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Functional and Structural Neural Effects of Emotionally Focused Therapy for Couples

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Abstract

There is increasing acknowledgement that problematic interpersonal relationships and negative emotions are key factors in the development and maintenance of various forms of psychopathology. Emotionally Focused Therapy (EFT) for couples centers on changing attachment behaviours as a means to improve distressed relationships by helping partners access underlying emotions and foster positive interactions that promote accessibility and trust. EFT is a highly effective therapeutic approach that encourages the development of adaptive emotion regulation observed in secure attachment. The development and emergence of non-invasive neuroimaging techniques, in particular functional magnetic resonance imaging (fMRI), provides a unique opportunity to investigate neural adaptations underlying successful psychotherapeutic change. Eighteen distressed couples received an average of 23 sessions of EFT, and the resulting functional and structural differences in the neural processing of threat were investigated before and after therapy using MRI methods. Female participants engaged in a stressful task in which they were confronted with the threat of electric shock, while they held their partner's hand, a stranger's hand, or were alone in the scanner. Results offered preliminary evidence that EFT can significantly impact emotional dysregulation, promote attenuation of neural threat by their partner, and result in structural change in a key region of emotion circuitry. Moreover, physiological data demonstrated that following EFT for couples, female partners were effectively soothed by their male partners, as demonstrated by decreased cortisol levels.

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Introduction

The development and emergence of non-invasive neuroimaging techniques, in particular functional magnetic resonance imaging (fMRI), has spurred a vast array of explorations into the underlying neural activity associated with innumerable physiological, behavioural, and psychological conditions. Until now, this level of insight has been unimaginable in the field of psychotherapy, where constructs and disorders are exceedingly complex, and etiology is still being determined.

Given our increasing knowledge of the human brain, a new discipline is emerging from the convergence of neuroscience and psychotherapy. With terms such as "Affective Neuroscience" (Atkinson et al., 2005) and "Interpersonal Neurobiology" (Siegel, 1999), it is easy to see that there is a clear focus on the role of emotion and relationships assumed to underlie psychopathology. These concepts merge nicely in the field of couple therapy, specifically in Emotionally Focused Therapy (EFT) for couples whose focus on attachment theory addresses both (Johnson, 1996, 2004).

Research into the benefits of couple therapy is increasingly important as its effects extend beyond resolving relationship distress. Indeed, a recent meta-analysis revealed a large correlation between depression and marital dissatisfaction (Whisman, 2001), and a recent review of the research by Dessaules, Johnson and Denton (2003) suggests that couple therapy is as effective as individual therapy for depression. This is of particular importance as the World Health Organization predicts that by 2020, depression will be responsible for the second highest rate of disability across all ages and sexes; it is already the second highest in those aged 15-44. Research has also shown that social connections and soothing behaviours promote well-being and health

(Berscheid, 2003), and that highly satisfied marriages are particularly beneficial in this respect (Coyne et al., 2001).

We therefore have a unique opportunity to investigate neural adaptations underlying psychotherapeutic change. This is important from a theoretical standpoint as a means to strengthen psychological models and theories, and it may also help distinguish effective psychotherapeutic approaches from those that are ineffective. The latter is of particular interest since there is a push, particularly in publicly funded programs, to selectively endorse and finance those psychological treatment paradigms which offer concrete, empirically validated support.

Attachment Theory

Bowlby (1969, 1982) believed that individuals have an innate, evolutionary drive to connect with others as a means to ensure safety and protection in their environment. This attachment system is known to motivate and organize our cognitions, emotions, and behaviours towards important relationships in our lives. Its main goal is to prompt care seeking under instances of threat, as a means to regulate the stress response both physiologically and emotionally. These processes begin at birth with respect to our primary caregiver, and extend into our adult lives where the focus shifts to our romantic partners (Bowlby, 1969).

This behavioural system is activated by both internal and external experiences of danger and anxiety. Once activated, individuals are prompted to seek proximity to their *attachment figure* (AF) who instils feelings of safety and security through soothing, comfort and protection (Bowlby, 1982). These attuned, caring responses by the AF provide a *safe haven* for the individual, and confer an experience of *felt security*, a sense that the world is safe (Mikulincer & Shaver, 2007). This serves to deactivate the attachment system, and permits individuals to

actively explore their environment from their AF who now serves as a *secure base* (Bowlby, 1969, 1982).

In children this secure base is provided by an attuned and caring AF who helps them to regulate their emotions and manage their arousal (Schore, 2001). As we mature into adulthood and the cortex completes its development, we acquire the ability to internalize mental representations of our responsive AF, which can be drawn on in times of distress and can preclude the need for proximity (West & Sheldon-Keller, 1994). Thus, it is the ability to regulate affect in a relationship that fosters security (Goldstein & Thau, 2004), and in this sense, attachment is also a theory of emotion regulation (Mikulincer & Shaver, 2007). Moreover, successful emotion regulation has been shown to be important in mental and physical health (Gross & Muñoz, 1995; Sapolsky, 2007), and relationship satisfaction (Murray, 2005).

In terms of the internalization of our experiences, attachment theory maintains that individuals develop *internal workings models* (IWM) of self and others, in response to repeated experiences with AFs in times of need (Bowlby, 1969, 1982). Over time, these experiences are encoded, processed and stored into memory systems. Specific events and interactions are stored as explicit memory, and IWMs are stored in implicit, unconscious memory. IWMs help organize and reflect our beliefs and perceptions of others in terms of their availability, supportiveness, and intentions, and also of ourselves in terms of our value, 'lovability' and personal competence (Bretherton & Munholland, 1999). In securely attached individuals, these are predominantly positive.

Conversely, attachment insecurity results from repeated experiences of AFs as non-responsive or unattuned to one's needs during the activation of the attachment system, and this leads to the development of IWMs that portray others as untrustworthy, inattentive, and

dangerous, and that represent the self as insignificant and inadequate (Hazan & Shaver, 1987). The absence or loss of the AF's attention contributes to the dysregulation of the psychological and physiological support provided by attachment (Sbarra & Hazan, 2008). In order to cope with the distressing emotions that arise from unmet needs and negative IWMs, and to prevent further abandonment and rejection, secondary attachment behaviours are developed. These behaviours attempt to compensate for the lost sense of felt security and represent their best approximation to regain it (Mikulincer & Shaver, 2007). Secondary attachment behaviours are typically classified as either anxious or avoidant in nature. Anxious individuals typically attempt to have their AF respond to their needs through 'hyperactivating strategies' (i.e., excessive concern for attention from partner, enmeshment), whereas avoidant individuals use 'deactivating strategies' (i.e., self-reliance, emotional inhibition and distancing from others) (Main & Hesse, 1990).

Attachment theory explains that our experiences of self and other can foster normative or dysfunctional development, promote well-being or psychopathology, and that these result from attachment security or insecurity, respectively (Bowlby 1969, 1982). Securely attached individuals report experiencing less negative affect (Simpson, 1990), and describe more trusting, happy, intimate, and friendly close relationships with others (Collins & Read, 1990; Feeney & Noller, 1990; Hazan & Shaver, 1987; Kafetsios & Nezlek, 2002; Mikulincer, 1998; Simpson, 1990) compared to insecure individuals. Conversely, strong connections between childhood adversity, insecure adult attachment and various types of psychopathology, in particular mood and anxiety disorders, have been reported in a large non-clinical population (Mickelson, Kessler & Shaver, 1997).

It is important to note that psychopathology does not necessarily arise from childhood experience. Bowlby (1969, 1982) himself acknowledges that early interactions with caregivers

are formative, but that IWMs are continually revised in light of new relationship experiences. Consistent with this notion, some researchers contend that adult attachment is strongly influenced by current relationship functioning (Kobak, 1994), and that insecure attachment may be related to psychopathology in adults because attachment needs are frustrated in their current relationship (Whiffen & Johnson, 1998).

Emotionally Focused Therapy

Emotionally Focused Therapy (EFT) is one of today's leading short-term interventions in couples' therapy (Baucom, Shoham, Mueser, Daiuto, & Stickle, 1998). It centers on changing attachment behaviours as a means to improve distressed relationships (Greenberg & Johnson, 1988; Johnson, 2004). According to EFT, marital distress stems from the way insecurely attached partners organize and make sense of their emotional experience. Specifically, it recognizes a breakdown in a couple's ability to communicate their emotions and cope with feelings of insecurity. Couples in distress are typically involved in a cycle of automatic emotional responses, linked to secondary attachment behaviours, which prompt them to behave rigidly with each other, and to view each other in a limited way (Johnson, 2004). This primarily occurs because they are absorbed in negative emotional states that have not been resolved, which means the attachment system remains activated. This leads to the development of negative interactional cycles or patterns (i.e. pursue-withdraw), and potentially compromised neural circuits. Thus, EFT aims to help the couple access underlying emotions and foster positive interactions that promote accessibility and trust between partners (Johnson, 2004).

EFT has been successfully applied to a broad range of populations, from those dealing with posttraumatic stress disorder (Greenman & Johnson, 2012; Johnson & Williams-Keeler,

1998), to couples dealing with chronic illness (Gordon-Walker, Johnson, Manion & Cloutier, 1996), childhood sexual abuse (MacIntosh & Johnson, 2008), sexual dissatisfaction (Honarparvaran, Tabrizy & Navabinejad, 2010), breast cancer (Couture-Lalande, Greenman, Naaman & Johnson, 2007), and depression (Denton, Wittenborn & Golden, 2012; Dessaulles, Johnson & Denton, 2003). EFT has also demonstrated relatively high treatment effects, and is associated with recovery rates between 70-73% (Johnson, Hunsley, Greenberg & Schindler, 1999). Moreover, EFT recovery rates in parents of chronically-ill children have been shown to be stable after two years (Clothier, Manion, Gordon-Walker & Johnson, 2001). This has been recently replicated at 3-year follow-up in couples recovering from attachment injuries (Halchuk, Makinen & Johnson, 2010). These results are particularly noteworthy in comparison to the 35% recovery in behaviourally focused interventions for couples (Jacobsen et al., 1984), which suffer from significant rates of relapse (Jacobsen & Addis, 1993).

Neurobiology of Attachment

The attachment behavioural system is complex, and requires the activity of a number of neural regions linked to pleasure and reward, emotion and its regulation, motivation, cognition, and personality (Coan, 2008, 2010).

The brain is roughly organized into three interconnected levels that increase in complexity. At the most basic level, the brainstem is responsible for coordinating vital activities such as heart rate, breathing and alertness. The limbic system is responsible for emotional processing, and includes the hypothalamus, the hippocampus, the amygdala, and several other areas nearby. Finally, the neocortex is responsible for higher functions such as sensory perception, generation of motor commands, spatial reasoning, language and conscious thought;

and includes the cortex of the four lobes (frontal, parietal, temporal and occipital), as well as the cingulate and insular gyri (Maclean, 1990).

Generally speaking, information enters our brain in such a manner that emotional cues are given primacy (LeDoux, 1996). These are processed in the limbic system, in particular in the amygdala, in a fast, automatic manner, before continuing onto the prefrontal cortex (PFC). The amygdala's role is to detect and encode emotionally relevant stimuli, as well as to learn associations between stimuli and orchestrate behavioural and physiological responses (Drevets & Raichle, 1998; LeDoux, 1996, Morris, Ohman, & Dolan, 1999; Whalen et al., 1998). The PFC plays a major role in a wide range of executive functioning processes, such as attention, working memory, cognitive control and emotion processing (Davidson & Irwin, 1999, 2003; Ochsner & Gross, 2005, 2007; Phan et al. 2002; Phelps, 2006; Phillips, Ladouceur & Drevets, 2008). It helps to translate processes that are happening outside of consciousness and bring them into awareness, and is deliberate and slower than the immediate amygdala reaction (Cozolino, 2006). These areas are integrated by the orbitofrontal cortex (OFC) (Price, Carmichael & Drevets, 1996; Stein et al. 2007), which is part of the PFC and is often considered part of the limbic system. The OFC is a key component of our ability to regulate our emotions (Miller & Cohen, 2001; Rule et al., 2002), and its location allows it to restrain impulsive amygdala activity, which permits us to make choices that are in line with our values, needs and goals. Indeed, research has shown that damage to the OFC results in compromised judgment, emotional processing, and self-control (Schwartz & Begley, 2002). Taken together, these three regions, the amygdala, OFC and other regions of the PFC, form an important neural circuit responsible for emotional processing and experience. When this circuit is balanced, people make fulfilling choices in their lives and

relationships leading to emotional and relational well-being, optimal functioning and good mental health (Fishbane, 2007).

Although interconnections in this circuit are bidirectional, they are not weighted equally, as connections from the amygdala to the PFC are stronger than the reverse (LeDoux, 1996). In the event that a cue is considered dangerous, the amygdala, which is known as "fear central" (LeDoux, 1996), signals distress, and what results is an overriding cascade of physiological and cognitive responses to manage the threat. Behaviourally, we are lead to perform fight, flight or freeze responses. At such times, the amygdala's automatic emotionally-driven systemic response can overtake healthy cortical functions, and compromise the ability of the PFC to perform rational, executive functions (Siegel & Hartzell, 2003). In this state, we are being driven by emotions without understanding them. Not surprisingly, the cost of protection from our limbic system can have significant consequences for our relationships.

Neurobiology of Relationship Distress

At the neural level, activation of the attachment system occurs in the limbic system as fear triggers amygdala activity. Without an available and attuned AF, the amygdala becomes chronically active. Moreover, attachment experiences also directly influence the wiring of the OFC to the limbic system, such that the circuit is structurally defective in insecurely attached infants which impacts long-term emotional fucntioning (Schore, 1996). Intrapersonally, this results in emotionally painful implicit memories becoming disconnected from explicit memories, and this lack of integration manifests in negative emotions and confusion (Fosha, 2003; Mikulincer & Shaver, 2007), as well as an impaired ability to self-regulate emotions (Amini et al., 1996).

Interpersonally, the activation of this system is so consuming that individuals cannot respond to others' needs in a caring an empathetic manner. Moreover, the automaticity of the amygdala's vigilance and activity means that our ability to avoid certain problematic reactions may be out of our control during times of threat; for example, anxiously attached individuals may lash out angrily at their partner, while avoidant individuals may withdraw emotionally and physically. In the realm of couple relationships, such uncontrollable, and potentially unwanted, responses may be particularly damaging, and the attachment bond itself may be compromised. Ironically, inherent in this survival process is the sense that one is acting appropriately and that their actions are justified (Atkinson et al., 2005). This is problematic for relationships as it works in stark contrast to our drive for connection, and contributes to the anguish experienced in distressed couples (Mikulincer & Shaver, 2007).

