed that basic emotions are shared across human cultures and species, with humans sharing antecedents from other vertebrates (Darwin, 1890; Ekman, 2003; Panksepp, 2005). This framework may be a useful operationalization of affective processing, but the extent to which it accurately describes felt emotion has been questioned.

Originally alluded to by Walter Cannon, the identification of distinct neural circuits underlying stereotyped emotional behaviors does not necessarily map on to what

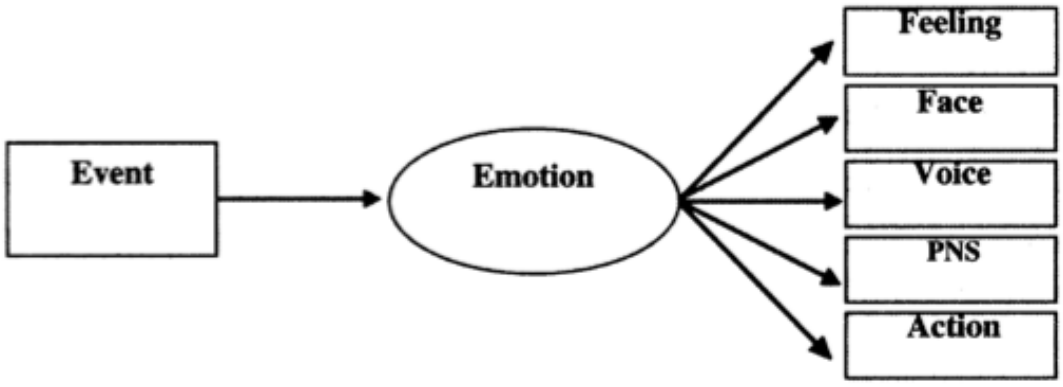


Figure 1.1: Schematic of affective expression under basic theories of emotion. These theories assume emotions are associated with stereotyped behaviors that are unique to each fundamental emotional type. Adapted from Barrett 2006.

is consciously felt (Cannon, 1927, p109). In addition to theoretical concerns, experimentation in humans has shown non-specificity in regions believed to underlie specific emotional types (Kesler-West et al., 2001; Winston et al., 2003; Wright et al., 2006; Fitzgerald et al., 2006). For example, Fitzgerald and colleagues (Fitzgerald et al., 2006) showed participants a series of 6 facial expressions (fearful, disgusted, angry, sad, neutral, happy) and compared brain activity in the amygdala for each of these conditions to a baseline image of a portable radio. In this way, the authors differed their analysis from the majority of prior studies, which compared emotional expressions to neural faces. Amygdala activity was most strongly associated with fearful faces, but was also significant in response to all expressions found in the other 5 conditions leading the authors to argue for an amygdalar role in the detection of "social salience".

Other challenges to basic theories include the long-standing claim that the autonomic nervous system is too broad and too slow to carry the needed specificity for the wide spectrum of emotions (Cannon, 1927, p112; Rolls, 2005, p26-30), and that facial expressions themselves are context-dependent (Aviezer et al., 2008) and more variable

across cultures than originally thought (Marsh et al., 2003; Elfenbein et al., 2007; Hess and Thilbault, 2009). Moreover, a pressing question that has disrupted the continuity between basic emotion theorists is how to define what can be considered a primary versus higher-order process. While the most commonly cited basic emotions are anger, happiness, fear, sadness, disgust, and surprise, there are no clear boundaries for making such categorizations (Ortony and Turner, 1990); however, the relevance of this criticism has been questioned (Panksepp, 1992). Considering these concerns, it has been suggested that basic emotional types are shorthand for linguistically identifying general emotional responses and that updated models are needed to better describe true affective experience (Barrett, 2006, Barrett et al., 2007). To this end, affective neuroscience has been gravitating toward a different type of description of emotional processing that abandons the categorical approach taken by traditional theories.

Dimensional Models

Rather than parse out what differentiates one feeling "state" from another, dimensional models seek a set of parameters that are common across all affective experiences. Such models are a parsimonious and powerful way to describe the full range of emotion without instantiating discrete neural, physiological, and behavioral representations for each putative emotional type. The components most frequently included in these models are *valence*, which describes the scale of positive to negative value, and *arousal*, referring to how intensely the emotion is perceived. More nuanced models include *duration* (Cabanac, 2002; Figure 1.2) and a bivariate form of the valence dimension (Cacioppo and Berntson, 1994; Norris et al., 2010). Although duration clearly

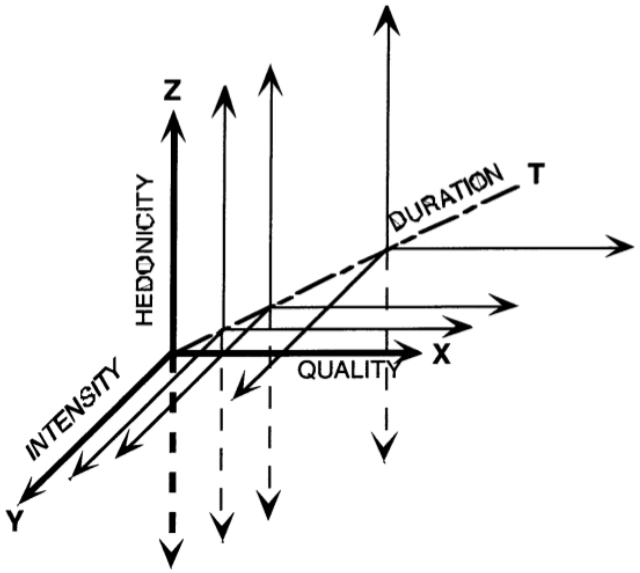


Figure 1.2: Example of a 4-dimensional model of emotion including quality and duration in addition to the traditional variables hedonicity (i.e. valence) and intensity. Adapted from Cabanac 2002.

affects the quality of a subjective feeling and "affective chronometry" is an important part of the study of emotions, it is believed to play a more pertinent role in inter-subject variations in the time-course of responses to mental or environmental challenges (Davidson, 1998; 2003) and is unlikely to signify a fundamental aspect of emotion per se. Also, bivariate models stipulate that there is not a single bipolar dimension for valence, but are instead two independent hedonic scales (i.e. positive and negative). Such a view is consistent with the observation that it is possible to possess both pleasant and unpleasant feelings simultaneously (Larsen et al., 2001), but such conflicts possess significant cognitive overlay and do not necessarily preclude the existence of a fundamental bipolar dimension (Barrett and Russell, 1998). For example, one may simultaneously feel somewhat negative while studying for high school exams, but severe displeasure at the threat of not gaining entrance to college; these concurrent beliefs do not

necessitate independent representations of varied forms of negative valence in a fundamental sense. Considering this, more work is needed before a bivariate form of valence can be accepted as a core component of affective experience.

An important point of agreement between categorical and dimensional models is that all emotions must have valence. This is a defining feature that separates emotion from other aspects of cognition (but see Pesssoa, 2008; 2010). Conversely, arousal maps more closely onto the strength of physiologic responses (e.g. cardiovascular, respiratory, sudomotor) in basic approaches, whereas dimensional theorists expect to find a neural representation coding for, not only the *inherent*, but also the *perceived* intensity of a stimulus. As a starting point, these distinctions have been used to define what constitutes an emotion (Cabanac, 2002), and work has begun to find evidence for this theoretical framework.

James Russell formulated a simple model (Russell, 1980), based on prior work using facial expressions (Schlosberg, 1952), that describes emotion as a circular arrangement of "affective concepts," that are placed along two principal axes: valence and arousal (Figure 1.3). Several lines of psychological evidence have been gathered to support the claim that the relationship between categorical labels of feelings (e.g. excited, sleepy, pleased, miserable) are related to one another by a circular pattern, denoted as an affective circumplex. The circumplex allows room for ambiguity in what is felt by not assuming the presence of distinct boundaries separating emotions (Russell and Fehr, 1994) and can account for important individual differences in the way emotions are perceived (Barrett, 1995). Several linguistic labels have been used to describe the model, such as positive/negative (Watson et al., 1999), approach/withdrawal (Lang et al., 1998),

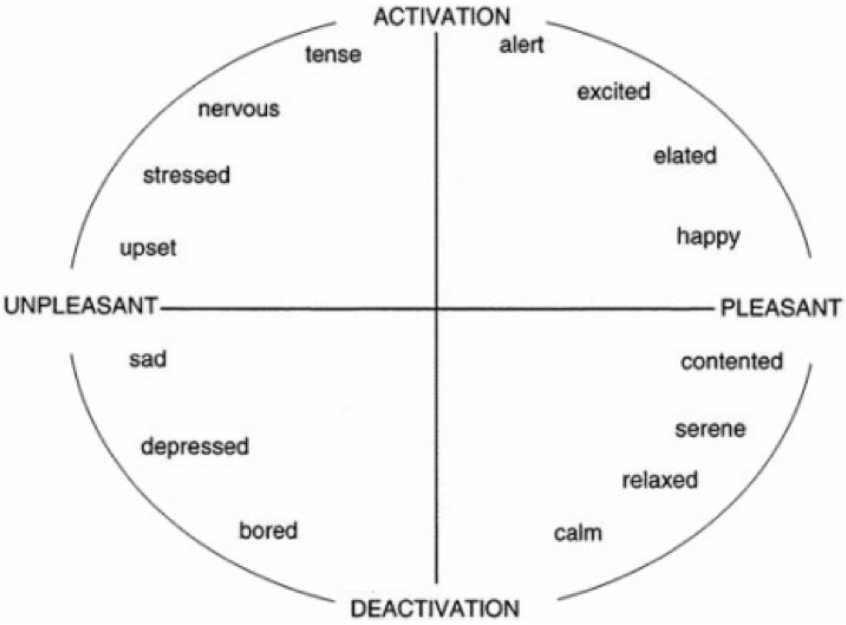


Figure 1.3: The classical circumplex model of emotion states that all affective experience may be ordered along two dimensions, valence (unpleasant – pleasant) and arousal (deactivation – activation). Adapted from Russell 1980.

and valence/arousal (Russell, 1980), but the affective arrangement is consistent across these variants (Posner et al., 2005). However, one crucial point that is frequently overlooked by studies that test predictions of the circumplex model is the meaning of the term "arousal." The model itself defines arousal as affective activation and does not refer to how intensely an emotion is felt (Russell, 1980). As explained in the following section, the intensity with which an emotional stimulus is felt may be a more tractable experimental measure of affective arousal, but the literature is currently undecided on the correct approach.

Evidence for a Circumplex Model

Functional imaging studies have provided some physiological evidence for the affective circumplex in humans by identifying neural correlates for both dimensions. For

example, using the olfactory system, Anderson and colleagues (Anderson et al., 2003) presented subjects with two olfactory stimuli representing pleasantness (citric acid) and unpleasantness (valeric acid), and manipulated the molar concentration of each smell to modulate the intensity with which they it was perceived. Participants provided significantly greater intensity ratings for the high relative to the low concentration stimuli and this was independent of their ratings of valence. Dissociating these two stimulus properties allowed the authors to look for dimension-specific brain activity in two regions of interest, which were the amygdala and OFC. The authors found that the magnitude of the blood oxygen level dependent (BOLD) signal in the amygdala, bilaterally, was greater for the high concentration stimuli, both for the pleasant and unpleasant smells. Conversely, the time-course in the amygdala did not show any change in the peak-response for citric versus valeric odorants. Together, these results suggest a role for the amygdala in intensity, but not valence, coding. Applying the same analysis to the medial OFC, the analysis revealed peak BOLD signal changes that were greater for the pleasant odor relative to the unpleasant odor, but there was no differentiation for high and low concentrations for either stimulus.

In a later study using a similar design, but with gustatory stimuli, the results of the olfactory study were replicated for both the amygdala and OFC (Small et al., 2003), but other regions were studied in a whole-brain analysis. Activity within multiple areas appeared to track either valence or intensity and there was a general trend for intensity coding in the mid- and hindbrain, while regions in the forebrain were more likely to be involved in valence. However, there were several exceptions, notably the bilateral insula, and multiple anatomical structures with voxels involved in both processes.

These studies took advantage of the unique aspect of chemosensory stimuli, in which valence and intensity may be decoupled. Taken together, they provide powerful evidence for specialized neural circuits underlying these two proposed dimensions of affect. However, since their publication, design and analytical limitations common to both studies have been considered and new evidence suggests a different interpretation of their results.

The investigations using olfactory and gustatory stimuli set out to compare positive and negative valence under high and low intensity conditions, but neither study included a neutral condition. This potential shortcoming was explored (Winston et al., 2005) and found to have considerable impact on the interpretation of BOLD signal changes in the amygdala, the only region of interest included in the analysis. Winston and coworkers presented subjects with citric and valeric acid, but also "phenolic" and "oily" odors, which were rated as being neither pleasant or unpleasant, but whose concentration could still be varied to manipulate their perceived intensity. Consistent with the findings of Anderson (Anderson et al., 2003) and Small (Small et al., 2003), peak activity in the amygdala was greater for the high concentration stimuli relative to the low, but there were no valence-specific differences in the BOLD signal. For the two neutral stimuli, amygdala activity did not change from baseline during either the high or low concentration trials. That the amygdala responded to intensity changes only in the presence of a stimulus with non-zero valence suggests that this region codes for an interaction between these two dimensions. Unfortunately, like the work of Anderson et. al., the entire brain was not studied and no conclusions could be drawn for any region other than the amygdala.

Subsequent studies have been performed using less technically challenging paradigms and have generally attempted to employ parametric stimuli to avoid misinterpreting valence-intensity interactions. The most commonly used stimuli in these studies are images from the International Affective Picture System (IAPS; Lang et al., 2005), for which subjects are asked to provide judgments of pleasantness/unpleasantness and the degree of *affective arousal* (Anders et al., 2004; Dolcos et al., 2004; Grimm et al., 2006; Anders et al., 2008; Viinikainen et al., 2010). An advantage of these studies is their ease in administering stimuli coupled with the large number of trials permitted by an event-related design, which is not possible in the chemosensory domain. However, although images vary parametrically along valence and affective arousal scales, these dimensions are highly correlated and impossible to orthogonalize. Finally, despite the available standard ratings for the IAPS battery, it is often difficult to balance the presentation of unpleasant images with pleasant ones, which may lead to oversampling of the negative range of the valence scale (Anders et al., 2004).

A similar approach has been attempted using linguistic stimuli, such as those from the Affective Norms for English Words (ANEW; Bradley and Lang, 1999), to require subjects to either recognize and subjectively rate the valence and affective arousal of a word (Lewis et al., 2007; Posner et al., 2009). As with pictures, the valence and affective arousal of words are highly correlated (Lewis et al., 2007) and difficult to disentangle. For both paradigms, a given stimulus is closely tied to its inherent valence and intensity – which confers validity to the standard IAPS and ANEW ratings – and a more powerful way to study the representation of each dimension in isolation would be to hold the valence of a stimulus constant while manipulating its intensity (and vice-versa). One

possible technique that may be employed for this purpose involves cognitive reappraisal of the affective images or words (Ochsner, 2002; 2004), which presumably would not modify the affective arousal of the stimulus, but this has yet to be tested.

