Ventral Prefrontal Cortex and Emotion Regulation

By

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CHAPTER 1

Introduction

1.1 Emotion Regulation

Emotion regulation is defined as processes that individuals utilize to change the trajectory (e.g., type, intensity, and time course) of their emotional experience (Gross, 1998; Gross & Thompson, 2007). These processes have been described as "multi-componential", with a collection of dynamic processes transpiring over time (Thompson, 1990). The emotion regulation process begins with a specific psychologically relevant situation (e.g., a grizzly bear crawls into my tent). Then, individuals devote attentional resources and assess the situation (i.e., appraisal). Subsequently, initial emotional responses (visceral subjective feelings as well as the outward physiological expressions) are engendered by one's interpretation or *appraisal* of the situation the individual experiences. After appraising a situation, emotion regulation can be employed as a functionally adaptive process that individuals utilize for the purpose of changing the intensity or the trajectory of one's emotional experience. For example, if a journal manuscript submitted for review was rejected with a long list of comments (situation), one may examine the details of the responses and your coauthor's reactions (attention), determine that the outcome of rejection was biased and unreasonable (appraisal) and subsequently experience, anger, despair, and fear (emotional response). As a method of regulating these emotions evoked by stressful situations, one can rethink or reinterpret (i.e., reappraise) the situation of manuscript rejection as a helpful process where authors are able to receive constructive comments from experts so an improved paper can be accomplished. As a method of emotion regulation that reframes the meaning of the situation, cognitive reappraisal is considered an *antecedent-focused* emotion regulation strategy (Gross, 1998, also see Figure 1 adapted from Cutuli, 2014). This regulation

strategy contrasts with *response-focused* strategies that rely on regulating outward expressions of emotional responses such as suppression.

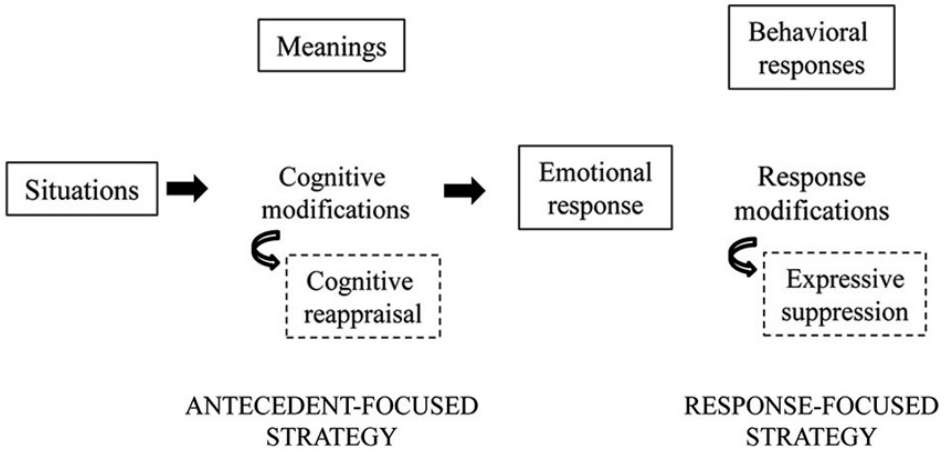


Figure 1. Process-Based Model of Emotion Regulation (adapted from Cutuli, 2014)

Cognitive reappraisal serves as an adaptive process among one's affective function because it helps to regulate mood states that can be detrimental in the long-term to one's mental health. In fact, faulty mood regulation and its resulting behavioral consequences are considered a hallmark feature of major psychiatric disorders such as depression and bipolar disorder (Aldao, Nolen-Hoeksema, & Schweizer, 2010). Critically, these psychiatric disorders commonly exhibit abnormal mood states, both in terms of intensity and duration (Bylsma, Morris, & Rottenberg, 2008). Furthermore, maintenance of anxiety disorders such as obsessive compulsive disorder, post-traumatic stress disorder, and specific phobias are thought to include emotion dysregulation as a core component (Suveg & Zeman, 2004; Hofmann, Sawyer, Fang, & Asnaani, 2012). More broadly, poorly-controlled and intensified emotional distress is widely considered one of the main pillars of many, if not most, psychopathological conditions diagnosed by current clinical standards (American Psychiatric Association, 2013; World Health Organization, 2008). This

common involvement of poor emotion regulation or emotion dysregulation in multiple psychiatric disorders necessitates an effort to examine the core mechanism that underlies both normal and abnormal emotion regulation. In this sense, identifying key neural components of emotion regulation can help better elucidate the neurobiological mechanisms that underlie distressing mood problems in many psychological disorders. Understanding the neurobiological mechanism of normal and abnormal emotion regulation can also make broader contribution to identifying specific treatment targets across multiple psychopathological conditions.

1.2 Neural Bases of Emotion Regulation

With the emergence and expansion of functional neuroimaging research, significant efforts in the field of emotion regulation have advanced our understanding of neural processes relevant to emotion regulation. Most of the neuroimaging studies of emotion regulation employ *reappraisal-based* emotion regulation, which is an *antecedent-focused* strategy that aims to control one's emotional response by reframing, or reinterpreting the situation or the meaning of emotional stimuli presented to individuals (Gross, 1998). The vast majority of neuroimaging studies in emotion regulation have implicated the ventral regions of the prefrontal cortex (PFC), and more specifically the lateral sub-region of the orbitofrontal cortex (OFC), as a key area involved in regulatory control of affective states (Ochsner *et al*., 2012). These studies have reported that lateral OFC is heavily recruited when subjects try to engage in such reappraisal-based emotion regulation (Ochsner *et al*., 2004). Although this specific strategy has been most commonly used in studies of emotion regulation, other studies that use other type of emotion regulation such as suppression and distraction have also shown similar ventral prefrontal involvement (Kim & Hamann, 2007; Goldin, McRae, Ramel, & Gross, 2008). Correlational evidence gleaned from these neuroimaging studies are also consistent with our current

knowledge of bidirectional structural connection between the amygdala and the caudolateral OFC (Ghashghaei & Barbas, 2002) as well as our knowledge of the existing cortical projection to the basolateral amygdala specifically from the ventrolateral region of the prefrontal cortex (Ghashghaei, Hilgetag, & Barbas, 2007).

A comprehensive review of data from neuroimaging studies points to the ventral prefrontal area as a core neural substrate that underlie emotion regulation processes regardless of valence (i.e., negative or positive affect) or direction (i.e., down- or up-regulation of emotional experience) of regulation (Ochsner *et al*., 2012). Attempted regulation of either the positive or negative emotions commonly recruited the left lateral OFC, regardless of the valence of affect being regulated (Kim & Hamann, 2007), providing more weight to the idea that attempt to regulate differently valenced affect may rely on common neural underpinnings that include the lateral OFC for cognitive control of emotions (Ochsner *et al*., 2012). This also suggests that while positive and negative valence systems have been traditionally theorized as orthogonal dimensions (Tellegen, 1985; Watson & Tellegen, 1985), they may still share a common regulatory control implemented by the ventral PFC.

Moreover, it has been speculated that modulation of amygdala activity, which likely reflects changes in affective salience of sensory stimuli, occurs as a function of regulatory control via activating regions of the ventral PFC. Accumulating evidence from multiple neuroimaging studies has revealed that emotion regulation is accompanied by the modulation of amygdala activity regardless of the valence (i.e., positive or negative) of the emotion being regulated. While amygdala activity is not strictly necessary for subjective experience of emotion (Wiest, Lehner-Baumgartner, & Baumgartner, 2006; Feinstein *et al*., 2013), changes in the perceived salience of sensory stimuli presented to an individual has been associated with

concomitant parametric modulation of amygdala activity (Zald, 2003). Neuroanatomically, vlPFC has a direct efferent projection to the amygdala (Ray & Zald, 2012) whereas other frontal areas such as dorsolateral prefrontal cortex lack a direct pathway. Moreover, studies have found that the degree of emotion regulation success as measured by self-report of changes in affect magnitude was correlated with OFC activity during regulation strategy deployment (Urry *et al*., 2006) and that tighter functional coupling between OFC and amygdala activity predicted greater emotion regulation success. In other words, closer linkage between OFC and amygdala activity predicted more successful emotion regulation (Banks, Eddy, Angstadt, Nathan, & Phan, 2007).

While greater ventrolateral prefrontal activity has been parametrically associated with more successful regulation of emotion (subjectively greater change in emotional response), more recent neuroimaging data on regulation has focused on identifying a more mechanistic understanding of the regulatory process. For instance, Wager and colleagues (2008) have shown some evidence that the vlPFC may play a key role in affect regulation by applying a novel statistical method to their neuroimaging data. They utilized the mediation effect parametric mapping (MEPM) method, which entails a type of structural equation modeling that identifies the neural mediator of successful emotion regulation. In this model, they highlighted that the vlPFC activity is positively correlated with greater success in regulation (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008).

A meta-analysis study by Kohn and colleagues (2014) integrated data from 23 fMRI and PET imaging studies of emotion regulation similarly concluded that vlPFC serves as a critical component of regulatory process. In their heuristic model of emotion regulation, vlPFC functions as a gatekeeper of emotion regulation such that activation of the region during emotion regulation serves a dual purpose of appraising the salience of the stimuli but also feeding forward

this information to other frontal areas to allow effective reappraisal when deemed necessary. These data in addition to a wealth of existing literature (Morawetz, Bode, Baudewig, Jacobs, & Heekeren, 2016; Hooker & Knight, 2006; for review see Buhle et al., 2014) that suggest vlPFC activity is likely critically involved in reappraisal-based emotion regulation.

1.3 Key Unaddressed Issues and Challenges

While growing evidence brings more weight to the hypothesized role of the ventral PFC in emotion regulation, there are at least two unaddressed key issues requiring further examination. First, data reported to date still have limited explanatory power to claim with confidence a causal relationship between ventral prefrontal cortex activities and emotion regulation process. There is little doubt that the ventral prefrontal lobe is a strong candidate as a neural substrate that serves a core role in emotion regulation (Ochsner *et al*., 2012). However, most current knowledge on the emotion-regulation related functions of the human ventral PFC stems from neuroimaging studies that are inherently correlational in nature. Traditionally, neuroimaging data reveal brain regions that are temporally co-activated during a task of interest (in this case, an emotion regulation task). Hence, data gathered from fMRI studies employing emotion regulation tasks cannot definitively link specific brain regions with neurocognitive processes necessary to accomplish the task (Wagner *et al*., 2007; Iacoboni *et al*., 2009). While functional neuroimaging data may be misconstrued as sufficient evidence that the ventral prefrontal lobe is where reappraisal-based emotion regulation takes place, it is still unclear whether there is indeed a causal link between ventral prefrontal lobe activity during emotion regulation tasks and the actual phenomenology of subjective change (either decrease or increase in affect intensity) in affective response to emotional stimuli. Because functional neuroimaging studies can only provide correlational evidence to brain-behavior relationships, emotion

regulation neuroimaging studies are not exceptions to this criticism. While these studies provide valuable clues and help generate hypotheses about ventral PFC's role in regulating emotions, these studies do not directly address the question of ventral prefrontal lobe's involvement in emotion regulation with *causal certainty*.

These data reviewed above are, to a limited extent, supplemented by additional observational clues from studies of individuals with OFC damage. These studies suggest that individuals who sustain OFC damage have measurable deficits in regulating mood and engaging in culturally appropriate behavior in social contexts, despite their generally intact ability to experience a full spectrum of emotions to a similar level as healthy normal individuals would. For instance, individuals with OFC damage have been reported to show disinhibited behavior (such as hypersexuality, substance use, and poor social interaction) and behavior that indicates the individual's disregard of moral and social decorum (Meyers, Berman, Sheibel, & Hayman, 1992; Berns & Swordlow, 2003). It has also been reported that OFC lesion patients exhibit lower levels of self-reported as well as outwardly visible facial expressions of embarrassment (Beer, Heerey, Keltner, Scabini, & Knight, 2003). One possible interpretation of these data is that subjective experience of socially relevant emotions, such as embarrassment, guilt, shame, and pride, may be associated with the OFC. One problem with this speculation is that most human OFC lesion studies report results from an aggregate of heterogeneous lesion cases that include multiple subregions within the OFC. Importantly, studies with a more homogeneous sample of OFC lesion foci have generally restricted their study sample to medial OFC lesion cases and rarely include ventrolateral OFC lesions. Furthermore, samples in such studies are commonly collected from neuropathological or clinically necessitated surgical lesions (as opposed to experimentally manipulated lesions in cases of non-human animal studies) that are inherently

heterogeneous sites within the larger OFC (Zald & Andreotti, 2010), making generalizable inferences more difficult. These weaknesses and idiosyncrasies in studies utilizing human subjects with existing OFC lesions make it challenging to draw conclusions about functions of specific foci of the OFC.

Conducting laboratory-controlled lesion studies (e.g., excitotoxic, surgical resection, electrical stimulation, and etc.) of non-human primates may be considered a viable approach to address this issue, albeit to a limited extent. For example, in one study, researchers induced excitotoxic lesion to the anterior OFC and ventrolateral PFC in marmoset monkeys. This revealed that both groups of lesioned marmosets exhibited observably increased anxious behavior and fear responses in response to the presence of human intruders, which is generally regarded as only "mildly threatening" (Agustín-Pavón *et al*., 2012). Interestingly, lesion targeted specifically to the vlPFC, but not the anterior OFC, influenced the monkeys' use of a coping mechanism of increasing proactive vocalization of alarm calls in response to the anxiety inducing stressor. Non-human primate lesion studies can be valuable sources to gain more precision when making inference about specific subregions of the frontal lobe and their dissociable functions in the context of affective control. However, an added layer of complication to this picture is the difficulty of ascribing to the behaviors of non-human primate subjects such a complex cognitive process as reappraisal-based emotion regulation. Note, this is not a question of whether non-human primates have emotion. In fact, it reaches one step further, as emotion regulation requires the addition of willful control of emotional experience. Because research into animal emotion regulation is a relatively unexplored area, it makes it even more difficult for researcher to employ an animal model to study it.

CHAPTER 2

Overview of Studies

2.1 Ventrolateral PFC and Reappraisal-based Emotion Regulation

2.1.1 *Using rTMS in Emotion Regulation Research*

An alternative method that combines the ability to probe emotion regulation process in humans while simultaneously allowing us to make more precise causal inferences about brain-behavior relationships is using a neurostimulation method called transcranial magnetic stimulation (TMS) (Schutter, Van Honk, & Panksepp, 2004). TMS is a neurophysiological technique that allows the induction of a current in the brain using a magnetic field to pass the scalp and the skull safely (Hallett, 2000). In TMS, a current passes through a stimulation coil that is held over the subject's head. As the current passes through the coil and rapidly changes the magnetic field, magnetic pulses are generated perpendicular to the direction of the coil and can penetrate the subject's scalp and skull to induce a small current that can cause - depending on the parameters used such as frequency and pattern of pulses delivered - depolarization or hyperpolarization in the underlying cortex of the subject's brain (Robertson, Théoret, & Pascual-Leone, 2003). TMS can be applied in trains of multiple pulses within a given period of time to a targeted cortical region. This form of TMS is called repetitive transcranial magnetic stimulation (rTMS). Depending on the stimulation parameters, rTMS is capable of changing the activity in a brain area for a brief period of time beyond the duration of the rTMS application itself. In other words, it is possible to increase or decrease activity level in a given cortical region for an extended periods of time (in order of minutes). Low-frequency rTMS (< 1 Hz) has been shown to suppress cortical excitability of the targeted region for several minutes following rTMS

stimulation (Robertson et al, 2003). This particular variant of TMS techniques allows researchers to transiently disrupt cortical activity within a targeted brain region, thus allowing examination of a focal cortical area's hypothesized involvement in specific cognitive functions. A number of previous studies have successfully used 1 Hz low-frequency rTMS over dorsal regions of the frontal cortex (Knoch, Gianotti, Pascual-Leone, Treyer, Regard et al, 2006; Knoch, Pascual-Leone, Meyer, Treyer, & Fehr, 2006; Van Honk, Schutter, d'Alfonso, Kessels, & de Haan, 2002), and the dorsomedial PFC (Mottaghy, Gangitano, Sparing, Krause, & Pascual-Leone, 2002). Note, it is possible to use stimulation frequency higher than 1 Hz, and applying such higher frequency is called the *rapid-rate* or *high-frequency* TMS. High-frequency rTMS, in contrast to low-frequency rTMS, enhances cortical excitability (Schutter, Van Honk, & Panksepp, 2004; Fierro *et al*., 2005).

Neuromodulation techniques such as transcranial magnetic stimulation (TMS) methods and emotion regulation tasks can be conjunctively utilized to investigate the impact of modulated cortical excitability in specific brain regions and their impact on regulation of one's emotional response. Using this approach, one can thus transiently disrupt brain excitability in a targeted cortical area and measure its effect on cognitive processes such as emotion regulation. Because the effects of rTMS-dependent cortical excitability modulation are transient, rTMS can safely test the hypothesis that the vlPFC function contributes to effective emotion regulation in healthy individuals. Directly manipulating cortical excitability using this technique provides an invaluable window of opportunity to gather crucial causal evidence where only correlation evidence currently exists (Schutter, Van Honk, & Panksepp, 2004). More specifically, this approach could help answer questions about the causal nature of ventral prefrontal lobe activity in emotion regulation. Utilizing the transcranial magnetic stimulation technique allows

recruitment of study sample comprised of healthy individuals, thus making it possible to recruit a significantly higher number of subjects.

To date, there has not been any published TMS study that targets ventrolateral frontal cortex to investigate its effect on emotion regulation. In fact, no previous human lesion patient studies or neurostimulation studies have directly addressed the question of the impact of ventral prefrontal cortex lesion or disruption on appraisal of emotional experience and subsequent emotion regulation.

A handful of TMS studies that have targeted other regions of the PFC examined the effect of TMS in the broader context mood and emotion, and not necessarily emotion regulation. One of the early TMS studies demonstrated that 5 Hz rTMS on dorsolateral regions of the frontal lobe could significantly shift mood states in healthy individuals (Steppel, Pascual-Leone, Basser, Hallett, & Post, 1996). Another study reported that repeated sessions of rapid-rate rTMS (10 Hz in this study) over the left dorsolateral PFC could significantly alleviate depressive symptoms in patients suffering from major depression (Pascual-Leone, Rubio, Pallardó, & Catalá, 1996). A meta-analysis of neurostimulation studies investigating the anti-depressant effect of high-frequency rTMS of the left DLPFC have shown that enhancing the cortical excitability of this region can have a lasting therapeutic effect compared to sham stimulation (Schutter, 2009). An integrative look at 30 double-blind sham-controlled studies (total n=1164) conducted in the last three decades showed a moderate effect size (Cohen's-d=0.39, confidence interval: .25-.54) which points to the efficacy of this method. Moreover, in meta-analysis studies by two different groups have also shown that therapeutic effect of low frequency right DLPFC rTMS is comparable to that of left DLPFC rTMS (Berlim, Van den Eynde, & Daskalakis, 2013; Chen et al., 2013).

In all of these studies, researchers have targeted the dorsal regions of the PFC, without additionally considering the effect of ventral PFC stimulation. Lack of ventral PFC rTMS studies is not surprising given that ventral prefrontal TMS stimulation is considered logistically more difficult due to the region's proximity to facial nerves and the anterior visual tracts. There are, however, a few exceptions. Among existing studies, Schutter and Van Honk (2006) reported that low-frequency rTMS specifically targeting the left frontopolar cortex (i.e., just anterior to medial OFC) facilitated study participant's memory for happy faces but not fearful faces. Interestingly, a relatively recent study reported that low-frequency rTMS to the cerebellum prevented stimulated individuals from suppressing negative mood (Schutter & Van Honk, 2009). However, there remains a dearth of TMS studies of emotion regulation that target the ventral frontal lobe. Even though previous functional neuroimaging data point to lateral regions of the ventral PFC as a prime candidate region associated with emotion regulation (Wager et al., 2008; Kim & Hamann, 2007), there is a contrasting void of data in the area of neurostimulation research that could complement the existing neuroimaging data, perhaps due to technical difficulties associated with targeting ventral regions of the frontal cortex.

There are a handful of TMS studies that target the inferior regions of the frontal lobe closer to the ventrolateral PFC; however, most of these studies have been conducted outside the context of affective processing, and none of the studies utilized a task specifically focused on emotion regulation. A few studies have used 1 Hz low-frequency over the inferior frontal gyrus of the PFC and demonstrated that low-frequency rTMS to regions of the inferior frontal gyrus (IFG) can disrupt aspects of semantic processing (Gough, Nobre, & Devlin, 2005; Nixon, Lazarova, Hodinott-Hill, Gough, Passingham, 2004; Thiel *et al*., 2005). But data gathered from these studies are not directly informative in regards to the effect of ventral PFC disruption on

one's ability to perform emotion regulations. Perhaps the most relevant study in this literature is a paper by Keuken and colleagues that reported disrupting the left IFG using low-frequency rTMS increased reaction time (but not accuracy) for recognition of emotional faces (Keuken *et al*., 2011). However, this study did not explicitly address differences in emotional appraisal or regulation associated with rTMS of the IFG.

In summary, although prior neuroimaging research has suggested a significant association between vlPFC activity and successful emotion regulation using cognitive reappraisal, little research has been done to causally link vlPFC activity and effectiveness of emotion regulation. In particular, to date, there has not been a TMS study that specifically examines whether disrupting activity in ventrolateral regions of the PFC influences individuals' ability to exert conscious and effortful control over externally elicited emotions. Previous TMS studies targeting regions near the ventral PFC have rarely focused on processes relevant to emotion regulation. Therefore, TMS stimulation studies specifically designed to target the ventral PFC to subsequently probe its effect on emotion regulation can greatly enhance our understanding of the frontal lobe's involvement in affective processes.

2.1.2 *Current Study 1*

The purpose of this first study was thus to examine the causal relationship between intact ventral prefrontal cortex function and effectiveness of reappraisal-based emotion regulation. By examining the process of emotion regulation using an rTMS technique that allows direct manipulation of cortical excitability, I aimed to assess the causal contribution of the ventral PFC in emotion regulation process. Data gathered from this rTMS study targeting the vlPFC provides

extremely valuable data that could more clearly evaluate the hypothesized role of frontal lobe involvement in emotion regulation.

The effect of rTMS on emotion regulation was specifically focused on down regulation (as opposed to up-regulation) of negative affect (as opposed to positive affect). Most emotion regulation neuroimaging studies have similarly focused more heavily on down-regulation of negatively valenced emotions. This is likely due to the greater clinical relevance of negative mood states on one's mental health and well-being than positive affect (Baumeister, Bratslavsky, Finkenauer, & Vohs, 2001). Accordingly, in daily living as well as in cases of clinical disorders, the problem of regulating negative affect is generally thought of as playing a bigger role in mental health than exerting similar control over positive affect (Folkman & Moskowitz, 2004). However, it is duly noted that cognitive control of emotion certainly extends beyond negative affect and can encompass regulating positive emotions (e.g., trying not to laugh at a friend tripping over a banana peel), as well as up-regulating positive or negative emotions (Gross, 1998). Therefore, completion of this experiment on the down regulation of negative affect can be conceptualized as a platform to expand upon this research in the future.