From this view, marital distress is conceptualized as resulting from a breach in the attachment system which manifests as chronic overarousal or underarousal of the nervous system. As partners can read social-emotional cues quickly, and tend to mirror each others' emotional states, secondary attachment behaviours promote disengagement, causing neural disconnection, and as a result partners cannot use each other to decrease their arousal and deactivate the attachment system. Essentially, distressed couples are unable to recover physiologically from their negative interactions (Schore, 2004).

Stress and Soothing

One of the predominant physiological stress-response systems is the hypothalamic–pituitary–adrenal (HPA) axis which is primarily moderated by the limbic system (Gunnar & Vasquez, 2006). This system is activated in response to psychological stressors (i.e. threat)

(Dickerson & Kemeny, 2004), suggesting clear links to the attachment system which is activated by the same stimulus (Mikulincer, Gillath, & Shaver, 2002). When activated, the hypothalamus releases corticotrophin releasing hormone (CRH), which stimulates the secretion of adrenocorticotropin hormone (ACTH) by the anterior pituitary, and leads to the secretion of cortisol into the blood by the adrenal glands. The effect of cortisol is to increase physiological arousal (such as heart rate and blood pressure) and attention levels in the autonomic nervous system (ANS) as the body prepares to deal with threat (Kemeny, 2003). Prolonged and frequent activation of the system, as in the case of insecure attachment, increases the risk of physical and mental health issues (Gunnar & Quevedo, 2007).

In a recent review, Diamond (2001) suggests that secure attachment to an AF can regulate HPA axis activity. Indeed, research has shown that supportive social behaviours, such as maternal soothing (Lewis & Ramsay, 1999) and touch in cardiac recovery (Weiss, 1990) can calm physiologic stress responses. The likely mechanism for this is the release of the neurotransmitters oxytocin and vasopressin which follow from positive experiences with AF and dampen HPA and ANS activity (Zeki, 2007).

This is supported by research which suggests that insecure attachment is associated with higher levels of HPA axis activation compared to secure attachment. Indeed, Carpenter & Kirkpatrick (1996) investigated physiological stress responses and the effect of partner proximity according to attachment style in 34 college women in serious relationships. Results indicated that both avoidant and anxiously attached women demonstrated higher blood pressure (systolic and diastolic) when in the presence of their partner, compared to their absence. Conversely, stress responses in securely attached women were unaffected by partner proximity. Authors believe this reflects the fact that insecure attachment impedes the ability to derive comfort from the AF,

despite a longing to be comforted and soothed, and whose presence appears to exacerbate their distress.

In another study of 124 heterosexual couples, insecurely attached individuals demonstrated increased levels of cortisol during a task invoking relationship conflict, compared to those securely attached. Moreover, the partners of insecurely attached individuals also demonstrated increased levels of cortisol compared to those with securely attached partners (Powers, Pietromonaco, Gunlicks & Sayer, 2006), suggesting that the overwhelming effects of insecurity extend beyond the individual.

Finally, women appear to be especially vulnerable to the effects of a distressed relationship compared to men. Research has shown that females' stress hormones increase when her partner withdraws angrily, and decrease when he is caring and compassionate (Goleman, 2006).

fMRI

Functional magnetic resonance imaging (fMRI) is a non-invasive neuroimaging technique that measures changes in neural activity in the human brain based on local changes in blood flow. This method was discovered by Ogawa, Lee, Kay and Tank (1990) who understood that increased neural activity in a brain area is accompanied by increased blood flow to that area to deliver the oxygen required for increased metabolism. Interestingly, they discovered that the relationship between blood flow and oxygen demand is disproportionate, as oxygen is consumed at a slower rate when blood flow increases. This leads to a relative increase in oxygenated hemoglobin in active brain regions. Although somewhat paradoxical, this curious phenomenon is stable and provides a quantifiable value known as the blood-oxygen-level-dependent (BOLD)

signal, which can be reliably used to identify neural changes associated with task performance. In particular, the greater the ratio of oxygenated to deoxygenated hemoglobin in a given region, the more intense the signal detected from that region. The BOLD effect is the basis of traditional fMRI experiments (Ogawa et al., 1990).

To generate such BOLD signals, subjects are placed inside a large magnet that exerts a powerful static magnetic field. This external field prompts protons within the nuclei of hydrogen atoms to align either in a parallel or anti-parallel orientation with the magnetic field. Subsequently, energy pulses are delivered and result in a perpendicular magnetic field that propels protons into a higher-energy state. As the protons relax, or *dephase*, back to their lower-energy state, a signal in the form of energy photons is emitted and quantified by the receiver coils in the scanner. The strength of the signal is dependent on the region in which the protons are located. In particular, protons dephase more slowly in regions with higher levels of oxygenated hemoglobin, as is the case in active cortical regions (Huettel, Song & McCarthy, 2004). fMRI has been used to investigate the myriad facets of executive functioning. With the recent advent of the "Affective Neuroscience" field, it has been recognized as an important tool to investigate clinical populations and interventions.

fMRI, Love, Couples, and Attachment Style

Several fMRI studies have examined the neural correlates of romantic love and have consistently found increased activity in dopamine-rich brain regions associated with pleasure, reward and motivation (Schultz, 2000), particularly in the caudate nucleus (CN) and the right ventral tegmental area (VTA) (Bartels & Zeki, 2000; Fisher, 2004; Aron et al., 2005). Relationships ranged from early-stage relationships where partners were intensely 'in love'

(Fisher, 2004; Aron et al., 2005), to more established relationships in which partners reported being 'truly, deeply, madly in love' (Bartels & Zeki, 2000). Interestingly, additional areas appear to be activated as relationship duration increases. These include the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) and the insula, which are implicated in emotion circuitry, and also the ventral pallidum, which is linked to attachment in prairie voles (Lim & Young, 2004). Ortigue, Bianchi-Demicheli, Patel, Frum & Lewis (2010) conducted a review of fMRI studies on various types of love (passionate, maternal and unconditional forms). Authors concluded that distinct neural networks are involved in each type, and that they are distinguished by the reward areas activated, in particular the VTA and CN are active in passionate love, whereas the periaqueductal grey matter (PAG) is involved in the other forms. It has been noted that neural areas associated with attachment and emotion become relevant as relationships establish themselves, and suggested that the CN, which has widespread afferents from the cortex, may be an appropriate region for the integration of regions involved in complex behaviour and emotion (Fisher, Aron & Brown, 2005).

Further support for the unique contribution of the CN in the attachment behavioural system, comes from a recent fMRI study on the neural correlates of grief, which Bowlby (1982) believed was an adaptive response to the phenomenon of separation anxiety and distress. In particular, Gündel, O'Connor, Littrell, Fort and Lane (2003) showed 8 bereaved women pictures of their beloved versus a stranger, and words specific to the death event or neutral words. Of particular interest was the specific activity observed in the CN when subjects looked at a picture of their deceased loved ones, which was not present with grief-eliciting words.

With respect to couples, the only fMRI study published to date examined the neural correlates of social soothing in 16 happily married couples, and how this interacts with externally

generated stress. To accomplish this, Coan, Schaefer and Davidson (2006) used fMRI to examine whether the act of holding someone's hand can attenuate the stress response evoked by threat of mild electric shock in female participants. Results indicated decreased activity in neural systems underlying emotional and behavioural threat responses when female partners held their husband's hand. Decreases were observed in the right anterior insula, superior frontal gyrus, and hypothalamus. This effect was observed to a lesser extent when holding a stranger's hand. Also, effects varied inversely with marital quality, with decreased threat-related activations associated with increased marital quality as measured by the Dyadic Adjustment Scale (Spanier, 1976).

With respect to the neural correlates of adult attachment styles, a handful of neuroimaging studies have been performed to date. In one fMRI study, researchers asked 20 healthy women to think about various relationship scenarios, and then to actively suppress this thinking (Gillath, Bunge, Shaver, Wendelken, Mikulincer, 2005). During negative scenarios (i.e., breakup, conflict), attachment anxiety was associated with increased activity in emotion-related regions, namely the anterior temporal pole and the ACC, and negatively related to regions involved in emotion regulation, namely the OFC. Thus, it appears that compared to non-anxious individuals, those with anxiety demonstrate higher levels of emotional reactivity and fail to utilize regions typically involved in suppressing emotional responsivity. Conversely, compared to non-avoidant individuals, avoidance was associated with fewer and smaller deactivations in regions that are typically observed with suppression and inhibition, in particular the subcallosal cingulate cortex (SCC) and the left medial PFC, suggesting that this ability is compromised.

Karremans and colleagues (2011) used fMRI to explore whether secure attachment could attenuate the neural activity associated with the pain of social rejection in 15 healthy participants. They used a computerized ball-tossing game (Eisenberger, Lieberman, & Williams, 2003)

designed to exclude the subject from a group, and examined whether the name of their AF could reduce the neural activity associated with exclusion observed in the lateral and medial PFC, ACC, temporal lobe and hypothalamus. Results showed that as attachment security increased, activity was less pronounced in emotion- and stress-regulation areas, and authors suggested that secure attachment protects an individual against negative social experiences, and reduces the need for emotion regulation processes.

Lemche and colleagues (2006) used fMRI to explore the neural correlates of attachment security in 12 healthy individuals. They employed a semantic priming task with stress (i.e. unpleasant attachment experiences) and neutral (i.e. nonsense statements) conditions designed to assess the working models of self and other believed to underlie attachment styles. Results showed that amygdala activity was associated exclusively with the stress condition and was positively correlated with attachment insecurity and autonomic response (as measured by a skin conductance test). Authors suggest the amygdala plays a central role in the autonomic activity, such as increased cortisol levels (Spangler & Schieche, 1998), associated with insecure attachment.

Bucheim et al. (2006) used fMRI to investigate the activation of the attachment behavioural system in 11 healthy females, as they told "attachment stories" in response to images. They classified subjects as either organized or disorganized, and found increased activations in the amygdala and hippocampus of disorganized subjects in response to distressing pictures compared to neutral ones.

Finally, Vrtička, Andersson, Grandjean, Sander and Vuilleumier (2008) used fMRI to explore how different attachment styles (i.e. secure, anxious, avoidant) influence responses to social cues. They had 16 healthy individuals perform a dot-counting task which provided

immediate accuracy feedback with happy faces denoting either angry or happy expressions, and either corresponding or non-corresponding verbal feedback. They noted differential responses to facial expressions based on attachment style; in particular, lower activation of the ventral striatum and VTA in response to happy faces in avoidant individuals, increased amygdala activation in response to angry faces in anxious individuals, and the opposite to these in secure individuals. They concluded that adult attachment shapes how individuals perceive and respond to social information.

Therefore, there are distinct neural areas that are linked to romantic love and adult attachment, as well as distinct patterns of activity noted according to relationship quality and attachment style. These results have important implications for emotional processing, regulation and stress responses.

fMRI and Affective Processing

Attachment is a complex construct that encompasses a variety of highly coordinated processes; for example: motivation, emotion generation, emotion regulation and social behaviours, such as proximity seeking. For that reason, it is speculated that numerous neural systems, collections of highly organized neurons that form a circuit within the brain, are required to support it (Coan, 2008). However, it is important to note that there is not a one-to-one correspondence between behaviours and brain regions, and therefore many processes will involve common regions. Thus, there is no simple attachment circuit in the brain, and observed neural activity depends highly on the behaviour of interest.

Motivation

As attachment processes involve motivation and goal-directed behaviour, it is conceived to be part of the dopaminergic reward system involving the VTA and nucleus accumbens (NA) (Tzschentke & Schmidt, 2000). In terms of establishing attachment bonds, the NA and VTA appear to be especially attuned to social cues, such as faces of the opposite sex (Aharon et al., 2001), and it is hypothesized that the activity of these regions prompts proximity seeking, a fundamental attachment behaviour. Moreover, the pleasure derived from this reward circuit is not only reinforcing, but is believed to promote the development of contextually explicit memories, which in turn prompt the establishment and maintenance of the attachment bonds that provide security support, comfort and regulation (Depue & Morrone-Strupinsky, 2005).

Emotion

Research has shown that the brain regions consistently associated with emotional activity are the amygdala, ACC, OFC, dorsolateral prefrontal cortex (DLPFC), insula, and ventral striatum (Phan, Wager, Taylor, & Liberzon, 2004). However, growing research suggests that parietal, temporal, occipital and subcortical activity is also commonly observed in emotional experiencing. This makes sense in light of the fact that emotions are considered to be *action tendencies* (Davidson 1993), which involve coordinated cognitive (i.e. evaluative, attentional), affective and behavioural responses, and require the activity of numerous neural areas to accomplish this.

Thus, it has been difficult for researchers to find consistent activations across studies. One reason for this is that researchers employ a number of different functional tasks to explore emotions, and tend to focus on a small subset of emotions (i.e. sadness, fear, love), making

generalization difficult. This is further complicated by the use of different strength magnetic fields and other fMRI-specific parameters (i.e. number of directions sampled, different anatomical atlases), different image pre-processing methods which introduce unique sources of sampling error, and differing neural models of emotion. Consequently, recent meta-analyses have attempted to determine more global aspects of emotional experience, such as the effects of different induction methods, the applicability of neural models of emotion, gender differences and functional patterns.

Of these, the most consistent findings support that there appear to be *affect programs*, or similar neural distributions of activity, for certain emotions (i.e. fear, disgust and anger) but not others (i.e. sadness and happiness), and there is often asymmetry observed in activity. In particular, in frontal regions the left hemisphere appears to be associated with more *approach* emotions, whereas *withdrawal* emotions are more bilateral (Murphy et al., 2003; Wager et al., 2003). Other findings of interest included that many non-limbic areas are activated with emotion, especially the basal ganglia and cerebellum, as well as parietal and temporal activity which indicate that a stimulus was emotionally arousing, but that no region is involved in all emotional tasks (Murphy et al., 2003; Phan, Wager, Taylor and Liberzon, 2002; Wager et al. 2003).