This growing body of work aimed at finding evidence for a circumplex model of affect has been met with several technical and analytical limitations that have hampered the interpretability of results. Moreover, a meta-analysis of this literature illustrates the lack of agreement for the most common regions identified as coding for either valence or intensity (Table 1.1).

Region of Interest	Valence (Unique Studies)	Intensity (Unique Studies)
Caudate	0	3
Hippocampus	1	4
L-amyg	1	6
L-dlpfc	3	1
L-ins	2	3
L-ofc	4	2
Putamen	1	2
R-amyg	1	3
R-dlpfc	3	1
R-ins	3	2
R-ofc	5	8
Thalamus	1	5
dACC	4	0
sgACC	3	2

Table 1.1: Analysis of functional imaging studies testing for a neural dissociation in valence and intensity. The most commonly reported regions of interest are listed along with the number of studies that found activity correlating with valence or intensity. Abbreviations: Left/Right amygdala (L/R-amyg), Left/Right dorsolateral prefrontal cortex (L/R-dlpfc), Left/Right insula (L/R-ins), dorsal anterior cingulate cortex (dACC), subgenual anterior cingulate cortex (sgACC).

In addition to the inherent relationship between valence and intensity discussed above, other factors have likely contributed to this sparse agreement across these studies.

For example, studies requiring participants to provide both types of ratings for each trial, whether simultaneously or in succession, risk further mixing of the perceptions of these two dimensions. Also, only primary sensory stimuli have a validated way of manipulating one of these dimensions while holding the other constant. Such stimuli are usually parametric in nature (e.g. concentrations of smells or tastants) and allow the inclusion of trials in the mid-range of valence and intensity (i.e. neutral conditions). Perhaps most important, primary sensory stimuli may be judged on their *sensory intensity*, with can be used as a proxy measure of arousal. Subjective ratings of the latter type, such as when participants are asked to rate the affective arousal of IAPS images, are more likely to show interactions with the valence dimension because of their inherent relationship. For these reasons, we employ parametric, primary sensory stimuli that are judged based on their sensory intensity.

Temperature to dissociate valence and intensity

Within the non-noxious range, temperature has no inherent affective value and is perceived as either pleasant or unpleasant independent of its physical intensity, lending itself to the phenomenon of alliesthesia. Alliesthesia is the condition where the hedonic aspect of a stimulus is based on the interior state of the body. For example, warm stimuli will be felt as pleasant when the environmental temperature is low, but will be unpleasant under hot conditions. Alliesthesia is present in several other sensory systems, such as gustation and olfaction (Cabanac, 1971), and provides an opportunity to alter the perceived hedonic value of a stimulus without changing its sensory properties (Figure 1.4).

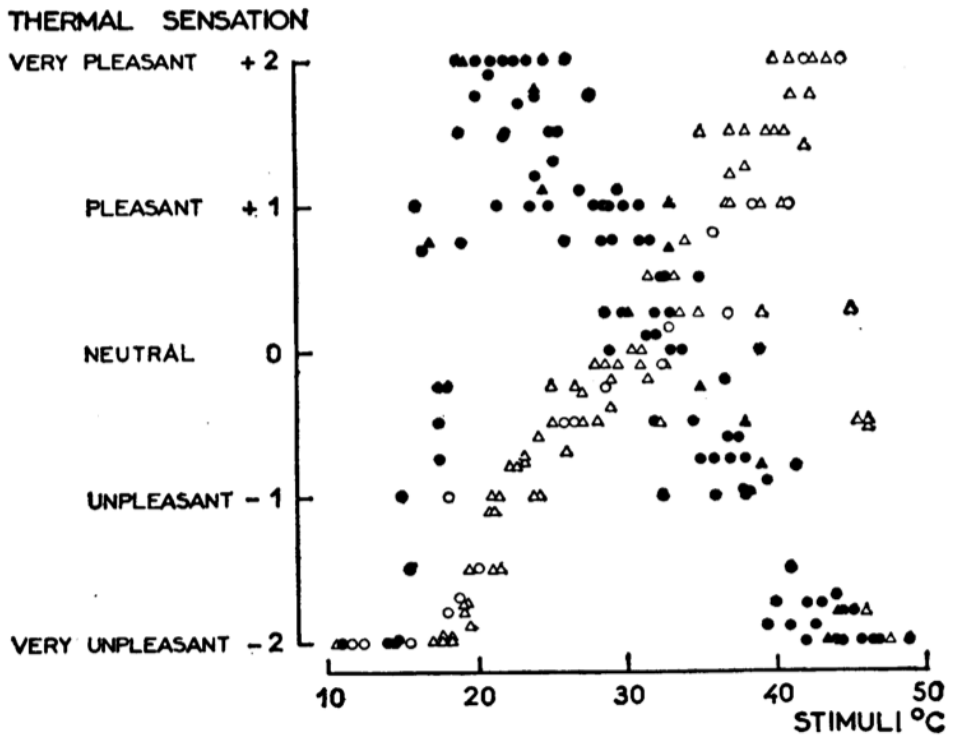


Figure 1.4: The classic demonstration of alliesthesia from Cabanac 1971 was generated by first having subjects lay in a bath of either hot (closed symbols) or cold (open symbols) water. Following acclimation to the bath, participants were then given a range of hot and cold thermal stimuli to the hand and asked to rate how pleasant or unpleasant it was. In the cold bath condition, subjects rated warmer stimuli to the hand as more pleasant. Conversely, warmer stimuli were correlated with unpleasantness in the hot bath condition. Circles and triangles represent different subjects.

Temperature has been explored as a possible means of dissociating valence and intensity in one functional imaging study, but alliesthesia was not included as an experimental condition. In the only study published to date, Rolls and others (Rolls et al., 2008) used two Peltier thermodes to deliver warm and cold stimuli to the palm and dorsum, respectively, of the hand. At the end of each trial, subjects were asked to indicate how "pleasant," unpleasant," and "arousing" the stimulus was and these ratings were used to probe for BOLD signal changes related to each measure. Unfortunately, arousal measures did not differ significantly across the 4 trial types, and no analysis was performed to disambiguate the arousal from valence.

The present study uses the phenomenon of alliesthesia to change the properties of a thermal stimulus to the hand such that its perceived valence is independent from its intensity. Our experiment is designed with a single Peltier thermode delivering a range of hot and cold stimuli to the palm of the hand under either warm or cool body conditions. To avoid misinterpreting interaction effects (Winston et al., 2005), temperatures that were only slightly above the threshold for detection, neutral trials, were included in the whole-brain analysis. Moreover, precautions are taken to minimize cognitive mixing of valence and intensity judgments, and trials were calibrated for each participant to maximize the range of these subjective reports.

Physiologic basis of temperature perception

Nearly all tissues in the body are innervated by nerve fibers originating in paravertebral ganglia (Craig 2002). Known as A-delta and C fibers, these relay a variety of sensory information (e.g. noxious, thermal, pruritic) to lamina I of the spinal cord at the thoracic and lumbar levels (Craig 1995; Sato and Schmidt 1973) . Temperature-sensitive ion-channels on these fibers lead to afferent signals that ascend the anterolateral system in the lateral spinothalamic tract. With thermal stimulation, peripheral nerves activate fibers in the spinothalamic tract that decussate and ascend the spinal cord and brain stem. The tract terminates predominantly in the ventral posterior lateral (VPL), ventromedial posterior (VMP), and medial dorsal (MD) nuclei of the contralateral thalamus. Additionally, some fibers synapse in the parabrachial nuclei of the brain stem before projecting to the thalamus or, along with connections with the hypothalamus and amygdala, are thought to be critical centers for autonomic reflex control (Craig 2003; Saper 2002). Major cortical targets of thalamic projections include primary sensory cortex, ACC, and insula (Craig 2002; Martin 2003) with the two latter regions appearing to play a particularly important role in the affective qualities of sensations arising from the periphery.

A-delta and C fibers refer many lines of information regarding the body's internal state to the brain and early MEG (Ploner et al. 2002; Tran et al. 2002) and EEG (Baumgartner et al. 2006; Opsommer et al. 2001) experiments began to determine their cortical targets. Recent studies have examined the cortical activation pattern of anterolateral system stimulation with the identification of neural correlates of pain. For example, Weiss and colleagues used high frequency laser pulses to the foot while neural

activity was being measured by fMRI (Weiss et al. 2008). In response to both A-delta and C fiber stimulation, robust activity was detected in the thalamus, anterior cingulate, inferior frontal gyrus, insula, and anterior and posterior operculum, supporting the use of this method of directly stimulating the afferent temperature pathway may be used to study their affective and sensory properties. With a somewhat less specific methodological means of stimulating A-delta and C fibers, another recent study (Rolls 2008b) attempted to model affective ratings of non-noxious thermal stimuli and found that neural activity related to the self-reported experience of temperature sensation differed from response patterns that correlated to the actual intensities of the same trials. In particular, pleasant ratings correlated to activity in the medial orbitofrontal cortex, anterior cingulate, and ventral striatum, while unpleasant stimuli evoked responses in lateral and anterior orbitofrontal cortices. Taken together, these studies begin to establish roles for afferent fiber pathways, brain stem nuclei (e.g. parabrachial and solitary nuclei), and subcortical (e.g. thalamus) and cortical (e.g. insula and cingulate cortices) regions in a broad network involved in thermal sensation, affective perceptions, and also homeostatic regulation.

With regard to the insula and anterior cingulate cortices, Craig affords a generous role for these regions relative to other models of temperature perception (Craig 2002; Craig 2009). Specifically, Craig's model attempts to identify a neural basis for interoception – the perception of the body's physiologic state. Within the framework of interoception, the posterior insula is thought to provide unconscious monitoring of afferent signals from the viscera (Craig 2002). Neuroanatomical support for this claim includes neuronal tracing studies and observations of the cytoarchitecture of the insula.

The posterior insula is populated with granular cells that receive unimodal input from all 5 sensory modalities, although direct gustatory and olfactory inputs may first track through the anterior insula (Augustine 1996). Across the entire anteroposterior axis of the insula, approximately 10% of the neurons respond to gustatory stimulation and, interestingly, approximately 20% appear to be involved in motor and touch (Augustine 1996; Mesulam and Mufson 1982 a,b;). These cellular properties along with its intimate connectivity between other sensory relay and integration sites, such as the thalamus, orbitofrontal cortex, and amygdala, the insula fits as a primary site of interoceptive processing. Empirical studies have begun to further the idea that the insula is involved in monitoring the state of the internal milieu. For example, Critchley and colleagues (Critchley et al. 2004) designed an experiment to quantify the accuracy with which subjects were able to track the beating of their own heart without using somatic cues (e.g. feeling their own pulse). The insula, operculum, and anterior cingulate cortex were activated when subjects were performing the task and the strength of the activity in the insula was positively correlated with the accuracy in the responses of individual participants. Further, the authors found that inter-subject variability in gray matter volume correlated with task performance and objective measures of trait anxiety, which supports their hypothesis that anxiety is associated with unbalanced focus on internal bodily functions.

As mentioned, Craig summarizes these separate lines of evidence into a general role for the insula as the primary site of representation of the physiologic state of the body (Craig 2002), but this model also takes into account additional findings that the insula is commonly co-activated with the anterior cingulate cortex. An extended model

specifically indicates that the right anterior insula represents a conscious awareness of changes to the internal state of the body and that the anterior cingulate cortex supports this function as an integrator of both the internal and external environment with a potential additional role in organizing emotional, cognitive, and behavioral adaptations (Craig 2009). One goal of hypotheses regarding the central representation of spinothalamic inputs is to better understand how hedonic aspects of sensory stimuli are coded and by what mechanism they serve to motivate behavior. One of the most commonly utilized systems in which this is studied is pain perception, which is drawing on both animal and human work to gain insight into how environmental stimuli are perceived as noxious and how internal mechanisms may modify this perception and the organism's behaviors.

Parallels between pain processing and general thermal sensation begin with common neuronal inputs to the spinal cord (i.e. A-delta and C fibers) and ascending spinal pathway (i.e. spinothalamic tract). Additionally, the aforementioned subcortical and cortical targets appear to be relevant in the perception and modulation of pain. In particular, subnuclei of the thalamus such as the ventral posterior, ventral medial, and medial dorsal have been implicated in both acute and chronic pain (Craig 2003; Pralong et al. 2004) as well as cortical targets that are commonly cited as components of the "pain matrix," such as the primary and secondary somatosensory cortices, insula, anterior cingulate cortex, and prefrontal cortex (Schweinhardt et al. 2006). Neuroimaging experiments have begun to elucidate what roles these brain areas might play in processing noxious stimuli and findings from studies of the affective aspects and

attentional control of pain are particularly relevant to the discussion of general thermal sensation.

Building upon from what is known regarding interoception, the insula has been a focus of much pain research and is implicated in a range of aspects of noxious stimulus processing, including subjective pain assessment, chronic pain, and psychogenic pain disorders (Apkarian et al. 2001; Apkarian et al. 2005; Tracey and Mantyh 2007; Witting et al. 2006). Paulus and Stein (Paulus and Stein 2006) posit that the insula's role in interoception extends to generating predictions signals arising from the spinothalamic system and may play a central role in generating affective responses to prediction errors. This hypothesis has wide implications for understanding psychiatric illnesses, particularly anxiety, where these authors suggest that genetic and environmental factors may lead to inappropriate predictive coding in the insula. Prediction errors are thought to lead to emotional reactions that motivate behavioral change and several lines of research suggest that the amygdala is involved in adding affective qualities to a painful experience. In one study of patients with chronic pain and depression, the sensory and affective dimensions of pain were dissociated and activity in the amygdala was correlated with depressive symptoms evoked by noxious stimuli, but not the physical intensity of the same stimuli (Giesecke et al. 2005). From these findings, the authors concluded that affective properties of pain may rely on a separate neural circuit than that coding for sensory properties and may be amenable to alternative treatment approaches, such as antidepressant medications. How affective value is integrated with the sensory aspects of a stimulus is closely related to the objectives of the thesis described below and findings

from recent animal and human studies have begun to build a neurobiological basis for this process.

