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Examination of the limbic system's role in emotional experience using a human lesion model

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EXAMINATION OF THE LIMBIC SYSTEM'S ROLE IN EMOTIONAL EXPERIENCE USING A HUMAN LESION MODEL

by

Justin Stanich Feinstein

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
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ABSTRACT

The current prevailing notion is that the limbic system is inextricably linked to emotion, and indeed, most textbooks, research articles, and scientific lectures tout the limbic system as being the predominant purveyor of emotional processing in the brain. Yet, more than a half-century of research has produced surprisingly little evidence in support of such a notion, suggesting that the concept of an emotional limbic system is overly simplistic. The primary objective of this thesis is to determine whether the limbic system is necessary for one aspect of emotion, namely, its conscious experience. Neurological patients with focal damage to different regions of the limbic system – including the hippocampus, amygdala, insular cortex, anterior cingulate cortex (ACC), and ventromedial prefrontal cortex (vmPFC) – underwent multiple emotion induction procedures using affectively-laden film clips. For comparison, two other groups of participants were tested: patients with brain damage outside of the limbic system and healthy participants without brain damage. Two emotion inductions aimed at eliciting diffuse emotional states of positive or negative affect, and five emotion inductions aimed at eliciting specific emotional states of happiness, sadness, anger, disgust, or fear. Immediately following the end of each film clip, the return of emotion back to its baseline state was tracked over a three minute "emotion recovery" time period. The results of the experiment revealed three main findings. First, limbic system damage did not disrupt the experience of emotion during the film clips, with patients reporting high levels of the induced target emotion at a magnitude comparable to both comparison groups. Second, patients with bilateral damage circumscribed to either the hippocampus or the vmPFC demonstrated an abnormally slow rate of emotion recovery, indicating that these limbic regions are important for the successful downregulation of emotion. Third, patients with large bilateral lesions affecting multiple limbic structures (including the medial temporal lobes and insular cortices) showed an abnormally rapid rate of emotion

recovery, with the induced emotion returning to baseline levels within 60 seconds following the end of each film. Based on these findings, it is concluded that the limbic system is not necessary for the experience of emotion, but is necessary for sustaining and regulating that experience after the emotion-inducing stimulus is no longer directly accessible to consciousness.

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CERTIFICATE OF APPROVAL

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PH.D. THESIS

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This is to certify that the Ph.D. thesis of

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TABLE OF CONTENTS

LIST OF TABLES

Table

LIST OF FIGURES

Figure

CHAPTER 1

INTRODUCTION

What is the limbic system?

There is currently no consensus in the field concerning the exact definition of what neural structures constitute the limbic system (Kotter & Meyer, 1992; LeDoux, 2000). As aptly stated by Ledoux, "*after half a century of debate and discussion, there are still no agreed upon criteria that can be used to decide which areas of the brain belong to the limbic system.*" (Ledoux, 2000, p.158). Rather than argue for or against the inclusion of a particular brain region, I will define the limbic system as a set of highly interconnected brain regions situated within the medial portion of the brain. This liberal definition encompasses all the cortical regions located along the medial fringe of the cortical mantle (Broca, 1878), as well as other adjacent cortical and subcortical structures that have been added to the limbic system over the years by several prominent investigators (Heimer & Van Hoesen, 2006; Maclean, 1952; Mesulam & Mufson, 1982; Papez, 1937; Yakovlev, 1972). These regions include (in no particular order): the orbitofrontal cortex, insular cortex, anterior and posterior cingulate cortices, temporopolar cortex, parahippocampal gyrus, hippocampal formation, amygdala, basal forebrain, anterior thalamic nuclei, and the hypothalamus.

Historically, the "limbic system" construct was conceived on purely anatomical grounds. In 1664, the preeminent physician and anatomist, Thomas Willis, observed that a cortical border appeared to encircle the brainstem and termed this the *cerebri limbus* (in Latin *limbus* means "border" or "edge") (Willis, 1664). Over 200 years later, Broca introduced the term, "le grand lobe limbique" to describe the same cortical regions forming the inner border of the cerebral hemispheres and speculated that these regions played a primary role in olfaction and were unique to the mammalian brain (Broca, 1878). The dawn of an emotion-related limbic system commenced in 1937 when James

Papez attempted to answer the quintessential question, "*Is emotion a magic product, or is it a physiologic process which depends on an anatomic mechanism?*" (Papez, 1937). Papez incorporated aspects of Broca's great cortical limbic lobe into the subcortically-mediated emotion theories of Cannon (1927) and Bard (1928) in order to construct his prescient emotional circuitry: "*It is proposed that the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus, and their interconnections constitute a harmonious mechanism which may elaborate the functions of central emotion, as well as participate in emotional expression."* (Papez, 1937, p.743). He went on to speculate that this circuitry represents "the stream of feeling" and made the specific prediction that emotional expression arises from subcortical structures (especially the hypothalamus) and emotional experience arises from cortical structures (especially the cingulate gyrus). Fifteen years later, MacLean formally introduced the term "limbic system" to describe an expanded version of the Papez circuit which he characterized as "*a visceral brain that interprets and gives expression to its incoming information in terms of feeling, being incapable perhaps of getting at the meaning of things at the level of symbolic language."* (Maclean, 1952, p.415). The high-reaching and tantalizing theories of Papez and MacLean inspired a whole movement toward understanding the emotional limbic system, a movement which continues to this very day.

At the very onset of this movement, Kluver and Bucy (1939) published their landmark studies involving rhesus monkeys who underwent bilateral temporal lobectomy (which includes the removal of two central limbic structures: the hippocampus and the amygdala). Immediately following the surgery, the emotional behavior of the monkeys was dramatically altered such that they readily approached and examined all objects, including objects which they had previously avoided and feared, such as the tongue of a large hissing snake. In addition, the monkeys were found to have a "*complete absence of all emotional reactions in the sense that the motor and vocal reactions generally associated with anger and fear are not exhibited*" (Kluver & Bucy, 1939). These marked

changes in emotional behavior in monkeys were replicated in a 19 year old man who underwent a bilateral temporal lobectomy in an attempt to alleviate his seizures (Terzian & Ore, 1955). Of note, the seizures triggered "paroxysms of aggressive and violent behavior" including attempts to strangle his mother and crush his younger brother. Quite strikingly, all violent behavior was completely eliminated immediately following the surgery. Moreover, it was noted that the patient "*lost the capacity to experience any emotion or to express it*" (Terzian & Ore, 1955).

As it turns out, cases where focal damage to the limbic system leads to a complete loss of emotion are extraordinarily rare. This became readily apparent during a meeting of the Harvey Cushing Society on April 23, 1953. Paul MacLean gave a presentation on the limbic system and its role in emotion, citing a large body of epilepsy and neurophysiology studies (many of which were conducted in non-human animals) as support for his theory (MacLean, 1954). In the presentation, MacLean focused on the hippocampus, which he labeled as the "heart of the limbic system." At the very end, he noted, "*animal experimentation can contribute next to nothing about the 'subjective' functions of the hippocampal formation… The animal cannot communicate how he feels. Here is the rub for the physiologist. Realizing that Aladdin's lamp is not for him, he obviously looks, as he has long been accustomed, to the neurosurgeon!*" (MacLean, 1954, p.41). The next presenter turned out to be a neurosurgeon by the name of William Beecher Scoville. Dr. Scoville discussed a radical surgical procedure he performed on a small number of human patients, where he removed the entire hippocampal formation, bilaterally (Scoville, 1954). Contrary to MacLean's hypothesis, Scoville claimed that the surgery "resulted in no marked physiologic or behavioral changes with the one exception of a very grave, recent memory loss." Unknown at the time, one of the patients whom Scoville performed the surgery on was Henry Molaison, more famously known as Patient HM (Scoville & Milner, 1957). From the pivotal case of Patient HM, we now know that bilateral damage to the human medial temporal lobes (including the hippocampus)

primarily disrupts the formation of new declarative memory, rather than disrupting emotion or feeling (Scoville & Milner, 1957). Future studies would confirm this finding and expand upon it by showing that damage to other limbic areas (such as the basal forebrain, thalamus, or mammillary bodies) also primarily disrupts memory, not emotion (for reviews see Tranel, Damasio, & Damasio, 2000; Zola-Morgan & Squire, 1993). Thus, the extant evidence strongly suggests that the functional role of many structures within the limbic system aligns more closely with memory than it does with emotion.

What role then, if any, does the limbic system play in emotion? Surprisingly, this question has never been adequately addressed and its answer remains unknown. This is not meant to insinuate that no work has been done in this area. Indeed, there exists a tremendous amount of data on individual limbic structures (such as the hypothalamus, amygdala, orbitofrontal cortex, anterior cingulate, and insular cortex) and their specific role in emotional processing. I will describe some of these findings in the subsequent sections. What remains to be deciphered is exactly how all of the different limbic structures work together to form an integrated network, and the precise functional role that this network plays in the instantiation of emotion. Due to the functional and anatomical elusiveness of the limbic system, some researchers have implored the scientific community to abandon the concept (e.g. Brodal, 1969; Kotter & Meyer, 1992; LeDoux, 2000). Others, however, continue to embrace the limbic system concept (e.g., see the recent special issue about the limbic system edited by Mokler & Morgane, 2006). These dissenting views do have one point of agreement; the preconceived notion of a limbic system that somehow represents all emotional processes is a dramatic oversimplification.

What is emotion?

Much of the confusion and conflict surrounding the notion of an emotional limbic system can be linked to the somewhat nebulous usage of the term *emotion* (Ekman &

Davidson, 1994; Kleinginna & Kleinginna, 1981; Kotter & Meyer, 1992). Without further specification, the emotional limbic system can be taken to represent everything and anything that pertains to emotion. In order to decipher the limbic system's precise functional role in the instantiation of emotion, it will be important to first provide a clear definition of emotion. For the purposes of this thesis, I will heed the foresight of James Papez and parse emotion into two components: emotional expression and emotional experience (Papez, 1937).

The expression of an emotion consists of a dynamically changing repertoire of responses triggered by any stimulus (i.e., any object, event, situation, thought, or body state) that is deemed relevant to one's needs, goals, or survival (Damasio, 2003; Watson, 2000). This emotion-inducing stimulus causes the central nervous system to orchestrate the complex cascade of reactions that comprise an emotional response (Damasio, 2003). These reactions can affect nearly every aspect of our being and include physiological changes (e.g., autonomic/visceral changes, surges in particular hormones and neurotransmitters, etc.), behavioral changes (e.g., approach/avoidance behaviors, facial expressions, crying, laughing, etc.) and cognitive changes (e.g., changes in attention, speed of processing, mood-congruent thoughts, appraisal processes, attribution processes, etc.). Together, these changes aim to regulate our homeostasis and promote behaviors intended to help us adapt to our ever-changing environment.

When certain combinations of physiological, behavioral, and cognitive changes occur in synchrony, they can elicit a distinct subjective feeling state in the form of an emotional experience or mood (Craig, 2002; Damasio, 2003; Watson, 2000). For example, following the appraisal of an emotion-inducing stimulus (e.g., hearing someone breaking into your home), a diverse repertoire of ensuing responses would be triggered including physiological changes (such as a surge in adrenaline and a sharp rise in heart rate), behavioral changes (such as the raising of the upper eyelids and a palpable urge to avoid the fear-inducing stimulus), and cognitive changes (such as an increase in vigilance

and an outpouring of negative thoughts related to death). The combination of all these changes, happening in close temporal proximity, produces the distinct and salient feeling of fear. Even though many of the changes that comprise an emotional response can occur unconsciously, the resultant subjective feeling state, by definition, is within the realm of our awareness (Craig, 2009; Craig, 2002; Damasio, 2003; Watson, 2000). Thus, humans have the capacity to consciously feel an emotion and subjectively describe what the emotion feels like. In this regard, the term "emotion experience" (as used in this thesis) always refers to the conscious feeling of an emotion.

Ever since William James and Carl Lange proposed that all emotions can be boiled down to their complex expression in the theater of the body (James, 1884; Lange, 1885), researchers have searched for specific bodily signatures that characterize each of the emotions. Although there has been some success in differentiating the basic emotions using patterns of autonomic activity or changes in facial expression (Ax, 1953; Ekman & Oster, 1979; Ekman, Levenson, & Friesen, 1983; Levenson, 1992; Rainville, Bechara, Naqvi, & Damasio, 2006), the picture becomes exponentially more complex when considering all possible subjective feeling states. No one, as of yet, has been able to find an objective set of indices that can definitively unveil the content of one's private subjective feelings. As it stands, the only way to validly and reliably determine how someone is feeling is by asking them (Barrett, 2004). For this reason, my thesis will focus on measuring the experience of emotion via self-report.

Based on a corpus of self-report data, our emotional experience can be organized into a two-tiered hierarchical arrangement (Watson, 2000). In the top tier are two broad dimensions that characterize the bulk of our emotional experience: Positive Affect (PA) and Negative Affect (NA). The higher order dimensions of PA and NA are largely independent and account for nearly three-quarters of the common variance in self-rated affect (Watson, 2000; Watson & Tellegen, 1985). In the lower tier are several correlated, yet ultimately distinguishable, specific emotional states. PA is composed of several

different positive states (including joviality, self-assurance, and attentiveness) and NA is composed of several different negative states (including fear, hostility, guilt, and sadness). Of note, the fundamental emotions of fear, anger, sadness, disgust, and happiness are all embedded within the lower level of this hierarchy. These particular emotions have been shown to be "universal" in the sense that they are expressed, perceived, and evoked in a similar manner across a wide range of cultures, and consequently, these specific emotional states tend to be the most heavily studied (Ekman et al., 1987; Ekman & Davidson, 1994; C. E. Izard, 1994). However, focusing only on specific emotional states fails to account for the higher order dimensions of PA and NA. As advocated by Watson (2000), any complete investigation of emotional experience should examine both levels of the hierarchy.

Emotion recovery

Affective chronometry refers to the complex process of how emotions unfold over time (Davidson, 1998). In its most basic format, an emotion can be parsed into three consecutive stages: (1) an emotion is elicited, (2) it rises to a peak, and (3) it descends ("decays") back down to baseline. While much research has explored the first two stages, very little is known about the latter stage which will be referred to as "emotion recovery." Emotion recovery begins once an emotion reaches its peak intensity and ends once the emotion has descended back down to its baseline level. Viewed in this framework, emotion recovery occurs over a discrete period of time that can be measured and systematically investigated. Of note, other terminology has been used to describe this same process, including "emotion decay" and the "sustained experience of emotion." The term "emotion recovery" was specifically chosen since it is the term most commonly used in the field of affective neuroscience (Davidson, 1998).

The idea of an emotional baseline state invokes the concept of homeostasis, the primary physiological mechanism for sustaining stable states and maintaining life

(Cannon, 1932; Schulkin, 2004). Indeed, a number of systems essential to our survival (such as body temperature and pH level) are tightly regulated by homeostatic mechanisms that treat the baseline state as a natural "setpoint". Any deviation away from this setpoint triggers an error signal that is quickly corrected through a negative feedback system. This simple set-up achieves the fundamental goals of homeostasis: *resistance to change* and *stability through constancy* (Cannon, 1932; Schulkin, 2004).

Homeostatic regulation of emotion stipulates that what goes up must come back down to baseline. The experience of any emotion outside of the normal baseline state would be considered a disruption to stability that needs to be immediately corrected. Such a model helps explain why an individual tends to experience affective states that are both stable over long periods of time and consistent across different situations in life; a concept which is commonly referred to as "trait affect" (Watson, 2000). Thus, one's baseline state (or trait affect) forms the backdrop from which each of our lives is experienced. It grounds us, providing a sense of continuity across time and also an invaluable point of comparison. Whenever we are not feeling like ourselves, it is usually because we notice that something has changed and we are no longer at our normal baseline state.

The baseline should not be construed as a neutral state with no emotional tone or feeling. Rather, most healthy people's baseline is a positive affective state of mild to moderate intensity, usually with little negative emotion (Diener & Diener, 1996; Ito & Cacioppo, 2005; Watson, 2000). Certain aspects of our baseline state tend to show rhythmic fluctuations, such as the robust finding that our positive affect tends to be highest during the daytime and lowest early in the morning and late at night (Clark, Watson, & Leeka, 1989). Moreover, each person has their own unique baseline state that is a product of their temperament and life experiences.

So, given a baseline state that forms our background ambient mood, and given a stimulus that triggers a cascade of emotional responses leading to the subjective

experience of an emotion or mood that feels qualitatively different from our baseline state, the question then becomes, "How quickly does the experience of an emotion return back to baseline?" As it turns out, much of the research that has been conducted on emotions has not looked at this important question. There are volumes of data exploring other affective processes: from determining the antecedents of an emotion, to tracking the cognitive, behavioral, and physiological components of an emotional response, to understanding and measuring the subjective experience of an emotion during both baseline and peak states. Yet, after an emotion is elicited and reaches its peak intensity, our state of knowledge is quite limited. Much more work is needed in order to better understand the temporal dynamics of emotion and its recovery back to baseline.

Based on a careful review of the literature (Feinstein, 2008), several comments can be made about the time frame of emotion recovery. Only 22 studies were found that induced an emotion in a laboratory setting and then tracked its recovery back to baseline. The amount of time needed for an emotion to recover varied widely depending on the type of emotion induction procedure, the specific emotion being induced, and individual differences in the population being tested. In the laboratory, nearly all induced emotions had fully recovered within 30 minutes (with most emotions taking between 5 to 10 minutes). In everyday life, most notable emotion experiences recovered within a few hours time. Significant life events, such as the death of a loved one or the end of a romantic relationship, were capable of extending the recovery process up to weeks and even months, but rarely ever for years. For the vast majority of people, even extreme emotional experiences tended to return to baseline levels within a few months time.

Instances where emotions failed to recover were often found in patients with severe psychiatric conditions. In fact, an important reason for studying emotion recovery emerges when considering its role in the diagnosis and treatment of mental illness. Nearly all forms of psychopathology include an element of subjective distress that endures for extended periods of time (American Psychiatric Association, 2000).

Posttraumatic stress disorder requires symptoms to endure for at least 1 month, and generalized anxiety disorder is excessive anxiety and worry occurring for a period of at least 6 months. A major depressive episode requires at least 2 weeks of persistent symptoms, a manic episode requires 1 week, and dysthymia is a chronically depressed mood that occurs for at least 2 years. For the millions of people who suffer from depression and anxiety, the failure of emotion recovery is a constant feature of their existence. Even with state-of-the-art treatments, many people never recover. Understanding emotion recovery is a critical step toward finding better treatments and regulation strategies that can expedite one's return to baseline and ameliorate the intense and prolonged periods of emotional suffering that pervade the lives of those with depression, anxiety, and other forms of psychopathology.

The previous findings have important implications for emotion researchers interested in capturing the entire emotional experience, from the onset to the offset. One-shot measures of state affect do not have the temporal resolution to capture emotion recovery, which requires that emotion experience be sampled at a minimum of three different time points: baseline, peak intensity, and recovery. The precise timing of the recovery measurement is dependent on the nature of the emotion induction procedure, as well as the emotion being probed. Currently, most laboratory-based experiments sample emotion on a "milliseconds to seconds" time scale. Thus, many emotion studies are entirely missing the process of emotion recovery, which tends to transpire over the course of many minutes (rather than seconds). In order for the study of emotion recovery to progress, it will be imperative for future work to extend the duration of emotion measurement in order to more fully capture emotion's downward slope back to baseline.

Film emotion induction procedure

Two review papers and a meta-analysis have concluded that an emotion induction procedure using film clips is the most effective and reliable way to induce an emotion in

a laboratory setting (Gerrards-Hesse, Spies, & Hesse, 1994; Martin, 1990; Westermann, Stahl, & Hesse, 1996). In its simplest format, the procedure has a research participant watch one or more highly emotional film clips and then report how they feel. Standardized sets of short film clips have been created and shown to reliably elicit specific target emotions (including happiness, sadness, anger, disgust, and fear), as well as more general states of positive and negative affect (Gross & Levenson, 1995; Philippot, 1993; Schaefer, Nils, Sanchez, & Philippot, 2010). An added advantage that the film induction procedure has over other types of emotion inductions (e.g., the Velten method, or other procedures using imagery or autobiographical recall) is that the demand characteristics are minimized since the induced emotion can usually be generated naturally by simply paying attention to the film clip (Martin, 1990; Rottenberg, Ray, & Gross, 2007). In addition, the emotions evoked while watching a film are often quite realistic, and can range from intense sobbing to hysterical laughing. For all of the aforementioned reasons, film clips were chosen as the primary method for inducing emotion in this dissertation experiment.

Brain regions implicated in emotion experience

Currently, very little is known about how the experience of emotion is instantiated in the human brain. Much of the extant literature investigating emotion in the human brain has focused on elucidating the neural substrates for emotion appraisal (e.g., recognizing emotion in facial expressions) and emotion expression (e.g., fear conditioning). This section will briefly summarize some of the relevant findings with regard to emotion experience, with a focus on four core limbic structures that have been strongly implicated in both the production and experience of emotion: the insular cortex, the anterior cingulate cortex (ACC), the orbitofrontal cortex, and the amygdala.

William James proposed that one of two things must be true with regard to special brain centers for emotion, *"Either separate and special centres, affected to them alone,*

are their brain-seat, or else they correspond to processes occurring in the motor and sensory centres already assigned, or in others like them, not yet known." (James, 1890, p.473). Over 120 years later, and neuroscientists continue to explore these two alternatives.

Some research supports James' first alternative, where specific emotions are represented by specific regions in the brain. For example, the insular cortex has been implicated in disgust (Adolphs et al., 2003; Calder, Keane, Manes, Antoun, & Young, 2000; Calder, Lawrence, & Young, 2001; Jabbi, Bastiaansen, & Keysers, 2008; Stark et al., 2003; Wicker et al., 2003), the amygdala has been implicated in fear (Calder et al., 2001; Davis, 1992; Feinstein, Adolphs, Damasio, & Tranel, 2011; Phan, Wager, Taylor, & Liberzon, 2002; Sprengelmeyer et al., 1999), and the subgenual ACC has been implicated in sadness (Drevets et al., 1997; Mayberg et al., 1999; Phan et al., 2002, Smith et al., 2011). Much of this research supports the notion that these structures are critical brain centers for triggering specific states of emotion (whether it be the insula for disgust, the amygdala for fear, or the subgenual ACC for sadness), and damage to these regions should diminish, or even abolish, one's ability to produce the cascade of reactions that comprise that specific emotional state. In line with this prediction, we have recently published a case study on patient SM, a woman with focal bilateral amygdala lesions who presented with a highly specific impairment in the induction of fear (Feinstein et al., 2011). However, findings in another patient with bilateral amygdala lesions failed to show a fear-specific impairment (Anderson & Phelps, 2000; Anderson & Phelps, 2002). Likewise, some patients with damage to the insular cortex have demonstrated disgust-specific impairments (Adolphs et al., 2003; Calder et al., 2000), whereas others have not (Straube et al., 2010; Vianna, 2005). Finally, the only study to examine sadness in patients with bilateral lesions to the subgenual ACC failed to detect any sadness impairment (Gillihan et al., 2011). While there are numerous potential reasons that can account for the discrepancy between some of the aforementioned findings, the mere fact

that there are discrepancies indicates that the notion of a specialized brain center for inducing a specific emotional state is more complex and nuanced than a simple one-to-one mapping between structure and function. The bedrock of good science is replication and these divergent findings highlight the need to study this issue in a much larger sample of lesion patients.

While the previous evidence lends some support (albeit mixed) for the existence of specialized brain centers involved in the expression of specific emotions, other research lends supports to William James' second alternative, where the experience of emotion, irrespective of the specific type of emotion, is instantiated by detailed body maps located within the brain's somatosensory cortices (Craig, 2002; Damasio, 2003). These somatosensory maps contain a moment-to-moment representation of the myriad changes happening in our body as the emotive process unfolds. A vast majority of the processing within these body maps occurs unconsciously. However, certain aspects of these neural maps produce perceptions that are accessible to consciousness. These perceptions, when attended to, allow "*for the subjective evaluation of one's condition, that is, how you feel*" (Craig, 2002, p.655).

A large body of neuroanatomical work proposes that these perceptions are formed via a dedicated lamina I afferent pathway that contains a detailed representation of the physiological condition of the entire body, including information related to pain, temperature, visceral sensation, and immune function (Craig, 2002; Damasio, 2003). This phylogenetically recent neural pathway is found only in primates and humans and has dual projections to limbic sensory cortex (i.e., the insular cortex) and limbic motor cortex (i.e., the ACC), which "*respectively engender the feeling and the motivation (agency) that constitute any emotion*" (Craig, 2009, p.62). Accordingly, most functional neuroimaging experiments involving the experience of emotion tend to jointly activate the insular cortex and the ACC (Craig, 2009; Damasio et al., 2000; Phan et al., 2002). The most anterior portion of the insular cortex marks the terminal endpoint for this

afferent pathway and is thought to play a critical role in the conscious awareness of all internal feeling states (Craig, 2002; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Damasio, 2003; but see Khalsa, Rudrauf, Feinstein, & Tranel, 2009). In fact, a recent review paper (reported as the most highly cited paper of the year in the prestigious journal, *Nature Reviews Neuroscience*) speculates that the anterior insula contains "*the ultimate representation of all of one's feelings*" and "*provides a unique neural substrate that instantiates all subjective feelings from the body and feelings of emotion*" (Craig, 2009, p.65).