A recent study by Kober et al. (2008) explored functional patterns across 162 studies to determine 'functional groups' associated with general emotion-related activity. This *data-driven* approach was unique and important as many studies have focused on exploring areas that are activated in response to basic emotions (i.e. fear, anger, etc.), despite the fact that there is little evidence to suggest that basic psychological constructs of emotion translate to specific constructs in the brain. They identified six functional groups of interest: the 'Occipital/Visual Association

Group & Medial Posterior Group' whose activity is related to visual processing and attention to emotional stimuli; the 'Cognitive/Motor Group' whose activity is not specific to emotion, but is instead related to its component processes (cognitive, affective, perceptual and motor), as well as appraisal of affect and shaping subsequent behavioural responses; the 'Lateral Paralimbic Group' whose activity is related to motivation, in particular assessing stimuli and rewards/punishment; the 'Medial PFC Group' whose activity is related to the generation and regulation of emotion; and, the 'Core Limbic Group' which serves as an integrative emotional centre and also regulates autonomic responses.

Taken together, there appears to be support for the idea that emotion can be conceptualized in terms of action tendencies (i.e. approach-withdraw) which demonstrate some lateralization across hemispheres, and that neural areas seem to function in distinct groups/patterns to generate specific emotions.

Emotion Regulation

When individuals are confronted with stress, they are naturally compelled to manage the resulting emotional response in some capacity. This emotion regulation can take various forms, such as suppressing the response, or re-appraising the situation (Gross, 1998, 2002). Unlike suppression which focuses on decreasing expressive behaviour, reappraisal changes the course of emotional responses by reformulating the meaning of a situation, and is more adaptable as it can be used to either increase (*up-regulate*) or decrease (*down-regulate*) reactions (Goldin, McRae, Ramel, & Gross, 2008). Although research on the neural correlates of emotion regulation is relatively new, there is a general consensus that reappraisal is a key factor in maintaining our psychological and physical well-being (Gross & John, 2003; Ochsner et al., 2002), and relies on

the combination of both cognitive control functions of the PFC and emotional appraisal functions of the limbic system (Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004; Ochsner & Gross, 2005).

Research on emotion regulation has not come to a consensus on a model of functioning. Ochsner and colleagues (2009) propose that emotion regulation occurs through two main routes, either *top-down* or *bottom-up processing*. Top-down processing refers to the activity of cortical areas to regulate limbic system activity, typically through cognitive control mechanisms, whereas bottom-up processing refers to limbic areas influencing the activity of cortical regions. Typically, it is believed that psychotherapeutic interventions that focus on cognitive changes such as cognitive-behavioural therapy (CBT) work through top-down mechanisms, whereas psychoactive medications target the activity of receptors in the limbic system and work through bottom-up processes (Fuchs, 2004).

Other research has focused on the various ways in which top-down processes can regulate emotion. Eippert and colleagues (2007) used fMRI to explore the emotional regulation associated with threat-related pictures in 24 healthy female volunteers. As the PFC can exhibit both inhibitory and excitatory effects on neural circuits (Knight, Staines, Swick, & Chao 1999), they were particularly interested in which prefrontal regions are involved in up- and down-regulation. They used reappraisal strategies to stimulate the two regulation approaches, asking subjects to either engage themselves with the scenario in the case of up-regulation, or to distance themselves in the down-regulation condition. Results showed that there was significant overlap between PFC regions involved in down-regulation and up-regulation which included the dorsal ACC, DLPFC and OFC, with down-regulation showing more left hemisphere activity, and up-regulation more bilateral activity. They also noted more dorsal ACC activity in the emotional

regulation processes, and concluded that ventral ACC is more likely to be a target for emotional regulation. Similarly, Goldin et al. (2008) used fMRI in a sample of 17 healthy women to understand the neural correlates of how two different emotion regulation processes, namely reappraisal, an antecedent-focused, cognitive form of emotion regulation, and suppression, a response-focused, behavioural strategy, work to reduce the experience of negative affect (watching disgust-inducing films). Results suggest that reappraisal strategies were employed earlier in the emotion generation process, whereas suppression strategies took longer to activate. Also, reappraisal was associated with decreased amygdala and insular activity, while suppression was characterized by increased activity in these areas. Although both strategies worked to decrease negative affect, reappraisal was more effective. In addition, both strategies activated a network of prefrontal areas, in particular the DLPFC and OFC, although reappraisal was more concentrated to the left hemisphere. Other studies have also observed similar effects with reappraisal strategies (Ochsner et al., 2002, 2004; Phan et al. 2005).

Although useful, the drawback of these conceptualizations is that they do not accommodate for the fact that many emotion regulation processes occur outside of our awareness and do not reflect a conscious attempt to change thoughts and emotions. A more comprehensive model is proposed by Phillips and colleagues (2008) who believe that a better way to classify emotion regulation processes is whether they reflect voluntary or automatic actions. They suggest that automatic and voluntary processes each include behavioural control (i.e. suppressing response to stimulus), attentional control (i.e. not paying attention to the emotional stimulus) and cognitive change functions (i.e. changing beliefs or perceptions of the stimulus). Authors suggest that voluntary processes are characterized by activity in the bilateral DLPFC activity, bilateral dorsomedial prefrontal cortex (DMPFC), bilateral dorsal ACC, and that limbic activity (in

amygdala, thalamus and ventral striatum) is modulated by the OFC. Conversely, automatic processes are associated with activity in the bilateral subgenual ACC, bilateral OFC, left rostral ACC, bilateral DMPFC, midline/dorsal ACC as well as the hippocampus and parahippocampus. Moreover, voluntary and automatic functions may act concurrently, and each can have adaptive or maladaptive benefits (Mauss et al., 2007).

Linking back to attachment it seems that IWMs, particularly negative ones, would be classified as automatic emotion regulation processes occurring outside awareness. However, distressed partners would also have explicit memories of their partner's unavailability and lack of responsiveness, and may also use conscious means to regulate distress. In all likelihood, both conscious and unconscious processes are present.

fMRI and Psychotherapy

Difficulties with emotion regulation are believed to be a major contributing factor to the development and maintenance of mood and anxiety disorders (Campbell-Sills & Barlow, 2007). With respect to unipolar depression, known neural effects include increased, prolonged amygdala activity (Drevets, 1999), particularly with respect to emotional processing (Siegle, Steinhauer, Thase, Stenger, & Carter, 2002), and decreased executive functioning, particularly in the DLPFC (Davidson, Jackson & Kalin, 2000; Drevets, 1999; Harvey et al., 2005). In addition, it is hypothesized that these areas form a network, where executive control is required for emotion regulation, and works to inhibit limbic system activity. From this perspective, decreased DLPFC function may result in amygdala overactivity (Davidson, 2001; Drevets & Raichle, 1998; Ochsner et al., 2002, 2004). These results appear to parallel regions implicated in relationship distress.

Several studies have examined the neural effects of psychotherapy in clinical populations. Symptom provocation techniques have been used to examine brain responses to stimuli before and after therapy to examine neural effects associated with treatment, primarily cognitive-behavioural therapy (CBT) or pharmacotherapy. With fMRI and positron emission tomography (PET), treatment effects for obsessive-compulsive disorder (OCD) (Baxter et al., 1992; Breiter et al., 1996; Nakao et al., 2005; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996), social phobia (Furmark et al., 2002), simple phobias (Paquette et al., 2003; Straube, Glauer, Dilger, Mentzel, & Miltner,, 2006) and major depression (Beauregard et al. 1998; Brody et al., 2001; Martin, Martin, Rai, Richardson, & Royall, 2001; Goldapple et al., 2004) have been investigated. Overall, results tend to show decreases in dysfunctional patterns of emotion reactivity and regulation post-therapy, although there are specific effects noted for particular disorders. For example, CBT and pharmacotherapy both resulted in decreased activity in the CN in OCD (Baxter et al., 1992; Schwartz et al., 1996), and decreased limbic activity in specific phobias (Paquette et al., 2003; Straube et al., 2006). However, differential effects are observed in depression depending on the treatment approach used. For example, pharmacotherapy appears to encourage increased PFC and decreased limbic activity (Mayberg, 2002), whereas CBT leads to decreased PFC, due to reported decreases in rumination and maladaptive memories, and increased limbic activity in response to emotional stimuli (Goldapple et al., 2003). As mentioned before, results appear consistent with the idea that psychotherapy is linked to top-down processing, and pharmacotherapy is linked to more bottom-up processes.

Fuchs (2004) suggests that psychotherapy works by changing both explicit and implicit memory systems. Explicit memory is linked to experiences that are available for recall, and its activity is linked to the hippocampus and the temporal lobe, whereas implicit memory is based

on automatic behaviours and tendencies, reflect IWMs, and is linked to activity in the basal ganglia, cerebellum and amygdala. Of the two, implicit memory is an especially important target in psychotherapy as it encompasses many instincts, beliefs and habits that are based on negative interactions with others, work outside of awareness, and impact secondary attachment behaviours (i.e. dysfunctional bonding patterns and dysfunctional emotion regulation). Fuchs contends that 'insight-based' approaches, such as CBT, target explicit memory systems and will have effects on cortical and hippocampal structures, with limited effects on the limbic system. However, as EFT provides new emotional experiences of the partner, in addition to encouraging insight into maladaptive patterns, changes to both the cortical and limbic systems are hypothesized to occur.

Structural Changes

In addition to the neurophysiological changes that occur after psychotherapy, there has also been a demand to focus on related structural changes. Advances in neuroscience have shown that re-structuring of neural circuits occurs across the lifespan and results from new personal experience (Björklund & Lindvall, 2000). This 'neuroplasticity' is understood to underlie all enduring changes in the brain, and has recently become a major interest to the field of psychology (Cozolino, 2006). It is believed that in order for psychotherapy to produce lasting effects, key regions in cortico-limbic circuitry associated with emotion generation and regulation, must be restructured (Fuchs, 2004).

Structural change can be explored with a technique known as voxel-based morphometry (VBM), which is a technique used to examine gray and white matter (GM and WM, respectively) differences in structural MRI images (Ashburner & Friston, 2000). To date, VBM

has been most frequently used to characterize GM and WM abnormalities associated with psychopathology, including schizophrenia (Schlösser et al., 2007; Witthaus et al., 2008), bipolar disorder (López-Larson, DelBello, Zimmerman, Schwiers, Strakowski, 2002; Strakowski et al. 1999), OCD (Radua & Mataix-Cols, 2009), generalized anxiety disorder (De Bellis et al., 2000), post-traumatic stress disorder (PTSD) (Chen et al., 2006; Villarreal et al., 2002), and depression (Alexopoulos et al., 2008; Frodl et al., 2002).

Recently, there has been increasing interest in applying VBM to explore treatment based changes, and there is increasing evidence for macroscopic neural changes following psychological and behavioural therapy for a number of disorders. de Lange and colleagues (2008) found that decreases in GM volume in the PFC, corresponding to cerebral atrophy, were reversed in patients with chronic fatigue syndrome following CBT treatment. Castro-Fornieles and colleagues (2009) noted increased GM volumes in posterior cortical regions in adolescent patients with anorexia nervosa following admission to an Eating Disorders Program. Gauthier and colleagues (2008) revealed increases in GM volume in motor and sensory areas in stroke patients following motor therapy.

Although interest has tended to focus on examining changes in cortical GM, which reflects an increased number of neurons, in response to new learning, there is emerging evidence that changes are accompanied by WM alterations, corresponding to increased numbers of axonal connections and supporting cells connecting neural regions. In a seminal study on neuroplasticity, Draganski and colleagues (2004) used VBM to show increased GM volume in cortical areas after subjects mastered the skill of juggling, but neglected to explore WM changes. It was not until Scholz, Klein, Behrens and Johansen-Berg, (2009) re-performed the study that

WM changes were also detected, and structural changes to GM and WM were recognized as interdependent processes.

Present Study

To date, of the handful of studies that have examined the effects of psychotherapy, none have examined the neural correlates of EFT for couples. This is unsurprising given the early stages of this type of study, but is important as EFT has been shown to be one of the most effective forms of psychotherapy in terms of recovery and relapse rates. There is also a general lack of research investigating structural changes following psychotherapy, and further research is required.

Thus, the purpose of this longitudinal study is two-fold. It aims to uncover the neural changes in both functional activity and structure of key regions involved in attachment and emotion, following EFT for couples using functional and structural MRI. It will focus on the emotion regulation aspects of the attachment bond, in particular the ability of handholding to attenuate neural responses associated with threat, by investigating three handholding conditions (Partner, Stranger and Alone). Outcome measures will include measures of relationship satisfaction and trust, strength of attachment bond, salivary cortisol levels, neuronal activity, levels of anxiety and pleasantness associated with fMRI task conditions, and structural MRI images.

It is hypothesized that:

1) Psychological intervention using EFT for distressed couples will result in changes in neural activity in several regions of interest (ROI) in emotion circuits from pre- to post-therapy.

These changes will be most pronounced in the Partner handholding condition, and least apparent in the Alone condition. Moreover, these changes will correlate with measures of relationship outcome and cortisol levels, with greater changes associated with increased levels of relationship satisfaction and trust, and decreased levels of attachment anxiety and avoidance, and salivary cortisol. Following therapy, decreased neural activity is expected in cortico-limbic structures associated with distress, negative emotion and threat, as well as IWMs, namely the amygdala, hippocampus, parahippocampus, basal ganglia, thalamus and insula; and increased activity is expected in structures related to emotion regulation and processing, specifically the OFC, ACC, PCC, and DLPFC. In addition, following therapy the Partner handholding condition will serve to effectively attenuate neural response to threat compared to the Stranger and Alone conditions.

2) Psychological intervention will manifest in structural brain changes in terms of GM and WM volumes in the neural regions associated with emotion processing and regulation.

Methods

Participants

Recruitment focused on distressed heterosexual couples in the Ottawa region. The following methods were used to obtain participants: posters in the university, community centers and agencies; media advertisements in local magazines and newspapers; and, referrals from the Centre for Psychological Services (CPS) and the Ottawa Couple and Family Institute (OCFI). Eligible couples received 20 free sessions of Emotion Focused Therapy (EFT).

To be eligible, female participants had to be between 25 and 55 years of age, to ensure the complete development of the PFC, and to avoid the potentially confounding effects of

cerebral atrophy, respectively. Couples had to characterize their relationship as being mildly to moderately distressed, and confirm their commitment to it, measured by the Dyadic Adjustment Scale (DAS; Spanier, 1976). The relationship also had to be established and exclusive (i.e. living together for at least one year).

Couples were excluded from the study if either partner reported: receiving current psychotherapeutic treatment, or anticipated doing so in the next 5 months; history of sexual abuse; history of sexual or physical abuse in the relationship; previous diagnosis of a psychotic disorder, or were taking medication to treat such a disorder; and meeting criteria for current drug or alcohol dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994), or consuming more than 14 drinks per week. Seizures, diabetes requiring insulin treatment, heart attack, stroke, blood clots, high blood pressure, and chronic pain also indicated exclusion.