One approach to studying valuation is through stimulus-reward learning paradigms. In a comprehensive study of a putative valuation network, Gaffan and Murray (Gaffan and Murray 1990) lesioned the amygdala, mediodorsal nucleus of the thalamus, ventromedial prefrontal cortex, or a combination of these in primates. The lesions were performed either all on the same side or one lesion was performed on one side and the anothers were completed on the contralaterally. For example, in three monkeys the right amygdala and the left thalamus and prefrontal cortex were lesioned while in a separate group of three monkeys all three areas were lesioned on the right side. The purpose of this study was twofold. First, the relevance of this network to stimulus-reward learning was determined with potential insights into how reward value is coded for arbitrary environmental stimuli. Second, the serial nature of a unilateral network was investigated by mixing ipsi- and contralateral lesions. Findings from this study support the hypothesis that this network is necessary for effective stimulus-reward associations and also suggest that a serial processing of information is utilized by this system.

Additional work has further supported the contributions of thalamus (Corbit et. al., 2003; Oyoshi et al. 1996), amygdala (Baxter and Murray 2002), and prefrontal cortex (Elliott et. al. 2000; Kringelbach and Rolls 2004) to valuation and current models place different weights on each of these and other regions as contributing to a functional pathway of stimulus perception and determination of biological significance. Particular focus has been paid to the role of the orbitofrontal cortex, which is thought to be broadly involved in establishing biological relevance for environmental stimuli and distinguishing

between different reward values to drive adaptive behaviors (Murray et. al. 2007; Wallis and Miller 2003). This heterogeneous cortex likely plays multiple roles in stimulus valuation as studies have implicated it in the discrimination between presence (Schoenbaum et. al. 1998) and size (Roesch and Olson 2004) of rewards and punishments, tracking the value of time (Roesch 2005), and in accounting for contextual influences such as the presence of competing rewards (Tremblay and Schultz 1999) and changing physiologic demands of the organism (Critchley and Rolls 1996). A popular consensus views the orbitofrontal cortex as a primary site coding for a value scale on which internal and external stimuli may be judged (Montague and Berns 2002; Rolls 2008a). This function is often described as developing a "common currency" that guides an organism's emotional, cognitive, and behavioral responses to dynamic environments.

In the following thesis, experiments are described that intend to isolate emotional aspects of thermal sensation from purely sensory perceptions. As stated above, the primary goal is to test the hypothesis that a distinction can be made between neural structures underlying sensory versus affective coding of these stimuli. Models of temperature, pain and valuation all share the common thread that external stimuli are perceived along their sensory dimension and colored with an affective dimension based upon physiologic demands. Aiming to further refine these models, the experiments described here account for inherent confounding factors between physical and affective properties of thermal stimuli and may thus differentiate brain activity between the two.

CHAPTER II

METHODS

Subjects

All subjects were recruited from the Columbia University Medical Center community and provided written informed consent according to the guidelines of the local institutional review board. Twenty participants (11 male, median age = 26, SD = 4.07, range 23-40) were recruited for a study of "temperature sensation" and compensated for their time.

fMRI acquisition

All scans were performed using a 1.5T GE Twin-Speed Excite scanner. Structural T1 SPGR images were acquired with: TE = 5 ms, TR = 19000 ms, flip angle = 20, FOV = 25.6, and voxel size = 1 x 1 x 1 mm. Functional imaging data were acquired with a spiral-in/out sequence to minimize susceptibility artifacts (Glover et al., 2001). Scan parameters were TE=36 ms, TR = 1600 ms, flip angle = 84, FOV = 22.4, and voxel size = 3.5 x 3.5 x 4.5 mm.

Experimental procedure

A custom set of temperatures was chosen for each subject to ensure a full range of non-noxious intensity values, and these were based on a range of thermal intensities that were judged prior to the session. Each subject participated in two experimental sessions that were administered on separate days. In one session, the subject experienced the 'cold body condition' and in the other, the 'hot body condition', with the session order counterbalanced across the subjects (Figure 2.1). During the cold body session, the ambient temperature of the fMRI scanning room was lowered to 65°F (18.3°C) and no

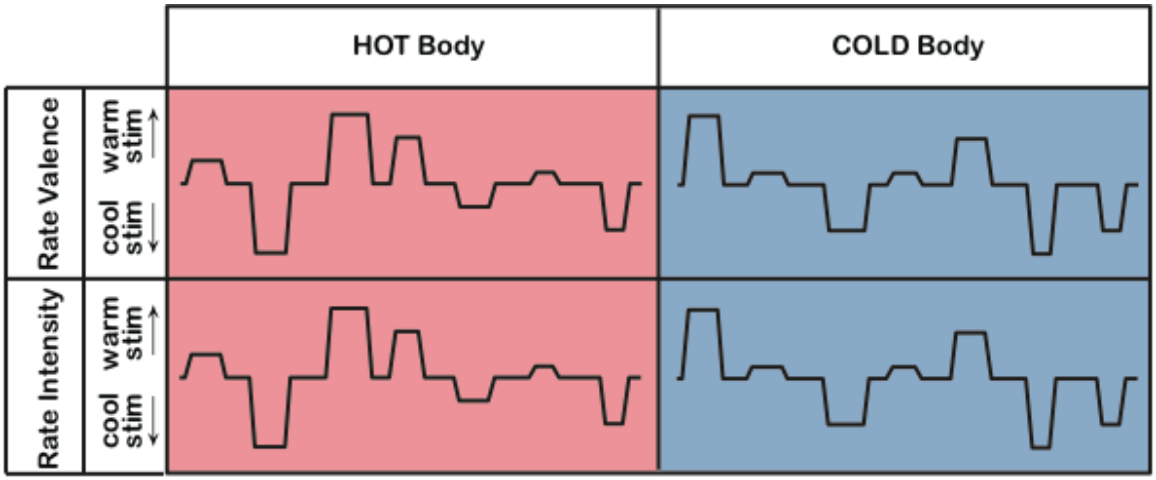


Figure 2.1: The experimental conditions consisted of two body temperatures: HOT (red) and COLD (blue). These were each performed on separate days. Within each body temperature condition, two runs were performed where the subject was asked to either rate the valence or intensity of thermal stimuli to the hand, which are represented as the trapezoidal boxcars within the red or blue shading. Continuous ratings were provided with a trackball guided by the visual analog scales for both valence and intensity.

blankets were given to the subject during the experiment. In the hot body session, the scanning room temperature was also lowered to 65°F to ensure no inter-session variability in equipment function, but subjects were wrapped in two MRI-compatible warming blankets – one was an electric blanket (Sunbeam; Boca Raton FL) and the other was an air-warming "Bair Hugger" (Arizant Healthcare; Eden Prairie, MN). In this way, the temperature of the air surrounding the body, below the neck, was increased to approximately 95°F (35°C). All subjects changed into hospital scrubs to control for differences in clothing. An example experimental setup is depicted in Figure 2.2. To provide time for acclimation to the hot and cold air temperatures, a structural scan was acquired before the thermal rating runs were begun. Air temperature was measured continuously throughout the experiment by a thermistor attached to the right inner thigh –

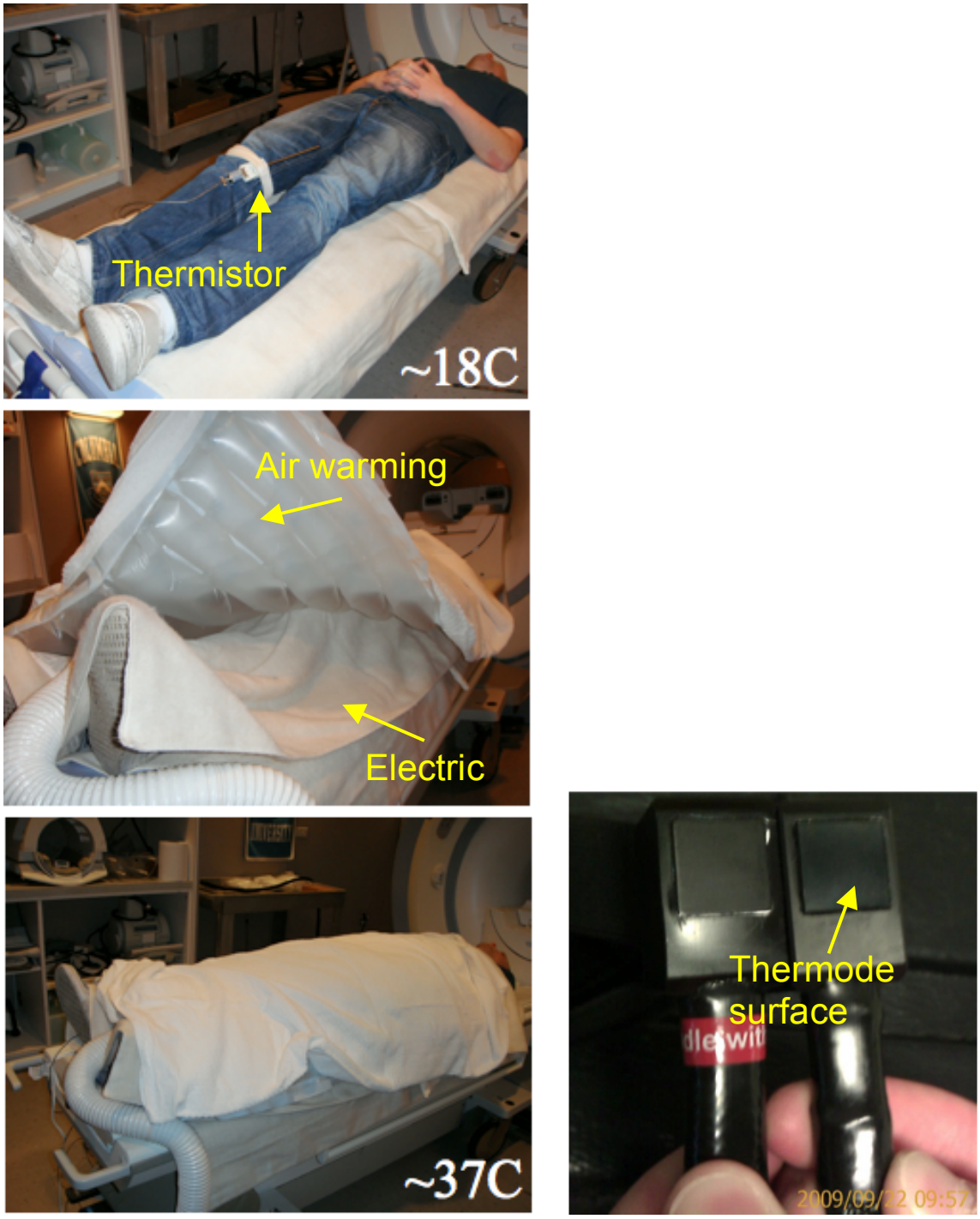


Figure 2.2: Experimental technique illustrating the two body temperature conditions. In the cold condition, top left, subjects were not covered with any blankets. The subject was given two warming blankets, middle left, for the hot condition, bottom left. The temperature within the blanket apparatus was measured continuously with a thermistor on the subject's right inner thigh. A single Peltier thermode, right, was placed on the palmar surface of the subject's left hand.

this was inside the blankets for the hot body condition – to confirm that the air temperature had stabilized by the start of the thermal rating portion of the study.

A 15 mm x 15 mm thermode (Medoc TSA 2001; Medoc Ltd., Chapel Hill, NC) was placed in the subject's left hand and a trackball was placed in their right hand. Five stimuli, 2 cold, 2 hot, and 1 near the baseline temperature of 32°F, were repeated 6 times each. Each stimulus lasted approximately 8 seconds and the inter-trial interval was randomized between 8 and 12 seconds. The time course of the stimulus presentation was trapezoidal with rise and fall times of approximately 1.5 seconds each and a plateau lasting 5 seconds.

On each scanning day, two experimental runs were performed, each lasting 9.5 minutes. Thermal stimuli presented during these runs were identical, but subjects were asked to either rate their valence or intensity. For valence runs, a visual analog scale was presented on the screen that ranged from -10 ("highly unpleasant") to +10 ("highly pleasant") where the middle value of 0 indicated "neutral." The intensity scale ranged from 0 ("low intensity") to 10 ("high intensity") where the middle value of 5 indicated "neutral." Subjects provided ratings continuously throughout the entire 9.5-minute run. The order of valence and intensity runs was counterbalanced between sessions and across subjects.

At the end of each scanning session, a 5-minute run was also performed for estimation of custom hemodynamic response functions (see below). During this run, a reversing checkerboard (10Hz) was displayed for a random duration of 3-6 seconds with a random inter-trial interval between 3-9 seconds. No thermal stimuli were given and the subjects were asked only to fixate on the center of the monitor.

Behavioral analysis

In the behavioral analysis, the peak valence or intensity judgment during trial periods was taken for each trial (i.e. 30 measurements per subject). Group-level analyses demonstrated that valence and intensity were best fit with linear and quadratic curves, respectively. For each subject, a linear fit was performed for ratings of valence versus thermode temperature and a quadratic fit was applied for ratings of intensity versus thermode temperature. Separate fits were performed for the hot and cold body conditions. Using these fits to test for an interaction of body-temperature on ratings of valence or intensity, a 1-sample paired t-test was performed using either the linear (valence) or quadratic (intensity) terms. All behavioral analyses were performed using Matlab R2009a (Mathworks, Inc., Sherborn, MA).

fMRI analysis

Analysis of functional imaging data was performed using FSL version 4.1.5 (Smith et al., 2004; Woolrich, et al., 2009). Pre-processing included brain extraction, motion correction, smoothing with a 5 mm Gaussian kernel, high pass filtering at 100s, and the derivation of transformation matrices to the 2 mm Montreal Neurological Institute (MNI 152) template using non-linear image registration. The design matrix for each experimental run consisted of one regressor for each temperature, totaling five, with each epoch duration equal to the duration of the subject's judgment period. Contrasts of parameter estimates were designed based on the behavioral data with models for the linearly increasing (for valence ratings in the cold body condition), linearly decreasing (for

valence ratings in the hot body condition), or quadratic (for intensity ratings for both hot and cold body conditions). For example, in the cold body session and when the subject was providing ratings of valence, the linear contrast for the 5-thermode temperatures was modeled as (-2 -1 0 1 2). Also for valence ratings, but in the hot body session, the linear contrast was modeled as (2 1 0 -1 -2). A fixed-effects analysis was performed for each subject in whom the parameter estimates for the hot and cold sessions were averaged, and these results were carried to the whole-brain mixed-effects group analysis. All statistical maps were corrected for multiple comparisons with spatial extent and voxel thresholds of $p \leq 0.001$. For cluster reporting, anatomically derived masks were employed to perform post-hoc clustering of the insula/operculum, putamen and caudate to delineate these structures.