Such strong claims regarding the functional role of the ACC and insular cortices (especially the anterior insula) are strangely reminiscent of the original claims made about the emotional limbic system. History repeats itself, for it turns out that these modern claims are grounded more in theory than fact. For example, recent work from our laboratory provides unequivocal evidence that neither the insular cortex nor the ACC are necessary for feeling the sensation of the heartbeat accelerating (Khalsa et al., 2009). Another study from our laboratory tested 18 stroke patients with significant damage to either their left or right insular cortex, including (in some cases) the anterior insula (Vianna, 2005). The patients all watched film clips designed to evoke one of four different emotions (disgust, sadness, fear, or happiness). Based on the strong claims about the role of the insula in emotional experience, one might predict that the insula patients would be unable to experience any emotion while watching the film clips. However, not only did the insula patients report feeling the target emotion (including disgust) while watching the film clips, but the intensity of their feeling was found to be of the same magnitude as a group of healthy participants (Vianna, 2005). These findings argue against the popular notion of the insula being the neural center of all feelings, and instead, support the possibility that the insula is not required for the experience of emotion.

Of all the structures in the limbic system, the amygdala has received the most attention with regard to its role in emotion. In particular, the amygdala is imperative for emotion-based learning, especially fear conditioning (Bechara et al., 1995; LeDoux, 1996) and emotional memory (Cahill, Prins, Weber, & McGaugh, 1994; Hamann, 2001). Damage to the amygdala can disrupt one's ability to detect threats in the environment, leading to impairments in recognizing fear in facial expressions, as well as impairments in the ability to judge the approachability and trustworthiness of strangers (Adolphs, Tranel, Damasio, & Damasio, 1995; Adolphs et al., 1999; Adolphs, Tranel, & Damasio, 1998). Likewise, in monkeys, amygdala damage often leads to dramatic changes in emotional behavior that often mimic elements of the Kluver-Bucy syndrome, including hypoemotionality, decreased aggression, increased tameness, and the indiscriminate approach of objects, including objects that previously were feared such as snakes (Aggleton & Passingham, 1981; Isaacson, 1974; Machado, Kazama, & Bachevalier, 2009; Weiskrantz, 1956).

The amygdala's role in the actual experience of emotion is less clear (Feinstein et al., 2011). Direct stimulation of the amygdala in human patients can induce both positive and negative emotions, including feelings of fear, sadness, and happiness (Lanteaume et al., 2007). Some evidence supports the idea that the amygdala is more involved during the initial stages of emotion induction than during the later stages of emotion experience. For example, a recent meta-analysis was conducted using a large dataset of 165 different emotion-related functional neuroimaging studies (Wager et al., 2008). A direct contrast was performed between studies examining emotion perception (e.g., viewing faces with different emotional expressions) versus studies examining emotion experience (e.g., autobiographical recall of highly emotional life events). The contrast revealed that the amygdala, bilaterally, was significantly more active during the perception of emotion than during the experience of emotion. Some have argued that the amygdala's role in emotional perception is mostly directed towards the appraisal of danger (Broks et al.,

1998). Others have argued that the amygdala plays a much more general role in the primary induction of emotion following the perception of emotionally-relevant stimuli in the immediate environment (Bechara, Damasio, & Damasio, 2003). Based on this latter account, the amygdala is involved in both the initial perception of an emotional stimulus and the subsequent induction of emotion via its direct projections to autonomic effector sites in the hypothalamus, basal forebrain, and brainstem (Davis, 1992; LeDoux, 1996). Furthermore, this account insinuates that the amygdala's role in emotion goes well-beyond fear, and includes the primary induction of arousal. Once the arousal is induced, the emotion can likely be experienced without significant involvement of the amygdala. Viewed in this light, the amygdala dynamically adjusts our moment-to-moment level of emotional arousal and vigilance based on our environmental context (Adolphs, Russell, & Tranel, 1999; Berntson, Bechara, Damasio, Tranel, & Cacioppo, 2007; Davis & Whalen, 2001; LeDoux, 1996). Some have even suggested that without the amygdala-mediated activation of our arousal systems, "*emotional states would be fleeting*" and would dissipate often as quickly as they are triggered (LeDoux, 1996, p.298). The amygdala, however, is not the only brain region involved in the initial induction of emotion. Other prominent emotion induction sites include the orbitofrontal cortex and the ACC, which also project downstream to autonomic effector structures in the hypothalamus, basal forebrain, and brainstem (Bechara et al., 2003; Damasio, 1999; Damasio, 2003). Thus, damage to the amygdala does not eliminate all emotional responses given the existence of alternative routes for the induction of emotion (Feinstein et al., 2011).

Both the orbitofrontal cortex and the ACC have been implicated in emotional experience, and damage to these regions has been associated with variable patterns of emotional dysregulation that is difficult to characterize given the diverse set of findings. Damage to the ventromedial prefrontal cortex (vmPFC; a brain region that includes the orbitofrontal cortex and ventral regions of the ACC and medial prefrontal cortex) tends to

cause specific deficits in the deployment of complex social emotions, including impairments in feeling empathy, embarrassment, regret, guilt, and other self-conscious emotions (Beer, Heerey, Keltner, Scabini, & Knight, 2003; Beer, John, Scabini, & Knight, 2006; Camille et al., 2004; Krajbich, Adolphs, Tranel, Denburg, & Camerer, 2009; Shamay-Tsoory, Aharon-Peretz, & Perry, 2008). Bechara et al. (2003) found reduced levels in the intensity of experienced emotion when vmPFC patients recalled highly emotional autobiographical memories. Other studies have shown that patients with vmPFC damage report both increases and decreases in their experience of emotions. For example, Hornak and colleagues (1996) reported some patients who claimed to have completely lost their ability to experience certain negative emotions like fear or sadness. Others patients, however, reported experiencing increases in these very same emotions, and no consistent pattern could be discerned between the different patients or the different emotions. A follow-up study interviewed patients with more focal brain injuries (Hornak et al., 2003). When the damage was circumscribed to the orbitofrontal cortex (bilaterally) or the ACC (bilaterally or unilaterally), the patients reported a significant change in the intensity and frequency in which they experienced sadness, anger, fear, happiness, and disgust. Overall, in this sample, the patients reported increases in their experience of these emotions nearly twice as often as decreases. Moreover, these changes happened across all of the different emotions, suggesting an overall increase in the lability of their mood. The findings were particularly notable for the patients with ACC damage who "*described themselves as having become far more emotional than before their surgery*" with a number of patients providing the example of having more exaggerated emotional responses to sad films (Hornak et al., 2003, p.1705). This is in stark contrast to the fascinating condition of akinetic mutism, whereby patients with bilateral damage, typically impacting both the ACC and adjacent territories (including the supplementary motor area), entirely lose their "motivation" to move or communicate, and consequently, show no emotional reactivity, and once the condition resolves, report that

they also did not feel any emotion while in their abulic state (Damasio & Van Hoesen, 1983). A review paper exploring emotional changes following frontal lobe damage found that patients with vmPFC lesions "*respond to trivial stimuli with outbursts of anger that pass quickly without a trace of remorse*" (Stuss, Gow, & Hetherington, 1992, p.353). Such was the case during the Ultimatum Game, where vmPFC-lesion patients tended to irrationally reject unfair financial offers (Koenigs & Tranel, 2007). Additional studies have highlighted increases in aggression and emotional lability in vmPFC-lesion patients, particularly in situations of frustration or provocation (Blair & Cipolotti, 2000; Grafman et al., 1996). Barrash et al. (2000) characterized the changes in emotionality following bilateral vmPFC damage into two categories: (1) a general dampening in emotional experience including low emotional expressiveness and apathy, and (2) poorly modulated emotional reactions including poor frustration tolerance, short-lived episodes of irritability, lability, and inappropriate affect.

It has been hypothesized that "*at least one important component of what the ventromedial and/or orbital prefrontal cortex 'does' in affective responding is modulate the time course of emotional responding, particularly recovery time*" (Davidson, 2002, p.8). In support of this hypothesis, the prefrontal cortex (including the vmPFC) has been shown to play an important role in the regulation of emotion. For example, functional neuroimaging studies in healthy individuals have revealed activation in the prefrontal cortex that is negatively correlated with activation in the amygdala and positively correlated with an individual's success in downregulating their emotional response to affectively-laden stimuli (Davidson, 2002; Eisenberger, Lieberman, & Williams, 2003; Hariri, Bookheimer, & Mazziotta, 2000; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Lieberman et al., 2007; Ochsner, Bunge, Gross, & Gabrieli, 2002; Banks et al., 2007). Likewise, an emerging line of work in the study of fear extinction has revealed a critical role for the vmPFC in suppressing the spontaneous recovery of fear (Milad & Quirk, 2002; Milad et al., 2007; Quirk, Russo, Barron, & Lebron, 2000), a process that is

thought to be mediated by inhibitory connections projecting from the vmPFC to the amygdala (Quirk, Likhtik, Pelletier, & Pare, 2003). A failure to extinguish a maladaptive fear response is one of the underlying deficits found in posttraumatic stress disorder (PTSD). A recent study examined a large cohort of Vietnam War veterans who had sustained various penetrating brain injuries during battle (Koenigs, Huey, Raymont et al., 2008). Whereas half of the veterans without brain injury were found to have PTSD, only 18% of patients with vmPFC damage and 0% of patients with amygdala damage had PTSD. These results suggest that the vmPFC and amygdala are both related to the long-term emotional suffering associated with PTSD, and damage to these regions can significantly reduce the amount of time it takes to emotionally recover from a traumatic event. Similar findings were found when examining depression; patients with bilateral vmPFC damage had significantly lower levels of depression than patients with damage elsewhere (Koenigs, Huey, Calamia et al., 2008). Together, these findings provide further evidence that PTSD and depression share a common core of symptoms related to high levels of distress and negative affect (Clark & Watson, 1991; Watson, 2005). Moreover, these findings suggest that damage to the vmPFC may confer resilience to disorders characterized by heightened levels of negative affect; an observation marred by the long and highly controversial history of psychosurgeries often aimed at damaging the vmPFC and its underlying fiber tracts (Malizia, 1997; Read & Greenberg, 2009).

Much of this background section has focused on a limited number of brain structures within the limbic system including the amygdala, insula, ACC, and vmPFC. While most of the available evidence points to these structures as playing an important role in emotion experience, there are many other brain regions that might also contribute. For example, certain nuclei within the hypothalamus, thalamus, basal forebrain, and brainstem are critical for the expression of emotion (Bard, 1928; Cannon, 1927; Damasio, 1999; Panksepp, 1998). The hypothalamus, in particular, has been shown to be essential for the expression of rage (Bard & Mountcastle, 1948). There are rare cases of damage to

the human hypothalamus caused by tumors that have induced altered mood states including manic episodes, depression, and anxiety (Alpers, 1940). Moreover, in Isaacson's monograph on the limbic system he states, "*the limbic system seems best defined in terms of its connections with the hypothalamus… many, if not all, of the effects produced by stimulation and lesions of the extrahypothalamic limbic structures can be replicated by stimulation or lesions of the hypothalamus*" (Isaacson, 1974, p.3). Panksepp (1998) views the hypothalamus, as well as midbrain structures (such as the periaqueductal gray) as being indispensable for emotion, including the beginning stages of emotional consciousness. Likewise, Damasio (2010) has recently speculated that specific nuclei in the brainstem are critical for creating the foundation of all feeling states (a concept he termed, "primordial feelings"). While certain brainstem nuclei (e.g., periaqueductal gray) are critical for triggering emotional responses in the body, other brainstem nuclei (e.g., nucleus of the solitary tract and the parabrachial nucleus) are critical for receiving the sensory signals arising from the body's interior (Damasio, 2010). Thus, the brainstem houses all of the necessary circuitry for both the basic expression and primordial experience of emotion. Such an anatomical framework is consistent with the striking presence of emotion found in children who are entirely missing their cortex (but not their brainstem) due to hydranencephaly (Damasio, 2010; Merker, 2007). Taken together, this evidence suggests that the diencephalon and brainstem likely play an important role in the experience of emotion.

There are other views that localize the seat of emotional consciousness to higher-order association cortices. For example, Ledoux (1996) postulates that the experience of emotion is no different from the conscious experience of any other perception or thought and merely involves the resonance of emotion-related information in brain structures known to be involved in working memory, such as the lateral prefrontal cortex and the posterior parietal cortex. While the notion of a working memory system responsible for the short-term maintenance of affective information is intriguing (Mikels, Reuter-Lorenz,

Beyer, & Fredrickson, 2008), Ledoux's postulation fails to entertain the possibility that there are specialized neural circuits for *holding onto* an emotional experience that are fundamentally different from the brain regions traditionally implicated in working memory. One of the primary goals of this thesis is to elucidate the specific brain regions that are vital for the sustained experience of emotion.

CHAPTER 2

PRELIMINARY STUDIES

Bilateral limbic system destruction in man

Much of the impetus for this thesis project comes from my experiences working with a rare neurological patient by the name of Roger, who, over 30 years ago, survived a life-threatening bout of herpes simplex viral encephalitis (Feinstein, Rudrauf, Khalsa et al., 2010). The encephalitis attack caused bilateral destruction to Roger's hippocampus, amygdala, parahippocampal gyrus, temporal poles, orbitofrontal cortex, basal forebrain, ACC, and insular cortex. In short, the lesion encompasses the vast majority of the limbic system, making Roger an exceptional test case for determining the limbic system's role in emotion experience.

In 2006, I had my first opportunity to meet Roger. Knowing full well the extent of Roger's limbic system damage, I envisioned a human devoid of all emotion. I quickly came to realize that my original expectation was altogether backwards. To begin, Roger's speech was fully animate, filled with gestures, prosody, puns, and a never-ending stream of one-line jokes. He laughed and smiled when he was happy, he sighed and slouched when he was upset, and on occasion, he even showed brief bouts of anger in situations where he felt his independence was being hindered. When I showed Roger a large battery of emotionally-evocative film clips, his reaction was quite unlike anyone else I have ever witnessed and included a constant barrage of emotional auditory vocalizations, replete with *eww's, aww's,* and *whoa's*, dynamically changing with the content of the film. Moreover, when asked what emotion he was feeling, Roger always reported experiencing high levels of intensity of the induced target emotion. These anecdotal behavioral observations in Roger are strangely reminiscent of the preserved emotional behavior found in another encephalitic, patient B., who is no longer alive, but who had a very similar pattern of brain damage to that of Roger's (Damasio, Damasio, &

Tranel, in submission). Together, the cases of Roger and patient B. provide preliminary evidence that the brain regions which form the core of the limbic system (including the hippocampus, amygdala, vmPFC, ACC, and insular cortex) are actually not necessary for the experience or expression of emotion; a finding which runs completely contrary to the widespread notion that the limbic system is the brain's vital hub for emotion.

Another striking feature of Roger's behavioral presentation was how quickly the emotions faded from his consciousness once the emotion-inducing stimulus was removed from his direct sensory experience (e.g., after an emotional film clip finished playing). Given Roger's intense (and sometimes excessive) emotional reactions, one might predict that the stimuli would have left a lingering emotional imprint. Instead, Roger's emotions often dissipated as rapidly as they were triggered. This observation was reinforced by the prescient insight made by Roger's parents (whom he lived with for over 24 years post-encephalitis), who claim that since Roger's brain injury, they have never witnessed a change in his mood that lasted for more than a few minutes. Such anecdotes highlight the intriguing possibility that the limbic system plays a critical role in the sustained experience of emotion. Since Roger's brain damage entails multiple limbic system structures, it is unclear whether his fleeting emotional states can be causally connected to damage related to an individual region within the limbic system, or whether the entire limbic system is involved in the maintenance of emotion. Additional research is necessary in order to determine the role of specific limbic territories in the sustained experience of emotion. The next section describes some of this preliminary work.

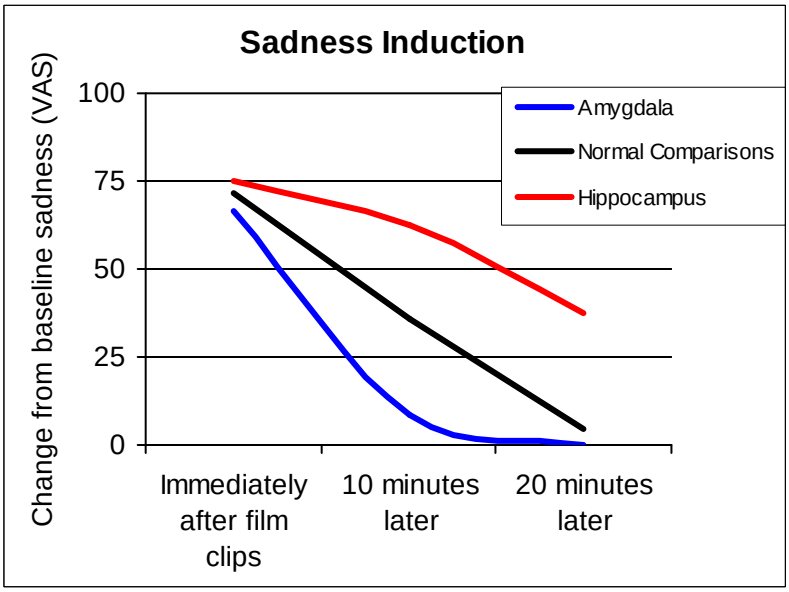
Hippocampus versus amygdala damage

A study of patients with severe amnesia was conducted in order to determine whether intact declarative memory was a necessary ingredient for the sustained experience of emotion (Feinstein, Duff, & Tranel, 2010). Specifically, I was interested in whether the experience of an emotion would persist once the memory for what induced

the emotion had evaporated from the amnesic patient's consciousness. Each patient underwent a sadness induction procedure that entailed watching 20 minutes of sad film clips, after which point they completed a memory test and provided ratings of their current emotional state. The results of the experiment clearly showed that the sadness persisted well beyond each patient's factual memory for the film clips. Similar results were found for other emotion inductions, including happiness and disgust. These findings present a striking dissociation between preserved conscious awareness of an emotional state and impaired conscious recollection for that state's origin.

An important aspect of the previous study is that all of the amnesic patients had circumscribed bilateral hippocampal brain damage that did not affect adjacent neural structures (such as the amygdala). Further testing was completed in a subset of amnesic patients (including Roger and another patient named SZ) who had damage that included both the hippocampus and the amygdala (in addition to other limbic regions). In these patients, not only did their memory for the film clips rapidly vanish, but their induced state of sadness also showed a rapid decay. In order to further clarify the nature of this rapid decay of emotion, I tested patient SM, who has circumscribed bilateral amygdala lesions that largely spared her hippocampus. In the case of SM, her memory for the film clips was intact, yet her level of sadness rapidly dissipated after the film clips were over at a similar rate to that seen in Roger and SZ. Taken together, these preliminary data provide evidence for a double dissociation between emotion and memory, with the amygdala supporting the sustained experience of emotion and the hippocampus supporting the memory for what caused the emotion (see Figure 1).

Figure 1. Results from a sadness induction procedure. The amygdala group is made up of 3 patients with bilateral amygdala damage (Roger, SZ, and SM), the hippocampus group is made up of 4 patients with focal bilateral hippocampal damage, and the healthy comparisons are 7 age- and sex- matched participants with no history of neurological or psychiatric illness. Each participant's level of sadness was measured using a 100-point visual analogue scale (VAS) that was completed at four separate time points: before the sad film clips (baseline), immediately after the sad film clips, 10 minutes later, and 20 minutes later. Memory was tested 5 minutes after the films.



Several aspects of Figure 1 are worth commenting on. First, all participants reported feeling sad when probed immediately after the film clips. This suggests that the films were effective at inducing sadness and that damage to limbic structures (such as the hippocampus or amygdala) does not disrupt the experience of sadness. Second, the hippocampal patients (who were unable to remember the film clips) reported a lingering state of sadness that lasted for over 20 minutes at a magnitude considerably higher than healthy comparison participants who have no brain damage and no memory impairment. This suggests that declarative memory is a not a necessary ingredient for the sustained experience of emotion. Moreover, this finding suggests that the hippocampus is not necessary for the sustained experience of emotion, and in some cases, focal damage to the

hippocampus may actually lead to an abnormally prolonged state of emotion. Third, due to the large time gap between emotion measurements, it is impossible to precisely determine how quickly the amygdala patients' sadness decayed and whether SM's sadness decayed at a rate similar to Roger and SZ. The only conclusion that can be made based on these data is that the amygdala patients' sadness had largely recovered at some time point within the first 10 minutes following the end of the film clips.

These preliminary results highlight a number of important issues ripe for further investigation: (1) exactly how quickly does emotion recover in patients who are missing only their amygdala (e.g., patient SM) versus patients who are missing both their amygdala and other limbic structures (e.g., Roger and SZ), (2) is the detected pattern of rapid emotion recovery specific to the emotion of sadness, or does it extend to other emotions (both positive and negative), and (3) considering that the hippocampus and amygdala are only two structures within a much larger limbic system, how is the experience and recovery of emotion altered when other limbic regions are damaged? These questions form the basis of my thesis.

CHAPTER 3

SPECIFIC AIMS AND HYPOTHESES

The primary aim of this dissertation project was to determine which structures in the limbic system are necessary for the conscious experience of emotion. Given the previously described anatomical elusiveness of the limbic system concept, the project focused on testing neurological patients with brain damage that impacted one or more of the 5 core limbic regions that have received the most attention with regard to their role in emotion, including: the hippocampus, amygdala, insular cortex, anterior cingulate cortex (ACC), and ventromedial prefrontal cortex (vmPFC). Accordingly, the term "limbic system" is used throughout this dissertation in specific reference to the aforementioned 5 brain regions. For comparison, two other groups of participants were tested: (1) a group of brain damaged comparison (BDC) patients whose brain damage lies outside of the limbic system, and (2) a group of non-brain damaged healthy participants (normal comparisons) who are of similar age, sex, and education to the lesion patients. All subjects underwent multiple emotion induction procedures using film clips. Two emotion inductions were aimed at eliciting diffuse emotional states of either positive or negative affect, and five emotion inductions were aimed at eliciting the specific emotional states of happiness, sadness, anger, disgust, or fear. Immediately following each induction, the return of emotion back to its baseline state was tracked over a 3-minute "emotion recovery" time period. Emotion experience was parsed into two separate components: (1) the "online" experience of emotion is defined as emotion that was experienced while watching the film clips, and (2) the "sustained" experience of emotion is defined as emotion that was experienced after the film clips were over.

Specific Aim #1: To determine which regions of the limbic system are necessary for the online experience of emotion.

Hypothesis 1a: The limbic system is not required for the online experience of emotion. It is predicted that the emotion inductions will successfully induce the target emotion in patients with limbic system damage at a magnitude that is not significantly different from the normal comparison group. The aforementioned observations in Roger (a patient with extensive bilateral damage to all 5 of the major target limbic regions) lend support to this hypothesis. It is possible however, that damage to specific structures within the limbic system could abolish or attenuate the experience of specific emotional states as articulated in hypothesis 1b.

Hypothesis 1b: It is predicted that patients with amygdala damage will show a fear-specific impairment, patients with insula damage will show a disgust-specific impairment, and patients with vmPFC damage (which includes the subgenual ACC) will show a sadness-specific impairment. These predictions are based on the body of evidence (see p.18) suggesting the presence of specialized centers in the brain for the induction of specific emotional states.

Specific Aim #2: To determine which regions of the limbic system are necessary for the sustained experience of emotion.

Hypothesis 2a: The limbic system is necessary for the sustained experience of emotion. Patients with large bilateral lesions affecting multiple limbic system structures (including the medial temporal lobes and insular cortices) will show an abnormally rapid recovery of emotion. Pilot data and anecdotal observations in both Roger and patient SZ lend support to this hypothesis (Figure 1).

Hypothesis 2b: The amygdala is important for the sustained experience of emotion. Patients with circumscribed bilateral amygdala damage will show a

rapid rate of emotion recovery, although not as rapid as in patients where the damage includes multiple limbic structures (in addition to the amygdala damage). The basis for this hypothesis stems from pilot data obtained in patient SM (Figure 1), as well as Ledoux's prediction that without the amygdala, "*emotional states would be fleeting*" (1996, p.298).

Hypothesis 2c: The vmPFC is important for regulating the sustained experience of emotion. Patients with circumscribed bilateral vmPFC damage will show an abnormally slow rate of emotion recovery. This prediction is based on the previously described evidence highlighting a prominent role of the vmPFC in the successful regulation of emotion (see pp.23-26).

Hypothesis 2d: The hippocampus is important for regulating the sustained experience of emotion. Patients with circumscribed bilateral hippocampal damage will show an abnormally slow rate of emotion recovery. This prediction is based on the previous finding showing that patients with focal bilateral hippocampal damage demonstrated a slow rate of sadness recovery (Feinstein, Duff, & Tranel, 2010; also see Figure 1).

