

Interoceptive Contributions to Motivational and Affective Modulators of Memory

Formation

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Dissertation submitted in partial fulfillment of  
the requirements for the degree of Doctor  
of Philosophy in the Department of  
Psychology & Neuroscience in the Graduate School  
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2015

ABSTRACT

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## **Abstract**

Biological drives such as hunger, thirst, and sexual reproduction are potent motivators of behavior. Extrinsic rewards in the environment (i.e. food, drink, money) are also important behavioral and cognitive motivators. In addition to the relevance of an extrinsic reward in meeting the needs of biological drives, an individual's sensitivity to the physiological state of their body (interoceptive awareness) would also be expected to mediate motivation for these extrinsic primary rewards (i.e. food, drink). Importantly, a better characterization of the predicted behavioral and neural interactions between interoception, motivation, and memory systems can highlight novel targets for interventions to facilitate motivation and memory for adaptive behaviors and/or impede motivation and memory for maladaptive behaviors (i.e. addiction, relapse, overeating).

The present dissertation examines how individual differences in interoceptive awareness may modulate motivated memory formation via motivational and affective mechanisms. Specifically, interoceptive accuracy is associated with increased motivation for relevant primary rewards and enhanced encoding for these rewards. However, anxiety, negatively predicted by interoceptive accuracy, negatively predicts memory the next day. Furthermore, memory for relevant primary rewards was negatively predicted by insula-parahippocampal and ventral tegmental area-hippocampal background

connectivity.

## **Dedication**

This dissertation is dedicated to my greatest teacher, Mrs. Alice Headley,

in loving memory of:

Mrs. Orina Wall,

Mrs. Gertrude Rainey, and

Dr. Gladys Bayse.

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# 1. General Introduction

Interoception refers to the collective cognitive processes involved in the representation of the physiological state of an organism's body (Craig, 2003). Interoceptive processing has been implicated in health conditions including anorexia nervosa (Eshkevari, Rieger, Musiat, & Treasure, 2014; Pollatos et al., 2008), obesity (B. M. Herbert, Blechert, Hautzinger, Matthias, & Herbert, 2013), irritable bowel syndrome (Craske et al., 2011; Labus et al., 2009; Song, Venkatraman, Ho, & Chee, 2006; Wolitzky-Taylor, Craske, & Labus, 2012), drug addiction (Berk et al., 2015; Kathryn L Lovero, 2009; Paulus, Tapert, & Schulteis, 2009; Verdejo-Garcia, Clark, & Dunn, 2012), depression (Dunn, Dalgleish, Ogilvie, & Lawrence, 2007; Pollatos, Traut-Mattausch, & Schandry, 2009), and anxiety disorders (Paulus & Stein, 2006; 2010; Sturges, Goetsch, Ridley, & Whittal, 1998). Importantly, several of the aforementioned health conditions present with motivational irregularities (eating disorders, obesity, and addiction), suggesting a role of interoceptive processing in motivation. Furthermore, individuals with Depression and Generalized Anxiety Disorder exhibit altered emotion/affective processing, implicating a role for interoceptive processes in affective cognition. This dissertation examines how interoception contributes to cognitive processes (e.g. memory formation) through its roles in motivational and affective processing. The current chapter will continue by first defining some of the most common interoceptive processes and their supporting neural

architecture before considering interoceptive contributions to motivation and emotion processing.

### ***1.1 Disambiguating Interoceptive Processes***

Somatic and visceral sensations falling under the umbrella of interoception include temperature, pain, hunger, thirst, itch, cardiac sensations, gastric sensations, and sensual touch (Craig, 2002). The process of interoception provides the nervous system with access to the mechanical, chemical, hormonal, thermal, and metabolic status of all tissues of the body (Craig, 2003). Eventually, interoceptive pathways in the brain integrate information from sensory afferents into a meta-representation of the body's internal states (Craig, 2003).

Recently, Garfinkel and colleagues proposed a three-dimensional model of interoception to distinguish between the cognitive processes of interoceptive accuracy, interoceptive sensibility, and interoceptive awareness. (Garfinkel, Seth, Barrett, Suzuki, & Critchley, 2015).

#### **1.1.1 Interoceptive Awareness**

According to this three-dimensional model, interoceptive awareness describes the correspondence between an individual's confidence in their interoceptive accuracy and their actual accuracy. Thus, interoceptive awareness can be computed with measurements of interoceptive accuracy and individual confidence levels as the area under the receiver operating characteristic curve.

### **1.1.2 Interoceptive Sensibility**

Interoceptive sensibility refers to an individual's subjective evaluation of their interoceptive ability. Interoceptive sensibility is normally assessed through self-report questionnaires like the Body Perception Questionnaire (Porges, 1993), the Multidimensional Assessment of Interoceptive Awareness (Cali, Ambrosini, Picconi, Mehling, & Committeri, 2015), and the Body Consciousness Questionnaire (Private subscale) (L. C. Miller, Murphy, & Buss, 1981).

### **1.1.3 Interoceptive Accuracy**

Interoceptive accuracy describes the precision with which an individual represents interoceptive information. Interoceptive accuracy is most often evaluated by calculating accuracy on heartbeat discrimination or heartbeat tracking tasks. In heartbeat discrimination tasks, subjects are asked to identify whether an externally presented stimulus (usually a tone) is presented almost synchronously with a heartbeat or with a short delay (i.e. 500 ms delay). Heartbeat tracking tasks require participants to count the number of heartbeats they detect within their bodies over varying periods of time (the subject is naïve to the length of each trial). A major advantage of studying cardiac interoception to determine interoceptive accuracy is that the procedure is non-invasive and tolerable to most individuals. It should be noted, however, that participants must be carefully instructed on the exact task they are to perform (count and report the number of heartbeats they feel – not produce a guess of the number of

heartbeats occurring within an approximated time period) because recent evidence has been presented indicating that an individual's knowledge about their heart rate can improve a participant's interoceptive accuracy (Ring, Brener, Knapp, & Mailloux, 2015).

Interoceptive accuracy has also been measured using more invasive techniques. Studies by Herbert et al. and Geliebter et al. employed stomach distension, whereby a balloon was inflated to different sizes within the stomach's lumen while participants rated the feeling of fullness induced by the balloon (Geliebter, 2013; B. M. Herbert, Muth, Pollatos, & Herbert, 2012). Inducing changes in bladder distension (through saline infusion) is another method used to access interoceptive accuracy (Jarrahi et al., 2015). Though more invasive than heartbeat discrimination and tracking tasks, bladder interoception has the added capability of measuring interoceptive accuracy along two dimensions: bladder distention pressure (amount of saline solution infused) and temperature of the infused saline.

## ***1.2 Neural Architecture of Interoception***

The processing of painful stimuli begins via peripheral fibers that synapse onto neurons in the ipsilateral ventral horn of the spinal cord (Craig, 2002). Axons from these ventral horn neurons cross the midline and travel up the contralateral spinal cord via the anterolateral system (Craig, 2002). Some axons in the anterolateral system of the spinal cord will terminate in the reticular formation, while other neurons synapse in the ventroposterior lateral nucleus of the thalamus (Craig, 2002). Thalamocortical projections then convey pain information to the somatosensory cortex (Craig, 2002).

Similarly, viscerosensitive information – interoceptive information as it pertains to visceral sensation (i.e. not those sensations covered by somatosensation) – is first transduced from the visceral periphery by peripheral and cranial nerves (X, XI and XII or the Vagus, Accessory Spinal and Hypoglossal nerves, respectively) (Craig, 2002). These neurons form synapses in the ipsilateral ventral horn of the spinal cord which then send axons through the solitary nuclear complex on to the parabrachial nucleus (Craig, 2002). The parabrachial nucleus in the brainstem sends projections to the ventroposterior medial nucleus of the thalamus (Craig, 2002). Eventually visceral information is projected via thalamocortical pathways to the gustatory cortex of the insula (anterior region of the insula) (Craig, 2002).

A lamina I spinothalamocortical pathway where pain and viscerosensitive information are eventually integrated in the insular cortex has been proposed (Craig, 2002). According to Craig's model, afferents from the periphery travel via the contralateral lateral spinothalamic tract and synapse in the ventromedial nucleus of the thalamus prior to reaching the insular cortex (Craig, 2002). Support for this proposed lamina I spinothalamocortical pathway include the observations that 1) Conventional pathways for pain sensation (which terminate in the somatosensory cortex) cannot explain the persistence of pain following somatosensory cortical lesions. 2) While conventional accounts of interoception do not preclude downstream projections of pain and viscerosensitive information to the insula, more direct thalamo-insular projections would be a more likely construal of interoceptive information (Craig, 2002). Furthermore, recent lesion and fMRI studies in humans and rodents implicate the insula in interoceptive processing and interoceptive awareness. Prior to expounding on the insula's role in interoception and motivational processes, the contributions of other limbic regions to appetitive (interoceptive) motivation will be considered.

### **1.2.1 Limbic Networks**

Many limbic neural regions with anatomical connectivity to the insula have been implicated in interoceptively-motivated behavior and learning. The hippocampus, a key neural structure for the encoding and retrieval of memories, has been implicated in exerting an inhibitory signal on motivated behaviors to

primary rewards (Ito, Everitt, & Robbins, 2005). Hippocampal lesions reduce conditioned locomotor activity to food stimuli (Ito et al., 2005). Additionally, bilateral hippocampal lesions simultaneously increase the frequency and decrease the latency to initiation of sign-tracking behavior (Ito et al., 2005). Sign-tracking, approach behavior directed at a reward-predicting stimulus that is not required to obtain the reward, is a behavioral index of a reward-predicting cue's acquired incentive salience (Meyer, Lovic, Saunders, Yager, & Flagel, 2012). These results thus suggest a potential inhibitory role for the hippocampus on incentive motivated behavior. This observation fits well with the hippocampus' known roles in binding important behavioral occurrences to the corresponding spatial or contextual information (Davachi, 2006), and also its role in pattern completion (Bakker, Kirwan, Miller, & Stark, 2008). In the first case of associating discrete pieces of information with its environmental context, attenuated incentive motivational influences on attention and behavior would appear to facilitate (or at least not inhibit) this hippocampus function. The fixation on a specific cue within the larger environment that is characteristic of incentive salience-motivated behavior would impede the formation of global associations between that cue (or indeed other stimuli) and the larger environment. A more global – less fixated view of the environment is similarly advantageous for pattern completion.

Decreases in sensitivity to devaluation of appetitive rewards have also been observed following hippocampal lesions. Flaherty and colleagues also observed that bilateral hippocampal lesions eliminated the decrease in approach speeds to downshifted rewards observed in control rats (Flaherty, Coppotelli, Hsu, & Otto, 1998). (Consummatory behavior on the other hand, was not affected by hippocampal lesions.) A study by Clifton et al. revealed that rats with excitotoxic hippocampal lesions ate smaller more frequent meals while eating the same quantity of food as control rats (Clifton, Vickers, & Somerville, 1998). Interestingly, the lesioned rats explored a novel olfactory stimulus less vigorously than their non-lesioned counterparts (Clifton et al., 1998). Another study implicates a role for the hippocampus in cost-benefit analysis, with hippocampal lesions leading to higher breakpoints in progressive ratio schedules (Schmelzeis & Mittleman, 1996). In other words, rats with hippocampal lesions are willing to exert more effort to obtain the same reward than intact animals. Furthermore, over time the hippocampal lesion group responded more efficiently (i.e more instrumental responses in a shorter period of time) than the control group.

Pavlovian-Instrumental Transfer data also supports roles for the basolateral amygdala and central nucleus of the amygdala in outcome-specific motivational processes and general motivational processes, respectively. During transfer tests, presentation of a Pavlovian trained conditioned stimulus (CS) is expected to increase operant behaviors to obtain that CS (instrumental

conditioning occurs in a separate context from the Pavlovian conditioning). Importantly, the Pavlovian CS and operant behavior must result in the same outcome for this increase to be observed. Lesions of the basolateral amygdala abolish the expected increase in operant responses to a Pavlovian-trained CS also presented during the transfer test (Corbit, 2005). Conversely, this increase is preserved in central nucleus of the amygdala-lesioned rats.

Pavlovian training of a CS-Unconditioned Stimulus (US) relationship for which a Response-US instrumental relationship is never trained, allows for the testing of general motivational effects of stimuli associated with an appetitive outcome (Corbit, 2005). Enhancements in operant behavior are preserved for animals with basolateral amygdala, but not lesions in the central nucleus of the amygdala. Work by Corbit and Balleine thus indicate specific roles for the basolateral and central nuclei of the amygdala in appetitive learning (Corbit, 2005). Ablation of the basolateral amygdala produced deficits in outcome-specific behaviors during non-rewarded extinction, rewarded extinction, and Pavlovian-Instrumental Transfer tests. Interestingly, central nucleus lesions resulted in non-outcome-specific (i.e. general) decreases in instrumental behavior, suggesting a role for the central nucleus in general appetitive motivational processes. For example, rats were first trained to press on one lever for one food outcome and a second lever for a second food outcome. After prefeeding the rats (providing ad libitum access) with one outcome (devalued

food outcome), the rats were presented with both levers. Sham-lesioned and central nucleus of the amygdala lesioned rats made significantly more lever presses for the lever associated with the non-devalued appetitive outcome. Basolateral amygdala lesioned rats were equally likely to make lever presses to the levers associated with the devalued (prefed) and the non-devalued food outcomes (Corbit, 2005). Although central nucleus lesioned animals demonstrated a preference for the non-devalued outcome, the number of lever presses these animals made overall was depressed from those produced by the sham-lesion group (Corbit, 2005). Furthermore, a separate study by Cardinal and colleagues found that the central nucleus of the amygdala is required for the acquisition of sign-tracking (conditioned motivated approach) responses, but not for the performance of these behaviors (Cardinal, Parkinson, Hall, & Everitt, 2002). In summary, the basolateral amygdala is implicated in outcome-specific appetitive motivation while the central nucleus of the amygdala is implicated in general (non-outcome specific) motivational processes.

### **1.2.2 Contributions of the Insular Cortex to Interoception and Motivation**

The insular cortex is situated between the frontal, parietal, and temporal lobes at the level of the Sylvian fissure. The insula is bounded laterally by the frontal/parietal and temporal opercula and the posterior region is contiguous with somatosensory cortex in the parietal lobe and auditory cortex in the temporal

lobe. Because of its proximity and anatomical connectivity to frontal, parietal, and temporal regions, the insula is well-positioned to contribute to somatosensory, attentional, executive, gustatory, language, and emotional processing.

Critically, the insula is thought to participate in the conscious awareness of internal states such as those that produce craving. For instance, lesions of the insula have been shown to disrupt consumption of drugs of addiction in humans and rodents (Contreras, Ceric, & Torrealba, 2007; Naqvi & Bechara, 2009). Furthermore, insula lesion patients who had previously been addicted to cigarettes were significantly more likely to report disruption in smoking habits (disruption was defined as smoking cessation that occurred within one day of neurological injury to the insula accompanied by perceived ease of quitting and absence of relapse) (Naqvi, Rudrauf, Damasio, & Bechara, 2007). One insula lesion patient experiencing a disruption in cigarette addiction asserted that their body had forgotten the urge to smoke (Naqvi et al., 2007). An animal model of drug-use disruption by Contreras and colleagues confirmed that insula ablation eliminated a learned place preference for amphetamine. However, the study did not further disambiguate between possible mechanisms for loss of this learned behavior.

Interpreting the Contreras et al. findings in the context of the human smoking literature, involvement in the experiencing of “urges” to use

amphetamine is a plausible mechanism for insular contributions to drug use; however, other explanations exist (Contreras et al., 2007). First, one must define what is meant by an “urge”; here, an urge might be conceptualized as a motivational state generally leading to approach behavior. Therefore, one might say that damage to the insula disrupts this motivational state partially or fully signaled by the insula. It is also a possibility, however, that damage to the insula disrupts retrieval of motivationally privileged representations – such as the location of amphetamine delivery. Insular damage might also block retrieval of relevant hedonic internal states that would promote approach and seeking behavior. On a related note, encoding hedonic interoceptive states would be expected to be critical in the formation of drug approach and drug-seeking behavior. Because the current lesion studies examine the effect of insular damage on previously acquired learning and habits/addiction, they leave the potential influence of the insular cortex on encoding unexamined.

Through its anatomical connections, the insula is well positioned to participate in the motivated acquisition of novel information (i.e. encoding). The anterior insula, which supports the translation of interoceptive information into internal representations in conscious awareness, has reciprocal connections with the ventral striatum (Chikama, McFarland, Amaral, & Haber, 1997). The ventral striatum is important in healthy and aberrant reward processing, and makes important contributions to learning (Wimmer, Daw, & Shohamy, 2012).

Additionally, these insulo-striatal relays may allow the insula's incorporation into medial temporal lobe memory processing. Current models of adaptive memory highlight the ventral striatum's indirect modulation of the ventral tegmental area (VTA) by way of the intermediary globus pallidus. The VTA in turn increases dopamine levels in the hippocampus through dopaminergic efferents (Shohamy & Adcock, 2010a). Increased activity in the VTA and the resulting increased dopaminergic tone in the hippocampus during encoding is predictive of successful retrieval of information (Shohamy & Adcock, 2010a).

The insula is anatomically and functionally connected to other limbic regions involved in appetitive learning. The granular insular cortex has reciprocal connectivity with the lateral nucleus of the basolateral amygdala (AUGUSTINE, 1996). The more anterior dysgranular insular cortex sends efferents to the central nucleus of the amygdala. The anterior hippocampus and anterior entorhinal cortex also receive afferents from the insular cortex.

Furthermore, there is direct evidence that the insula may play a role in appetitive learning. For instance, there is evidence that the insula, particularly gustatory cortical regions, are necessary for goal-directed instrumental behavior to obtain food outcomes. Balleine and Dickinson observed an insensitivity of rats with gustatory cortex lesions to the sensory-specific devaluation of a food outcome (Balleine & Dickinson, 1998). While rats with this lesion did not decrease the number of instrumental responses they had been trained to perform

to obtain the devalued outcome (as did sham-lesioned controls), the rats showed no general deficits in instrumental behavior acquisition or contingency learning (Balleine & Dickinson, 1998). Furthermore, the gustatory cortex-lesioned rats performed identically to the sham-lesion group in a rewarded extinction test. A follow-up experiment revealed that the mechanism for gustatory cortex lesions in influencing sensitivity to devaluation lies in the animal's ability to retrieve the incentive value of the food outcome (Balleine & Dickinson, 1998). Gustatory cortex-lesioned rats were able to acquire instrumental responses for food outcomes, but again, when one food had been devalued by re-exposure in sated states (the other outcome was only exposed in a state of high deprivation), they showed no difference in the number of instrumental responses for the devalued and valued outcomes in an unrewarded extinction test (Balleine & Dickinson, 1998). (Again, sham-lesioned rats show decreased performance of instrumental behaviors leading to the devalued outcome relative to instrumental behaviors leading to the non-devalued outcome.) These results suggest that the gustatory cortex is vital to the retrieval of attributes of a food stimulus that would be vital in determining the outcome's value in accordance with the animal's internal state and/or recent experience.