Meta-analysis

For the meta-analysis, presented in the introduction, neuroimaging articles that specifically tested for disparate valence and intensity networks were reviewed (Table 2.1). Analyses that were aimed at targeting interactions between these two processes were excluded (i.e. identification of regions that respond to valence only for high intensity). Voxel coordinates that were in Talarach space were converted to standard FSL MNI152 2x2x2 mm space using GingerALE (brainmap.org). Using these coordinates, voxels were then plotted on the standard brain and a 3 mm sphere was inflated around each to reduce the possibility that minor differences in registration quality

would affect the results. To identify the anatomical structure corresponding to each coordinate sphere the Harvard-Oxford atlas was used. If a voxel did not fall within one

First Author	Year	Stimulus	N
Anders	2004	IAPS	16
Anders	2008	IAPS/IADS	40
Anderson	2003	Olfactory	16
Colibazzi	2010	Induction	10
Cunningham	2004	Induction	20
Dolcos	2004	IAPS	16
Grimm	2006	IAPS	29
Heinzel	2005	IAPS	13
Lewis	2007	Linguistic	18
Posner	2009	Words	10
Rolls	2008	Thermal	12
Small	2003	Gustatory	9
Viinikainen	2010	IAPS	17
Winston	2005	Olfactory	18

Table 2.1: List of studies included in the meta-analysis. Results from this analysis are listed in Table 1.1.

of the anatomical regions identified by this atlas, masks created by a separate investigator based on anatomical landmarks were used. Within a single study, if a voxel from an inflated sphere intersected with one of these masks or a region from the anatomical atlas, that brain region was said to code for either valence or intensity. The sum across studies was computed and entered into Table 1.1.

Quantification of overlap between activity associated with valence and intensity

To test the hypothesis that there are segregated (i.e. non-overlapping) patterns of neural activity associated with perceptions of valence and intensity, we calculated the Dice coefficient (Dice, 1945). This similarity coefficient measures the degree of overlap between two images and has been used extensively in neuroimaging for test-retest

reliability estimates (Rombouts et al., 1997; Raemaekers et al., 2007; Clement and Belleville, 2009) and meta-analyses (Salimi-Khorshidi et al., 2008). This value ranges between 0 (no overlap) to 1 (complete overlap) and is computed with the following equation, were **D** is the Dice coefficient, and **A** and **B** are the two activity maps:

$$D = \frac{2|A \cap B|}{|A| + |B|}$$

Alone, the Dice coefficient is a qualitative measure that is most commonly used as an index of reliability in test-retest measures, without providing any statistical inferences. To quantify the statistical output, we performed a Monte Carlo simulation. The simulation began by down-sampling the test images (i.e. valence and intensity activity maps) for each subject according to the number of image resels for that subject. These images were then randomized and the Dice coefficient was calculated. This procedure was repeated 100,000 times to generate a distribution of Dice coefficients that represent the amount of overlap that two activity maps will have when their spatial patterns defined at random. This distribution was divided by its sum for conversion to a probability distribution to allow direct comparison to the observed value in the original test images. To describe the probability distribution, the full width half maximum (FWHM) was calculated, assuming normality, with the equation:

$$\mathrm{FWHM} = 2\sqrt{2\ln 2}\,\sigma$$

Custom HRF estimation

fMRI analyses often assume a canonical hemodynamic response function (HRF), but inter-subject variability may reduce the explanatory power of models of the BOLD

signal (Handwerker et al., 2004; Grinband et al., 2008). A customized HRF was generated for all subjects using an independent component analysis (ICA) on images acquired during a 5-minute reversing checkerboard run (Eichele et al., 2008). The component corresponding to primary visual cortex was identified with a cross-correlation with an anatomical mask of V1. This automated procedure was then checked manually and the primary visual component was fit with three flexible basis functions. The parameter estimates from this analysis were then multiplied by their corresponding basis function to generate the best-fit curve estimating the subject's HRF. The HRFs from each flashing checkerboard run were averaged and this function was used in the convolution step for the analysis of valence and intensity judgments (Figure 2.3).

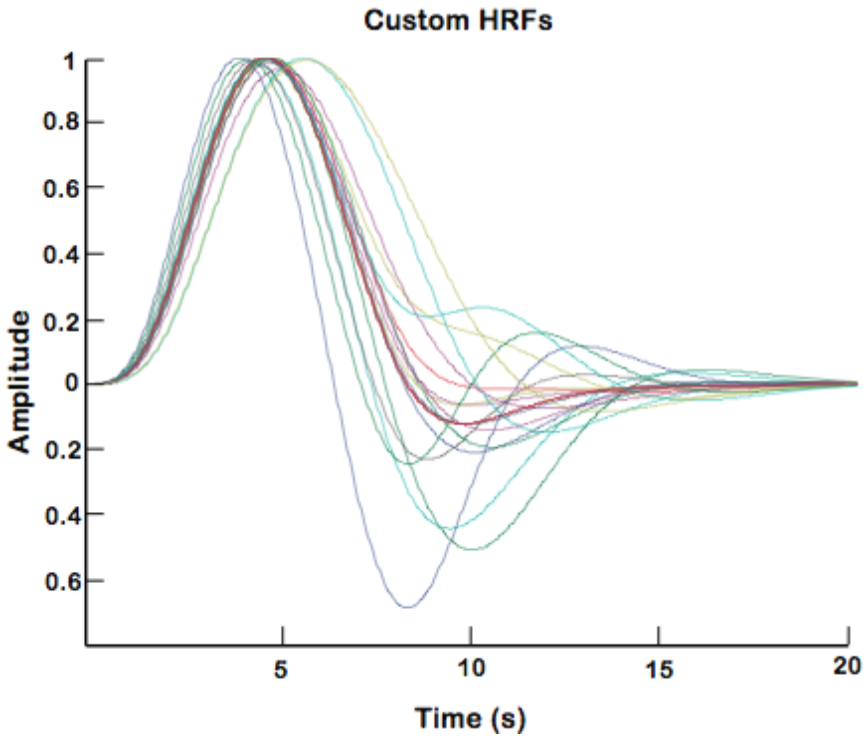


Figure 2.3: Custom hemodynamic response functions. The HRF for all 20 subjects was estimated to establish more accurate explanatory variables in the analyses using the general linear model. All 20 estimates are overlayed and illustrate the small differences in slope and time to peak, as well as variability in the overall shape of the curve.

CHAPTER III

RESULTS

Ratings of valence and intensity

Subjective ratings of valence and intensity are plotted for both the hot (red) and cold (blue) body temperature conditions (Figure 3.1a). As hypothesized and consistent with previous findings (Cabanac, 1971), the relationship between stimulus temperature and ratings of valence was dependent on body temperature ($p \leq 0.001$, 1-sample paired ttest of individual subject fits). As expected, the perceived intensity of thermal stimuli to the hand increased with both positive and negative deviation from the baseline temperature (Figure 3.1b). In contrast to ratings of valence, intensity judgments were not affected by body-temperature condition ($p = 0.48$). An analysis of only those subjects demonstrating a significant behavioral effect is described at the end of this section.

Functional imaging data and valence

The relationship between thermode temperature and valence judgments provided by the subjects was modeled for both the hot and cold sessions. Data from both sessions were averaged at the first-level and included in the higher-level group analysis. Brain regions that covaried with thermode temperature and subjective ratings of valence for the two body-temperature conditions are included in Table 3.1. This network included two clusters of activity in the medial OFC in the right hemisphere (x = 30, y = 22, z = -26; Z-score = 3.82) and medially (x = 12, y = 50, z = -14; Z-score = 5.31) (Figure 3.2a). The subgenual anterior cingulate cortex (sgACC) was also significantly activated (x = 4, y = 22, z = -8; Z-score = 3.60) as was a cluster in the posterior cingulate cortex (pCC, x = 0, y = -52, z = 28; Z-score = 5.73). Within the amygdala, significant activity was detected with peak voxels found at (x = -28, y = -2, z = -22; Z-score = 4.17) on the left and (x =

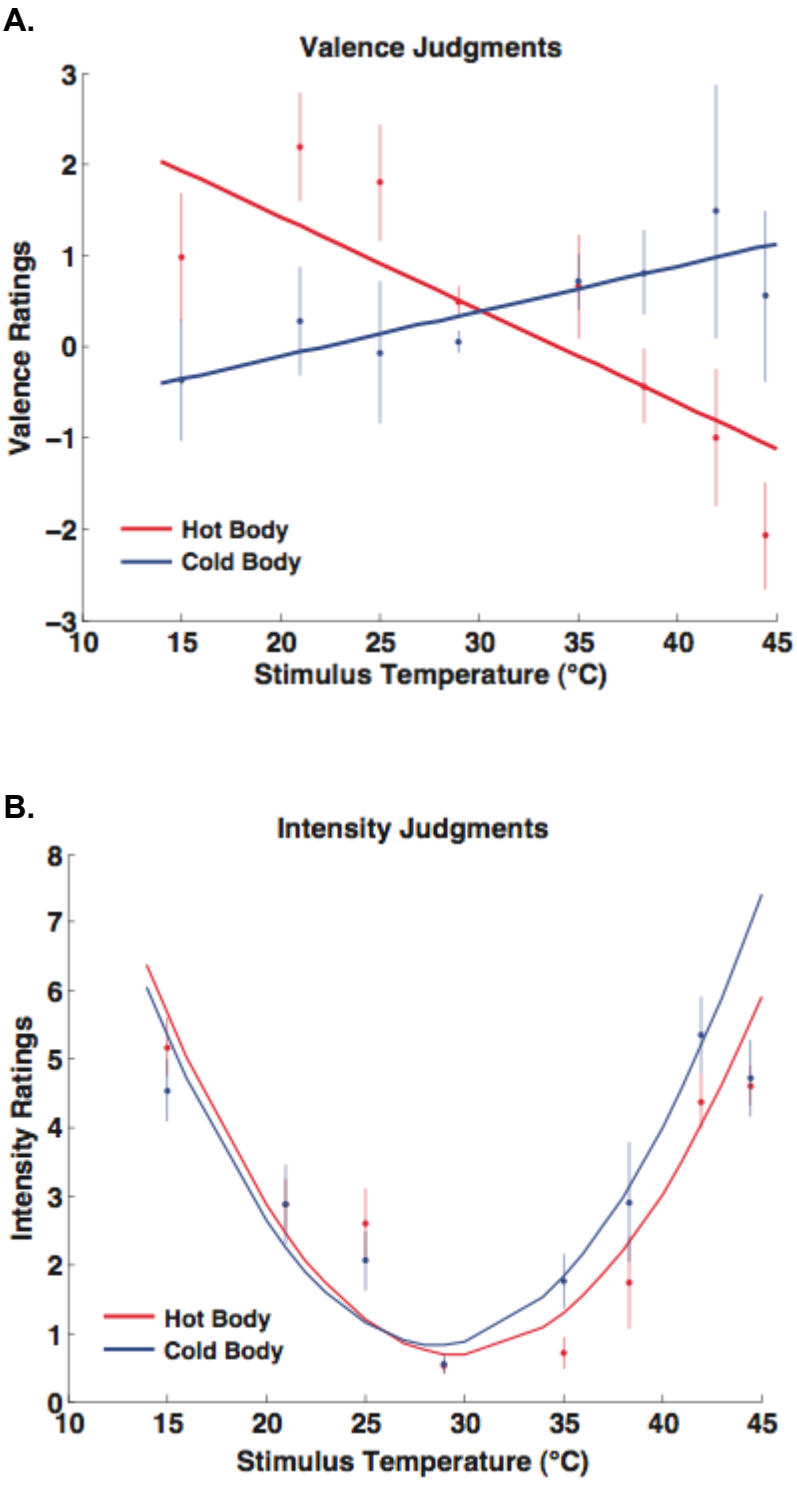


Figure 3.1: Behavioral analyses (n = 20). **A)** Subjective ratings of valence were given with negative values representing increasing unpleasantness and positive values representing increasing pleasantness. In the cold body condition (blue line), warmer stimuli were considered more pleasant (i.e. positive slope) while this relationship was reversed in the hot body temperature condition (red line). There was a significant interaction between body temperature condition and the

slope of the rating x stimulus relationship ($p \leq 0.001$, 1-sample paired ttest, errors are SEM). **B)** On a separate experimental run, ratings of the physical intensity of the thermal stimuli to the hand were taken. In both the hot and cold body temperature conditions, stimuli near baseline (30 °C) were described as very low intensity and these judgments increased in magnitude as temperatures became either warmer or colder. There was no statistical difference in the intensity ratings in the hot and cold body temperature conditions ($p = 0.48$, 1-sample paired ttest, errors are SEM).

Peak Z-score	X	Y	Z	Anatomical Region
5.73	0	-52	28	pCC
5.31	12	50	-14	mOFC
4.36	-48	-72	30	L-LOC
4.17	-28	-2	-22	L-amyg
4.18	2	4	-12	vStr
3.92	-26	-92	22	L-LOC
4.36	-56	-58	-26	L-Inf temp
3.89	-28	-64	20	L-LOC
3.77	-46	8	-34	L-temp pole
3.68	28	-4	-24	R-amyg
3.81	36	-22	46	R-PoCG
3.81	12	-80	14	Intracalc
3.52	14	-30	62	R-PrCG
3.82	30	22	-26	R-OFC
3.6	-56	-2	-20	L-Mid temp
3.63	-44	-70	48	L-LOC
3.6	4	22	-8	sgACC
3.65	10	-60	44	Precuneus
3.28	-36	-78	40	L-LOC

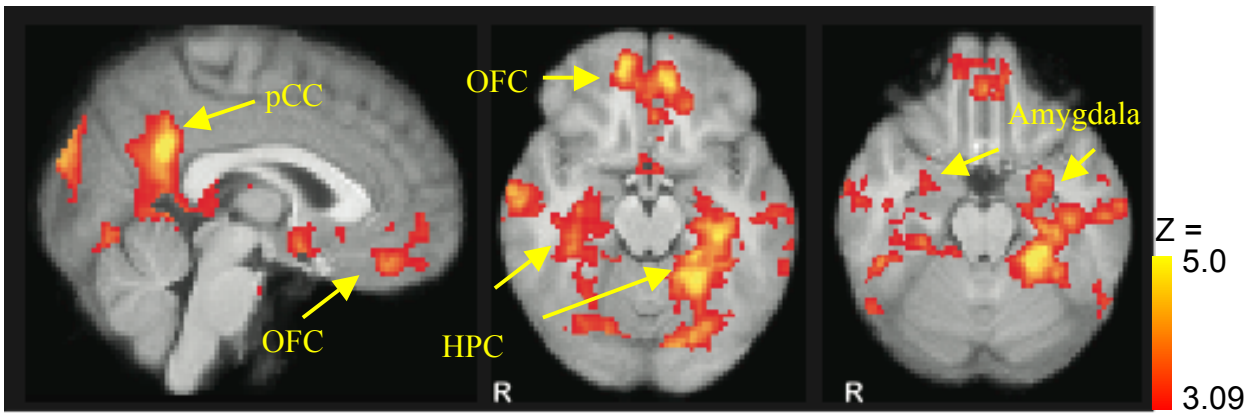
Table 3.1: Peak voxels and MNI coordinates resulting from the fMRI analysis of valence. Abbreviations: posterior cingulate cortex (pCC), medial orbitofrontal cortex (mOFC), lateral occipital cortex (LOC), amygdala (amyg), ventral striatum (vStr), interior temporal gyrus (Inf temp), temporal (temp), post-central gyrus (PoCG), intracalcarine cortex (Intracalc), pre-central gyrus (PrCG), orbitofrontal cortex (OFC), subgenual anterior cingulate cortex (sgACC).