Additional exclusion criteria that would have precluded fMRI participation applied to female partners who underwent the scanning. In particular, females with significant back problems or past accounts of claustrophobia, which would have prevented lying comfortably and still in the scanner for an extended period of time, were excluded. Females who were pregnant or nursing were also excluded. Likewise, anyone with mechanically activated or metal implants, permanent retainers, piercing(s) that could not be removed, or electrical implants were excluded. Finally, failure to meet any required inclusion criteria or refusal to complete any research or therapy components resulted in exclusion.

Measures

The Dyadic Adjustment Scale (DAS). The DAS (Spanier, 1976) is a 32-item self-report rating scale designed to measure the quality of adjustment between married or cohabiting couples. It is currently considered the instrument of choice for the assessment of relationship adjustment. The scale yields a total adjustment score, as well as scores on four subscales: Satisfaction, Consensus, Cohesion, and Affectional Expression. Using Cronbach's Coefficient Alpha (Cronbach, 1960), internal consistency for the total measure was determined to be .96 for the total scale, and high degrees of internal consistency were found for all four subscales (Cronbach's alphas ranged from .73- .94) (Spanier, 1976). In terms of convergent validity, scores on the DAS are highly correlated with partners' scores on the Locke Wallace Marital Adjustment Scale (Spanier, 1976).

The DAS is scored by summing the weights of each fixed response, and has a theoretical range of 0-151. Lower scores indicate more distress and lower adjustment. Mean total scale scores of 114.8 are indicative of happily married couples and 70.7 for divorced couples (Spanier, 1976). Clinically, it has been established that scores lower than 97 indicate marital distress, with scores lower than 80 indicating severe distress, thus a range of 80-95 is considered to represent mild to moderate distress (Jacobson, Schmaling & Holtzworth–Munroe, 1987).

Relationship Trust Scale (RTS). The RTS (Holmes, Boon, & Adams, 1990) is a 30-item self-report inventory designed to assess interpersonal trust in married or cohabiting couples. This scale consists of five subscales: Responsiveness, Dependability-Reliability, Faith in Partner's Caring, Conflict Efficacy, and Dependency Concerns. Reliability for this scale has been determined to be .89, which was established for the total scale using Cronbach's Coefficient Alpha. In addition, high levels of internal consistency have been found for each of the subscales;

Responsiveness (.89), Dependability-Reliability (.83), Faith in Partner's Caring (.84), Conflict Efficacy (.84), Dependency Concerns (.83) (Holmes et al., 1990). In terms of discriminate validity, the RTS has been shown to correlate negatively with measures of self-disclosure, anger, and ambivalence (Holmes et al., 1990).

To obtain a score for this scale, individuals are asked to respond to the 30 items on a 7-point Likert scale ranging from "Strongly Disagree" (1) to "Strongly Agree" (7). The theoretical range of scores is 30-210. Subscales are summed to provide an overall score. High scores indicate a stronger presence of trust between partners.

Experiences in Close Relationships (ECR). The ECR (Brennan, Clark & Shaver, 1998) is a 36-item measure of adult attachment comprised of two 18-item self-report scales: attachment anxiety and avoidance. Internal consistency was determined for both subscales using Cronbach's Coefficient Alpha (Cronbach, 1960). Reliability coefficients for the avoidance and anxiety scales were .94 and .91, respectively (Brennan et al., 1998). In terms of convergent validity, the ECR has been shown to correlate highly with other measures of attachment security, namely the Relationship Questionnaire (RQ) (correlations ranging from -.29 to -.70) (Griffin & Bartholomew, 1994).

To obtain a score for this scale, individuals are asked to respond to the 36 items on a 7-point Likert scale ranging from "Disagree Strongly" (1) to "Agree Strongly" (5). Items 3, 15, 19, 22, 25, 27, 29, 31, 33, and 35 are recoded. The two scales are individually summed with a total score ranging from 18 to 126; odd numbers create the avoidance score, and even numbers create the anxiety score. High scores indicate avoidance and anxiety. For this study, questions were slightly modified as original question stems did not inquire specifically about one's current

partner. Question stems were changed accordingly, with permission from P.R. Shaver, who attested that this would not jeopardize the scale's utility.

The Self-Assessment Manikin Scales. The SAM scales (Bradley & Lang, 1994) are nonverbal, pictoral assessments that directly measure an individual's affective reaction to stimuli. In this experiment, SAM assessed the degree of pleasantness and anxiety. Participants were given one rating along a 5-point scale for each dimension. For the pleasure dimension, SAM ranges from a smiling, happy figure (5), to a frowning, unhappy figure (1). The anxiety dimension ranges from an extremely agitated figure (5), to a relaxed, sleepy figure (1). SAM has been used effectively to measure emotional responses in a variety of situations, including reactions to painful stimuli (McNeil & Brunetti, 1992). Correlations between the SAM and longer, verbally based rating methods of experienced pleasure and felt arousal have been high, at .96 and .94, respectively.

All measures were self-report and were administered by a graduate level student at the Emotionally Focused Couple Research Laboratory at the University of Ottawa. Moreover, the order of measures was counterbalanced, except for the SAM ratings.

Materials

Imaging Protocol. All imaging was performed using a 1.5 Tesla Siemens Magnetom Symphony MR scanner. Participants laid supine with their head secured in a standard head holder. A conventional T1-weighted spin echo localizer was acquired to confirm that the anterior commissure–posterior commissure (AC–PC) line in the sagittal view was at right angles to the slice select gradient. Structural MRI and whole brain echo planar fMRI based on the BOLD effect was performed using a gradient echo pulse sequence: TR/TE 2000/30 ms, flip angle 90º, FOV 288mm, 64x64 matrix, slice thickness 4.5 mm, 26 transverse slices, bandwidth 2.5 kHz.

Hand-holding Task. To study brain activations associated with neural threat response, and its attenuation, a replication of the fMRI task by Coan and colleagues (2006) was used. Female partners were fitted with two Ag-AgCl shock electrodes on their left ankle, along with a birdcage head piece with a mounted mirror so they could observe a screen positioned at their feet upon which task stimuli were presented.

The event-related design procedure involved presentation of 12 threat and 12 safety cues in random order across three conditions. Cues were randomized within subjects, and conditions counterbalanced between subjects. Conditions consisted of one trial where the female partner was alone in the scanner, another with her right hand holding an anonymous experimenter's right hand, and lastly, her right hand holding her partner's right hand. These conditions were counterbalanced for each participant but remained constant for the second imaging session.

All task stimuli appeared on a black background. Threat cues appeared as a red 'X' indicating that there was a 20% chance of receiving an electric shock, whereas safety cues appeared as a blue 'O' indicating no chance of shock. Participants received 2 electric shocks per condition, delivered using an isolated physiological stimulator (Coulbourn Instruments, Allentown, PA) at 2mA with 20ms duration. The task was programmed and run by the *e-prime*^{TM} application system which is widely used in fMRI experiments requiring complex timing.

With respect to the experimental design, trials began with a 1-s threat or safety cue, followed by a 4- to 10-s anticipation period where the cue was replaced by a white fixation cross, a 1-s end cue (a small white circle) marking the end of the trial, and a 4- to 10-s rest period (blank screen). Following each condition, subjects were asked to rate feelings of pleasantness and anxiety on the SAM scales (Bradley & Lang, 1994). This was administered verbally over the

intercom system in the scanner, and at the same time it was confirmed that subjects received shocks.

Schunck and colleagues (2008) used a threat paradigm similar to Coan et al. (2006), and evaluated the test-retest reliability of the task in healthy volunteers in terms of the reproducibility of anticipatory anxiety. The importance of evaluating the task was due to the fact that prior research had shown there to be a decrease in activity over time in salient neural areas linked to fear (i.e. amygdala, cingulate gyrus) during emotionally-laden tasks (Büchel & Dolan, 2000; LaBar, LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Phan, Liberzon, Welsh, Britton, & Taylor, 2003). Authors found that the task elicited moderately intense anticipatory anxiety based on clinical scales and self-rated apprehension. They also noted no habituation to the threat stimuli across 2 separate sessions, which were conducted 10 days apart. Using interclass correlation coefficient (ICC) of percent signal change, a standard measure of reproducibility for fMRI results, authors found that threat stimuli were associated with reliable functional activity in the DLPFC, inferior frontal gyrus (IFG), OFC, premotor areas, insula, lentiform nucleus, temporal pole, visual cortex and ACC. Of note, they did not observe physiological changes in the autonomic system, but were unsurprised given the moderate level of anxiety reported. Authors concluded that their study offered support that a functional marker can be both sensitive and reliable. Therefore, this task seemed appropriate to study the treatment effect of EFT for couples on brain activity and neural circuits.

Cortisol Sampling. To quantify changes in stress levels before and after therapy, cortisol samples were collected from both partners prior to and following the fMRI task. Participants placed a cotton ball under their tongue, or at the side of their mouths, for 1 to 2 minutes. Once saturated, the cotton was removed and placed in a plastic test tube (*Salivette* ™). Saliva samples

were transported from St. Joseph's MRI clinic, in an insulated cooler with ice to the neuroscience laboratory at the University of Ottawa, and stored in a -80°C laboratory freezer until ready to be tested. Salivary cortisol assays were conducted with the ImmuChem Cortisol ^{125}I Kit (MP Biomedicals, Orangeburg, NY). Sensitivity of this kit for salivary cortisol is 0.02 µg/dL, and inter- and intra-assay coefficients of variation range from 7.6 to 9.3% and 6.1 to 8.9% (low to high doses), respectively.

Cortisol levels naturally vary throughout the day, with levels peaking in the morning shortly after awakening and decreasing through afternoon and evening. Therefore, experimental samples were collected in the afternoon to help control for variance. In addition, to ensure that couples demonstrated normative cortisol patterns, baseline cortisol was sampled based on the procedure outlined by Cunningham-Bussel and colleagues (2009); four samples were collected on a normative, non-testing day, at the following time points: upon awakening (WU), 30 min after awakening (WU+30), at noon and at 5 pm. Partners were asked to refrain from brushing teeth, chewing gum, eating, drinking and smoking the hour before each sample collection; this was verbally verified at testing sessions.

As suggested by Pruessner, Kirschbaum, Meinlschmid and Hellhammer (2003), the repeated baseline measurements were converted into an 'Area Under the Curve' (AUC) Score to both simplify the statistical analysis, and increase its power by limiting comparisons. This was achieved using the two recommended, standardized formulas for AUC, based on the trapezoid method; namely 'area under the curve with respect to ground' (AUC_G) and 'area under the curve with respect to increase' (AUC_I). The AUC_G is used to examine any changes occurring with time, whereas the AUC_I is used to examine the overall intensity of the response.

Procedure

When participants arrived at the clinic, couples completed an MRI compatibility questionnaire which was reviewed by the MRI technician on site. Despite having verbally screened for MRI exclusion criteria over the phone, this was a precautionary measure to ensure that no aspects were overlooked before removing all ferromagnetic objects and entering the scanner. After eligibility of both partners was ensured, two cortisol samples were taken from each participant. Following this, the fMRI task was explained in detail to the participants and any questions were answered.

Once in the scanning room, female participants were provided with ear protection (i.e. ear plugs and head phones) and an emergency call bell, and positioned into the head coil. Electrodes were applied to the left ankle, the mirror on the birdcage was adjusted so that the projection screen was properly situated in their field of vision, and any further adjustments were made to ensure physical comfort. Participants were informed that they would communicate through the intercom in the head coil, and assured that they could ring the emergency bell in the event of a problem. Male participants remained in the waiting room until the fMRI task began, at which point they were escorted by the experimental, or stranger, handholder into the scanning room. Male participants were also provided with ear protection (i.e. ear plugs).

The study began with the acquisition of a series of anatomical T1 weighted structural MRI images. The subject was instructed to lie still and to relax for this portion of the experiment. Once this was complete, the subject was informed over the intercom that the task would begin, and instructed to keep their eyes open the entire time. At this point, the male partner and the experimenter entered the magnet room, and all lights were turned off so that the task images could be seen on the projector screen. A series of instructions appeared for the subject to review

the task; subjects had button response pads that permitted scrolling through the instructions at their own pace. The order of the handholding conditions was revealed one at a time to subjects in the task directions that preceded each condition. Once instructions were completed, the scanner triggered the *e-prime*^{TM} software to begin the task. Subjects observed 24 cues per condition. At the end of each condition, the female participant was asked to verbally report her SAM scale ratings of pleasantness and anxiety which were recorded manually. The subsequent two conditions proceeded in the same manner.

Once the fMRI task was completed, the female participant exited the scanner, and the final two cortisol samples were collected from both partners. Cortisol samples were drawn in duplicates for quality assurance purposes (i.e. low volume, contamination, etc.). Any additional questions the couple had were answered at this time. Lastly, participants were informed that a radiologist would examine the structural brain images, and in the event that an abnormality was detected, would contact the family doctor of the female participant to inform them, who in turn would inform the participant; female participants provided this contact information during their first visit to the clinic.

These procedures were performed again following EFT sessions. Similarly, all data cleaning and fMRI data post-processing was performed for both the pre-therapy and post-therapy imaging sessions.

Data Cleaning

Outcome data, in particular the self-report questionnaires and cortisol levels, was entered into a Statistical Package for the Social Sciences (SPSS) spreadsheet, and data was cleaned according to standard procedures outlined by Tabachnick and Fidell (2001). To start, possible

data entry errors were investigated by running descriptive statistics for each variable, and output frequencies and histograms were visually inspected for each individual. This helped determine whether or not any missing value codes were improperly input into the computer syntax. It also helped detect any out of range values, by allowing comparison of the actual versus intended range values from the methods section.

Next, a Missing Values Analysis (MVA) was performed on the questionnaire data and cortisol data, and demonstrated that approximately 3% of the data was missing; when less than 5% of the data is missing, this suggests a random pattern and permits expectation maximization (EM) to be performed. EM is a technique which entails the formation of a missing data correlation matrix in order to estimate the shape of the distribution for the partially missing data, and then bases inferences about the missing values under that distribution (Tabachnick & Fidell, 2001). EM was used accordingly to calculate estimated means for missing values.