As an outcome measure of emotion regulation, physiological data was concomitantly collected alongside self-report of subjective affect rating. Most emotion regulation studies exclusively report changes in self-report affect rating as a sole metric of emotion response and emotion regulation success. While collecting subjective affect rating has the clear benefit of explicitly asking study participants to judge their own emotional experience, using this as the only measure of emotion regulation effectiveness can restrict one's interpretation of the data due to the subjective nature of self-report data. To remedy this and complement the subjective data with an objective index of affective response changes, skin conductance response (SCR) data

were also collected during the emotion regulation task following rTMS. SCR is a type of electrodermal activity (EDA) and an index of autonomic arousal and has been widely used as a measure of emotional arousal intensity in psychological studies (Crone, & Van der Molen, 2007; Hinson, Whitney, Holben, & Wirick, 2006; Jenkinson, Baker, Edelstyn, & Ellis, 2008; Wagar & Dixon, 2006). Critically, individuals show heightened levels of SCR during emotional arousal (Dunn, Dalgleish, & Lawrence, 2006), which allows for a real time monitoring and recording of physiological changes as a result of emotional response to task stimuli and subsequent emotion regulation. This measure augmented the self-report data and served as an added dimension that elucidated changes to physiological response following rTMS.

Additionally, individual differences in difficulty with emotion regulation were measured using relevant questionnaires in order to take into account each participants' disposition to engaging in emotion-regulation. Studies suggest that individuals vary in the type of emotion regulation strategy they prefer to use (e.g., reappraisal vs. suppression) and how effectively they use these regulation methods (Gross & John, 2003; John & Gross, 2004). Addressing this latent complexity embedded within the study participant pool enhanced the interpretability of this study. For instance, if a hypothetical study participant who is very adept at reappraising negative emotions received TMS stimulation and showed no significant change in her ability to down-regulate negative emotions, this participant may reduce the overall effect size of TMS influence on emotion regulation. Conversely, if the hypothetical study participant dispositionally has much difficulty reappraising negative situations regardless of the TMS stimulation condition given, she may similarly reduce the overall effect size of the study. Therefore, explicitly measuring the individual differences in trait-level emotion regulation capability and integrating this variance in hypothesis testing could improve the explanatory power of the collected data. Accordingly, TMS

study participants were asked to fill out the Difficulties in Emotion Regulations Scale (DERS). This is a self-report questionnaire originally developed to measure self-reported dysregulation in various domains of emotional functioning within the larger context of emotion regulation (Gratz & Roemer, 2004). The questionnaire consists of 36-items scored on a 5-point Likert scale ranging from 1 ("*almost never (0-10%)*") to 5("*almost always (91-100%)*") and has good internal consistency (α=.93) and test-retest reliability across 4-8 weeks ($p<.01$) (Perez, Venta, Garnaat, & Sharp, 2012). This questionnaire is an ideal inventory to include as an index of individual differences in emotion regulation, because it simultaneously measures multiple dimensions within the larger category of emotion regulation (or dysregulation). Subscales of this questionnaire include: non-acceptance of emotional-responses (*non-acceptance*), difficulties engaging in goal-directed behavior (*goals*), impulse control difficulties (*impulse*), lack of emotional awareness (*awareness*), limited access to emotion regulation strategies (*strategies*), and lack of emotional clarity (*clarity*). This six-factor conceptualization of the questionnaire structure has been supported in both adults (Gratz & Roemer, 2008) and adolescent populations (Neumann, Van Lier, Gratz, & Koot, 2010). Total scores and specific subscale scores from this study were utilized as covariates when conducting statistical analysis to test the hypothesized effect of TMS on emotion regulation.

2.2 Ventral PFC Damage and Emotion Regulation

2.2.1 *Experience Sampling to Harness Data from Naturalistic Settings*

The second issue that I aimed to address was the disconnect between laboratory-controlled emotion regulation studies that explicitly cue for conscious and effortful modulatory control of emotion, as opposed to more spontaneous regulation that likely happens in our day to

day life. As Gross (1998) suggested, emotion regulation can be "automatic or controlled," "conscious or unconscious." This inclusive definition reminds us of the multidimensional nature of emotion regulation which laboratory-based studies can only partially capture. In other words, dominant emotion regulation task paradigms used in research settings are generally restricted – though understandably – to consciously controlled and explicitly cued instruction based experimental paradigms. For example, two dominant strategies that study participants are frequently instructed to use in emotion regulation tasks involve reappraisal and suppression. In the reappraisal strategy, study participants are instructed with visual cues (e.g., words or figures on screen) to actively reinterpret and reframe the salient emotional stimuli presented. In suppression strategy, participants are directed to inhibit their emotional response without actively engaging the salient features of the emotional stimuli. Both strategies are known to manipulate one's primary emotional experience (Quirk & Beer, 2006), but necessarily call on conscious and effortful mechanisms that are somewhat unnaturally elicited in a laboratory controlled setting. Because studies conducted in a laboratory setting present emotional stimuli explicitly salient to study participants, it does not necessarily replicate the natural experience of daily living where individuals attend to environmental stimuli on their own volition and voluntarily extract emotional significance from them. It is possible that in a more naturalistic setting, individuals with orbitofrontal or more broadly ventral frontal damage may show a greater deviation from the norm in terms of the course or periodicity of emotional experience and emotion regulation. A study conducted by Beer and colleagues (2003) has shown that within the context of more spontaneous interactions, individuals with orbitofrontal damage tended to generate socially inappropriate emotions and reactions, although it is largely unknown to what extent this is caused by emotion regulation problems. In this regard, studying the effect of frontal lobe lesion

on emotion regulation within the context of daily life can provide valuable data that has not yet been reported in the literature.

One possible approach to harness ecologically valid data when studying mood and emotion regulation is to utilize experience-sampling methods. Experience-sampling methods refer to a technique in which data gathering related to affect and activities are done at the moment of the experience (or at a time that is temporally proximal to the moment of experience), within the context of individuals own daily living environment (Larson & Csikszentmihalyi, 1983). This method can be utilized to not only examine the frequency and patterns of emotional experience embedded within the context of everyday life situations (Csikszentmihalyi & Larson, 1987), but also can be used to connect a specific emotional experience with an antecedent event or situation (Scollon, Prieto, & Diener, 2009). Therefore, experience-sampling methods can be exploited to gather potentially illuminating data that stretches beyond the mere inference of group difference in emotion regulation, and reaches a more integrated and descriptive understanding of what aspects of emotional experience or regulatory control go awry, if any.

There are some recent efforts, albeit not involving OFC lesion samples, to provide a more ecologically valid data on mood regulation by utilizing this experience-sampling method. For example, Gruber and colleagues (2013) reported daily experience-sampling data of mood and emotion regulation effort, comparing remitted bipolar disorder and remitted major depressive disorder patients to healthy normal individuals. In this study, self-report data regarding subjective experience of positive and negative affect as well as related emotion regulation effort were collected over six continuous days. As expected, patients with bipolar disorder showed patterns of increased emotionality and accordingly increased effort to regulate emotions. Another experience-sampling study by O'Toole and colleagues (2014) compared college students high

and low in social anxiety, and reported that individuals with high social anxiety used a maladaptive emotion regulation strategy to ineffectively regulate their emotion. This study also revealed that individuals with high social anxiety also showed high correlation between daily instances of suppressing emotional expression and positive affect such that highly anxious individuals who used more suppression also had diminished positive emotional experience (O'Toole, Jensen, Fentz, Zachariae, & Hougaard, 2014).

While these experience-sampling studies provide intricate insight into the linkage between emotion and emotion regulation among different clinical populations, it is unclear whether there are significant individual differences in periodicity, or level of fluctuation in affective experience or subsequent emotion regulation effort. For example, the Gruber *et al*. (2013) study did report useful measures of emotion regulation effort, but this study did not specifically examine periodicity in bipolar disorder patients' emotionality or emotion regulation effort. Given the longitudinal nature of most experience-sampling data, it will be a valuable addition to examine the presence of periodicity, if any. Periodicity in this case refers to a cyclical pattern of fluctuation in mood (either positive or negative affect) of which previous studies have demonstrated as a feature of human affective experience (Larsen & Kasimatis, 1990; Chow et al., 2005). A specific aspect of interest in mood periodicity is the question whether there are clinically meaningful individual differences in the fluctuation of affective experience. In other words, is there a significant difference in the magnitude of change in affect over a defined unit of time between healthy individuals and those believed to experience emotion regulation difficulties? One way to answer this question is to measure a change in intensity of sadness between two time-points t_1 and t_2 and change of intensity between two time-points (i.e., $\mathbf{\Delta} = t_1 - t_2$) as a measure of momentary fluctuation. This change measure reflective of momentary

fluctuation can then be aggregated into simple index measure of mood fluctuation across a longer period of time by deriving the root-mean-square of the change measures (see equation below).

$$* \textit{ mood fluctuation index} = \sqrt{\frac{\sum_1^{i-1}(t_n - t_{n+1})^2}{i-1}}$$

* i represents number of sampling events; n represents serial order of sampling event

This mood fluctuation index can be derived for both positive and negative affect dimensions for each study participant. Using this metric allows for an examination of quantifiable mood fluctuation and thus helps to investigate the presence of abnormal emotionality and emotion dysregulation. Given the chronological nature of the experience-sampling data, it is possible to analyze whether the continuous observations over time exhibit any cyclical periodicity by utilizing autocorrelation analysis (Siderides & Greenwood, 1997).

To date, there is no published study of frontal lobe lesion patients that utilizes experience-sampling methods to examine self-report data containing subjective mood experience and emotion regulation effort. The experience-sampling study of patients with OFC lesion may provide invaluable data that could address several key questions that will help better characterize the OFC's role regarding regulation of affect in more settings (as opposed to explicitly instructed emotion regulation in the laboratory). First of all, this experience-sampling study will establish whether OFC lesion patients experience an abnormal level of positive and negative affect in either direction. One study with OFC lesion patients described that this group self-reported greater anger and decreased happiness compared to healthy normal individuals (Berlin, Rolls, & Kischka, 2004). However, this study did not attempt to measure whether this group difference in specific emotions stayed constant over time or whether these individuals engaged in less effective emotion regulation effort.

2.2.2 *Current Study 2*

In order to investigate the effect of OFC lesion on the intensity, duration, and periodicity of positive and negative emotionality as well as related emotion regulation effort and their effectiveness, a group of OFC lesion patients provided subjective report of their emotional experience and emotion regulation effort over time by utilizing an experience-sampling method. This study is the first to attempt measuring subjective self-report of mood and emotion regulation over time in this population. Exploiting such a study design provides valuable data by tracking study participants' emotional experience and emotional control over time. In addition, chronologically collected data could inform whether there is any group difference in time dependent changes in mood intensity and frequency within the context of emotion regulation. More specifically, experience-sampling of mood and mood regulation attempts over an extended period of time may yield valuable data that put to the test the anecdotal evidence and previous case studies that suggest lesion to the OFC disrupts regulation of affect.

The experience-sampling study enrolled a group of OFC lesion patients, amygdala lesion patients and an equal number of demographically matched healthy controls for comparison. Three sampling events (epochs) occurred each day for 14 consecutive days in order to capture and characterize the continuously changing affective experience. Each experience-sampling event included subjective ratings of positive and negative emotions, subsequent emotion regulation effort used if any, and study participant's report of their own perceived daily functioning level. Previous studies that reported OFC lesion patients' abnormal subjective emotionality could not discern between changes in the intensity of emotionality per se or failure of regulatory control over emotional experience. In comparison, for this study, I collected self-reports of participants' emotion regulation effort and perceived regulation success in addition to

subjective report of affect, with the intent to gather and examine a data set that illustrates a more integrative picture of participants' emotion regulation experience. The measures of emotion regulation effort in addition to measures of emotionality can be used to tease apart the distinction that has been lacking in previous studies. Therefore, measuring both emotionality and related emotion regulation effort was a clear strength of this study compared to previous experience sampling studies.

Self-report measures gathered from this experience-sampling study of OFC lesion patients have the potential to provide informative data that could more clearly examine the role of the OFC in emotion regulation.

In order to advance our knowledge of emotion regulation and the role of frontal lobe regulatory control, I used two complementary studies designed to specifically attend to issues that were unaddressed by previous data presented by other researchers. While these two studies utilized different methodologies and techniques, both studies broadly address the causal involvement of the ventral PFC in emotion regulation: one in the context of conscious and effortful emotion regulation, and another in the context of spontaneous emotion regulation embedded in the context of daily life activities. Data gathered from these two studies augments the existing data from neuroimaging and lesion studies and will further advance our knowledge of the role of the frontal lobe in affect regulation.

CHAPTER 3

Low Frequency rTMS of Ventrolateral PFC and Reappraisal-Based Emotion Regulation

3.1 Background

The experiments described in this chapter evaluated the impact of transient disruption of the ventrolateral PFC, using rTMS, on reappraisal-based emotion regulation. In order to investigate the contribution of the frontal lobe in emotion regulation, study participants engaged in an emotion regulation task following a repetitive transcranial magnetic stimulation (rTMS) to the ventral PFC. The goal of this study was to investigate whether low-frequency rTMS (1 Hz) over the ventrolateral frontal cortex in healthy controls would impair effective down-regulation of negative affect during reappraisal-based emotion regulation. Since TMS dependent influence on behavior have generally been shown to last for approximately half the duration of low-frequency rTMS stimulation over the PFC (Mottaghy, Gangitano, Sparing, Krause, & Pascual-Leone, 2002), ventrolateral prefrontal regions were stimulated using 1800 pulses delivered every 1 second (i.e. 1 Hz rTMS for 30 mins), which was designated to be twice as long as the expected duration of the reappraisal-based emotion regulation task (< 15 min). Study participants performed the behavioral task immediately following the stimulation procedure (i.e., Off line TMS procedure). The rationale for utilizing offline stimulation (task performance after rTMS stimulation) was that it allowed participants to perform the task without the distracting auditory and tactile sensations from repetitive TMS pulses. Furthermore, the advantage of using rTMS over single pulse TMS was that rTMS allowed cortical excitability to be reduced for much longer periods of time – minutes as opposed to milliseconds (Robertson et al, 2003) – allowing participants to perform an entire task following modulation of cortical excitability in the target

stimulation region. The duration of pulse delivery was precisely controlled using computerized script on Matlab (Mathworks, 2013), ensuring participants received no more than 1800 pulses of rTMS stimulation.

The right and left vlPFC were targeted for low frequency transcranial stimulation in separate sessions, in each case with stimulation occurring prior to participants' performing an emotion regulation task. The main purpose of this study was to investigate the effects of unilateral rTMS on down regulation of negative affect within the context of reappraisal-based emotion regulation. It was predicted that rTMS of the vlPFC (either left of right) would interfere with participants' ability to effectively down regulate negative affect using reappraisal-based emotion regulation. A comprehensive review of emotion regulation neuroimaging studies (Ochsner *et al*., 2012) suggests that the left ventrolateral PFC may serve a more critical role in reappraisal-based emotion regulation strategies compared to the right vlPFC, because reinterpretation of presented emotional stimuli requires more left-hemisphere based semantic processing. Given these data, it was predicted that a greater decrement on the reappraisal effectiveness would be observed after the left rTMS compared to the right rTMS.

3.2 Methods

3.2.1 *Participants*

Thirty-three healthy, right-handed, female adults with a mean age of 22.1 years (SD = 3.2) were recruited from the Vanderbilt University psychology department subject pool through the SONA systems website (http://vanderbilt.sona-systems.com/). Interested prospective participants completed a written informed consent approved by the Vanderbilt University Institutional Review Board. Because this study involves MRI scanning and rTMS techniques as

essential components, interested individuals were also screened to ensure their safety and eligibility of MR imaging and transcranial stimulation. All participants were screened for, and excluded if they had a positive history of neurological or psychiatric disorder. Individuals currently taking psychotropic medication, possessing a family history of epilepsy and 3 Tesla MRI ineligible persons were also excluded from the study.

3.2.2 *Materials and Design*

MRI and Frameless Stereotaxy Using BrainSight™

While many previous rTMS studies have utilized the 10-20 EEG system to identify and stimulate the *dorsolateral* prefrontal cortex (Essex, Clinton, Wonderley, & Zald, 2012), a pilot rTMS study of the vlPFC revealed that this method was not suitable for this stimulation target. Because of a larger margin of precision, the 10-20 EEG system frequently caused unintended peripheral facial nerve stimulation. Therefore, I used an identification method using a frameless stereotaxy software (BrainSight™ 2, Rogue Research, Montreal, Canada) that registers T1-weighted MRI scans of the participants' cerebral cortex to more precisely guide the TMS coil to stimulate the vlPFC without stimulating the facial nerves. For this, all participants completed a structural MRI scan, which was processed and loaded into this frameless stereotaxy software, to precisely place the TMS coil to target the vlPFC region (see Figure 2 and 3).

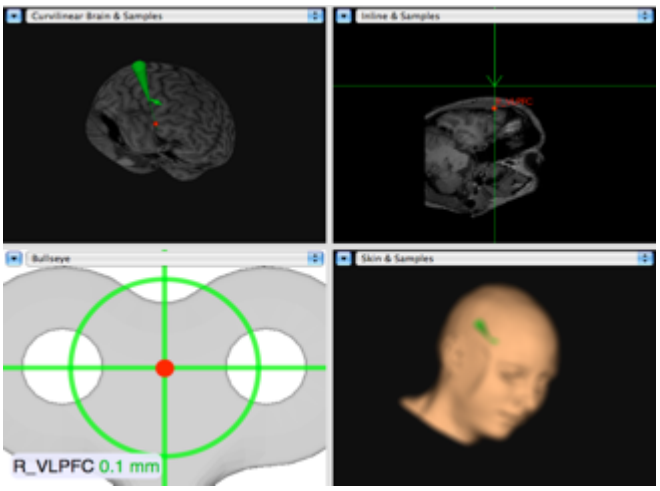


Figure 2. TMS Coil Stereotactically Positioned Over the Right VLPFC Using BrainSight™

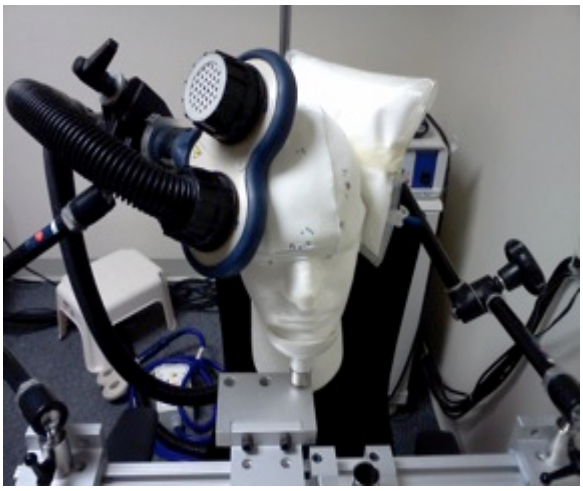


Figure 3. Demonstration of TMS Coil Positioned Over a Mannequin Head

TMS Set-up

TMS stimulation target coordinates were selected based on a previous fMRI study with a relatively large sample size (n=30) that identified the vlPFC as a critical region whose blood-oxygen-level-dependent (BOLD) activity showed positive correlation with reappraisal success (Wager *et al*., 2008). This vlPFC target coordinate corresponded to the orbital portion of the inferior frontal gyrus [MNI coordinates: x = 52, -52; y = 31; z = -9]. The specific vlPFC coordinates identified by this study were of particular interest as Wager and colleagues (2008) performed a pathway mapping analysis which illustrated that activities in the vlPFC region influenced the effectiveness of reappraisal-based emotion regulation by mediating activities in subcortical structures such as the amygdala and the nucleus accumbens.

Offline TMS

Immediately prior to performing the emotion regulation task, participants received a 30-minute course of low-frequency (1 Hz) rTMS stimulation (i.e., 1800 pulses) delivered with a

MagStim™ TMS double 70 mm (*Figure-8*) coil (Magstim, Wales, UK) at 54% power (see Figure 2). An identical stimulation parameter setting was successfully and safely used in a previous rTMS study in our laboratory for targeting the dorsolateral prefrontal cortex (Essex, Clinton, Wonderley, & Zald, 2012).

Emotion Regulation Task

Immediately following the completion of a 30-minute low-frequency rTMS, participants completed an emotion regulation task (see Figure 4). On each trial, participants were first

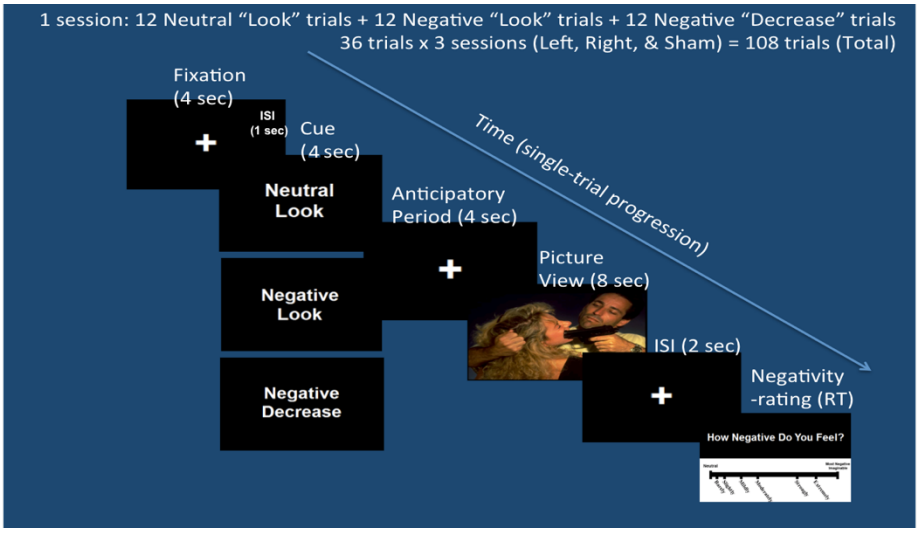


Figure 4. Schematic of Reappraisal-Based Emotion Regulation Task

presented with a fixation cross for 4 seconds. Then, after 1 second of inter-stimulus-interval, participants were presented with a cue screen that indicated the *valence* of an upcoming visual stimulus: "NEUTRAL" or "NEGATIVE". On the same screen where the valence cues appeared, participants were also presented with an *instruction* cue: "LOOK" or "DECREASE", which appeared directly below the valence cue. For the look cues, participants were told to attend to the picture but not try to alter any feelings elicited by it. By contrast, for the decrease cues,

participants were instructed to reinterpret and reframe the picture presented so that it no longer elicits a negative response. In total, three different cuing conditions were used: "NEUTRAL LOOK", "NEGATIVE LOOK", and "NEGATIVE DECREASE". Each cue was immediately followed by a 4-second anticipatory period, after which a picture was presented for 8 seconds. For the "NEUTRAL" condition, participants viewed a neutral picture, a photograph of an everyday object such as a book or a chair. For the "NEGATIVE" condition, participants viewed an aversive picture, most of which depict scenes of violence and gore. Negative and neutral images were selected from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2008) and were balanced for valence and arousal between different sets assigned to each session. After two seconds after the offset of picture presentation, a visual analog rating scale appeared and stayed on the screen until the study participant input a response using a mouse. This scale allowed participants to rate the current strength of their negative affect on a continuous scale with empirically determined label spacings (Lishner, Cooter, & Zald, 2008). Participant responses of self-reported negative affect after picture-viewing served as a subjective measure of negative affect for each trial. Prior to each experimental session, participants completed a practice version of the emotion regulation task with the experimenter present to ensure every participant fully comprehended the task and conformed to the type of emotion regulation instructed they were instructed to use (i.e., reappraisal-based emotion regulation) during the task. Each participant viewed 12 pictures associated with each of the three cue combinations (i.e., "NEUTRAL LOOK"; "NEGATIVE LOOK"; and "NEGATIVE DECREASE") for a total of 36 pictures in a given session. Thus, for participants completing all 3 different types of stimulation sessions (left real rTMS, right real rTMS, left or right sham rTMS), a total of 108 pictures were presented, 72 of which were negative (further divided into 36

associated with the "LOOK" cue and the other 36 associated with the "DECREASE" cue) and 36 of which were neutral. Picture stimuli were selected to ensure equivalence in valence, arousal, and luminosity across sets. A series of one-way analysis of variance (ANOVA) indicated that neither valence, arousal, nor luminosity were significant different among picture sets (all *F*-test p-values >.05). Mean and standard deviation of valence, arousal, and luminosity ratings are presented below (see Table 1).