Unsurprisingly, gustatory cortical lesions have also been shown to affect learned taste aversion in rats. In a study by Kiefer and Orr, gustatory cortex-lesioned rats did not display the same aversive reactions to food outcomes that

had been paired with lithium chloride (and thus illness) (Kiefer & Orr, 1992). These rats did, however, learn to avoid the taste that had been paired with illness, albeit at a slower rate than control animals (Kiefer & Orr, 1992).

### ***1.3 Interoception and Motivational Processing***

A role for interoception has previously been proposed for motivational disorders such as drug addiction (Goldstein et al., 2009; Paulus et al., 2009; Paulus & Stewart, 2014). The model put forth by Goldstein and colleagues purports that impaired interoception is part of a larger suit of impairments in insight experienced by the drug-addicted patient. According to this model, lack of meta-awareness of interoceptive states may lead to denial of the severity of the disease. Conversely, Paulus et al. argue that individuals with impaired interoceptive awareness may be at increased risk for drug addiction due to decreased accuracy in calculating body prediction errors. If a high-risk individual experiences lower accuracy in calculating current or predicted interoceptive states, the ability to select and alter behaviors adaptively will necessarily be impaired (Paulus & Stein, 2006).

A role for interoceptive processing in adaptive motivational evaluations has also been demonstrated. For example, prefeeding animals before instrumental tasks alters the which behaviors are most adaptive in a given environment. For example, when animals are prefed before an instrumental task,

they reduce their effort exertion for the food received during prefeeding (DeMarse, Killeen, & Baker, 1999; Salamone et al., 1991; Seward, Pereboom, Butler, & Jones, 1957). In fact, prefeeding a rat with as little as 0.5 gram of food increases the amount of time it takes the rodent to traverse a runway to a second location containing food (Seward et al., 1957).

Food deprivation also results in context-specific behavioral sensitization; deprived rats that were fed in a given experimental context demonstrated increased locomotor activity in that specific context, but not in other unrelated contexts (Le Merrer, 2006). In the same experiment, prefed rats failed to exhibit this behavioral sensitization (Le Merrer, 2006). Similarly, in a concurrent-choice paradigm, prefed rodents reduced the amount of chow consumed *ad libitum* as well as reduced the number of lever presses to obtain higher quality (i.e. preferred) food rewards (Salamone et al., 1991).

Prefeeding also reduces sensitivity to reinforcer frequency and discrimination accuracy; in other words, food satiety reduced an animal's response bias towards choices with greater probability of being reinforced and reduced the animal's accuracy in discriminating between food-predictive stimuli (Ward & Odum, 2006). Another experiment found that prefeeding scrub jays with one flavor of food biased their behavior away from the prefed flavor to retrieve cached food of an alternate flavor (Clayton & Dickinson, 1999). Thus internal

states and meta-representations of internal states influence the application of memory in real-world situations.

The evidence presented above all demonstrate that internal states conveyed by interoceptive processing influence motivated behavior for extrinsic rewards. The next section will consider a role for interoceptive processing in another potent modulator of behavior, emotion.

## ***1.4 Interoception and Emotion Processing***

### **1.4.1 James-Lange Theory**

The theory of emotions proposed by William James and Carl Lange centered around the necessity of the body's physiological responses to stimuli for cognitively experience emotions. According to this theory, emotion processing began when a stimulus evoked a physiological change (increased heart rate, increased perspiration) in the body (James, 1884). These physiological changes then set the groundwork for subsequently occurring metacognitive experiences of emotion. This theory flipped the existing "common-sense" conceptualization of emotion on its head by suggesting that the subjective experience (appraisal of emotion) presumed to be the instigator in emotional processing (i.e. instigating bodily changes) was actually the evoked response. Many of these instigating bodily changes reflect changes in interoceptive state such as physiological arousal (changes in heart rate and parasympathetic perspiration); suggesting a role for interoception in emotion processing.

### **1.4.2 Somatic Marker Hypothesis**

A little over one hundred years later, Antonio Damasio and his colleagues proposed that somatic (as well as interoceptive) bodily states contribute to cognition by acting as “markers” that serve as input in decision-making and other cognitive processes (A. R. Damasio et al., 1996). Under this theory, as a somatic or interoceptive state (i.e. somatic marker) becomes associated with an environmental stimuli or context, future encounters with or retrieval of that stimuli/context will reactivate the representation of the associated somatic marker. The Somatic Marker Hypothesis arose from a litany of studies of emotional and decision making deficits in patients with lesions in the ventromedial prefrontal cortex. Despite the preservation of several measures of cognition important in “rational” decision-making (i.e. working memory, attention, intellect), vmPFC lesion patients presented with real-life decision-making deficits that were later interrogated in the laboratory using the Iowa Gambling Tasks. Somatic markers are thought to contribute to both implicit and explicit cognitive contributions to decision making (i.e. learning to avoid the “bad” deck in the Iowa Gambling task before conscious awareness that this is the “bad” deck). Importantly, unlike the James-Lange postulate, this hypothesis does not require somatic markers to originate in the body; rather somatic markers can also originate as the brain’s representation of the body (as opposed to reflecting the current state of the body).

### **1.4.3 Recent Findings Linking Interoception and Emotion Processing**

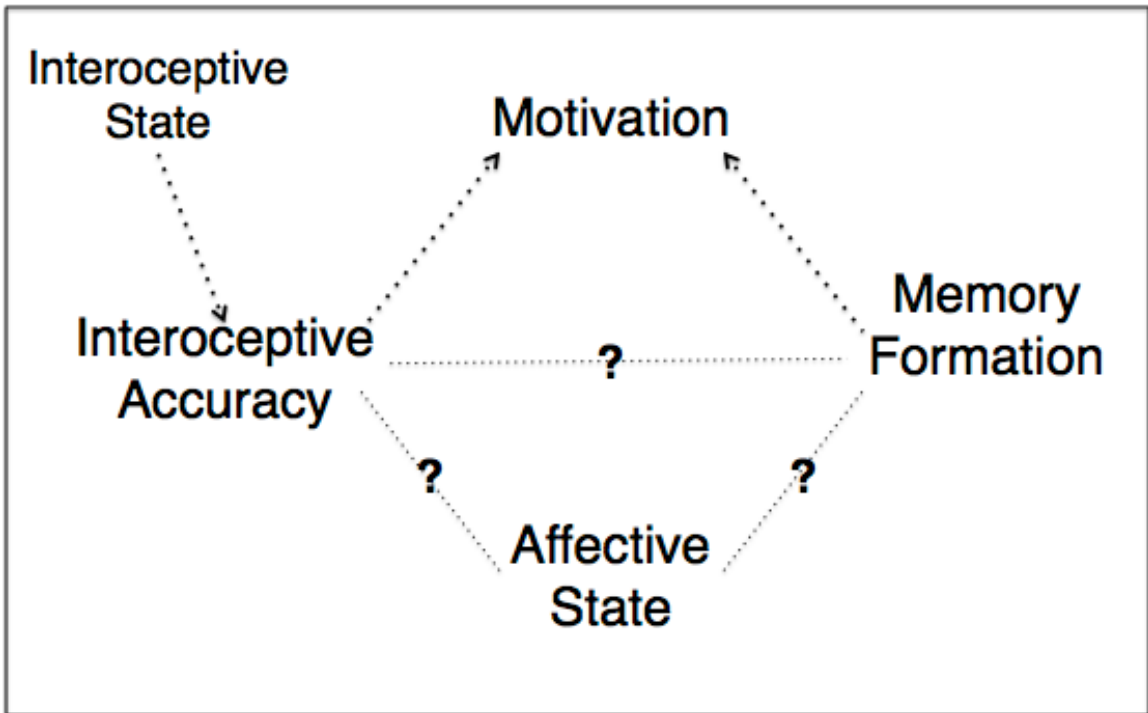
Recent studies continue to link interoception to emotion processing. Intact interoceptive afferents have been demonstrated to be critically important in the identification of one's own emotional state (i.e. "What emotion am I experiencing right now?") (Pistoia et al., 2015). Moreover, differences in the subjective experience of emotion intensity and arousal, and neural activations resulting from emotionally evocative stimuli have been reported to be increased in individuals with high interoceptive accuracy (compared to individuals with low interoceptive accuracy) (B. M. Herbert, Pollatos, & Schandry, 2007; Pollatos, Kirsch, & Schandry, 2005; Pollatos, Schandry, Auer, & Kaufmann, 2007a). Recently, Ondobaka and colleagues even proposed a model of interoceptive predictions in theory of mind, a cognitive construct important in understanding and predicting the emotions of others (Ondobaka, Kilner, & Friston, 2015).

### ***1.5 Interoception, Motivation, and Encoding***

This dissertation explores the relationships between interoception and encoding as modulated through interoceptive contributions to motivation and/or affective processing.

Chapter 2 will characterize the relationships between interoceptive state, interoceptive accuracy, motivation, and memory formation using a liquid incentivized encoding paradigm. Chapter 3 then explores the relationship between interoceptive processing and affective states (anxiety). Chapter 4

investigates individual differences in neural connectivity that predict successful memory formation for relevant information. And finally, Chapter 5 will consider findings reported in Chapters 2-4 in the context of current models of interoceptive contributions to cognition before culmination in future directions and applications of the research.



**Figure 1.1 Conceptual Framework I: Relationships to Be Elucidated Between Interoception, Motivation, Affect, and Memory Formation**

The study described in the upcoming chapter (Chapter 2) will investigate possible direct relationships between interoceptive accuracy and memory formation (following the induction of a deprived interoceptive state – thirst), and the relationship between aversive affective state (i.e. anxiety) and memory formation.

## **2. Interoception, Motivation, and Memory Formation**

### ***2.1 Introduction***

Interoceptive processing is an important modulator of motivational processes important in addiction (such as craving and relapse) ((Paulus & Stewart, 2014; Volkow, Wang, Fowler, Tomasi, & Baler, 2011; Volkow, Wang, Tomasi, & Baler, 2012; Xie et al., 2012). However, the potential influence of interoceptive processes on healthy motivated cognition largely remains to be explored. Given their importance in addiction, interoceptive processes involved in the conscious representation of the body's interoceptive state would be expected to mediate the effect of biological deprivation on motivation for interoceptive-state relevant rewards. While much processing occurs to convert biochemical information in tissue periphery to conscious awareness, interoceptive accuracy, a measure of the fidelity of interoceptive representations, is an informative proxy for these processes.

One challenge in investigating the role of interoceptive awareness in motivating behavior for interoceptive state-relevant rewards is that these primary rewards (e.g. food, drink, copulation) are also rewarding independent of interoceptive states. Because cognitive processes such as attention, decision-making, and memory are modulated by reward, delineating the contributions of interoceptive-dependent processing and interoceptive-independent processing

may be a particularly fruitful line of research (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006a; Failing & Theeuwes, 2014).

Episodic memory represents a particularly interesting collection of cognitive processes that may be modulated by incentives. Some of the processes involved in memory formation and maintenance, such as encoding may be modulated independently by rewards. Prior work utilizing incentivized encoding paradigms has observed enhanced memory for stimuli where successful recognition leads to reward (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006a; Dillon, Dobbins, & Pizzagalli, 2014; Wolosin, Zeithamova, & Preston, 2012a) or the prevention of punishment (Murty, LaBar, & Adcock, 2012). Other memory processes, occurring downstream of encoding (consolidation, retrieval, reconsolidation), may be influenced indirectly through cascading cognitive effects (i.e. changes in encoding result in changes in consolidation, altering retrieval success).

The current study aims to characterize the influence of interoceptive state and interoceptive accuracy on motivation and memory. The present protocol includes an interoceptive state manipulation (thirst or satiety); it was anticipated that motivation for interoceptive state-relative rewards will be greater in the deprived thirst condition when compared to the sated condition. This increased motivation for state-relevant rewards in the thirst condition was then predicted to increase memory for rewarded stimuli relative to unrewarded scenes as a

function of interoceptive state. Specifically, memory enhancement for rewarded stimuli was expected to increase as a function of interoceptive condition (i.e. higher memory enhancement in the thirst condition compared to the sated condition). Importantly, individual differences in interoceptive accuracy are expected to modulate memory success for relevant primary rewards (at least at the shorter delay).

## **2.2 Methods**

### **2.2.1 Participants**

Forty-seven participants who were 18-35 years old, fluent in English, without psychiatric diagnosis and not taking psychoactive medication completed the study (23 female). Additionally, participants were required to fast from all food and drink for three hours prior to the experiment and for the duration of the experiment except as instructed by the experimenter. Two participants that completed the study were excluded due to high indices of depressive symptoms as measured by a score exceeding 14 on the Beck Depression Inventory. Five participants were excluded for technical difficulties in heart rate or behavioral data recording. Finally, five participants were excluded for noncompliance with task instructions. (Thirty-five participants were included in the final analysis.)

All participants provided informed consent to participate in the current study, which was approved by the Duke University Medical Center Institutional Review Board.

### **2.2.2 Materials**

The stimulus set used in this experiment consisted of pictures of 240 indoor and 240 outdoor scenes (void of people). Each participant completed the experiment in two counterbalanced conditions: a thirst condition, and a sated condition. 120 indoor scenes and 120 outdoor scenes were presented during the thirst condition, and likewise for the sated condition. Within conditions, participants viewed 60 indoor and 60 outdoor scenes during encoding; 120 scenes during the immediate retrieval (of which 60 scenes had been presented during encoding); and finally, the remaining 120 scenes during the next day retrieval (including the 60 scenes from encoding that were not presented in the same-day retrieval).

All stimuli were presented and keyboard responses were recorded using PsychToolbox 3 and Matlab R2010a.

Cardiac activity was recorded using the BioPac Systems MP150, Measurement Computing Corporation USB Data Acquisition Board 1208FS, and Acqknowledge 4.1.

### **2.2.3 Procedure**

Each participant completed the following procedure in the thirst and sated conditions. **(See Figure 2.1.)** (The order of conditions was counterbalanced across subjects.) After providing informed consent, participants filled out a brief survey describing their regular drinking habits as well as indicating the time of

their most recent consumption of food and their most recent consumption of drink (to ensure compliance with the three-hour instructed fast prior to completing the thirst condition). Participants then underwent a thirst manipulation before being instructed and trained on the study tasks. Next, participants completed an encoding task and completed self-report survey measures of their anxiety, mood, and arousal during the encoding task.

Participants then completed a heart beat detection task to assess interoceptive awareness and were given free access to water (surprise satiation) prior to a self-paced recognition test. Following this recognition test, participants received their earned liquid compensation before being asked to complete ancillary survey measures. Finally, all participants returned the next day to complete the next-day retrieval. The steps of this procedure are described in further detail below.

#### **2.2.3.1 Thirst Manipulation**

Prior to the experiment, participants were instructed to either refrain from consuming any food or drink for three hours prior to the appointment (thirst) or to consume food and drink at will (sated). In both the thirst and sated conditions, participants consumed 28 grams of Snyder's Pretzel Rods (200 mg sodium). The consumption of this salty, chalky-textured snack induced dry mouth as has been previously demonstrated in the literature (O'Brien & Ellsworth, 2012). In the sated condition, participants were given free access to water and instructed to

drink until they were no longer thirsty immediately after consuming the salty snack. Thus in the thirst condition, participants continued with dry mouth, but in the sated condition participants progressed at satiety. (As the thirst manipulation was designed to be an encoding manipulation only, participants were not required to fast prior to the next-day retrieval.)

### **2.2.3.2 Instructions and Training**

Following the thirst manipulation, participants were instructed on the structure and timeline of the experiment. Participants were informed that they could earn liquid rewards (juice, soda, or water) for successfully recognizing pictures presented during the encoding task at a recognition memory test to take place approximately 90 minutes later in the appointment. Importantly, participants were told that they would be required to complete an additional 30-45 minutes of tasks (surveys) following the memory test; thus, if they did not earn any liquid rewards, they might not have access to drink for 120-135 minutes (until the end of the experiment). These instructions served the purpose of motivating participants to intentionally encode scenes for the liquid rewards since they would not be able to otherwise obtain drink immediately after finishing the recognition test. (i.e. The experiment did not end with the memory test.)

Participants then completed a brief training run of the encoding and retrieval tasks and received a demonstration of the amount of liquid they would have theoretically won. For this demonstration, the amount of liquid received for

remembering rewarded scenes (maximum possible reward: 4 ounces) was poured into one cup and the amount of liquid received for remembering unrewarded scenes (always 0 ounces) was displayed in a separate (empty) cup. Any penalties received for false alarms was poured out of the reward earnings cup in sight of the participant with the explanation, “This is your reward after penalties.”

### **2.2.3.3 Incentivized Encoding Task**

Participants were presented with and asked to remember 120 stimuli (indoor and outdoor scenes) across four runs of this motivated memory paradigm. **(See Figure 2.2.)** Half of the scenes were worth one ounce of liquid for successful recognition at a later (same-day and next-day) memory test (“rewarded scenes”), while correct memory performance for the other half would not earn liquid rewards for successful recognition (“unrewarded scenes”).

Each trial commenced with a 1-s cue indicating the trial type (three drop cue: rewarded or empty drop cue: unrewarded). Following the cue, a fixation crosshair was presented for 2.5-6.5 s, after which the scene to be remembered appeared for 3s. To constrain encoding time to the 3 seconds the stimulus was presented, stimulus presentation was immediately followed by three sequentially-presented distractor arrows; upon each distractor arrow presentation, participants were required to indicate arrow direction (0.667 s/arrow presentation; 0.333 seconds ITI between arrows).

#### 2.2.3.4 Heartbeat Detection Task

To access interoceptive accuracy/awareness, participants completed a heart beat detection task (Schandry, 1981). **(See Figure 2.24.)** At the beginning of each trial, participants were instructed, “Without manually checking, please begin counting the number of heartbeats you feel within your body.” Participants completed 6 trials of durations: 25 s, 30 s, 35 s, 40 s, 45 s, and 50 s. Trial durations were pseudorandomized and the participants were not made explicitly aware of trial length. Special emphasis was put on instructing participants to only report the number of heartbeats they actually felt and not to merely guess how many heartbeats had occurred during the elapsed time. The experimenter remained in the testing room for the duration of the task to ensure contraband strategies (manually checking pulse at neck or wrist) were not employed. During each trial heartbeat data was collected via BioPac MP150 electrodes applied to the subject’s right wrist, and left and right ankles. Comparison of the recorded heartbeat data was then compared to the number of heartbeats reported by the subject over the same epoch to calculate an interoceptive accuracy score (percent error):

$$\text{Interoceptive Accuracy \% Error} = \frac{|(\text{Heartbeats}_{\text{actual}} - \text{Heartbeats}_{\text{reported}})|}{\text{Heartbeats}_{\text{actual}}} * 100$$

Percent error close to 0 indicates strong accord between detected and recorded heartbeats, whereas percent error approaching 100 represents the

lowest possible interoceptive accuracy.

#### **2.2.3.5 Surprise Satiation**

Following the heartbeat detection task and completion of the State-Trait Anxiety Inventory (measure of state anxiety levels), all participants (in both the thirst and sated conditions) received a surprise satiation. During the surprise satiation, participants were presented and left alone with two 500 mL bottles of water to consume. They were asked to retrieve the experimenter when they were completely sated or to receive an additional supply of water. Participants were also explicitly instructed that there were no time limits for the surprise satiation to make sure water consumption was not limited by perceived time constraints. Once the participant indicated they were sated, all bottles were removed and the volume of water consumed was calculated as: mL provided to subject – mL remaining in bottles of water.