CHAPTER 4

METHODS

Participants

All procedures were approved by the Institutional Review Board at the University of Iowa, and all subjects provided their informed written consent prior to participation. All lesion patients were recruited from the Patient Registry at the University of Iowa's Division of Behavioral Neurology and Cognitive Neuroscience, under the auspices of which they have been fully characterized, both neuropsychologically and neuroanatomically, according to standard protocols (Frank, Damasio, & Grabowski, 1997; Tranel, 2009). Importantly, all lesion data were collected during the chronic epoch of recovery (i.e., at least three months after lesion onset), at which point the patients have focal and stable brain damage. Normal comparison subjects were recruited from either a registry of healthy participants who have participated in prior research studies or through an advertisement placed in a daily hospital newsletter, and were screened over the phone prior to testing and excluded if they reported any current or past neurological or psychiatric conditions. At the beginning of the experiment, all participants completed a series of baseline questionnaires including the trait version of the Positive and Negative Affect Schedule (PANAS) and the general depression scale on the Inventory of Depression and Anxiety Symptoms (IDAS) (Watson, Clark, & Tellegen, 1988; Watson et al., 2007). All subjects were paid $12.50 per hour for their participation.

Table 1 shows the basic demographics of the brain damaged patients and the normal comparisons. As can be seen, subjects are closely matched in age, sex, education, and handedness. The brain damaged patients are split into 7 groups based on lesion location: (1) focal bilateral hippocampal damage (hipp), (2) focal bilateral amygdala damage (amy) (Figure 2), (3) focal bilateral dorsal ACC damage (dACC) (Figure 3), (4) bilateral limbic system damage that affects the entire medial temporal lobe in addition to

the insular and frontal cortices (MT+) (Figure 4), (5) unilateral insular cortex damage (ins) (Figure 5), (6) focal bilateral vmPFC damage (vmPFC) (Figure 6), and (7) brain damaged comparison patients with lesions outside of the limbic system (BDC). The gender, etiology, and lesion location for each patient are shown in Table 2. For the focal bilateral hippocampus group, volumetric tracings using MRI revealed that patient 1846 is missing ~47% of her hippocampus and patient 2363 is missing ~28% of his hippocampus (Allen et al., 2006), with neither patient having significant atrophy in their amygdala. Reductions in hippocampal volume in the range of 40% typically signify a complete loss of hippocampal neurons (Gold & Squire, 2005). The other 2 hippocampal patients (2563 and 3139) have cardiac pacemakers and were unable to undergo MRI scanning. Therefore, the presence of hippocampal damage in these latter patients is inferred based on their shared presentation of severe anterograde amnesia caused by an anoxic event. Detailed descriptions and MRI scans of Roger's extensive bilateral lesions to the limbic system have been previously reported (Feinstein, Rudrauf, Khalsa et al., 2010).

Table 1. Basic subject demographics.

group	# of subjects	males/ females	age	education	hand	years since onset
Normal comparisons	40	20 M 20 F	56.7 (15.8) range: 22-80	15.9 (2.5) range: 12-20	34 R 6 L	NA
Brain damaged patients	37	22 M 15 F	57.3 (12.3) range: 21-80	14.2 (2.3) range: 11-20	32 R 5 L	12.7 (8.9) range: 2-37

Note: Numbers in parentheses represent the standard deviation. Years since onset are the total number of years since the onset of brain damage.

Table 2. Etiology and lesion location for the brain damaged patients.

Group	Subject	Sex	Lesion location	Lesion etiology
amy	1465	M	bilateral amygdala + right medial temporal lobe	herpes simplex encephalitis
amy	AM	F	bilateral amygdala	Urbach-Wiethe disease
amy	BG	F	bilateral amygdala	Urbach-Wiethe disease
amy	SM	F	bilateral amygdala	Urbach-Wiethe disease
BDC	1815	M	bilateral dorsomedial prefrontal cortex	meningioma resection
BDC	2355	F	right parietal cortex	AVM resection
BDC	2855	M	bilateral supplementary motor area	meningioma resection
BDC	3001	M	right frontopolar cortex	meningioma resection
BDC	3277	F	right parietal cortex	ischemic stroke
BDC	3319	F	right frontoparietal cortex	meningioma resection
BDC	3348	M	left anterior temporal cortex	hemorrhagic stroke
BDC	3379	M	left parietal cortex	meningioma resection
dACC	3082	M	bilateral ACC+supplementary motor area	meningioma resection
hipp	1846	F	bilateral hippocampus	status epilepticus
hipp	2363	M	bilateral hippocampus	anoxia
hipp	2563	M	bilateral hippocampus	anoxia
hipp	3139	M	bilateral hippocampus	anoxia
ins	650	M	right insula+	ischemic stroke
ins	747	M	right insula+	ischemic stroke
ins	1188	M	left insula+	ischemic stroke
ins	1580	M	right insula+right medial temporal lobe	herpes simplex encephalitis
ins	1656	M	right insula+	ischemic stroke
ins	1711	F	right insula+	ischemic stroke
ins	3196	F	right insula+	ischemic stroke
ins	3202	M	left insula+	ischemic stroke
ins	3341	F	left insula+	ischemic stroke
ins	3363	M	right insula+	ischemic stroke
MT+	Roger	M	bilateral limbic system	herpes simplex encephalitis
MT+	SZ	M	bilateral limbic system	herpes simplex encephalitis
vmPFC	318	M	bilateral vmPFC	meningioma resection
vmPFC	1983	F	bilateral vmPFC	ACoA aneurysm
vmPFC	2352	F	bilateral vmPFC	ACoA aneurysm
vmPFC	2391	F	bilateral vmPFC	meningioma resection
vmPFC	2577	M	bilateral vmPFC	ACoA aneurysm
vmPFC	3349	F	bilateral vmPFC	meningioma resection
vmPFC	3350	M	bilateral vmPFC	meningioma resection
vmPFC	3534	F	bilateral vmPFC	meningioma resection

Note: “+” sign indicates additional damage to surrounding territories.

Figure 2. MRI scans of 4 patients with focal bilateral amygdala lesions. Patient 1465's lesion extends into additional territories in the right medial temporal lobe (including the hippocampus) and only infiltrates a small section of the left amygdala. Patients AM and BG are identical twins and both have additional minor damage to their entorhinal cortices. Patient SM's lesion also extends into the entorhinal cortex and has recently progressed into the basal ganglia and adjacent white matter. There are no evident signs of damage to the hippocampus in patients AM, BG, or SM.

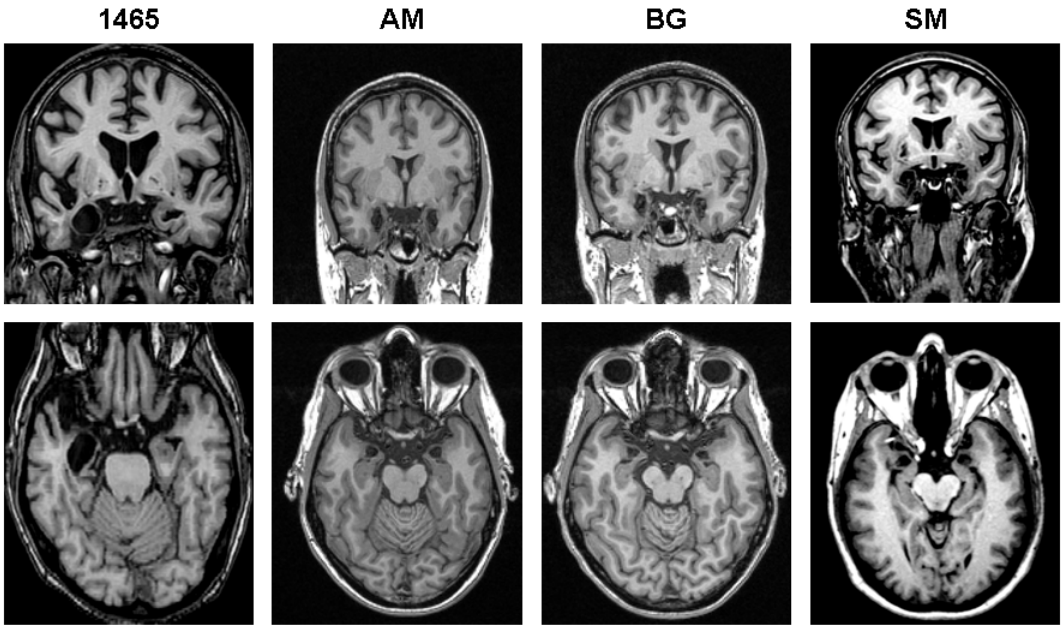


Figure 3. MRI scans of patient 3082 showing bilateral damage (left hemisphere greater than right hemisphere) to the supplementary motor area and the dorsal sector of the ACC.

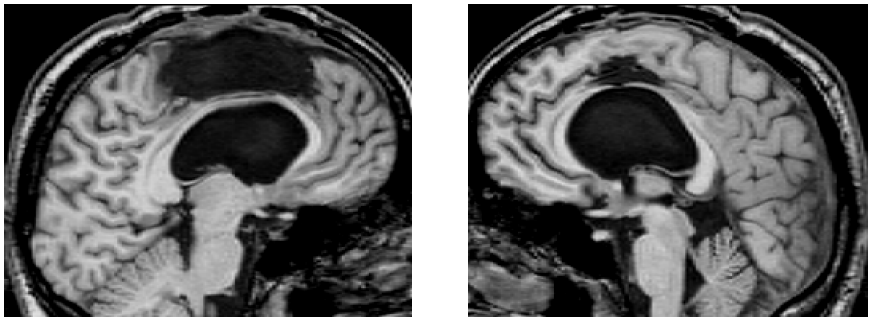


Figure 4. MRI scans of patient SZ's brain. (A) Axial slice depicting bilateral damage to the medial temporal lobe, medial temporal poles, and unilateral damage to a large region of the left temporal lobe. (B & C) Axial slices depicting bilateral damage to the insular cortex and left-sided damage to the basal forebrain and posterior orbitofrontal cortex. (D) Coronal slice depicting bilateral damage to the temporal poles (with only the medial temporal pole affected on the right side), and unilateral damage in the region of the left basal forebrain. (E) Coronal slice depicting bilateral damage to the amygdala and insula, and unilateral damage to a large region of the left temporal lobe damage. (F) Coronal slice depicting bilateral hippocampal damage and some residual damage to the left temporal cortices and left posterior insula.

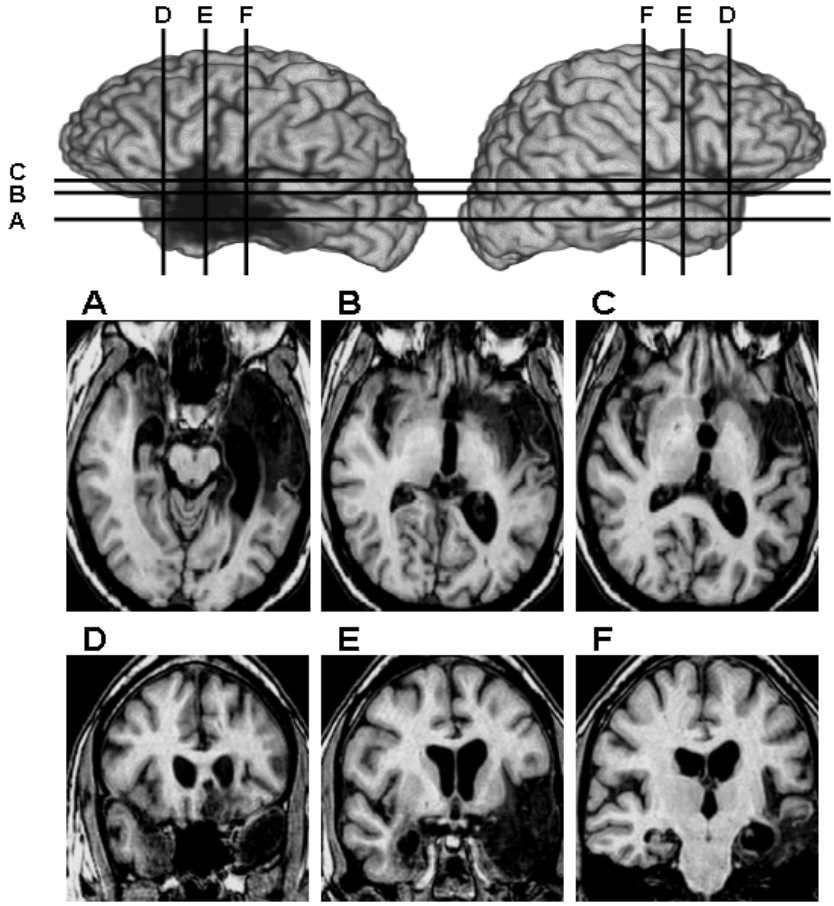


Figure 5. Lesion overlap map of the 10 insula-lesioned patients (7 patients with unilateral right insula damage and 3 patients with unilateral left insula damage). The surface of the brain has been removed to expose the underlying insular cortices. While the lesions include many of the surrounding territories, maximum overlap in each hemisphere occurs in the region of the anterior insula.

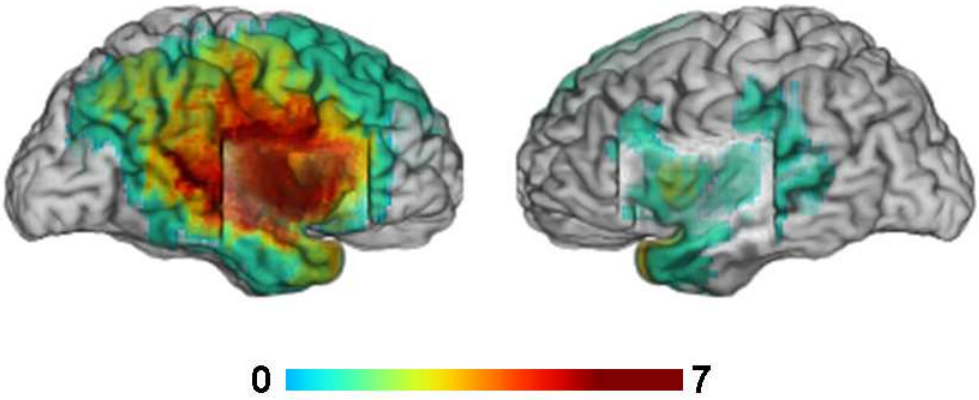
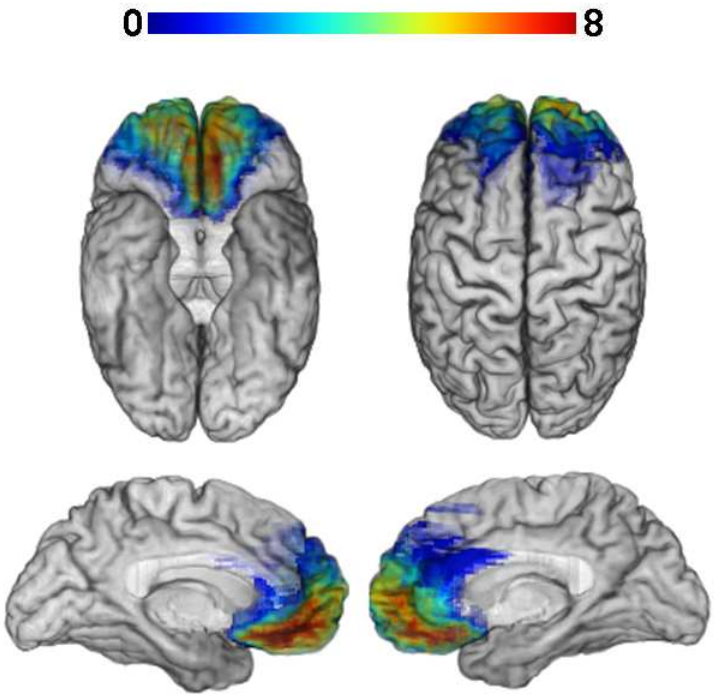


Figure 6. Lesion overlap map of the 8 bilateral vmPFC-lesioned patients. Maximal overlap occurs in the medial orbitofrontal/prefrontal cortices extending into the subgenual anterior cingulate.



Basic neuropsychological data

As previously noted, all patients have been extensively characterized across a large number of different neuropsychological tests. Table 3 reports several basic summary scores for each group of participants including their general intellectual functioning (Full-Scale IQ), their general ability to remember information over a long delay (General Memory Index), their basic attention and capacity for holding onto information over a short delay (Working Memory Index), their basic reading abilities (Reading), their aural comprehension (Token test), and their ability to perceive and discriminate complex visual information (Benton faces). In sum, none of the patients had severe defects in intellectual functioning, basic attention, language, or visual perception that would confound the interpretation of their performance on the experimental task. Their scores were largely within normal limits on nearly all of the tests. The only exception is the severe memory defect found in the hippocampal and MT+ groups; all patients within these groups demonstrated at least a 25-point difference between their general intelligence and memory (i.e., FSIQ – GMI $\geq$ 25). Furthermore, on other tests of declarative memory, both the hippocampal-lesioned and MT+ patients were unable to retain information over a 30-minute delay, consistent with a severe anterograde amnesia.

Basic emotional functioning data

Prior to starting the experiment, all participants completed a series of baseline questionnaires aimed at probing their basic emotional functioning (Table 4). The PANAS provided a measure of trait positive and negative affect, whereas the IDAS provided a measure of each participant's current level of depression. As compared to a normative sample of 370 healthy community adults living in eastern Iowa (Watson et al., 2007), both the patients and the comparisons reported experiencing less depression, on average. Likewise, both the patients and the comparisons reported levels of trait negative affect that were typically several points lower than the normative mean (cf. Watson,

Clark, & Tellegen, 1988). Thus, most participants in this study did not report elevated levels of negative affect or depression. There were, however, some participants with reduced levels of trait positive affect. In general, none of the participants reported values on these measures that would be indicative of severe emotional turmoil, and as previously noted, all participants explicitly denied having any current psychiatric conditions.

Table 3. Basic neuropsychological data.

Group	FSIQ (WAIS-III)	GMI (WMS-III)	WMI (WAIS-III)	Reading (WRAT-R)	Token test	Benton faces
amy (4)	98.8 (9.2) 88-110	89.0 (2.8) 87-91	87.0 (1.4) 86-88	88.0 (12.7) 79-97	43.5 (0.7) 43-44	43.8 (6.4) 36-50
BDC (8)	106.8 (12.0) 85-120	104.2 (7.7) 92-112	106.1 (13.7) 86-126	98.3 (8.8) 81-109	43.3 (1.1) 41-44	44.8 (4.6) 39-52
dACC (1)	85.0	95.0	92.0	87.0	44.0	49.0
hipp (4)	97.8 (9.9) 84-107	70.8 (9.4) 57-78	92.5 (6.4) 88-102	95.3 (5.4) 90-102	43.0 (1.4) 41-44	46.0 (1.2) 45-47
ins (10)	102.2 (11.0) 82-116	109.0 (16.2) 92-130	96.6 (7.7) 84-106	96.6 (10.1) 76-112	42.1 (2.6) 36-44	44.5 (4.2) 39-50
MT+ (2)	96.5 (13.4) 87-106	51.0 (8.5) 45-57	97.0 (15.6) 86-108	107.0 (2.8) 105-109	44.0 (0) 44-44	45.5 (2.1) 44-47
vmPFC (8)	109.9 (16.6) 84-143	106.0 (16.7) 74-132	107.3 (10.8) 86-121	103.1 (8.7) 86-116	43.9 (0.4) 43-44	45.8 (4.1) 41-50

Note: Each cell contains the group mean (with the SD in parentheses) and the range of scores immediately below. Scores are reported as standard scores except the Token Test and Benton Facial Discrimination Test which are reported as raw scores. WAIS–III = Wechsler Adult Intelligence Scale–Third Edition; WMS–III = Wechsler Memory Scale–Third Edition; WRAT–R = Wide Range Achievement Test–Revised; FSIQ = Full-Scale IQ; GMI = General Memory Index; WMI = Working Memory Index. The total number of participants in each group is displayed next to the group name in parentheses.

Table 4. Basic emotional functioning data.

Group	General PA (PANAS)	General NA (PANAS)	General Depression (IDAS)
Previously reported norms	35.0 (6.4)	18.1 (5.9)	44.99 (14.75)
Normal comparisons (40)	34.6 (6.5) 18 - 47	12.7 (3.0) 10 - 20	30.0 (6.7) 20 - 59
amy (4)	27.3 (13.5) 13 - 42	16.8 (3.5) 15 - 22	34.7 (4.2) 30 - 38
BDC (8)	28.5 (9.9) 15 - 42	14.4 (4.9) 10 - 24	36.0 (11.0) 22 - 56
dACC (1)	31.0	11.0	38.0
hipp (4)	39.8 (6.5) 34 - 49	14.8 (4.9) 10 - 21	32.0 (12.2) 21 - 48
ins (10)	28.3 (8.9) 17 - 43	13.4 (4.7) 10 - 22	33.8 (8.3) 24 - 50
MT+ (2)	36.0 (11.3) 28 - 44	10.5 (0.7) 10 - 11	23.0 (1.4) 22 - 24
vmPFC (8)	33.5 (7.2) 24 - 47	11.4 (1.3) 10 - 13	30.8 (5.6) 25 - 40

Note: Each cell contains the group mean (with the SD in parentheses) and the range of scores immediately below. All scores are raw scores. The previously reported norms are derived from large samples of healthy participants. The total number of participants in each group is displayed next to the group name in parentheses.

Film emotion induction procedure

The procedure entailed 9 separate emotion inductions using film clips (see Table 5). Five inductions aimed at inducing specific emotions (i.e., anger, disgust, fear, sadness, and happiness) and two inductions aimed at inducing more diffuse emotional states (i.e., positive affect and negative affect). These seven emotion inductions were chosen to provide a broad sampling across the hierarchical organization of emotion experience alluded to in the introduction section. Additionally, there were two neutral control inductions using film clips that were largely unemotional in nature.

Table 5. Description of the 9 different film inductions.

Emotion	Title	Source	Length	Brief Description
Anger	The Burning Bed	Movie	4:21	A woman is physically abused by her husband
Disgust	Pink Flamingos* & Trainspotting*	Movies	2:08	A man searches through a filthy toilet & a transvestite eats dog feces
Fear	The Grudge	Movie	6:06	An evil supernatural force tries to possess and then kill its victims
Sadness	The Champ*	Movie	2:46	A little boy's father dies from a boxing accident
Happiness/ Amusement	America's Funniest Home Videos	Television	2:45	A collage of funny scenes involving babies laughing and practical jokes
Positive Affect	Ladder 49 & Love Actually	Movies	2:39	A celebration after a man learns his wife is pregnant & scenes of friends and family members greeting each other at the airport
Negative Affect	Schindler's List	Movie	2:59	Nazi liquidation of a Jewish ghetto during the Holocaust
Neutral-NA (NeuNA)	Antiques Roadshow	Television	2:03	A man discusses antique perfume bottles
Neutral-PA (NeuPA)	Physics Lecture	Internet	1:35	A college professor gives a lesson on quantum mechanics

Note: * denotes emotional film clips that have been validated in previous studies.

The film clips were specifically chosen based on the following criteria:

(1) Short duration: The average film length is just over 3 minutes, making it feasible to test multiple emotions in a single experimental session. Utilizing short film clips improves the probability that a severely amnesic patient will still be able to successfully follow the storyline without losing track of the details occurring during the early portion of the film. While the fear film is longer than the others, this was done on purpose since a key ingredient for the effectiveness of horror films requires the build-up of anticipation. Furthermore, research suggests that the total length of the film clips should not significantly alter the post-film affective ratings (Fredrickson & Kahneman, 1993).

(2) Self-contained: The film clips were specifically selected and edited to be self-contained inducers of the appropriate emotion. In other words, all of the information

necessary to evoke an emotional response was contained within the clip, and thus, an understanding of the context and plot surrounding each clip was not a prerequisite for the success of the emotion induction.

(3) Intensity: Film clips were selected based on their ability to induce high levels of emotional intensity (with the exception of the neutral clips). Great effort was spent editing each film clip in order to maintain a high level of intensity throughout the entirety of the clip, with an aim of making the final segment of each clip the most intense.

(4) Specificity: For the specific emotion inductions (i.e., anger, disgust, fear, sadness, and happiness), films were specifically chosen based on their ability to elicit the target emotion. Other emotions may be also be elicited during the film, but their intensity is typically experienced at much lower levels compared to the intensity of the target emotion (Gross & Levenson, 1995; Philippot, 1993; Schaefer et al., 2010). All films have been extensively piloted in our laboratory and three of the films used in this study have been validated by previous studies (Gross & Levenson, 1995; Schaefer et al., 2010).