		Set 1	Set 2	Set 3	F	p-value
Valence (lower is more negative)	Neutral Look	4.82 (.15)	4.99 (.16)	4.88 (.19)	2.98	.06
	Negative Look	1.86 (.38)	2.11 (.58)	1.81 (.43)	1.49	.24
	Negative Decrease	1.93 (.34)	2.05 (.52)	1.86 (.57)	.47	.63
Arousal (higher is more arousing)	Neutral Look	2.91 (.67)	3.10 (.67)	2.87 (.64)	.41	.63
	Negative Look	6.53 (.78)	6.33 (.65)	6.83 (.51)	1.77	.18
	Negative Decrease	6.46 (.81)	6.29 (.73)	6.46 (.55)	.23	.79
Luminosity (higher is brighter)	Neutral Look	78.5 (42.8)	69.6 (34.3)	83.5(35.0)	.42	.66
	Negative Look	81.4 (29.9)	83.6 (37.5)	82.9 (20.2)	.02	.98
	Negative Decrease	88.4 (35.0)	79.1 (41.4)	72 (35.8)	.57	.57

Table 1. Mean Rating of Valence, Arousal, and Luminosity by Trial Type and Picture Set

In addition, a series of t-tests were conducted comparing the "NEGATIVE LOOK" and "NEGATIVE DECREASE" conditions. No statistically significant difference was found in mean ratings of valence, arousal, or luminosity between the two conditions within each picture set (all t-test p-values >.05). In order to mitigate the possibility of uncontrolled variable biasing study results, the three picture sets were pseudo-randomly assigned to stimulation types. Thus, assignment of picture-sets to the type of TMS session was counterbalanced across study sample.

While participants were completing the behavioral task, skin conductance response (SCR) was simultaneously recorded as a measure of physiological arousal. This SCR data collected during emotion regulation task performance augmented the subjective mood rating as an objective measure of physiological arousal, and were later analyzed both independently and in conjunction with participant's subjective mood ratings. SCR data harnesses the variation of electrical properties of the skin in response to sweat secretion. Such variation in SCR can be measured non-invasively by applying a low constant voltage to the skin near the palm or the phalange area of fingers (Fowles *et al*., 1981). Because of the relative ease of acquisition of physiologic data, SCR measures have been extensively used in research studies relevant to affective processes (Dawson *et al*., 2007). To measure autonomic signals using SCR, participants were fitted with two Ag-AgCl electrodes with finger cuffs placed on their left hand index and ring fingers. Each electrode was placed on the palmar surface of the middle phalanx. SCR data were recorded continuously with a sampling rate of 200 Hz for the entire duration of the emotion regulation task using a research-grade sampling device (*Biopac*-GSR100C, BIOPAC systems Inc., USA) including amplifiers for SCR collection.

3.2.3 *Procedure*

Procedure Overview

Session 1	Session 2	Session 3*	Session 4*	Session 5*
Questionnaires Time: 15 minutes	MRI Time: 20 minutes	rTMS for 30 minutes Total Time: 1 hour	Fake rTMS for 30 minutes Total Time: 1 hour	rTMS for 30 minutes Total Time: 1 hour

Table 2. Outline of Procedure for Each Session in the Emotion Regulation TMS Study: order of sessions 3 through 5 are pseudo-randomized to ensure balanced order types across all participants

Recruited participants completed five sessions (see Table 2 for an outline of this study). Prior and subsequent TMS sessions (i.e., between-session interval) were separated by a

minimum of 48 hours. Session 1 served as a screening session to ensure participants' eligibility for MRI and TMS procedures. Session 2 involved acquisition of T1-weighted MRI images of the participants' brain, that were used to localize the bilateral vlPFC TMS targets using computer assisted stereotaxic interface (BrainSight™ 2, Rogue Research Inc., Montreal, Canada). Sessions 3, 4, and 5 involved a real or sham TMS stimulation. All participants participated in the following three types of TMS sessions: a real stimulation of the left VLPFC, a real stimulation of the right VLPFC, and a sham stimulation of either the left or the right VLPFC (specific participant's assignment to left or right sham condition was pseudo-randomly decided to ensure balance across participants). Order of the stimulation type was pseudo-randomly predetermined and randomly assigned to participants to ensure study results are not confounded by the sequence of stimulation type assigned to participants. Study procedure for each of these three sessions were identical, with the exception of the type (i.e., real or sham) and the hemisphere (i.e., left or right) of the stimulation involved.

Individual Session Procedures

Session 1 – Screening:

All participants completed a written consent approved by the Vanderbilt University Institutional Review Board. After being consented, participants completed the TMS, and MRI screening questionnaires. To ensure participant safety standards were met, prospective participants were screened to ensure they had no history of any major neurological or psychiatric disorder. Prospective participants were also screened to ensure they were not currently taking any psychotropic medication, and have no family history of epilepsy in first-degree relatives. Prospective participants who had risks for MRI scanning or other conditions that would interfere

with MRI scanning, such as claustrophobia and extreme obesity, were excluded from the study. Additionally, individuals with post-traumatic stress disorder (PTSD) or history of trauma were excluded due to the graphic nature of visual stimuli included in the behavioral tasks. Additionally, for participants who could not rule out pregnancy, a urine pregnancy test was conducted at this initial screening session and prior to all TMS sessions (including sham TMS).

Session 2 – MRI Scan:

Structural MRI scans were conducted using a Philips Achieva 3T MRI scanner (Philips Healthcare, Inc., Best, The Netherlands) using an 8-channel head coil. For each study participant, high-resolution 3-D T1-weighted anatomical images were acquired (TR = 8.969 ms; TE = 4.6 ms; in-plane resolution = 1 mm^2; FOV=24x24cm^2; matrix size=256x256; slice thickness = 1 mm; no gap). The total time each participant spent in the MRI scanner was approximately 20 minutes.

Sessions 3, 4, and 5 – TMS Sessions:

Participants first completed the TMS/rTMS Acute Side Effects questionnaire, which is a brief measure of discomfort or cognitive and mood changes. Then participants were given the Mini-Mental Status Exam (MMSE). After completing the two forms, participants took a urine pregnancy test if they had been sexually active in the past 90 days (determined by giving female participants the "sexual activity questionnaire"). Next, they completed a practice version of the emotion regulation task. Following this, either sham stimulation using a MagStim placebo coil or 1 Hz rTMS using a MagStim air-cooled double 7-ohm coil system (Magstim Company, UK; peak discharge = 1.8 kV; 70-mm figure-eight) was applied to either the left or right vlPFC. The sequence of stimulation types assigned to each participant was randomly assigned and

counterbalanced. Individual participants received real rTMS stimulation no more than twice, and never in the same location. Sham stimulation using a placebo coil produced a clicking noise that emulated the sound of real TMS without any magnetic pulse being delivered. Sham or real rTMS stimulation lasted exactly 30 minutes (1800 pulses). Immediately following stimulation, participants completed the emotion regulation task described above, which took approximately 15 minutes to complete. After participants completed the task, the TMS/rTMS Acute Side Effects questionnaire and MMSE were administered for the second time to screen for any adverse effects of rTMS impacting changes in cognitive status.

3.2.4 *Predictions and Statistical Analyses*

It was hypothesized that stimulation to the vlPFC would significantly change the magnitude of difference in negative affect rating between attend negative ("*negative look*") and reappraise negative ("*negative decrease*") conditions. It was also predicted that disruption of cortical activity to the vlPFC on either hemisphere would result in decreased effectiveness of reappraisal-based emotion regulation. Furthermore, the left vlPFC rTMS was expected to have a stronger impact on participants' ability to regulate negative affect based on prior research findings. Kim & Hamann (2008) reported that left vlPFC was activated in both up-regulation as well as down regulation conditions, whereas right vlPFC only came online during down-regulation conditions (i.e., down-regulation related vlPFC activity was more bilateral). Given that study participants generally report down-regulation to be more difficult than up-regulation (Ochsner *et al*., 2004), this suggested left vlPFC likely serves as a more basal or default involvement in emotion regulation. By contrast, when the task becomes more difficult, the right vlPFC may come online to augment the emotion regulation effort. Given these findings, rTMS to the vlPFC on either hemisphere was expected to hamper participants' ability to successfully

engage in the emotion regulation task, only more strongly so when participants receive rTMS on the left hemisphere.

A series of analyses were performed to test the hypothesis that low-frequency rTMS to the vlPFC influences participants' ability to down regulate negative emotions in the reappraisal-based emotion regulation task. To examine the effect of vlPFC disruption on emotion regulation success, a repeated-measures ANOVA was conducted, in which *Stimulation Type* (left rTMS, right rTMS, and sham rTMS) served as a repeated-measures variable and *Reappraisal Success Index* derived from subjective rating scores served as a dependent variable. Subjective ratings of negative affect were tabulated across each of the three instruction combinations: neutral look, negative look, and negative decrease. The *reappraisal success index* (RSI) was derived for each subject by subtracting the mean subjective rating score of *negative decrease* trials from that of the *negative look* trials (i.e., reappraisal success = mean rating on negative look - mean rating on negative decrease). This RSI was calculated for each rTMS session, thus yielding three different RSIs for each participant: left rTMS RSI, right rTMS RSI, and sham TMS RSI.

SCR data was analyzed using Ledalab V3.4.8 (Benedek and Kaernbach, 2010). Raw SCR data were preprocessed with a unidirectional 1st order Butterworth low pass filter with a cut off frequency of 5Hz. Data were then down sampled to 20Hz. The data were visually checked for artifacts, but no formal artifact rejection was implemented.

After these preprocessing steps, SCR data for each session was decomposed by continuous decomposition analysis (CDA). The CDA essentially decomposes SCR data into continuous signals of phasic and tonic activity. This method was used to parse the recorded SCR data into unbiased components of phasic and tonic activity. An example of the decomposition

can be seen in Figure 4, where SCR data from a single session was decomposed into tonic (dark gray shading) and phasic (blue shading) activities for further comparative analysis between conditions and across sessions.

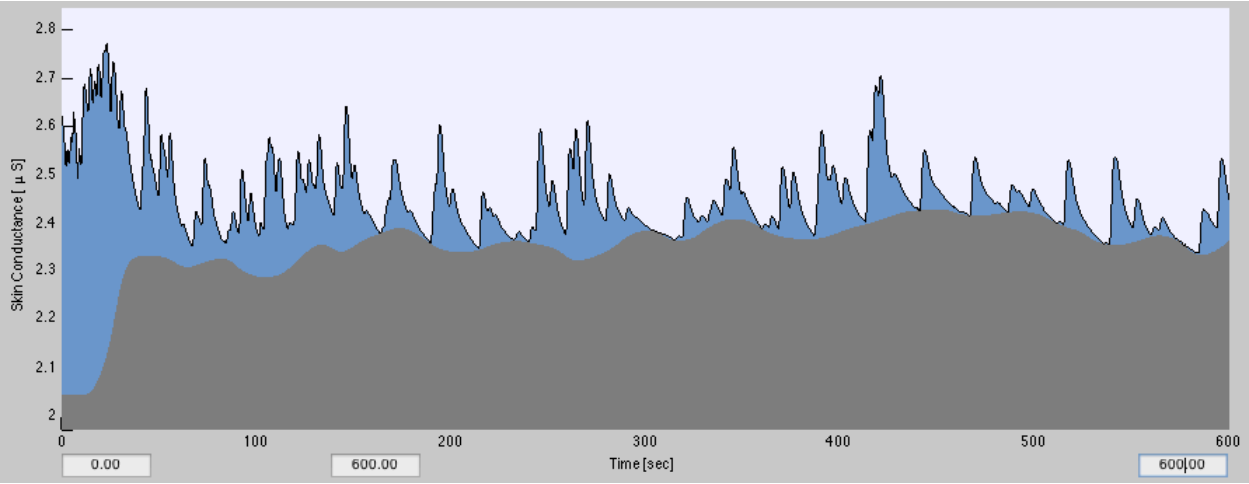


Figure 5. Example of SCR Data Decomposed into Tonic and Phasic Activity (gray-shading: tonic, blue-shading: phasic)

Within each session, the decomposed SCR data were spliced into distinct components within each trial. Specifically, the post-CDA SCR data were further spliced into *anticipation* (a four-second period immediately after instruction cue onset), *initial appraisal* (a four-second period immediate following picture stimuli onset), and *pre-rating period* (a four-second period immediately prior to self-report rating). Four-second window was chosen as optimal based on data reported by Benedek and Kaernbach (2010), which indicated this duration as demonstrating optimal sensitivity to phasic SCR following stimulus onset. Because the emotion regulation task completed in each session included a mix of different instructional cues ("NEUTRAL LOOK", "NEGATIVE LOOK", "NEGATIVE DECREASE") pseudo-randomly mixed into the overall task within a given session, both SCR and behavioral data from each of the three categories were aggregated into three separate conditions: *neutral look, negative look, and negative decrease*.

To examine the effect of TMS stimulation type on physiological arousal, a series of two-way repeated-measures ANOVA were conducted for each of the three within-trial components (i.e., baseline, anticipation, and emotional response). First of all, SCR magnitude was measured as the largest conductance change greater than .02 μS (micro-siemens) observed within a one to four second time window immediately subsequent to a stimulus onset (e.g., IAPS picture onset or cuing onset). A logarithmic transformation was applied to the derived SCRs in order to normalize the positively skewed SCR data (i.e., log [SCR + 1]). In general, the SCR data associated with the emotion regulation task were analyzed using a repeated-measures analysis of variance (ANOVA). The effects of emotion regulation on autonomic arousal was investigated using a three-by-three repeated-measures ANOVA, with Stimulation Type (left rTMS, right rTMS, and sham rTMS) serving as the first within-subjects factor and Trial type (attend-neutral, attend-negative, and reappraise-negative) serving as the second within-subjects factor.

It was hypothesized that SCR data acquired subsequent to a real rTMS to either hemisphere of the vlPFC would show smaller down-modulation of phasic activity compared to sham conditions. This would indicate that disruption of vlPFC activity decreases participants' modulation of autonomic arousal signal, which is considered to reflect study participants' difficulty regulating the magnitude of their negative mood states. While study participants' tonic SCR activities were not expected to be affected by rTMS type or trial type, tonic SCR activity patterns were nonetheless compared across different TMS session types and trials types in order to investigate the potential influence of vlPFC rTMS on participants' tonic arousal level.

The associations between post-picture-viewing ratings of negative affect and SCRs were investigated across Trial types and Stimulation types using Spearman's rank-ordered correlation coefficient. The Spearman's ρ is considered a nonparametric equivalent of the Pearson-product

moment correlation and is recommended for use in skewed (i.e., non-normal) data sets to examine the strength of association between two variables, when monotonic relationship is expected. Because SCR data was highly positively skewed, spearman's ρ ("rho", rank correlation coefficient) was calculated rather than a pairwise Pearson's correlation coefficient.

In order to ensure obtaining an adequate sample size, a power analysis was conducted with the power calculation package *G*Power3* (Faul, Erdfelder, Lang, & Buchner, 2007). A previous study in the lab that targeted the dorsolateral PFC used an identical TMS stimulation parameter of 1 Hz low-frequency repetitive TMS at 54% power for 30 minutes. Results from this study revealed an average effect size of (*Cohen's d* = 0.1868). This effect size is considered to be in the *small* range. However, it was notable that the study showed a stronger effect on the right than left dlPFC stimulation: the average effect size of rTMS on the right dlPFC was d = 0.34 whereas it was only d = 0.03 on the left dlPFC. It should be noted, however, that one study comparing different TMS targeting methods revealed that MRI-guided TMS had significantly greater effect sizes than 10-20 EEG system-based targeting (Sack *et al*., 2009)

Assuming the proposed rTMS study would show at least a moderate effect size (*f* = 0.25; cf. Cohen, 1977) on emotion regulation as measured by the *reappraisal success index*, the power to detect an effect of this size in the three conditions of Study 1 was determined to be $1-\beta = 0.88$, critical $F = 3.14$ (numerator df=2, denominator df=64). The power to detect a small effect (*f* = 0.1) was 0.22, and power to detect a large effect (*f* = 0.4) was 0.99. Thus, if the rTMS manipulation were to show a moderate to large effect size, the current sample size was expected to be adequate to detect a true effect, if any.

3.3 Results

3.3.1 *Self-reported Negative Affect*

The influences of reappraisal based emotion regulation on self-reported negative affect was investigated using a 3 by 3 repeated measures ANOVA, with Stimulation Type (left rTMS, right rTMS, and sham) serving as the first within-subjects factor and Instruction Type (attend-neutral, attend-negative, and reappraise-negative) serving as the second within-subjects factor. Study participants' responses on the Difficulties in Emotion Regulations Scale (DERS) and the Emotional Intolerance (EI) subscale of the Frustration Discomfort Scale (FDS) were z-transformed and summed to form an Emotion Regulation Trait (ERT) variable which was added as a covariate to the repeated-measures model tested. Given that the three levels of stimulation types and instruction types were expected to show unequal variances of differences between conditions, Mauchly's test of sphericity was performed prior to the ANOVA. This indicated that there were significant difference between the variance of differences in Instruction Type, $\chi^2(2) = 16.81, p < .001$, as well as the Stimulation Type by Instruction Type interaction, $\chi^2(9) = 21.33, p < .05$. Accordingly, the Greenhouse-Geisser correction was applied for the repeated measures ANOVA of Instruction Type and Stimulation Type by Instruction Type interaction. A Stimulation Type by Instruction Type interaction was predicted from the repeated measures ANOVA such that the magnitude of reduction in negative affect as a result of reappraisal was expected to be smaller after participants received real rTMS.

Table 3 presents means and standard deviations of negative affect ratings stratified by Stimulation Type and Instruction Type, and Figure 6 presents the same results in a bar graph format. Results of the 3 by 3 repeated measures ANOVA revealed that there was a significant

main effect of Instruction Type, $F(1.32, 31.61) = 189.98, p < .001$ but no significant main effect of Stimulation Type, $F(2,48) = .09, p > .1$. Furthermore, there was a significant interaction effect between Instruction Type and Stimulation Type such that the effect of Stimulation Type on self-reported negative affect was dependent on the Instruction Type that participants engaged in, $F(2.85, 68.5) = 3.89, p < .05$.

		Instruction Type		
		Attend Negative	Reappraise Negative	Attend Neutral
Stimulation Type	Sham	44.6 (17.0)	35.2 (14.6)	4.0 (4.3)
	Left rTMS	45.6 (14.7)	38.5 (14.6)	4.1 (5.0)
	Right rTMS	45.8 (13.5)	33.0 (11.9)	3.4 (3.3)

Table 3. Mean Ratings of Self-Reported Negative Affect

From the self-reported negative affect rating, *reappraisal success index* (RSI) was calculated for each study participant by subtracting their mean rating score of *negative decrease* trials from that of the *negative look* trials (i.e., reappraisal success = mean rating on negative look – mean rating on negative decrease). These RSIs calculated for each rTMS session, yielded three different RSIs for each participant who completed all three sessions: left rTMS RSI, right rTMS RSI, and sham TMS RSI (see Figure 7). One-way repeated-measures ANOVA of RSI with Stimulation Type as a within-subjects factor revealed a statistically significant effect of Stimulation Type, $F(2, 24) = 8.29, p < .005$. Further pairwise comparison of Stimulation Type pairs revealed that RSIs were significantly different among all three stimulation type pairs: Right rTMS RSI > Left rTMS RSI, $t_{25} = 4.09, p < .0005$; Sham rTMS RSI > Left rTMS RSI, $t_{25} = 1.98, p < .05$; Right rTMS RSI > Sham rTMS RSI, $t_{25} = 3.41, p < .005$.

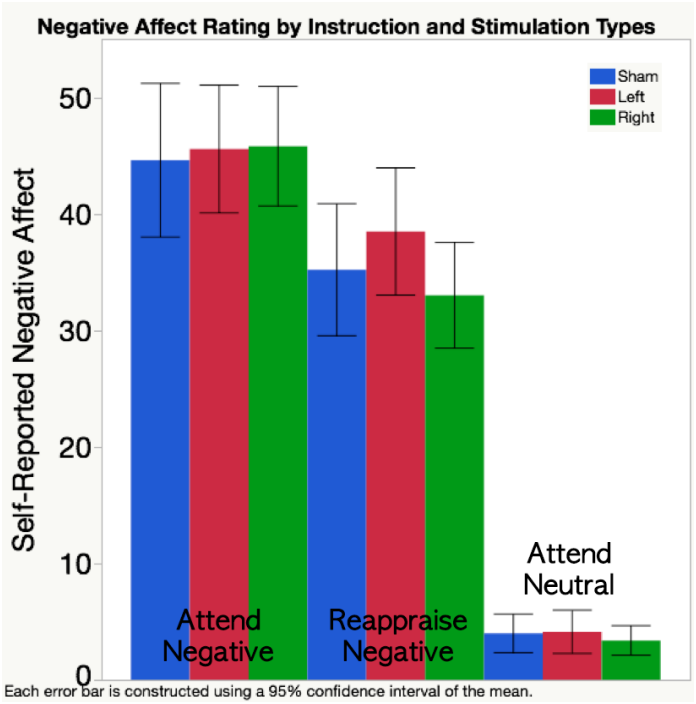


Figure 6. Mean Self-Reported Negative Affect by Stimulation Type and Instruction Type

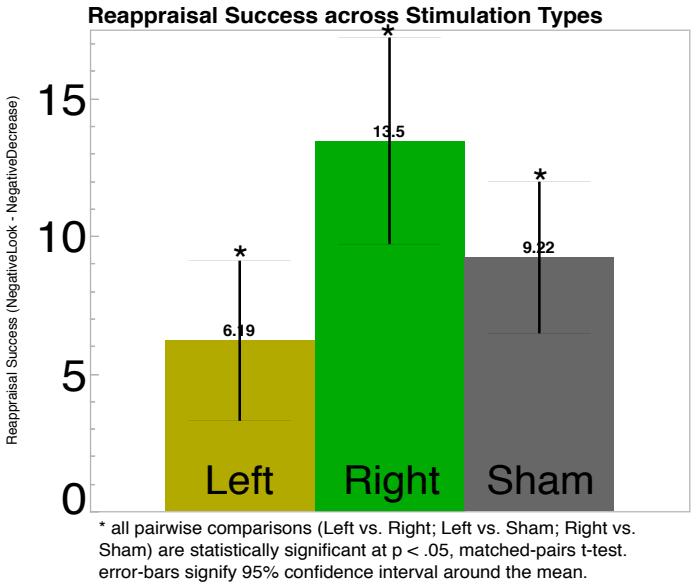


Figure 7. Mean Reappraisal Success Index (RSI) by Stimulation Type

3.3.2 *Questionnaire Data and Self-Reported Negative Affect*

Study participants' Emotion Regulation Trait (ERT) score was correlated with their RSI score for each session respectively. Because RSI data was negatively skewed, spearman's ρ ("rho", rank correlation coefficient) was calculated rather than a pairwise Pearson's correlation coefficient. RSI score for the sham, $\rho(26) = n.s., p>.1$, and the left rTMS session, $\rho(28) = n.s., p>.1$, was uncorrelated with the ERT score. However, RSI score for the right rTMS session was negatively correlated with study participants ERT score such that greater endorsement of emotion regulation difficulties tended to be associated with lower RSI score subsequent to the right rTMS session, $\rho(27) = -.4335$, $p=0.0188$.