#### **2.2.3.6 Retrieval Task**

The current protocol included a same-day memory test (administered approximately 30 minutes following the completion of the encoding task) as well as a next-day memory test for each condition to examine the relationship between interoceptive state and interoceptive accuracy on memory over shorter and longer delays (**See Figure 2.3**). Half of the stimuli originally presented during encoding were presented during the same-day recognition test and the remaining half of the encoding stimuli appeared in the next-day recognition test.

An equal number of novel lures were included for each recognition test.

Participants were asked to indicate whether each scene presented during the recognition test was “New” or “Old” before being asked to gauge their confidence (“Sure”, “Pretty Sure”, “Guessing”) of their “New”/“Old” judgement.

#### **2.2.3.7 Reward Payout**

Participants received one ounce of their chosen liquid for every rewarded scene they correctly remembered during the immediate and next-day retrievals. Participants did not earn any liquid for successfully recognizing unrewarded scenes during the recognition test. To discourage guessing, a penalty of 0.5 ounces was implemented for each new scene a participant incorrectly identified as “old.” Participants received their liquid payout, rounding up to the nearest bottle of juice, water, soda, immediately after completing the recognition memory test (for both the immediate and next-day retrievals).

#### **2.2.3.8 Subjective Thirst and Hunger Ratings**

Participants were instructed to rate their thirst level at seven different time points in the experiment. To indicate their rating, participants completed a 7-point Likert scale ranging from 1 (Not thirsty at all) to 7 (Extremely thirsty) in paper and digital formats. These subjective thirst ratings were recorded at the start of the experiment, immediately following the thirst manipulation, after each of the four encoding runs, and immediately after the surprise satiation.

Participants were instructed to rate their hunger at two different time points using an identical Likert scale at the start of the experiment and then again following the surprise satiation. Participants' subjective thirst was queried at more time points than subjective hunger to encourage reflection on the thirst (or sated) state and further motivate performance on the encoding task.

#### **2.2.3.9 Ancillary Measures**

Participants completed several surveys of motivation-related individual difference measures following the recognition memory test to prolong the experiment past the end of the memory test (to imbue the rewarded scenes with greater value during encoding). These surveys include the State-Trait Anxiety Inventory (STAI), Tridimensional Personality Questionnaire (TPQ) (Cloninger, Thomas, & Dragan, 1991), Motivational Trait Questionnaire (MTQ) (Kanfer & Heggestad, 2000), Behavioral Inhibition and Activation Scales (BIS/BAS) (Carver & White, 1994), and the Temporal Experience of Pleasure Scale (TEPS) (D. E. Gard, Gard, Kring, & John, 2006a).

#### **2.2.4 Behavioral Data Analysis**

All trials for which a participant indicated “pretty sure” or “sure” confidence during retrieval were included in the analyses. Hit rates for rewarded and unrewarded scenes were calculated by dividing the number of “Old” rewarded scenes correctly identified as “Old” with medium and high confidence during retrieval by the total number of “Old” rewarded scenes presented during the

retrieval task (30). (The same procedure was used to calculate hit rate for unrewarded scenes.) A participant's false alarm rate (for medium and high confidence levels combined) was calculated by dividing the number of "New" items incorrectly classified as "Old" with medium and high confidence during retrieval by the total number of "New" items presented during the memory test (60). Memory was then corrected by subtracting a participant's false alarm rate from her hit rate. (Memory was computed in this manner for the same-day and next-day recognition tests.) Two participants with corrected memory performance two standard deviations above or below the group's mean were determined to be outliers and excluded from further analysis.

Participants with STAI-State Anxiety or STAI-Trait Anxiety scores that were two standard deviations above or below the mean were excluded from all analyses (one participant). Additionally, two participants were excluded from the analyses for interoceptive accuracy scores two standard deviations above or below the group mean. Finally, two participants were excluded due to corrupt or unavailable memory response data or heartbeat data (these data were critical to the current hypotheses), leaving 33 subjects in the final analysis.

To query the efficacy of the thirst manipulation on inducing subjectively distinctive interoceptive states (from the completion of the thirst manipulation to the end of encoding), a 2 x 5 x 2 ANOVA (Condition X Thirst Rating Time Point X Condition Order) was conducted. Furthermore, to investigate whether the thirst

manipulation induced distinctive motivational states, 2 x 2 x 2 ANOVAs of condition, stimulus value (rewarded vs. unrewarded), and condition order were conducted for subjective mood and arousal ratings. A paired t-test was also carried out on the amount of water consumed during the surprise satiation of the THIRST and SATED conditions to confirm behavioral expression of distinct motivational states. Lastly, it was important to verify that the manipulation was selective to the encoding phase (as intended), thus a paired t-test was conducted on subjective thirst ratings immediately following the surprise satiation (i.e. immediately before the same-day retrieval).

A 2 x 2 x 2 ANOVA was conducted to assess the effects of interoceptive condition (THIRST vs. SATED), stimulus value (rewarded vs. unrewarded), and retrieval delay (same-day vs. next-day) on memory (corrected). The between-subject factor of condition order was included to investigate possible order effects.

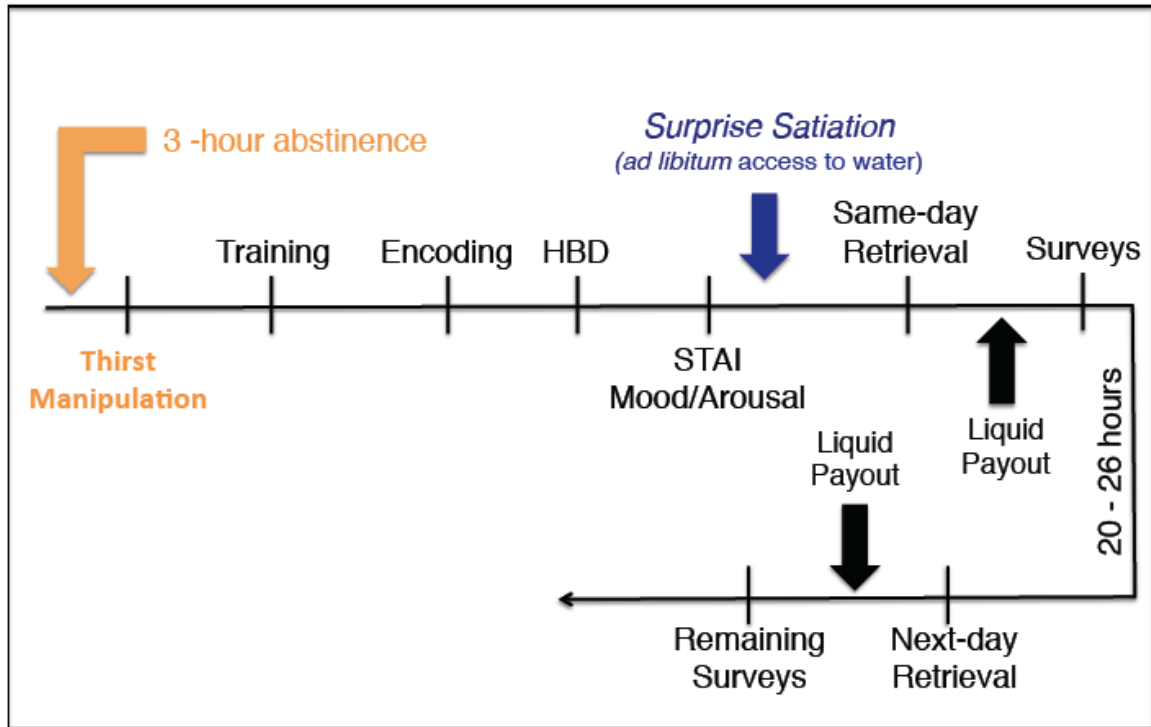
Rewarded memory benefit for each interoceptive condition (Thirst or Sated) was calculated by subtracting each participant's corrected memory for unrewarded scenes from their corrected memory for rewarded scenes. For the thirst condition, this score provides a measure of the degree to which state-relevant information (rewarded scenes) was successfully remembered relative to irrelevant information (unrewarded scenes). The sated rewarded memory benefit

score describes the extent to which rewards more generally enhanced memory performance (compared to memory for unrewarded scenes).

### **2.2.5 Correlation Analyses**

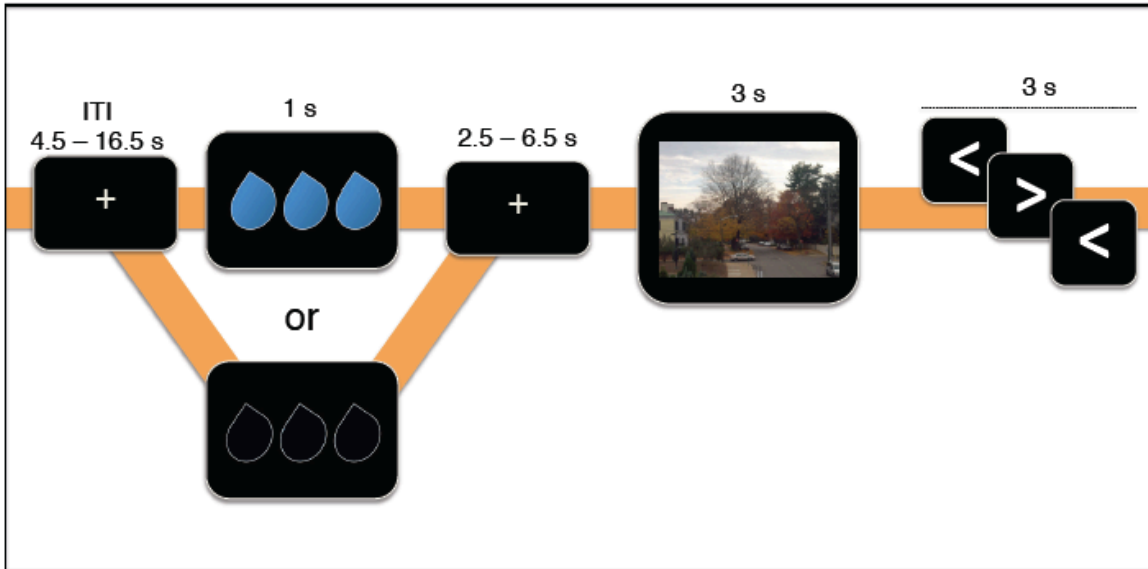
To investigate the relationship between interoceptive awareness and rewarded memory benefit, linear regression analyses were conducted with average interoceptive accuracy during the heart beat detection task as the independent variable and same- and next-day rewarded memory benefit (for both the thirst and sated conditions) as the dependent variables (for a total of four analyses).

To investigate the relationship between anxiety and rewarded memory benefit, linear regression analyses were conducted with the participant's score on STAI-Trait Anxiety as the independent variable and same- and next-day rewarded memory benefit (for both the thirst and sated conditions) as dependent variables (four analyses were conducted).



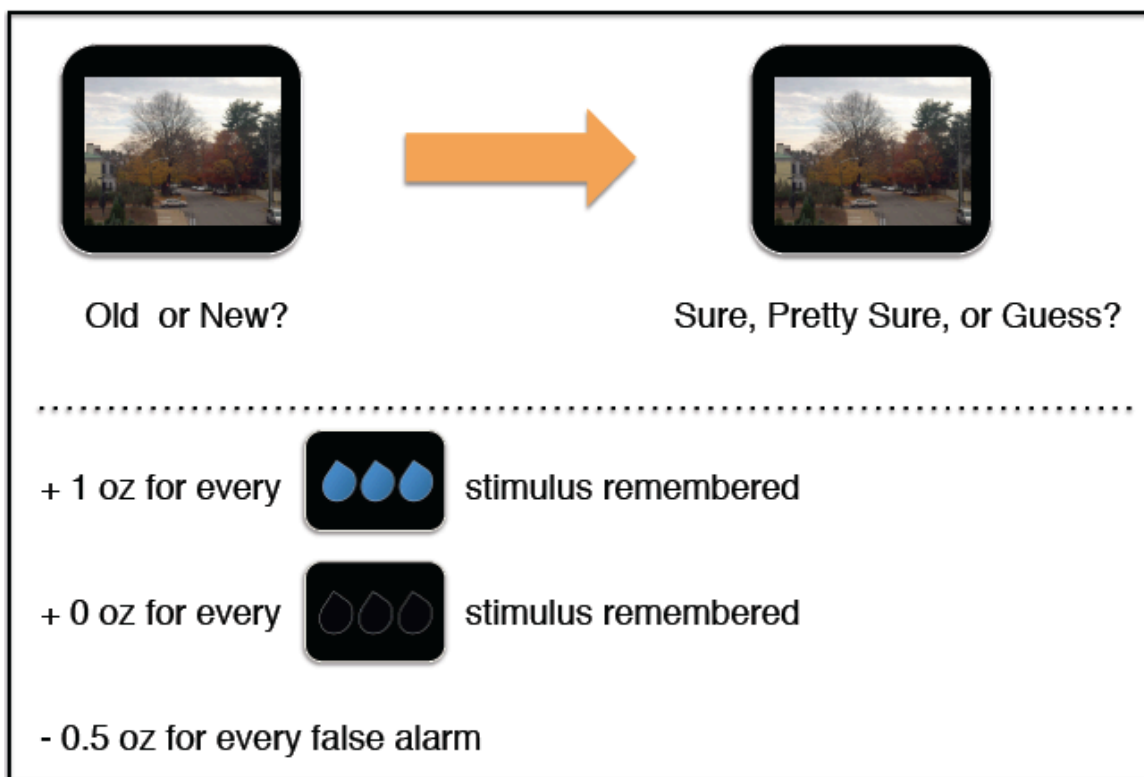
**Figure 2.1: Experimental Procedure**

Each participant completed this within-subject protocol in both the thirst and sated conditions. The protocol was identical on both days except participants fasted from food and drink for 3 hours prior to the experiment during the thirst condition. Additionally, when completing the sated condition participants were offered water following the thirst manipulation.



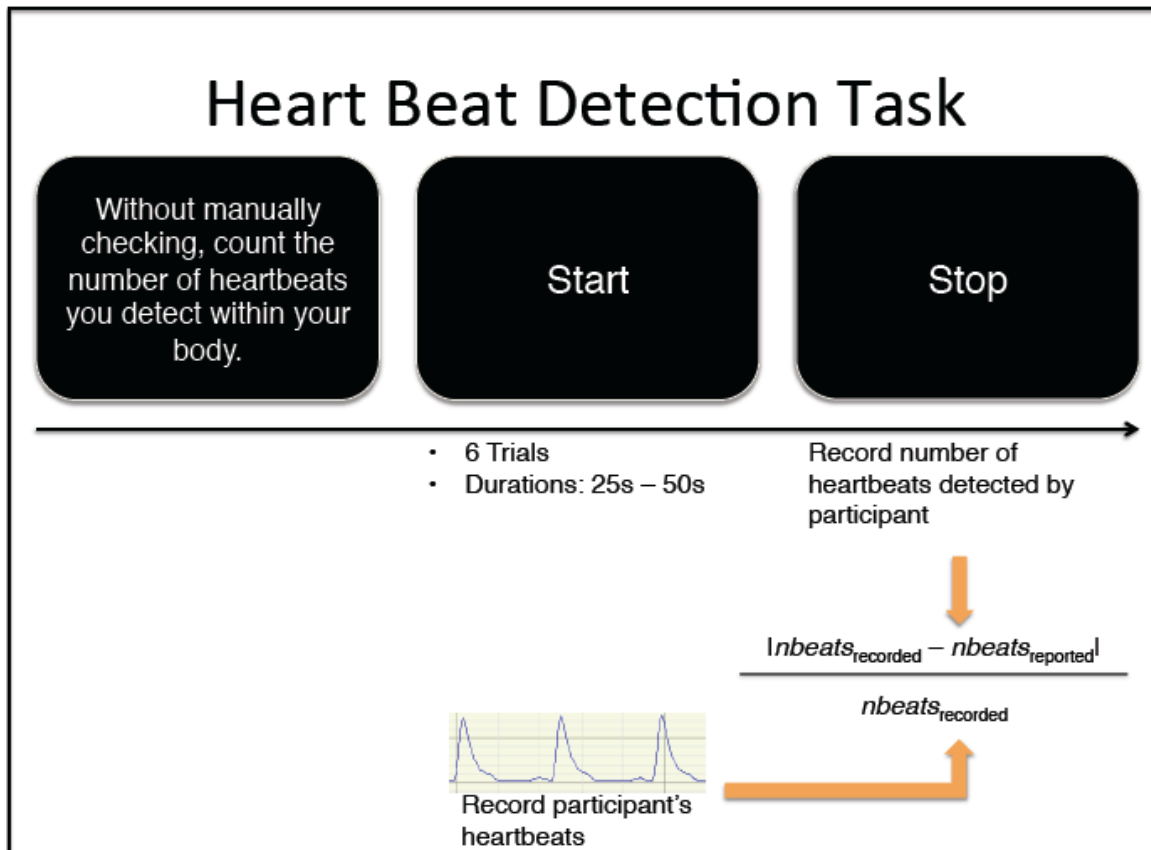
**Figure 2.2: Liquid Incentivized Encoding Task Trial Structure**

Participants completed the encoding task with the opportunity to receive juice, soda, or water rewards for 3-drop scenes that were successfully remembered at subsequent retrieval tasks. Each trial began with a cue to indicate the upcoming value of the scene (3-drop cue = 1 ounce of liquid if later remembered; 0-drop cue = 0 ounces of liquid if remembered later), which was followed by presentation of the scene to be remembered. Each trial ended with the presentation of three distractor arrows (participants pressed a button to indicate which director each arrow was pointing while it was on the screen) to limit encoding to the time the target scene was presented on the screen.



### Figure 2.3: Same-day and Next-Day Retrieval Task

Participants completed two retrieval tasks, one at a 30 min delay after encoding and the second at a 20 – 26 hour delay. During the first retrieval task, participants were shown 60 “Old” scenes (scenes that were presented during encoding and 60 “New” foils (novel scenes). During the next day retrieval task, participants were presented the remaining 60 “Old” scenes from encoding (that were not presented during the first retrieval task), and 60 novel foils. After indicating whether a presented scene was “Old” or “New,” participants were asked to indicate their confidence for the preceding judgement (to allow for the elimination of “Guess” trials from analysis). Participants received an ounce of liquid for every 3-drop scene correctly identified as “Old”, no liquid for every 0-drop scene correctly identified as “Old,” and were penalized 0.5 ounce of liquid for incorrectly identifying a novel foil as “Old.”



**Figure 2.4: Heart Beat Detection Task (Measures Interoceptive Accuracy)**  
 For six trials of varying lengths (25 – 50), participants were asked to count the number of heartbeats they detected within their body. Simultaneous collection of pulse data allowed for a calculation of the cardiac interoceptive accuracy.