Following this, univariate and multivariate outliers were identified. For the univariate outliers, this was achieved by transforming data into standardized z-scores, running a frequency analysis to show the degree of skewness and kurtosis for each variable, and generating histograms to visually identify outliers within range. Any cases with *z*-scores greater than ±2.58 were deemed univariate outliers (Tabachnick & Fidell, 2007). For the questionnaire data, there were no univariate outliers. The cortisol data revealed 12 univariate outliers across scores for 3 subjects. Outlying scores were adjusted so that they continued to be the most extreme score in the dataset, but so that the discrepancy was reduced. This adjustment eliminated significantly skewed data (no results exceed ±2.58 (*z* score, $p = .01$), and no transformations were required to obtain a normal distribution. There were no multivariate outliers, identified through the inspection of the residuals plot, for the questionnaire and cortisol data ($p<0.001$).

Finally, the assumptions underlying use of statistical tests, namely t-tests, ANOVA and Pearson's r, were verified. These included: normality, homogeneity of variance, and linearity, as well as an absence of multicollinearity, singularity and sphericity (Tabachnick & Fidell, 2001). The normality of variables was examined using normal probability plots to identify any violations to test assumptions. The assumption of normality was checked for each variable, and was found to be true; skewness scores for variables were divided by the standard error of skewness for the corresponding variable, and no results exceeded ±2.58 (*z* score, $p = .01$).

Statistical analyses involved: paired samples t-tests to explore changes to cortisol secretion and questionnaire data (DAS, RTS, ECR), and repeated measures ANOVA for SAM ratings.

fMRI Pre-processing

In BOLD fMRI, small yet meaningful changes in brain activity are concealed within highly variable measurements (Huettel et al., 2004). For this reason, the collected images underwent extensive pre-processing before they were used for analysis to eliminate any systematic variation before the statistical modelling occurred. From the outset, data files from the scanner for each participant were converted from their native DICOM format, into a format that was compatible with the Statistical Parametric Mapping (SPM) software program. This was performed for each participant's structural and functional images. Of note, all images were visually inspected to ensure that data was valid.

Next, in order to correct for head movements in the scanner, which can be a major source of noise in the fMRI data and ultimately obscure results, the images were realigned (Ashburner & Friston, 1997). By applying a range of standard test transformations, consisting of planar

translations and rotations, the transformation that yielded the minimum difference in magnitude between the paired images was selected as the optimal correction for the subject movement. This involved setting the first image as the reference image, to which all subsequent slices were aligned. Afterwards, the images were resliced so that they matched the reference image voxel-by-voxel. Finally, a structural image for each subject was used as a reference image to co-register all the functional images to a unifying, stationary template. No large movements of the head appeared to occur (>1.5 mm translation), and therefore no motion regressors were included in further analyses (Huettel et al., 2004).

Due to the human brain's remarkable variability in its morphology, images were normalized to compensate for these shape differences. This was achieved by normalizing data into a common space (using the EPI template supplied by the Montreal Neurologic Institute (MNI)), and permitted the combination of data across individuals (Huettel et al., 2004). Finally, images were smoothed with a 10 mm Gaussian kernel full-width at half maximum in order to eliminate noise interference in the data. By smoothing the images, the signal-to-noise ratio and the resolution of each image was balanced to optimal levels. This step also ensured that there was inter-voxel dependence in the fMRI data, an important assumption for statistical corrections (Huettel et al., 2004). All four of these pre-processing steps were performed using SPM8 (Statistical Parametric Mapping) software (Wellcome Trust Centre for Neuroimaging, University College of London) running under the MATLAB environment (Mathworks, Inc.), which is used to organize and interpret functional neuroimaging data.

At this point, it is generally accepted that potential noise and artefacts in the data have been eliminated, and that the data has been primed to maximize the sensitivity of later analyses (Smith, 2004).

fMRI Analyses

Before describing the types of analyses that were performed, it is worthwhile to explain the difference between *fixed effects* and *random effects* models. Both models can be used to explore treatment effects, but they differ in the way that they accommodate for variability in the sample. A fixed effects analysis assumes that subjects do not differ to any considerable extent from each other, and therefore only explores one source of variability, from the subjects themselves (within); accordingly, inferences can only be made about the sample itself. Conversely, a random effects analysis assumes that subjects do differ in important ways from each other, and therefore partitions variability both within and between subjects, allowing inferences to be made about the population from which the sample was drawn. The benefits of a fixed effects analysis, is that they are more powerful because there are as many degrees of freedom as functional images per subject, whereas a random effects analysis only has as many degrees of freedom as subjects and is therefore more stringent. In neuroimaging studies, both models are typically used. A first-level fixed effects analysis is performed to explore results for each subject, and a second-level random effects analysis is subsequently performed to explore between subject and group differences (Penny & Holmes, 2003).

Another important form of analysis frequently used in neuroimaging studies is the region of interest (ROI) analysis, which focuses on examining BOLD signal for particular neural regions. Researchers often choose to use an ROI analysis to further explore their data following a whole brain analysis to get more details of the pattern of activation being observed. This is sometimes exploratory in nature, but more often than not, analyses are based on a set of regions that have been identified *a priori* from the literature as relevant and important (Poldrack, 2007).

Fixed effects

To assess effects of the threat task on females' brain activity when alone in the scanner, a fixed effects analysis was performed. Specifically, the neural response associated with viewing the safety stimulus was subtracted from the activity associated with the threat stimulus. The ROIs chosen were focused on those originally outlined by Coan et al. (2006), as well as frequently activated regions associated with normative threat responding (Schunck et al., 2008; Sinha et al., 2004; Wager et al., 2003), yielding a total of 17 regions, namely the OFC, DLPFC, DMPFC, IFG, precentral gyrus, supplementary motor area (SMA), ACC, PCC, insula, precuneus, superior parietal lobe, superior temporal gyrus, amygdala, hippocampus, parahippocampus, basal ganglia, and thalamus.

To determine the extent that voxels were activated in our subjects, individual analyses were performed to generate statistical maps, or contrast images, that show where each brain was activated in response to the threat stimulus. This was achieved using a standard univariate general linear model (GLM) analysis to independently explore the time series for each voxel. As the timings of stimulus presentations differed across and within conditions, an event-related approach was used to define timings. In fMRI research, there are two commonly used designs, event-related and block designs. Event-related designs vary the presentation and timing of experimental conditions of interest, whereas block designs present conditions continually for set periods of time. Event-related designs permit more accurate temporal and spatial resolution of the BOLD signal in the brain, as compared to block designs, which is especially important when investigating tasks which depend highly on novelty (such as threat tasks) (Josephs, Turner & Friston, 1997). Original regions of interest (ROI) in the Coan article (2006) were converted from Talairach coordinate space to MNI space, and ROIs were labelled using the Automated

Anatomical Labeling (AAL) software (Tzourio-Mazoyer et al., 2002). To discover how our population of distressed couples changed their neural threat response across time, these ROIs were examined before and after EFT at the $p = .001$ significance level (uncorrected), with a cluster-wise correction at $p_{FWE} = .05$, and only included those clusters with more than 10 significantly activated voxels.

Random effects

To assess neural effects of therapy and handholding condition on brain activity, a random effects analysis was performed. This involved using the contrast images of the threat minus safety stimuli for each subject from the fixed effects analysis into the appropriate statistical model. To evaluate the hypothesized main effects of time and condition, as well as their interactions, a 2 x 3 repeated-measures ANOVA was warranted. However, due to limitations in the SPM8 models for repeated measures, a few accommodations were necessary to ensure that correct error terms were applied. To examine the main effect of time, an average image for pre- and post-therapy times were created by averaging the 3 conditions, and a paired t-test was used with DAS and cortisol as covariates. Similarly, to assess the main effect of condition, an average image for all 3 conditions for each subject was created by averaging across time, and a 1-way ANOVA was performed with subject and condition factors along with DAS and cortisol. Finally, a 2x3 repeated measures flexible factorial was conducted at the whole brain level to explore hypothesized interactions ('main effects') between time and condition, with DAS and cortisol as covariates. To control for multiple comparisons, a family-wise error (FWE) rate of 0.05 was used for all results, and only clusters with more than 10 activated voxels were reported. Coordinates

of activated voxels are reported in MNI space, and activation maxima are labelled according to the AAL atlas (Tzourio-Mazoyer et al., 2002).

To further examine neural changes across time with each handholding condition, an ROI analysis was performed. Regions were selected based on neural activity reported in the literature associated with emotion regulation and threat tasks, yielding a total of nine distinct regions including the: DLPFC, OFC, ACC, PCC, insula, thalamus, amygdala, hippocampus and parahippocampus. The ROI investigations were conducted at a set threshold of $p = .001$ significance level (uncorrected), with a cluster-wise correction at $p_{FWE} = .05$, and a cutoff of 10 activated voxels was set for cluster size.

Structural MRI

To explore structural changes in GM and WM volumes associated with EFT, VBM was used. Similar to functional data, VBM requires pre-processing steps (i.e. spatial normalization, smoothing) before statistical analyses can be performed. To accomplish this, T1 weighted images were processed and examined using SPM8 software and the VBM8 toolbox, set with default parameters. Spatial normalization involved estimating the optimum 12-parameter affine transformation (3 translations, 3 rotations, 3 zooms and 3 shears) for matching each participant's image to common space (Ashburner & Friston, 2005). The normalized images were then tissue classified, and segmented into GM, WM and cerebrospinal fluid (CSF) probability maps, stripped of extracerebral voxels, modulated with the Jacobian determinants from the spatial normalization and smoothed with a 12 mm Gaussian kernel full-width at half maximum.

Subsequently, analyses were performed on GM and WM segmented volumes. Voxel-wise GM and WM differences before and after therapy were examined using independent

samples t-tests with DAS and cortisol as covariates. To avoid possible edge effects between different tissue types, voxels with GM or WM values of less than 0.1 (absolute threshold masking) were excluded.

Whole brain and ROI investigations were conducted at a set threshold of $p = .001$ significance level (uncorrected), with a cluster-wise correction at $p_{FWE} = .05$, and a cutoff of 10 activated voxels was set for cluster size. ROIs included the same nine regions used in the random effects functional analyses, reflecting neural activity reported in the literature associated with emotion regulation and threat tasks.

Results

Descriptive Statistics

Demographic variables for our sample are presented in Table 1, and reflect age, mother tongue, marital status, length of relationship, duration of living together, number of children, ethnicity, highest educational level, gross annual income, and number of therapy sessions received.

Subjective Reports of Unpleasantness and Anxiety

Subjects' reports of SAM ratings for both pleasantness and anxiety levels experienced in each condition across time were examined in order to determine the effectiveness of the experimental task. A repeated measures analysis of variance (with Condition and Time as within-subject variables) showed that there was a main effect of hand-holding condition on SAM ratings of pleasantness, (F (2, 16) = 3.82, $p = .032$), but not anxiety (F (2, 16) = 2.98, $p = .64$). There

were also significant interactions between time and condition for both pleasantness, (F (2, 16) = 6.62, p = .004), and anxiety (F (2, 16) = 4.28, p = .022).

Post hoc t-test comparisons showed that pleasantness was significantly higher in the partner condition across time, (T (1, 17) = 2.83, p = .012), and that anxiety was significantly lower (T (1, 17) = 2.50, p = .023). Also, pleasantness was significantly higher for the partner versus stranger handholding condition post therapy (T (1, 17) = 3.76, p = .002) (this was non-significant pre-therapy (T (1, 17) = 0.7, p = .50)). Similarly, pleasantness was significantly higher for the partner versus alone handholding condition post therapy (T (1, 17) = 1.17, p = .028) (this was non-significant pre-therapy (T (1, 17) = 1.14, p = .27)). Anxiety was significantly lower in the partner versus stranger handholding condition post therapy (T (1, 17) = 3.69, p = .002) (this was non-significant pre-therapy (T (1, 17) = 0.00, p = 1.00)). There were no other significant differences across time by condition for either pleasantness or anxiety. See Table 2 for a summary of descriptive statistics.

In order to determine if there was an effect of the order of runs (independent of condition) another repeated measures analysis of variance was performed. Results indicated that there was a main effect of run on SAM ratings of anxiety (F (2, 16) = 3.59, p = .039), but not for pleasantness (F (2, 16) = 0.29, p = .75). Pair-wise comparisons revealed that there was a significant decrease in anxiety pre therapy between run1 and run3, (T (1, 17) = 4.12, p = .001), and between run3 and run 2, (T (1, 17) = 2.36, p = .03). Therefore there is a clear decrease in anxiety after the first run at the initial testing session. There was also a significant decrease in anxiety reported for the first run of the second testing session, compared to the first run of the initial session (T (1, 17) = 2.65, p = .017).

Questionnaire Data

To determine whether there was a significant change in couples' ratings of satisfaction, trust, and attachment avoidance and anxiety after EFT, paired t-tests were used to examine each variable. Results were explored for males and females separately, and the same pattern was observed in each case. In particular, there was a clear increase in the level of satisfaction reported by participants across time (DAS; males T (1, 17) = 2.403, p = .0028; females T (1, 17) = 5.596, p = .000). There was also a significant change in attachment avoidance, but this was noted only for male participants (ECR-Avoid; males T (1, 17) = 2.190, p = .043). No other variables demonstrated significant changes. As only the DAS showed a significant change for female participants, this was the only variable used as a covariate with the MRI data. See Table 3 for descriptive statistics.

Cortisol

As a preliminary measure, baseline cortisol data was compiled into a graph to examine baseline cortisol patterns of participants on a typical day; these were comparable to the diurnal rhythm described by Cunningham-Bussel et al. (2009), see Figure 1 (error bars reflect the standard error of the mean). In addition, there were no extreme z-scores, and normality was verified (the skewness of each total value was divided by the standard error of skewness). AUC for cortisol secretion for females and males, revealed no significant differences either across time (AUC_G, T (2, 16) = 0.736, p = .472), or in overall intensity (AUC_I, T (2, 16) = 0.233, p = .818), suggesting that both groups demonstrate similar patterns of total overall cortisol release after awakening, as well as in terms of cortisol increase after awakening. See Table 4 for descriptive statistics.

For experimental data, there were 3 participants that had outlying data which were adjusted to reduce their discrepancy from the group (z-scores greater than 2.58). Of note, as two cortisol samples were taken from each individual at each time point of interest (before and after fMRI threat task presentation) for both pre- and post-therapy scanning sessions, an average for each time was calculated for each subject, and these averages were used for the analyses.