3.3.3 *Skin Conductance Response Data*

Manipulation Check

A series of Spearman rank-order correlations were conducted within the sham condition in order to determine if affective dimensions of picture stimuli such as arousal and valence ratings were associated with autonomic arousal during picture viewing phase of the emotion regulation task. In order to ascertain that pictures presented during the emotion regulation task elicited detectable physiological autonomic arousal, study participant's SCR associated with picture-viewing was aggregated into a mean SCR score for each unique picture stimuli and separately correlated with arousal and valence ratings associated with the picture presented (ratings were extracted from previously published normative data from Lang, Bradley, & Cuthbert, 2008). Because SCR data was highly positively skewed, spearman's ρ ("rho", rank correlation coefficient) was calculated rather than a pairwise Pearson's correlation coefficient. Phasic SCR during picture-viewing in the sham condition was negatively correlated with

published pleasure (i.e. positive affect) rating of the pictures (Lang, Bradley, & Cuthbert, 2008) such that pictures with lower pleasure rating tended to evoke greater SCR score during picture viewing, $\rho(106) = -.32$, $p<0.001$. Furthermore, presented pictures with greater arousal rating were associated with higher SCR response during picture-viewing, $\rho(106) = .36$, $p<0.001$. However, luminosity of the presented pictures was not associated with autonomic arousal, $\rho(106) = .08$, $p=0.4154$. These results suggested that as expected, greater autonomic arousal was associated with pictures known to evoke greater level of arousal and negative affect.

Relationships between self-reported ratings of negative affect and autonomic arousal as measured by SCR were examined across stimulation types and instruction types using Spearman's correlation coefficient ρ. In order to test whether self-report of negative affect was related to autonomic arousal, phasic SCR level during picture-viewing was correlated with participants' self-reported rating of negative affect. SCR during the first 4 seconds of picture-viewing was positively correlated with self-report rating of negative affect, such that greater SCR during picture viewing predicted higher self-report rating of negative affect $\rho(106) = .28$, $p<0.005$.

Prior research has suggested that faster responses as well as greater magnitude of skin conductance responses are associated with autonomic arousal (Witvliet & Vrana, 1995). Therefore, trough to peak (TTP) SCR latency, which is a measure of lag between stimuli onset and phasic electrodermal activity were tested for correlation with participants' self-report rating of negative affect experience after viewing the picture. TTP SCR latency immediately following picture viewing was uncorrelated with self-report rating of negative affect when examined across instructional cues ($p>.1$). However, when self-report ratings of negative affect were tested for

correlation with TTP SCR latency in trials with passive viewing only (i.e., Negative Look and Neutral Look conditions, but excluding the Negative Decrease conditions), TTP SCR positively correlated with self-reported negative affect such that faster autonomic arousal predicted higher self-report rating of negative affect, $\rho(287)=-.11$, $p<.05$. This indicated that under passive viewing of pictures, shorter latency to peak autonomic arousal was associated with greater magnitude of negative affect.

In order to test the effect of rTMS and emotion regulation (i.e., reappraisal) on autonomic arousal, a series of 3 by 3 repeated measures analysis of variance (ANOVA) were performed with Stimulation type (Right rTMS, Left rTMS, Sham) and Instruction type (Negative Decrease, Negative Look, and Neutral Look) as within-subjects factors. Dependent measures used for these analyses included SCR activity level during 1) the anticipatory period after the onset of instructional cue but before picture viewing; 2) picture-viewing period; 3) a period immediately prior to negative affect rating but after picture off-set. ANOVA results are described in greater detail below. Post hoc analyses were performed in case of significant ANOVA results. In order to control for false discovery (type I error) due to multiple comparisons of post hoc testing, Benjamini-Hochberg method (Benjamini & Hochberg, 1995) with family-wise error rate of $p=.05$ was used.

SCR during anticipatory period before picture onset: *first 3 seconds after instruction onset*

Event-related phasic SCR activities in the 4-second window (note, due to the canonical 1 second lag in SCR response phasic SCR was extracted from 1 second post instruction onset to 4 seconds post instruction onset) immediately following the instruction stimulus (“Neutral Look” / “Negative Look” / “Negative Decrease”) were extracted using the continuous decomposition

analysis (CDA, Benedek and Kaernbach, 2010) and used as the dependent measure. Because the phasic autonomic activity data were highly positively skewed, median SCR values for each stimulation type by instruction type cell were extracted and log-transformed for the repeated measures ANOVA analyses (see Table 4 for summary SCR values and Figure 8 for visual representation of these values). There was a significant main effect of stimulation type, $F(2, 50) = 3.758$, $p = .03$ which indicated that autonomic response during anticipation of visual stimuli varied with the type of stimulation the subject received prior to starting the emotion regulation task. Subsequent pairwise comparison of stimulation types among the stimulation conditions revealed that autonomic arousal in anticipation of viewing pictures was trending toward having higher magnitude after left rTMS compared to sham, *matched-pairs-t*$(25) = 2.34$, $p = .027$, and compared to right rTMS, *matched-pairs-t*$(25) = 1.89$, $p = .078$. However, there was no autonomic arousal activity differences between the right rTMS and sham stimulation condition for the anticipatory period, *matched-pairs-t*$(25) = .30$, $p = .764$. There was no main effect of instruction type, $F(1.42, 35.507) = .391$, $p = .609$, nor a stimulation by instruction type interaction, $F(2.232, 55.811) = .374$, $p = .712$.

		Instruction Type		
		Attend Negative	Reappraise Negative	Attend Neutral
Stimulation Type	Sham	.00642 (.00722)	.00535 (.00553)	.00610 (.00643)
	Left rTMS	.00934 (.00770)	.00964 (.01039)	.00986 (.01258)
	Right rTMS	.00528 (.00445)	.00535 (.00446)	.00649 (.00679)

Table 4. Log of Median Phasic SCR Values During the Anticipation Period (i.e., viewing of verbal instruction cue).

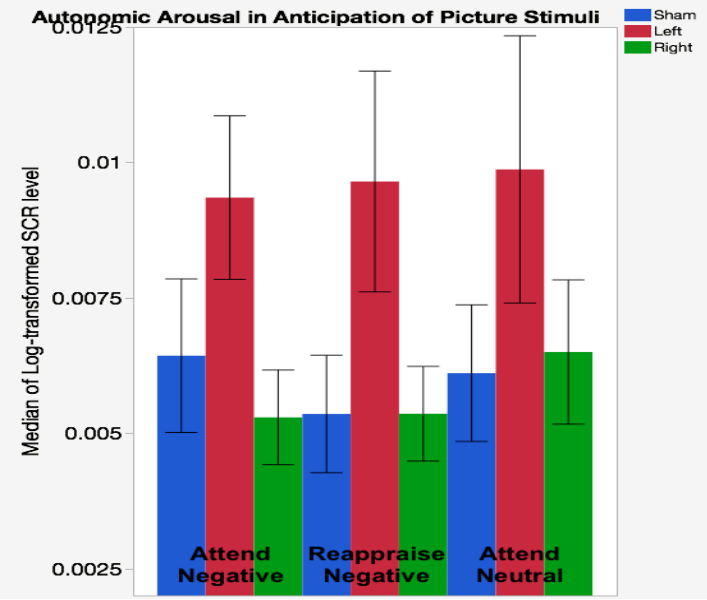


Figure 8. Phasic SCR During the Anticipatory Period
(error-bars: 1 standard error around the mean)

SCR during picture viewing: *first 4 seconds after picture onset*

Event-related phasic SCR activities in the 4-second window (note, same as above, effective analysis window was between 1 second post picture onset to 4 seconds post picture onset) immediately following the picture stimulus onset were extracted from the continuous decomposition analysis and used as the dependent measure. Because the phasic autonomic activity data were highly positively skewed, median SCR values for each stimulation type by instruction type cell were extracted and log-transformed for the repeated measures ANOVA analyses (see Table 5 for summary SCR values and Figure 9 for visual representation of these values). There was no main effect of Stimulation Type, $F(2, 50) = 1.7$, $p = .193$, nor Instruction Type, $F(1.509, 37.729) = 1.978$, $p = .161$. However, there was a Stimulation Type by Instruction Type interaction, $F(4, 100) = 3.534$, $p = .01$, which means the effect of Instruction Type varied with the Stimulation Type (or the vice versa, effect of Stimulation Type dependent on the Instruction Type). Because of this significant interaction effect, a series of post-hoc pairwise

comparisons were performed across each instruction type. As expected, when self-report data for the "Attend Neutral" condition was examined, there was no significant effect of different stimulation types on phasic SCR activity, $F(2, 50) = .372$, $p = .691$. In the "Attend Negative" condition, there was a trend toward a significant effect of stimulation type on phasic SCR activity, $F(2, 50) = 2.637$, $p = .081$. Subsequent post hoc, pairwise comparisons revealed that median phasic SCR activity during Negative Attend conditions in the Left rTMS stimulation session (mean=.00711) was trending toward having larger magnitude compared to that of the Right rTMS stimulation session (mean=.00434), *matched-pairs-t*(25) = -2.42, p=.023 (however, this p-value did not survive the Benjamini-Hochberg correction for multiple comparison). In the "Reappraise Negative" condition, there was a significant effect of stimulation type on phasic SCR activity, $F(2, 50) = 3.912$, $p = .026$. Pairwise comparison of stimulation types within the "Reappraise Negative" condition revealed that phasic SCR activity during the left rTMS condition (mean=.00586), was significantly (albeit modestly) higher in magnitude compared to median phasic SCR activity during the sham TMS (mean=.00361) condition, matched-pairs-t(25) = -2.62, p =.0149.

		Instruction Type		
		Attend Negative	Reappraise Negative	Attend Neutral
Stimulation Type	Sham	.00545 (.00489)	.00361 (.00316)	.00424 (.00451)
	Left rTMS	.00711 (.00524)	.00586 (.00378)	.00508 (.00553)
	Right rTMS	.00434 (.00330)	.00477 (.00372)	.00498 (.00489)

Table 5. Log of Median Phasic SCR Values During the Picture Viewing Period

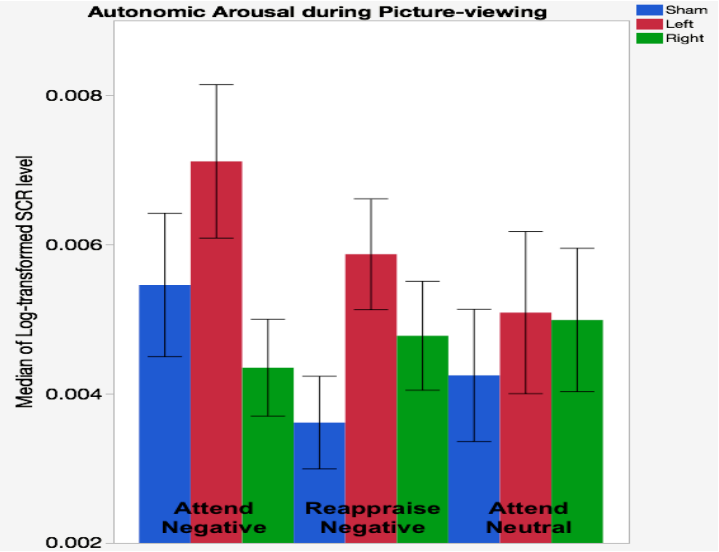


Figure 9. Phasic SCR During the Picture-Viewing Period
(error-bars: 1 standard error around the mean)

SCR Immediately Prior to Affect Rating: *4 seconds before rating until rating onset*

Event-related phasic SCR activities in the 4-second window immediately prior to the negative affect rating (mouse click) were extracted from the continuous decomposition analysis and used as the dependent measure. Because study participants were asked to self-report their negative affect by reflecting on their mood precisely at the moment of rating, autonomic arousal data sampled most proximal to the mouse click of self-reporting was believed to be associated with the self-report data. Because the phasic autonomic activity data were highly positively skewed, median SCR values for each stimulation type by instruction type cell were extracted and log-transformed for the repeated measures ANOVA analyses (see Table 6 for summary SCR values and Figure 10 for visual representation of these values). There was a trend toward a main effect of Instruction Type, $F(1.145, 28.634) = 3.890$, $p = .053$. This indicated that the magnitude of phasic SCR activity immediately prior to subjective negative affect rating potentially varied depending on the instruction type, but the effects were modest at best. None of the post hoc

pairwise comparisons were significant after the Benjamini-Hochberg correction. However, there was a trend toward statistical significance between autonomic arousal in the pre-rating period during the reappraise negative condition (mean=0.00469), and the attend negative condition (mean=0.00448), being lower relative to the neutral look condition (mean=0.00755), p=.058 and p=.051 respectively. There was no main effect of Stimulation Type, $F(1.314, 32.862) = 1.383$, $p = .257$, or stimulation type by Instruction Type interaction, $F(1.398, 34.954) = .652$, $p = .474$. A summary of aforementioned SCR ANOVA analyses is presented in Table 7.

		Instruction Type		
		Attend Negative	Reappraise Negative	Attend Neutral
Stimulation Type	Sham	.00441 (.00730)	.00361 (.00395)	.00676 (.01666)
	Left rTMS	.00552 (.00416)	.00587 (.00850)	.01005 (.01496)
	Right rTMS	.00351 (.00268)	.00458 (.00502)	.00583 (.00550)

Table 6. Log of Median Phasic SCR Values During the Pre-Rating Period

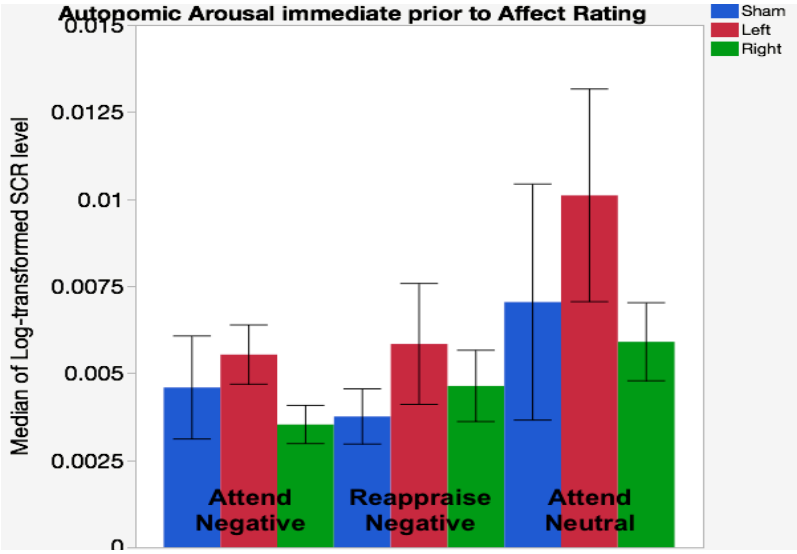


Figure 10. Phasic SCR During the Pre-Rating Period

	Instructional Cue (anticipatory period)	Picture-viewing (initial appraisal)	Pre-rating (proximal to rating)
Attend Negative	Left > Sham * Left > Right *	Left > Right *	Attend Negative < Attend Neutral ** Reappraise Negative < Attend Neutral **
Reappraise Negative	n.s.	Left > Sham	
Attend Neutral	n.s.	n.s.	

* $p<.05$ but did not meet statistical significance after Benjamini-Hochberg correction
** $.05 < p < .1$

Table 7. Summary of SCR Analyses Results

Contrasting physiological arousal between reappraisal and passive viewing conditions

A series of analyses were conducted by utilizing a calculated SCR measure analogous to the Reappraisal Success Index (RSI) previously used with self-report data. Specifically, physiological RSIs were calculated by taking the difference in phasic SCR between the two negative picture viewing conditions (i.e., mean SCR Attend Negative – mean SCR Reappraise Negative). Resultant summary SCR RSI data were used to perform a series of pairwise matched-pairs tests among the three rTMS conditions. No paired differences were statistically significant in either the picture-viewing phase or the pre-rating phase (matched-pairs t-tests: all $p > .1$)

3.4 Discussion

Summary of the Effect of rTMS and Emotion Regulation on Affect Rating and SCR

The main objective of this study was to examine the causal role of ventrolateral PFC function on reappraisal-based emotion regulation of negative emotions. This question was investigated by disrupting study participants' ventrolateral PFC excitability using low frequency rTMS and subsequently measuring subjective negative affect rating as well as measuring concomitant autonomic arousal changes indexed by using SCR during a behavioral task with instructions to either engage in emotion regulation or attend to emotional or neutral images.

Behavioral Data Results

Across all stimulation conditions, instructions to down-regulate ("negative decrease") emotional responses resulted in self-reported subjective negative affect that is significantly lower than that of instructions to maintain emotional responses ("negative look"). Furthermore, a measure of emotion regulation effectiveness (Reappraisal Success Index), calculated as the difference of self-reported negative affect between the negative look and negative decrease instructions was significantly different across the stimulation types such that disruption of left vlPFC subsequently resulted in significantly lower reappraisal effectiveness compared to that of the sham (or control) stimulation condition. This indicated that, consistent with the original hypothesis, left ventrolateral PFC function is causally involved in reappraisal-based emotion regulation. More specifically, because disruption of the left vlPFC attenuated the effectiveness of reappraisal, we can infer that left vlPFC function facilitates effective reappraisal-based emotion regulation. Interestingly, right vlPFC PFC stimulation paradoxically enhanced the effectiveness of reappraisal-based emotion regulation. In other words, after right vlPFC disruption, study participants were able to reappraise negative stimuli more effectively compared to left-sided disruption or sham stimulation, resulting in greater attenuation of negative affect in response to the reappraise instruction ("decrease negative"). This is particularly puzzling given previous functional imaging study finding of bilateral vlPFC activity level being parametrically and positively correlated with reappraisal success (Kim & Hamman, 2007). In other words, at the surface level, the current results of right vlPFC disruption subsequently increasing individuals' reappraisal effectiveness appears to be inconsistent with prior evidence from neuroimaging studies discussed before (Kim & Hamann, 2007, Wager, 2008). There are several possible ways to reconcile the current pattern of findings of lateralized effect of vlPFC disruption with previous

neuroimaging study data. First of all, it is important to acknowledge that the degree of neural activities in both left and right vlPFC have been parametrically associated with greater success in down-regulating negative affect (Urry et al, 2006; Wager, 2008). However, in detailed examination of previous study results, activation patterns across these studies tended to consistently show asymmetry in the area of recruitment between the two hemisphere's vlPFC. Specifically, there is evidence that recruitment of the left vlPFC region were broader and more reliable compared to the right vlPFC region. Indeed, recent neuroimaging data suggests that left vlPFC is consistently activated in reappraisal of low and high intensity negative emotions, but right vlPFC is only activated in response to the demand of reappraising high intensity negative emotions (Silvers, Weber, Wager, & Ochsner, 2015). In light of this previously reported data, it is possible to speculate that cognitive mechanism of emotion regulation preferentially recruit the left vlPFC during active reappraisal and may additionally recruit the right vlPFC as necessary. This possibility of recruiting additional neural resources for reappraisal may be more pertinent to situations requiring greater effort to reappraise. Therefore, when key neural substrate of reappraisal, that is when the left vlPFC is disrupted, greater difficulty with emotion regulation can be expected, which is consistent with our current findings. In the same vain, when the right vlPFC, which likely comes online as additional support of reappraisal effectiveness, is disrupted it is possible to imagine the rTMS-dependent disruption not as much of a detrimental impact on emotion regulation, especially if the emotion regulation task is not too difficult or challenging.

However, there are further puzzling finding of current data's result of right-sided vlPFC disruption-dependent enhancement of reappraisal effectiveness. In contrast to left rTMS-dependent disruption of reappraisal effectiveness, right rTMS caused an opposite effect of enhancement of reappraisal effectiveness. Is it possible that disruption of right vlPFC somehow

enhanced left vlPFC functioning? Although speculative at best, there is some evidence from other previous studies to suggest that low frequency TMS to a specific frontal cortical region can cause cross-hemisphere facilitation of homologous area of the brain on the contralateral hemisphere (Plewina, Lotze, Gerloff, 2003; Gilio et al., 2003). These studies have shown that unilateral low frequency rTMS to the motor cortex increased the excitability of the motor cortex in the opposite hemisphere while simultaneously exerting an inhibitory effect on the stimulation site. This suggests that right sided inhibition of cortical activity may have potentially facilitated of cortical excitability in the contralateral (left vlPFC) as an unintended effect. In other words, it is possible to speculate that by disrupting the right vlPFC, left vlPFC function was facilitated to make study participants' reappraisal-based emotion regulation more effective. This hypothesis maybe worth further investigating given evidence from the literature demonstrating such effect in motor-control. While current data of contralateral cortical *disinhibition* effect after low-frequency rTMS has been largely limited to the motor cortex, it is not certain whether such contralateral facilitation of cortical excitability may in fact generalizes to non-motor cortical regions. Given the current data showing right sided low frequency rTMS causing enhancement in emotion regulation effectiveness, it is possible to envision translating such an effect to test possible therapeutic utility in psychiatric conditions with known mood dysregulation component such as depression and anxiety. Replication of this data will be an appropriate first step.