## **2.3 Results**

### **2.3.1 Behavioral Results**

#### **2.3.1.1 Efficacy of thirst manipulation**

A 5X2 ANOVA with five timepoints during which the thirst manipulation was active (i.e. immediately following the thirst manipulation (post-TM) and the rating time points after each of the four encoding runs: ENC1, ENC2, ENC3, ENC4) and interoceptive condition (thirst, sated) revealed a main effect of interoceptive condition,  $F(1, 29) = 217.22, p < .001, \eta_p^2 = .882$ . This effect was qualified by an interaction between condition and timepoint,  $F(4, 26) = 17.69, p < .001, \eta_p^2 = .379$ . Follow-up t-tests revealed participants reported increased subjective thirst ratings in the thirst condition vs. the sated condition at each of the five time points, post-TM:  $t(32) = 18.15, p < .001$ , two-tailed; ENC1:  $t(31) = 12.62, p < .001$ , two-tailed, ENC2:  $t(31) = 12.57, p < .001$ , two-tailed, ENC3:  $t(31) = 10.90, p < .001$ , two-tailed, ENC4:  $t(30) = 10.15, p < .001$ , two-tailed. **(See Figure 2.5.)** Additionally, participants consumed more water during the surprise satiation in the thirst condition than in the sated condition,  $t(32) = 6.70, p = .003$ , two-tailed. **(See Figure 2.6.)** These results confirm that participants were subjectively thirstier in the thirst condition as revealed by their increased subjective thirst ratings and their increased water consumption relative to the sated condition.

Importantly, there was no significant difference in post-satiation subjective thirst ratings. These findings confirm that the thirst manipulation was confined to encoding and the interoceptive accuracy tasks.

Lastly, potential effects of the thirst manipulation on subjective hunger were considered. Analysis of variance with timepoint (post-thirst manipulation, post-surprise satiation) and interoceptive condition (thirst, sated) revealed main effects of timepoint,  $F(1, 32) = 12.35, p = .001, \eta_p^2 = .278$ , and interoceptive condition,  $F(1, 32) = 15.87, p < .001, \eta_p^2 = .331$ . **(See Figure 2.7.)**

#### **2.3.1.2 Order effects**

Because the experimental protocols were nearly identical on both days, there was the concern that participants that had completed the sated condition first might anticipate a surprise satiation while completing the thirst experiment. Such anticipation would be expected to decrease motivation for learning scenes to earn liquid rewards. However, we observed no effect of condition order on subjective thirst ratings (condition order was entered as a between subjects factor in the ANOVA discussed in 2.3.1.1.) Similarly, no interactions between condition order and same-day memory or next day memory were observed (condition order was also entered as a between subjects factor in the ANOVA discussed in 2.3.1.3.) These findings suggest that the order of condition completion did not significantly impact participants' subjective experience or memory performance.

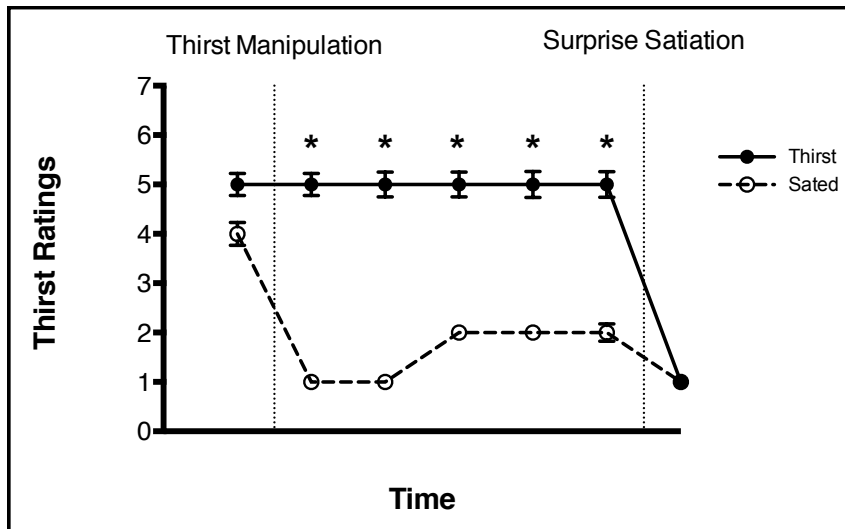
### 2.3.1.3 Memory performance

Analysis of variance with condition (thirst, sated), stimulus value (rewarded, unrewarded) and delay (same-day retrieval vs. next-day retrieval) as within-subject factors revealed main effects of stimulus value,  $F(1, 31) = 22.50, p < .001, \eta_p^2 = .421$ , and retrieval delay,  $F(1, 31) = 88.24, p < .001, \eta_p^2 = .740$ , but not a main effect of condition,. No significant interactions were observed. Participants had higher memory for scenes that were rewarded relative to unrewarded scenes (rewarded scenes:  $M = 0.43, SD = 0.17$ , unrewarded scenes:  $M = 0.35, SD = 0.16$ .) Also, as expected, memory was higher during the same-day retrieval than for the next-day retrieval. **(See Figure 2.8.)**

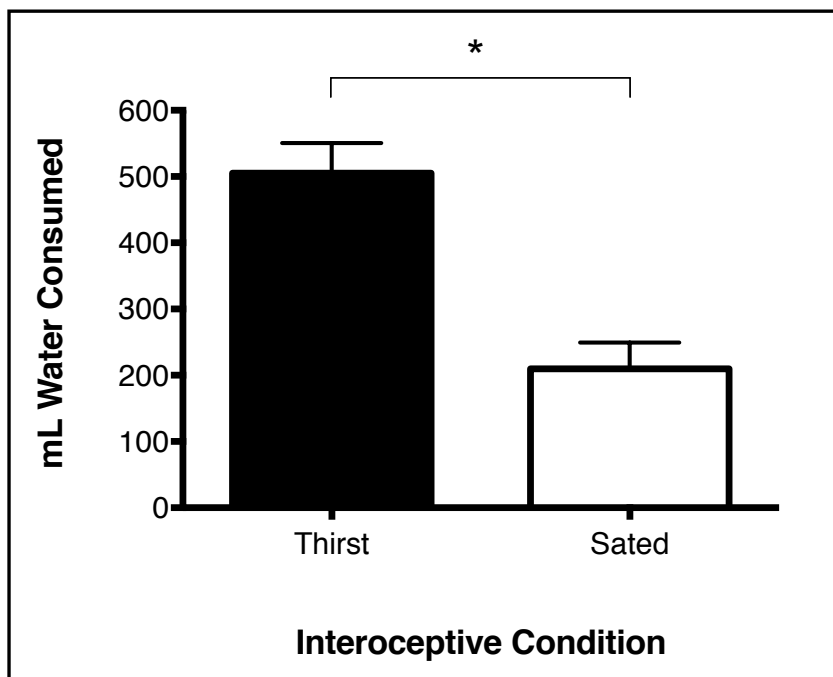
### 2.3.1.4 Correlations between memory performance and trait measures

The relationship between interoceptive accuracy, as measured by accuracy on the heartbeat detection task), and memory benefit was best fit with a quadratic function, Pearson's  $r(28) = .449, p = .043$ . (No significant relationship between interoceptive accuracy and memory benefit for rewards at next-day retrieval was observed.) **(See Figure 2.9.)**

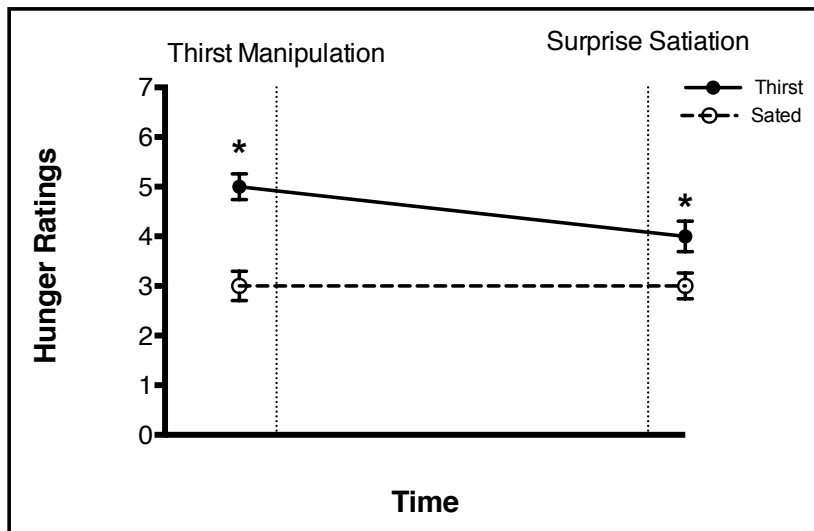
Increased anxiety, as measured by participants scores on the STAI-Trait Scale, was associated with decreased memory benefit (of trending significance) for rewards at next-day retrieval only, Pearson's  $r(30) = .342, p = .055$ . (No significant relationship between anxiety and memory benefit for rewards at same-day retrieval was observed.) **(See Figure 2.10.)**



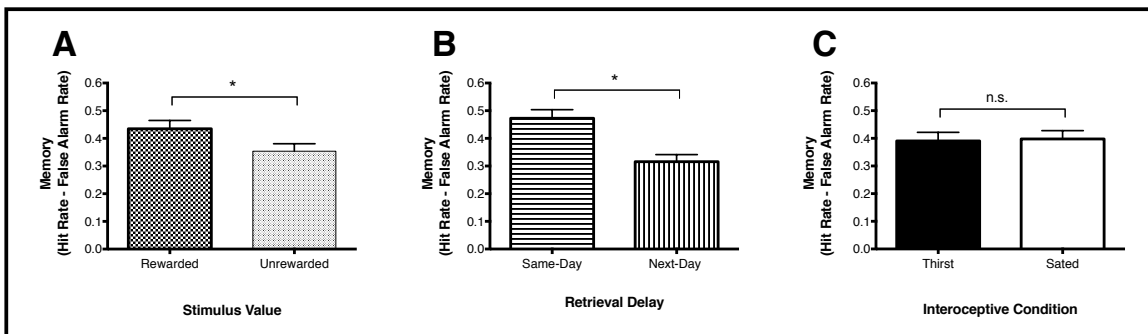
**Figure 2.5: Participants Report Increased Thirst in the Thirst Condition**  
 Each data point represents participants' average thirst ratings at seven timepoints during the experiment ( $p < 0.05$ ).



**Figure 2.6: Water Consumption is Increased in the Thirst Condition Relative to the Sated Condition** ( $p < 0.05$ )

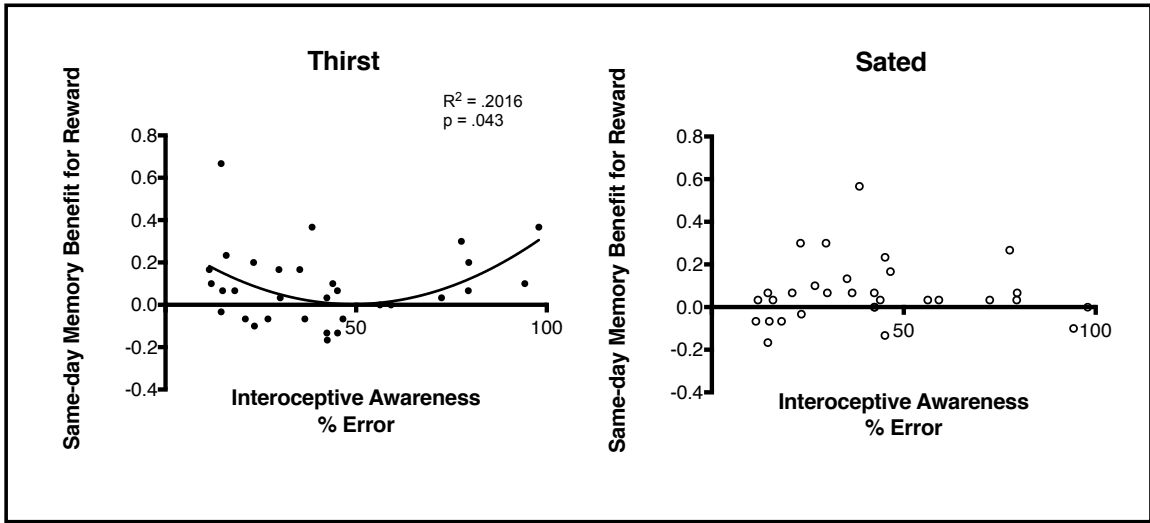


**Figure 2.7: Participants Report Increased Hunger in the Thirst Condition Relative to the Sated Condition ( $p < 0.05$ )**

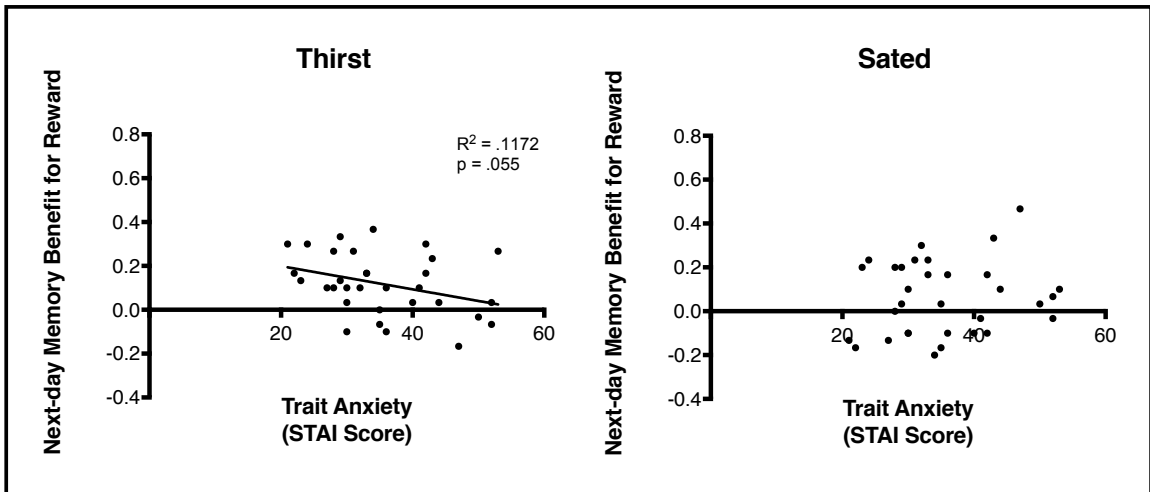


**Figure 2.8: Main Effects of Retrieval Delay and Stimulus Value (but not Interoceptive Condition) on Memory**

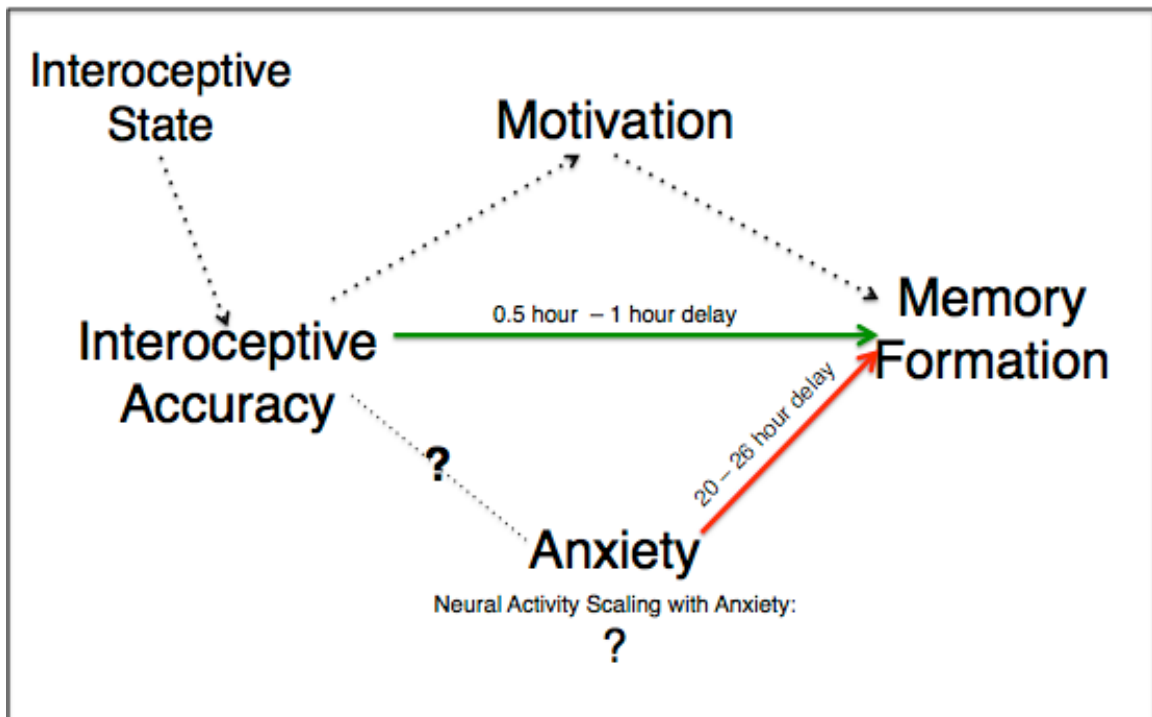
Main effects of reward value (3-drop/1 ounce vs. 0-drop/0 ounces) (A) and retrieval delay (same day vs. next day) (B) were observed. However there was no effect of interoceptive condition (thirst vs. sated) (C) on memory performance.



**Figure 2.9: High and Low Interoceptive Awareness Predict Rewarded Memory Benefit at Same-Day Retrieval**



**Figure 2.10: Trait Anxiety Negatively Predicts Rewarded Memory Benefit at Next-Day Retrieval**



**Figure 2.11: Conceptual Framework II** Following induction of a deprived interoceptive state (thirst), interoceptive accuracy positively predicted memory formation for relevant information when memory was tested the same day. Conversely, trait anxiety negatively predicted memory formation for relevant information when memory was tested the next day. The following chapter (Chapter 3) will examine the relationship between interoceptive accuracy and anxiety during a deprived interoceptive state (thirst).

## **2.4 Discussion**

The present study examined interactions between interoceptive state, interoceptive accuracy, and motivation on (primary rewards-) incentivized encoding. Greater memory success was observed for rewarded scenes than unrewarded scenes in this liquid-incentivized encoding paradigm. Previous studies have demonstrated that secondary rewards enhance memory performance (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006b; Wittmann, Schiltz, Boehler, & Duzel, 2008; Wolosin, Zeithamova, & Preston, 2012b; 2012a). The current findings extend this work by demonstrating that primary rewards also enhance memory processes. Furthermore, the results here indicate that primary rewards enhance memory when delivered 30 minutes – 26 hours (i.e. not immediately) after presentation of the stimuli to be remembered.

Increased consumption of water during a surprise satiation in the thirst condition relative to the sated condition indicates interoceptive condition increased motivation for state-relevant primary rewards. However, this observed increase in motivation for liquid rewards in the thirst condition did not translate to an observed increase in memory performance for these rewards. Additionally, no interactions between interoceptive condition and reward value were observed for memory at immediate or 24-hour recognition tests. Liquid-rewarded images were subsequently remembered better than unrewarded images independent of interoceptive condition, suggesting that deprivation alone is insufficient to

enhance memory for state-relevant rewards. Alternatively, the absence of interaction between condition and reward value may be the result of receiving primary rewards at a delay. It might reasonably be expected that delayed primary rewards may be processed more akin to secondary rewards when they will be delivered on a timescale less compatible with interoceptive need.

Individual differences in interoceptive accuracy were observed to predict rewarded memory benefit (the difference between rewarded memory and unrewarded memory) at short delays (approximately thirty minutes after completion of the encoding task). The observation of this relationship at a short delays and not at longer delay (next day) suggest that interoceptive accuracy exerts an influence on encoding directly (or cognitive processes that support encoding like attention) to enhance memory for relevant information and decrease memory for irrelevant items.