To determine whether there was a significant change in couples' cortisol levels, paired t-tests were used to look at changes across time; for both within an experimental session (before and after fMRI task), as well as pre- and post-therapy. Results were explored for males and females separately, and the same pattern was observed in each case. In particular, there was a significant decrease in cortisol levels post-therapy compared to pre-therapy (using after fMRI task levels from testing sessions); males (T (1, 17) = 5.025, p = .000); females (T (1, 17) = 4.264, p = .001)). No significant changes were detected within a given testing session; for testing session pre-therapy, (T (1, 35) = 0.109, p = .914), and testing session post-therapy, (T (1, 35) = 1.450, p = .156). See Table 5 for descriptive statistics.

Covariates

To determine the appropriate use of significant variables as covariates in analyses of fMRI activations, the Pearson's r correlations (2-tailed) between questionnaire variables for female participants were examined. As only the DAS, cortisol and SAM ratings of pleasantness and anxiety showed significant change with time, these were the only variables investigated in this manner. Results indicated that there were significant correlations between related variables (i.e. pre-therapy DAS, post-therapy DAS), and that unrelated variables did not correlate with

each other. The one exception to this was that the level of reported anxiety during the Alone handholding condition post-therapy, was significantly correlated with post-therapy levels for the DAS (r = .517, p = .028) and cortisol (r = .499, p = .035). See Table 6 for full details. As it is important to use uncorrelated covariates to ensure that each accounts for unique variance, and to minimize the number of covariates used to maintain adequate power in the analysis, only 2 covariates were used in the analyses. In particular DAS and cortisol were selected as appropriate covariates as they significantly impacted results when incorporated into statistical models; there was not enough diversity in the SAM scores, noted by a lack of significant impact in results, to warrant their use as an effective covariate.

fMRI Fixed Effects ROI Analysis

Prior to receiving therapy, female participants demonstrated significant activity in the following areas for the threat minus safety contrast: DLPFC, OFC, insula, putamen, superior parietal cortex, and the superior temporal gyrus. Following therapy, there was increased activity noted in the: DLPFC, DMPFC, IFG, OFC, ACC, SMA, superior parietal cortex and superior temporal gyrus. All significant activity noted reflects a significance level of p =.001 (uncorrected), with a cluster-wise correction at p_{FWE} = .05, and a cluster size cutoff of 10 voxels. Results are summarized in Table 7 for pre- and post-therapy times, respectively.

fMRI Random Effects Analysis

All significant results noted reflect a significance level of p = .05 (FWE), with a cluster size cutoff of 10 voxels. Results for comparisons of interest are summarized in detail in Table 8, and include significance levels, cluster sizes, x y z coordinates, and Z-scores.

Paired t-test

There was no main effect of time (between post- and pre-therapy) for the paired sample t-test after averaging across conditions.

1-way ANOVA

A one-way within subjects ANOVA was conducted to explore the main effect of handholding (between Alone, Partner and Stranger conditions) after averaging across time. There was a significant effect of stress on neural activity for the three conditions in the following areas: IFG (Z (1,34) = 5.51, cluster size 19, *x y z* coordinates, -44 12 4, p = .000), hippocampus (Z (1, 34) = 5.44, cluster size 19, *x y z* coordinates -12 -54 -32, p = .000), and inferior temporal gyrus (Z (1, 34) = 5.25, cluster size 25, *x y z* coordinates 52 -60 -12, p = .000). As there were considerable differences between handholding conditions despite having averaged across time, these were further investigated in the flexible factorial model results described below.

2x3 Repeated Measures Flexible Factorial

Handholding Conditions across Time

For the Partner condition, there was more activity post-therapy in the left OFC and less activity post-therapy in the left postcentral gyrus. For the Stranger condition, there was no significant difference in activity post-therapy compared to pre-therapy. For the Alone condition, there was more activity observed post-therapy in the right SMA, left cerebellum, and lingual gyrus.

Interactions across Time and Conditions

Partner minus Stranger

Pre-therapy there was significantly more activity in the Partner minus Stranger condition in the frontal and temporal lobes as well as limbic areas. In the frontal areas, there was more activity in the OFC, IFG, DLPFC, SMA, ACC and insula. In the temporal lobe, there was more activity in the inferior and middle gyri. Post-therapy there were no significant differences between the Partner minus Stranger conditions.

Partner minus Alone

Pre-therapy there was significantly more activity in the Partner minus Alone condition in frontal, parietal, occipital and temporal lobes, as well as subcortical areas. In the frontal areas, there was more activity in the OFC, IFG, DLPFC, DMPFC, ACC, insula, SMA, and precentral gyrus. In subcortical areas, there was more activity in the hippocampus, parahippocampus, thalamus, amygdala, and cerebellum.

Post-therapy, there were considerably fewer differences in activity in the Partner condition compared to the Alone condition. Of the initial areas there remained significantly more activity in the IFG, insula, superior parietal lobe, the inferior, middle and superior areas of the temporal lobe, as well as the temporal pole, and the hippocampus, thalamus and cerebellum.

Stranger minus Alone

Pre-therapy there was significantly more activity in the Stranger versus Alone condition in the parietal, occipital and temporal lobes, as well as subcortical areas. There was more activity

in the postcentral gyrus, precuneus, lingual gyrus, middle temporal gyrus, temporal pole, hippocampus, caudate and cerebellum.

Post-therapy, there were considerably more differences in activity in the Stranger condition compared to the Alone condition. In particular there were frontal activations noted in the OFC, IFG, and insula. There was also activity in the postcentral gyrus, inferior parietal lobe, lingual gyrus, middle occipital gyrus, hippocampus, thalamus and cerebellum, as well as the temporal gyrus.

Alone minus Partner

Pre-therapy there was significantly less activity in the Partner condition compared to the Alone condition in frontal, parietal, occipital, temporal and limbic areas. Frontal activations were less in the DMPFC, DLPFC, IFG, OFC, ACC, PCC, and insula. In subcortical areas, there was less activity in the putamen, thalamus and cerebellum.

Post-therapy there was significantly less activity in the Partner condition compared to the Alone condition in frontal, parietal, occipital, temporal and limbic areas. Frontal activations were less in the Precentral and premotor gyri, DMPFC, DLPFC, IFG, OFC, and ACC. In subcortical areas, there was less activity in the thalamus, parahippocampus, amygdala and cerebellum. Figure 2 demonstrates the neural attenuation observed for the Partner handholding condition compared to the Alone condition.

Alone minus Stranger

Pre-therapy there was significantly less activity in the Stranger condition compared to the Alone condition in frontal, parietal, occipital, temporal and limbic areas. Frontal activations were

less in the Precentral gyrus, SMA, DMPFC, DLPFC, IFG, OFC, ACC and insula. In the limbic and non-cortical areas, there was less activity in the putamen and cerebellum.

Post-therapy there was significantly less activity in the Stranger condition compared to the Alone condition in frontal, parietal, occipital, temporal and limbic areas. Frontal activations were less in the precentral gyrus, SMA, DMPFC, DLPFC, IFG, OFC, ACC and PCC. In subcortical areas, there was less activity in the hippocampus, parahippocampus, putamen and cerebellum.

Stranger minus Partner

There were no significant differences pre-therapy in the Stranger minus Partner contrast. However, post-therapy there was less activity in the Partner condition in the ACC.

fMRI Random Effects ROI Analysis

Following therapy, for the Partner condition results showed increased activity in the OFC, thalamus, hippocampus and parahippocampus, and decreased activity in the DLPFC, at a significance level of $p = 0.001$ (uncorrected), with a cluster size of 10 or more significantly activated voxels. The insula and PCC showed significant activity before and after therapy, although coordinates were associated with different regions, and in different hemispheres for the insula. Also, following therapy, there was increased activity in the DLPFC and hippocampus noted in the Stranger condition, and in the thalamus for the Alone condition. See Table 9 for full details. Figure 3 demonstrates the differences in neural activity for the Partner handholding condition following therapy.

Structural MRI Analysis

White matter

There was a significant group difference in WM volume following therapy in the dorsal ACC (T (1, 17) =3.44, $x\ y\ z$ = -3 11 30, p = .015) at the whole-brain level at p = .05 (uncorrected). Figure 4 demonstrates structural differences in WM volumes following therapy. ROIs were selected from functional and structural studies exploring neural changes in emotion regulation and reactivity following psychotherapy. Extracted regions included the amygdala, insula, ACC, PCC, hippocampus, parahippocampus, OFC and other PFC regions. There were no significant ROIs for WM volume, apart from the ACC.

Gray matter

There were no significant differences in GM volume following psychotherapy at the whole-brain level when conducting t-tests, even with the addition of DAS and cortisol as covariates. There were no significant ROIs for GM volume.

Discussion

The main goal of this study was to determine if Emotionally Focused Therapy (EFT) for couples affects the neural processing of female partners during a stressful threat task. The results from this study offer preliminary evidence that this may be the case. In our sample of distressed couples, EFT promoted differences in normative neural threat response, physiological reactivity, ability to derive comfort from their male partner's touch, and white matter structural volume.

Normative Neural Threat Response

More specifically, female partners demonstrated distinctly different patterns of responding to neural threat after receiving therapy compared to before EFT when alone in the scanner. The need to explore changes to this neural response is important because the Alone condition serves as a benchmark for examining the amount of attenuation conferred by their partner's touch.

In terms of the threat response, there were brain areas that were commonly activated across time which are associated with threat stimulation (Schunck et al., 2008). This confirms the effectiveness of the threat task, and reflects processing emotionally salient stimuli (parietal and temporal lobes) (Desimone & Duncan, 1995; Murphy et al., 2003), emotional distress and anticipation of threat (putamen and insula) (Sinha et al., 2004; Wager et al., 2003), and emotion regulation (DLPFC and OFC) (Phelps, 2006; Phillips et al., 2008).

Prior to EFT there was evidence of emotional dysregulation. This is consistent with insecure attachment, which is characterized by intense feelings of stress and threat and, which we can intuit, likely serves to alter the experience of the fMRI threat task by increasing negative affect. Insecurely attached females were expected to be highly upset about participating in a task with a partner who, prior to therapy, serves as an additional source of threat. This added threat stimulus appeared to activate the limbic system, in particular the insula, to such an extent that partners were not able to process emotion effectively. This was reflected in the lack of activity noted in the ACC, an area that is consistently activated in conjunction with insula activity during emotional experiences and processing (Medford & Critchley, 2010). In fact, this relationship is so commonly observed that current hypotheses believe that the insula and ACC are integral components of a system, with the insula constituting the 'input' of the system, integrating

cognitive, affective and physiological information, and the ACC as the 'output' of the system, translating emotions into responses (Medford & Critchley, 2010; Pollatos, Gramann, & Schandry, 2007). Research on PTSD, a population known to struggle with emotion dysregulation, has shown that during a task in which subjects re-experience their trauma, there was a positive correlation with insula activity, and a negative correlation with activity in the ACC (Hopper et al., 2007). This phenomenon has been thought to reflect an inability of medial prefrontal structures, such as the OFC, to regulate limbic activity. Decreased ACC activity in PTSD subjects has also been noted by other researchers (Lanius et al., 2003), and similar dysfunctional patterns between cortical and limbic areas are also evident in depressed patients (Anand et al., 2005). Although trauma history was an exclusion criteria for our sample, findings from PTSD research may be relevant as the effects of insecure attachment bonds, particularly emotional inaccessibility, have been conceptualized as constituting a small 't' trauma, and are known to have devastating effects on individuals' ability to effectively emotionally regulate (Johnson, 2002). It seems that prior to receiving therapy, female partners find the forced experience of holding their partner's hand distressing, and doing so may induce re-experiencing memories of the lack of support in their relationship causing emotional dysregulation.

What is of particular interest is that after receiving EFT for couples, the neural response to threat observed in our sample more closely approximated normative responses (Pichon et al. 2011, Schunk et al., 2008), as well as those observed in a population of happily married couples (Coan et al., 2006). In particular, there was increased activity in areas expected to be involved in the detection, processing and regulation of negative emotion (ACC, OFC, SMA, DMPFC) (Eippert et al., 2007; Pichon et al., 2011; Whalen et al., 1998; Vogt, Berger, & Derbyshire, 2003; Yamasaki, LaBar & McCarthy, 2002), indicating increased ability to attend and respond

appropriately to relevant stimuli. There was also decreased activity in areas responsive to negative emotion (insula and putamen), suggesting that after therapy, female partners were better able to demonstrate normative responses to stress and showed healthier emotion regulation.

Physiological and Self-Report Changes

This renewed ability to effectively emotionally regulate is also apparent in the couples' physiological stress responses, as measured by HPA axis activity. In particular, EFT for couples appeared to contribute to changes in HPA axis activity, as both female and male partners demonstrated significantly reduced levels of cortisol after therapy in response to the threat task. This is in line with research which suggests that the ability to regulate affect is the hallmark of secure attachment (Goldstein & Thau, 2004; Mikulincer & Shaver, 2007), and that secure attachment behaviours such as intimacy and trust are linked to lower levels of cortisol (Ditzen, Hoppmann, & Klumb, 2008; Takahashi et al., 2005). Females also tend to direct more of their attention to how they feel in response to emotional stimuli (Orozco & Ehlers, 1998), are particularly sensitive to stress hormones, and demonstrate increases in these when their partners demonstrate avoidant behaviours and decreases when they are attentive and caring (Goleman, 2006). Indeed, prior to receiving therapy, female partners had higher levels of cortisol compared to post-therapy and rated the Partner handholding condition as the least pleasant and most aversive. This is consistent with research that has shown that increased HPA axis activity, demonstrated by increased levels of cortisol, impedes one's ability to derive comfort from their AF (Carpenter & Kirkpatrick, 1996). This finding also offers physiological support for the increased limbic activity observed prior to receiving therapy. To be sure, another possible explanation for the decreased cortisol levels following therapy relates to response habituation to

the fMRI task. Prior research has shown such declines in humans in response to repeated stress exposure (Gerra et al, 2001; Kirschbaum et al, 1995; Wüst, Federenko, van Rossum, Koper & Hellhammer, 2005). However, there is also significant inter-subject variation noted for this phenomenon, where as much as 35 - 40% of individuals not do show such a response (Gerra et al, 2001; Kirshbaum et al, 1995), which may complicate such effects.

Results also support that successful emotion regulation is linked to relationship satisfaction (Murray, 2005), as couples reported significantly higher scores on the DAS following therapy. This is further reflected in self-report ratings of pleasantness and level of anxiety experienced during the threat task across the three handholding conditions. After therapy, females reported a significant increase in pleasantness and decrease in anxiety when holding their partner's hand. Interestingly, there was no significant change observed when females were alone in the scanner, or held an experimenter's hand. Together, these findings suggest that EFT's impact was uniquely suited to affect the romantic relationship, and contributed to a significant change in the perception of their partner, as well as their ability to utilize their partner as a source of comfort and soothing.