Physiological Data Results

Results from analyses of the autonomic arousal data further puts the self-report data in a broader context and help elaborate the contribution of vlPFC on the neural mechanism underlying reappraisal-based emotion regulation. As predicted, across instruction types, autonomic arousal measured during viewing of negatively valenced IAPS pictures showed

positive correlation with arousal ratings and negative correlation with valence ratings (from published data by Lang, Bradley, & Cuthbert, 2008) of the pictures presented. This meant that pictures that evoke negative emotions that are considered more arousing and negative tended to also evoke greater autonomic response during picture viewing. Moreover, study participants' self-reported level of negative affect subsequent to viewing negative pictures was significantly predicted by their autonomic arousal during picture viewing. This gives support to the idea that even though autonomic arousal as measured by SCR level and self-reported rating of negative affect may not be considered analogous, they do show some convergence in the context of the current study's emotion regulation task. Interestingly, latency of SCR onset measured from picture-viewing was inversely related to the degree of self-reported negative affect, meaning that swifter emergence of autonomic arousal (i.e., shorter SCR response latency) in response to picture viewing predicted higher level of negative mood. One possibility is that shorter SCR response latency is reflective of a robust affective response which results in higher level of negative affect at rating phase of the emotion regulation task. In a previous study by another group, shorter latency of SCR response was associated with high arousal conditions compared to lower arousal conditions (Witvliet & Vrana, 1995) showing a similar relationship as our results on latency of SCR being predicted by stronger negative affect. Importantly, this relationship was observed only for passive-viewing of negative pictures (i.e., when the reappraisal condition was excluded from the analysis). This may provide some insight into the mechanism of the reappraisal-based regulation. It is possible to that trials with instructions to reappraise resulted in greater decoupling of autonomic arousal and subjective experience or report of negative affect. This contrasts with general convergence of autonomic arousal and negative affect in passive viewing conditions where autonomic arousal more reliably predicted one's subjective affective

response. Is it possible that even though autonomic arousal is still present, reappraisal allows individuals a method to reframe the experience of heightened arousal? Consistent with this possibility, further analyses of the SCR using a similar contrast measure subtracting the difference between reappraise and negative attend conditions did not show significant difference between stimulation conditions. These results together could suggest that cognitive reappraisal may not necessarily attenuate the consequence of physiological arousal as a result of emotional response, but rather change one's cognitive interpretation of it. In a relevant study of mindfulness and emotion regulation, a group of researchers have shown that state level mindfulness, that is individual differences in taking a non-judgmental stance on observing emotionally evocative situations, is correlated with one's ability to reappraise emotional situations (Garland, Hanley, Farb, & Froeliger, 2015). It is possible that while arousing negative stimuli tend to create a robust autonomic arousal, cognitive reappraisal may in a sense be allowing individuals to suspend judgment of the arousal as "good" or "bad". This is very consistent with the essence of mindfulness which has been a very active area of research in the past decade (Davidson, 2010; Vago & Silbersweig, 2012). Further research in delineating the neural mechanism of reappraisal-based regulation should examine the mechanism underlying the separation of perceived autonomic arousal and individual's interpretation of the arousal state as negative affect.

Effects of rTMS on autonomic arousal during the three phase of the emotion regulation task

Anticipation

When the effect of rTMS on phasic SCR level was compared across three different instruction types, anticipation of emotional stimuli evoked greater SCR after left-sided disruption

of vlPFC activity. This indicated that left rTMS resulted in greater autonomic arousal during instruction cuing phase, regardless of the specific instruction type.

Appraisal

There was a trend toward left vlPFC disruption causing greater phasic SCR activity in response to passively viewing negative pictures compared to right vlPFC disruption. This points to the idea that modulation of vlPFC can significantly impact autonomic arousal evoked in response to emotional stimuli, and thus influencing subsequent appraisal of negative stimuli as more arousing. When study participants were shown instructions to down-regulate negative affect, left rTMS resulted in greater phasic SCR activity compared to sham stimulation during picture viewing phase of the emotion regulation task. While one may hypothesize that left-sided vlPFC disruption resulted in a generalized "heightened sensitivity" to any stimuli, the counter evidence of lack of significant difference in SCR response to viewing neutral pictures argue against that idea. If indeed rTMS dependent effect exerted a generalized effect on appraisal of any stimuli, the data results would have shown a consistent finding across different instruction conditions. In other words, only the two different instruction types, "Negative Look" and "Negative Decrease", that signal study participants to view emotionally salient pictures resulted in higher increase in arousal after left vlPFC disruption compared to right vlPFC disruption or sham stimulation. One possible interpretation is that a disrupted function of the left vlPFC in the context of emotion regulation may hamper one's ability to regulate autonomic arousal that occur in response to emotionally salient cues. This suggests that disengaging the putative neurocognitive component subserved by left vlPFC effectively increases one's sensitivity to affective stimuli, making study participants more prone to over-arousal in response to emotional stimuli. Interestingly consistent with this idea, when study participants received left vlPFC

disruption, trait level emotion regulation difficulty correlated with self-reported negative affect associated with viewing neutral picture stimuli (i.e., Negative Affect rating of neutral picture stimuli was correlated with the ERT variable in the sham stimulation condition, $\rho(26) = .38$, $p<0.05$; left rTMS condition, $\rho(28) = .38$, $p<0.05$; and trending toward significant correlation for the right rTMS condition, $\rho(27) = .33$, $p=0.0768$)

Pre-rating Period

Data from physiological arousal during the window of time immediately leading up to the subjective rating of affect did not differentiate well between stimulation types but showed consistently lower SCR level for pre-rating period associated with viewing negative picture. One possibility is that the influence of instructions to reappraise or disruptions to vlPFC has an impact on subjective negative affect without significant changes to physiological arousal. Another possibility is that whatever impact the instructions or rTMS have on subjective negative affect happens sufficiently early on in the process (anticipation or appraisal) and fairly rapidly that the autonomic arousal captured immediately prior to rating is not reflective of the impact of instruction or rTMS on affective modulation. Eippert et al. (2007) similarly indicated that down-regulation of negative affect did not show different of phasic SCR level between passive viewing and reappraisal. Our data is consistent with this previous data in that we did not observe a significant difference in autonomic arousal during reappraisal.

Limitations & Future Directions

There are limitations of current data that should be noted. First of all, limited spatial coverage of the effect of rTMS on the target cortical area may have limited the effects of cortical stimulation. While the precise spatial resolution of the effect of rTMS is considered to vary

somewhat by the equipment and parameter used during stimulation (Bolognini & Ro, 2010), it is generally believed to deliver stimulation over the target area in the order of approximately .5 to 1cm in diameter. vlPFC area however covers a wide region along the lateral portion of the orbitofrontal cortex that cannot be captured within a 1cm diameter. Therefore, it is important to acknowledge that our current method of focal stimulation of peak activation area as suggested by previous neuroimaging research likely insufficiently disrupted the influence the entire vlPFC area. This may also be one of the key reasons behind rTMS manipulation significantly modulating reappraisal effectiveness but not completely attenuating it. For greater effect of rTMS dependent cortical inhibition, it is possible in future to combine using two figure 8 coils for a greater coverage of the vlPFC which may result in greater larger effect size. Second, the power of cortical stimulation exerted to each participant using the stimulation coil was not individually tailored to the cortical excitability of the individual. Motor thresholding is a method that can be used to precisely measure the amplitude of stimulation at which each individual's excitatory cortical response for the motor cortex (M1) occurs. This method was not used in the current study in the interest of most efficiently allocating the limited time and resources (i.e., monetary compensation) expendable with each participant. However, it is possible that not controlling for or measuring individual differences in cortical excitability introduced unmeasured variances in the data. Taking into account individual differences in cortical excitability in future neurostimulation studies of emotion regulation may help maximize the power to detect the impact of experimental manipulation. Third, study sample exclusively included young female participants complicating the generalization of study results to a wider more diverse set of populations. Future studies with a more diverse set of samples will help broaden the generalizability of findings from this study.

CHAPTER 4

Experience-Sampling Study of Individuals with Ventral PFC Damage

4.1 Background

The findings reported in the previous study showed that in the healthy normal adult sample, disrupting the ventrolateral PFC activity can causally influence effectiveness of reappraisal-based emotion regulation. As described earlier, neuroimaging studies and studies with human lesion sample show converging evidence that indicates ventral PFC likely serves an important role in emotion regulation. However, to date, there has not been any study that specifically measured emotion regulation differences in the ventral PFC lesion sample. The study reported in this chapter extends previous work by investigating the consequence of ventral PFC damage on spontaneous emotion regulation in day to day living situations. The experience sampling method used in this study can complement laboratory-based studies and offer additional perspectives and dimensions to evaluating the role of the ventral PFC in emotion regulation. Critically, existing literature does not address to what extent individuals with known ventral PFC damage shows impairment in emotion regulation in a naturalistic setting, and how abnormal emotionality relates to impaired emotion regulation, if any. Experience sampling data were collected using experience sampling over 2 weeks in three groups: ventral PFC lesion sample, amygdala lesion sample, and demographically-matched healthy normal sample. The rationale for adding the amygdala lesion sample was to test potentially dissociable role of the amygdala and the ventral prefrontal cortex as they related to subjective emotional experience and emotion regulation. It was predicted that the amygdala lesion group may show abnormal affective experience (for example, relatively attenuated negative affect) but not abnormal mood regulation per se, and the frontal lobe lesion group may show abnormal mood regulation, as well as an abnormal

experience of affect. It was hypothesized that greater difficulty with emotion regulation would be more prominently observed in the ventral PFC lesion sample, compared to the healthy demographically-matched sample and the amygdala lesion sample. It was also hypothesized that greater fluctuation in mood would be observed in the ventral PFC lesion sample compared to both the amygdala lesion sample and healthy controls.

4.2 Methods

4.2.1 *Participants*

OFC Lesion Patients

Identification and recruitment of Ventral PFC and amygdala lesion patients:

Eleven patients with Ventral PFC lesion were included in the study. The Vanderbilt University Medical Center electronic data repository, Star-Panel, was used to identify OFC lesion patients eligible for participation in the study. Star-Panel's Neurosurgery and Radiology clinic databases were queried using Ventral PFC-related keywords: e.g., "*orbitofrontal*"; "*inferior frontal*"; "*subfrontal*"; "*gyrus rectus*"; "*anterior communicating artery*" to identify patients with relevant lesion foci. This initial search identified 3,047 cases. Medical records of these identified patients were thoroughly reviewed to determine their eligibility, and eligible individuals were contacted in writing, to which they could respond and elect to participate in the study. Only patients with brain lesion affecting the orbitofrontal cortex (i.e., ventral surface of the prefrontal cortex that include gyrus rectus; medial orbital gyrus; anterior and posterior orbital gyri; and lateral orbital gyrus) were included in the lesion sample of this study. The sites of the lesion were ascertained by visually inspecting an existing brain MRI or CT scan in addition to radiologists' or neurosurgeons' reports. Exclusion criteria included evidence of damage outside

the orbitofrontal cortex, only diffuse damage to the orbitofrontal cortex resulting from edema and encephalomalacia (as evidenced by CT/MRI images and/or reports by a neuroradiologist), alcohol or drug dependence, and when available, a full-scale intelligence quotient (FSIQ) below a cut-off of 75 (1 standard deviation below the mean) in the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III, Wechsler, D., 1997).

For the amygdala lesion sample, previous study participants with intractable epilepsy who have undergone unilateral resection of the amygdala matching demographic characteristics were identified and contacted for a follow-up study. These were participants who have previously completed a study examining the impact of amygdala lesion on emotion and attention and also have agreed to being contacted for future study participation. Same exclusion criteria were applied to potential amygdala lesion study participants.

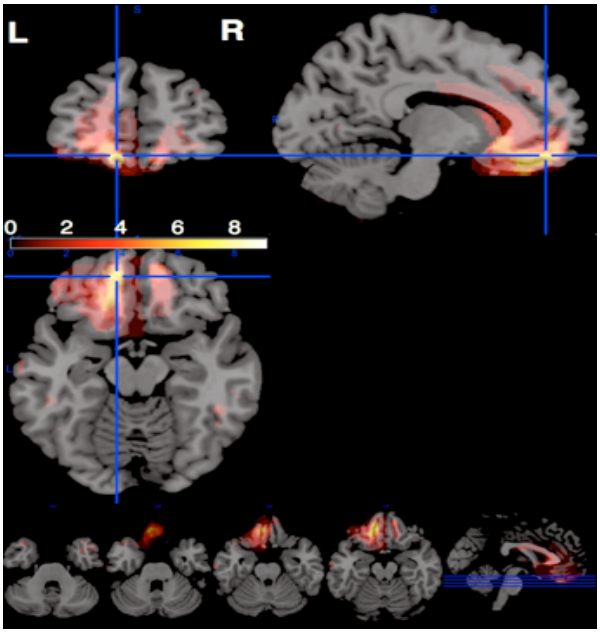


Figure 11. Overlap of Cortical Damage in OFC Lesion Patients: Heat-map indicates the density of lesion-overlap analysis (i.e., number of patients showing lesion to the colored area). Neurological Convention is used (Left is Left, Right is Right).

From the twenty OFC lesion patients identified, eleven OFC lesion patients completed the study. This final OFC lesion sample consisted of 4 males and 7 females aged 32 to 59 years

(mean = 51.1 years, SD =7.6 years). The time between surgery and their taking part in the study ranged from 3 to 14 years. Two of these participants had suffered from ruptured anterior communicating artery aneurysm which was clipped, 1 had suffered from focal head injury, and 8 other patients had undergone resection of portions of the OFC due to the following: 4 from meningioma, 2 from intractable focal epilepsy, 1 from cavernous angioma, and 1 from neurofibroma. A map of lesion overlap of recruited OFC patients is illustrated in Figure 11. Mean lesion volume was 6129 mm^3(SD=6726 mm^3 , Median= 4078 mm^3, Minimum=866 mm^3 , Maximum=20269 mm^3). Examination of the lesion overlap revealed a primarily left-sided overlap with more medially-centered lesions, near the anterior OFC area (anterior portion of the middle orbitofrontal gyrus and gyrus rectus).

Amygdala Lesion Patients

Five amygdala lesion patients participated in the study consisted of 3 males and 2 females aged 35 to 57 years (mean=48.4 years, SD=9.2 years). All of the amygdala lesion patients were unilateral surgical resection cases (clinical resection for treatment of intractable epilepsy). Three of these participants were selective amygdalohippocampectomy cases (two left and one right), and two of them were temporal lobectomy cases (one left and one right).

Healthy Matched-controls

Ten healthy controls were recruited through advertisements posted on a local craigslist webpage, a high-traffic online community featuring advertisements and forums. Whenever possible, control subjects were recruited to match, within a pre-defined margin of difference, the demographics of a OFC lesion patient. Specifically, matched-controls were no more than 3 years younger or older; and within 2 years of difference in formal education level compared to the

patient subject they were matched to. Controls were also matched for gender and handedness. Whenever possible, ethnicity of the subject was matched as well. Exclusion criteria included past history of head injury or loss of consciousness greater than 1 minute, history of drug and alcohol dependence, current use of psychotropic medications, past or current diagnoses of major psychiatric disorders, and a full-scale intelligence quotient (FSIQ) below a cut-off of 75 (1 standard deviation below the mean) as measured by the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, D., 1999).

4.2.2 *Procedure*

Recruited study participants came into the laboratory for the consent procedure and in person screening. A written informed consent approved by the Vanderbilt Institutional Review Board was provided and verbally explained to each prospective participant. For participants who already had visited the laboratory for consent and screening process for other previous laboratory studies, an online electronic consent was provided. In lieu of a physical signature, individuals interested in participating in the study signed an electronic version of the consent by typing in their name and the current date. This online consent method was approved by the Vanderbilt Institutional Review Board.

Experience-sampling events occurred within the context of each study participant's daily life setting by administering questionnaires via the world-wide-web (i.e., online) in their respective environments. All participants were provided with a unique link to the online study. Every day, participants received three messages to their phone (text or e-mail) asking them to complete a series of questions on an online survey. For those who did not own a smartphone or a tablet, a courtesy smartphone was offered in order to facilitate participation. Messages were sent

to participants at randomized times, 3 epochs a day for 14 consecutive days between 9am-9pm (i.e., 9am-1pm, 1-5pm, and 5-9pm) for a total of 42 possible experience-sampling events for each study participant. Participants were allowed up to 3 hours to respond to the message and fill out the online survey, after which the online survey responses were deemed invalid. Participants responded on average 95.6% (SD=4.2%, minimum=85.7%, maximum=100%) of the requested surveys (i.e., fewer than 3 of the 42 total experience-sampling events were missed on average). The questionnaires that participants were asked to fill out were posted on an online survey platform, REDCap (www.redcap.com), which is a secure, web-based application for building and managing online surveys and databases, approved by the Vanderbilt Institutional Review Board. Questions included in the online survey assessed type and intensity of emotion experienced in the past 3 hours, and what, if any, methods they used to regulate their emotions and how successful they were in regulating. Each sampling event required no more than 5 to 10 minutes to complete in order to ensure high participation rate. After completing the emotion regulating ratings over a two-week period, participants completing over 90% of the questionnaires were compensated $65 by either check (via mail) or as a gift certificate (via email). For participant completing below 90%, compensation was paid as a prorated amount depending on the percentage of survey response. Sampling questions were presented to participants in the order described below.

4.2.3 *Materials and Design*

Emotion Ratings (positive and negative emotionality)

Participants rated the types and intensity of emotions experienced three times a day using mood descriptors from the modified differential emotion scale (mDES; Cohn, Fredrickson,

Brown, Mikels, & Conway, 2009). The version of mDES utilized in this study included 10 positive emotion types (amusement, awe, compassion, contentment, gratitude, hope, interest, joy, love, and pride) and 10 negative emotion types (anger, anxiety, boredom, contempt, disgust, embarrassment, fear, guilt, sadness, and shame). Participants were asked to indicate emotion types experienced, if any ("Indicate emotion (feeling) experienced in the past 3 hours"), and rate the intensity of each emotion type experienced in the past 3 hours on a Likert type scale of 1 ("not at all") to 5 ("extremely"). Positive emotionality and negative emotionality scores were calculated for each sampling event by summing across all emotion types within the same valence category. Maximum emotional intensity scores (of any of the 10 types within positive or negative emotionality) were extracted for each sampling epoch, yielding two maximum intensity scores, one positive and one negative, for each sampling event. In a similar manner, minimum emotional intensity scores were calculated for each valence dimension as well. Therefore, each study participant's summary experience sampling scores were derived by calculating the mean scores of 42 or fewer (if completion rate was less than 100%) sampling event responses of the following: within-epoch sums of affect ratings, within-epoch maximum of affect ratings, and within-epoch minimum of affect ratings. Positive and negative affect ratings were separately calculated.

Emotion Regulation

Use of emotion regulation strategies were measured immediately following participant's emotion ratings. This assessment used procedures adapted from a previous study measuring emotion regulation effort in individuals with mood disorders (Gruber *et al.*, 2013). The questions were designed to measure whether and how participants attempted to regulate their emotions. Participants were asked to identify and indicate the level of their emotion regulation effort from

one of the four following strategies: reappraisal ("Thinking about a situation differently"), calming ("Trying to calm body by taking deep breathes or relaxing muscles"), suppression ("Trying not to show emotions on the outside"), and distraction ("Turning my attention away from what is making me feel emotional"). After completing the emotion rating, participants were asked to indicate how much they were utilizing each of the four regulation strategies on a Likert scale of 1 ("not at all") to 5 ("extremely"). Subsequently, participants were asked to gauge the effectiveness of the emotion regulation strategy used ("How effective was this at controlling or changing your emotion in this instance?"), to which study participants rated on a Likert scale of 1 ("not at all") to 5 ("extremely").

Additional Questionnaires

Before the beginning of the 2-week experience sampling surveys, each participant filled out a set of questionnaires that consisted of the following: the 60-item NEO Five Factor Inventory (NEO-FFI; Costa & McRae, 1992), the 20-item Toronto Alexithymia Scale (TAS-20; Bagby, Parker, and Taylor, 1994). After the last experience sampling trial, participants filled out a set of questionnaires that consisted of the following: the 5-item Life Satisfaction Assessment Scale (LSAS, Goldberg & Harrow, 2005), the 36-item Difficulties in Emotion Regulation Scale (DERS,), and the 43-item Holmes and Rahe Stress Scale (Holmes & Rahe, 1967). These survey measures of personality, stress, and life satisfaction were included to ensure these potentially impactful confounding variables did not better explain putative group differences experience sampling data results.

The NEO Five Factor Inventory (NEO-FFI; Costa & McRae, 1992) was used to obtain a general profile of each participants five domains of personality: neuroticism, extraversion,

openness, agreeableness, and conscientiousness, on a Likert-type 1 ("Strongly Disagree") to 5 ("Strongly Agree") scale. The Toronto Alexithymia Scale (TAS-20; Bagby, Parker, and Taylor, 1994) was included as a measure of deficits in understanding, labeling, and describing one's own emotions, and is designed to assess agreement to statements such as, "I am often confused about what emotion I am feeling", on a Likert-type 1("Strongly Disagree") to 5 ("Strongly Agree") scale. The Life Satisfaction Assessment Scale (Goldberg & Harrow, 2005) was used to measure overall life satisfaction in key life domains: economic security, social relationships, living arrangement, and occupation domains on a Likert-type 1 ("very satisfied") to 5 ("very dissatisfied") scale and an additional question regarding participant's overall assessment of life satisfaction. Items on this questionnaire were reverse scored (i.e., greater scores indicated higher life satisfaction). The Difficulties in Emotion Regulation Scale was used to measure trait level facility with utilizing emotion regulation. This measure was included to account for individual differences in emotion regulation usage, if any. On the Holmes and Rahe Stress Scale, participants were asked to indicate any significant events or stressors that occurred in the past year, or expected to occur in the near future. This measure was included to account for situational factors significantly impacting mood ratings and emotion regulation usages, if any.

4.2.4 *Predictions and Statistical Analyses*

The first goal of this study was to test whether there are group (control, amygdala lesion, and ventral PFC lesion) differences in the intensity of positive and negative emotions experienced as well as frequency and preference of emotion regulation efforts and their perceived effectiveness. This goal was accomplished by evaluating the following: (a) the overall magnitude of positive and negative emotion intensity ratings reported throughout the 2-week long experience sampling period, (b) frequency of regulation effort within all sampling events

where any emotional experience was reported (c) relative preference among four regulation strategy-types (i.e., reappraisal, calming, suppression, and distraction) (d) perceived subjective outcome of regulation effort as measured by self-report of regulation effectiveness yoked to reported use of any regulation strategies.

Therefore, for positive and negative valence dimensions separately, each participant had the following experience sampling summary scores: 1) an overall affect intensity rating score derived by calculating the mean of affect-ratings summed within the valence category (10 positive emotion scores summed to form a positive affect rating, 10 negative emotion scores summed to form a negative affect rating), 2) a regulation effort frequency score calculated as a proportion of experience sampling events where specific regulation strategy was used out of all experience sampling events where some affect was reported, 3) a regulation success score for each strategy type by calculating the mean of all reported effectiveness of regulation within each strategy-type.

To test group differences in emotion regulation effort, a series of repeated measures ANOVAs were conducted with each of the summary emotion regulation effort scores serving as the dependent variable for these analyses. Summary scores associated with different strategies were treated as different levels of a repeated within-subjects factor whereas the sample group (control, amygdala lesion, ventral PFC lesion) was included as a between-subjects factor. It was predicted that the ventral prefrontal cortex lesion patients would show greater positive and negative affect intensity compared to controls, as well as relatively greater utilization and preference for non-reappraisal-based regulation strategies (calming, suppression, distraction). It was also hypothesized that the lesion patients would experience less effective reappraisal-based emotion regulation as evidenced by lower effectiveness rating score relative to other strategies',

given the previous findings that suggest intact ventral prefrontal cortex serves a critical role in reappraisal-based emotion regulation.