By contrast, anxiety was negatively correlated with rewarded memory benefit, suggesting individual differences in anxiety may be more important in predicting differences in consolidation of relevant versus irrelevant information. retrieval.

One limitation in interpreting the same-day memory performance is participants reported being hungrier in the thirst condition than in the sated condition at both timepoints of measurement. These findings prevent the current study from cleanly dissociating motivation due to food deprivation from motivation

due to drink deprivation. The subjective experience of increased hunger at the start of the experiment (presumably extending through the encoding task) would not be expected to affect the interpretation of the data, as it is irrelevant for the current hypotheses whether an individual was motivated for these rewards by thirst or hunger. However, increased hunger ratings immediately prior to the same-day recognition test suggest that participants completed the same-day recognition test in an interoceptive state that was more hunger deprived in the thirst condition than in the sated condition. While it is unknown how experienced hunger might be expected to impact retrieval processes and/or performance on a recognition memory test, this finding may affect interpretation of the results.

Another limitation is the possibility that the thirst manipulation depressed successful encoding. This would particularly affect interpretation of the results reported here if the thirst manipulation selectively depressed encoding for rewarded scenes. Selective depression of memory for rewarded scenes by the thirst manipulation would potentially mask a main effect of interoceptive condition or a condition-stimulus value interaction on memory performance. A previous study by Ganio et al. observed decreased working memory performance in a dehydrated state (Ganio et al., 2011). Working memory decrements would be expected to impair encoding success in the paradigm employed here; however, the Ganio et al. thirst manipulation, which combined exercise-induced dehydration with a diuretic, most likely produced a level of hydration significantly

higher than the thirst manipulation employed in the present study. Future work should investigate how deprivation states may differentially influence cognition for rewards. One option for future work would be to examine the effect of induced interoceptive deprivation on encoding for rewards that are irrelevant to one's experienced interoceptive states. For example, a monetary incentivized encoding paradigm could be used following the induction of a thirst interoceptive state. Another option would be to employ a liquid-incentivized encoding paradigm identical to the one described here, except to limit the rewards to calorie-free liquids following the induction of a hunger interoceptive state. Either of these experimental paradigms would be expected to provide additional insight into how deprivation states (thirst or hunger) influence encoding for rewards more generally.

## **3. Individual Differences in Interoceptive Accuracy & Anxiety**

### ***3.1 Introduction***

Interoception has been linked to affective state since at least 1884 when William James' asserted, "whatever moods, affections, and passions I have, are...constituted by, and made up of, those bodily changes we ordinarily call their expression or consequence" (James, 1884). According to the James-Lange theory of emotion, physiological changes in the body are necessary prerequisites for the experience of emotion. More recent work has elaborated the relationship between interoception and emotion processing. For example, increased interoceptive accuracy is associated with enhanced emotion processing (as assessed by arousal responses to and subjective intensity of emotions elicited by emotional images) (Pollatos et al., 2005; Pollatos, Traut-Mattausch, Schroeder, & Schandry, 2007b). Similarly, spinal cord injury patients (with reduced integrity of interoceptive afferents) experience greater difficulty evaluating their individual emotional response to fear- and anger-evoking scenes (Pistoia et al., 2015).

There is additional evidence that differences in emotion processing modulated by interoception are valence-specific. Werner and colleagues observed attention interference for negative words during an emotional Stroop task in persons with high interoceptive accuracy (Werner et al., 2014). In this same study, individuals with poor interoceptive accuracy demonstrated attention

facilitation for positive words. A study by Olga Pollatos and colleagues finding increased sensitivity and decreased tolerance for pain among participants with high interoceptive accuracy corroborates this tendency towards negative attentional bias with increasing interoceptive accuracy (Pollatos, Füstös, & Critchley, 2012).

A close link between interoceptive accuracy and anxiety has also been suggested, though different studies have deduced different relationships between the two variables. While some studies report an association between higher interoceptive accuracy and higher trait anxiety (Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004; Dunn, Stefanovitch, et al., 2010b; Pollatos et al., 2009; Pollatos, Gramann, & Schandry, 2006b; Richards & Bertram, 2000) others report no relationship (Steptoe & Vögele, 1992) or a negative correlation between interoceptive accuracy and anxiety (de Pascalis, Alberti, & Pandolfo, 1984).

However, it is argued here, that awareness of interoceptive changes (i.e. heart rate) may not rigidly lead to negative affect. It is very adaptive for an organism to appraise its interoceptive information within the context of its environment. For instance, appraisal of an increase in heart rate following a loud gunshot heard while on a walk would necessarily be different from a gunshot attributed to a television show. The aforementioned divergent findings may be explained by another cognitive process modulating the relationship between interoceptive accuracy and anxiety. Cognitive appraisal may be a candidate

cognitive process in defining interoceptive contributions to anxiety.

Cognitive appraisal is described in the emotion literature as strongly influencing resulting affective states (Lazarus & Folkman, 1984). It then follows that appraisal, especially threat appraisal of interoceptive information may also be an important factor in understanding the relationship between interoceptive awareness and affective state.

The current study further investigates the relationship between interoceptive awareness and affective state, by identifying the neural substrates underlying anxiety and threat appraisal of interoceptive information.

## ***3.2 Methods***

### **3.2.1 Participants**

Twenty-five right-handed participants were scanned while completing a heartbeat detection task. Participants were fluent in English, 18-35 years old, without psychiatric diagnosis and not taking psychoactive. Additionally, to be eligible for the study, participants had to be able to fast from all food and drink for three hours prior to the experiment and for the duration of the experiment except as instructed by the experimenter. One of the participants that completed the study was excluded due to high indices of depressive symptoms as measured by a score exceeding 14 on the Beck Depression Inventory (Beck et al. 1987), since Depression and anxiety have high comorbidity.) Additionally, two participants

were excluded as the result of technical difficulties, leaving 22 participants in the final analyses.

### **3.2.2 Materials**

Structural and functional magnetic resonance images were collected using a 3.0 Tesla Siemens scanner.

Stimuli were presented using PsychToolbox 3 and Matlab R2010a. Cardiac activity was recorded using a pulse oximeter and MP150, Measurement Computing Corporation USB Data Acquisition Board, and Acqknowledge.

### **3.2.3 Procedure**

Participants completed the current study as part of a larger experimental protocol (described in Chapter 4). Upon arrival to the experiment, all participants underwent a thirst manipulation (consumption of chalky-textured, high sodium snacks following a three hour abstinence from all food and drink). Compliance with the instructed abstinence was confirmed by asking participants to indicate the time of their most recent food and drink consumption via a paper survey.

Participants then underwent a brief training on the heartbeat detection task to ensure proper interpretation of task instructions and success in recording trial responses prior to entering the scanner. Because the number of heartbeats detected by participants could theoretically, if not practically, range from zero to infinity, participants were asked to record responses (i.e. number of heartbeats or “T”s detected for a given trial) by writing responses on a large notecard. Training

was critical here because writing in the scanner required participants to write their responses under the following unfamiliar constraints: 1) using a crayon as a writing utensil, 2) writing without being able to see the writing hand or writing paper (resulting from the supine positioning during an fMRI scan), and 3) manipulating both the writing utensil and writing paper with the same hand (participants were asked to not move the non-writing hand to which the pulse oximeter was attached to avoid adding noise to the data). Participants were able to successfully write with crayon and maintained an index of their responses (i.e. order of responses) using tactile orienting cues in the writing paper (cut-out holes in one corner of the writing paper). Participants confirmed the order of their written responses and the value of each response with the experimenter immediately following the scan. Participants returned to the lab the next day to complete questionnaires and inventories.

### **3.2.3.1 Heartbeat Detection Task**

The heart beat detection task consisted of three conditions: HEART, COUNT, and REST. There were 6 trials of each condition of lengths 25, 30, 35, 40, 45, and 50 seconds. Trial type and length were pseudorandomized so that participants were not explicitly aware of the length of any trial.

Each trial consisted of the presentation of a visual cue or visual stimuli to indicate the task to be performed ( the word “Count” was displayed for HEART trials, a visual stream of “T’s” and distractors were presented during COUNT

trials, and the word “REST” was displayed for REST trials) a period of time to record participant response (on HEART and COUNT trials only) (8s), and a message indicating the identity of the upcoming condition (3s).

On HEART trials, participants were instructed to count the number of heartbeats they could detect within their bodies with special emphasis on reporting the number of heartbeats actually felt and not merely guessing. During COUNT trials, participants counted the number of T’s (of any orientation) that appeared in a visual stream of stimuli. Lastly, during REST trials, participants engaged in open-eyed rest and were explicitly instructed not to count their heartbeats during this time.

At the end of each HEART and COUNT trial, participants recorded their responses using the provided, fMRI-compatible index card and crayon.

Additionally, pulse data was collected throughout the task via a pulse oximeter attached to the volunteer’s left index finger. The pulse data obtained from the oximeter would eventually be compared to the participant’s self-reported heartbeats over the HEART trials.

### **3.2.3.2 Inventories and Questionnaires**

The next day, participants completed a number of surveys including the Spielberger Trait Anxiety Inventory (Spielberger, Gorsuch, & Edward, 1970), the Body Sensations Questionnaire (Chambless, Caputo, & Bright, 1984), and the Body Consciousness Questionnaire (L. C. Miller et al., 1981).

The STAI is a 20-item inventory designed to measure trait anxiety. Participants indicate the frequency (“Never”, “Almost Never”, “Sometimes”, “Often”, and “Almost Always”) with which they endorse survey items such as: “I am ‘calm, cool, and collected’” or “I feel nervous and restless.”

The Body Sensations Questionnaire (17 items) asks participants about the level of fright (“not frightened or worried by this sensation” to “extremely frightened by this sensation”) induced by several bodily sensations. Many of these sensations map onto the interoceptive states of thirst (“dry throat”) or cardiac activity (“heart palpitations”), which map directly onto the interoceptive states investigated in the present study (Chambless et al., 1984).

The Body Consciousness Questionnaire queries the self-reported frequency (“extremely uncharacteristic” to “extremely characteristic” with which participants experience somatosensory and interoceptive sensations (15 items). For the present study, individual items relevant to interoception like, “I know immediately when my mouth or throat gets dry.” or “I can often feel my heart beating.” were of particular interest. The summed score of these 5 interoceptive-relevant items (termed the “interoceptive sensibility score” here) was also of interest (L. C. Miller et al., 1981).

### **3.2.4 Behavioral Data Analysis**

Comparison of the recorded heartbeat data was then compared to the number of heartbeats detected by the subject over the same period to calculate

an interoceptive accuracy using the following equation:

$$\frac{1}{3} \sum (1 - (|\text{recorded heartbeats} - \text{detected heartbeats}|) / \text{recorded heartbeats})$$
 (Pollatos, Gramann, & Schandry, 2006a).

Scores close to 1 indicate strong accord between detected and recorded heartbeats without distinguishing between over- and underestimation of heartbeats.

### **3.2.5 Correlational Analyses**

To examine the relationship between interoceptive awareness and trait anxiety, a linear regression analysis was conducted with the interoceptive accuracy during the heart beat detection task as the independent variable and trait anxiety as the dependent variable. To increase the power of the analysis, data from the study described in Chapter 2 was combined with data from the present study. The heartbeat detection trials in the present study were identical in length and instruction as the trials in the previous study. Similarly, both studies use scores on the Spielberger Trait Anxiety Inventory to measure anxiety. Thus, data from both groups of participants would be expected to be comparable.

### **3.2.6 Imaging Analysis**

Images were acquired on a GE MR750 3.0 Tesla Scanner using an eight-channel head coil. Stimuli were presented to participants via computer projection onto a screen in the scanner bore. Respiration and cardiac data were recorded

with a respiration belt and pulse oximeter that remained attached to the participant for the duration of the scan.

The scan session began with a localizer scan and was followed by structural and functional brain scans. The T1-weighted structural images were collected before full-brain coverage functional images were collected. (Functional images were collected with the following parameters: 2 s TR, 27 ms TE, 34 oblique slices with identical prescription to the structural images, 3.8 mm slice thickness (3.8 mm x 3.8 mm x 3.8 mm voxels), and 77 degree flip angle.)

All imaging analyses were carried out using FSL 5.0.6 (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). The first six volumes of the functional run were discarded prior to preprocessing (brain extraction, slice timing correction, motion correction, and spatial smoothing). Images were spatially smoothed using a 4 mm FWHM Gaussian kernel due to the relatively small size of some of the regions of interest (i.e. ventral tegmental area). Each individual's anatomical scan was registered to a Montreal Neurological Institute (MNI) template with the same transformation later being applied to the functional images.

Events of interest were convolved with a double gamma hemodynamic response function for each participant. Following first-level (individual-level) analyses consisting of the following events: HEART trials, COUNT trials, and REST trials, group-level analyses were conducted. The contrasts of interest included HEART > COUNT and HEART > REST. In the group-level analyses,

thirst interoceptive appraisal ratings, heart interoceptive appraisal ratings, and trait anxiety scores were included as covariates of interest.

### **3.3 Results**

#### **3.3.1 Behavioral Results**

##### **3.3.1.1 Correlations between interoceptive accuracy and affective measures**

Increasing interoceptive accuracy (heartbeat detection task accuracy) was associated with decreased trait anxiety (Figure 1), Pearson's  $r(47) = -0.32$ ,  $p = .02$ . (See Figure 3.1.)

##### **3.3.1.2 Correlations between interoceptive accuracy and interoceptive sensibility (self-report of subjective interoceptive experience)**

A linear regression analysis was also performed to examine the relationship between participant's interoceptive sensibility (as measured by the sum of self-reported interoceptive items on the Body Consciousness Questionnaire) and interoceptive accuracy (accuracy on HEART trials). No significant correlation was observed.

#### **3.3.2 Neuroimaging Results**

##### **3.3.2.1 Main effect of interoceptive task**

The main effect of interoceptive task was queried by assessing which brain regions showed increased activations during HEART trials compared to REST or COUNT trials (HEART > REST or HEART > COUNT). Both contrasts yielded activations in regions previously identified to be important in interoceptive

focus such as the left and right insula, anterior cingulate, and somatosensory cortex (refs). The general pattern of activation was very similar between the HEART > REST and HEART > COUNT trials; for simplicity, only the HEART > COUNT activation maps are shown here. **(See Table 3.1, Figure 3.2.)**

### **3.3.3 Neural activations scaling with trait anxiety**

Interoceptive accuracy has previously been linked to trait anxiety (Critchley et al., 2004; de Pascalis et al., 1984; Dunn, Stefanovitch, et al., 2010b; Pollatos et al., 2009; Pollatos, Gramann, & Schandry, 2006b; Richards & Bertram, 2000).

While some studies demonstrate a positive correlation between interoceptive awareness and anxiety, the present study observed a negative correlation between these two traits. To further tease apart the relationship between interoceptive awareness and anxiety, fMRI analyses were conducted to examine the contributions of interoceptive accuracy, interoceptive appraisal, and anxiety on neural activity during an interoceptive task. Specifically, participants' threat appraisal scores for "dry throat" and trait anxiety scores were entered into the General Linear Model as regressors of interest.

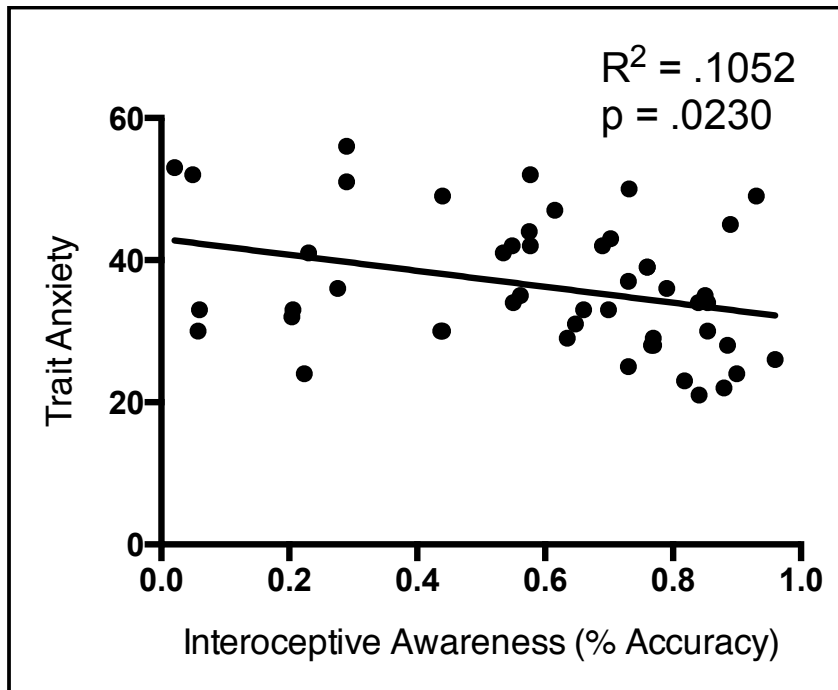
Increasing trait anxiety was associated with increasing activation in the dorsal anterior cingulate cortex/ dorsal medial prefrontal cortex (HEART > REST). **(See Table 3.2, Figure 3.3.)**

### **3.3.4 Neural activations scaling with interoceptive threat appraisal**

Next, to identify regions associated with increased threat appraisal of

interoceptive information, participant's scores of how frightened they were by the sensations of "dry throat" (item from Body Sensations Questionnaire) were entered as separate regressors. Bilateral activations in the vmPFC and ventral striatum scaled with increasingly aversive appraisal of thirst (HEART > COUNT). The vmPFC and ventral striatum are strongly implicated in reward/salience processing indicating a potential role for these regions in evaluating or representing the significance (or affective salience) of interoceptive information.