28, y = -4, z = -24; Z-score = 3.68) on the right. This analysis was aimed at isolating brain regions involved in valence coding, by modeling the interaction between body-temperature condition and judgments of valence for varying thermal stimuli.

Functional imaging data and intensity

Perceptions of varying intensity evoked by thermal stimulation of the hand were modeled as a parabolic curve for both hot and cold body-temperature sessions. These sessions were averaged and entered into a group-level analysis, which indicated a network that included distinct regions of activity relative to the analysis for valence coding (Figure 3.2b). In particular, peak activity was identified in the insula (left, x = -40, y = 6, z = 6; Z-score = 5.19), and thalamus (right, x = 18, y = -24, z = 8; Z-score = 3.49). Several other regions were identified in this analysis and are listed in (Table 3.2). A post-hoc clustering analysis was performed using anatomically derived masks to further discriminate clusters of activation within the insula, putamen, caudate and thalamus (see Methods). This analysis revealed additional cluster peaks in the striatum in the left (x = -24, y = -4, z = 2; Z-score = 4.76) and right (x = 22, y = 4, z = 4; Z-score = 4.86) hemispheres as well as several additional peak voxels in the insula (right, x = 38, y = 4, z = 6; Z-score = 4.88; left, x = -38, y = 16, z = -2; Z-score = 4.73) and thalamus (right, x = 14, y = -4, z = 12; Z-score = 3.82; left, x = -16, y = -18, z = 2; Z-score = 4.8 (Table 3.3). This analysis was designed to identify activity in neural regions correlating with intensity ratings and found several clusters that were distinct from those correlating with judgments of valence.

A.



B.

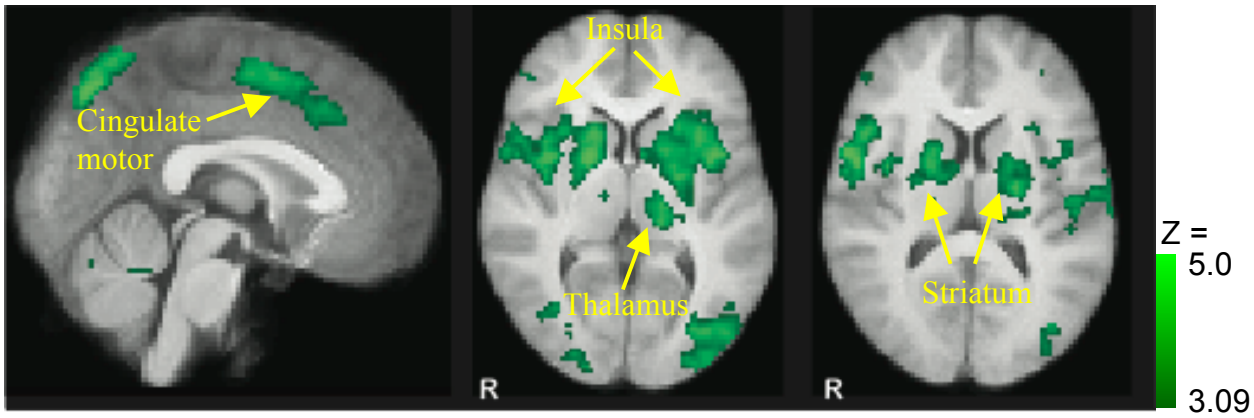


Figure 3.2: fMRI analysis of valence and intensity ratings. **A)** Subjective ratings of valence correlated with activity in several brain regions including the OFC, pCC, and amygdala bilaterally. **B)** Ratings of intensity were correlated with the BOLD response in a separate network of brain regions that included the insula, thalamus, and striatum. A complete list of voxel clusters is reported in Tables 1 & 2. Abbreviations: posterior cingulate cortex (pCC), orbitofrontal cortex (OFC), hippocampal and parahippocampal gyrus (HPC).

Peak Z-score	X	Y	Z	Anatomical Region
6.36	-30	-16	56	L-PrCG
5.19	-40	6	6	L-ins/opr
5.47	-48	-82	-4	L-LOC
4.85	26	-54	-28	R-CBL
4.25	24	-92	-2	R-OCC Pole
4.16	-26	-60	-28	L-CBL
3.55	-44	8	30	L-PrCG
4.26	-8	-104	-2	L-OCC Pole
3.49	18	-24	8	R-Thal

Table 3.2: Peak voxels and MNI coordinates for clusters of activity identified in the analysis of intensity. Abbreviations: pre-central gyrus (PrCG), insula (ins), operculum (opr), lateral occipital cortex (LOC), cerebellum (CBL), occipital (OCC), thalamus (Thal).

Peak Z-score	X	Y	Z	Anatomical Region
4.76	-24	-4	2	L-Put
4.86	22	4	4	R-Put
4.8	-16	-18	2	L-Thal
4.88	38	4	6	R-ins
4.73	-38	16	-2	L-ins
3.82	14	-4	12	R-Thal

Table 3.3: Peak voxels and MNI coordinates for a post-hoc region of interest clustering analysis. Regions of interest were used to delineate between structures that were grouped in the initial analysis of intensity. Abbreviations: putamen (Put), thalamus (Thal), insula (ins).

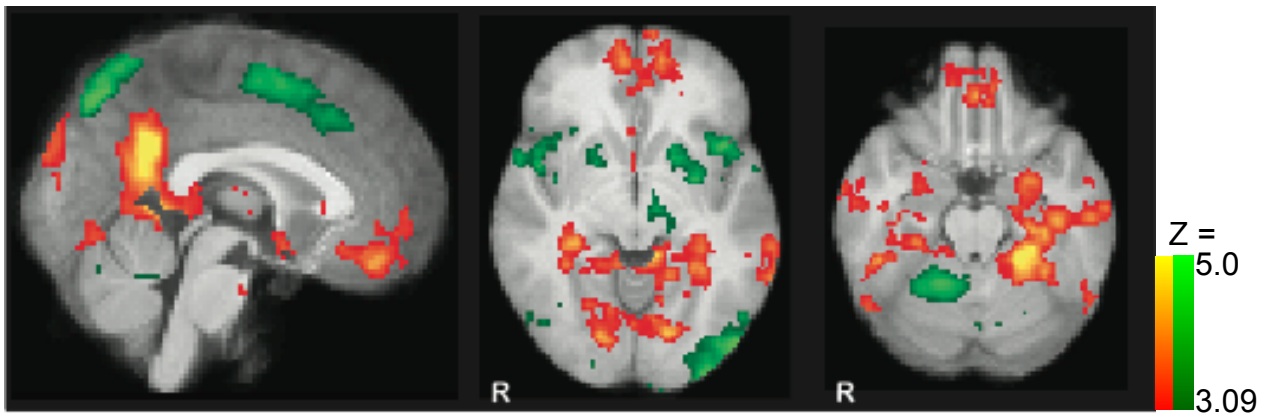
Comparison of valence and intensity networks

Regions identified in the analyses described above suggest little overlap between valence and intensity networks. The overlayed images qualitatively illustrate the segregation of these two activity maps (Figure 3.3a) and to quantify the degree of overlap we calculated the Dice similarity coefficient (Dice, 1945). With a low threshold for each activity map ($p \leq 0.05$), the degree of overlap was low (Dice = 0.017). To test for statistical significance in this value, we performed a Monte Carlo simulation by randomizing the valence and intensity activity maps, and then calculating the Dice coefficient for each pair. This method provides a distribution of randomly generated coefficients from a given volume of activity (i.e. valence and intensity maps) to determine the probability of the observed measure arising by chance. The left side of the resulting probability distribution describes the chances of obtaining a low degree of overlap, or low Dice coefficients, while the right side of the distribution describes high degrees of overlap, or high Dice coefficients. The distribution of randomly acquired Dice coefficients was centered at 0.251 with a full width half maximum (FWHM) of 0.031 (Figure 3.3b) and demonstrates that the observed overlap in the valence and intensity activity maps would occur by chance at $p \leq 0.001$.

Comparison of hot and cold conditions

To satisfy the requirements of the experimental design, subjects were scanned on two separate occasions under either hot or cold body conditions. Each session was analyzed separately to identify regions that fit the models of valence or intensity obtained from the behavioral measures. These data were then averaged at the individual subject

A.



B.

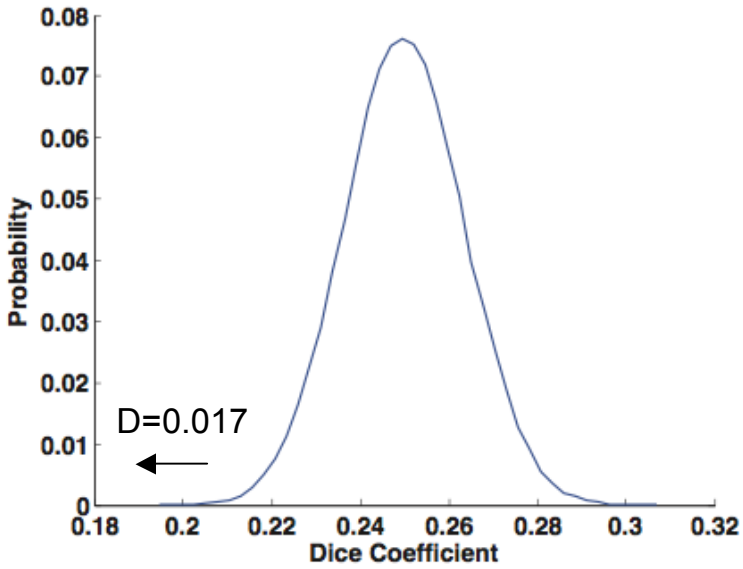


Figure 3.3: Quanitification of overlap for valence and intensity networks. **A)** Overlayed fMRI activity maps for valence (red) and intensity (green) on which the Monte Carlo simulation was based. **B)** The simulation generated a distribution of Dice coefficients and the cumulative probability was computed. Comparing this to the observed Dice coefficient of 0.017 demonstrates the low degree of overlap between these two networks ($p \leq 0.001$).

level, but it is possible that hot and cold conditions were associated with differential patterns of activity for either the valence or intensity correlations. To ensure that this effect was not lost in averaging, a post-hoc analysis was performed for hot and cold body conditions separately using the same threshold as was applied during averaging.

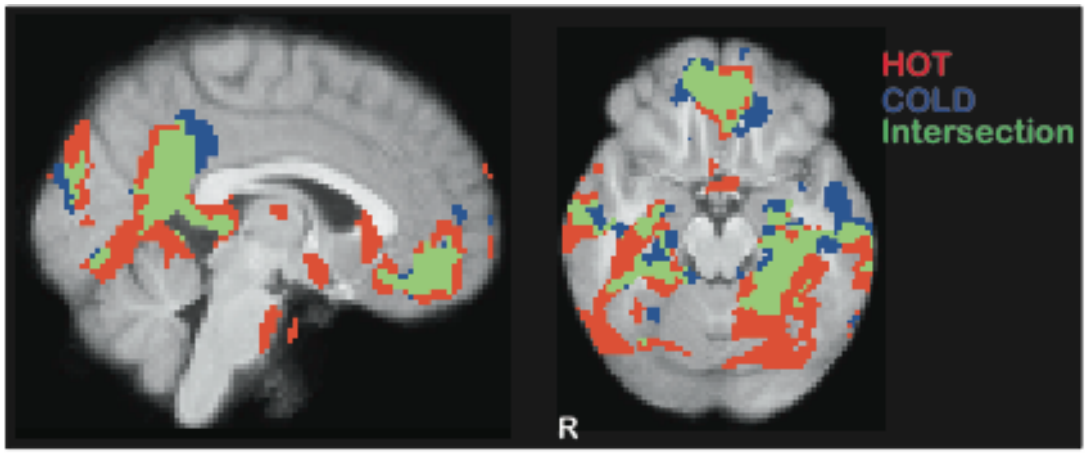
Results from the analysis of valence runs are shown in Figure 3.4a. A conjunction analysis using the thresholded ($p \leq 0.001$) activity maps depicts large clusters of shared voxels between conditions with only sparse areas of non-overlap. The Dice coefficient for these maps was calculated to be 0.636. A Monte Carlo simulation was performed as above, but instead used the hot and cold activity maps for valence coding. The resulting distribution was centered at a Dice coefficient of 0.166 with FWHM = 0.035. Therefore, the observed coefficient would not likely have arisen by chance ($p \leq 0.001$) as illustrated by the probability distribution (Figure 3.4b).

Finally, regions coding for intensity were also identified for hot and cold body conditions and a conjunction analysis was performed on the thresholded images (Figure 3.4c). As in the valence analysis, major clusters of activity were overlapping between these conditions and a high Dice coefficient was observed (Dice = 0.747). The simulation using the intensity maps generated a random distribution of coefficients centered at Dice = 0.149 with FWHM = 0.036, again demonstrating the low probability of this degree of overlap being found by chance ($p \leq 0.001$; Figure 3.4d).

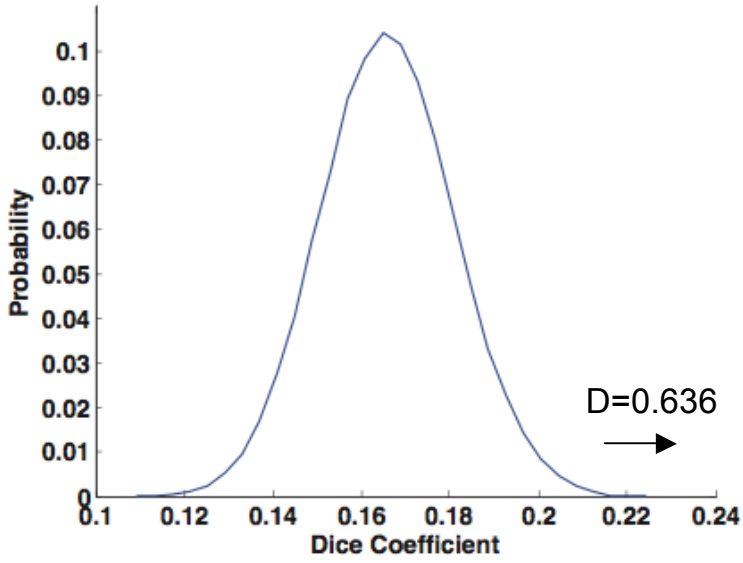
Analysis of data subset

In the group-level behavioral results we observed that the relationship between ratings of valence and stimulus temperature was dependent on body temperature.