The second goal was to examine whether Ventral PFC lesion patients experience greater intensity and volatility of positive and negative affect compared to healthy controls. The potential group difference in the volatility, or fluctuation of emotional experience was examined by taking advantage of the repeated-measures data generated by the current study. The current experience-sampling study was designed to probe each study participant three times per day, every day for two weeks. This allowed for an invaluable opportunity to test hypotheses that pertain to the time course of positive and negative emotionality. Consistent with the hypothesis that ventral prefrontal cortex is critically involved in regulation of mood, it was expected that the ventral PFC lesion sample would show greater mood intensity fluctuation in both positive and negative emotionality domains. In order to test this hypothesis, a summary measure of time-dependent volatility in mood change, the *fluctuation index score* was derived for each participant by calculating the magnitude of mood intensity change for consecutive experience sampling events. This summary measure was generated from participants' responses in the modified differential emotions scale (mDES) and tabulated separately for positive and negative emotionality dimensions. Total positive and negative emotionality scores were derived from each experience sampling event. Then, emotionality scores from adjacent time points (e.g., assuming participant responded to all 42 experience sampling events, t_1 and t_2, t_2 and t_3, ... t_{41} and t_{42}) were subtracted to create mood change scores ($\Delta = t_1 - t_2$). These mood change scores were squared and summed across time points to generate a Mean Square Successive Difference score (MSSD, Von Neumann, Kent, Bellinson, & Hart, 1941). A square root of the MSSD score was calculated to for the mood fluctuation index score used in this study (see equation below). This

$$mood\ fluctuation\ index^{*} = \sqrt{\frac{\sum_{1}^{42}(t_n - t_{n+1})^2}{42}}$$

*assumes study participant responded to all 42 experience sampling events. Precise formula will vary according to how many consecutive experience sampling responses were completed.

method has been used in previous studies (Carstensen et al., 2011; Wood & Trull, 2008) as an index of "mood instability" or "lability" in a time-series data. These mood fluctuation indices were derived separately for both positive and negative affect dimensions within each study participant. Then, they were utilized as dependent measures of subsequent ANOVA analyses comparing the three sample groups. Greater mood fluctuation index was predicted for both positive and negative emotionality in the frontal lesion patients compared to healthy controls.

In order to estimate the likelihood of detecting the hypothesized effect of OFC lesion on intensity of affect and emotion regulation effort, a power analysis was conducted using the power calculation package *G*Power3* (Faul *et al*., 2007). Assuming there is indeed a moderate effect size (*Cohen's d* = 0.5) to be detected, the power to detect an effect of this size using a one-way ANOVA (i.e., *F*-test) was determined to be $1\text{-}\beta = 0.56$, critical $F = 3.42$. The power to detect a small effect (*Cohen's d* = 0.2) was 0.13, and power to detect a large effect (*Cohen's d* = 0.8) was 0.94. Because there is a directional a priori hypothesis such that the OFC lesion patient group will show greater intensity in positive and negative affect and greater difficulty with emotion regulation compared to healthy controls, a separate power calculation for one-tailed t-test was also conducted. In this instance, power to detect a moderate effect (*Cohen's d* = 0.5) was $1\text{-}\beta = 0.29$, critical $t_{19} = 1.73$ (one-tailed). Additionally, power to detect a small effect (*Cohen's d* = 0.2) was 0.11, and power to detect a large effect (*Cohen's d* = 0.8) was 0.55.

4.3 Results

4.3.1 *Sample Demographics and Characteristics*

As shown in Table 8, the three groups were similar in key demographic variables. A series of one-way ANOVA with three groups showed that the sample did not significantly differ by group in terms of age, $F(2,23) = .81$, $p > .1$; and education, $F(2,10.036) = 2.57$, $p > .1$. Moreover, The percentage of participants that were female did not differ by group, $\chi^2(2, N = 26) = 0.41$, $p > .1$. Comparison of questionnaire responses among groups indicated no significant group differences in difficulty identifying and labeling emotions (TAS-20), overall life satisfaction (LSAS), stressors experienced in the past 12 months (HRSS), and dispositional difficulties in regulation emotions (DERS); see Table 8 for complete list of means and test-statistics for comparison of demographic variables. Moreover, four (extraversion, agreeableness, conscientiousness, neuroticism) of the five factors were not significantly different among the three groups. Interestingly, the *openness* subscale of the NEO-FFI-3 was significantly different between the control and OFC lesion group such that participants in the OFC lesion group endorsed significantly lower level of openness compared to participants in the control group $F(2,22) = 4.20$, $p = .0285$ (for follow-up analyses and discussion, see results from this chapter under 4.3.6*)*.

4.3.2 *Preliminary Analyses*

Preliminary analyses of the data were conducted in order to ensure missing data patterns and compliance rates did not differ across sample groups. All participants met the minimum criteria of completing at least 80% of 42 experience sampling surveys. Missing data was addressed prior to analyzing the longitudinal experience sampling data. In order to assess the

potential impact of missing data a systematic analysis was made between the three groups to ensure that there were no group differences in the frequency of missing data. Overall, there was a very high compliance rate (mean=95.6%, SD=4.2%) across the whole sample. There was a trend toward a significant difference in the number of surveys completed out of 42 sampling events among the three groups: Control (n=10, mean=41.0, SD=.5), Amygdala (n=5, mean=39.2, SD=.8), OFC lesion (n=11, mean=39.6, SD=.5), $F(2,23) = 2.79$, p=.0822. However, post-hoc pairwise comparison of each pair using Tukey-Kramer HSD test revealed no group differences (all ps>.1).

Possible group differences in contextual behavior immediate prior to submissions of experience sampling responses (i.e., activities performed immediately prior to experience sampling) were also examined. In the study sample as a whole, "Work" was the most highly endorsed activity (31.0%), followed by "Other" (12.5%), "Home Chore" (12.0%), and "Social Activity" (10.8%). "Exercise" was the least endorsed (4.3%) activity of all available choices. The overall distribution of endorsed contextual activities indicated that the sampling captured a broad range of study participants' daily activities.

For the analysis of mood fluctuation, only consecutive sampling events were included in deriving the mood fluctuation index. For example, if a participant responded to sampling epoch 1, 2, 4, and 5 (i.e., thus missing sampling event 3), then mood fluctuation index was derived from taking into account the change in affect magnitude between epoch 1 and 2, and 4 and 5 (i.e., magnitude change between epochs 2 and 4).

See Table 9 for a list of means and test-statistics for experience sampling variables.

	Control (n=10)	Amygdala (n=5)	OFC (n=11)	Statistic
Demographics Age	46.3 (9.4)	48.4 (9.2)	51.1 (7.6)	F=.81
Education	14.5 (1.4)	15.2 (2.3)	16.9 (3.1)	F=2.57
% Female	50% (5/10)	60% (3/5)	64% (7/11)	χ^2 = .41
NEO-Five Factor Inventory (NEO-FFI-3) Extraversion	39.9 (9.3)	44.8 (10.0)	48.2 (7.2)	F=2.33
Agreeableness	47.4 (6.2)	44.8 (9.0)	47.6 (9.3)	F=.22
Conscientiousness	49.4 (6.2)	51.0 (6.8)	48.4 (9.7)	F=.19
Neuroticism	27.8 (7.9)	25.8 (3.9)	34.1 (13.1)	F=1.57
Openness	54.7 (4.6)	49.6 (9.1)	45.5 (7.7)	F=4.20 *
Toronto Alexithymia Scale (TAS-20)	42.1 (13.0)	45.0 (14.8)	48.9 (13.7)	F=.62
Life Satisfaction Assessment Scale (LSAS)	12.0 (1.1)	10.2 (1.5)	12.0 (1.0)	F=.58
Holmes & Rahe Stressor Scale (HRSS)	524.1 (118.3)	543.2 (158.7)	549.8 (107.0)	F=.01
Difficulties in Emotion Regulation Scale (DERS) Non-Accept	10.3 (1.5)	10.0 (2.0)	11.9 (1.4)	F=.45
Goals	13.1 (1.6)	9.8 (2.1)	11.4 (1.4)	F=.86
Impulse	8.7 (1.4)	7.6 (1.9)	9.6 (1.3)	F=.40
Aware	12.8 (1.7)	13.0 (2.2)	14.4 (1.5)	F=.28
Strategies	12.8 (4.8)	13.4 (6.0)	14.2 (4.9)	F=.19
Clarity	8.8 (.9)	7.8 (1.2)	9.7 (.8)	F=.87

* $p < .05$ for Control and OFC lesion; For DERS, Non-Accept: Non-acceptance of emotional responses; Goals: Difficulties engaging in goal directed behavior; Impulse: Impulse control difficulties; Aware: Lack of emotional awareness; Strategies: Limited access to emotion regulation strategies; Clarity: Lack of emotional clarity.

Table 8. Descriptive Statistics of Demographics Variables and Questionnaire Responses

Category	Dimension		Control (n=10)	Amygdala (n=5)	OFC (n=11)	Cohen's *d* (OFC vs Control)
Emotionality	PA Sum		5.3 (3.2)	6.4 (3.6)	8.0 (4.8)	.66
	PA Maximum		3.4(1.3)	4.2 (0.4)	4.0 (0.7)	.51
	PA Minimum		2.9 (1.2)	3.4 (0.5)	3.4 (0.7)	.48
	NA Sum		1.0 (1.3)*	.4 (.9)	.1 (.3)*	.94
	NA Maximum		1.0 (1.3)*	.4 (.9)	.1 (.3)*	.94
	NA Minimum		.9 (1.2)*	.4 (.9)	.1 (.3)*	.93
Regulation Effort	Reappraisal	PA	0 (0)	.13 (.20)	.04(.03)	n/a
		NA	.13 (.09)	.20 (.18)	.18 (.03)	1.71
	Calming	PA	0 (0)	.05 (.11)	.004(.01)	n/a
		NA	.06 (.07)	.07 (.08)	.09 (.08)	.49
	Suppression	PA	0 (0)	.12 (.18)	.02 (.03)	n/a
		NA	.06 (.05)	.14 (.11)	.14 (.09)	1.05
	Distraction	PA	0 (0)	.06 (.14)	.03 (.05)	n/a
		NA	.09 (.08)	.11 (.10)	.17 (.09)	.88
Regulation Effectiveness	Reappraisal	PA	n/a	.44 (.65)*	.11 (.19)*	n/a
		NA	.34 (.19)	.63 (.63)	.49 (.28)	.62
	Calming	PA	n/a	.16 (.37)	.01 (.02)	n/a
		NA	.15 (.16)	.21 (.26)	.19 (.11)	.28
	Suppression	PA	n/a	.42 (.57)*	.05 (.08)*	n/a
		NA	.14 (.11)*	.42 (.32)*	.33 (.24)	.98
	Distraction	PA	n/a	.19 (.42)	.08 (.12)	n/a
		NA	.23 (.20)*	.30 (.28)	.49 (.30)*	1.02
Behavioral Context	Eating		6.5% (8.2)	1.9% (1.9)	6.3% (7.7)	
	Sleep		7.7% (6.4)	5.8% (7.6)	8.9% (7.8)	
	Work		40.2% (13.9)*	36.9% (5.6)^	19.6% (15.2)*^	
	Social Activity		6.0% (3.6)*	12.4% (11.8)	14.5% (9.8)*	

	Media Entertainment	9.9% (12.2)	6.4% (8.7)	6.5% (7.1)	
	Exercise	1.9% (3.2)	5.3% (4.4)	5.9% (7.3)	
	Other Leisure	8.1% (6.8)	8.4% (4.7)	8.4% (5.2)	
	Home Chore	12.9% (10.3)*	2.4% (1.7)*^	15.9% (9.8)^	
	Other	6.9% (7.7)	20.5% (22.0)	14.0% (10.4)	

**Note*. Control = Healthy control group; Amygdala = Amygdala lesion group; OFC = Ventral PFC lesion group; PA-Positive Affect; NA-Negative Affect. Means and standard deviation values are in parentheses where applicable. Experience-sampling event ratings (i.e., positive affect, negative affect, Emotion regulation attempt, effectiveness and contextual behavior variables) reflect average values across the 42 sampling epochs. Because distribution of positive and negative affect ratings was highly positively skewed, for affect ratings, median values (i.e., median of summed affect rating, median of maximum affect rating, and median or minimum affect rating) from all available sampling events were derived from each participant and used to represent each individual's overall positive and negative affect. Each cell represents mean and standard deviation of these median scores. Means with a common symbol *, ^ indicate statistically significant difference in t-test group comparison at the one-tailed α=.05. Percentages for context represent the percent of all responses summed across all participants within each group. Standard deviations are included in parentheses.

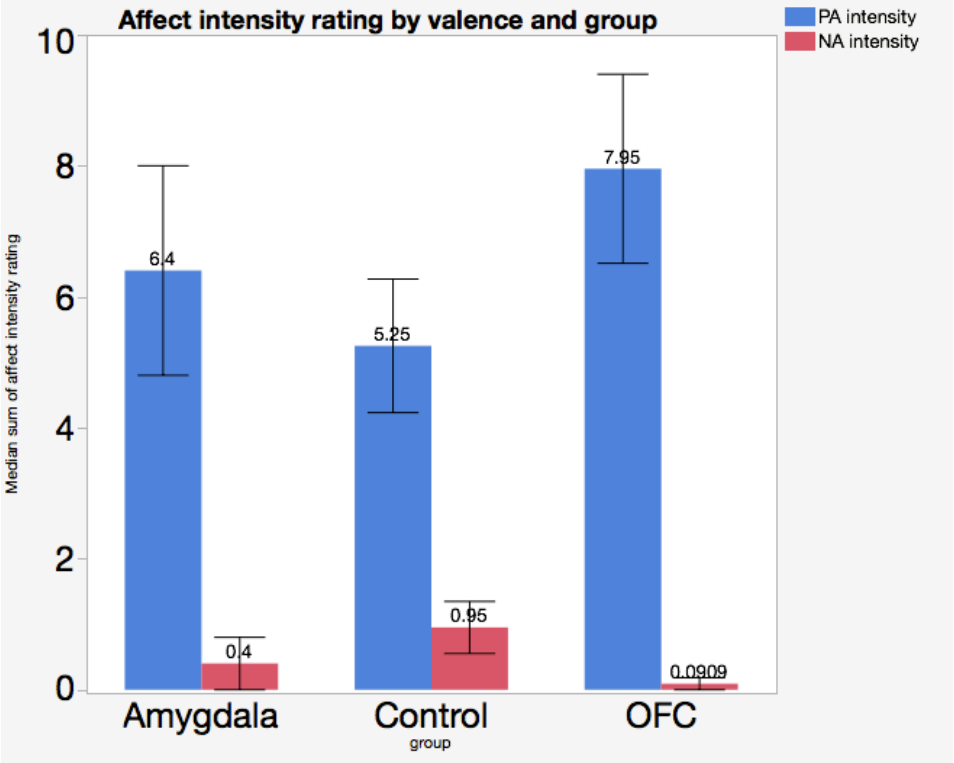
Table 9. Descriptive Statistics of Experience Sampling Response Variables

4.3.3 *Group Differences in Positive and Negative Emotionality*

There was no significant difference in self-reported positive affect intensity among the three groups. A one-way ANOVA with sample group as a between-subjects factor with three levels (healthy control, amygdala, and ventral PFC lesion groups) and median of summed affect intensity rating (note that this summary parameter used for analysis of both positive and negative affect rating because of the distribution being highly positively skewed) revealed that the sum of positive affect rating, $F(2,23) = 1.19$, $p > .1$ was not significantly different among the three groups. A planned comparison of the ventral PFC lesion sample and controls revealed only a weak trend toward greater self-reported positive affect rating in the ventral PFC lesion sample compared to healthy controls, $t(19) = 1.50$, $p = .15$.

On the other hand, there was a trend toward possible group differences in negative affect as measured by the sum of all negative affect rating, $F(2,23) = 2.45$, $p = .1085$. A planned comparison of negative emotionality ratings between the ventral PFC lesion sample and healthy

controls revealed significantly lower overall negative affect rating in the ventral PFC lesion sample compared to controls, $t(19) = -2.20$, $p = .0401$. See Figure 12 for graphic illustration of positive and negative affect ratings by Group and Valence.



Each error bar is constructed using 1 standard error from the mean.

Figure 12. Self-Reported Positive and Negative Affect Ratings Across Experience Sampling Events

4.3.4 *Group Differences in Emotion Regulation*

Group Differences in Probability of Emotion Regulation Attempt

Because Levene's test of unequal variances for the proportion of sampling events with regulation attempt was significant for the three groups, $F(2,23) = 14.4$, $p < .0001$, a series of non-

parametric tests (using Wilcoxon's method) was conducted in order to adequately compare the group differences in proportion of sampling events with emotion regulation attempt. Across all sampling events, Ventral PFC lesion patients were more likely to attempt emotion regulation (mean = 25.8%, SD = 11.9%) compared to controls (mean = 14.8%, SD = 8.5%), z = 2.22, p=.0264. Neither the comparison of amygdala lesion patients and controls, z = .74, p>.1, nor the comparison of amygdala lesion patients and ventral PFC lesion patients, z = -.11, p>.1 was significant. See Figures 13 and 14 for graphic illustration of regulation attempt comparison.

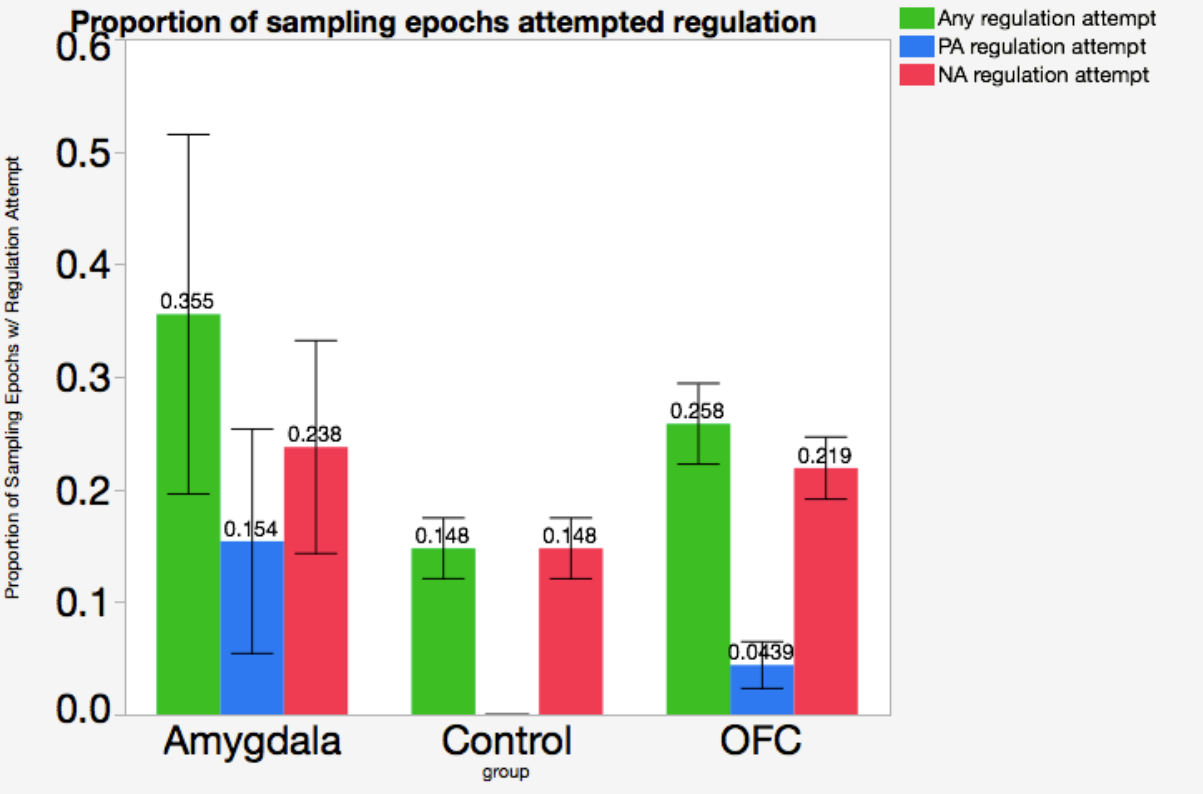
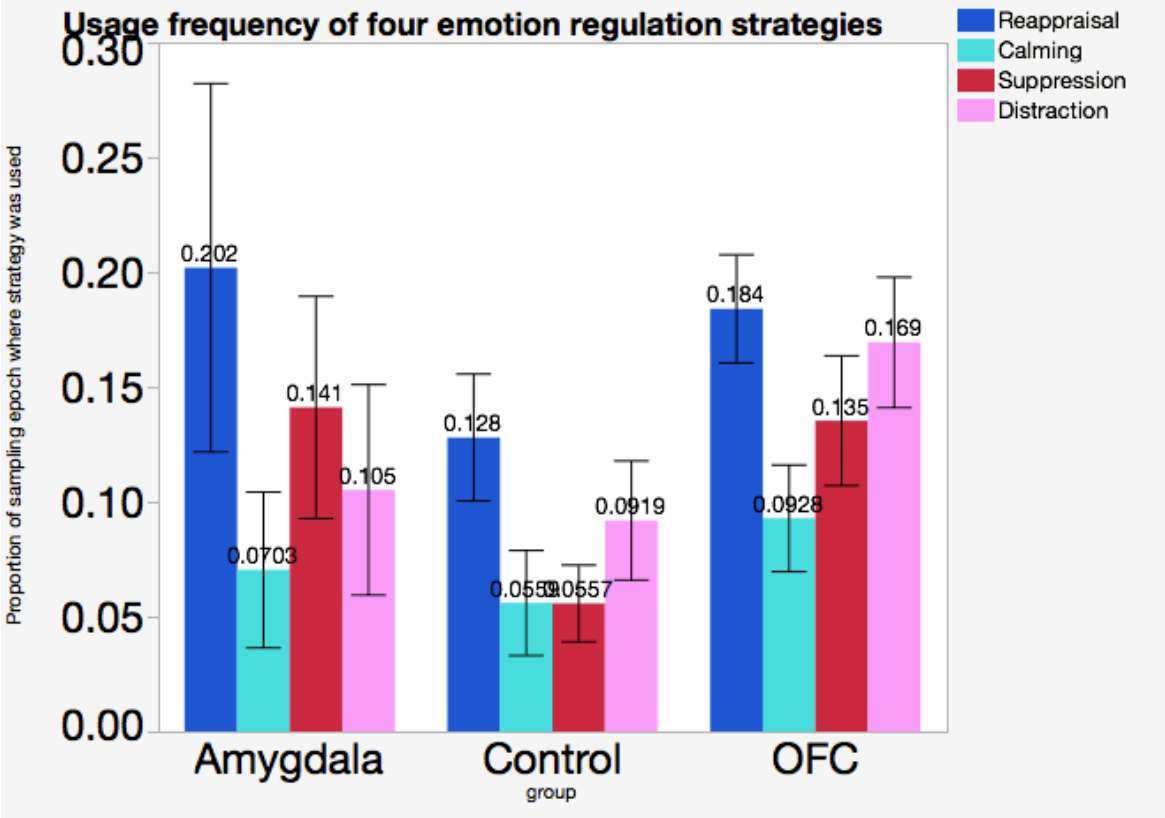


Figure 13. Overall Emotion Regulation Attempt Frequency by Valence



Each error bar is constructed using 1 standard error from the mean.