Outline of procedures

The entire experiment was completed in an approximately 2-hour testing session with a short break in the middle. Each subject was individually tested in a private room with dimmed lights while seated in a comfortable chair approximately five feet away from a computer monitor with external speakers. All subjects passed a brief visual screening test to ensure they could read the questions on the computer monitor. All stimuli were presented using a paradigm designed in Matlab, ensuring accurate and consistent timing across subjects, while minimizing the experimenter interactions with the subject. The experimenter was seated behind a wall outside of the subject's view. All emotion ratings were made by pressing a left or right arrow button on an Ergodex

DX1 keyboard. Electrodes were used to measure each participant's skin conductance and heart rate. In addition, a small webcam with a built-in microphone was used to record each participant's facial expression, body posture, and vocalizations during the experiment. The psychophysiological recordings and video/audio recordings will be the subject of a separate analysis (not reported in this thesis) because the specific aims of the present investigation are focused on emotion experience rather than on the physiological or behavioral aspects of emotion expression.

Before starting the emotion induction procedure, participants were read the following statement in order to minimize demand characteristics, "Every person experiences emotions differently. Some people experience a lot of emotion; some people experience very little emotion. Sometimes the emotion goes up over time, sometimes the emotion goes down over time, and sometimes it just stays the same. Throughout this experiment, there are no right or wrong answers. All that we ask is that you answer as honestly and accurately as possible."

Timeline of emotion induction

Each emotion induction followed the same timeline. First, participants underwent a standardized 1-minute breathing relaxation exercise meant to mitigate any crossover effects of residual emotion from the previous induction. Second, participants completed a series of baseline questions asking them to rate their current level of fear, sadness, anger, happiness, disgust, overall positive emotion, and overall negative emotion. Third, participants watched one of the film clips (see Table 5). The films were shown in a pseudo-randomized order such that each negative film was always followed by either a positive film, a neutral film, or a ~5-minute break, in order to control for any additive effects of showing two films of the same valence, one after the other (Branscombe, 1985). For all subjects, the order of the films was as follows: Negative Affect, Neutral-NA, Sadness, Happiness, Fear, break, Disgust, Neutral-PA, Anger, and Positive Affect.

Immediately following the end of each film, participants answered a series of 6 questions (Table 6).

Table 6. Questions asked during specific time intervals within the 3-minute emotion recovery period immediately following the end of each film clip.

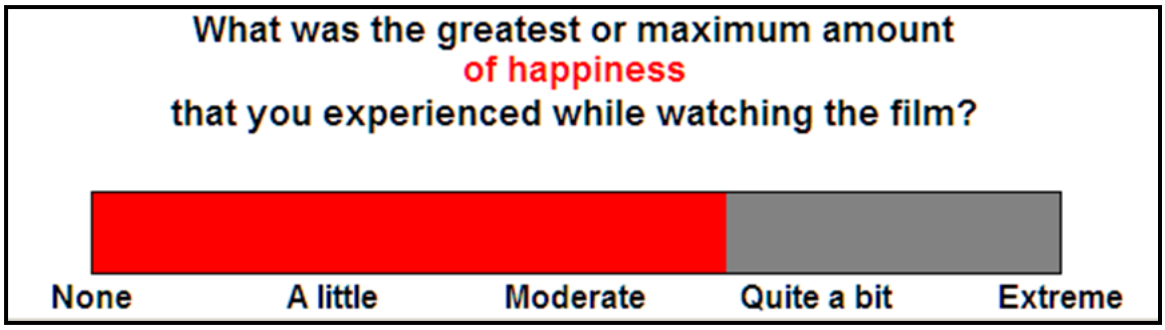
Q1)	1-22 seconds post-film: "Which emotion BEST describes the film you just watched? (Choose one) Neutral – Happy – Sad – Fear – Anger – Disgust"
Q2)	23-45 seconds post-film: "What was the greatest or maximum amount of [target emotion] that you experienced while watching the film?"
Q3)	60-75 seconds post-film: "How much [target emotion] do you feel right now?"
Q4)	90-105 seconds post-film: "How much [target emotion] do you feel right now?"
Q5)	120-135 seconds post-film: "How much [target emotion] do you feel right now?"
Q6)	165-180 seconds post-film: "How much [target emotion] do you feel right now?"

The [target emotion] will be one of the following terms based on the particular film shown (see Table 5): "anger", "disgust", "fear", "sadness", "happiness", "positive emotion" (for the Positive Affect and Neutral-PA films), and "negative emotion" (for the Negative Affect and Neutral-NA films). Question 1 probes for whether a participant can correctly recognize the target emotion of the film clip. Question 2 probes for the peak intensity of the target emotion that was experienced while watching the film clip. Questions 3-6 measure the recovery of emotion up to 3-minutes post-film. A fixation cross was displayed during the interval between questions and no explicit instructions were given during this time period.

The specific timing of each question was chosen following extensive piloting and taking into consideration the slowed processing speed in patients with brain damage. All questions remained on the screen for the entirety of the specified time period, even if the

subject had finished answering the question. Answers to question 1 were provided by pressing the left or right arrow buttons until the desired choice was highlighted. Answers to questions 2-6 (as well as all baseline questions) were provided using a 100-point modified visual analogue scale (VAS) that used a sliding red thermometer that could be adjusted using the left or right arrow buttons (Figure 7). The VAS contained 5 anchor terms (None, A little, Moderate, Quite a bit, Extreme) located at the 0, 25, 50, 75, and 100 point-markers. The anchor terms were derived from the PANAS and helped ensure that subjects were using the VAS in a consistent manner.

Figure 7. 100-point modified visual analogue scale used by participants to report their emotional state. This is an example screen shot of question 2 following the happiness film clip, where a subject indicated that they experienced a level of happiness equal to 65 (out of 100).



Data analysis

Dependent variables

For each emotion induction, subjects rated their emotion experience across 6 time points:

- t1 = baseline emotion (measured immediately before each film)
- t2 = peak emotion (measured shortly after each film)
- t3-t6 = emotion recovery (measured during the previously specified time intervals over the course of 3-minutes)

Based on these measurements, 3 primary dependent variables were computed and compared between individual patients and the comparison samples (see section on analysis strategy below):

1. The effectiveness of each emotion induction was computed as the change score from baseline to peak emotion (i.e., t2-t1).
2. The short-term magnitude of emotion recovery was computed as the change score from peak emotion to the first emotion recovery measurement assessed 60-seconds after the film (i.e., t2-t3).
3. The sustained experience of emotion was computed as the change score between baseline and the emotion remaining at the end of the 3-minute recovery time period (i.e., t6-t1).

Analysis strategy

The small number of target patients in each lesion group limits the ability to make strong inferences or conclusions based on robust statistical tests. In particular, small and unequal sample sizes often violate core assumptions of parametric tests, including the normal distribution of data and homogeneity of variance. While nonparametric tests can help overcome violations of normality, they often assume equal variance, and by their very nature, are insensitive to the degree of abnormality of an individual patient's score (since all data are rank-ordered). Beyond statistical issues, there are also other important issues that should be considered when conducting group studies of lesion patients. For example, group studies eliminate individual differences that could potentially offer important insights for understanding brain-behavior relationships. Also, it is difficult to account for all of the factors that are different between the lesion patients who are being grouped together, including differences in the lesion size and location, the specific etiology that caused the lesion, the elapsed time since the onset of the lesion, and myriad differences in the premorbid functioning of each patient. Some researchers have even

argued that single-case studies are a more valid method than group studies for making inferences about the functional organization of the brain (e.g., Caramazza, 1986; Shallice, 1979). For all of the aforementioned reasons, I decided to approach the analysis by examining each patient, individually. By treating each patient as a single-case study, the analysis offers the chance to make more precise inferences with regard to the reliability of specific brain-behavior relationships. While group averages for different lesion sites will be presented in figures as an efficient means of conveying the results, the data for each lesion patient will be systematically compared (as described in the paragraph below) to the distribution of scores obtained for each dependent variable in a healthy gender-matched sample.

A special method has been devised for analyzing neuropsychological data pertaining to single-case studies (Crawford & Howell, 1998). The method uses a modified t-test in order to estimate the abnormality of an individual patient's score and to test whether it is significantly different than the scores of a comparison sample. Based on this method, the presence of a deficit has been operationalized as follows (using the criteria proposed by Crawford, Garthwaite, & Gray, 2003): (a) if the modified t-test reveals that the patient's score is significantly different than the comparison sample ($p<0.05$, one-tailed), it is concluded that the patient is "impaired" or "has a deficit", (b) if the test is not significant then, for present purposes, it is considered that the patient is "not impaired" or "within normal limits". Importantly, this method controls for Type 1 error rate significantly better than using z-scores to determine a deficit, and is robust even in the face of a comparison sample that is small and a distribution that is skewed and/or leptokurtic (Crawford & Garthwaite, 2005; Crawford, Garthwaite, Azzalini, Howell & Laws, 2006).

Exponential decay analysis

Finally, an exploratory analysis was undertaken to examine whether a model of exponential decay would provide a good fit to explain the average recovery of negative emotions. Due to the large variation in baseline positive affect and the sizeable minority of subjects who failed to show a meaningful increase in positive emotion after the happiness and PA films, I was unable to apply such a model (at least in its simplest form) to the positive emotion recovery data.

A model of exponential decay has the following formula: $N(t) = N_o e^{-\lambda t}$, where $N(t)$ is the quantity at time t, N_o is the quantity at time 0, and λ (lambda) is the decay constant. Exponential functions were fitted to the emotion ratings for each subject in order to estimate the corresponding exponential parameters, including the rate of decay (lambda). Unconstrained nonlinear optimization was used, which finds the minima of unconstrained multivariable functions using derivative-free methods (Lagarias et al, 1998). Each subject's observed ratings at t2 were used as the initial parameter for the estimation of N_o (i.e., the amplitude at time 0). Each subject's curve was visually inspected for quality control. All analyses were completed in Matlab.

CHAPTER 5

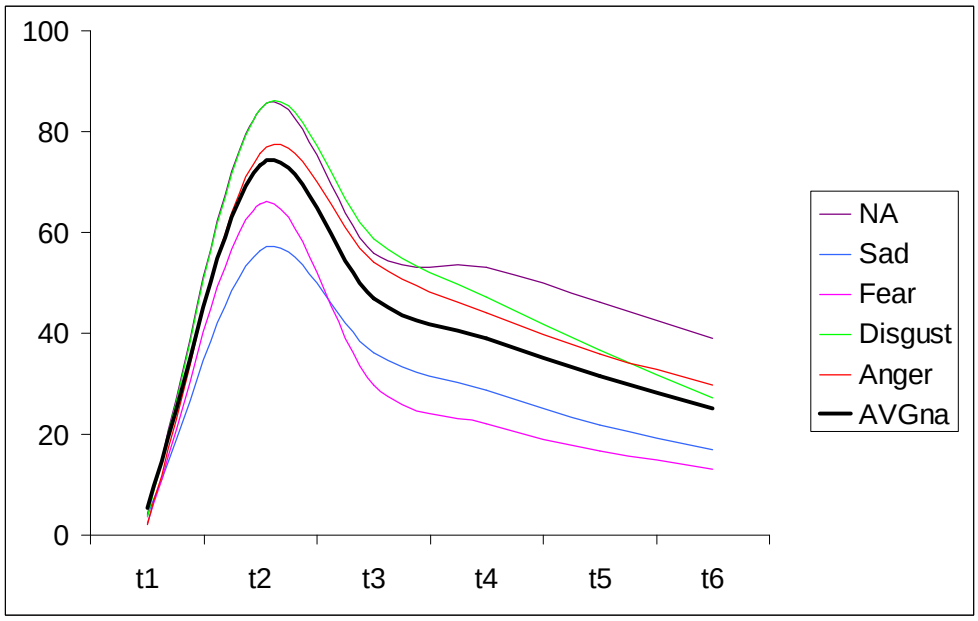
RESULTS

Preliminary analyses

Inspection of the normal comparison data

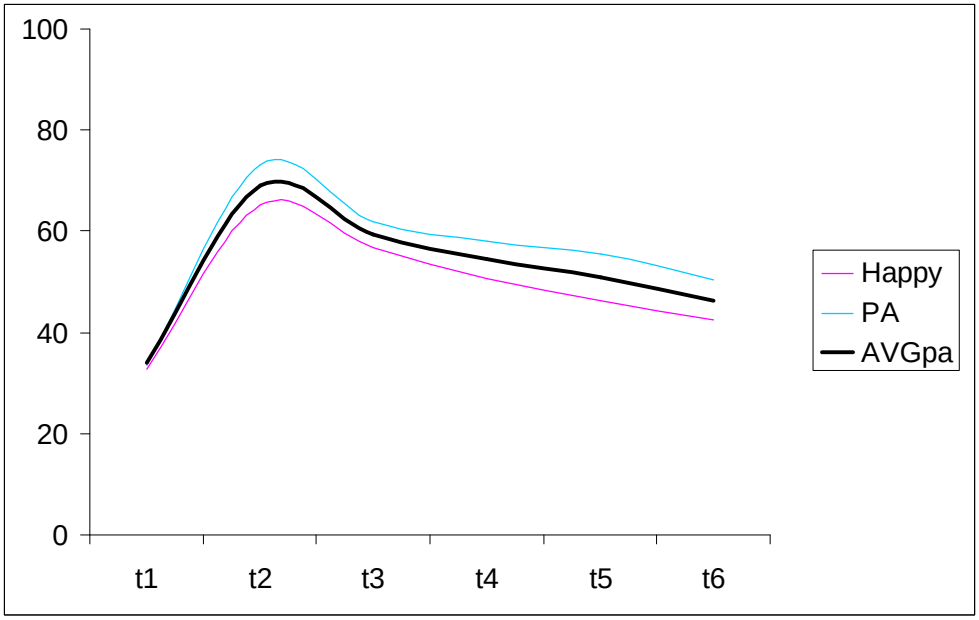
The 5 negative film clips each followed a similar pattern (Figure 8): (1) a low baseline level of the respective negative emotion prior to watching the film, (2) a sharp rise to the peak level of induced emotion during the film, and (3) a gradual, but incomplete, recovery of the induced emotion over the 3-minute emotion recovery period after the film. A composite average of the data for the 5 negative films appears to provide a decent model of this overall pattern (see "AVGna" line in Figure 8). On average, the disgust and NA films induced the highest level of emotion, whereas the sad film induced the least. Fear showed a slightly quicker recovery than the other film clips, whereas the negative emotion induced by the NA film showed the slowest recovery.

Figure 8. Average amount of emotion reported by the normal comparisons for each of the 5 negative film clips, as well as a composite average of all the negative films ("AVGna"). The y-axis ranges from 0-100 using the modified VAS. The x-axis contains the 6 time points of each induction (t1=baseline, t2=peak emotion, t3-t6=recovery).



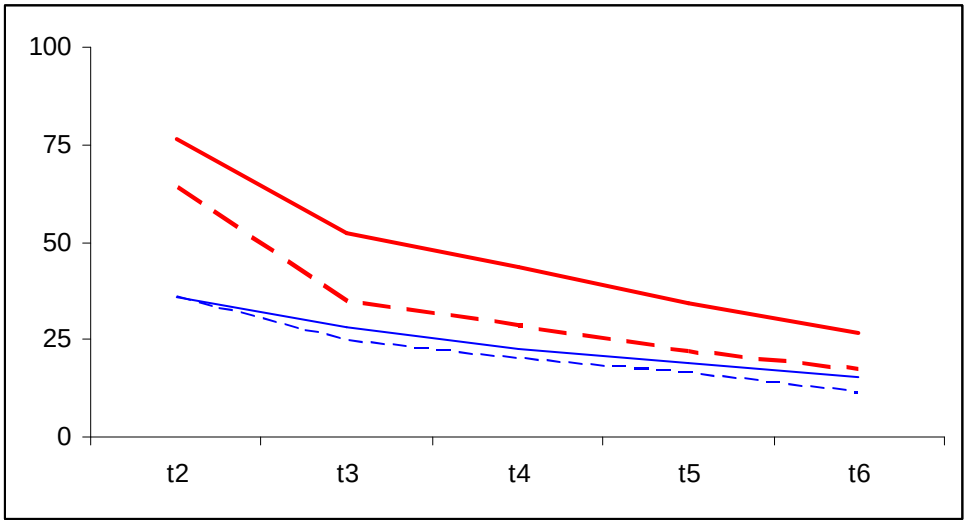
The 2 positive film clips each followed a similar pattern (Figure 9): (1) a high baseline level of positive emotion prior to watching the film, (2) a moderate rise to the peak level of induced emotion during the film, and (3) a gradual, but incomplete, recovery of the induced emotion over the 3-minute emotion recovery period after the film. A composite average of the data for the 2 positive films appears to provide a decent model of this overall pattern (see "AVGpa" line in Figure 9). On average, the PA film induced slightly higher levels of emotion than the happiness film. Even though the maximum level of induced emotion for the 2 positive films is comparable to the peak intensity levels induced during the negative films, the overall change from baseline is far smaller for the positive films (due to the high baseline level of positive emotion).

Figure 9. Average amount of emotion reported by the normal comparisons for the 2 positive film clips, as well as a composite average of both positive films ("AVGpa"). The y-axis ranges from 0-100 using the modified VAS. The x-axis contains the 6 time points of each induction (t1=baseline, t2=peak emotion, t3-t6=recovery).



Previous studies using films to induce emotion have found that women experience significantly more intense levels of negative emotion than men (e.g., Gross & Levenson, 1995; Hagemann et al., 1999; Schaefer et al., 2010). Consistent with this finding, the data from this study revealed a significant main effect of gender for the normal comparisons, $F(1,38)=6.3$, $p<.05$, indicating that females experienced more intense levels of negative emotion as compared to men (Figure 10). There was no significant difference found for the positive films, $F(1,38)=0.2$, *ns*. Given this significant gender difference for the negative films, all statistical tests with individual brain damaged patients will be computed using gender-matched normal comparison data.

Figure 10. Gender differences. A significant difference between genders was found in the normal comparisons for the average of the negative emotion inductions (red), but not for the average of the positive emotion inductions (blue). Specifically, females (solid lines) reported significantly more intense states of negative emotion than men (dashed lines). All values on the y-axis represent the change from baseline. The x-axis contains the five post-film ratings (t2=peak emotion, t3-t6=recovery).



Emotion recognition

Immediately after watching each film clip, the participant was first asked to identify the emotion that best describes the film they just watched using a 6-option alternative forced-choice response (neutral, happy, sad, fear, anger, or disgust). This question was primarily aimed at ensuring that subjects have a basic understanding and recognition for the primary target emotion of each film.

The results for the normal comparisons will first be discussed (see Table 7). The NA film (which aimed to elicit a diffuse and varied state of negative emotion) generated a range of responses characterized by a mixture of sadness, anger, and disgust. In addition, both the fear and anger films generated some disgust responses, and the NeuNA film generated some happy responses. A small number of subjects rated some of the emotional films as being neutral. No subject rated any of the negative films as being happy. A single subject rated the happy film as disgust, claiming that they were disgusted by some of the practical jokes. Another subject rated the PA film as sad because it caused her to reflect on the loneliness in her own life. With the exception of the NA film (which has no definitive correct response), healthy subjects correctly recognized the primary target emotion of the film 87% of the time (on average), ranging from 60% for anger to 100% for disgust.

The brain damaged patients showed similar recognition scores in comparison to the healthy non-brain damaged sample (Table 8). Once again, the NA film generated a range of responses characterized by a mixture of disgust, sadness, anger, and fear. In addition, the anger film generated some disgust and fear responses, and the NeuNA film generated some happy responses. A small number of subjects rated some of the emotional films as being neutral. No subject rated any of the negative films as being happy or any of the positive films as being negative. The one exception is patient BG, a woman with focal bilateral amygdala damage, who rated the disgust film as happy. Of note, patient BG was observed intensely laughing throughout the duration of the disgust

film and found it to be highly amusing, even though she stated that most people would find it disgusting. With the exception of the NA film (which has no definitive correct response), brain damaged patients correctly recognized the primary target emotion of the film 88% of the time (on average), ranging from 58% for anger to 100% for the happiness and PA films.

Table 7. Emotion recognition for the normal comparisons.

	NA	Fear	Disgust	Anger	Sad	PA	Happy	NeuNA	NeuPA
Neutral	2.5%	5%	0	0	2.5%	2.5%	5%	82.5%	90%
Happy	0	0	0	0	0	95%	92.5%	17.5%	2.5%
Sad	35%	0	0	10%	95%	2.5%	0	0	2.5%
Fear	2.5%	82.5%	0	5%	0	0	0	0	2.5%
Anger	35%	0	0	60%	2.5%	0	0	0	0
Disgust	25%	12.5%	100%	25%	0	0	2.5%	0	2.5%

Note: Each column represents one of the 9 film inductions and each row represents one of the 6 possible response options. Each cell contains the percent of subjects (out of 40) that chose that response.

Table 8. Emotion recognition for the brain damaged patients.

	NA	Fear	Disgust	Anger	Sad	PA	Happy	NeuNA	NeuPA
Neutral	0	2.5%	0	2.5%	2.5%	0	0	76%	85%
Happy	0	0	2.5%	0	0	100%	100%	24%	5%
Sad	24%	0	0	8%	95%	0	0	0	2.5%
Fear	11%	95%	0	13%	0	0	0	0	0
Anger	22%	0	0	58%	0	0	0	0	2.5%
Disgust	43%	2.5%	97.5%	18.5%	2.5%	0	0	0	5%

Note: Each column represents one of the 9 film inductions and each row represents one of the 6 possible response options. Each cell contains the percent of subjects (out of 37) that chose that response.

Taken together, these results indicate that both brain damaged and healthy subjects clearly recognized the primary emotion that each film aimed to induce. On average, healthy subjects correctly recognized the target emotion 87% of the time and brain damaged patients correctly recognized the target emotion 88% of the time. This suggests that the films were successful at conveying the appropriate emotion. Moreover, it suggests that deficits in the realm of emotion experience are unlikely to be directly attributable to a primary deficit in emotion recognition. For example, all of the amygdala-lesioned patients tested during the present experiment correctly recognized fear as being the primary emotion during the fear film, even though some of these same patients have previously shown deficits in recognizing fear in static pictures of faces (e.g., Adolphs et al., 1995; Becker et al., in press). Static pictures of faces offer no contextual cues and only stimulate the visual pathway. On the other hand, the film clips display numerous contextual cues using a dynamically changing presentation that stimulates multiple pathways (including vision and hearing). Thus, it is not surprising that most patients (including those with amygdala lesions) were able to easily recognize the target emotion.

While the intended emotion was patently obvious for most films, there appeared to be some ambiguity for three of the films: NA, anger, and NeuNA. The NA film was purposefully meant to induce a range of negative emotions, and the emotion recognition data suggests that it did, with responses encompassing all of the different negative emotions. On the other hand, the anger film was meant to induce mostly anger, but the responses revealed a mix of negative emotions comprised mostly of anger and disgust, which is in accordance with the observation that many subjects later reported feeling a high degree of "contempt" for the male aggressor in the film. The NeuNA film was meant to be mostly neutral, however, a sizeable minority of subjects rated it as happy, suggesting that it was not perceived as being entirely neutral. The remaining films – including fear, disgust, sadness, happiness, PA, and NeuPA – showed far less ambiguity,

with an average correct recognition of 92.5% for normal comparisons and 95.4% for brain damaged patients.

Neutral films

There were 2 different neutral films presented. One film (NeuNA) probed for overall changes in negative emotion and the other film (NeuPA) probed for overall changes in positive emotion. The NeuNA film induced essentially no negative emotion, and overall levels of negative emotion remained at floor level throughout the recovery period (Figure 11). Interestingly, there was a slightly elevated level of negative emotion during the baseline period (before the NeuNA film) for some individuals, a likely residue from the previous emotion induction using the NA film. The NeuPA film induced very little positive emotion (often less positive emotion than present during baseline), and during recovery the positive emotion quickly returned to its baseline level (Figure 12). Overall, these findings indicate that the neutral films did not induce an increase in either positive or negative emotion in both healthy subjects and brain damaged patients. Moreover, it provides evidence that subjects were not simply providing random ratings or following a rule-based system (e.g., always rating the peak emotion question high, and then rating less and less emotion with each recovery measurement).

Overall effectiveness of the emotion induction procedure

For any emotion induction procedure, the primary dependent variable for assessing the effectiveness of the induction is the overall change from baseline to the maximum or peak state of emotional experience (i.e., t2-t1). For the negative film clips, the average change from baseline to peak was consistently on the high end of the scale (around a 75-point change) for all subjects, healthy and brain damaged (Figure 13). In fact, many lesion groups reported experiencing intensity levels that were even higher than

the normal comparisons. This indicates that the negative film clips were highly effective at inducing the target emotion, even in patients with extensive bilateral limbic system damage.

For the positive film clips, the average change from baseline to peak was much more variable (Figure 14a), both within-groups and between-groups. However, much of this variability appears to be related to differences at baseline, since the average group values are very similar when examining the peak raw score (t2) without subtracting the baseline (Figure 14b). In order to further examine this issue, the baseline values for both negative and positive emotions were compared across groups. The negative emotions were consistently at floor level during baseline (Figure 15), whereas the positive emotions were much higher at baseline (Figure 16), especially for the MT+ group. This indicates that in many subjects, the positive film clips failed to induce a meaningful increase from baseline in either happiness or general positive affect, an unfortunate by-product of high baseline levels of positive emotion.

Figure 11. Average amount of negative emotion reported during the NeuNA film.