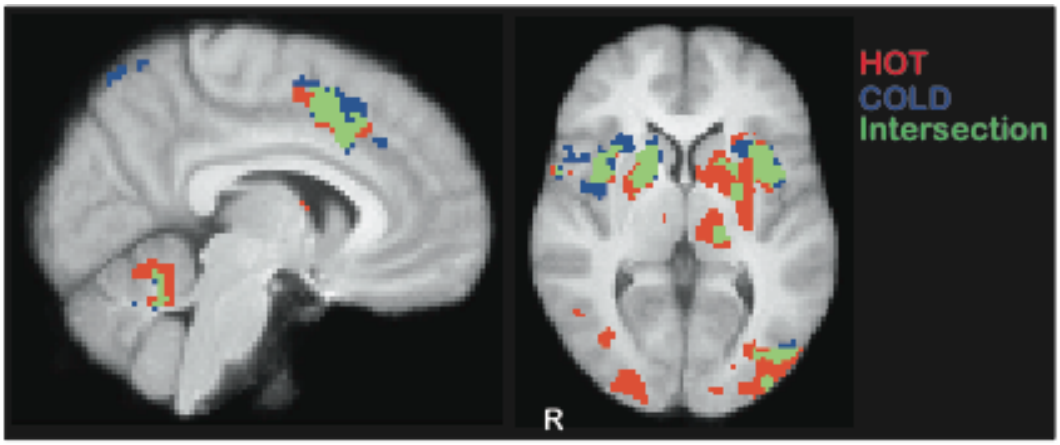
A.


HOT
COLD
Intersection
R

B.


Probability
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0.1
0.12
0.14
0.16
0.18
0.2
0.22
0.24
Dice Coefficient
D=0.636

C.



D.

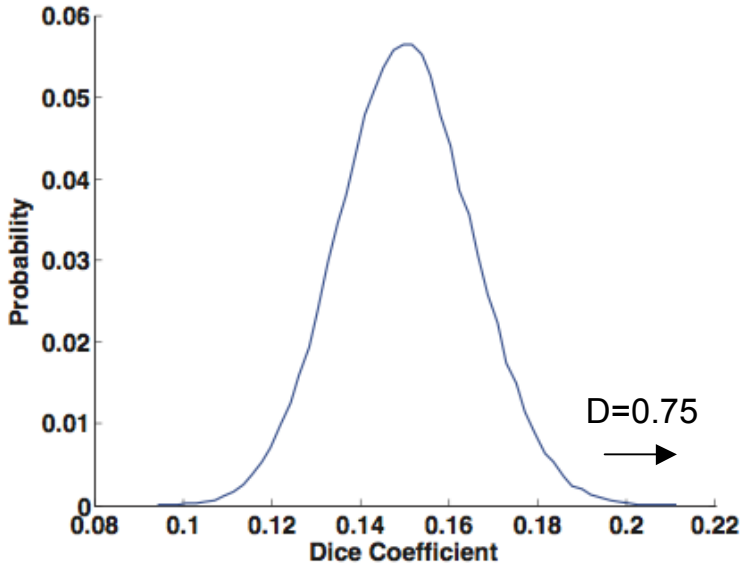
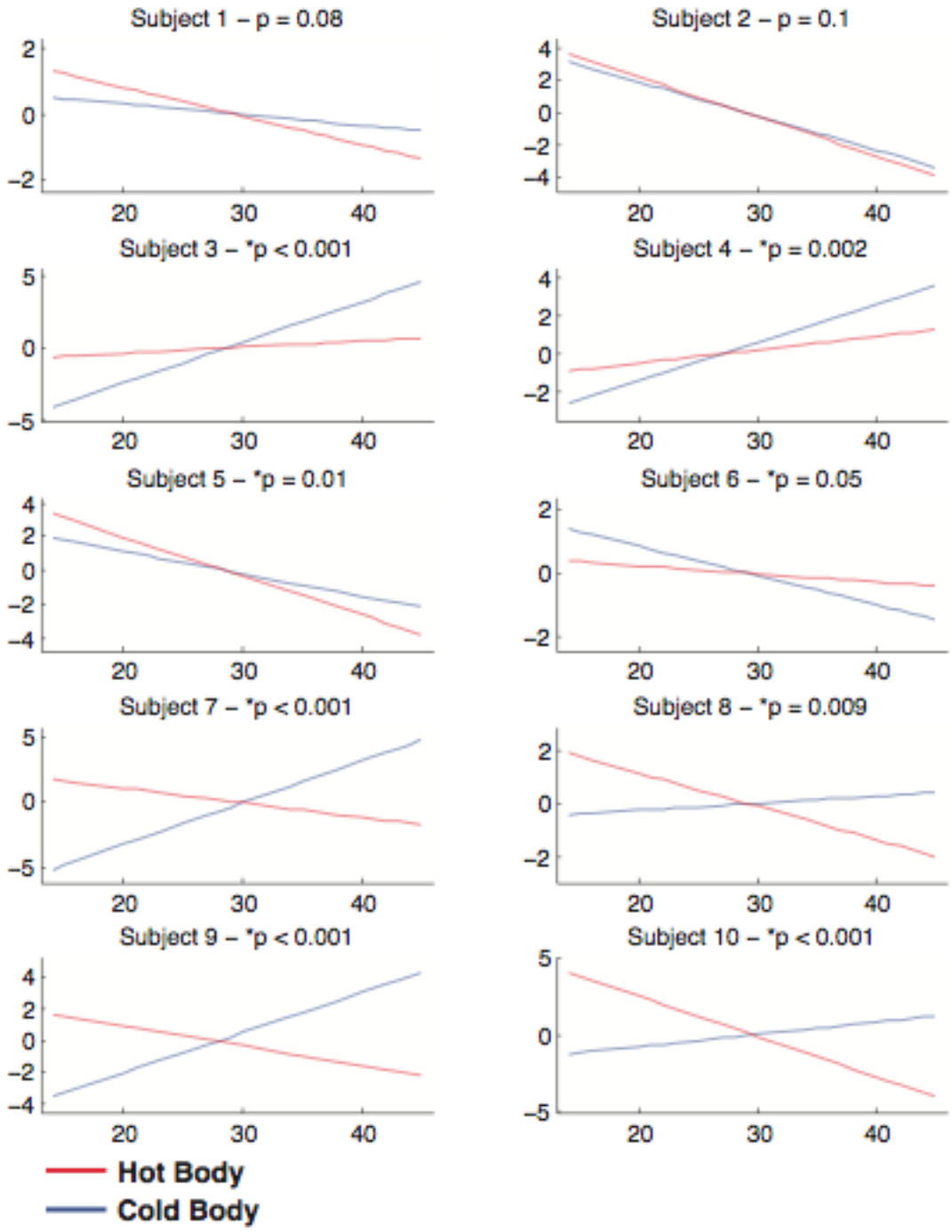


Figure 3.4: Quantification of overlap for hot and cold body temperature conditions. **A)** Conjunction analysis of valence runs for the hot (red) and cold (blue) body temperature conditions along with their intersection (green). Main clusters of BOLD activity are overlapping. **B)** A Monte Carlo simulation was performed using the thresholded activity maps for valence under the hot and cold body temperature conditions. As in Figure 4, the probability of the random distribution of Dice coefficients was computed for comparison to the observed overlap value of 0.636. The simulation demonstrates that the degree of overlap between these activity maps would not have arisen by chance ($p \leq 0.001$). **C)** Overlap of intensity activation maps also demonstrates the high degree of overlap between the hot and cold body temperature conditions. **D)** The simulation of the intensity data generates a probability curve that confirms the significant overlap (Dice = 0.75) between conditions ($p \leq 0.001$).

However, not all subjects demonstrated a significant interaction and it is possible that these outliers are drivers of our results. To test this, we performed individual fits for the stimulus temperature x valence data and excluded those subjects that did not show a significant ($p \leq 0.05$) interaction with body temperature (Figure 3.5). Six subjects were identified as not showing a significant effect and we again performed our group-level fMRI analysis excluding these participants. The analysis of valence and intensity yielded a similar pattern of activity, but with smaller cluster sizes, as was described for the full 20 subjects, using the same statistical thresholds (Figure 3.6a; Table 3.4). Lowering this statistical threshold demonstrates that reducing the number of subjects has the effect of lowering the statistical power of the analysis, but that the overall patterns for valence and intensity remain disparate (Figure 3.6b). Finally, results from behavioral analyses removing either the non-significant (Figure 3.7 a,b) or significant (Figure 3.8 a,b) subjects are shown.


Subject 1 – p = 0.08
Subject 2 – p = 0.1
Subject 3 – *p < 0.001
Subject 4 – *p = 0.002
Subject 5 – *p = 0.01
Subject 6 – *p = 0.05
Subject 7 – *p < 0.001
Subject 8 – *p = 0.009
Subject 9 – *p < 0.001
Subject 10 – *p < 0.001
Hot Body
Cold Body

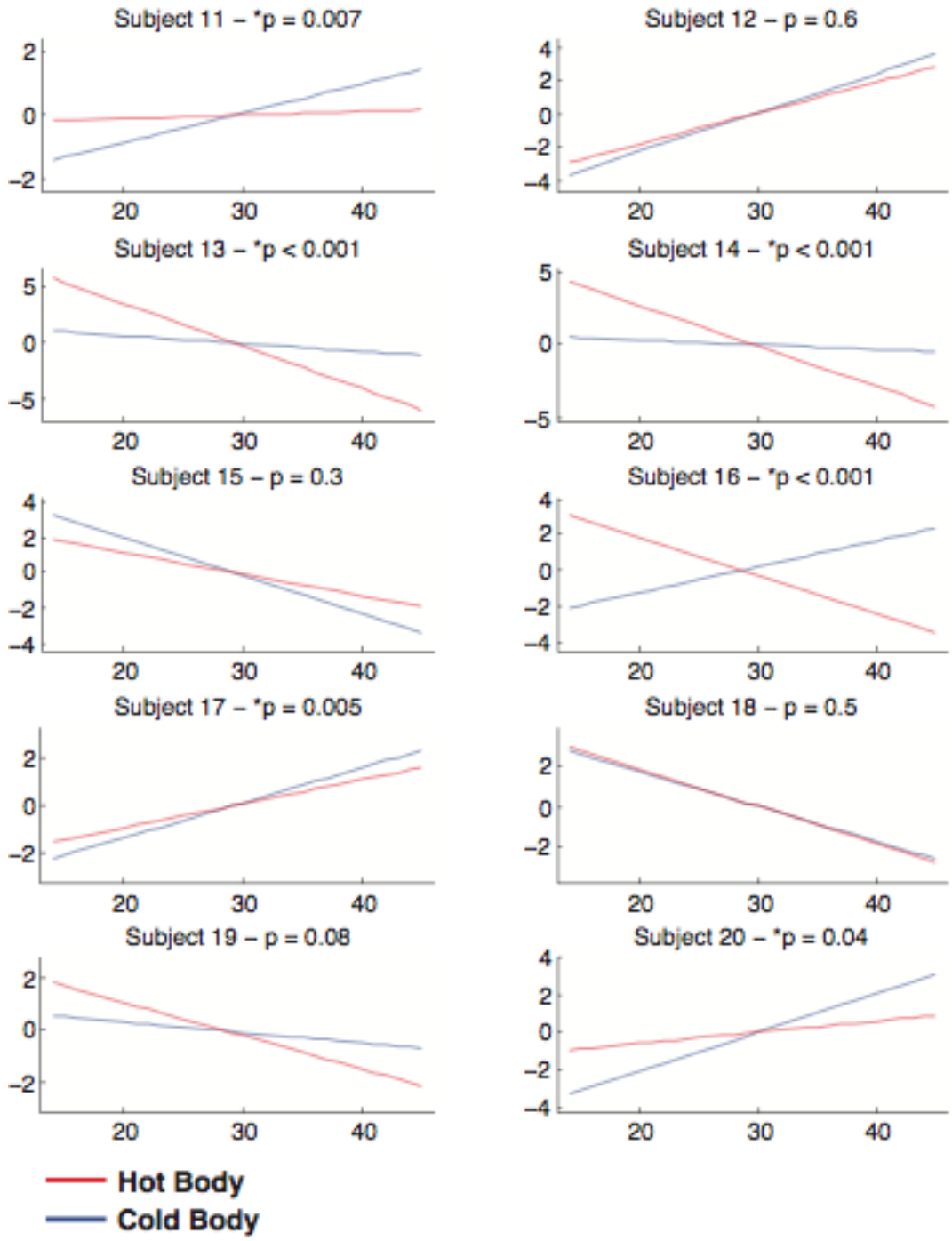
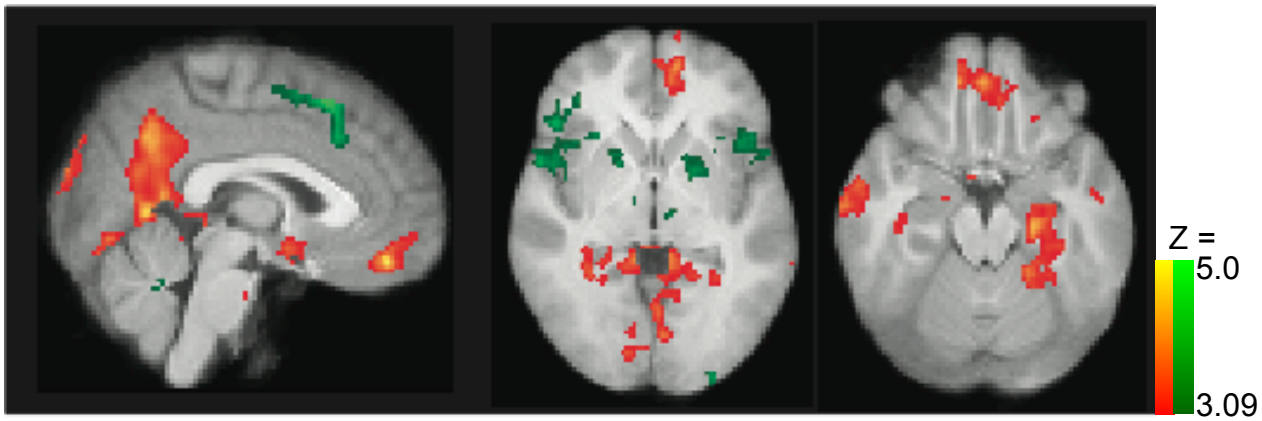


Figure 3.5: Individual subject behavioral data plots for valence ratings of thermal stimuli. Data are shown for both hot (red) and cold (blue) body temperature conditions. Six subjects did not show a significant interaction with body temperature condition and were excluded in the analysis of the data subset.

A.



B.