**(See Table 3.3, Figure 3.4.)**



**Figure 3.1 Interoceptive Awareness Negatively Predicts Anxiety**

**Table 3.1: Main Effect of Interoceptive Task (HEART > COUNT)**

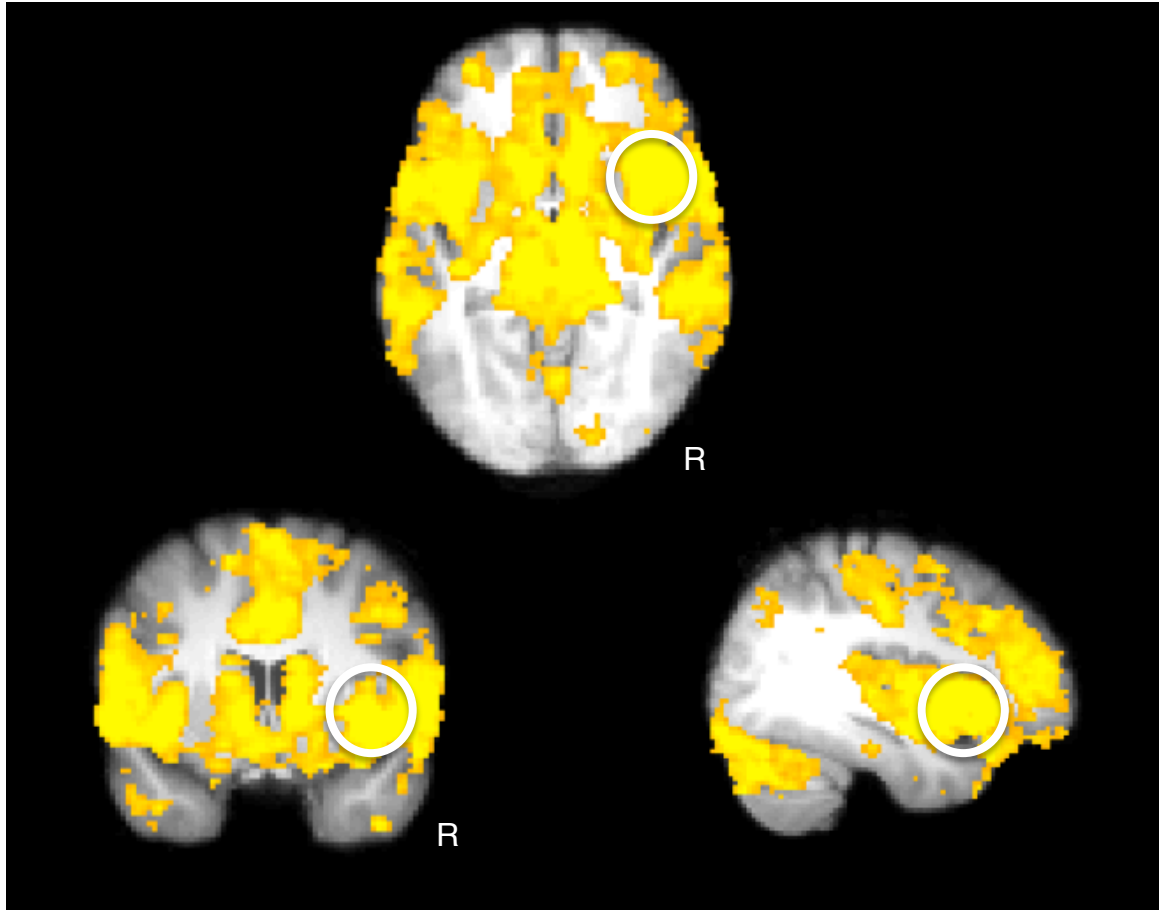
<u>Regions</u>	<u>Hemisphere</u>	<u>MNI Coordinates</u> <u>(x,y,z)</u>	<u>Cluster Extent</u> <u>(voxels)</u>	<u>Z</u>
Right Anterior Insula	R	(38, 8, -4)	97501	6.18
<i>Subpeaks:</i>				
Temporal Pole				
Thalamus				
Left Insula				
<i>Significant Activations in Nonpeak Regions:</i>				
Postcentral Gyrus	L	(-22, 32, 66)		3.13
Postcentral Gyrus	R	(22, 32, 66)		4.51
Anterior Cingulate		(0, 20, 36)		4.93

**Table 3.2: Peak Activations of Neural Regions Positively Correlated with Anxiety**

<u>Regions</u>	<u>Hemisphere</u>	<u>MNI Coordinates</u> <u>(x,y,z)</u>	<u>Cluster Extent</u> <u>(voxels)</u>	<u>Z</u>
Precentral Gyrus	L	(-44, -2, 32)	865	4.27
<i>Subpeaks:</i>				
Precentral Gyrus				
Postcentral Gyrus				
Opercular Cortex				
Postcentral Gyrus	L	(-60, -26, 30)	704	3.98
<i>Subpeaks:</i>				
Supramarginal Gyrus				
Angular Gyrus				
Anterior Cingulate	L	(-6, 12, 40)	619	4.04
<i>Subpeaks:</i>				
Superior Frontal Gyrus				
Middle Frontal Gyrus				

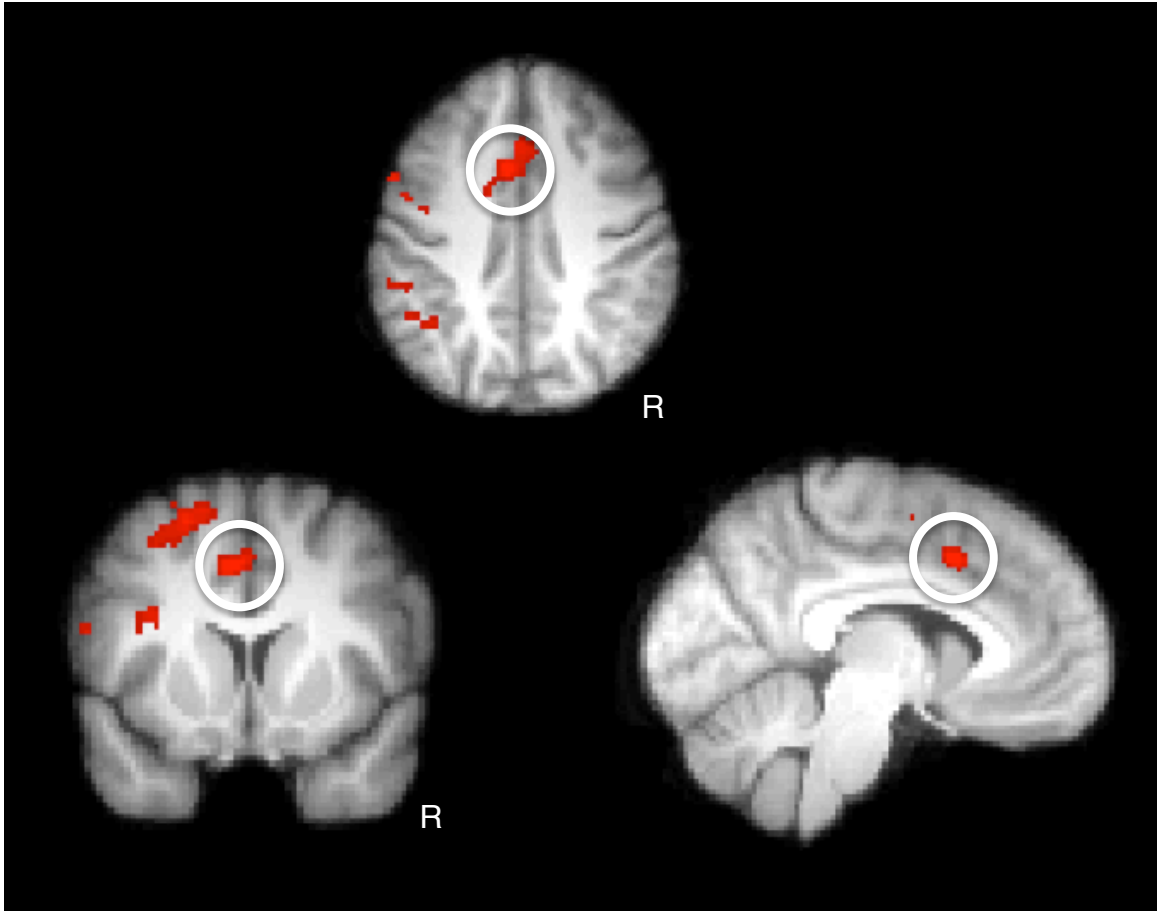
**Table 3.3: Peak Activations of Neural Regions Positively Correlated with Interoceptive Threat Appraisal**

<u>Regions</u>	<u>Hemisphere</u>	<u>MNI Coordinates (x,y,z)</u>	<u>Cluster Extent (voxels)</u>	<u>Z</u>
Frontal Pole	R	(16, 56, -20)	2520	4.23
Thalamus	L	(-4, -30, 8)	883	3.6
Frontal Pole	L	(-34, 44, -2)	666	3.4
<i>Subpeaks:</i>				
Occipital Fusiform Gyrus	L	(-26, -86, -18)	625	3.28
Superior Parietal Lobule	R	(42, -42, 54)	598	3.36
Lateral Occipital Cortex	L	(-38, -60, 52)	320	3.42
Frontal Pole	R	(44, 50, 0)	308	4.25
<i>Significant Activations in Nonpeak Regions:</i>				
Nucleus Accumbens	R	(6, 12, -6)		2.61
Putamen	L	(-16, 10, -6)		3.16
Putmen	R	(16, 10, -8)		2.95
Insula	L	(-34, 20, -4)		3.08



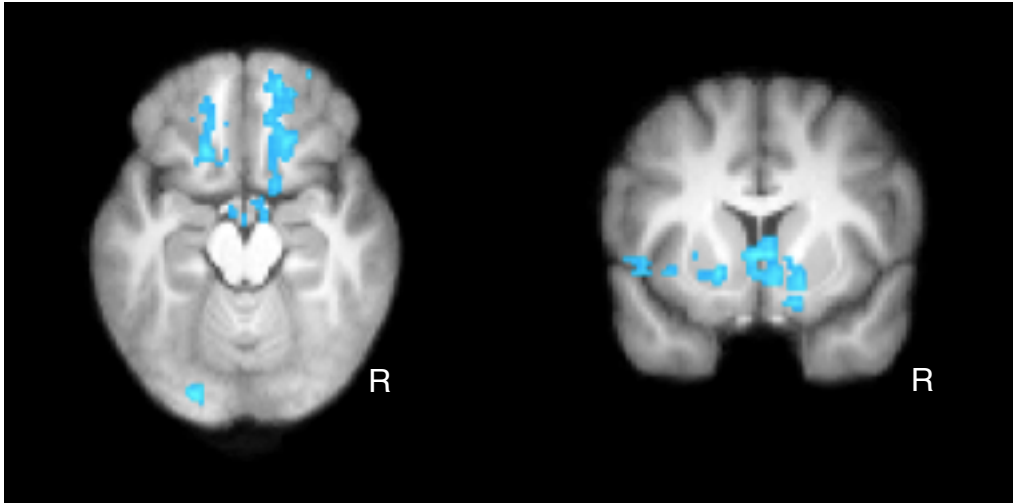
**Figure 3.2: Main Effect of Interoceptive Task**

The pattern of activation closely resembles those reported in previous fMRI studies of interoceptive tasks. Specifically, increased activations were observed bilaterally in the insula, somatosensory cortex, and anterior cingulate. (Activation peak was observed in the right anterior insula, circled above.)  
 (HEART > COUNT during thirst state, Cluster Corrected:  $z = 3.08$ ,  $p = 0.001$ )



**Figure 3.3: Neural Correlates of Trait Anxiety**

A regression analysis identified a region in the anterior cingulate cortex (ACC)/ dorsomedial prefrontal cortex (dmPFC) that scales with increasing trait anxiety. (HEART > COUNT during thirst state, Cluster Corrected:  $z = 2.33$ ,  $p = 0.05$ )



**Figure 3.4: Neural Correlates of Interoceptive Threat Appraisal**

A regression analysis identified regions in the bilateral ventromedial prefrontal cortex (vmPFC) and ventral striatum (VS) that scale with increasing threat appraisal of thirst sensations.

(HEART > REST during thirst state, Cluster Corrected:  $z = 2.33$ ,  $p = 0.05$ )

### **3.4 Discussion**

The present study aimed to further elucidate the relationship between interoceptive accuracy and anxiety. Performance of an interoceptive task (relative to open-eyed rest or performance of an exteroceptive, visual discrimination task), activated regions previously implicated in other interoceptive fMRI studies (insula, anterior cingulate, somatosensory cortex) (Critchley et al., 2004; Pollatos et al., 2007a; Simmons et al., 2012).

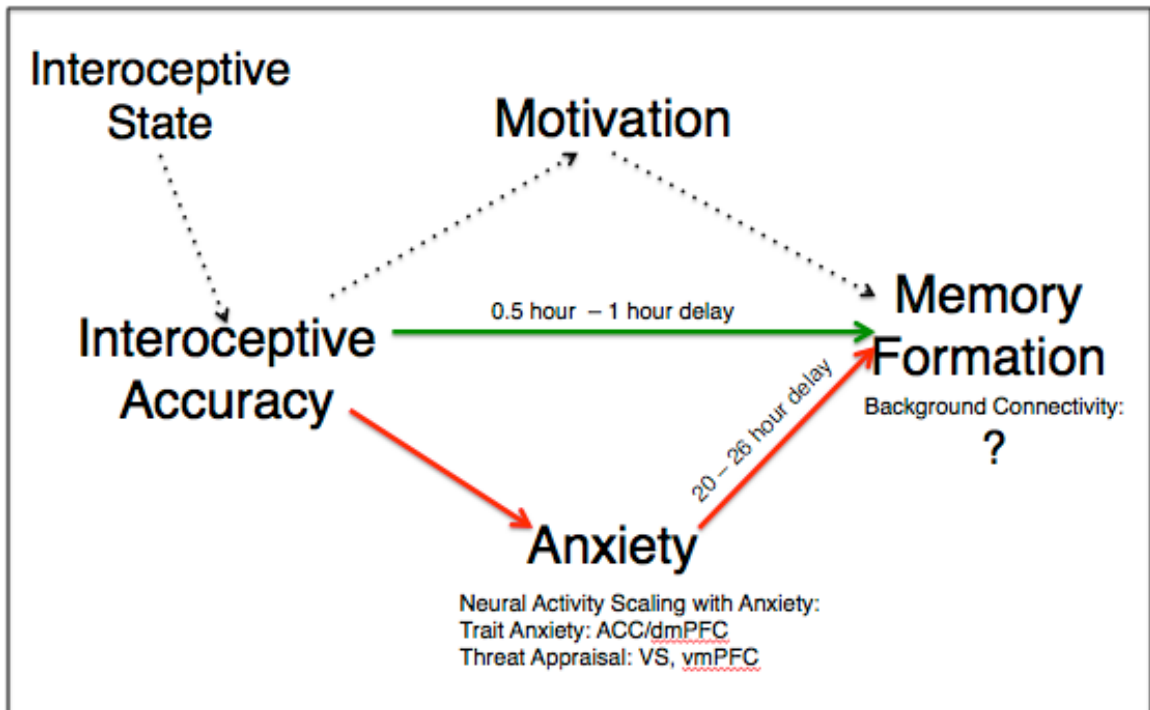
The current study revealed a negative correlation between interoceptive accuracy and trait anxiety. These results contradict the previously reported positive correlation between interoceptive accuracy and trait anxiety (B. M. Herbert et al., 2007; Pollatos, Gramann, & Schandry, 2006b). One interpretation of these divergent findings is that interoceptive accuracy and anxiety may not be invariably linked, but may be modulated by another cognitive process, threat appraisal. Supporting evidence for this hypothesis includes the observation that activation in an anterior cingulate/dmPFC region previously associated with threat appraisal in a meta-analysis of anxiety literature by Kalisch and Gerlicher, scaled with increasing anxiety during the performance of the current interoceptive task (relative to open-eyed rest) (Kalisch & Gerlicher, 2014).

Future work to further elucidate the role of cognitive appraisal in interoceptive influences on affect would be a significant contribution to the field. In addition to the identification of bilateral regions in the vmPFC and ventral

striatum that scale with the threat appraisal of interoceptive information, contributions to this line of research includes examining defensive mobilization (potentiation of startle reflex) following interoceptive threats (interoceptive state resulting from guided hyperventilation) as a function of anxiety sensitivity (Melzig, Michalowski, Holtz, & Hamm, 2008). Importantly, in a related study, both controls and individuals with high anxiety sensitivity expressed defensive mobilization to exteroceptive threat, but only individuals with high anxiety sensitivity expressed defensive mobilization to interoceptive threats (Melzig, Holtz, Michalowski, & Hamm, 2010). Meanwhile Fustos et al. reported enhanced emotion reappraisal in individuals with higher interoceptive accuracy relative to those with lower interoceptive accuracy (Fustos, Gramann, Herbert, & Pollatos, 2013). In summary, these studies are an important beginning to understanding the relationship between anxiety, the appraisal of interoceptive information, and emotion processing.

Finally, no correlation was observed between interoceptive sensibility (self-reports of interoceptive awareness) and heart beat detection accuracy. This finding replicates the lack of association reported by Critchley and colleagues (Critchley et al., 2004) and suggests that self-reports of interoceptive sensibility and heart beat detection accuracy (interoceptive accuracy) may represent different processes. A study by Garfinkel and colleagues found a positive correlation between interoceptive accuracy (accuracy on the Schandry heartbeat

tracking task) and interoceptive sensibility (questionnaire self-report of interoceptive experience) only for individuals with high interoceptive accuracy (Garfinkel et al., 2015). Thus, interoceptive accuracy may be a reflection of the fidelity of the representation of interoceptive information and/or an individual's ability to volitionally access interoceptive information. By contrast, subjective reportings of interoceptive awareness may be a better indicator of the salience of interoceptive information at the point that it reaches consciousness in an individual. This is a potentially important distinction because interoceptive awareness is measured interchangeably as a function of accuracy or subjective ratings throughout the literature. While Garfinkel et al.'s recent publication is a seminal start to disambiguating these processes, further work is needed to understand the relationships between accuracy and subjective ratings.



**Figure 3.5 Conceptual Framework III**

The present study observed a negative predictive relationship between interoceptive accuracy and anxiety (following a thirst manipulation). Bilateral ventromedial prefrontal cortex (vmPFC) and ventral striatum (VS) activity scaled with threat appraisal of interoceptive (thirst) sensations. Additionally, a region in the anterior cingulate cortex/ dorsomedial prefrontal cortex (ACC/dmPFC) was observed that scaled with trait anxiety. Given Chapter 2 identified a negative relationship between anxiety and next-day memory performance the final study (Chapter 4) aims to complete the conceptual framework through the identification of individual differences in background (neural) connectivity that predict memory formation.

## **4. Insula modulation of memory networks**

### ***4.1 Introduction***

The preceding studies of this dissertation have described relationships between interoceptive accuracy, motivation, anxiety and memory formation. The aim of the current study is to identify the neural substrates that support and/or predict these reported relationships.

With respect to the relationship between motivation and memory formation, previous encoding studies reveal important roles for the ventral tegmental area and amygdala (and their functional connectivity with medial temporal lobe structure) in enhancing memory for incentivized stimuli relative to unincentivized (or less incentivized) stimuli (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006a; Dillon et al., 2014; Murty et al., 2012). The interoceptive dimension of the current study points to a potential role for the insula in predicting subsequent memory success as well. A study in non-human primates has observed increased firing in insula neurons to anticipated rewards (Mizuhiki, Richmond, & Shidara, 2012). Furthermore, the insular cortex's anatomical connectivity to the medial temporal lobe makes it an ideal candidate to influence memory processes in this interoceptively-motivated encoding paradigm (Augustine, 1996). Another potential role for the insula in an encoding paradigm under interoceptive challenge is this region's involvement in affective

processing (Gasquoine, 2014; Kirk, Gu, Harvey, Fonagy, & Montague, 2014; Levens & Phelps, 2010; Smith, Henson, & Rugg, 2005). Affect processing in the insula might be predicted to contribute to memory processes indirectly through this region's reciprocal connections to the amygdala, a region known to modulate consolidation processes in the hippocampus (McGaugh, 2015).

The present study seeks to identify individual differences in background connectivity that predict enhanced memory for interoceptive state-relevant rewards in a deprivation state. It is hypothesized that background connectivity between the right insula and medial temporal lobe structures may be more predictive of memory success than amygdala or ventral tegmental area connectivity with the medial temporal lobe.

## **4.2 Methods**

### **4.2.1 Participants**

Twenty-five right-handed participants were scanned while completing a liquid-incentivized encoding task. Participants were from the same cohort described in Chapter 3 and were fluent in English, 18-35 years old, without psychiatric diagnosis and not taking psychoactive medication. Additionally, to be eligible for the study, participants had to be able to fast from all food and drink for three hours prior to the experiment and for the duration of the experiment except as instructed by the experimenter. One of the participants that completed the study was excluded due to high indices of depressive symptoms as measured by

a score exceeding 14 on the Beck Depression Inventory. Additionally, three participants were excluded as the result of technical difficulties. Finally, two participants were excluded from analyses due to low response rates during the scan (i.e. excessive fatigue) and one participant was excluded because of failure to report to their second-day appointment. The final analyses included data from 18 participants.