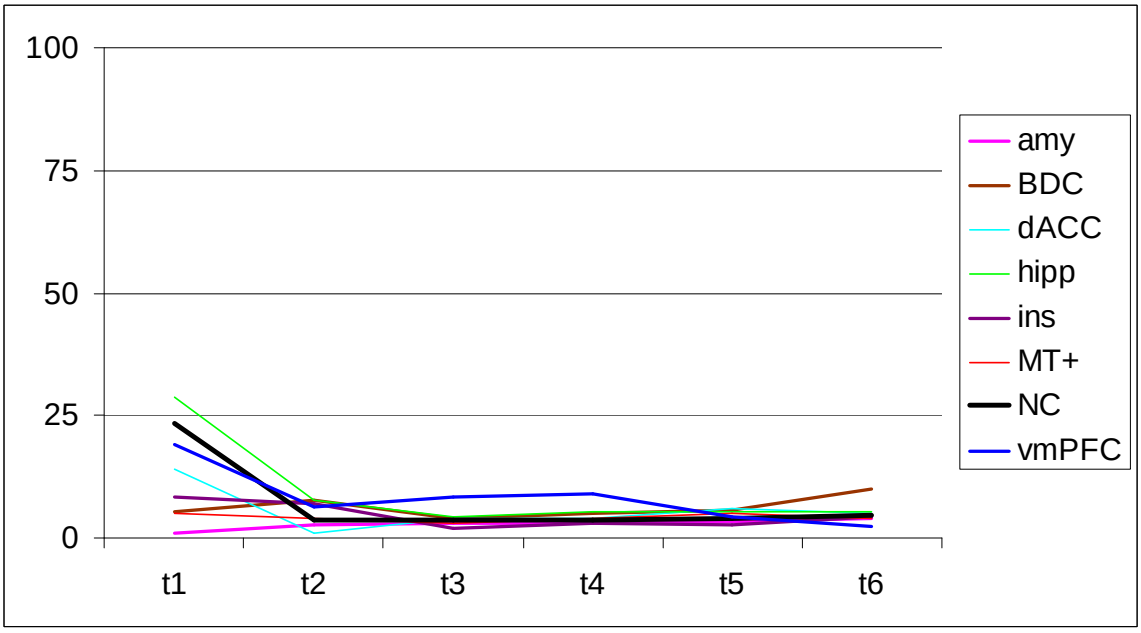


Figure 12. Average amount of positive emotion reported during the NeuPA film.

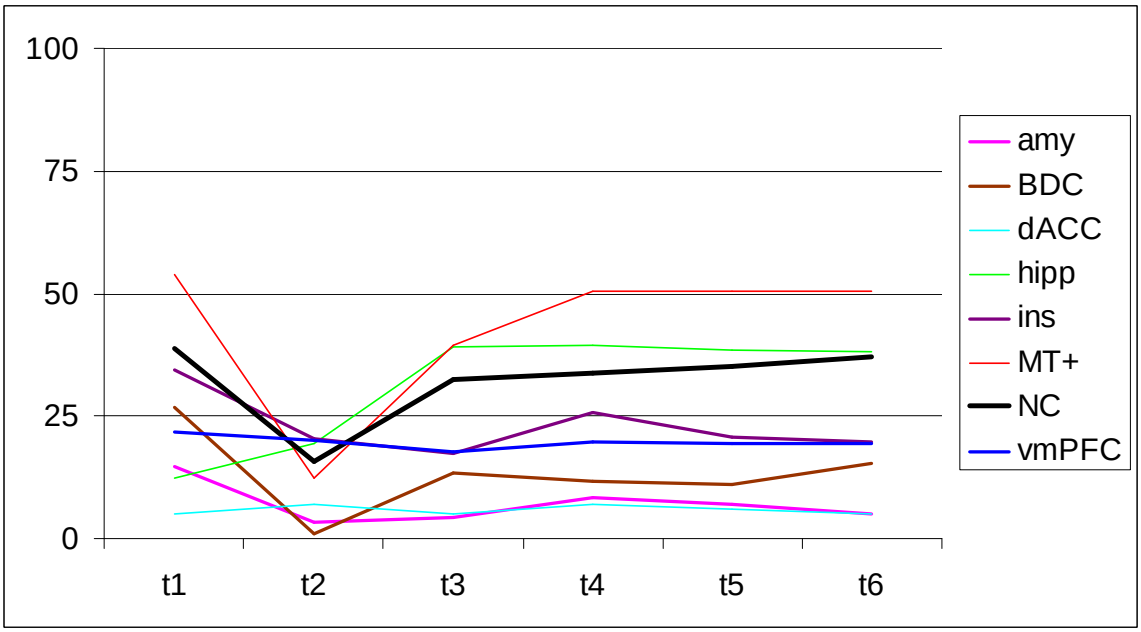


Figure 13. Average change from baseline to peak emotion for the composite average of the 5 negative film clips. Error bars represent the SD.

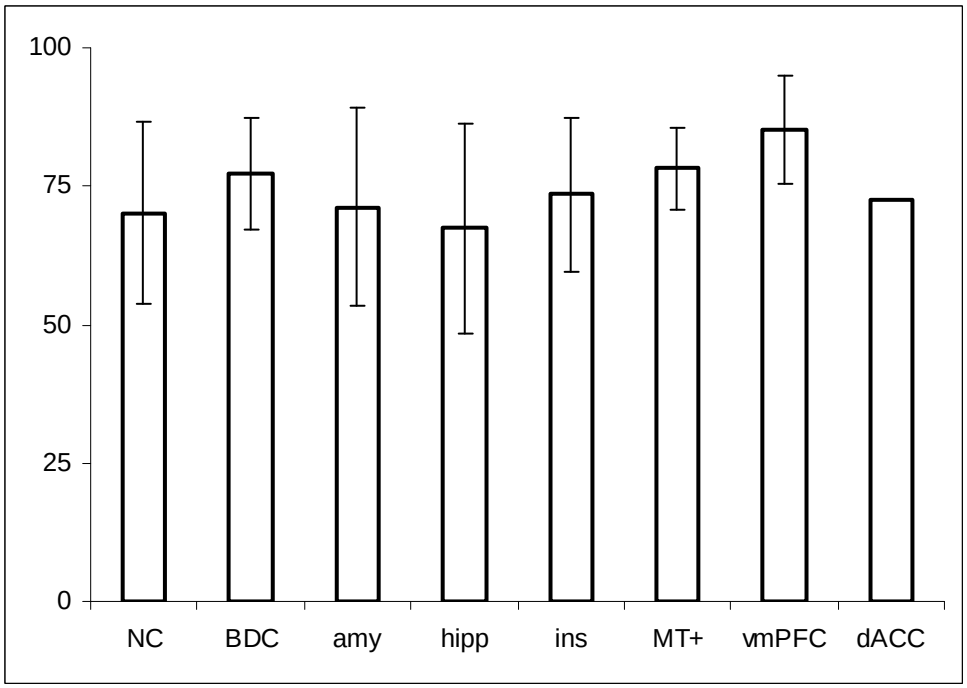


Figure 14. Effectiveness of the positive emotion inductions. (A) Average change from baseline to peak emotion, and (B) average peak emotion raw score (without subtracting baseline) for the composite average of the 2 positive film clips. Error bars represent the SD.

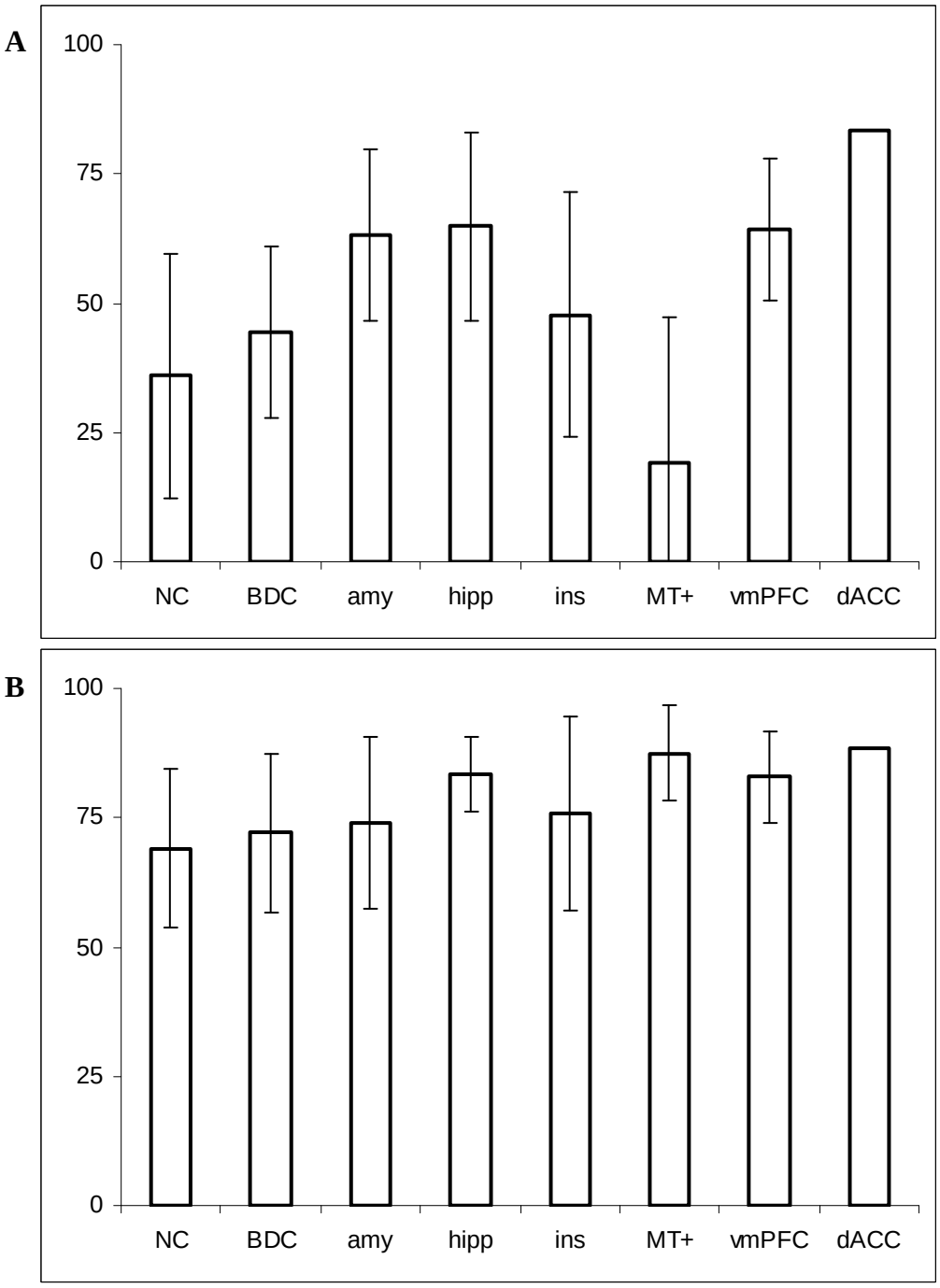


Figure 15. Average negative emotion reported at baseline. The higher mean for the hippocampus group is due to a single subject who reported high levels of negative emotion at baseline. Error bars represent the SD.

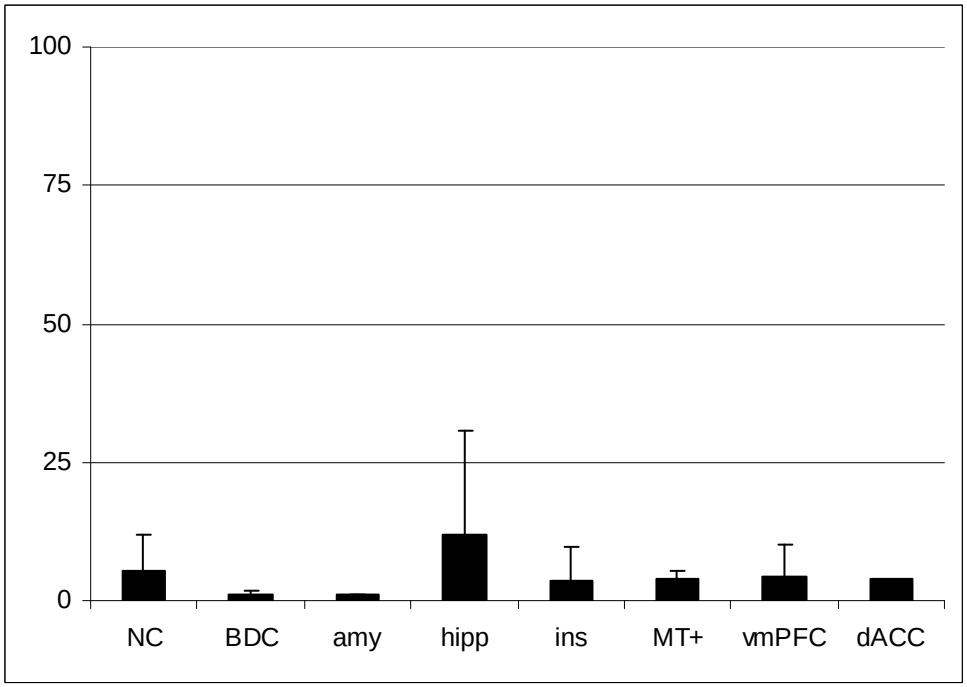
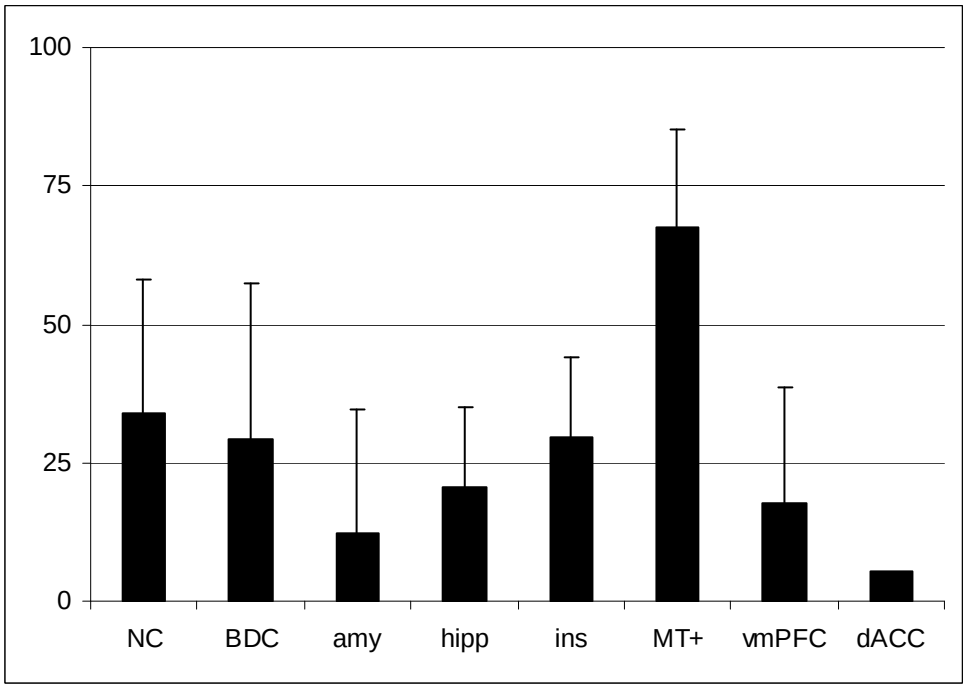


Figure 16. Average positive emotion reported at baseline. Error bars represent the SD.



Effectiveness of the specific emotion inductions

In order to examine for changes in specific emotions, several analyses were conducted at the individual subject level. The first analysis examined how many subjects (in each group) failed to show at least a small increase in emotion. A small increase was operationalized as a minimum 25-point increase from baseline to t2 (i.e., t2-t1). For example, in cases where the baseline is at floor level, a 25-point increase (based on the modified VAS) would indicate that the subject reported feeling at least "a little" of the target emotion. Table 9 shows how many subjects (in each group, for each induction) showed less than a 25-point increase from baseline to t2.

For both neutral inductions, nearly every subject met this criterion, which provides further evidence that the neutral films did not induce any meaningful increases in either positive or negative emotion. In contrast, for the negative emotion inductions, very few subjects met this criterion, whereas, for the positive emotion inductions, about a third of the normal comparisons failed to show at least a 25-point increase from baseline. Interestingly, across both negative and positive inductions, there were generally fewer brain damaged patients (in total) than normal comparisons who met this criterion, even though the total number of brain damaged patients (37) is nearly equal to the total number of normal comparisons (40). Furthermore, no consistent pattern within each patient group and across each emotion induction could be discerned. This suggests that, in general, the emotional film clips induced at least a little emotion in the vast majority of patients.

Table 9. Number of subjects in each group who reported less than a 25 point change from baseline to peak emotion (i.e., t2-t1), broken down by the 9 different inductions.

	NA	Fear	Disgust	Anger	Sad	PA	Happy	NeuNA	NeuPA
Normal (40)	0	5	0	2	5	12	16	40	38
BDC (8)	0	0	0	0	1	1	1	8	8
vmPFC (8)	0	1	0	0	0	1	2	8	7
dACC (1)	0	0	0	0	0	0	0	1	1
amygdala (4)	0	1	1	1	0	0	1	4	4
hipp (4)	1	1	0	0	0	0	1	4	3
insula (10)	1	0	1	0	1	0	2	10	8
MT+ (2)	0	0	0	0	0	1	2	2	2

Note: Numbers in parentheses represent the total number of subjects in that group.

The second analysis examined how many subjects in each group reported significantly less overall change in emotion (t2-t1) than the normal comparison sample using Crawford and Howell's (1998) modified t-test and gender-matched norms. Table 10 shows how many subjects (in each group, for each emotion induction) met the criteria for a significant impairment ($p<.05$). Once again, no consistent pattern emerged when examining each patient group separately for each emotion induction, suggesting that none of the lesion sites probed in this study generated a consistent emotion-specific impairment. The only possible exception would be for anger, where 2 out of 4 focal bilateral amygdala lesion patients met criteria for a significant impairment. Upon further inspection, it was found that these two patients were identical female twins from Germany. Their detected anger impairment may be more related to a language or cultural issue since both denied feeling "anger" during the film, but when further probed after the experiment, both reported feeling anger towards the male aggressor in the film. It is not

clear how or why they differentiated between these two types of anger. Nevertheless, neither twin has any notable anger impairment in everyday life since each of their husbands reported numerous instances where they were on the receiving end of their wife's anger.

Table 10. Number of subjects in each group who demonstrated a significant impairment ($p<.05$) of a specific emotion induction, broken down by the 7 different emotion inductions, as well as the average composite score for the negative and positive films.

	NA	Fear	Disgust	Anger	Sad	PA	Happy	AvgNA	AvgPA
BDC (8)	0	0	0	0	1	0	0	0	0
vmPFC (8)	1	1	0	0	0	0	0	0	0
dACC (1)	0	0	0	0	0	0	0	0	0
amygdala (4)	0	1	1	2	0	0	0	1	0
hipp (4)	1	0	1	0	0	0	0	1	0
insula (10)	0	0	1	0	0	0	0	0	0
MT+ (2)	1	0	0	0	0	0	0	0	0

Note: Numbers in parentheses represent the total number of subjects in that group.

The final analysis examined the three specific hypotheses with regard to emotion specific impairments: (1) amygdala damage elicits a fear impairment, (2) insula damage elicits a disgust impairment, and (3) subgenual ACC damage elicits a sadness impairment. With regard to the first hypothesis, there were 6 patients with bilateral amygdala lesions, 4 of whom reported fear levels within the normal range, 1 with a relatively low level of fear (BG), and only 1 patient (SM) who met criteria for a significant fear impairment (Figure 17). The detected fear impairment in SM replicates previous work (Feinstein et al., 2011), as does the noted discrepancy between low fear in BG and normal fear in her twin sister, AM (Becker et al., in press). The three cases with

adult-onset bilateral amygdala lesions (1465, Roger, and SZ) reported fear levels that were entirely within the normal range. With regard to the second hypothesis, 12 patients were tested with insula damage, and only a single patient with unilateral left insula damage (patient 1188) met the criteria for a significant disgust impairment (Figure 18). Interestingly, this same insula patient has previously reported feeling high levels of disgust triggered by the smell of cigarette smoking (Naqvi et al., 2007), suggesting that the detected disgust impairment may be specific to the film clip itself and not generalizable to his everyday life. The remaining 11 insula patients, including 2 patients with bilateral insula damage (Roger and SZ), reported peak disgust levels that were entirely within normal limits. Likewise, with regard to the third hypothesis, 10 patients were tested with damage that included aspects of the subgenual ACC, and all 10 patients reported peak sadness levels that were actually higher than the average sadness reported by both the normal comparison group and the brain damaged comparison group (Figure 19). Thus, none of the three hypotheses with regard to specific emotion impairments are supported by the current data.

Figure 17. Peak fear experience (minus baseline) for the fear film clip in patients with amygdala damage. Data are shown for 6 patients with bilateral amygdala damage, as well as the group average for the brain damaged comparisons (BDC) and normal comparisons (NC). 4 patients have relatively focal amygdala lesions (SM, BG, AM, and 1465) and 2 patients have damage throughout the limbic system (Roger and SZ). Error bars represent the SD.

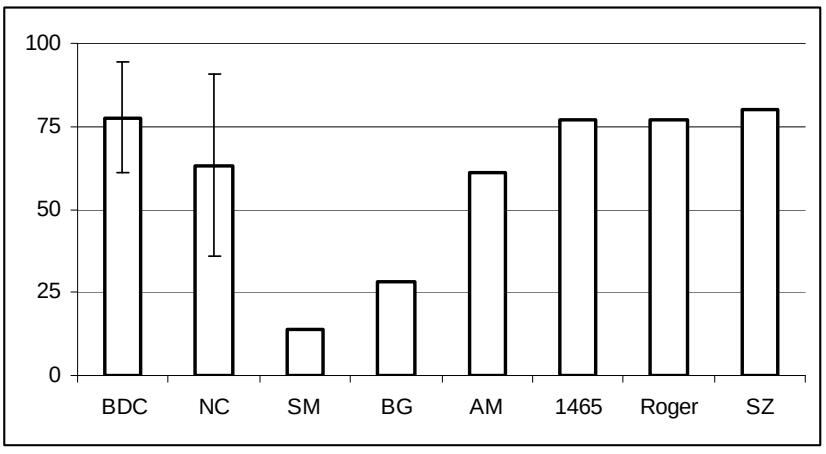


Figure 18. Peak disgust experience (minus baseline) for the disgust film clip in patients with insula damage. Data are shown for 3 patients with left insula damage (1188, 3202, 3341), 7 patients with right insula damage (650, 747, 1580, 1656, 1711, 3196, 3363) and 2 patients with bilateral insula damage (Roger and SZ), as well as the group average for the brain damaged comparisons (BDC) and normal comparisons (NC). Error bars represent the SD.