Figure 14. Frequency of Emotion Regulation Attempt of Negative Affect by Strategy Type

The following section separately describes regulation attempt patterns of negative and positive affect.

Regulation Pattern of Negative Affect

On average, out of 42 maximum possible sampling events, healthy controls reported at least some negative affect in 16.3 (SD=12.7) of all sampling events, ventral PFC lesion sample reported negative affect in 12.5 (SD=4.5), and amygdala lesion sample in 12.2 (SD=9.4) of all sampling events. Welch's test (alternative to conventional ANOVA) was conducted due to unequal variances among groups: Levene's test, $F(2,23) = 4.92$, $p=0.0166$. Results of the Welch's

test indicated no significant difference among groups in the number of sampling events reporting negative affect.

Proportion of sampling events with attempted regulation of negative affect was compared among the three groups. Healthy controls reported attempts to regulate negative affect in 14.8% (SD=8.5%) of all sampling events, whereas ventral PFC lesion sample reported attempts to regulate negative affect in 21.9% (SD=9.1%) of all sampling events, and amygdala lesion sample reported attempts to regulate in 23.8% (SD=21.1) of all sampling events. A one-way ANOVA indicated that proportion of regulation attempt of negative affect did not vary by group, $F(2,23) = 1.32$, $p > .1$. However, direct comparison of ventral PFC lesion patients and healthy controls indicated that ventral PFC lesion patients trended toward attempting regulation of negative affect more frequently compared to controls, $t(1,19) = 1.84$, $p = .0816$.

In order to capture putative differences in preference of using different regulation strategy types, further group comparisons of regulation strategy usage were made within all sampling events where any usage of emotion regulation strategies was reported (see Figure 15 below for illustration of regulation strategy type usage by Group). A repeated-measures ANOVA with Group as a between-subjects factor and Strategy-Type as a within-subjects repeated factor with 4 levels (Reappraisal, Calming, Suppression, and Distraction), and Regulation Attempt as a proportion of all regulation attempts was used as the outcome measure. There was a significant within-subjects main effect of Strategy-Type, $F(3,69) = 10.096$, $p < .0001$, indicating that for the group as a whole, frequency of regulation attempt varied with the type of regulation strategy. Further post-hoc analysis of pairwise comparison of the four Strategy-Types revealed that usage of reappraisal (whole sample mean=37.9%, SD=18.6%) was greater than calming (whole sample mean=14.4%, SD=10.9%), *matched-pairs-t*$(25) = -4.93$, $p < .0001$; greater than suppression

(whole sample mean=18.6%, SD=11.3%), *matched-pairs-t*(25) = -4.12, *p*=.0004; and greater than distraction (whole sample mean=25.3%, SD=14.0%), *matched-pairs-t*(25) = -2.40, *p*=.0241. Additionally, distraction was preferred over calming, *matched-pairs-t*(25) = 3.08, *p*=.0049. There was no significant main effect of Group, or Group by Strategy-Type interaction, (all p>.1).

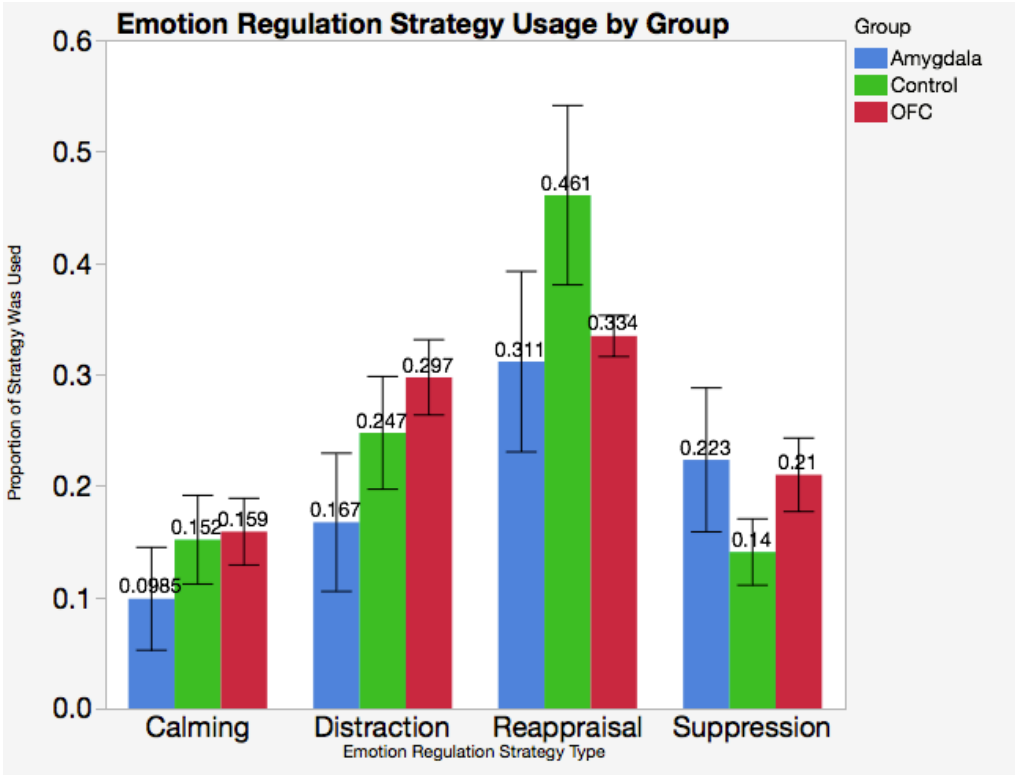


Figure 15. Regulation Strategy Used within All Sampling Events with Any Regulation Attempt

Exploration of Association between Reported Emotion Rating Intensity and Emotion Regulation

Correlational analyses were conducted to explore the relationship between subjective report of negative affect intensity and likelihood of using regulation strategies. First of all, for the sample as a whole, there was a robust positive correlation between individual differences in the intensity of negative affect rating and subject's likelihood of attempting to regulate negative affect using any of the four strategies (see Figure 16), r(24) =.68, p<.0002.

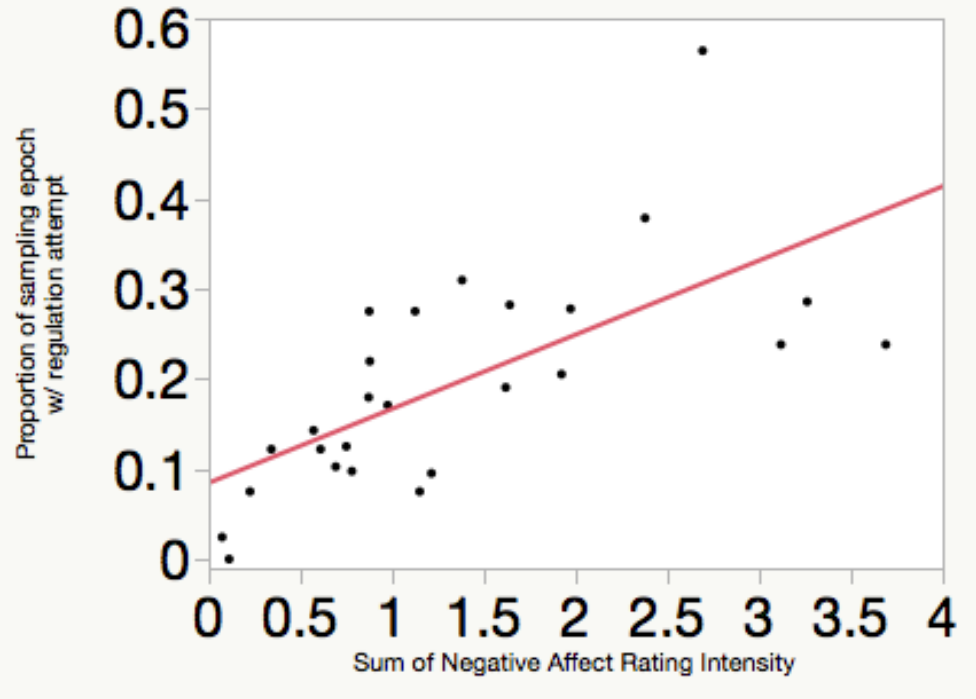


Figure 16. Correlation between Negative Affect Ratings and Frequency of Regulation Attempt

When the same relationship explored separately for the four different types of regulation strategies, a contrasting pattern of emotion regulation strategy usage was revealed between the ventral PFC lesion group compared to healthy controls. For example, in the control group, the overall sum of negative affect intensity rating was highly correlated with tendency to utilize *reappraisal*, r(8) =.86, p=.0014, *suppression*, r(8) =.74, p=.0138, and *distraction*, r(8) =.86, p=.0014, but not *calming*, r(8) =n.s., p>.1. In contrast, in the ventral PFC group, only the likelihood of using *distraction* as a regulation strategy was significantly predicted by the sum of negative affect intensity, r(9) =.69, p=.0179.

Moreover, subjective report of regulation effectiveness was compared among groups and strategy types. First of all, across the sample as a whole, regardless of regulation strategy type used, individuals who more frequently attempted regulation of negative affect also tended to

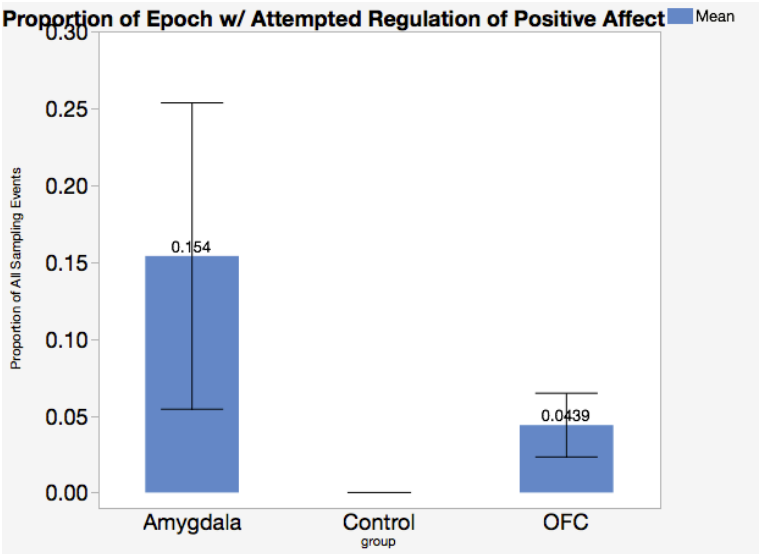
endorse greater regulation success: *reappraisal*, r(24) =.90, p<.0001; calming, r(24) =.86, p<.0001; *suppression,* r(24) =.91, p<.0001; and *distraction*, r(24) =.93, p<.0001.

A two-way repeated measures ANOVA was conducted with self-reported Regulation Strategy Type as a repeated within-subject factor with 4 levels (regulation success-reappraisal, regulation success-calming, regulation success-suppression, and regulation success-distraction) and Group (control, amygdala, ventral PFC) as a between subject factor. There was a significant main effect of strategy type on regulation success such that for the sample as a whole, self-reported success of emotion regulation varied with the type of regulation strategy used, $F(3,69) = 9.33$, p<.0001. However, there was no significant main effect of Group, $F(2,23) = 1.09$, p>.1, or Group by Regulation Strategy Type Interaction $F(6,69) = 1.06$, p>.1. A post-hoc pairwise comparison of four strategies revealed that mean regulation success for reappraisal was greater compared to calming, *matched-pairs-t*(25) = -4.72, *p*<.0001, as well as suppression, *matched-pairs-t*(25) = -3.88, *p*=.0007. In addition, distraction was comparatively endorsed as being more effective when compared to calming, *matched-pairs-t*(25) = 3.13, *p*=.0044. Reappraisal showed a trend toward being more effective than distraction, *matched-pairs-t*(25) = 2.01, *p*=.055 and suppression greater than calming, *matched-pairs-t*(25) = -1.96, *p*=.0614. however, neither of the two pairwise comparisons survived the Benjamini-Hochberg correction for multiple comparison.

Further pairwise analyses comparing the ventral PFC lesion sample and controls in terms of regulation effectiveness for each of the four strategy types revealed significantly higher perceived effectiveness of suppression and distraction. Whereas the two groups did not differ on their self-reported effectiveness of reappraisal, t(19) =1.41, p>.1, or calming, t(19) =.69, p>.1, the OFC lesion group did endorse experiencing greater effectiveness of suppression, t(19) =2.21, p=.0396; and greater effectiveness of distraction, t(19) =2.32, p=.0314.

Regulation Pattern of Positive Affect

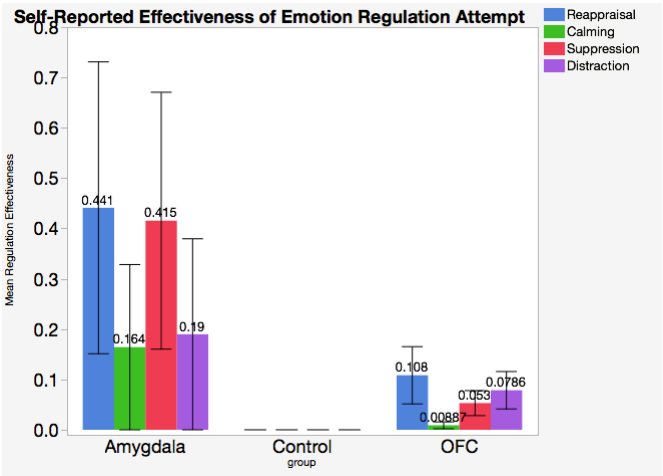
Interestingly, while none of the healthy controls endorsed attempting to regulate positive affect, six ventral PFC lesion patients and two amygdala lesion patients reported attempts to regulate positive affect (proportion of all sampling events indicating any attempt to regulate positive affect for the 6 ventral PFC patients: 12.2%, 11.1%, 9.8%, 2.5%, 2.4%, 2.0%) and 48.7%, 28.2% for the two amygdala patients). Follow-up interview of these participants suggested that attempts to regulate positive affect generally reflected efforts to curb outwardly expression of positive affect in situations where it was considered socially obtuse to do so (e.g., feeling happy about good news of a job offer when an unemployed friend was present). A series of non-parametric pairwise comparison using the Wilcoxon method revealed that regulation attempt for positive affect was more frequent in the ventral PFC lesion sample (mean=4.4%, SD=6.9%), z = 2.31, p=.021, and the amygdala lesion sample (mean=15.4%, SD=22.2%) compared to healthy controls (mean=0.0%, SD=0.0%), z = -1.97, p=.0492 (see Figure 17 below).



Each error bar is constructed using 1 standard error from the mean.

Figure 17. Proportion of Sampling Events where Regulation of Positive Affect was Reported

A two-way repeated measures ANOVA was conducted with self-reported Regulation Strategy Type as a repeated within-subject factor with 4 levels (regulation success-reappraisal, regulation success-calming, regulation success-suppression, and regulation success-distraction) and Group (control, amygdala, ventral PFC) as a between subject factor. Mauchly's test of sphericity performed prior to the ANOVA indicated that there were significant difference between the variance of differences in Strategy Type, $\chi^2(5) = 38.417$, $p < .0001$. Accordingly, the Greenhouse-Geisser correction was applied to the repeated measures ANOVA of Strategy Type. There was a significant main effect of Strategy Type on regulation success such that for the sample as a whole, self-reported success of emotion regulation varied with the type of regulation strategy used, $F(1.721,39.590) = 5.671$, p=.009. Moreover, there was a significant main effect of Group, $F(2,23) = 3.856$, p=.036, and a significant Group by Regulation Strategy Type interaction $F(6,69) = 3.026$, p=.011 (See Figure 18 below for illustration). A post-hoc pairwise comparison of four strategies revealed that there was a trend toward reappraisal being more effective in regulating positive affect compared to calming, *matched-pairs-t*(25) = -2.21, p=.0363, however, this p-value did not survive the Benjamini-Hochberg correction for multiple comparison.

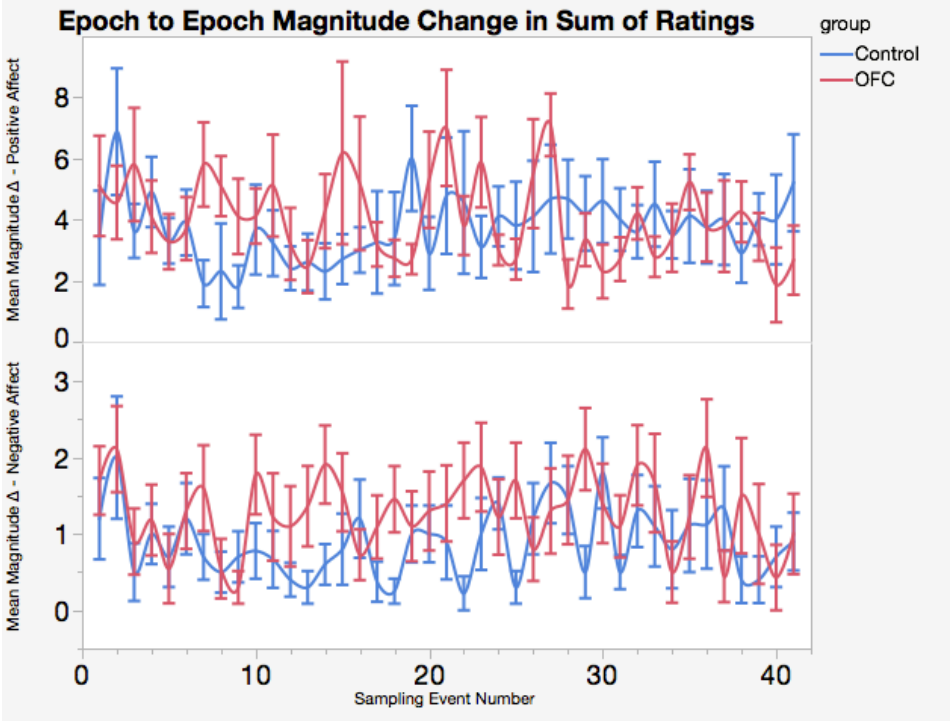


Each error bar is constructed using 1 standard error from the mean.
Note, controls reported no attempts to regulate positive affect.

Figure 18. Self-Reported Effectiveness of Regulating Positive Affect by Strategy Type

4.3.5 *Group Differences in Emotionality Fluctuation*

An analysis of group differences in fluctuation index representing epoch to epoch affect intensity change revealed no difference in the magnitude of fluctuation in positive affect when comparing sum of positive affect intensity rating, $F(2,23) = .40$, $p>.1$; maximum positive affect rating, $F(2,23) = .62$, $p>.1$; or minimum positive affect rating, $F(2,23) = .38$, $p>.1$. In the negative affect domain, there was a trend toward group difference in epoch to epoch fluctuation in overall sum of negative affect intensity rating, $F(2,23) = 3.38$, $p=.0518$, a significant difference in the fluctuation index of maximum negative affect rating, $F(2,23) = 3.72$, $p=.0397$ as well as a trend toward significant difference in the fluctuation index of minimum affect rating $F(2,23) = 2.97$, $p=.0711$. A planned follow-up analysis directly comparing the ventral PFC lesion sample and controls indicated that the ventral PFC lesion sample exhibited greater magnitude of epoch to epoch fluctuation in: sum of negative affect intensity rating, $t(19) =2.28$, $p=.0346$; maximum negative affect intensity rating, $t(19) =3.31$, $p=.0057$; and minimum negative affect intensity rating, $t(19) =3.05$, $p=.0048$. Note, while this result showing greater negative affect fluctuation in lesion patients may seem to be at odds with results reported in the previous section showing decreased negative affect rating in the lesion patient group, the lower negative affect result was based on comparing median of negative affect ratings whereas the fluctuation index analyses were done using mean affect ratings. A graphic illustration of fluctuation in affect rating is described in Figures 19 A and B below.



Each error bar is constructed using 1 standard error from the mean.

Figure 19.A Mean Epoch to Epoch Magnitude Change in Sum of Ratings

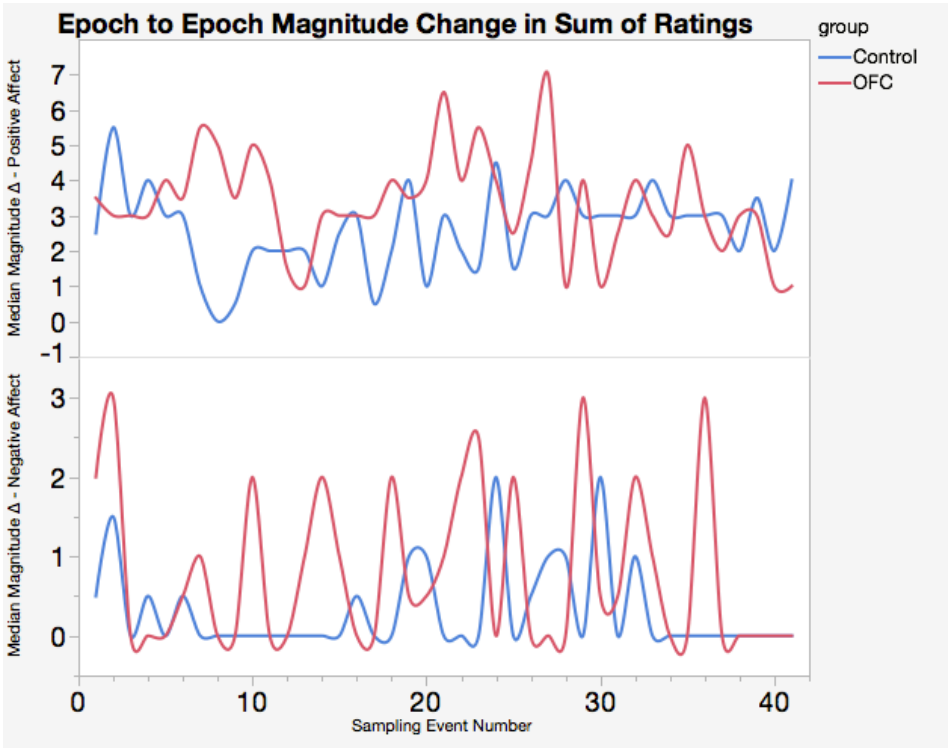


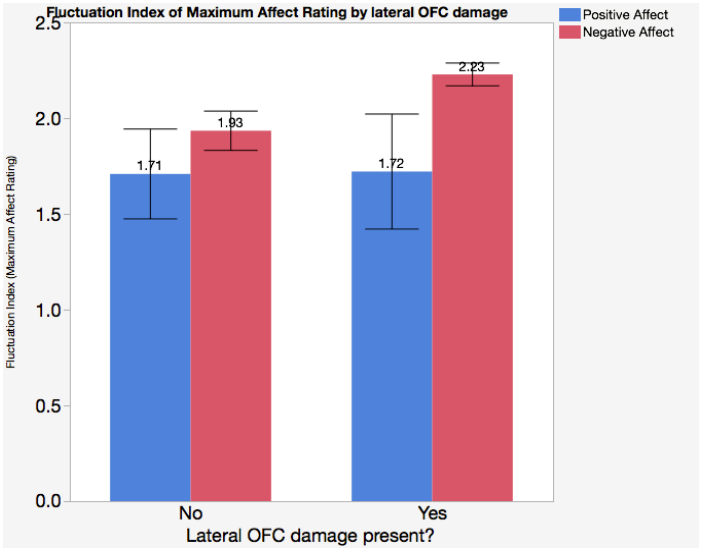
Figure 19.B Median Epoch to Epoch Magnitude Change in Sum of Ratings

In order to investigate the possible association between this measure of mood lability and regulation attempt frequency and effectiveness, a series of correlational analyses were conducted between negative affect fluctuation index and regulation attempt frequency as well as effectiveness. In healthy controls, individuals with greater mood fluctuation index also tended to utilize to a greater extent: reappraisal, $r(8) = .65$, $p = .0436$; suppression, $r(8) = .87$, $p = .001$; and distraction, $r(8) = .65$, $p = .0427$. Greater mood fluctuation was also associated with higher level of self-reported effectiveness of reappraisal, $r(8) = .71$, $p = .0225$; suppression, $r(8) = .78$, $p = .0077$; and distraction, $r(8) = .71$, $p = .0218$. However, with the exception of greater mood fluctuation being associated with increased usage in distraction, $r(9) = .66$, $p = .0279$, in the OFC lesion sample there was no other significant association between the degree of mood fluctuation and frequency or effectiveness of regulation strategy usage (all $p > .1$).