#### **4.2.2 Materials**

Structural and functional magnetic resonance images were collected using a 3 Tesla Siemens scanner. Stimuli were presented and participant responses (via a 4-button right-handed response box) were recorded using PsychToolbox 3 and Matlab R2010a.

#### **4.2.3 Procedure**

Participants completed a protocol very similar to the one described in Chapter 2 (Figure 2.1). Briefly, participants underwent a thirst manipulation before being instructed and trained on an encoding task. Following the scanning of the encoding task, participants completed self-report survey measures evaluating their anxiety, mood, and arousal during the encoding task, then were given free access to water (surprise satiation) prior to a brief recognition memory test. Following this recognition test, participants received their earned liquid compensation before being asked to complete ancillary survey measures.

Finally, all participants returned the next day to complete a next-day recognition test.

As the current experimental protocol is very similar to a previously described protocol, the current subsection will focus on highlighting differences between the present and previous protocol. (For a more detailed description of the following experimental tasks and measures, please refer to descriptions and figures in Chapter 2.)

#### **4.2.3.1 Thirst Manipulation & Subjective Thirst Ratings**

Our previous study revealed that interactions between interoceptive awareness, motivation, and memory were driven by significant relationships in the thirst condition; thus, participants completed the current fMRI protocol in the thirst state only. All participants were instructed to refrain from consuming any food or drink for three hours prior to the appointment. Following a survey to ensure compliance with the instructed food and drink abstinence, participants were asked to consume 30 grams of Snyder's Pretzel Rods (290 mg sodium). Participants then continued with induced thirst until the surprise satiation. Again, to limit the effect of the manipulation to encoding, abstinence and the thirst manipulation only occurred on Day 1 of the experiment.

#### **4.2.3.2 Training and Incentive Structure**

Following the thirst manipulation, participants were instructed on the structure and timeline of the experiment. Participants were informed that they could earn

liquid rewards (juice, caffeine-free soda, or water) for successfully recognizing pictures presented during the encoding task at a recognition memory test occurring approximately 90 minutes later in the appointment. As in the previous (Chapter 2 protocol), participants were told that they would be required to complete 30 – 45 minutes of additional tasks (surveys) following the memory test to further motivate participants to encode scenes for the liquid rewards.

Departing from the previous protocol, participants in this fMRI experiment were informed that they would earn points for successfully recognizing images at a memory test later in the appointment (as well as a penalty for false alarms). Participants were told that if they earned sufficient points, they would be rewarded with their choice of a bottle of soda, juice, or water. Unbeknownst to the participant, this threshold was set at negative infinity, so that all participants would earn the liquid reward (to control for differences in mood that might arise based on receipt of different amounts of reward.) This points system decreased the transparency of the contingency between subject memory performance and liquid payout, which allowed for a very brief, same-day recognition test (consisting of only nine trials) to determine liquid reward payout.

#### **4.2.3.3 Incentivized Encoding Task**

Participants were asked to remember 150 stimuli (indoor and outdoor scenes) across five runs of this motivated memory paradigm. Participants earned points towards a performance threshold for successfully recognizing “rewarded scenes”,

but did not receive any points towards the threshold for recognizing “unrewarded scenes” that had been presented during the Incentivized Encoding Task.

Each trial commenced with a 1-s cue indicating the trial type (rewarded or unrewarded). Following the cue, a fixation crosshair was presented for a jittered epoch ranging from 2.5 - 6.5 s, after which the scene to be remembered appeared for two seconds. To constrain the time for encoding to the two seconds the stimulus was presented, participants were then asked to indicate the direction of three sequentially-presented distractor arrows (0.667 s/arrow) using a four-button response box.

#### **4.2.3.4 Retrieval Task**

The current protocol included a token same-day memory test (administered approximately 30 minutes following the completion of the encoding task) and a next-day memory test (taken 20 – 26 hours following the start of the encoding appointment). Importantly, only the next-day memory test was of experimental interest; the token same-day memory test was included to motivate participants to encode scenes to earn a liquid reward. To enhance motivation to encode scenes during the task, participants would need to believe their memory performance could help them earn a bottle of juice on a timescale that would sate their deprivation. For example, if a participant is thirsty now, a bottle of juice in 30 minutes would be useful, but a can of juice delivered tomorrow (if they could obtain liquid before then on their own) would be useless. Since the same-day

memory test was merely symbolic, only three rewarded stimuli, three unrewarded scenes, and three novel scenes were included in the same-day recognition test and the remaining 144 stimuli were presented during the next-day recognition test. As in the previous protocol, participants were asked to indicate whether each scene presented during the recognition test was “New” or “Old” before being asked to gauge their confidence (“Sure”, “Pretty Sure”, “Guessing”) of their “New”/“Old” judgement.

#### **4.2.3.5 Reward Payout**

All participants received a bottle of their choice of drink following the symbolic same-day and next-day memory tasks. Participants earned points towards a threshold for receiving a drink reward for recognizing rewarded scenes, and were penalized points for incorrectly identifying novel retrieval stimuli as “Old” (i.e. false alarms). It is reiterated here that the performance threshold was set at negative infinity (participants were not made aware of the exact value of the performance threshold), so that all participants received the reward.

#### **4.2.3.6 Subjective Thirst and Hunger Ratings**

Participants were instructed to rate their thirst level at eight different time points in the experiment. To indicate their rating, participants completed a 7-point Likert scale ranging from 1 (Not thirsty at all) to 7 (Extremely thirsty) in paper and digital formats. These subjective thirst ratings were recorded at the

start of the experiment, immediately following the thirst manipulation, after each of the five encoding runs, and immediately after the surprise satiation.

Participants were instructed to rate their hunger at two different time points using an identical Likert scale at the start of the experiment and then again following the surprise satiation. Participants' subjective thirst was queried at more time points than subjective hunger to encourage reflection on the thirst (or sated) state and further motivate performance on the encoding task.

#### **4.2.3.7 Ancillary Measures**

Additionally, participants completed several survey measures of motivation-related individual differences to prolong the experiment past the end of the memory test (to imbue the rewarded scenes with greater value during encoding). These surveys include the STAI-Trait (Spielberger et al., 1970), Tridimensional Personality Questionnaire (TPQ) (Cloninger et al., 1991), Motivational Trait Questionnaire (MTQ) (Kanfer & Heggstad, 2000), Behavioral Inhibition and Activation Scales (BIS/BAS) (Carver & White, 1994), Temporal Experience of Pleasure Scale (TEPS) (D. E. Gard, Gard, Kring, & John, 2006b).

#### **4.2.4 Behavioral Data Analysis**

All trials for which a participant indicated “pretty sure” or “sure” confidence during retrieval were included in the analyses. Hit rates for rewarded and unrewarded scenes were calculated by dividing the number of “Old” rewarded scenes correctly identified as “Old” with medium and high confidence during

retrieval by the total number of “Old” rewarded scenes presented. (The same procedure was used to calculate hit rate for unrewarded scenes.) A participant’s false alarm rate (for medium and high confidence levels combined) was calculated by dividing the number of “New” items incorrectly classified as “Old” with medium and high confidence during retrieval by the total number of “New” items presented during the memory test. Memory was then corrected by subtracting a participant’s false alarm rate from his hit rate.

#### **4.2.5 Imaging Analysis**

Image acquisition and preprocessing procedures were identical to those described in section 3.2.6. The main effect of reward modeled during the cue was voxel corrected at the liberal threshold  $p = 0.05$ .

##### **4.2.5.1 Correlation Analyses between Anxiety, Anterior Cingulate Activation, and Memory Performance**

A negative relationship between anxiety and rewarded memory benefit was reported in Chapter 2 and was followed by the identification of an ACC/dmPFC region whose activity scaled with individual differences in anxiety during interoceptive task performance. Linear regression analyses were carried out to see if data from the present study would replicate the negative correlation between trait anxiety and rewarded memory benefit observed previously. Additionally, a linear regression analysis was performed to test for a relationship between the mean activation of the aforementioned ACC/dmPFC region to the

cue (independent of cue value) and rewarded memory benefit.

#### **4.2.5.2 Background Connectivity Analyses**

To investigate the relationship between connectivity in motivation and memory-related brain regions and memory performance, physio-denoised time series were extracted for the following Harvard-Oxford subcortical atlas-defined regions: left amygdala, right amygdala, left hippocampus, right hippocampus, left parahippocampal gyrus, right parahippocampal gyrus. Time series were also extracted for the left and right ventral tegmental areas using a probabilistic mask (Murty et al., 2014). Background connectivity between ipsilateral amygdala and parahippocampal gyrus, ipsilateral VTA and hippocampus, ipsilateral insula and hippocampus, and ipsilateral insula and parahippocampal gyrus was then correlated with high confidence memory for rewarded stimuli.

### **4.3 Results**

#### **4.3.1 Behavioral Results**

##### **4.3.1.1 Memory Performance**

A paired t-test revealed better memory performance for scenes that were rewarded relative to unrewarded scenes (rewarded scenes:  $M = 0.25$ ,  $SD = 0.15$ , unrewarded scenes:  $M = 0.14$ ,  $SD = 0.14$ ,  $t(18) = 4.30$   $p < .001$ , two-tailed.) The results observed here are consistent with the pattern of increased memory for rewarded scenes reported in Chapter 2.

## **4.3.2 Imaging Results**

### **4.3.2.1 Main effect of reward**

The main effect of reward was queried by assessing which brain regions showed increased activations during Rewarded trials vs. Unrewarded trials. The Rewarded > Unrewarded contrast yielded activations in left and right anterior cingulate, left ventral striatum, right caudate and were similar to previously reported regions in an incentivized encoding paradigm (Murty et al., 2012). Additionally, increased left insula activation was observed to the reward cue in this interoceptive-encoding paradigm.

### **4.3.2.2 ROI Analysis**

The prior identification of a dmPFC/ACC region associated with increasing trait anxiety during an interoceptive task implied that the connectivity of regions associated with anxiety may also play an important role during encoding. Here, it was hypothesized that mean activation in this region (modeled during the cue) scaling with trait anxiety would negative correlate with rewarded memory benefit (memory for rewarded scenes – memory for unrewarded scenes). No significant correlations were observed between activation in this ROI and memory performance.

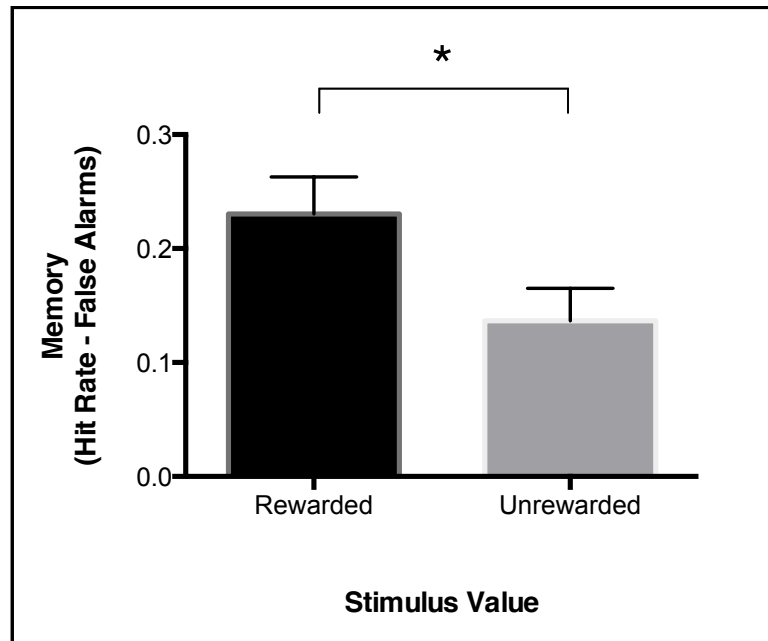
### **4.3.2.3 Background Connectivity**

Previous incentivized encoding studies have observed that connectivity between the amygdala and parahippocampus (Murty et al., 2012) or connectivity

between the ventral tegmental area and hippocampus (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006a) predict successful memory performance for rewarded items. Importantly, Murty et al. demonstrated that memory predictive connectivity depended on the valence of encoding incentives. Encoding success for monetary rewards was associated with increased VTA-hippocampus connectivity, whereas encoding success to avoid electrical shock was associated with increased amygdala-parahippocampus connectivity. The incentive structure in the present paradigm was more ambiguous in valence than the previously cited studies; mainly, the incentive structure might be experienced as the opportunity to earn appetitive rewards or the opportunity to avoid an aversive thirst state. Thus, VTA-hippocampal and amygdala-parahippocampal background connectivity were both queried as potential predictors of memory success for rewards. Amygdala-parahippocampal connectivity was not observed to correlate with memory performance for rewarded or unrewarded scenes. However, a negative correlation between left VTA-left hippocampal connectivity and rewarded memory performance was observed, Pearson's  $r(16) = 0.54$ ,  $p = .02$ . (No significant correlations between R VTA – R Hippocampal connectivity and rewarded memory were observed.)

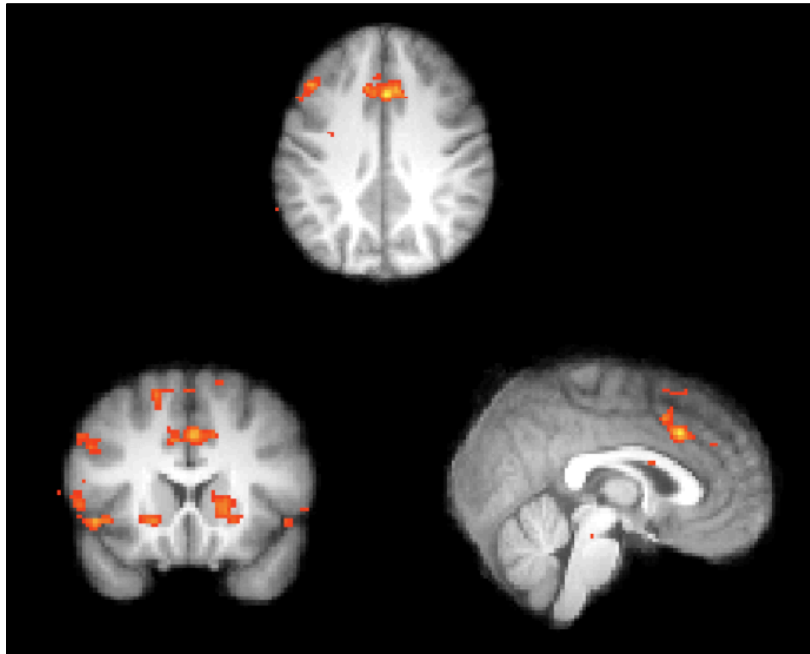
Additionally, it was expected that connectivity between regions involved in interoceptive processing and the medial temporal lobe might also be important in this interoceptive state-induction encoding paradigm. Thus, insula-hippocampal

and insula-parahippocampal connectivity measures were also examined. Correlation analyses found no relationship between insula-hippocampal connectivity strength and memory performance for rewarded or unrewarded scenes. However, right insula-right parahippocampal background connectivity and memory for rewarded items were negatively correlated, Pearson's  $r(16) = 0.55$ ,  $p = .02$ . Also, there was a trending negative correlation between left insula–left parahippocampal connectivity and rewarded memory performance: Pearson's  $r(16) = 0.54$ ,  $p = .087$ .



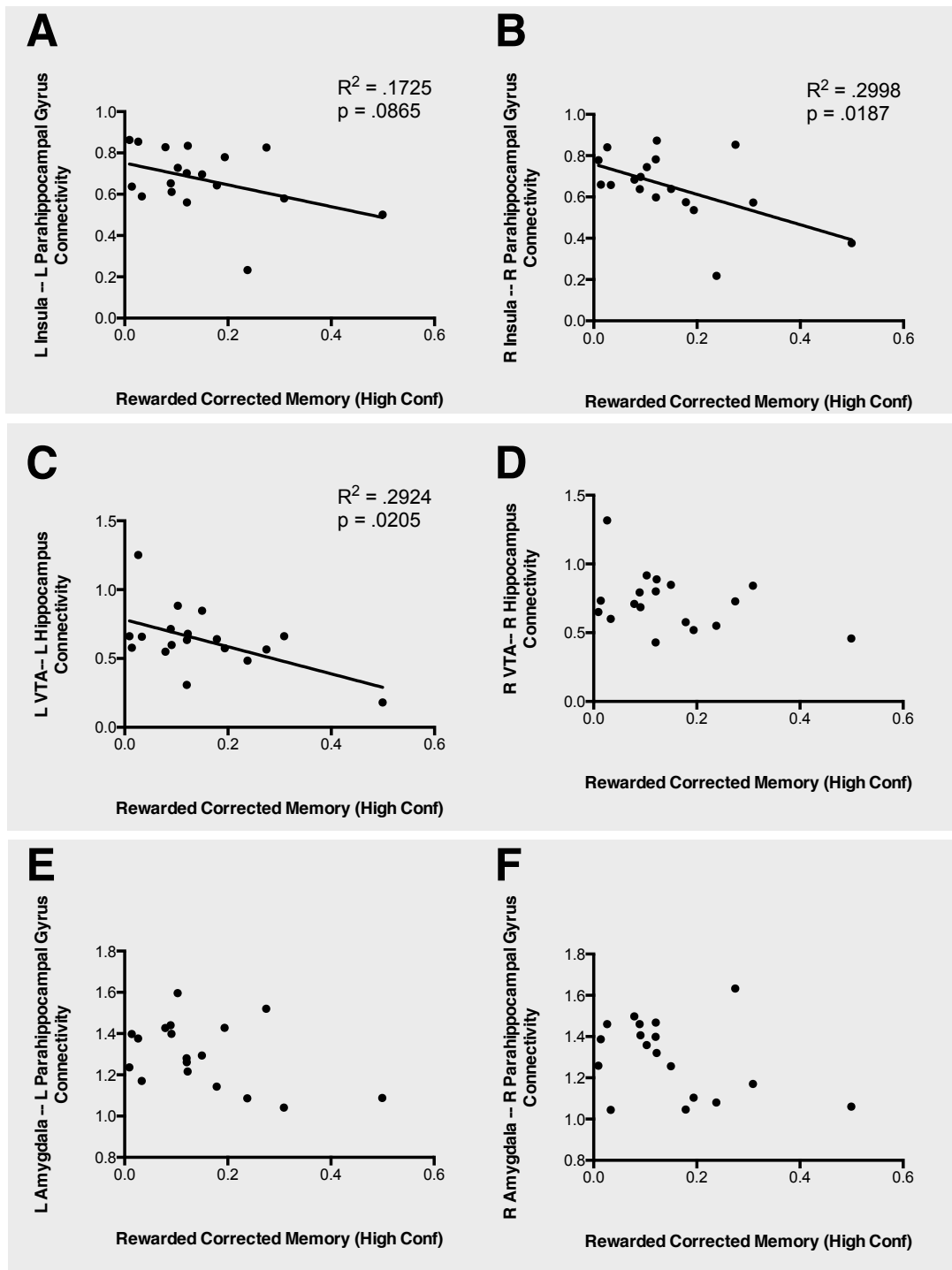
**Figure 4.1: Reward Enhances Memory**

Replicating the results presented in Figure 2.8, a main effect of reward was observed on memory performance (Memory by Stimulus Value,  $p < 0.05$ ).