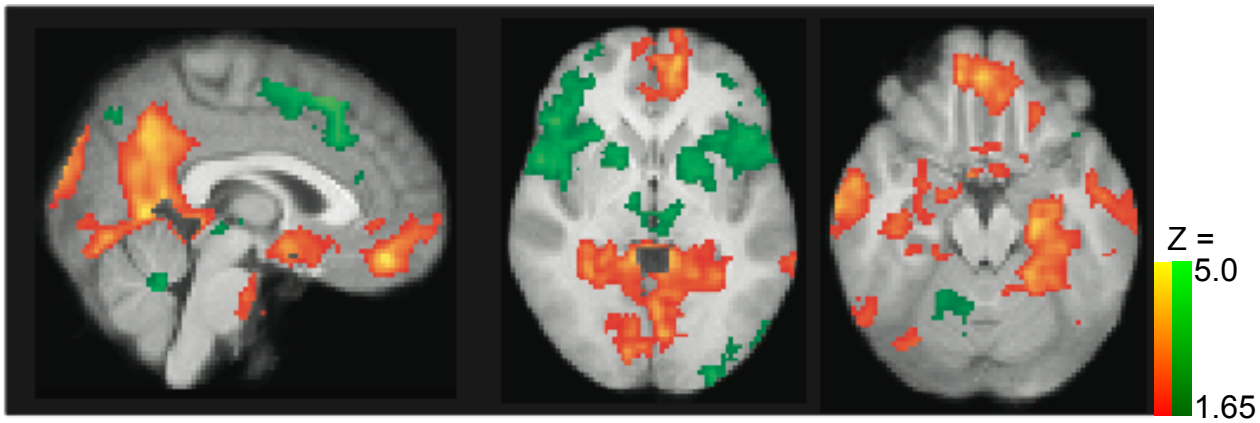
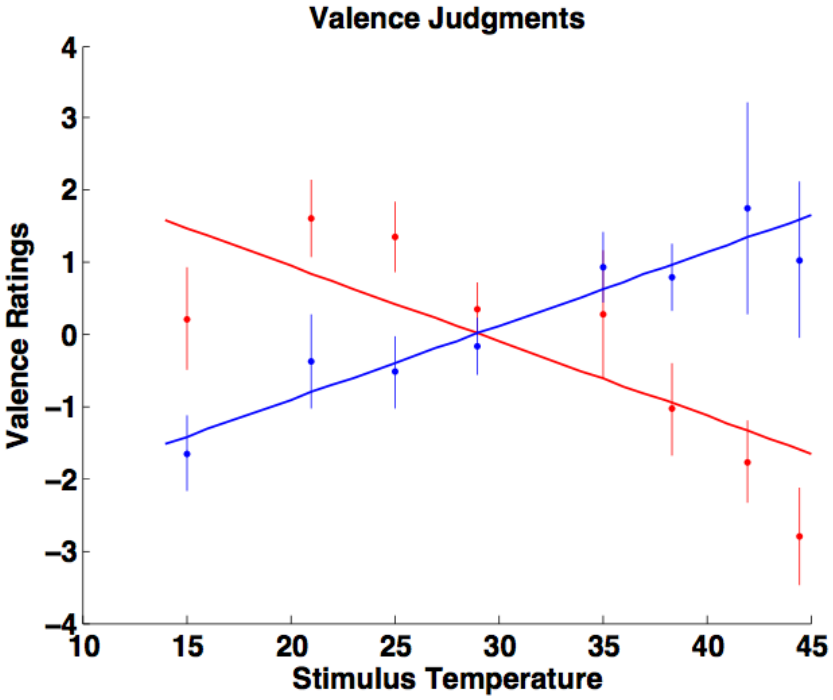


Figure 3.6: Analysis of the data subset containing only the 14 subjects that demonstrated a significant behavioral effect (see Figure 3.5). **A)** Using the same statistical thresholds as were applied in the imaging analysis of all 20 subjects demonstrates smaller cluster volumes, but conservation of the distinct neural representations of valence (red) and intensity (green). **B)** Reducing the number of subjects decreases statistical power and we, therefore, lowered our statistical threshold to z = 1.65 to illustrate the effect on cluster size.

A.



B.

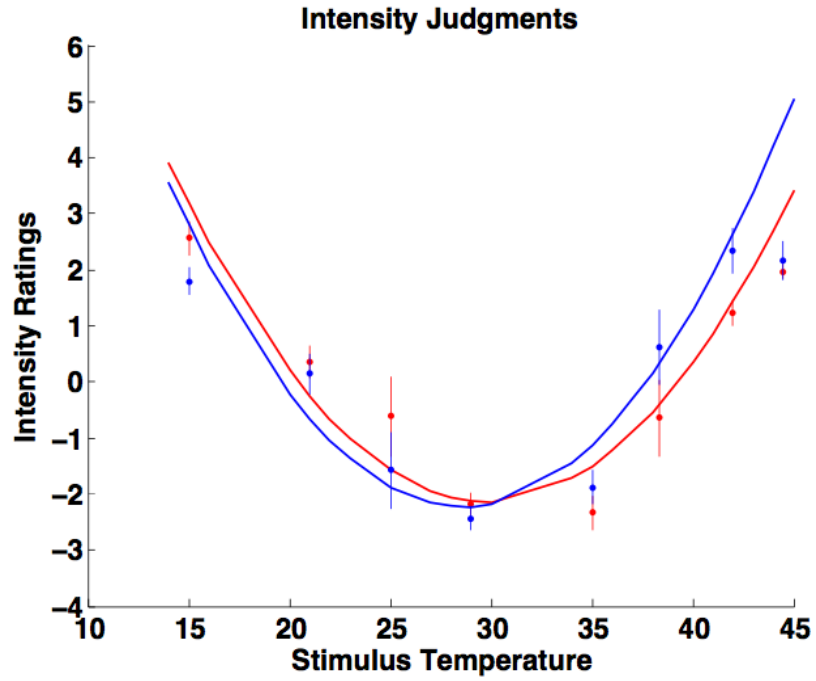
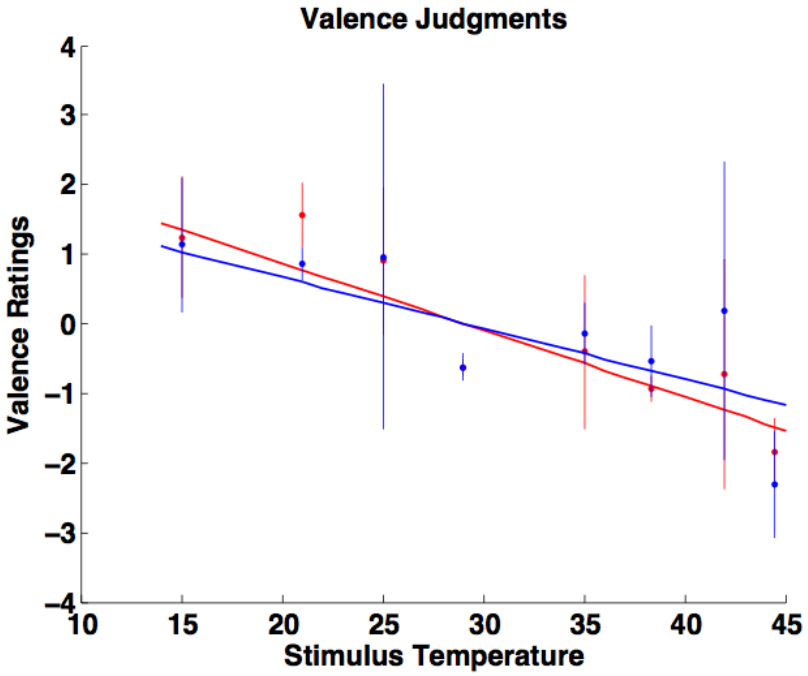


Figure 3.7: Group behavioral analysis of the data subset containing only the 14 subjects that demonstrated a significant effect for valence ratings. Comparison for hot and cold body conditions was significantly different for valence ($p<0.001$) and not for intensity ($p=0.384$).

A.



B.

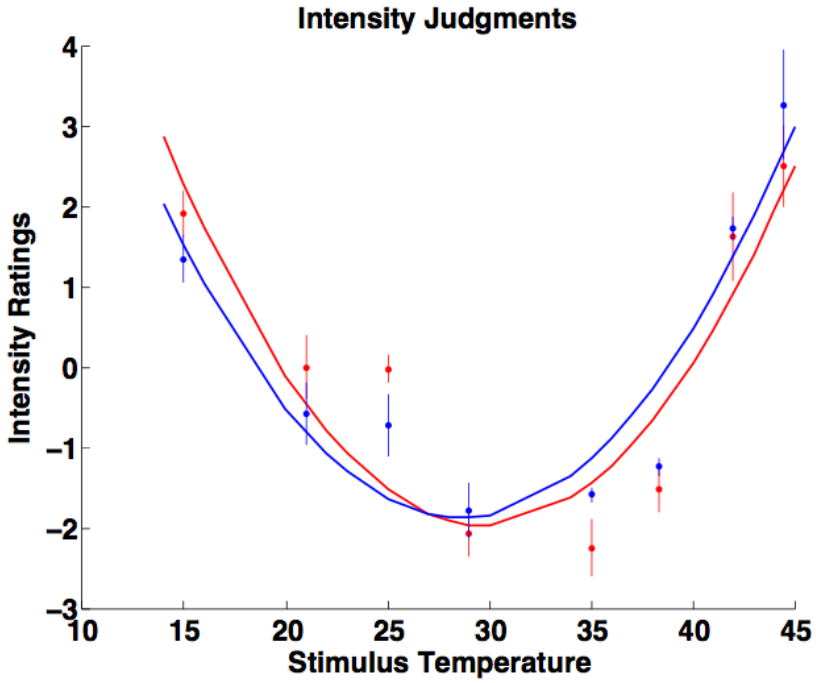


Figure 3.8: Group behavioral analysis of the data subset containing only the 6 subjects that did not have a significant effect for valence ratings. Comparison for hot and cold body conditions was not significantly different for valence ($p<0.41$) or for intensity ($p=0.602$).

Peak Z-score	X	Y	Z	Anatomical Region
5.33	8	-84	-14	R-OCC Pole
4.92	2	46	-18	mOFC
4.19	-58	-64	26	L-LOC
4.49	4	-88	36	OCC Pole
4.6	68	-12	-18	R-Mid Temp
4.27	6	-2	-14	Mam body
3.8	-60	-44	-12	L-Mid Temp
4.2	-10	-16	-44	Brain stem
3.63	-54	-4	-28	L-Mid Temp
3.65	-26	-80	46	L-LOC
3.76	-28	14	-40	L-Temp pole
3.93	-14	-28	-30	Brain stem
3.45	54	-62	-22	R-Inf Temp
3.39	10	-18	-42	Brain stem
3.46	-60	-16	-28	L-Inf Temp

Table 3.4: Peak voxels and MNI coordinates for the analysis of the data subset. The data set consisted of 14 subjects for whom the relationship between thermode temperature and valence ratings was dependent upon body temperature. Abbreviations: occipital (OCC), medial orbitofrontal cortex (mOFC), middle (Mid), temporal (Temp), mammilary body (Mam body), lateral occipital cortex (LOC), inferior (Inf).

CHAPTER IV

DISCUSSION

Overview

In the present study, subjects rated a series of hot and cold thermal stimuli to the hand on scales of either valence or intensity. Creating two body temperature conditions altered the relationship between these two highly correlated parameters, allowing for dissociation of their underlying neural substrates. The successful separation of these variables was confirmed by our replication (Figure 3.1a,b) of the classic representation of alliesthesia for temperature (Cabanac, 1971). Results from the fMRI data analysis provide strong evidence for disparate networks coding for these proposed dimensions of affective processing. The network identified for valence included regions such as the medial OFC, ACC, and amygdala while arousal was represented by a different set of brain areas including the insula, striatum, and thalamus. These results support the claim of dimensional theories of emotion, which posit that valence and intensity are fundamental components of affective processing (Russell, 1980).

Several past investigations have initiated this field of research, but limitations in design and analytical approaches have not resolved the question of how valence and intensity are represented in the brain. Our study was specifically designed to avoid conflating valence and intensity judgments by having these ratings done on separate experimental runs and never concurrently on a single trial basis. The most significant element in our experimental design is the use of temperature as the chosen stimulus type because it is parametric, alliesthesia can be used to change the hedonics of a stimulus at a given intensity and it may be judged on its physical intensity rather than its affective intensity.

Stimulus choice is a crucial aspect of study design because valence and intensity are confounded and the negativity bias must be accounted for. The negativity bias, or the tendency to attend to *unpleasant* rather than *pleasant* inputs and to perceive them as more intense, is believed to confer an evolutionary advantage (Taylor, 1991; Norris et al., 2010) by helping organisms respond quickly to noxious triggers, and several studies have identified changes in the time-course of neural responses to this effect (Carretie et al., 2001, 2004; reviewed in Carettie et al., 2009a). This bias is present in all stimulus types, including emotional words (Pratto and John, 1991) and faces (Hansen and Hansen, 1998; Ohman et al., 2001), and is often difficult to control; however, stimuli such as olfactory, gustatory, and thermal have the potential avoid this confound.

Temperature has been employed previously (Rolls et al., 2008) and the present study adds to those findings. Rolls and colleagues found that activity in the ACC, lateral OFC, and ventral striatum correlated with both valence and intensity, but their study lacked a range of thermal intensities, as demonstrated in the group behavioral results, and these results must be interpreted with caution. In the present study, the use of whole-body warming and cooling as opposed to local stimulus changes to the hand permitted the dissociation of valence and intensity in the results presented here (Figure 3.1). This method yielded brain activity that was spread over two largely bilateral networks that were congruent with several findings of Rolls et. al. 2008. Most notably, there was agreement over the role of the ACC and OFC in valence responses, which is also consistent with studies using different modalities (ACC: Small et al., 2005; Lewis et al., 2007, Colibazzi et al., 2010. OFC: Dolcos et al., 2004; Cunningham et al., 2004; Small et al., 2005; Lewis et al., 2007; Colibazzi et al., 2010).