Within-group Differences of Fluctuation Index in the Ventral PFC Sample

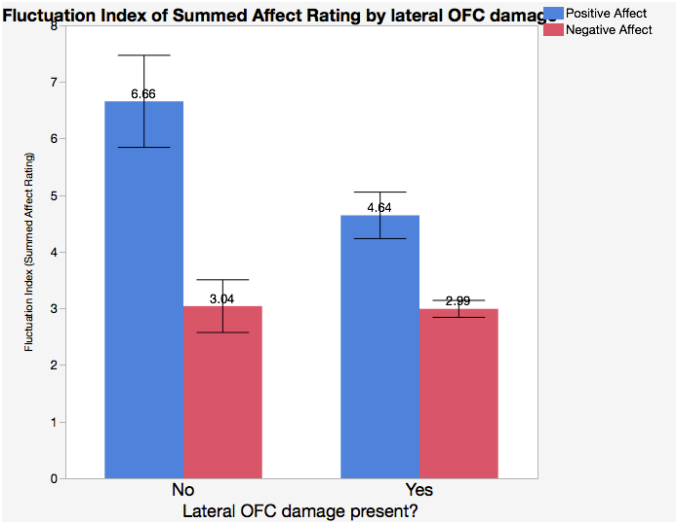
Based on functional neuroimaging studies demonstrating that the ventrolateral PFC plays a key role in emotion regulation, it was hypothesized that a subset of ventral PFC lesion sample with any lateral OFC damage would endorse lower degree of reappraisal effectiveness and greater affect fluctuation index compared to those without lateral OFC damage. Six of the eleven ventral PFC lesion sample were identified as having at least some lesion in the lateral OFC area. There was no significant difference in the self-reported effectivenes of reappraisal of negative emotions between the ventral PFC lesion sample with lateral OFC damage (mean=.42, SD=.17), and those without lateral OFC damage (mean=.57, SD=.13). However, there was a greater degree of fluctuation in experience of highest level of negative affect intensity (see Figure 20A), as measured by the fluctuation index of maximum negative affect rating, in the subset of ventral

PFC lesion sample who had lateral OFC damage (mean=2.23, SD=.15) compared to those without lateral damage (mean=1.93, SD=.23), t(9)=2.59, p=.0292. Interestingly, the two groups also differed in the level of fluctuation in overall positive affect (see Figure 20B), as measured by the fluctuation index for the sum of all positive affect rating, such that ventral PFC lesion sample with lateral OFC damage had smaller sum of positive affect rating (mean=4.64, SD=1.01), compared to those without lateral OFC damage (mean=6.66, SD=1.82).



Each error bar is constructed using 1 standard error from the mean.

Figure 20A. Fluctuation Index for Maximum Affect Rating by Lateral OFC Damage Presence



Each error bar is constructed using 1 standard error from the mean.

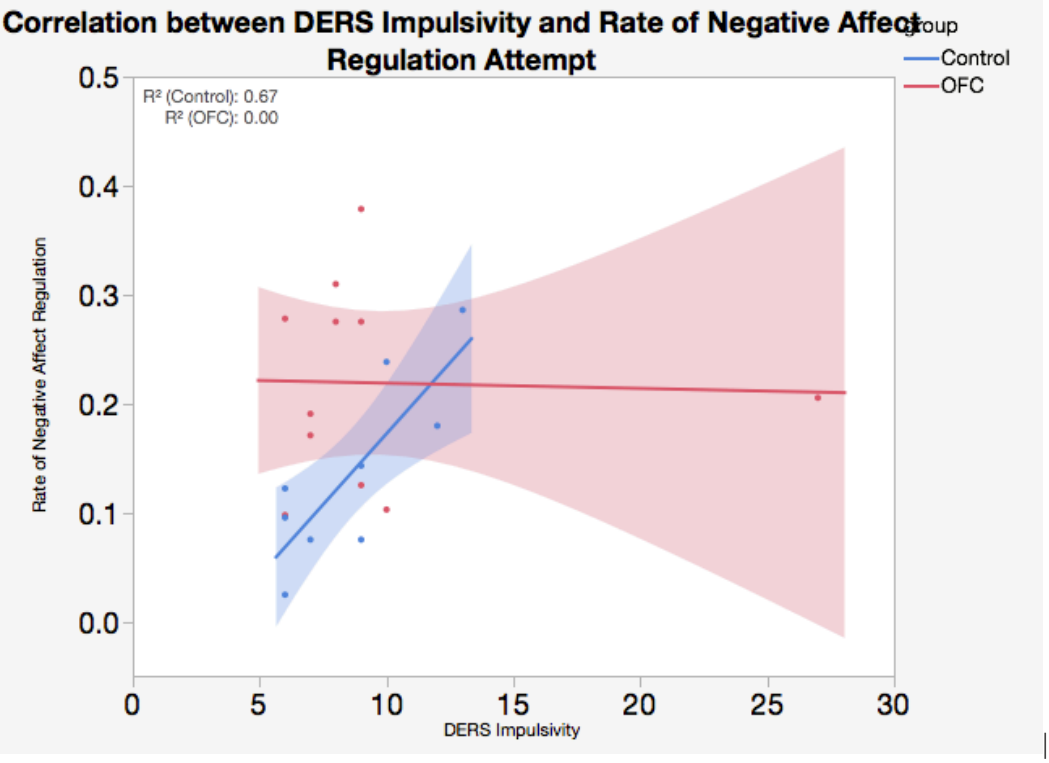
Figure 20B. Fluctuation Index for Summed Affect Rating by Lateral OFC Damage Presence

4.3.6 *Exploring Associations between Individual Differences Measures and Regulation*

The association between study participant's self-reported trait level difficulties in emotion regulation was examined in conjunction with experience sampling response of regulation strategies used and their effectiveness. It was predicted that trait level impulsivity represented by the impulsivity subscale of the DERS questionnaire would significantly predict the frequency of emotion regulation attempt. It was also predicted that greater endorsement of limited accessibility to regulation strategies would be associated with greater usage of maladaptive regulation strategies. Because control subjects did not endorse regulation attempt of positive affect, the comparative analyses were limited to negative affect regulation.

In the control group, greater difficulty with impulse control of negative affect, as measured by higher score in the DERS: impulse subscale, predicted more frequent attempt to regulate negative affect (see Figure 21), $r(7) = .82$, $p = .0069$, as well as an increased usage of reappraisal, $r(7) = .82$, $p = .0067$; suppression, $r(7) = .78$, $p = .0136$; and distraction $r(7) = .68$, $p = .0454$, but not calming, $r(7) = .45$, $p > .1$. On the other hand, ventral PFC lesion sample did not show any association between impulse control difficulty and overall regulation attempt of negative affect, $r(9) = -.03$, $p > .1$, usage of reappraisal, $r(9) = .05$, $p > .1$, calming, $r(9) = -.04$, suppression, $r(9) = .33$, $p > .1$, or distraction, $r(9) = -.23$, $p > .1$. Testing for significant differences in correlation coefficients for the two groups revealed that the two groups significantly differed in their correlation between impulse control difficulty and overall regulation attempt frequency, $z = 2.2$, $p = .0278$. Furthermore, the two groups showed significantly different correlations between impulse control difficulty and the frequency of using specific types of emotion regulation strategy for: reappraisal attempt frequency, $z = 2.05$, $p = .0404$, distraction attempt frequency, $z = 1.97$, $p = .0488$, and a trend towards a difference in correlation with suppression attempt

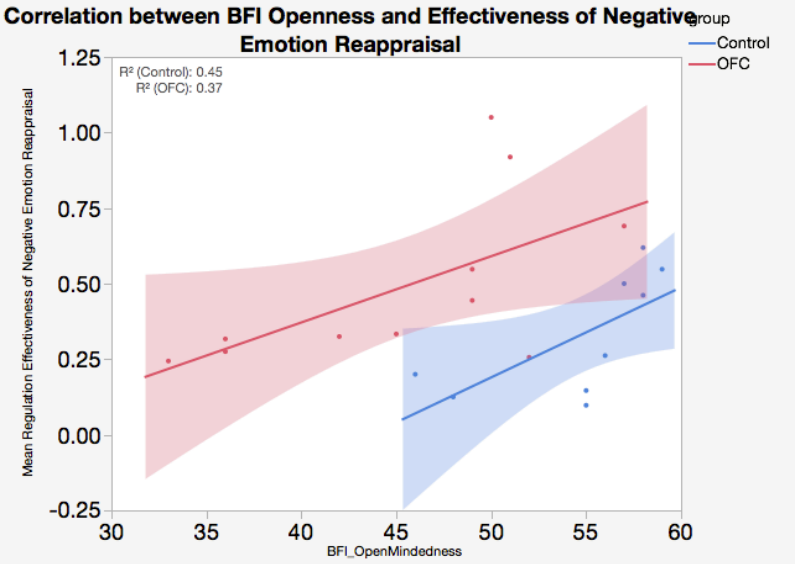
frequency, z=1.84, p=.0658, but no significant group difference in correlation with calming attempt frequency, z=.97, p>.1. Moreover, a subscale of the individual differences measure of emotion regulation difficulty, DERS that assesses perceived limited access to emotion regulation strategies predicted greater suppression and distraction regulation strategy usage in controls, but not in ventral PFC lesion sample. In the control group, greater endorsement of limited access to regulation strategies predicted higher frequency of utilizing suppression, r(7) =.70, p=.0346, as well as distraction, r(7) =.69, p=.0384 but not reappraisal or calming, r(7) =n.s., ps>.1. On the other hand, ventral PFC lesion sample did not show any association between perceived lack of access to emotion regulation strategies and frequency of using regulation strategies, all r(9) =n.s., all ps>.1.



shading indicates 95% confidence interval around the linear regression line of fit

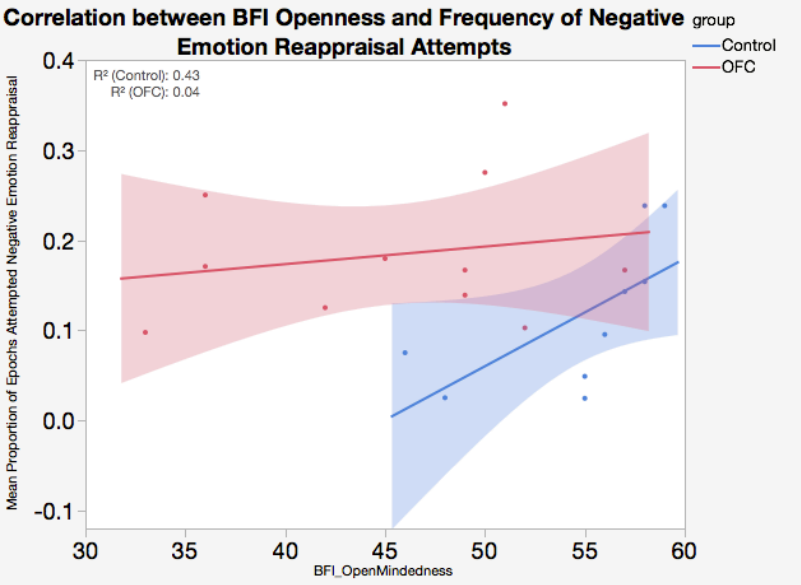
Figure 21. Association Between Emotional Impulse Control and Regulation Attempt Frequency

Because of recent research showing a robust association between the Openness factor of the Big Five personality dimensions and a measure of individual differences in ability to generate possible reappraisal scenarios: or "Reappraisal Inventiveness" (Weber, Loureiro, Martin, Westmeyer, & Geisler, 2014). A series of correlational analyses were conducted between participants NEO-FFI-3: openness subscale score and reappraisal attempt as well as effectiveness ratings of negative emotions (analyses were limited to negative emotions as none of the controls reported attempts to regulate positive affect). In both groups, greater score on the openness subscale predicted higher self-reported reappraisal effectiveness (see Figure 22A): controls, $r(7) = .61$, $p = .0466$; ventral PFC lesion patients: $r(9) = .61$, $p = .0486$. Interestingly, while healthy controls showed a trend toward a positive association between NEO-FFI-3: openness score and frequency of reappraisal attempt, $r(7) = .65$, $p = .0604$, ventral PFC lesion sample did not show any evidence of potential association between the NEO-FFI-3: openness score and the frequency of negative emotion reappraisal attempt usage, $r(9) = .47$, $p > .1$ (see Figure 22B). However, difference between the two correlation coefficients were not significantly different: $z = .49$, $p > .1$



shading indicates 95% confidence interval around the linear regression line of fit

Figure 22.A Association Between Openness and Reappraisal Effectiveness



shading indicates 95% confidence interval around the linear regression line of fit

Figure 22.B Association Between Openness and Reappraisal Attempt Frequency

4.4 Discussion

The main goal of the analyses reported in this second study was to investigate the extent to which ventral PFC damage is associated with abnormal affective experience in terms of intensity and frequency of positive and negative affect as well as aberrant periodicity or fluctuation in change of affect intensity, and to evaluate the degree to which ventral PFC lesion sample actually shows differences in real-world emotion regulation. Damage to the ventral PFC region was significantly associated with greater fluctuation in magnitude of negative affect experienced. This greater lability in negative affect was only associated with increased frequency of using distraction as a regulation strategy. This clearly contrasted with healthy controls, whose magnitude of negative affect fluctuation index was positively associated with increased frequency of usage of a diverse set of strategies (reappraisal, suppression, and distraction) as well as increased perceived effectiveness of the strategies used.

For regulation of negative affect, while the sample as a whole showed robust association between frequency of regulation attempts and degree of self-reported regulation success, there were also significant group differences in self-reported success of emotion regulation depending on the type of regulation strategies used. For example, healthy controls and ventral PFC lesion sample did not differ on perceived effectiveness of reappraisal or calming, but the ventral PFC lesion sample did endorse greater effectiveness using suppression and distraction as regulation strategies. Integrating these results with findings of individuals with ventral PFC damage experiencing greater negative affect intensity fluctuation suggest that ventral PFC damage is associated with dysregulation of normative stability of emotional experience that is distinct from difficulty with voluntary and willful emotion regulation. Indeed, correlational analysis between fluctuation index (indicator of greater epoch to epoch emotional intensity magnitude change) and self-reported effectiveness of reappraisal of negative emotions revealed that while healthy controls and amygdala lesion sample show a robust positive correlation between reappraisal effectiveness and fluctuation index, individual in the ventral PFC lesion group do not show this relationship. In other words, fluctuation in negative affect magnitude embedded in experience sampling responses from individuals with ventral PFC damage is less likely to be the product of voluntary reappraisal-based emotion regulation, which goes contrary to ventral PFC sample's self-report of intact emotion regulation effectiveness. However, there was no direct supporting evidence of trait level group differences in difficulties with emotion regulation (as shown by no significant difference in the DERS) or dispositional difficulties in appraising emotions (as shown by no significant group difference in the TAS-20).

Another possibility (that is not mutually exclusive with the previous explanation) is that there indeed was a significant group difference in effectiveness of emotion regulation, but

individuals with ventral PFC damage have poorer judgement of regulation effectiveness. Indeed, findings from functional MRI studies suggest that one of the multifarious cognitive functions subserved by the ventral PFC function is self-referential judgment (Denny, Kober, Wager, & Ochsner, 2012). Without experience-sampling of an external rater, this hypothesis is more difficult to test. It would be helpful and important to address this possibility in future studies.

Interestingly, greater difficulty with impulse control of negative emotions predicted greater attempts to regulate negative affect in controls, but not in individuals with ventral PFC damage. These results add some support to the idea that what ventral PFC may be lacking in emotion regulation may not necessarily be the effectiveness of emotion regulation per se, but the inability to deploy emotion regulation strategy appropriately when deemed helpful to do so.

It was also predicted that ventral PFC damage would be associated with greater fluctuation in affect compared to healthy controls. Consistent with this prediction, there was a greater fluctuation in negative affect intensity rating in ventral PFC lesion group. This is supportive of the idea that intact ventral PFC likely contributes to stability of affective experience, and individuals with damage to this area can experience greater dysregulation of affect as evidenced by greater fluctuation index. Interestingly, within the ventral PFC lesion sample, when the sample was further segregated into those with and without lateral OFC damage, those with damage to the lateral OFC demonstrated decreased fluctuation in positive affect but increased fluctuation in negative affect. This seems to suggest a possible divergent impact of lateral OFC in appraisal and regulation of affect depending on the valence of emotional experience. Wager et al. (2008), demonstrated that two independent networks connected by the ventrolateral PFC respectively influenced: 1) inhibition of negative emotions by down-regulating the amygdala, and 2_ generation of positive reappraisal by vlPFC's

functional connection with the nucleus accumbens and ventral striatum. Results from this study are consistent with these previous findings, and further demonstrate that the ventrolateral OFC damage is associated with increased fluctuation of negative affect.

There are a few notable limitations of the current study that must be acknowledged. First of all, conclusions drawn about the effects of ventral PFC damage did not include examination of baseline functioning of the lesion sample prior to damage to the cortical area. Specifically, it is unclear whether abnormal patterns of affect stability were present prior to these individuals incurring prefrontal damage. In other words, the possibility that abnormal affect intensity fluctuation in the ventral PFC sample measured in the current study predated the lesion cannot be ruled out. Because of this limitation, inferences regarding the effects of ventral PFC must be qualified. Importantly, findings from the rTMS study described in chapter 3 showing disruption of ventral PFC (in particular, vlPFC which was the focal region of rTMS stimulation) activity resulting in changes in affect regulation is critically complementary. Future lesion studies should further address the issue of baseline functioning by including supporting data such as structured peer ratings as well as self-reported ratings about lesion patient's baseline (i.e., pre-lesion) affective functioning. Second, even though the current study's sample size was not small considering many other published lesion studies with only single digit sample sizes, power calculations of the current study (see methods under chapter 4) revealed a potential complication of being underpowered, especially if the true effect was less than *large* (i.e., Cohen's $d < .8$). This possibly limited detection of true effects of lesion on emotion regulation. Specifically, modest per cell sample size for factorial ANOVA analyses likely contributed to underpowered ANOVA analyses. Third, the ventral PFC lesion patients had a wide range of lesion foci making any functionally-localizing inferences of emotion regulation difficult. Several patients had only

medial ventral PFC damage, whereas a few patients had both medial and lateral ventral PFC damage, which further complicated drawing conclusions about the association between lesion location and emotion regulation. Future studies, with recruitment of a larger sample size, should address the issue of the impact of lesion to specific subregions of the ventral PFC on emotion regulation. In the current project, review of over 3000 candidate cases resulted in a final yield of fewer than two dozen study-eligible ventral PFC lesion patients. Given the scarcity of eligible participants, in the future, it would be advantageous to coordinate multiple study sites executing a collaborative data collection effort for a larger sample size.

In summary, findings from this study offer additional support to the idea that damage to the ventral PFC is associated with abnormal affective experience and differences in emotion regulation patterns compared to healthy individuals. Future studies in patients with ventral frontal lobe damage may provide more detailed understanding of the role of subregions of the ventral PFC and connected regions on emotion regulation and will help us gain a more systematic understanding of the functional circuitry of emotion regulation.

CHAPTER 5

Conclusion

The main goal of this project was to test the hypothesized role that the ventral PFC plays in emotion regulation, and the degree to which disruption to ventral PFC function or structural damage to the same area is associated with emotion regulation patterns different from that of a healthy brain. The two studies described in this manuscript aimed to investigate the impact of compromised ventral PFC function by employing two complementary methods: i) effects of transient disruption of the ventrolateral PFC activity on reappraisal-based emotion regulation; ii) effects of structural damage to the ventral PFC region on day to day appraisal and regulation of real-world affective experience.

Findings from the first study demonstrated that disrupting ventrolateral PFC function resulted in significant change in positive and negative affect rating in the context of reappraisal-based regulation efforts. However, findings of differential left versus right hemisphere vlPFC disruption suggests a potentially lateralized role of the vlPFC. Physiological data (SCR) also demonstrated that disrupting the ventrolateral PFC resulted in increased physiological response to emotionally salient negative stimuli, showing convergent evidence that manipulation of vlPFC activity results in subjective experience of reappraisal effectiveness as well as objectively measureable physiological responses. Importantly, SCR data also showed evidence that left-sided disruption of vlPFC resulted in generally increased reactivity to negative visual stimuli compared to right-sided vlPFC disruption, which is consistent with behavioral data.

Results described in the second study aimed to examine the impact of ventral PFC damage on appraisal of positive and negative emotions, as well as emotion regulation patterns in

a naturalistic setting. Findings from this study provided further evidence that intact ventral PFC is critically involved in stability of positive and negative affect appraisal, as well as involved in normative patterns of effective emotion regulation. Results from this study further suggest possible differences in socioaffective experience of individuals with frontal lobe damage. Specifically, a series of analyses comparing the ventral PFC lesion sample and healthy controls demonstrated that individuals with ventral PFC damage show abnormal fluctuation in negative affect. Moreover, while healthy controls indicating greater endorsement of negative affect intensity also indicated greater utilization of a diverse set of regulation strategies, this was not the case with individuals with ventral PFC damage, who showed only higher utilization of distraction as a regulatory strategy being associated with greater level of negative affect intensity. These results together suggest that intact ventral PFC function may play a key role in maintenance of affect stability as well as adaptive utilization of various regulation strategies important in voluntary control of affective experience.

Future studies should further clarify the role of subregions of the ventral PFC, as current results also suggest the critical role that lateral OFC may play in regulating the stability of positive and negative affect. Further investigations should also address whether and how differences in appraisal and regulation of emotional experience can translate to real-world differences in functional adaptiveness (e.g., adaptive social functioning, work performance, satisfaction in long-term relationship quality).

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