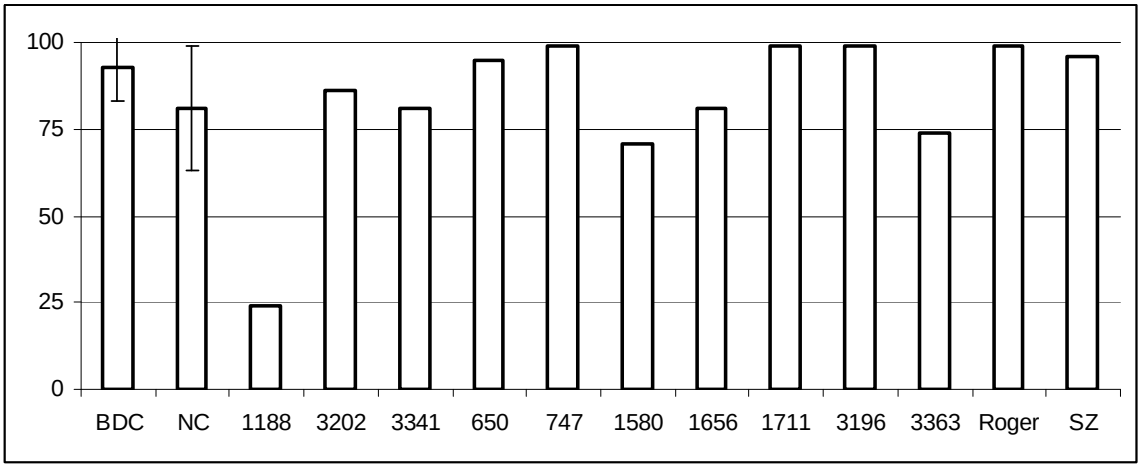
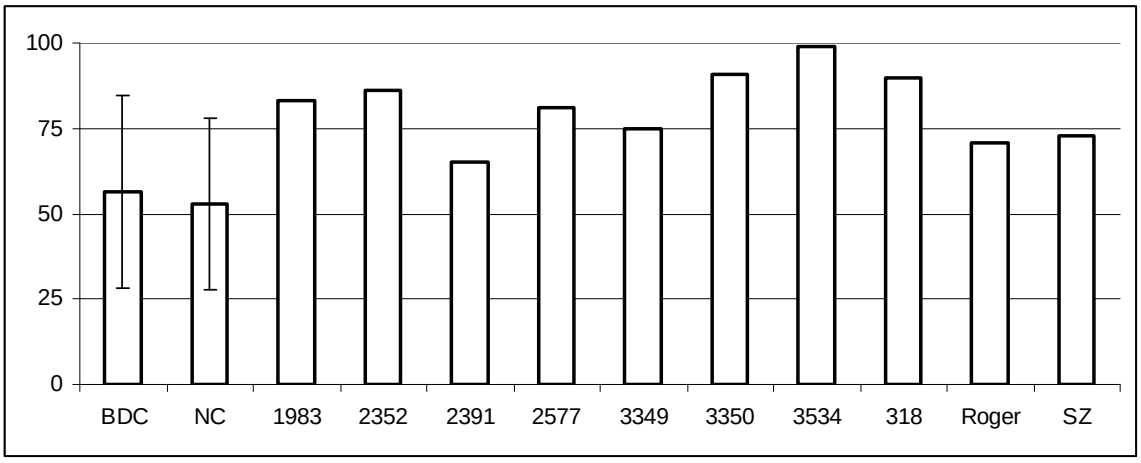


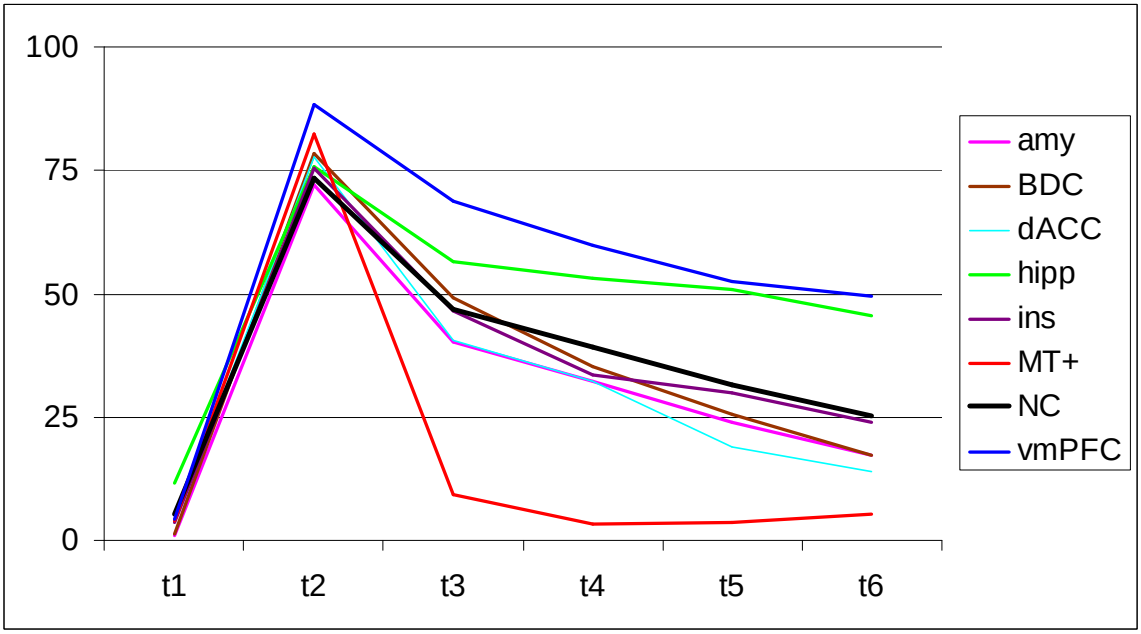
Figure 19. Peak sadness experience (minus baseline) for the sad film clip in patients with vmPFC damage. Data are shown for 10 patients with vmPFC damage (which includes damage to the subgenual ACC), as well as the group average for the brain damaged comparisons (BDC) and normal comparisons (NC). 8 patients have focal bilateral vmPFC lesions, whereas 2 patients (Roger and SZ) have damage throughout the limbic system. Error bars represent the SD.



Emotion recovery

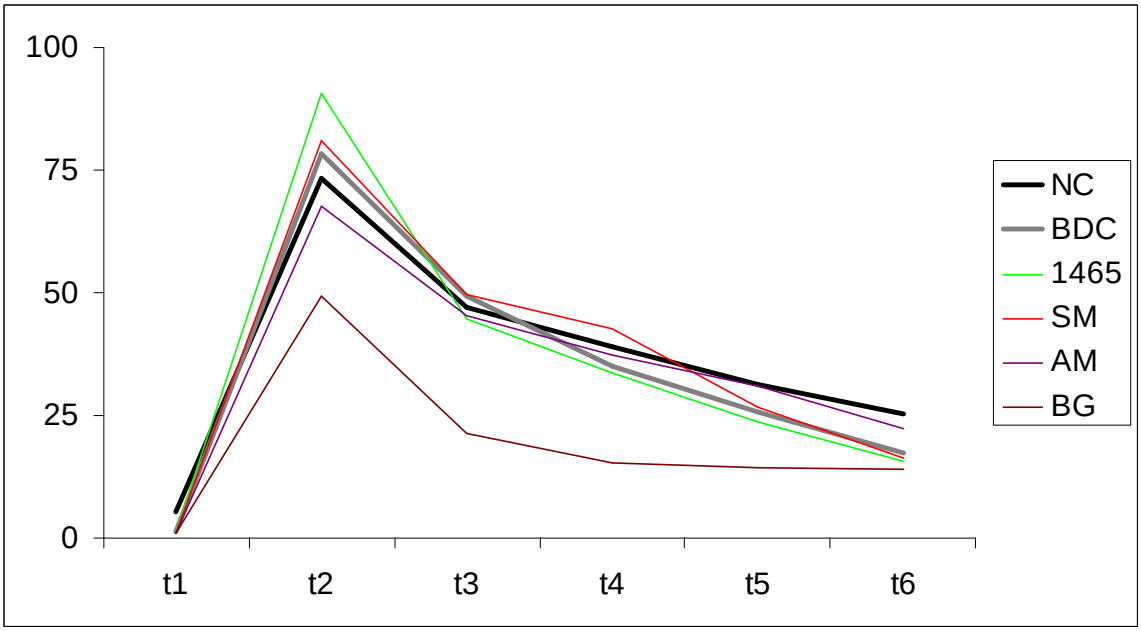
As a first inspection of the emotion recovery data, the average raw composite scores for each group are graphed below for the negative film clips (Figure 20). The first notable finding to stand out from the graph is that the MT+ group showed a rapid recovery of emotion that was most prominent between peak emotion (t2) and the first recovery measurement (t3) assessed 60-seconds following the end of each film. Secondly, the vmPFC group, and to some extent the hippocampus group, showed a relatively slow recovery of negative emotion, with both groups reporting high levels of negative emotion throughout the 3-minute recovery period. Third, the remaining subject groups (including the amygdala group) all tended to cluster together, demonstrating a gradual, but incomplete recovery of the induced negative emotion.

Figure 20. Average composite score for the negative film clips shown for each group. The y-axis ranges from 0-100 using the modified VAS. The x-axis contains the 6 time points of each induction (t1=baseline, t2=peak emotion, t3-t6=recovery).



Given the apriori hypothesis that the amygdala patients would show a rapid rate of recovery, a separate figure examined each patient's individual recovery curve separately (Figure 21). In general, the recovery trajectory for all of the focal bilateral amygdala-lesioned patients was remarkably similar to the comparison subjects. The only notable difference was patient BG, who showed significantly less peak negative emotion than the other subjects (cf. Table 10), but a largely normal recovery thereafter.

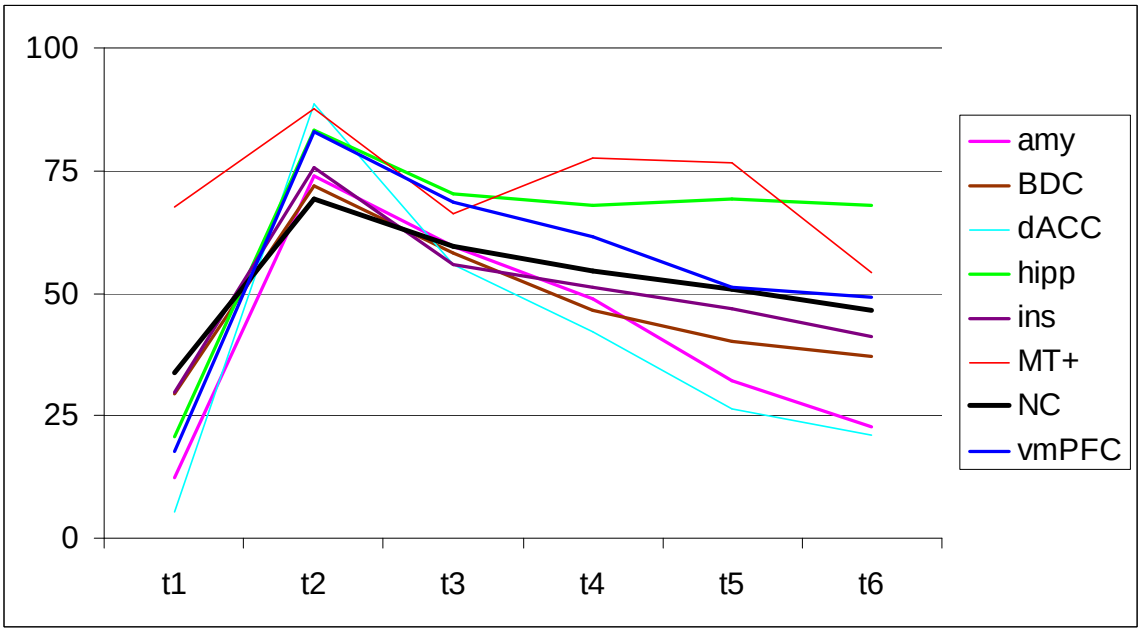
Figure 21. Individual raw scores for the focal bilateral amygdala-lesioned patients for the average of the negative films graphed alongside the average of the comparison groups.



The findings for the positive films (Figure 22) generally showed the same patterns as the negative films, although at a smaller scale due to the high baseline levels of positive emotion found in some subjects. The MT+ group, in particular, reported such high levels of positive emotion at baseline, that it was difficult to interpret any of their recovery measurements since the inductions largely failed to produce a meaningful

increase in positive emotion. On the other hand, the hippocampus group, and to some extent the vmPFC group, showed a relatively slow recovery of positive emotion, with both groups reporting high levels of positive emotion throughout the 3-minute recovery period. While the amygdala and dACC groups reported the least amount of positive emotion at the end of the recovery period, both of these groups also reported the least amount of positive emotion at baseline.

Figure 22. Average composite score for the positive film clips shown for each group. The y-axis ranges from 0-100 using the modified VAS. The x-axis contains the 6 time points of each induction (t1=baseline, t2=peak emotion, t3-t6=recovery).



Assessing the short-term magnitude of emotion recovery

The overall change between peak emotion and the first recovery measurement (i.e., t2-t3), provided a good measure to assess the short-term magnitude of emotion recovery. The average group values for t2-t3 are shown below for the negative films (Figure 23) and the positive films (Figure 24). Based on these graphs, the only notable

pattern to emerge is the uniformly high magnitude of recovery evident in the MT+ group for the negative films. Using Crawford and Howell's (1998) modified t-test and gender-matched norms, Table 11 reports the number of subjects in each group who showed a significantly faster rate of recovery ($p<.05$) than normal comparisons. For the average of the negative films, the only consistent pattern to emerge was that both subjects in the MT+ group showed an abnormally rapid recovery of negative emotion. For the average of the positive films, no clear patterns could be discerned, with 1-2 subjects in several different groups showing an abnormally rapid recovery of positive emotion. Examining the individual film clips, there was no evidence indicating a rapid recovery of emotion in any of the patients with damage to regions previously hypothesized to be important for the induction of a specific emotion: none of the amygdala patients demonstrated a rapid recovery of fear, none of the insula patients demonstrated a rapid recovery of disgust, and only 1 of the vmPFC patients had a rapid recovery of sadness. Interestingly, 3 of the 4 amygdala patients demonstrated a rapid recovery following the NA film, which provides some limited evidence in support of hypothesis 2b.

As a final way of assessing the short-term magnitude of emotion recovery, the t2-t3 values for all 77 subjects were rank-ordered for the average composite score of the negative films. The 2 subjects in the MT+ group (Roger and SZ) had the two highest values (SZ=72.6 and Roger=71.8) of the entire subject pool. The next closest subject had a value of 54.6 which is ~25% lower than Roger and SZ. The average value for the rest of the subjects was 26.4 which is ~64% lower than Roger and SZ. Thus, Roger and SZ clearly had the most rapid recovery of negative emotion at a magnitude that was far greater than all other subjects.

Figure 23. Average magnitude of short-term emotion recovery (t2 minus t3) for each group using the average of the negative film clips. Error bars represent the SD.

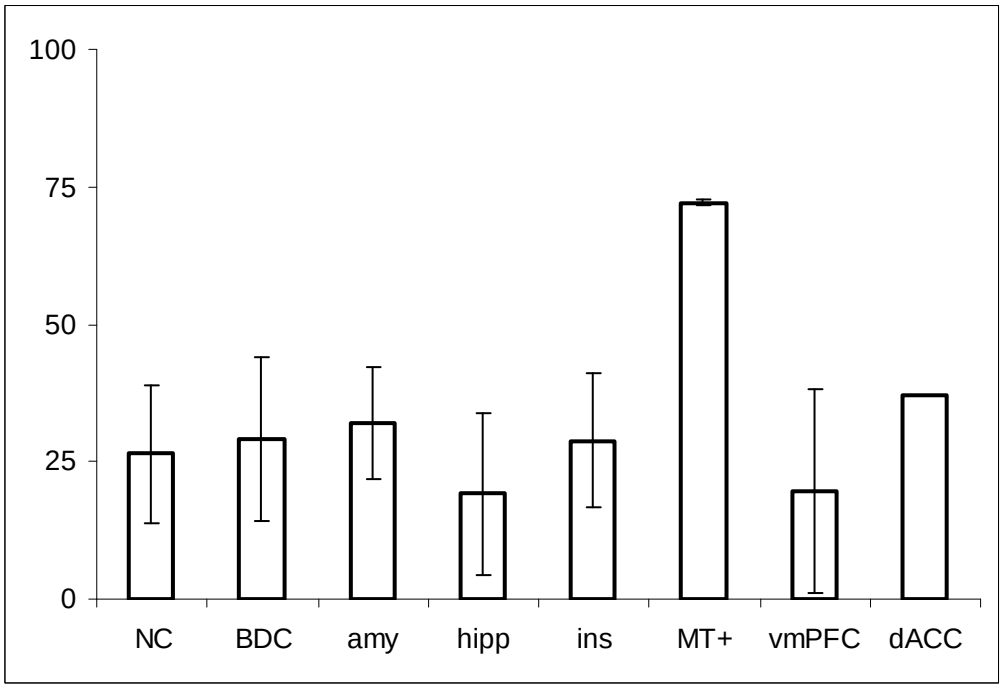


Figure 24. Average magnitude of short-term emotion recovery (t2 minus t3) for each group using the average of the positive film clips. Error bars represent the SD.

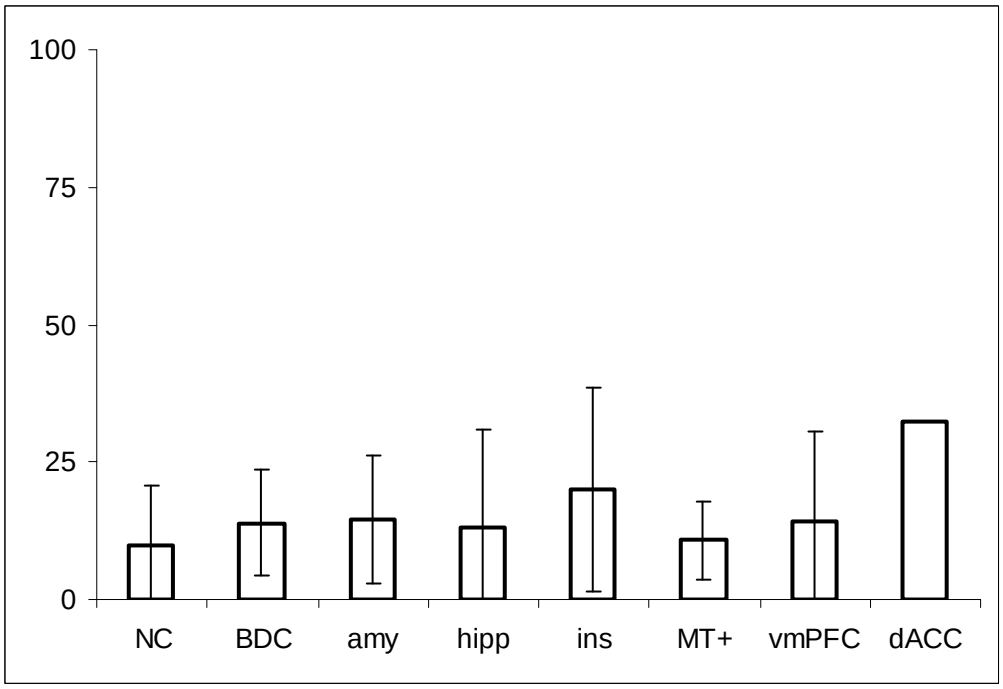


Table 11. Number of subjects in each group with an abnormally fast rate of emotion recovery (t2-t3; $p<.05$) broken down by the average composite score for the negative and positive films, as well as each film individually.

	AvgNA	AvgPA	NA	Fear	Disgust	Anger	Sad	PA	Happy
BDC (8)	1	0	0	2	2	0	0	1	0
vmPFC (8)	1	2	0	1	1	1	1	2	1
dACC (1)	0	0	0	0	0	0	0	0	0
amygdala (4)	0	1	3	0	1	0	1	2	0
hipp (4)	0	1	0	0	0	0	0	1	0
insula (10)	0	2	0	1	0	1	0	3	2
MT+ (2)	2	0	0	0	1	2	2	0	0

Note: Numbers in parentheses represent the total number of subjects in that group.

Assessing the sustained experience of emotion

The sustained experience of emotion was computed as the change score between baseline and the emotion remaining at the end of the 3-minute recovery time period (i.e., t6-t1). Higher values generally indicate slower emotion recovery, since this measure provides a basic approximation of how much induced emotion remains at the end of the recovery period. The average values for each group are shown below for the negative film clips (Figure 25) and the positive film clips (Figure 26). For both the negative and positive inductions, the main pattern that stands out is the higher mean values for the vmPFC and hippocampus groups. However, both groups also appear to have a large amount of within-group variance based on the large error bars. To further examine this issue, the average scores for each subject in the vmPFC and hippocampus group were graphed alongside the average of the comparison groups (Figures 27-30). For the negative films, 5 out of 8 vmPFC patients showed a slow recovery of negative emotion (Figure 27). Likewise, the same 5 vmPFC patients showed a slow recovery of positive

emotions (Figure 28). The other 3 vmPFC patients generally showed a quicker recovery than the comparison groups, including 1 patient (2391) whose rate of recovery was significantly quicker for both negative and positive emotions (cf. Table 11). Interestingly, patient 2391 happened to have the best memory out of all the brain damaged patients, with a general memory index of 132. In the hippocampus group, 1 of 4 patients showed a slow recovery of negative emotion (Figure 29), and 3 of 4 patients showed a slow recovery of positive emotion (Figure 30).

In order to examine whether these qualitative observations were significant, each subject was compared to gender-matched norms using Crawford and Howell's (1998) modified t-test. Table 12 reports the number subjects in each group who showed a significantly slower rate of recovery ($p<.05$) than normal comparisons. For the average of the negative films, 4 of 8 vmPFC patients and 1 of 4 hippocampal patients were significantly slower. A rank-ordering of all 77 subjects revealed that these 5 patients (4 vmPFC and 1 hippocampal) also had the 5 highest values of the entire subject pool, with an average value of 79. In comparison, the remaining subjects had an average value of 20, which is ~75% lower than the vmPFC and hippocampal patients who had a significantly slow recovery of negative emotion. Examining the individual negative films, a similar pattern emerged: 5 vmPFC patients were significantly slower to recover after the sadness and anger films, and 3 hippocampal patients were significantly slower to recover after the disgust film. For the average of the positive films, 3 vmPFC patients and 3 hippocampal were significantly slower. A rank-ordering of all 77 subjects revealed that these 6 patients (3 vmPFC and 3 hippocampal) were amongst the 10 highest values of the entire subject pool, with an average value of 60.5. In comparison, the remaining subjects had an average value of 12, which is ~80% lower than the vmPFC and hippocampal patients who had a significantly slow recovery of positive emotions. Thus, these data reveal that vmPFC and hippocampal patients generally showed the slowest

recovery of both negative and positive emotions (although not every patient with damage to these regions demonstrated this pattern).

Figure 25. Average level of emotion remaining at the end of recovery (t6-t1) for each group using the average of the negative film clips. Error bars represent the SD.

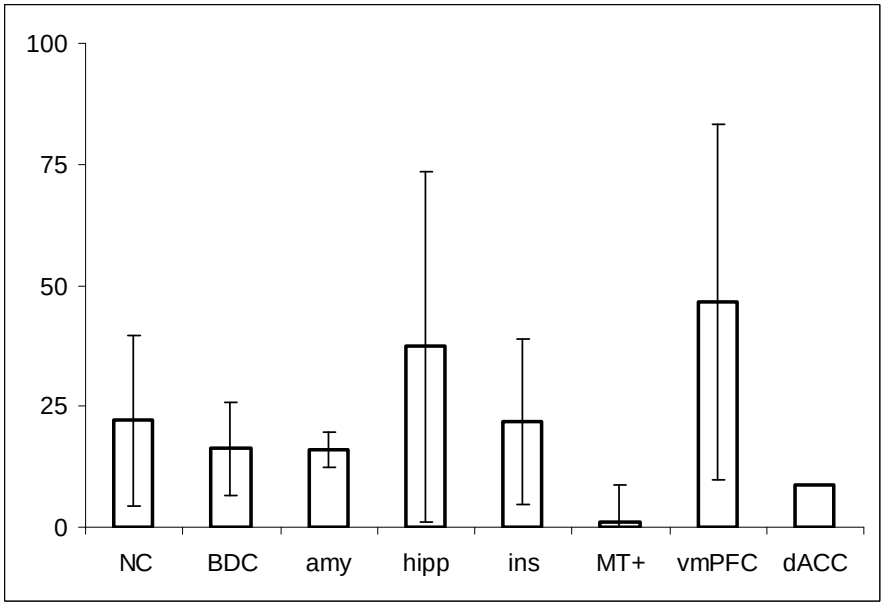


Figure 26. Average level of remaining emotion at the end of recovery (t6-t1) for each group using the average of the positive film clips. Error bars represent the SD.

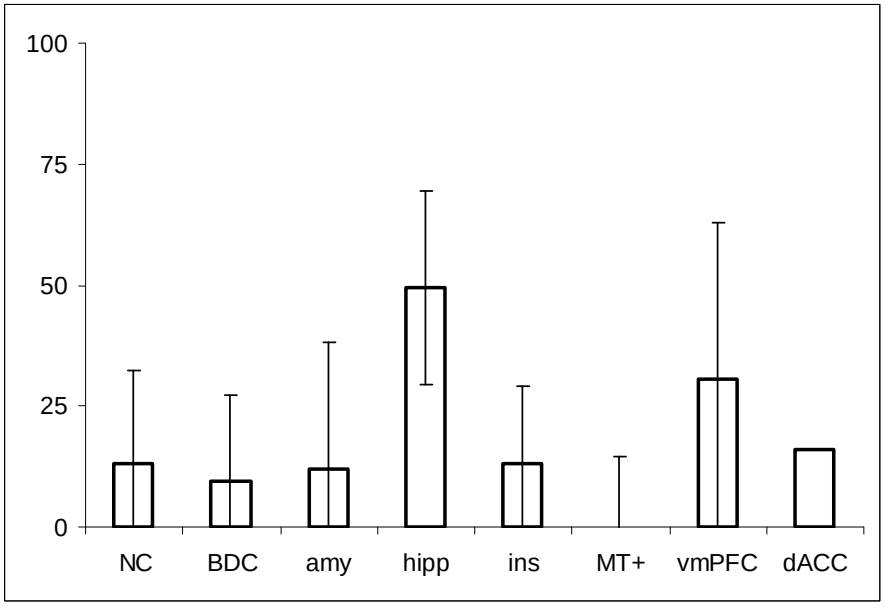


Figure 27. Individual raw scores for the vmPFC-lesioned patients for the average of the negative films graphed alongside the average of the comparison groups.