Stimulus valuation

Of particular interest in our results is the specific role of the mOFC in valence responses, a region that is hypothesized to play a role in value coding in a manner that is irrespective of modality (Elliot et al., 2000; O'Doherty et al., 2001; Kim et al., 2006). For example, Chib and coworkers (Chib et al., 2009) scanned subjects with fMRI while they made value decisions on food, non-food items, and monetary quantities, which identified a common area of activity in the mOFC that tracked value for all decision types. This subspecialization within the prefrontal cortex is related to findings of lesion studies, which suggest that the OFC, in contrast to other regions in the prefrontal cortex, is involved in updating the reward-value of a stimulus (Buckley et al., 2009). The results presented here are consistent with OFC involvement in stimulus valuation, as was found in similar imaging studies aimed at dissociating valence and intensity (Anderson et al., 2003; Small et al., 2003; Rolls et al., 2008), but there is a discrepancy in the proposed role of the amygdala. It is thought that the OFC and amygdala are closely aligned with respect to valuation (Salzman and Fusi, 2010), but the specific contributions of each to valence and intensity coding is unknown. Studies in the chemosensory domain have argued for functional specialization of the amygdala for intensity (Anderson et al., 2003; Small et al., 2003), which is consistent with its demonstrated function in the skin conductance response (SCR; Mangina and Beuzeron-Mangina, 1996), an index of general arousal. However, this is a complex point because amygdala function is nonessential for SCRs to some stimuli, such as loud noises (Tranel and Damasio 1989; 1994). An alternative explanation for the findings of both the Small et al. and Anderson et al. can be

tested on the cellular level and is not only restricted to the putative role of the amygdala in intensity coding. An assumption that these studies have made is that pleasantness, unpleasantness and intensity tracked by brain regions that are distinguishable at the resolution of fMRI. However, there may, for example, be populations of neurons that respond to the pleasantness and unpleasantness of a stimulus separately, but if they are spatially adjacent and below the resolution of fMRI, then together they will appear to track intensity. Although this specific hypothesis has yet to be tested, studies of amygdala function at the cellular level suggest a close association with valence coding.

Convincing evidence for representations of valence in the amygdala comes from several single-cell recording studies in monkeys. For example, it has recently been demonstrated that the amygdala is heterogeneously populated with neurons that respond to either appetitive or aversive stimuli, suggesting a representation of positive and negative valence irrespective of stimulus intensity (Paton et al., 2006). Moreover, chemical inactivation of the amygdala impairs devaluation of sated food rewards in macaques both with permanent (Malkova et al., 1997) and temporary (Wellman et al., 2005) lesions. In summary, studies in humans and other animals provide a mixed view of amygdala involvement with respect to emotional processing. This structure is clearly involved in stimulus valuation, but imaging studies have provided evidence for a role in arousal as well. The only other study performing this dissociation with temperature did not report any findings for the amygdala (Rolls et al., 2008) and results from our study were consistent with valence coding in the amygdala. As highlighted previously (Winston et al., 2005), this structure is likely to be multifaceted in its role in emotional

processing and these seemingly conflicting findings may be explained by differences in experimental manipulations along with the inherent heterogeneity of the amygdala.

Reward and punishment

The present work was motivated by competing theories of emotional representation in the brain, but valence and arousal are confounded across many other types of studies and our results may have implications to other related fields, including reward and pain processing. In particular, the correlation we identified between intensity ratings and striatal activity has interesting implications for the reward literature.

The connection between the striatum and valence has been made in numerous studies across species. This region has a demonstrated role in goal-directed behavior (Hollerman et al., 1998), incentive salience (Ravel et al., 1999; Apicella et al., 2009), and reward preference (Hassani et al., 2001; Cromwell et al., 2005). Response profiles of individual striatal neurons have been shown to correspond to the presence or absence of a rewarding liquid (Tobler et al., 2003), and a population of neurons in the nucleus accumbens (NAc) has been shown to respond to either reward- or punishment-related cues (Roitman et al., 2005). Similarly in fMRI of human subjects, rewarding and punishing stimuli were used to demonstrate different response profiles such that appetitive cues induced sustained (approximately 3 seconds) responses whereas aversive cues led to an initial activation, followed by a rapid inhibition in the BOLD response (Delgado et al., 2000). The finding that the striatum responds differentially for positively and negatively valenced stimuli was replicated in a later study, which also identified an interaction between the hedonic value of a stimulus and its magnitude (Delgado et al.,

2003). A similar interaction was also described in other work, but was found to be specific to subregions of the striatum (Knutson et al., 2001). Knutson and coworkers parametrically manipulated reward and punishment, and found that both positive and negative stimuli were associated with increased activity in the caudate nucleus while the NAc responded only to rewards. These responses were modulated by the size of the reward in both areas of the striatum, whereas punishments were parametrically represented only in the caudate.

It has been suggested that the differential responses of the caudate to positive and negative stimuli is related to differences in stimulus intensity (Carretie et al., 2009b). By attempting to equate valence and arousal in stimuli presented to human subjects, Carretie et. al. identified a quadratic response in the caudate nucleus that closely resembles the relationship described in the results presented here. These authors argued that arousal must be equated across stimuli of varying hedonic content to gain an understanding of the neural response of the striatum. Such findings further highlight the difficulty in dissociating these confounded stimulus properties that, given the results of the literature discussed above, are likely to both be represented in the striatum to some degree. In the present study, we found that the BOLD response in the striatum correlates with thermal intensity, which is consistent with what others have found with manipulations of reward magnitude (Hassani et al., 2001; Knutson et al., 2001; Rolls et al., 2008; Carretie et al., 2009b). However, the analysis of valence ratings of the same thermal stimuli did not identify significant correlations with the response of the striatum. Though the cause of this is likely multifactorial, one important consideration is the nonlinear response of the caudate demonstrated in Carretie et. al., 2009b. In Carretie et. al., the relationship

between valence and the BOLD signal was quadratic, while our study strictly probed for linear correlations. Assumptions about linearity were made based on the subjective ratings derived from the behavioral measure of valence, whereas only intensity judgments were described by a quadratic relationship.

Pain processing

Our results may also add to the pain literature, where the specificity of the neural substrates of pain processing is being debated. Pain is complex and involves several other conscious and unconscious mental processes including sensation, attention, affect, and motor control. Some findings have even demonstrated a role for reward in pain processing because the striatum is believed to underlie an endogenous form of analgesia. For example, Becerra and colleagues (Becerra et al., 2001) found that painful thermal stimuli led to increased BOLD signal in the NAc and ventral striatum, along with other brain regions classically thought to be involved in pain including the insula, ACC, thalamus, and somatosensory cortex. The interpretation that activation in the striatum has an anesthetic role in pain processing is congruent with animal studies that have demonstrated an anti-nociceptive effect by stimulating the NAc (Altier and Stewart, 1997; Gear et al., 1999) as well as human studies using PET to examine opioid receptor binding (Zubieta et al., 2001).

It is important to note that several neural substrates of pain have also been shown to respond to noxious stimuli that are social in nature. A recent example of this comes from paradigms that attempt to simulate social rejection as a form of an abstract painful experience. Eisenberger and coworkers (Eisenberger 2003) scanned subjects with fMRI

while playing a ball-tossing game where several trials would lead the participant to feel socially excluded. The authors found activity in the anterior cingulate cortex that correlated with the degree of exclusion and went on to show, through functional connectivity analyses, that this relationship may have been modulated by the right ventral prefrontal cortex. The prospect for a general "alarm system" for all types of disadvantageous stimuli and experiences carries the implication that there is a neural system reserved for an abstract sense of pain that may act irrespective of contextual cues (Panksepp 2003; Eisenberger 2004). In addition to gaining a better understanding of the physiology of these important aspects of pain, these studies may explain why many psychiatric disturbances of an emotional nature are co-morbid with a number of seemingly organic complaints.

Several brain regions that are classically thought to underlie pain have also been found to track a range of non-noxious stimuli including the anterior and posterior cingulate, primary and secondary somatosensory cortices, insula, thalamus, and others (Becerra et al., 1999). It has been noted that there are inconsistencies in reported neural activation across pain studies, with some regions having very limited reproducibility, which might be explained by differences in stimulus intensity (Derbyshire et al., 1997). Coghill and others (Coghill et al., 1999) noted that the widespread pattern of activity seen in many pain studies is actually modulated by the physical intensity of the stimulus, which the authors argue accounts for the interesting phenomenon that judgments of pain intensity are maintained even after extensive cerebral lesions (Knecht et al., 1995). In support of this claim, we found an extensive cortical and subcortical network where activity correlates with stimulus intensity. The thermal stimuli employed in the current

work not only fell within the non-noxious range, but many trials were rated as pleasant. Still, our network of activity correlating with intensity overlapped with many regions that are frequently activated under painful conditions.

Our finding of increased amygdala activity as a correlate of valence is interesting in light of an established phenomenon from the pain literature. Many studies have found that anticipation of pain is associated with a decreased BOLD signal in the amygdala, which has been interpreted as an adaptive cognitive mechanism to suppress the stress response (Becerra et. al., 1999; Petrovic et. al., 2004). Because the amygdala is involved in fear and stress, this hypothesis states that in the presence of an impending noxious experience, higher cognitive centers attenuate the response in the amygdala as a coping mechanism. Although our experiment was not designed to evaluate the neural response associated with the anticipation or experience of pain, results from our study may suggest an alternative view to this observation of amygdala deactivation. Namely, amygdala may follow a positive correlation with valence and thus deactivates with negatively valenced stimuli. This hypothesis is in accord with findings from pain studies that identify amygdala deactivation with pain anticipation and is more parsimonious than explanations that involve complex top-down regulatory mechanisms of stress attenuation.

Summary

Experimental research on animal emotion has progressed rapidly over the past 100 years and many inroads have been made into understanding how affective experience is represented in the brain. Theories of emotion have evolved along with the methodologies used to test their predictions, but agreement on a framework for defining

what an emotion is and how it comes about has yet to be reached. Psychological proposals have recently moved away from traditional theories of basic emotional *types* toward fundamental *dimensions*. One prominent model attempts to place all affective experience along a two-dimensional circumplex that is defined by valence, ranging from unpleasant to pleasant, and intensity, which varies from low to high arousal. Evidence has been found to support this parsimonious cognitive construct and recent neuroimaging studies have been aimed at elucidating possible neural components of these dimensions.

Along these lines, many imaging studies have been performed but are often limited by the inherent relationship between valence and arousal. The aim of the study presented here was to dissociate these highly confounded stimulus properties by using thermal stimuli to the hand, coupled with whole-body warming or cooling. This whole-body manipulation changed the hedonic component of the hand stimuli and caused subjects to rate a stimulus of given intensity as pleasant under one condition and unpleasant under another. This experimental paradigm permitted an analysis of the neuroimaging data that was fully dissociated for valence and intensity.

In summary, results from the current study confirm that whole-body temperature manipulations can be used to modify judgments of hedonic value for thermal stimuli to the hand, as was suggested in a previous study that was not performed in the fMRI scanning environment (Cabanac, 1971). Using these behavioral findings as models for our neuroimaging data, we found activity correlating with valence judgments in the anterior and posterior cingulate cortex, orbitofrontal cortex, and amygdala, among others. Several of these regions have been shown in related studies to have a role in integrating the sensory properties of a stimulus in determining its hedonic value. In regions that

were largely segregated from this valence network, activity was found to correlate with the subjective intensity of the temperature stimuli. These areas included the insula, thalamus, and striatum, all bilaterally. These regions are often implicated in pain processing, but it has been hypothesized that they are involved in intensity sensation more generally. Together with our quantifications of spatial overlap, we conclude that valence and intensity are represented by separate neural substrates and may indeed underlie these putative fundamental dimensions of emotion.

Our evidence for segregated networks of neural activity underlying valence and intensity raises an interesting additional question of how the brain constructs a unified emotional percept from its independent parts. There are many possible explanations that may be grouped as either serial or parallel processes. For example in a serial model, the physical intensity of a stimulus may first be processed as a pure sensory event without affective value. The location, quality, quantity, and strength of the stimulus may be integrated and then processed by centers involved in monitoring homeostasis and internal physiologic drives. Moreover, additional contextual information, such as predictions about future environmental changes, may influence valuation at a higher cognitive level. In this way, environmental stimuli may begin with the basic senses and this information may gradually evolve into a more emotionally substantive percept in a linear fashion. An additional possible gross mechanism of how valence and intensity are processed may be in a more parallel manner. One can imagine a dynamic development whereby valence and intensity become gradually more integrated as they move along separate processing streams. Future models should address the role of attention, which may vary with increases in both valence and intensity, or may correlate with the degree of integration

between these two systems. Interestingly, our study found evidence for involvement of the precuneus, a region implicated in a diverse set of attentional functions (Cavanna and Trimble, 2006), in intensity coding that may suggest intensity as a driver of attention. Obviously, these hypotheses are highly speculative and nonspecific, but may lend themselves as models to be refined and tested in future studies.

Limitations and future directions

Several important limitations must be considered in regards to the results presented here. First, we chose to use temperature as our experimental probe for reasons outlined above, but this stimulus type is closely associated with pain at high intensities. Because pain is correlated with the extremes of intensity, known as Wundt's schema (Pfaffmann, 1980), it cannot be ruled out that pain-specific brain activity was present in our analysis of high intensity trials. However, we minimized this possibility by calibrating each subject's intensity range before beginning the experiment such that no subject rated any thermal stimulus as painful.

Another potential drawback of the experimental design implemented here is the use of only one sensory modality. The goal of this study was to describe the neurobiology of valence and intensity with the assumption that thermal stimulation would generalize to other modes of perception. We note that some discrepancy exists between our findings and those of similar studies in the chemosensory domain (Anderson et al., 2003; Small et al., 2003), particularly in the proposed roles of the amygdala and striatum. The causes for discrepancy are multifactorial, but differences in stimulus modality may have some role.

Finally, this study shares the same approach as others (Anderson et al., 2003; Small et al., 2003; Rolls et al., 2008) that used sensory intensity as an index of affective arousal. Although this distinction is commonly overlooked, we believe it is an important point of consideration. Tracking the subjective intensity of a physical stimulus is advantageous because participants possess a clear understanding of the task and can provide subtle differences in judgments across similar stimuli. However, a drawback is that it indirectly measures how arousing the stimulus is and may not be as specific as a direct, objective measure of arousal.

To control for these limitations and extend the present work, future studies may benefit from applying alliesthesia to other sensory modalities. To accomplish this, a replication of the two chemosensory studies may be performed, but with the added conditions of fasted and fed. This is applicable to gustatory stimuli in particular, and would avoid the possibility of high intensity trials being perceived as painful. Moreover, an extension of the current study to another mode of perception would broaden the generalizability of our results.

A key advance that has yet to be made is the objective measurement of affective arousal without indirect judgments of intensity. One methodological modification to our design that may assist future studies with this aim is the use of the skin conductance response (SCR), which is a general measure of sympathetic arousal. We did not employ this measure because we required the use of both of the subject's hands for our experiment; however, this would not be the case in olfactory or gustatory studies. It may also be possible to place SCR electrodes on the plantar surface of the feet, but this method may be less sensitive than when used on the hands (Naqvi and Bechara, 2006).

In addition to methodological changes, a study design employing cognitive reappraisal (Ochsner, 2002; 2004) may provide a means of altering stimulus valence without manipulating arousal. As mentioned in the introduction, this avenue has yet to be explored, but may present a solution to studying valence and arousal of common stimuli, such as affective images and words.

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