Of note, there was a significant decrease in anxiety reported for the first run/condition of the task after therapy compared to before therapy. This likely reflects familiarity with the task, which was thought not to be problematic in light of the fact that decreases in anxiety and increases in pleasantness were not observed for all handholding conditions. Since these were solely observed for the Partner condition (levels remained relatively unchanged for the Alone condition, and became more aversive and unpleasant in the Stranger condition), it was determined to be a normal by-product of previous exposure that was adequately accommodated with counterbalancing conditions.

Neural Changes Following Therapy

Following EFT for couples, there was more activity in areas that play a central role in emotion regulation for the Partner handholding condition. This was consistent with our hypothesis that there would be increased activity in areas related to emotion regulation when holding one's partner's hand after receiving EFT for couples, as the male partner would help to soothe the female partner's distress. ROI analysis showed increased activity in cortical and limbic structures associated with both explicit (temporal gyrus, hippocampus, parahippocampus) and implicit memory (insula), as well as increased automatic emotion regulation (OFC, PCC).

The OFC is an integral component to emotion regulation processes. It is thought to mediate dorsal and lateral PFC activity during 'voluntary' emotion regulation (Phelps, 2006; Phillips et al., 2008), and play a role in 'automatic' emotion regulation tasks (Ochner & Gross, 2005, 2007; Mauss et al., 2007). From the ROI analysis, it appears that the OFC activity may be linked to the ventral circuit, as no dorsal PFC activations were observed to be significant post-therapy; of note, prior to receiving therapy there was significant activity in the DLPFC, which is known to be involved in cognitive control and voluntary emotion regulation activities (Phan et al., 2002). This suggests that following therapy, the ability to rely on one's partner as a source of support and emotion regulation may have become an adaptive, automatic response, and may reflect processes such as reappraisal and monitoring their partner's behaviours. The increased hippocampal, parahippocampal and PCC activity observed post-therapy also provides some support for this idea as these areas are known to be involved in emotion regulation (Philips, Ladouceur & Drevets, 2008), and recently have been hypothesized to have a role in automatic cognitive change processes (Mauss et al., 2007; Phillips et al. 2008). Moreover, the hippocampus has been hypothesized to act as a facilitator of goal directed behaviours, especially in exploratory

rather than defensive patterns (Gray & McNaughton, 2000), which is consistent with adaptive attachment behaviours.

It could be argued that automatic emotion regulation could also be occurring because of maladaptive, defensive reactions or repression (Mauss et al., 2007). However, this is unlikely as participants rated the Partner condition post-therapy as the most pleasant and least anxiety provoking of the entire study, and cortisol levels were significantly decreased post-therapy compared to pre-therapy. This last point is particularly relevant as research has shown that during defensive and repressive reactions, physiological reactivity remains detectable even when self-reported distress is denied (Shedler, Mayman, & Manis, 1993; Schwartz, 1995). This is further supported by the fact that following therapy, there were decreases in neural activity in areas related to vigilance to emotion, negative affect, emotional reactivity, defensive reactions and motor preparation in response to anticipated aversive stimuli (superior parietal lobe, CN, ACC, postcentral and precentral gyri) (Bingel et al., 2002; Carter, 2009; Le, Pardo & Hu, 1998; Peyron, Laurent, & García-Larrea, 2000). In fact, ROI analysis revealed an overall shift from right to left hemisphere activity following therapy in the OFC and insula. Left hemisphere PFC activity has been associated with more approach-related behaviours (Murphy et al., 2003; Wager et al., 2003). Therefore, it is unlikely that the neural activity observed post-therapy is suppressive or defensive in nature, and more likely reflects automatic, adaptive emotion regulation activity and a willingness to reach for one's AF for support.

Interestingly, there were entirely different neural patterns of activity observed in the Alone and Stranger handholding conditions post-therapy. When alone in the scanner, female partners showed increased activity in areas related to vigilance to threat stimuli (lingual gyrus) (Lang et al., 1998), emotional processing (cerebellum) (Kober et al., 2008; Murphy et al., 2003),

and defensive reactions (SMA) (Pichon et al., 2011). Coupled with higher ratings of unpleasantness compared to the Partner condition, this suggests that the threat task continues to be an aversive experience at the second testing session, requiring multiple neural resources to respond to threatening stimuli in the absence of one's AF. This is consistent with findings by Coan et al. (2006) who observed that resources related to vigilance, evaluation and self-regulation are recruited in response to stress in the absence of one's spouse.

There were no neural differences observed in the Stranger condition following therapy, which suggests that EFT does not improve distressed couples' ability to receive support from non-AFs during times of stress. In fact, female partners reported significantly less pleasantness and increased anxiety when holding a Stranger's hand following therapy. This is not surprising as the focus of EFT is to foster an increased ability to rely on one's AF for security and support. AFs are not simply a close individual, they are unique in that they are the individual a person turns to when support or protection is needed (Mikulincer & Shaver, 2007). Therefore, the inability for a stranger to confer similar emotion regulation benefits makes sense. Perhaps over time, as security in the attachment bond strengthens, these benefits may transfer to other relationships in a person's life, which are part of their attachment network, although the possibility of this including strangers in unlikely.

Attenuation of Neural Threat

Further support that couples can better regulate negative emotion after receiving EFT comes from the male partners' enhanced ability to attenuate their partner's neural threat responses with touch. This improved ability is highlighted because before receiving EFT holding their partner's hand was particularly aversive. Compared to holding a stranger's hand, holding

their partner's hand resulted in increased activity in prefrontal and temporal areas linked to detecting and processing emotionally salient stimuli (insula, ACC, DLPFC, OFC) (Medford & Critchley, 2010; Phan et al., 2002, Eippert et al., 2007; Kober et al., 2008; Rolls 1999), as well as defensive reactions (SMA) (Pichon et al., 2011). These results are the complete opposite of findings reported by Coan et al. (2006) who found that spousal handholding attenuated neural stress responses in happy marriages, which was reflected in subjective reports of increased pleasantness and decreased anxiety when holding their spouse's hand. In our sample, female partners reported significantly higher levels of unpleasantness and anxiety pre-therapy compared to post-therapy. This makes sense in light of the fact that in distressed marriages, one's partner acts as a source of anxiety and distress, rather than security and support, and the emotional regulation benefits of the attachment bond are compromised (Mikulincer & Shaver, 2007). Moreover, insecurely attached individuals' distress is exacerbated by their AF's presence (Carpenter & Kirkpatrick, 1996).

This idea was echoed when comparing the Partner and Alone conditions pre-therapy, which was characterized by similar but more extensive activity than compared to the Stranger condition. Specifically, there was significantly more activity in regions associated with the detection of emotionally salient stimuli and the experience of threat (fusiform gyrus, inferior and superior parietal cortices, superior temporal gyrus, visual cortex, and cerebellum) (Lang et al., 1998; Murphy et al., 2003; Schunck et al., 2008). This increase in activity was also observed in components of the striatal-limbic-prefrontal circuit that are activated in emotional distress (hippocampus, parahippocampus, thalamus, basal ganglia and amygdala) (Sinha et al., 2004), which suggest a greater experience of threat. These results are consistent with signs of attachment insecurity. In particular, there was increased activity in the temporal pole, which has

been shown to be highly activated in insecurely attached partners when thinking negatively about one's relationships (Gillath et al., 2005). Similarly, there was increased activity in areas related to automatic emotion regulation (dorsal ACC, hippocampus, parahippocampus), which may reflect negative IWMs of partner. Increased hippocampal activity has been observed during recollection of emotional and contextually-rich memories (Maratos, Dolan, Morris, Henson, & Rugg, 2001). In addition there appeared to be greater activity in ventrolateral PFC and dorsomedial PFC areas, which have been shown to reflect additional emotion regulation areas that anxiety-prone individuals require to reduce negative emotions effectively (Campbell-Sills et al., 2011). There was also extensive bilateral activity observed across the hemispheres, which correlated significantly with withdrawal behaviours in a study by Murphy et al. (2003). Therefore, it seems that processes beyond simple emotion regulation, such as those linked to insecure attachment were present prior to receiving therapy, and negatively impacted females' abilities to regulate distress.

Consistent with this idea, and particularly notable, is the increased activity in the right amygdala which is linked to experiences of negative affect such as fear (Ochsner et al., 2004; Phan, et al. 2002). Moreover, its activity correlates with attachment insecurity during times of stress (Lemche et al., 2006), and is chronically activated in this condition (Price et al., 1996; Schore, 2004). That the activity was localized to the right hemisphere of the amygdala is especially significant, as it has been associated with more subconscious processes, such as implicit emotional memory, and emotional learning (Morris et al., 1998; Tillfors, Furmark, Marteinsdottir, & Fredrikson, 2002). These processes could reflect activation of IWMs which in insecurely attached individuals would further increase distress, as they likely constitute negative beliefs about their partner's availability and responsiveness, as well as their own importance.

Negative IWMs are known to contribute to impaired emotion regulation abilities (Amini et al., 1996). As the amygdala was only active during the Partner condition, it appears that female partners were exposed to two significant sources of threat, from the fMRI task itself, and from their negative IWMs of their partners. It seems that in a distressed marriage, holding a partner's hand during times of stress exacerbates the stressful experience, possibly due to the activation of IWMs, and induces greater negative emotion than enduring stress alone. It also seems to require additional compensation and emotional regulation, observed by increased activity in numerous neural areas, to manage it.

It is interesting that this pattern was markedly more extensive than what was observed when comparing the Stranger versus Alone condition or the Partner versus Stranger condition. This may reflect the fact that in distressed marriages, partners have learned to turn inward, to rely on themselves to cope during times of stress, and the forced act of relying on one's partner is particularly distressing. Similar results were observed by Carpenter and Kirkpatrick (1996) who noted that when insecurely attached women were faced with a stressful task, the aversive stimuli were perceived as more psychologically threatening when their partner was present.

Post-therapy this neural pattern of activity appears to reverse itself, and suggests that the male partners' ability to attenuate neural threat responses with touch was significantly enhanced. Compared to Coan and colleagues' (2006) initial study, following therapy our sample looked increasingly similar. In particular, there was decreased activity in 'general regulatory structures' such as the postcentral gyrus and supramarginal gyrus, as well as in more 'evaluative, attentional, and affective components typically involved in emotional processing and regulation activities, namely the DLFPC, OFC, ACC and parahippocampus. There was also decreased activity in the right amygdala, suggesting that their partner is no longer a source of threat, but

instead serves as a support. This is also consistent with decreased levels of cortisol noted post-therapy, as the amygdala is a key moderator of cortisol activity (Gunnar & Quevedo, 2007), and its decreased activity is linked to secure attachment (Vrtička et al., 2008). Such findings are consistent with research on secure attachment bonds which are protective against negative experiences and reduce the need for emotion regulation strategies, shown by decreased neural activity in corresponding areas (Karremans et al., 2011). These findings support our initial hypotheses and suggest that EFT for couples restores the ability for the partner to effectively attenuate and regulate their partner's experience of emotional distress by decreasing activity in neural areas associated with neural threat and regulation of emotion. These findings were further supported by subjective reports of experience which revealed that following therapy, female partners reported that holding their partner's hand resulted in significantly more pleasant and less anxious feelings compared to the Stranger and Alone conditions.

What is interesting to observe, is that despite low ratings of pleasantness and high levels of anxiety, the Stranger condition did serve to attenuate neural response to threat after therapy, albeit to a lesser degree than the Partner condition. It is difficult to determine why this would be the case, although one explanation could be that during EFT for couples, partners experienced their AF in new ways which likely served to change their IWMs, or beliefs about themselves and their partner. In particular, they would likely see their partner as more accessible and supportive, and believe that they are important to their partner. These new IWMs would help them become more adept at regulating their emotions both with and without their partner's presence. Indeed, securely attached relationships are characterized by implicit representations of their partner that can be drawn on effectively in their absence (Mikulincer & Shaver, 2007). What did distinguish the Partner condition from the Stranger condition was decreased activity in the amygdala and

thalamus, which suggests that following therapy the male partner served as an enhanced source of support and regulation demonstrated by increased threat attenuation in the limbic system. This is particularly noteworthy, as many forms of therapy are believed to selectively target prefrontal structures and work from a top-down perspective, which would not likely yield changes in implicit memory or affect limbic activity (Fuchs et al., 2004). However, as EFT relies heavily on emotional experiencing and enactments in session, which are bottom-up processes, its effects are noted in such structures, and may reflect a key reason as to why EFT is associated with such high recovery rates.

Structural changes

In addition to the functional changes observed, there was also a significant structural difference following EFT. In particular, there was significantly more white matter (WM) noted in the dorsal ACC. The ACC has many functions which are commonly divided into ventral affective and dorsal cognitive components (Bryant et al., 2008; Bush, Luu & Posner, 2000). The affective component is thought to be a target for modulation in emotion regulation (Beauregard, Levesque, & Bourgouin, 2001; Ochsner et al., 2002), and the cognitive component has been shown to be involved in response conflict and competition (Barch et al., 2001, Carter et al., 2000), in particular directing attention to relevant stimuli (Weissman, Gopalakrishnan, Hazlett, & Woldorff, 2005). These are important monitoring functions involved in emotion regulation processes. White matter is the main substrate of neural circuits, representing myelinated axons that conduct electrical impulses. An increase in WM suggests enhanced connectivity between brain regions. More WM in the dorsal ACC suggests that there are more synaptic connections present in a key region of neural circuitry linked to emotion detection, generation and regulation.

Structural changes to the ACC following treatment with either psychotherapy or medication have also been reported and seem to reflect therapy responsiveness. For example, Anand, Li, Wang, Gardner, and Lowe (2007) used fMRI to examine the effects of antidepressants on the functional connectivity of the mood regulating circuit in patients with unipolar depression, and found increased connectivity between the ACC and the limbic system, as well as decreased limbic responsiveness to negative stimuli. Also, Li, James, Mayberg and Hu (2008) used MRI tractography to examine differences between treatment-resistant and treatment-responsive clients with unipolar depression and found that resistance was associated with decreased fiber track integrity connecting the ACC, thalamus and cerebellum, and that responsiveness was associated with greater integrity. Abnormalities in WM have been shown to be at least partially reversible following pharmacological treatment of OCD (Yoo et al., 2007), and electroconvulsive therapy for depression (Nobuhara et al., 2004).