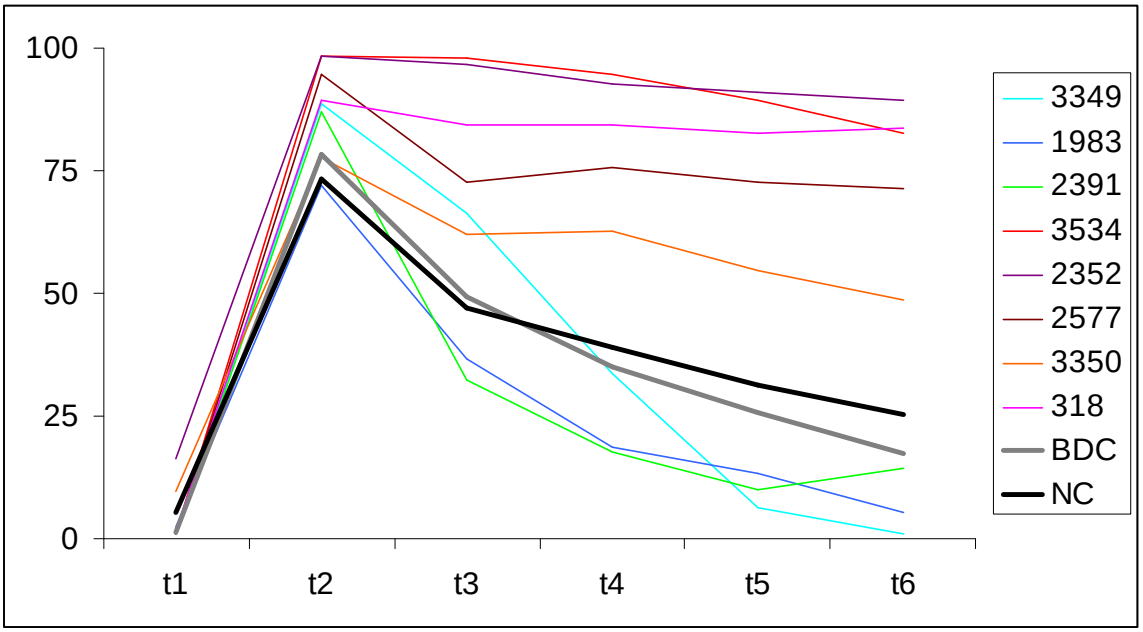


Figure 28. Individual raw scores for the vmPFC-lesioned patients for the average of the positive films graphed alongside the average of the comparison groups.

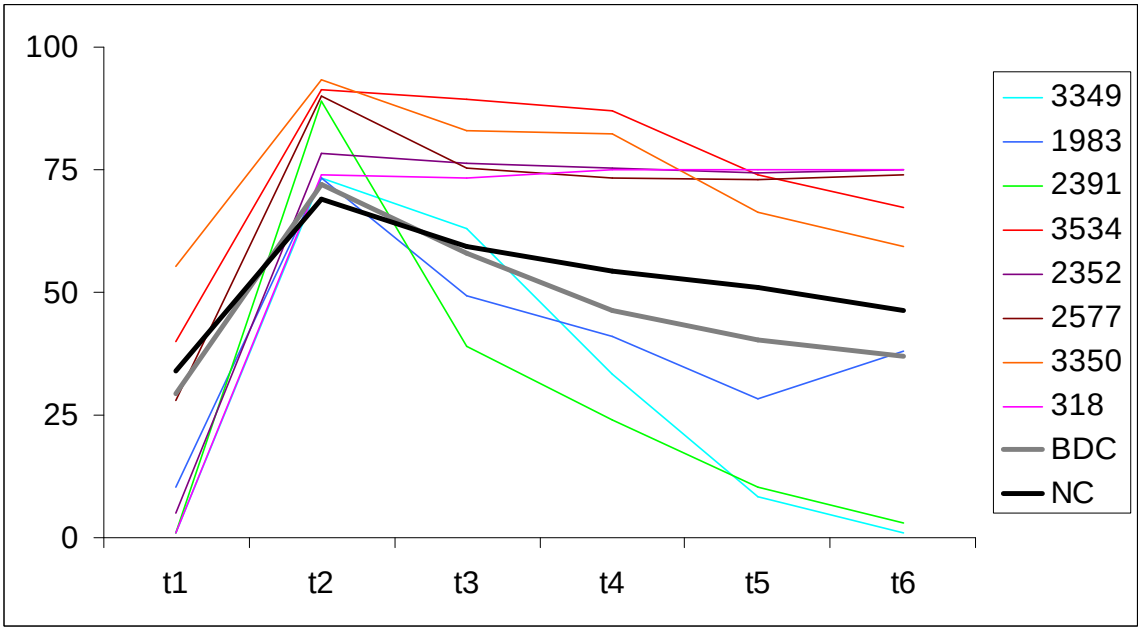


Figure 29. Individual raw scores for the hippocampal-lesioned patients for the average of the negative films graphed alongside the average of the comparison groups.

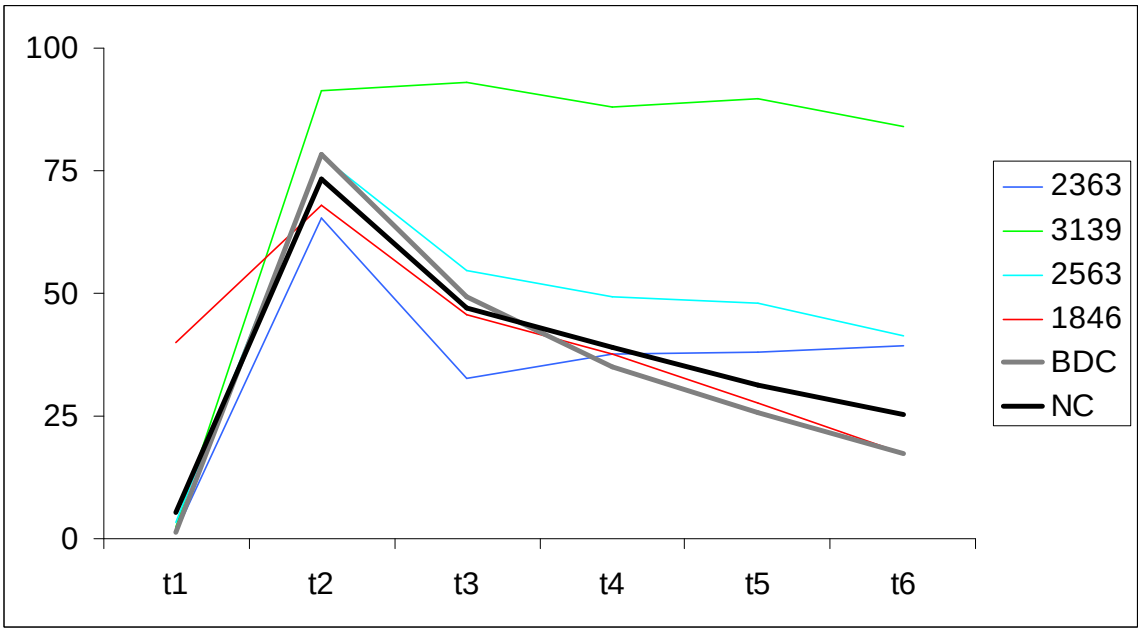


Figure 30. Individual raw scores for the hippocampal-lesioned patients for the average of the positive films graphed alongside the average of the comparison groups.

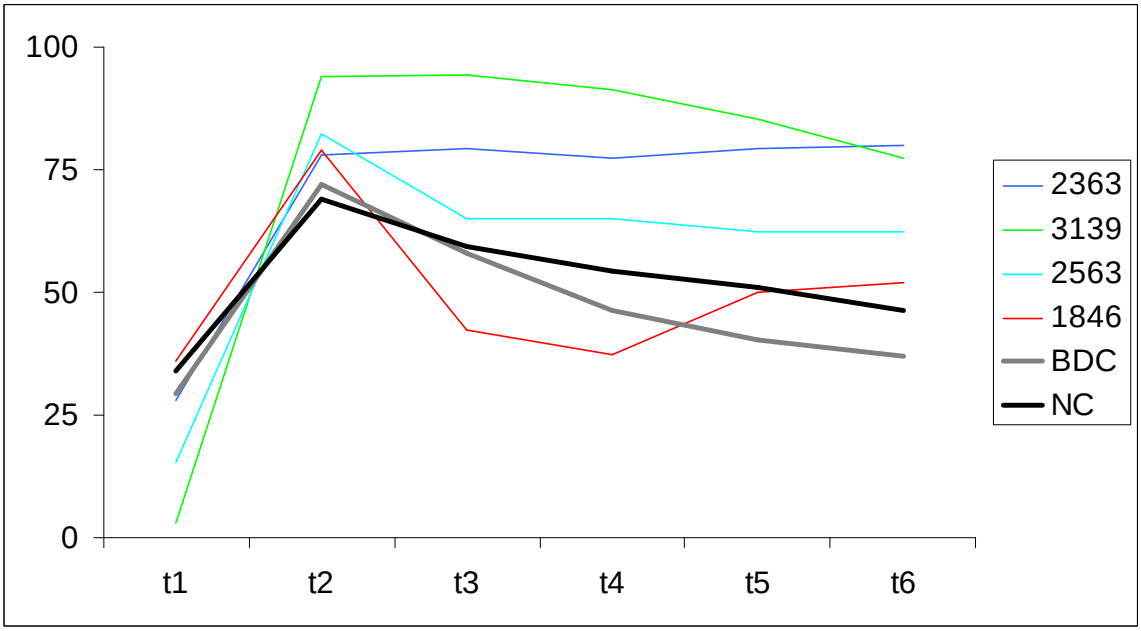


Table 12. Number of subjects in each group with an abnormally slow emotion recovery (t6-t1; $p<.05$) broken down by the average composite score for the negative and positive films.

	AvgNA	AvgPA	NA	Fear	Disgust	Anger	Sad	PA	Happy
BDC (8)	0	0	0	0	0	0	0	1	0
vmPFC (8)	4	3	1	3	3	5	5	3	2
dACC (1)	0	0	0	0	0	0	0	0	0
amygdala (4)	0	1	0	0	0	0	1	1	0
hipp (4)	1	3	1	1	3	1	2	3	1
insula (10)	1	1	0	2	2	1	0	2	0
MT+ (2)	0	0	0	0	0	0	0	0	0

Note: Numbers in parentheses represent the total number of subjects in that group.

Exponential decay

The previous analyses all focused on specific time points during the recovery process, often times to the exclusion of other time points. There would be advantages (both in terms of efficiency and inclusiveness) to finding a single model that could simultaneously incorporate all time points of the recovery process and still detect the core differences between patients. For this reason, a preliminary attempt was made to fit each subject's average negative emotion ratings to a model of exponential decay. Since the emotion recovery ratings for most subjects tended to decrease over time at a rate proportional to the initial value of peak emotion at t2, the data generally adhered to a model of exponential decay. Figure 31 demonstrates that exponential functions provide a relatively good fit for describing the emotion recovery data. Moreover, extracting the estimated decay rate for each subject revealed that for negative emotions, the MT+ patients have the fastest rate of decay and the vmPFC and hippocampal patients have the

slowest rate of decay (Figure 32). Thus, a model of exponential decay appeared to provide a good explanatory framework for modeling emotion recovery and was able to reproduce the main findings of the study.

Figure 31. Exponential decay analysis. Average of the fitted exponential functions (dashed lines) for five groups of participants (NC=black, BDC=green, MT+=red, vmPFC=blue, hippocampal=yellow). Each group's actual average composite rating for the negative film clips are displayed on the graph as bullet points with standard error bars.

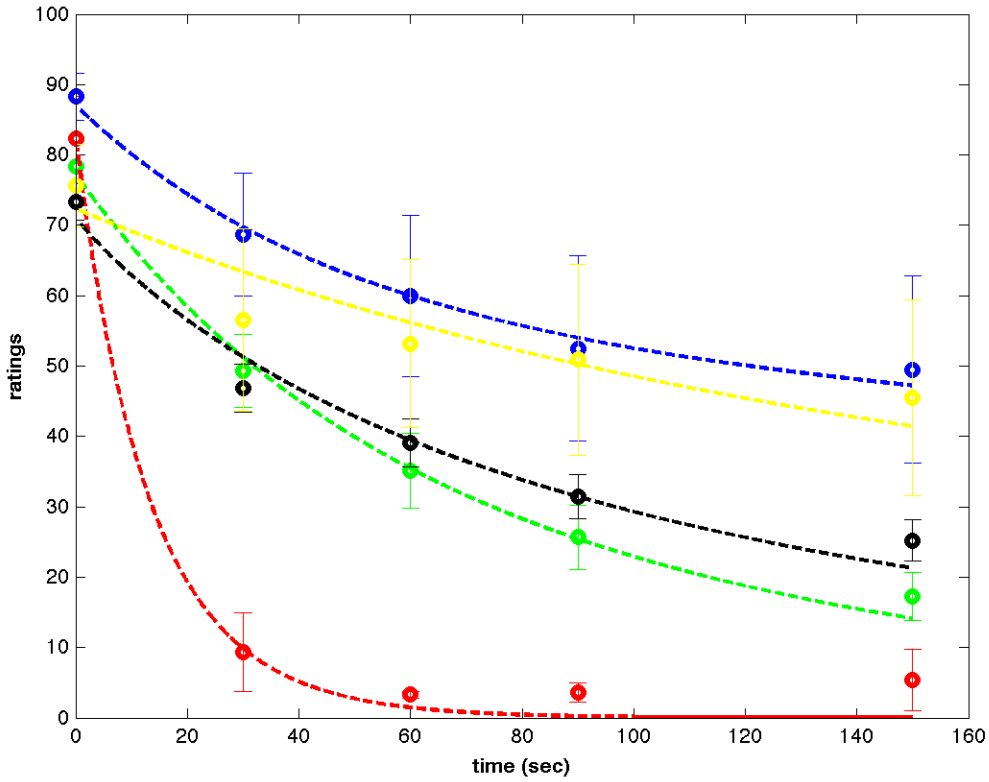
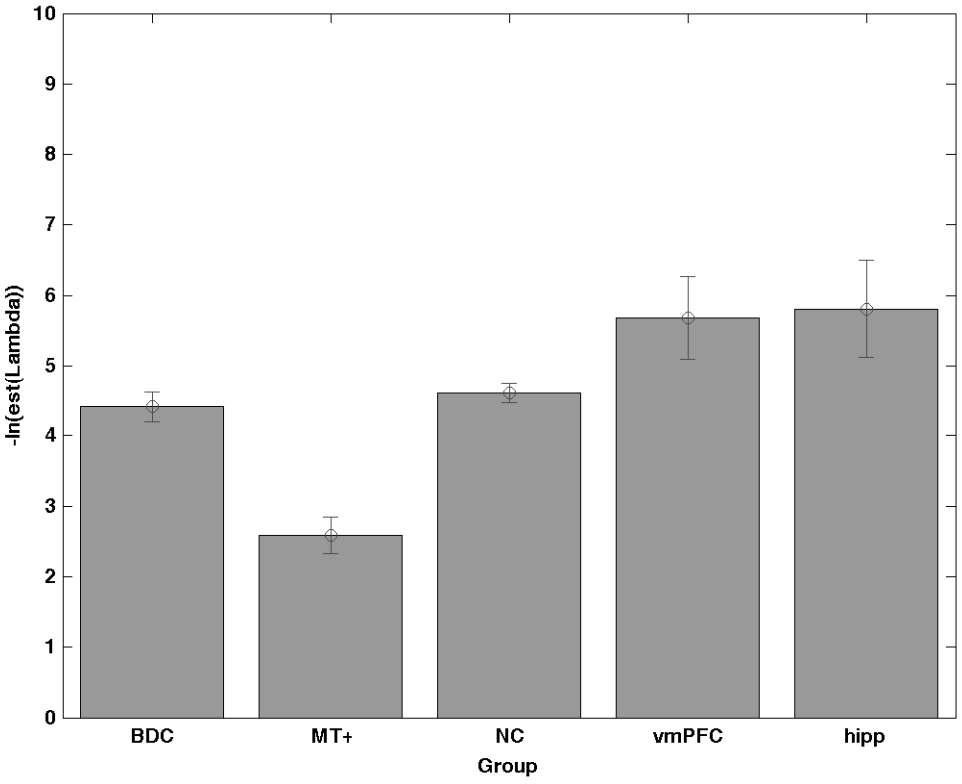


Figure 32. Rate of exponential decay. Average log transformed lambdas with standard errors for five groups of participants (BDC, MT+, NC, vmPFC, and hippocampal). The log transform was used to normalize the distribution of lambda, and is defined as lambda* = -ln(lambda). Higher values indicate a slower rate of decay.



CHAPTER 6

DISCUSSION

The concept of an emotional limbic system has been around for the better part of the past century, yet, we remain unable to define exactly what is "emotional" about the limbic system. This thesis aimed to shed light on this issue by examining whether the core brain structures that comprise the limbic system (including the hippocampus, amygdala, insular cortex, ACC, and vmPFC) are necessary for one aspect of emotion, namely, its conscious experience. The results provide a promising foundation from which we can begin to define a more precise functional role of the limbic system with regard to emotion.

Below, the different findings are discussed in reference to the specific hypotheses of the study, and are separated based on the type of emotional experience (i.e., online vs sustained). The online experience of emotion is defined as emotion that was experienced while watching the film clips, and the sustained experience of emotion is defined as emotion that was experienced after the film clips were over. Separating these two types of emotional experiences provides a valuable framework for the interpretation of the results. Notably, the primary distinction between *online* and *sustained* emotional experience is whether the emotion-inducing stimulus is directly accessible to consciousness. By "directly," I am specifically referring to stimuli that are being perceived, in the present moment, through one or more sensory channels. There are 7 primary sensory channels capable of inducing an online experience of emotion: vision (e.g., the sight of a predator), hearing (e.g., the sound of a baby crying), smell (e.g., the odor of spoiled milk), taste (e.g., the rich flavor of biting into a piece of chocolate cake), touch (e.g., the feeling of intimate contact with another person), proprioception/vestibular (e.g., the vertigo experienced at elevated heights), and interoception (e.g., the burning sensation of a stomach ulcer). As long as the emotion-inducing stimulus is actively

stimulating one of these sensory channels, the emotion experienced in response to this stimulation is "online." However, the moment this stimulation stops, is the precise moment in time when the experience of emotion transitions to being "sustained." In the case of the present experiment, this critical transition point occurs as soon as the emotion-inducing film clip comes to an end.

The online experience of emotion

The results of this study support the hypothesis that the limbic system is not required for the online experience of emotion. Such a finding runs completely counter to the widespread notion that the limbic system is the seat of all emotion. It also runs counter to the recently proposed hypothesis that claims the insular cortex (especially the anterior insula) contains "*the ultimate representation of all of one's feelings*", including feelings of emotion (Craig, 2009, p.65).

By using the lesion method, this experiment establishes that the core structures which comprise the limbic system (including the hippocampus, amygdala, insular cortex, ACC, and vmPFC) are not essential for feeling emotion. Damage encompassing any of these regions (or in the case of Roger, all of these regions) had no detectable effect on the patients' experience of emotion while watching the film clips. The intensity of the patients' emotional experience was entirely within the normal range (Figures 13-14; Tables 9-10), and cases outside of the normal range typically reported experiencing even more intense emotion than normal, not less (e.g., Figure 19). Moreover, the range of their reported emotional experiences was diverse, and included episodes of anger, sadness, fear, disgust, and happiness, as well as more diffuse states of negative and positive affect. While there were rare instances of individual patients who reported that a specific film failed to affect them emotionally, these cases were few and far between, showed no consistency with other patients who shared the same region of brain damage, and never occurred at a rate higher than would be expected amongst the normal

population. Indeed, not every film will affect every person, and this is a common finding in the emotion induction literature, where, on average, a film clip will fail to induce a meaningful change in emotion in about 10-20% of healthy subjects (e.g., Martin, 1990; McHugo et al., 1982; Westermann et al., 1996). For this reason, the experiment used many different film clips, and while a patient may have been unaffected by a specific film, there was always another film that affected them greatly. Taken together, these findings provide clear evidence that a variety of different emotional states can be experienced at high levels of intensity in human patients with extensive bilateral damage affecting the limbic system.

One possible interpretation of this finding is that subjects were simply not being honest and were reporting high levels of emotion even when they didn't actually feel any emotion. This issue, which relates to demand characteristics, is not unique to this study or the patients who were tested. There is in fact no definitive way to entirely rule out this interpretation, since, by definition, emotional experience is subjective. However, several points argue against such an extreme interpretation. Firstly, all subjects were explicitly instructed to answer the questions as honestly and accurately as possible. Furthermore, they were told that there are no right or wrong answers and that every person experiences emotion differently. Thus, any subject who did not follow these instructions would actually be going against the explicit demands of the experiment. Secondly, while one's true emotional experience may be hidden from the world, its close counterpart, emotional expression, is visible for the world to see. Though the psychophysiological data and video/audio recordings of emotional behavior still await analysis (and will certainly help address this issue), anecdotal observations, including in patients such as Roger, documented multiple instances of emotionally expressive behavior that would be consistent with the subjective experience of intense emotion. Thirdly, subjects were able to accurately recognize the emotion being conveyed by the film (Tables 7-8), which indicates that they were not simply rating their emotional state at random. Finally, and

perhaps most importantly, patients did not report experiencing elevated levels of emotion during the two neutral films (Figures 11-12; Table 9). This argues against the notion that patients were arbitrarily rating their emotion as always being high, and supports the notion that patients genuinely felt high levels of emotion, but only during the emotional film clips.

There are many possible brain regions that could account for the spared emotional experience following limbic system damage. For example, in Roger we recently demonstrated that his intact somatosensory cortices played a critical role in his preserved feeling for his own heartbeat (Khalsa et al., 2009), leaving open the possibility that his preserved emotional experiences rely on a similar circuitry. Indeed, there are multiple brain regions outside of the limbic system, especially within the parietal cortices, that contain detailed maps of the body that can potentially instantiate feelings of emotion (Berlucchi & Aglioti, 2010). Recently, Damasio has argued that sensory nuclei within the brainstem, including the nucleus of the solitary tract and the parabrachial nucleus, form the critical platform from which all feelings are based (Damasio, 2010). Other possibilities include the hypothalamus and the posterior cingulate, the two regions of the limbic system that were not probed in this study due to the paucity of patients with damage in these locations. Finally, regions within our brain that motivate behavior, including the ventral striatum and the supplementary motor area, may also be critical for generating feeling. For example, the striatal dysfunction inherent in Parkinson's disease can lead to a state of apathy and anhedonia (Kaji & Hirata, 2011). Likewise, bilateral damage to the supplementary motor area (in addition to the anterior cingulate) can lead to a state of akinetic mutism characterized by not only a complete loss of motivation to move or communicate, but an equally profound loss of emotion (Damasio & Van Hoesen, 1983). Thus, there are multiple territories outside the limbic system that provide a feasible substrate for the experience of emotion following extensive bilateral limbic system damage.

Specific emotions

The hypothesis of specialized brain centers for the induction of specific emotional states was not supported by the results of this study. In particular, amygdala damage did not lead to a consistent fear-specific impairment (Figure 17), insula damage failed to produce a disgust-specific impairment (Figure 18), and damage affecting the subgenual ACC failed to produce a sadness-specific impairment (Figure 19). Moreover, there was no evidence of reliable emotion-specific impairments for any of the other target emotions or lesion sites (Table 10). Most of the prior work examining this issue has been conducted in single-case studies. Given the relatively large number of cases tested in the current study, the striking lack of evidence in support of specialized brain centers for specific emotions is rather surprising and suggests that the induction sites of individual emotions are distributed across multiple regions of the brain. It is possible that more subtle emotion-specific deficits could have been detected with different induction and/or measurement procedures. Additionally, it is important to realize that most of the past research supporting this hypothesis predicts that these brain regions are specialized for inducing the specific emotional states (i.e., triggering the cascade of physiological, behavioral, and cognitive changes that comprise a particular emotional state), and not necessarily for feeling them. This leaves open the possibility that fine-grained analyses of each patient's facial expression and psychophysiological responses during the films may lead to the detection of an emotion-specific impairment. Nevertheless, the mere fact that the patients experienced such high levels of the target emotion indicates that alternative pathways must exist for inducing the specific emotional state, otherwise the patients would not have felt any emotion. More generally, these results suggest that there are multiple pathways and built-in redundancies in the brain for triggering specific emotional states such as fear, disgust, and sadness.

The findings with regard to the amygdala and fear were mixed. On the one hand, patient SM did demonstrate a fear-specific impairment, consistent with previous findings

(Feinstein et al., 2011). Additionally, patient BG reported a highly diminished level of fear, which is also consistent with previous findings (Becker et al., in press). On the other hand, all of the other amygdala-lesioned patients demonstrated remarkably normal levels of fear. One such patient, 1465, had some remaining tissue in his left amygdala, which can potentially explain his intact fear. Roger and SZ, however, have complete bilateral destruction of their amygdala, yet still reported high levels of fear. One possible explanation is that Roger and SZ sustained their amygdala damage during adulthood, whereas SM and BG sustained their amygdala damage much earlier in life causing them to have a more pervasive fear impairment than the adult-onset cases. Unfortunately, this explanation fails to account for the preserved fear experience found in BG's identical twin sister, patient AM. Both sisters presumably acquired their amygdala damage during the same time frame in life and there are no clear differences between their lesions. A previous report documents this striking difference in fear between the twin sisters and provides preliminary evidence suggesting that AM compensates for her amygdala damage by recruiting her mirror-neuron system (Becker et al., in press). While a conclusive explanation for when amygdala damage will or will not lead to a fear-specific impairment is lacking, the findings in this study clearly show that the relationship between the amygdala and fear is much more complex and nuanced than a simple one-to-one mapping between structure and function.