**Figure 4.2: Main Effect of Reward Value**

Increased activations in the bilateral anterior cingulate, right caudate, and left ventral striatum were observed for “reward” cues compared to “no reward” cues. (Rewarded > Unrewarded at Cue, cluster corrected  $z=2.33$ ,  $p = 0.05$ )



**Figure 4.3: Insula – Parahippocampal and Ventral Tegmental Area - Hippocampal Connectivity Negatively Predicts Rewarded Memory**

Individual differences in background connectivity predict memory performance at a 20-26 hour delay. Background connectivity between the right insula and right parahippocampal gyrus was associated with decreased memory for rewarded scenes. A similar trend was observed for background connectivity between the left insula and left parahippocampal gyrus. Additionally, ventral tegmental area-hippocampal connectivity in the left hemisphere negatively predicted memory for rewarded scenes. Finally, no significant relationships were observed between amygdala-parahippocampal background connectivity and rewarded memory.  
(Regression lines drawn for significant or trending relationships.)

#### **4.4 Discussion**

The present study examined the neural correlates predicting enhanced memory for interoceptive state-relevant vs. irrelevant stimuli (i.e. stimuli rewarded with liquid relative to unrewarded stimuli) in an interoceptive-encoding paradigm. Replicating findings in Chapter 2, memory for rewarded scenes was higher than unrewarded scenes at a next-day recognition test. The negative correlation between trait anxiety and memory benefit for reward was not replicated in the current study sample (18 participants). However, the previously reported relationship held significant when data from Chapter 2 were combined with the current data set.

Despite this relationship, activation in an ACC/dmPFC ROI defined by neural correlates of anxiety during an interoceptive task (Chapter 3) was not significantly correlated with rewarded memory benefit. It is possible that the present data set was insufficiently powered to observe the expected negative correlation between activation in this region and rewarded memory benefit.

Increased activation was observed in reward neurocircuitry (left insula, left nucleus accumbens, right caudate, and bilateral anterior cingulate) for a contrast of rewarded compared to unrewarded trials modeled at the cue. The caudate is a reward-sensitive region previously implicated in delay discounting; more specifically, increasing caudate volume and increasing caudate activation is associated with decreased delay discounting (Benningfield et al., 2014; Szamosi,

Nagy, & Keri, 2013). Successful performance of the current interoceptive encoding paradigm requires reward processing for liquid rewards that will be received at a 30 minute – 26 hour delay. In the context of cues indicating potential to earn a reward for remembering an upcoming scene versus absence of potential to earn a reward, increased insular activation may reflect reward anticipatory processes previously reported (Cho et al., 2013; Mizuhiki et al., 2012).

Increased background connectivity between the left ventral tegmental area and left hippocampus predicted decreased memory for rewarded stimuli. This finding contradicts previous findings of a study by Adcock et al., which observed a positive correlation between VTA-hippocampal connectivity and memory for rewarded stimuli (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006a). Additionally, connectivity between the amygdala and parahippocampal gyrus did not predict subsequent memory for rewarded scenes. These relationships have been previously reported in encoding paradigms where pleasant and aversive incentives (monetary gains and shock avoidance, respectively) were utilized to motivate encoding (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006c; Murty et al., 2012; Murty, LaBar, Hamilton, & Adcock, 2011). Due to the more ambiguous incentive valence of the present paradigm, VTA-hippocampal and amygdala-parahippocampal connectivity were both queried for potential predictive relationships with rewarded memory. The

absence of a significant relationship between amygdala-parahippocampal background connectivity and rewarded memory may suggest the absence of stress hormone amygdala activation, one mechanism through which the amygdala is thought to modulate memory consolidation (McGaugh, 2015). One important limitation in this interpretation are that Adcock et al. and Murty et al. findings were the result of PPI analyses, whereas the present study employed background connectivity analyses. Another important limitation is that stress hormone levels were not measured in the present paradigm due to constraints of the thirst manipulation. (Salivary cortisol measurement protocol requires participants to rinse their mouth prior to saliva collection to avoid contamination of the sample with food. As abstinence from all liquid followed by the consumption of salty, chalky-textured food was critical to increasing participant's subjective experience of thirst, the current paradigm was not amenable to collecting a saliva sample.) Future studies should employ a similar paradigm, perhaps with a hunger paradigm instead of a thirst paradigm, as not to preclude salivary cortisol collection.

Background connectivity between the right insula and the right parahippocampal gyrus was also negatively correlated with subsequent memory for rewarded scenes. Interestingly, this relationship between insula connectivity and subsequent memory was exclusively observed for rewarded scenes. Insula activation during encoding has been previously associated with memory

detriments (Daselaar, Prince, & Cabeza, 2004; Xie et al., 2012). However, to the authors' knowledge, this is the first report that connectivity of the right insula, a region whose anterior portion supports conscious interoceptive representations, predicts episodic memory of interoceptively-relevant information. These findings underline the need to carry out additional studies to better understand interoceptive contributions to episodic memory (see Chapter 5).

## 5. General Discussion

The present set of experiments investigated the interoceptive contributions to motivational and affective modulators of memory formation. The initial experiment (outlined in Chapter 2) examined interoceptive contributions to motivation and memory formation. This study revealed a reliable effect of interoceptive state on motivation as revealed by increased consumption of water in a thirsty interoceptive state compared to a liquid-sated interoceptive state. Additionally, subjective ratings of experienced thirst level were higher at all timepoints following the thirst manipulation (save the timepoint following an *ad libitum* satiation) in the thirst condition than the sated condition. Taken together, these observations point to an enhanced motivational state for liquid rewards that was dependent on interoceptive condition.

Investigating the effect of the interoceptively-enhanced motivational state on memory, individual differences in interoceptive accuracy and anxiety were observed to be important predictors. Interoceptive accuracy was observed to predict memory performance for relevant (rewarded) compared to irrelevant (unrewarded) information at a short delay, indicating a main modulatory effect of interoceptive accuracy on encoding processes. Conversely, individual differences in anxiety negatively predicted memory for relevant compared to irrelevant information between 20 – 26 hours later suggesting a modulatory role of anxiety on consolidation. In conclusion, individual differences in trait measures

of interoceptive accuracy and anxiety, two measures that have themselves been previously linked to one another, differentially modulated memory processes (encoding and consolidation, respectively).

Chapter 3 followed-up on this line of inquiry by interrogating the relationship between these two trait measures demonstrated to differentially modulate encoding and consolidation processes. A negative predictive relationship was observed between the two variables such that individuals with higher interoceptive accuracy reported decreased trait anxiety. This result contradicts previous work by Pollatos and colleagues (Pollatos et al., 2007a), but is consistent with other studies and models of interoceptive processes in anxiety (Paulus & Stein, 2006). Briefly, it is proposed that the suite of behavioral expressions and cognitions attributed to anxiety disorders is purported to be the result of the body's compensatory mechanisms for noisy interoceptive signaling (Paulus, 2013; Paulus & Stein, 2006; 2010). Higher interoceptive accuracy may be a proxy measure for the fidelity of interoceptive signaling as reporting accurate cardiac interoceptive information would require sufficiently reliable/accurate interoceptive signals to reach consciousness. (This predictive coding approach to interoceptive processing in anxiety will be discussed in further detail in section 5.2.) Finally, a region in the anterior cingulate/dmPFC was observed to predict anxiety during the performance of an interoceptive task. This region has been implicated in cognitive processes associated with heightened anxiety such as

threat appraisal, suggesting that cognitive appraisal of interoceptive information may be an important factor in the relationship between anxiety and interoceptive accuracy.

Chapter 4 aimed to elucidate the neural underpinnings of interoceptive contributions to motivation and affective processes during memory formation. Reward trials (relative to unrewarded encoding trials) were associated with increased activation in reward processing regions such as the dorsal and ventral striatum. This is consistent with the literature supporting a role of the striatum in reward processing (DELGADO, 2007). Additionally, increased activation in interoceptive regions (left insula and bilateral anterior cingulate) were also observed.

While no relationship between mean activation in a anterior cingulate ROI (identified in Chapter 3) with rewarded memory benefit was observed, predictive relationships between rewarded memory and connectivity between medial temporal lobe regions and regions implicated in interoceptive, affective, and motivation processes were identified. Background connectivity between the left ventral tegmental area and left hippocampus negatively predicted memory for rewarded information. Similarly, increased insula connectivity with the parahippocampus predicted decreased subsequent memory for rewards.

In this final chapter, results from Chapters 2-4 will be integrated and interpreted in the context of popular motivated memory and interoceptive

predictive coding models. Additionally, practical applications of the work as well as future directions for the research will be discussed.

### ***5.1 Integration of interoceptive processing into current memory models***

Future studies should investigate mechanisms through which the insula may modulate memory. Here, a negative relationship between insula-parahippocampal background connectivity and rewarded memory performance was observed. Previous studies reveal negative associations between insula activation during encoding and subsequent memory (Daselaar et al., 2004). However, it is yet unknown whether the observed relationship between insula activity and memory success reflects modulation of encoding or consolidation processes. One possible mechanism through which insular activation might be expected to modulate memory processes would be this region's involvement in stress hormone cascades. There is emerging evidence in rodent studies that the insula cortex may mediate glucocorticoid effects on consolidation. In a rodent study, glucocorticoid administration immediately following an episodic encoding experience (foot shock training) reduced activity in insular neurons and enhanced subsequent retention (Wichmann, Fornari, & Roozendaal, 2012). The current results are consistent with those previously reported in that increased insula activation was observed in rewarded compared to unrewarded encoding trials

and decreased insula-parahippocampal connectivity was associated with memory success for these rewarded trials.

## **5.2 Future Directions**

A movement to consider interoceptive contributions to cognition in the context of predictive coding models has been gaining increasing traction (Anil K Seth, 2011; L. F. Barrett & Simmons, 2015; Sel, 2014; Seth, 2013). The cognitive neuroscience field is increasingly discussing potential roles for interoceptive prediction errors in cognition, as discussed below. Although, the evidence in support of interoceptive predictive coding models is indirect at present, these models propose an intriguing mechanism for the integration of interoceptive and exteroceptive information.

Interoceptive predictive coding models counter tacit assumptions of unidirectional processing of interoceptive information whereby interoceptive processing is exclusively the result of bottom-up signaling of physiological changes in the body. Predictive coding models such as the newly-minted Embodied Predictive Interoception Coding (EPIC) model, argue that top-down predictions regarding interoceptive state are integrated with bottom-up interoceptive actuality signals to produce a prediction error that can then be fed into subsequent cognitive processes (L. F. Barrett & Simmons, 2015).

Predictive coding models conceptualize the brain as an “active inference generator” employing Bayesian active inference principles to make predictions

about interoceptive and exteroceptive input. The goal of this “inference generator,” then is to minimize prediction errors computed as the difference between predicted interoceptive input and actual interoceptive input (L. F. Barrett & Simmons, 2015). Importantly, reduction of these prediction errors can take the form of 1) updating the prediction (by propagating prediction errors back to top-down prediction-generating systems), 2) acting to produce predicted interoceptive signals, or 3) altering attentional weights or sampling of interoceptive input (L. F. Barrett & Simmons, 2015).

The system’s compensatory efforts to minimize prediction errors may explain symptoms of interoceptively-linked health conditions like anxiety disorders. Specifically, hypothesized noisy amplification of afferent interoceptive signals produces larger prediction errors, which lead to compensatory cognition and behaviors to produce interoceptive signals that approach signal predictions (Paulus, 2013). For example, worrying and catastrophizing tendencies in anxious individuals may actually be top-down compensatory cognitions to minimize interoceptive prediction errors.

The observed negative correlation between interoceptive accuracy and trait anxiety observed in the current dissertation (see Chapter 3) is readily interpreted in a predictive coding context. High interoceptive accuracy is presumably a measure of the fidelity with which bottom-up interoceptive signals are incorporated into conscious experience; thus, under this model, individuals

with high interoceptive accuracy would be expected to have higher fidelity in these bottom-up signals and would be less susceptible to behaviors and cognition to compensate for a noisier signal.

Predictive coding models may also be beneficial in interpreting the association between high interoceptive accuracy and rewarded memory benefit at an immediate recognition test (Chapter 2). In high interoceptive accuracy individuals, computed prediction errors would be predicted to precisely motivate actions to minimize this prediction error (i.e. encode scenes to earn liquid rewards selectively in a thirsty state). This hypothesis is supported by a study by Herbert et al., where high interoceptive accuracy was associated with intuitive eating and decreased body mass index (reflecting appropriate actions to minimize prediction error between predicted hunger and actual hunger) (B. M. Herbert et al., 2013).

Much groundwork remains before interoceptive predictive codings can be validated empirically, thus knowledge regarding the neural architecture supporting proposed interoceptive predictive coding is limited to hypothesized roles of the anterior insular cortex (in the integration of interoceptive and exteroceptive signals to compute interoceptive prediction errors) (Seth, 2013) and agranular visceromotor cortices (L. F. Barrett & Simmons, 2015) in these processes. Once significant progress has been made with validating or rejecting the significance of interoceptive prediction errors, potential roles for prediction

errors in downstream cognitive processes, such as encoding, should be investigated.

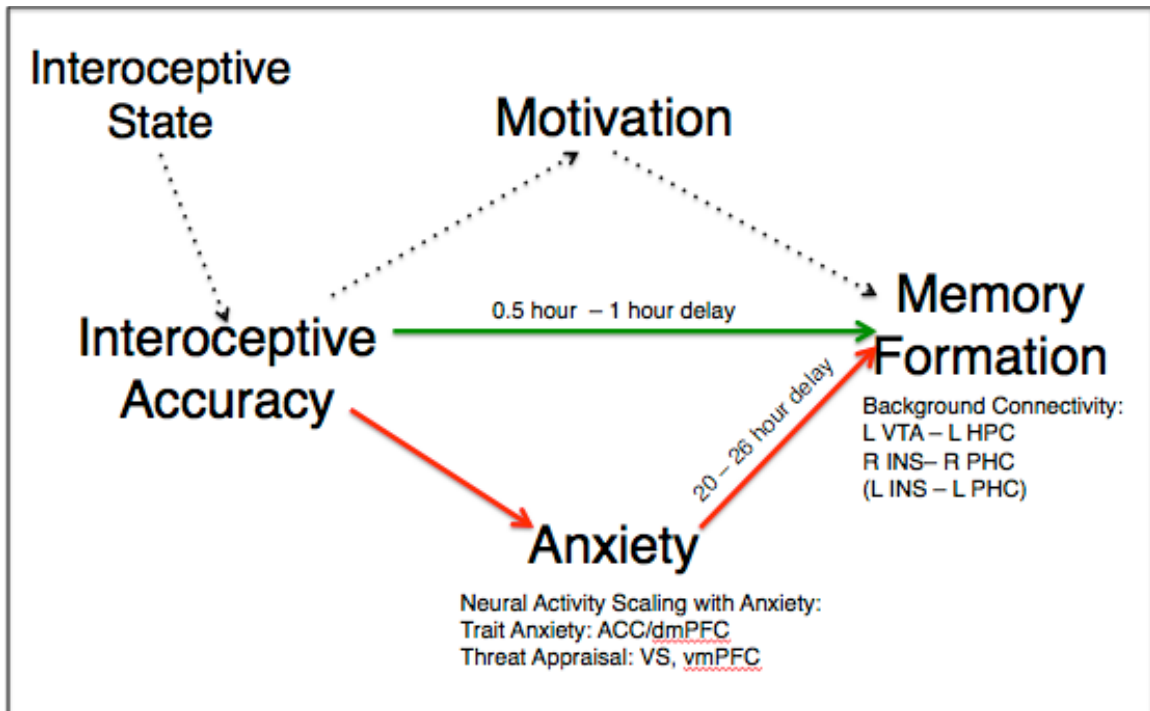
### ***5.3 Closing Thoughts***

The findings presented here suggest a constellation of relationships between interoceptive processing, anxiety, encoding, and consolidation. Modulation of encoding by interoceptive processes is more apparent at short delays (30 minutes) whereas indirect modulation of consolidation via interoceptive processes that interact with anxiety appears at longer delays (20 – 26 hours).

The current description of interoceptive contributions to affective and motivational modulation of episodic memory formation has immediate applications in interoceptive exposure therapy. Interoceptive exposure therapy is a technique employed under the umbrella of cognitive based therapies that has been used in the treatment of patients with anxiety disorders (Dixon, Kemp, Farrell, Blakey, & Deacon, 2015). The aim of interoceptive exposure therapy is to evoke the interoceptive symptoms associated with anxiety disorder so that maladaptive associations can be extinguished and presumably more adaptive associations may be formed (i.e. extinguishing the maladaptive association between hyperventilation as a precursor to a panic episode). Thus, one could state the goal of interoceptive exposure as the formation of durable new memories (and associations) with the conscious experience of interoceptive

stimuli. The catch-22 is that interoceptive exposure is utilized to treat patients with high anxiety and high anxiety is associated with decreased long-term memory for interoceptively-relevant information. Thus, findings from the present study suggest that this type of learning may be the most challenging for individuals who need it the most.

Additionally, the work presented in the current dissertation points to the increased need to understand the contributions of interoceptive information in episodic memory formation. Interoceptive processing abilities have been shown to color the experience of emotionally evocative stimuli (Dunn, Galton, et al., 2010a; Garfinkel & Critchley, 2013; Mallorquí-Bagué et al., 2014; Terasawa, Moriguchi, Tochizawa, & Umeda, 2014; Uddin, Kinnison, Pessoa, & Anderson, 2014; Werner, Mannhart, Reyes Del Paso, & Duschek, 2014) that have been demonstrated to influence episodic memory. Furthermore, the results here suggest that interoceptive processing (accuracy) may directly affect encoding of interoceptively-relevant information (Chapter 2). Future studies to examine how interoceptive information is represented in memory and how these representations' are associated with features of external stimuli in memory will provide a deeper richness to how we understand memory overall.



**Figure 5.1 Conceptual Framework IV: Final Conclusions**

Very high or very low interoceptive accuracy predicts enhanced memory for information that is relevant to one’s interoceptive state. Low interoceptive accuracy is associated with increased anxiety, which is associated with increased activation in the ACC/dmPFC during an interoceptive task and negatively predicts rewarded memory at ~24 hours. Rewarded memory (tested the next day) is negatively predicted by individual differences in background connectivity between the right insula and right parahippocampal gyrus (this relationship was trending in the left hemisphere), and the left ventral tegmental area and left hippocampus.

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## **Biography**

Courtnea Rainey was born in Durham, NC in the same hospital where she would eventually complete her dissertation research (Duke University). Courtnea Rainey holds a B.S. in Biochemistry from Spelman College (2005) and a M.A. in Psychology from Duke University (2012). Courtnea is the recipient of a National Science Foundation Graduate Research Fellowship (2010 – 2015), a Bass Instructional Fellowship (Duke University, 2014), a James B. Duke Fellowship (Duke University, 2009 - 2013), a University Scholars Fellowship (Duke University, 2009 - 2010) and a Dean's Fellowship (Duke University, 2009 - 2013).