Insula damage, whether bilateral or unilateral, failed to produce a disgust-specific impairment. This finding is consistent with other insula-lesion studies failing to find a disgust impairment (Straube et al., 2010; Vianna, 2005). In fact, there have only been two previous case studies documenting disgust-specific impairments in patients with insula damage (Adolphs et al., 2003; Calder et al., 2000), and in neither of these cases was the damage limited to the insula, leaving open the possibility that the detected disgust deficit was due to damage outside of the insula. A recent study has shown mild deficits in insula-lesioned patients when evaluating static emotional pictures (Berntson et

al., 2011). In contrast, the present study used a highly aversive film clip and it remains possible that more subtle disgust-related deficits would have been detected had a less intense stimulus been used.

None of the vmPFC patients (including patients with bilateral damage to the subgenual ACC) showed any evidence of a sadness-specific impairment. If anything, the findings revealed that the patients actually experienced heightened levels of sadness (Figure 19). A previous study also failed to show any sadness impairment in vmPFC patients (Gillihan et al., 2010). Thus, there is no evidence that damage to the subgenual ACC leads to a loss (or even a reduction) in sadness. This suggests that the underlying mechanism for the decreased rate of depression – found in lesion patients with bilateral vmPFC damage (Koenigs et al., 2008) and depressed patients following deep brain stimulation of the subcallosal region of the subgenual ACC (Holtzheimer et al., in press) – is likely unrelated to alterations in the ability to experience sadness.

A recent meta-analysis of 91 different functional neuroimaging studies examining emotion "found little evidence that discrete emotion categories can be consistently and specifically localized to distinct brain regions" (Lindquist et al., in press). In particular, there were no significant associations between amygdala activity and the experience of fear, insula activity and the experience of disgust, and subgenual ACC activity and the experience of sadness (Lindquist et al., in press). The experience of emotion (irrespective of the specific type of emotion) often triggered activation across a widespread network of brain regions, both cortical and subcortical (Wager et al., 2008). Furthermore, this network was activated across different types of emotion induction procedures, including film clips (e.g., Karama et al., 2011) and autobiographical recall (e.g., Damasio et al., 2000). These functional neuroimaging data are consistent with the human lesion data reported here, and together, these convergent findings argue against the existence of specialized brain centers for the induction and experience of specific emotions.

The sustained experience of emotion

The hypothesis that the limbic system is necessary for the sustained experience of emotion was supported by the data. Specifically, Roger and SZ, the only 2 patients tested with extensive bilateral lesions affecting multiple limbic system structures, were also the only 2 patients who demonstrated a rapid and complete recovery of all negative emotions within the first minute following the end of the film clips. This finding is made even more striking by the fact that both Roger and SZ reported experiencing highly intense states of emotion while watching the films. Their robust and precipitous drop-off in emotion immediately following the end of each film clip suggests that the areas in their brain which are damaged form the critical substrate for holding onto an emotional experience once the emotion-inducing stimulus is no longer directly accessible to consciousness.

Both Roger and SZ share a widespread matrix of lesioned-tissue throughout the limbic system, with maximal overlap in the medial temporal lobe (including the hippocampus, amygdala, parahippocampal gyrus, and the medial temporopolar cortices) and insular cortices. Roger's lesion extends anteriorly to encompass the basal forebrain, anterior cingulate and most of the vmPFC, whereas SZ's lesion only infiltrates a small region of the left basal forebrain and posterior orbitofrontal cortex. In general, Roger's damage is more prominent in the right hemisphere and SZ's damage is more prominent in the left hemisphere. Despite these differences, both share a common substrate of bilateral damage affecting the hippocampus, amygdala, and insula; the 3 most likely candidate structures contributing to their abnormally expeditious recovery of negative emotion.

Since both patients reported highly elevated levels of positive emotion at baseline, the positive emotion inductions failed to induce a meaningful increase in happiness or other positive emotions. For this reason, I am unable to conclusively comment on whether their rapid recovery of emotion extends into the domain of positive emotions, although several anecdotal observations suggest that it does. For example, Roger was

once observed in a state of pure elation while watching a live comedy show, laughing for over an hour straight at every joke that was told. As soon as the show was over, his exuberance quickly dissipated, and upon leaving the theater, he showed no obvious signs of lingering positivity above and beyond his typical baseline state. Similarly, he was observed celebrating after bowling an impressive 5 strikes in a row. While the team of onlookers continued to excitedly cheer his accomplishment, Roger's outward expression of joy seemed to dissipate as soon as the next bowler stepped up for their turn. SZ has been observed playing saxophone in a large orchestra in front of hundreds of people. An obvious glow of pride and joy was evident in his face and demeanor as he stood up at the end of the show and proudly bowed to the sea of cheers erupting from the audience during an extended standing ovation. As soon as he left the stage, however, his affect and demeanor quickly reverted to his usual baseline state, and there were no signs that he even remembered having played the concert. While these anecdotes are suggestive of a rapid recovery of positive emotion, they are no substitute for a rigorously controlled laboratory experiment. Future studies need to firmly establish whether Roger's and SZ's positive emotion recovery follows the same trajectory as their negative emotions.

Finally, the hypothesis that patients with focal bilateral amygdala lesions would also show a rapid rate of emotion recovery was not supported by the data. The only possible exception is that 3 of the 4 amygdala-lesioned patients showed a quick recovery of negative emotion, but only after the NA film. For the other films, their recovery appeared to be very similar to the comparison groups (e.g., Figure 21). In contrast, Roger and SZ showed a rapid recovery for all of the negative films, irrespective of the specific emotion being targeted. It is possible that had the recovery period been extended beyond 3 minutes, more differences may have emerged between the amygdala patients and the comparisons, which would also be consistent with the pilot data collected in patient SM (Figure 1).

Emotion regulation

vmPFC damage

The hypothesis that patients with bilateral damage to the vmPFC would show an abnormally slow rate of emotion recovery was supported by the data. Specifically, 5 of the 8 patients with bilateral vmPFC damage showed a slow recovery of both negative and positive emotion (Figures 27-28). Of these 5 patients, 4 exceeded the significance threshold for the negative film clips and 3 exceeded the significance threshold for the positive film clips (Table 12), indicating that these patients experienced significantly more emotion than the normal comparisons at the end of the 3-minute recovery period. Interestingly, the 3 vmPFC who did not show a slow recovery of emotion generally had the opposite pattern (i.e., a rather fast recovery). In fact, one patient's recovery was significantly faster than normal for both negative and positive emotions (Table 11). It is not clear why some patients showed the hypothesized pattern of slow recovery and others did not. Closer inspection of their individual lesions failed to reveal any obvious anatomical differences that could account for the discrepancy. As noted in the introduction, the heterogeneity of behavior between individual vmPFC patients is one of the most commonly reported findings, and also one of the main reasons why it has been so difficult to succinctly characterize the behavioral deficits following vmPFC damage (e.g., Teuber, 2009). Nevertheless, the evidence from this study supports the conclusion that bilateral damage to the vmPFC disrupts the natural process of emotion regulation (the word "natural" is used to highlight the fact that no explicit regulation instructions were provided to any of the subjects).

These findings are consistent with the large body of research showing a pervasive pattern of emotional dysregulation following vmPFC damage (see pp. 23-26). Likewise, functional neuroimaging studies in healthy individuals have revealed activation in the prefrontal cortex that is positively correlated with an individual's success in downregulating their emotional response to affectively-laden stimuli (Davidson, 2002;

Eisenberger, Lieberman, & Williams, 2003; Hariri, Bookheimer, & Mazziotta, 2000; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Lieberman et al., 2007; Ochsner, Bunge, Gross, & Gabrieli, 2002; Banks et al., 2007). While the location of this prefrontal activity varies between studies, a recent meta-analysis concluded that a small region within the vmPFC is the most consistently activated area during the successful downregulation of negative affect (Diekhof et al., 2011). As it turns out, this small region of activity is located in the same area where the vmPFC lesion patients (from the current investigation) share a maximal overlap of brain damage (Figure 6). Interestingly, this same region also shows a significant negative correlation with activity in the amygdala (Diekhof et al., 2011), suggesting that the success of downregulating negative emotion is directly related to how well the vmPFC is able to inhibit activity of the amygdala. Since the vmPFC patients in the present study all have intact amygdalae, one possible explanation for their prolonged state of negative emotion is because their brain damage has destroyed their primary pathway for downregulating the amygdala, in essence creating a situation of amygdalar disinhibition. Such an explanation also fits with the data from Roger and SZ, who both have vmPFC damage (Roger's being far more extensive). One rationale for why Roger and SZ did not exhibit sustained states of negative emotion (like the other vmPFC patients) is because they also have damage to their amygdala, and thus, there is no negative affect to be regulated. The explanatory power of this model falls short, however, when examining the data from the focal bilateral amygdala lesion patients. If the amygdala is the primary generator of sustained negative emotion, then amygdala-lesioned patients should have demonstrated a rapid recovery of emotion. The fact that they didn't suggests that other brain regions (perhaps the insula and/or hippocampus) are capable of sustaining negative emotion in the absence of the amygdala.

One previous study has examined emotion recovery in patients with bilateral damage to the vmPFC (Gillihan et al., 2011). The study induced states of sadness or

happiness using a combination induction method. First, patients viewed an emotion-inducing film clip (for the sadness condition they actually used the same film that was used in the current investigation). Next, patients recalled a sad or happy memory while listening to emotion-congruent music. Finally, the recovery of induced emotion was measured over the course of 6 minutes. The first result found that patients reported experiencing high levels of the induced target emotion (for both sadness and happiness) immediately after the induction, and at a level no different than the normal comparisons. This finding is consistent with the results from the current investigation. The second result found that patients showed a completely normal recovery for both sadness and happiness, which is inconsistent with the slow recovery found in the majority of vmPFC patients tested in the current investigation. One possible explanation for the discrepancy between studies is due to differences in the induction method. While both studies used a film emotion induction procedure, Gillihan's study also included an autobiographical memory induction procedure. Previous work in our lab has shown that vmPFC patients report less intense emotional states using an autobiographical memory induction procedure (Bechara et al., 2003). Thus, it remains possible that the vmPFC patients in the Gillihan study would have also shown a slow emotional recovery had they only used the film clips to induce emotion.

Hippocampal damage

The hypothesis that patients with focal bilateral hippocampal damage would show an abnormally slow rate of emotion recovery was mostly supported by the data. Specifically, 1 of the 4 patients showed a slow recovery for all negative emotions and 3 of the 4 patients showed a slow recovery for all positive emotions (Figures 29-30), with all of these patients meeting the significance threshold (Table 12). For the negative films, patient 1846 had an unusually high level of negative emotion at baseline which likely contributed to her relatively quick recovery. On the other hand, patient 3139 was

consistently slow to recover across all emotions, both negative and positive. The remaining 2 patients (2363 & 2563) showed an abnormally slow recovery of positive emotion, and a largely normal recovery of negative emotion, except for disgust and sadness where their recovery was abnormally slow (Table 12). Thus, the majority of hippocampal patients showed a pattern consistent with a slow recovery for both negative and positive emotions.

These findings essentially replicate those from a previous study (Feinstein et al., 2011), which examined the influence of declarative memory on emotion experience in a group of patients with severe anterograde amnesia due to focal bilateral hippocampal damage (including 2 patients who were also tested in the current investigation). In the study, the amnesic patients continued to experience elevated levels of emotion even after they could no longer remember the content of the film clips which had originally induced the emotion. Quite strikingly, their level of sadness persisted even longer than the normal comparison subjects (whose memory for the film clips was entirely intact). One potential explanation for the persistence of emotion in hippocampal amnesics relates to the adaptive value of knowing the cause of our emotions, which in turn can help expedite the recovery of emotion. Since both the amygdala and insula are intact in these patients, they continue to experience an emotion, even when they can no longer remember the cause. This free-floating state of emotion (especially when it is a negative emotion) likely triggers a search process aimed at discovering the source of the emotional disturbance. Unfortunately, their severe amnesia often times prevents any conclusive discovery from occurring, and this attribution failure may draw additional attention toward their aberrant emotional state, in effect creating a positive feedback loop that hijacks the natural recovery process and ultimately leads to an abnormally prolonged state of emotion. Viewed in this light, the functional role of the hippocampus with regard to emotion regulation is centered on the binding of an emotional experience to the context which generated that experience. This contextual information can then be used by emotion

regulation sites within the prefrontal cortex (including the vmPFC) to dynamically modulate our emotional experience in a context-appropriate manner. Thus, the slow recovery of emotion evident in patients with focal hippocampal damage may be a by-product of their failure to link the emotional state with its source.

Although it is tempting to conclude that the reason Roger and SZ have such transient emotional states is completely due to their severe amnesia, the findings in the hippocampal amnesic patients strongly suggest otherwise. Since the experiment in the present study did not examine whether participants were able to remember the films, it is difficult to comment on whether Roger, SZ, or any of the hippocampal amnesics were able to hold onto any knowledge about the previous film during the emotion recovery period. Given the relatively brief time frame of the recovery period (i.e., 3 minutes) it is likely that many of the amnesics still retained at least a little knowledge about the previous film clip. Future iterations of this experiment will need to examine whether the amount of knowledge retained had any impact on their reported emotional experience during recovery.

Limitations and future directions

While the results of this study begin to provide a clearer picture of the functional role of the limbic system with regard to emotional experience (see Conclusion section below) there were several limitations that need to be addressed. The first limitation is the small number of patients in each group. This is a common issue in lesion studies due to the extreme rarity of certain types of brain damage. Great effort was made to find such patients, including flying them into Iowa from other states, and in some cases, from other countries. In comparison to other lesion studies (which are typically single-case studies), the number of patients in certain groups was actually quite large. For example, being able to test 4 patients with focal bilateral amygdala damage is very uncommon. However, in other groups there were only 1 or 2 patients and this makes it difficult to

draw firm conclusions. This was the case for the ACC. While many of the vmPFC patients had damage to the ventral region of the ACC, there was only a single patient with focal damage to the dorsal region of the ACC, and only Roger had damage that entirely encompassed the ACC (both ventral and dorsal). Since Roger's data looked remarkably similar to patient SZ (who did not have ACC damage), and the data from the dorsal ACC patient revealed no apparent deficits, very little can be concluded about the specific impact that ACC damage had on emotional experience. Furthermore, certain regions of the limbic system were unable to be studied due to an inability to locate any patients with the requisite bilateral lesion. In particular, the posterior cingulate and the hypothalamus are completely missing from this investigation, and as noted earlier, both structures could very well be playing a prominent role in emotion experience.

The second limitation deals with the inherent difficulty of reliably inducing positive emotion in the laboratory. The main reason for this difficulty is due to the well-known fact that most people report experiencing elevated levels of positive emotion at baseline (Diener & Diener, 1996; Ito & Cacioppo, 2005; Watson, 2000). Such high baseline levels make it extremely difficult to detect meaningful increases in positive affect following an emotion induction procedure, an all-too-common finding in other emotion induction studies (Albersnagel, 1988; Gerrards-Hesse et al., 1994; Monteil & Francois, 1998; Westermann et al., 1996). In the current investigation, about a third of the normal comparisons failed to report a meaningful increase in positive emotion after the happy and PA films (Table 9). Luckily, this lack of an effect was not as prevalent amongst the brain damaged patients, although it was certainly an issue for both Roger and SZ. Since all emotion induction procedures compute the effectiveness of the manipulation as the change in emotion from baseline to post-induction, there is no clear solution for overcoming this limitation.

A third limitation deals with the measurement of emotion recovery. While the modified VAS was successful at detecting changes in emotion over time, it was unable to

capture the nuances of the induced affective experience since it only probed a single emotion for each induction. Great effort was spent selecting films that targeted a specific emotion, but nonetheless, past research has shown that other emotions are likely to be induced as well (Gross & Levenson, 1995; Philippot, 1993; Schaefer et al., 2010). It would have been interesting to examine these other emotions. For example, one experiment used the same disgust film as this study and found that even though the experience of disgust had fully recovered 20 minutes after the film was over, positive emotion had not fully recovered (Hemenover, 2003). Ultimately, I decided to focus on individual emotions given the time-sensitive nature of the recovery process and the limited time period that was being probed. This limited time period created another limitation in that the induced emotion had not fully recovered for many subjects by the end of the 3-minute recovery window. While many interesting differences between the lesion patients and comparisons emerged within the first 3-minutes, it is possible that a longer recovery period may have revealed additional findings. Due to the large number of emotion inductions (9 in total), I decided to cut-off the recovery measurement after 3 minutes. Future studies, especially in vmPFC and hippocampal patients, should continue measuring the emotion until it has fully recovered. In addition, future studies should consider using real-time measurement devices in order to more precisely understand the temporal dynamics of emotion recovery. A continuous rating dial can capture changes in emotion while viewing film clips (Mauss et al., 2005), and may be even more effective than retrospective ratings at measuring emotion in patients with brain damage (Wittling & Roschmann, 1993). However, it is important to consider the possibility that having a subject continuously monitor their affective state may fundamentally alter the emotion recovery process. Since emotions in real-life are rarely accompanied by self-report rating scales, it will be important for future research to investigate how emotion recovery is affected by the different types of ratings (e.g., VAS, questionnaires, continuous rating dials) and the frequency in which subjects are asked to make these ratings.

Since the measurement of emotion recovery is still in its infancy, there remains a pressing need to develop more rigorous analysis strategies. Preliminary data from this study suggests that exponential decay may provide a good model for the analysis of emotion recovery (Figures 31-32). It will be important to examine other functions, such as the power-law, to see which model provides the best overall fit. The utility of deriving such a model offers many possibilities for future investigation. For example, it would allow for the derivation of prediction curves that could be used to estimate the total time or half-life of a particular emotion that is experienced at a particular level of peak intensity. Indeed, a recent study successfully used a model of exponential decay to predict how long a student would experience states of boredom and frustration while learning a new concept during a tutoring session (D'Mello & Graesser, 2011). Additional variables could also be integrated into the model that would offer the ability to adjust the rate of decay based on a multitude of factors, such as the area of brain damage or the particular emotion being experienced. As enough data is collected, the model's predictive power would improve, and could eventually be used to investigate patterns of brain activity (e.g., using intracranial electrode recordings from neurosurgical patients) to see if particular firing patterns correlate with the process of emotion recovery.

CHAPTER 7

CONCLUSION

The results from this thesis argue for the existence of two distinct states of emotional experience. The first state, termed the *online* experience of emotion, encompasses the diverse array of possible feeling states that are experienced in relation to a specific emotion-inducing stimulus being directly conveyed to consciousness through one or more of our sensory channels. The second state, termed the *sustained* experience of emotion, is the raw and relatively undifferentiated feeling that persists after the emotion-inducing stimulus is no longer directly accessible to consciousness. The findings from this experiment indicate that the brain structures which comprise the limbic system, especially the medial temporal lobes and insular cortices, are essential for the sustained experience of emotion, but are not required for the online experience of emotion.

Of the 77 subjects tested in the current experiment (both healthy and brain damaged), only 2 subjects (patients Roger and SZ) were unable to hold onto the experience of emotion following the end of the film clips. For both Roger and SZ, the induced emotion that was intensely experienced while watching the films had fully recovered a mere 60 seconds later. This profound deficit in sustained emotion suggests that both Roger's and SZ's brain is missing the critical substrate for holding onto an emotional experience once the emotion-inducing stimulus is no longer directly accessible to consciousness.

The dual cases of Roger and SZ provide powerful evidence that the structures which comprise the limbic system are in fact an integrated system. While the brain damage in Roger and SZ is extensive and includes multiple regions, they share a common core of bilateral damage impacting the medial temporal lobes (including the hippocampus and amygdala) and the insular cortices. In contrast, damage localized to any single

region of the limbic system (whether it be the hippocampus, amygdala, insula, ACC, or vmPFC) never caused a pattern of emotion recovery that came close to approximating the rapid speed and completeness so readily apparent in Roger and SZ. This was an important finding, since it suggests that only a combined lesion to multiple limbic structures is capable of producing a rapid recovery of emotion. More specifically, there appears to be an additive effect of damage to the hippocampus, amygdala, and insula (and the white matter connections between these structures), which is not found when only 1 of these 3 territories is lesioned. It would have been interesting to test a patient with bilateral insula damage that did not affect the medial temporal lobe, but such a case is unlikely to be found. There are, however, some rare cases of bilateral medial temporal lobe damage (that includes both the hippocampus and amygdala), but does not extend into the insula. If such a case were tested, and showed the same pattern of recovery as Roger and SZ, this would further narrow the prime regions of interest to the medial temporal lobe. There is, in fact, some anecdotal evidence to support the crucial role of the medial temporal lobe in sustained states of emotion. For example, Broks and colleagues (1998) describe the interesting case of a female encephalitic patient (YW) who had bilateral medial temporal lobe damage that did not infiltrate the insula. While on vacation with her husband, they were mugged and physically accosted. The husband was left feeling traumatized for several days, yet YW was reportedly "unperturbed" and "showed no sign of concern". This general lack of distress and concern, combined with relatively short-lived emotional responses and unchanging mood states, is a very characteristic pattern found in amnesic patients with bilateral medial temporal lobe damage (O'Connor et al., 1995; Tate, 2002), including patients such as Roger and SZ.

One plausible theory that can account for how the medial temporal lobes and insular cortices are sustaining the experience of emotion is as follows: (1) highly processed information from the 7 different sensory channels converge in the medial temporal lobes and insular cortices on a moment-to-moment basis, (2a) the medial

temporal lobes filter through this torrent of sensory information and "capture" the salient features (especially those aspects which are emotional in nature), (2b) at the same time, a highly malleable meta-representation of the current state of the internal milieu of the body (including the viscera) is constructed within the anterior insula and provides a relatively rudimentary composite of the dynamically changing internal landscape of the body, (3) the medial temporal lobes (especially the amygdala) links the captured sensory information (from part 2a) with the raw internal feeling represented in the anterior insula (from part 2b), in effect binding together the emotion-inducing stimulus with the emotion that was induced, (4a) once the emotion-inducing stimulus is removed from direct conscious experience, the experienced emotion begins to recover as attention is diverted toward new incoming sensory information, (4b) the vmPFC, in conjunction with the hippocampus, uses contextual cues to help regulate the rate of recovery, (5a) as the emotion recovery process is underway, the medial temporal lobes can reconstruct the memory for the emotion-inducing stimulus, and at the same time, temporarily reactivate the raw internal feeling associated with that memory, (5b) some of this reactivation occurs by actually triggering the physiological, behavioral, and cognitive changes that accompanied the original online emotional experience, (5c) most of this reactivation, however, is achieved by reconstructing the meta-representation (formed in part 2b) within the anterior insula. This 5 step process culminates in the sustained experience of emotion. Notably, this proposed sequence of events occurs in parallel with the online experience of emotion, which does not require the limbic system, but likely requires multiple structures outside of the limbic system including the brainstem, diencephalon, basal ganglia, and primary/secondary sensory cortices. Once the emotion-inducing stimulus is no longer directly accessible to consciousness, the online experience of emotion rapidly dissipates (most likely in a matter of seconds). Shortly thereafter, the sustained experience of emotion is likely triggered in bursts, as the meta-representation of the raw internal online feeling is temporarily reactivated by the medial temporal lobes.

A noteworthy feature of this theory is that the sustained experience of emotion feels qualitatively different than the online experience of emotion. On the one hand, the online experience of emotion is vivid, complex, and nuanced, replete with detailed representations of all the different sensory channels that are being simultaneously activated by the emotion-inducing stimulus. On the other hand, the sustained experience of emotion is a much more vague and poorly differentiated reconstruction of the raw internal feeling experienced during the online state. Some have called this reconstruction an "as-if" feeling (Damasio, 1999 and 2003) because it feels as if you are experiencing the emotion that was felt during the online state, but yet there is no immediately present emotion-inducing stimulus that can be directly experienced in tandem with the feeling. While a memory for the emotion-inducing stimulus is often times associated with the as-if feeling, this is not a necessary requirement, since the feeling of emotion can persist without any explicit memory for its cause (Feinstein, Duff, & Tranel, 2010). Interestingly, in one of MacLean's original formulations of the limbic system, he described similar as-if feelings that occurred during the aura immediately preceding a medial temporal lobe seizure, and said they represent "raw, poorly differentiated, and impersonalized feelings" that are "viscerally related" (Maclean, 1952, p.413).

In conclusion, the evidence presented in this thesis argues against a critical role for the limbic system in the online experience of emotion. It appears that evolutionary pressure has created a significant degree of redundancy within our brains to ensure that we continue to experience emotion in response to certain stimuli and situations, even in the aftermath of extensive bilateral limbic system destruction. Despite this extraordinary resiliency, the brain is simply unable to hold onto an emotional experience without the limbic system, especially the medial temporal lobes and the insular cortices, for this network forms the fundamental substrate that allows the experience of emotion to persevere even after the emotion-inducing stimulus has left the realm of consciousness.

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