Most notably, Bryant et al. (2008) explored a sample of subjects with PTSD and observed increased GM volume in the dorsal ACC in therapy-responders following CBT. Dorsal ACC activity facilitates conflict resolution by directing attentional resources to relevant stimuli, which is a particularly important aspect of emotion regulation, especially when confronted with threat (Weissman et al., 2005). Authors concluded that its activity reflected an increased capacity to regulate emotion effectively, and hypothesized that changes were linked to the extinction learning associated with CBT, in which previously conditioned responses are replaced by newly learned associations. EFT promotes new emotional experiences of one's partner as a source of support and comfort rather than distress, which corresponds closely to the concept of extinction learning in CBT, and likely reflects changes to IWMs, which even Bowlby (1969, 1982) acknowledged were revised in light of new experience. Therefore, it seems that changes in

circuitry involving the dorsal ACC reflect differences in attachment-related constructs and are consistent with the increased capacity for emotion regulation observed in the functional results. The fact that this change was observed in the left ACC corresponds with the decreased functional activity observed in the right ACC following therapy, and may reflect neural compensation so that the right ACC does not require as much activity to function effectively. Given that the anatomical connectivity of subregions of the ACC is still being determined, future research should focus on understanding neural changes at this level to gain a better understanding of the therapeutic mechanisms of change.

Limitations

There are a number of limitations to this study that should be acknowledged. Most importantly, our study lacks a control group. This certainly poses a threat to the internal validity of this research as only a single group was used and no random assignment was possible. Unfortunately the addition of a control group would have been difficult, expensive and inefficient. From an ethical standpoint, researchers would have had to provide the control group with therapy afterward, and this was simply beyond the means of the researchers to do so. Also, as this study was exploratory in nature, as there is no prior research on the neural effects of EFT for couples, a control group was simply beyond its scope at the present time. Given the extent of our findings, it is strongly recommended that future research incorporate a group of distressed couples as controls in a randomized controlled trial, to further strengthen and validate the effectiveness of EFT on neural processing and structure. In terms of choosing a control group, it would be best to compare EFT to another form of couples therapy (i.e. CBT), as well as a no-therapy group.

Other major limitations stem from the collection, processing and analysis of the fMRI data. There were some important constraints associated with the power of the magnet used. Although adequate to acquire basic functional and structural information, a 1.5 Tesla scanner does not provide sufficient signal to noise to permit advanced resolution of structural changes. For this reason, although we had planned to investigate structural changes using diffusion tensor imaging (DTI), this was not possible. In future, it would be recommended to use a 3.0 Tesla magnet to remedy this problem.

In terms of pre-processing of neural data, the processes of normalization and smoothing onto a template loses some of the inter-subject variability observed in brain morphology, and could equally serve to mask or inflate actual differences. However, the absolute best approximation is achieved by a highly controlled process in which countless iterations of configurations are generated to find the solution which best minimizes any error. Finally, as with many statistical analyses lacking a control group, the results achieved with fMRI can not be used to argue causality, but must instead be used to infer associations between variables.

Also related to the collection of fMRI data, was the lack of physiological measures acquired during the task itself, which would have been useful to determine the immediate activation of the autonomic response, as well as engagement with the visual task. Although cortisol is a good estimate of the autonomic stress response, because it is a hormone, its effects are not immediately observed, and it would be helpful to complement with another more direct measure. This could easily be achieved by measuring skin conductance level (SCL), which is highly sensitive to emotional and psychological stimuli, and easily tested by placing electrodes on the palms of one's hands or feet. Lemche et al. (2006) effectively used SCL in a study of stress responses and adult attachment. With respect to visual engagement with the threat task,

there was concern that subjects may have closed their eyes as a means to reduce distress instead of looking at the target stimuli. Although we did verbally check with participants after each run, it would have been preferable to have a more reliable source than self-report to verify this. There is eye-tracker software available for use with fMRI equipment which has been successfully used with threat paradigms (Eippert et al., 2007). Along these same lines, we also did not inquire as to how participants regulated their distress across conditions. It would have been helpful to have a measure of whether this changed before and after therapy. A major question of interest is: did subjects tend to use more distraction or suppression strategies before receiving therapy, and if so did this change after EFT? This should have been explored after the fMRI testing session, when it was confirmed that subjects kept their eyes open.

Another limitation pertains to the fact that our study employed two distinct sources of data, in particular neural functioning and more classic physiological and self-report questionnaires, each requiring distinct forms of statistical analysis. The problem lies in the fact that the threshold for detecting robust findings is very different for both types of data. In particular, a much smaller sample size is needed to detect significant changes in fMRI data, whereas a larger one is typically needed for more classic variables. This was a problem in terms of detecting significant differences in non-neural variables of interest, specifically the subscales of the ECR. It would have been preferable to have been able to include it in our analysis, as there is extensive research detailing significant differences between anxiously and avoidantly attached individuals. It is possible that with a greater sample size, significant differences would have emerged for this scale. For the present study, there were no significant differences noted for female participants.

Future Directions

There are several recommendations that would help to strengthen future studies. The use of a control group would allow a more stringent analysis of the results, and would permit causal inferences to be made. Also, as research has shown that EFT's effects strengthen with time (Halchuk et al., 2010) it would be interesting to reassess the current population at 2-year follow-up to determine how functional and structural neural changes evolve. It would also be advised to explore the neural effects of EFT in male subjects to compare with those observed in our female population.

Another important suggestion would be to use a stronger magnet that would allow greater resolution and permit the exploration of specific changes to neural circuitry using DTI. It would also be helpful to acquire a measure of baseline neural activity, known as resting state fMRI, for each individual. This would provide a better measure of how controls and distressed couples differ in terms of neural responses, and help to more accurately detect and localize the impact of therapeutic intervention.

Conclusion

This is the first study performed on pre- and post-EFT neural processing showing that with only 23 sessions of this treatment, not only does EFT significantly affect important psychological constructs but it also changes our physiology. In particular, EFT can significantly alter the quality of relationships through functional and structural brain changes. EFT resolves emotional dysregulation, promotes attenuation of neural threat by AFs, results in structural change in a key region of emotion circuitry, and accomplishes this through attachment-related structures and concepts (i.e. amygdala, IWMs, HPA axis). There is evidence from both neural

and physiological data, that following EFT for couples, female partners are effectively soothed by their male partners, as demonstrated by decreased cortisol levels observed post-therapy, as well as attenuated neural activity observed in neural areas associated with threat and emotion regulation.

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Table 1
Sociodemographic Information for Couples

Variable		Male	Female
Age			
(mean ± SD; years ± months)		47 ± 7.1	46 ± 5.4
Mother tongue			
	English	13	14
	French	3	2
	Spanish	1	2
	Dutch	1	
Marital Status			
	Married	16	
	Common law	2	
Length of Relationship			
(mean ± SD; years ± months)		20.5 ± 7.76	
Living Together			
(mean ± SD; years ± months)		19.0 ± 7.38	
Number of Children			
(mean ± SD)		2 ± 1.3	
Ethnicity			
	White/Caucasian	17	16
	Latino/Hispanic	1	1
Highest Educational Level			
	University	13	15
	College	3	2
	High School	2	1
Annual Personal Gross Revenue (in dollars)			
(mean ± SD)		93692 ± 51062.7	58666 ± 29803.3
Number of EFT sessions received			
(mean ± SD)		22.8 ± 7.70	

n = 18 for all variables
Abbreviation: SD = Standard Deviation

Table 2
Means and Standard Deviations of Pleasantness and Arousal Ratings Pre- and Post-therapy by Handholding Condition

	Time	Partner		Stranger		Alone	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Pleasantness	Pre	2.72	0.895	2.83	0.618	2.89	0.758
	Post	3.33[a]	0.840	2.56[b]	0.922	2.78[b]	0.808
Anxiety	Pre	2.78	0.878	2.78	0.878	2.83	1.200
	Post	2.17[a]	0.618	3.06[c]	0.873	2.67	1.085

$n = 18$ for all variables
[a] Denotes significant difference Post-therapy for the Partner handholding condition (post-hoc paired t-test, $p < 0.05$).
[b] Denotes a significant difference Post-therapy for the Stranger and Alone conditions compared to the Partner condition (post-hoc paired t-test, $p < 0.05$).
[c] Denotes a significant difference Post-therapy for the Stranger condition compared to the Partner condition (post-hoc paired t-test, $p < 0.01$).

Table 3
Means and Standard Deviations for Self-Report Questionnaire Variables Pre- and Post-therapy

Variable	Time	Males		Females	
		Mean	Standard Deviation	Mean	Standard Deviation
DAS	Pre	91.28	7.36	82.89	12.49
	Post	98.00 [b]	12.86	95.06 [a]	15.00
RTS	Pre	130.08	12.26	127.75	13.96
	Post	135.44	13.71	131.39	11.03
Avoidance ECR	Pre	63.78	13.37	65.67	20.68
	Post	71.17 [c]	5.53	74.22	9.87
Anxiety ECR	Pre	72.06	16.80	73.56	18.26
	Post	71.33	16.16	67.22	18.95
Total ECR	Pre	136.38	25.25	139.22	19.02
	Post	142.50	18.28	141.44	24.80

$n = 18$
[a] Denotes significant difference Post-therapy (paired t-test, $p < 0.001$).
[b] Denotes significant difference Post-therapy (paired t-test, $p < 0.01$).
[c] Denotes significant difference Post-therapy (paired t-test, $p < 0.05$).
Abbreviations: DAS = Dyadic Adjustment Scale, RTS = Relationship Trust Scale, ECR = Experiences in Close Relationships

*Figure 1.*Diurnal cortisol rhythms for male and female participants.
Abbreviations: Awakening = WU, 30 minutes after awakening = WU + 30.

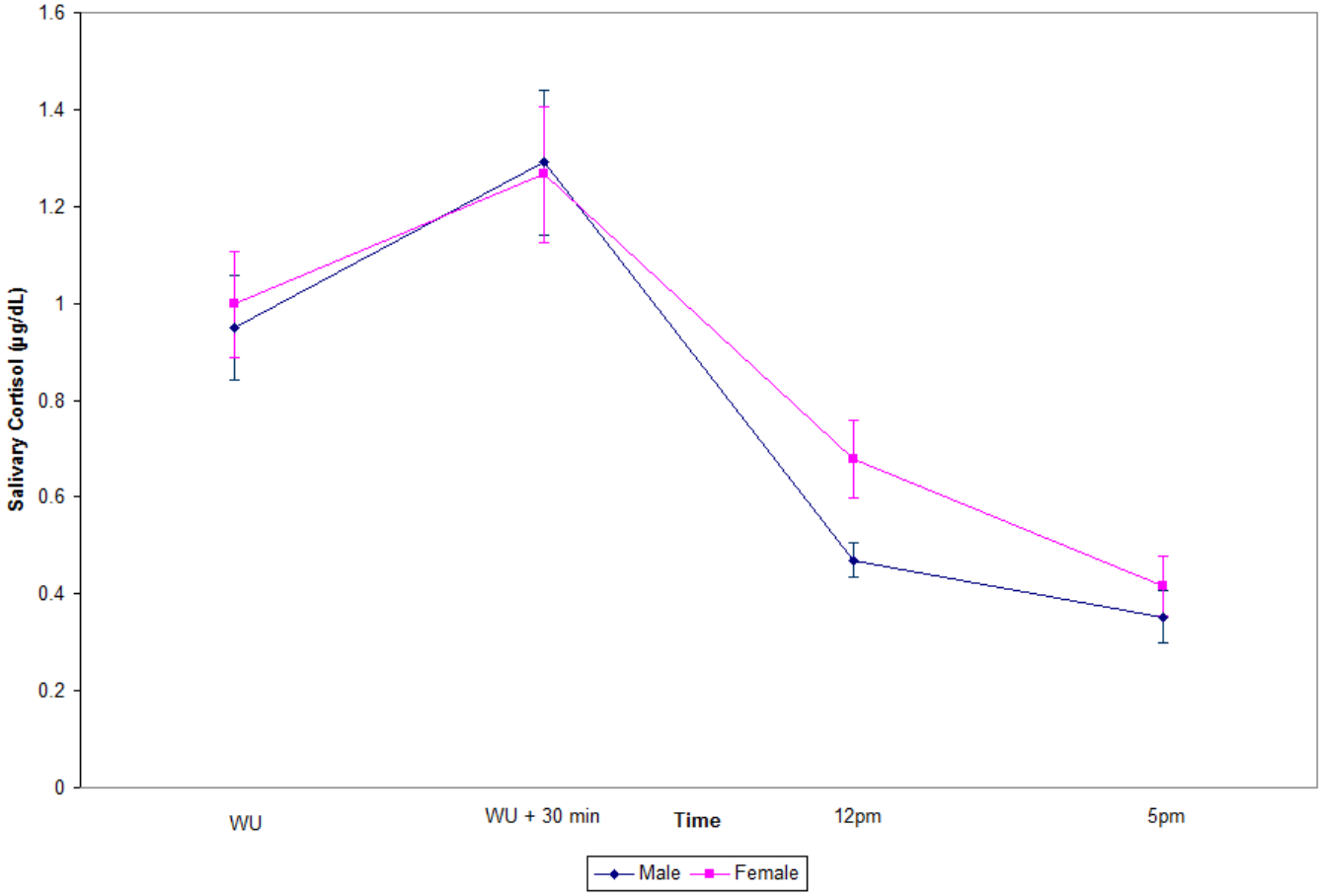

1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Salivary Cortisol (µg/dL)
WU
WU + 30 min
Time
12pm
5pm
Male
Female

Table 4
Means and Standard Deviations of Baseline Cortisol Data for Male and Female Participants

Group	Sample Time	Mean	Standard Deviation
Male	WU	0.95	0.326
	WU +30min	1.29	0.448
	Noon	0.47	0.108
	5pm	0.35	0.165
Female	WU	1.00	0.325
	WU +30min	1.27	0.421
	Noon	0.68	0.238
	5pm	0.42	0.187

$n = 9$
There were no significant group differences.
Abbreviations: Awakening = WU, 30 minutes after awakening = WU+30.

Table 5
Means and Standard Deviations for Cortisol Levels Pre- and Post-therapy and Before and After fMRI Threat Task Presentation

Group	Time	fMRI Task	Mean	Standard Deviation
Males	Pre-therapy	1	1.09	0.418
		2	0.69	0.304
	Post-therapy	1	1.07	0.355
		2[a]	0.63	0.177
Females	Pre-therapy	1	0.96	0.248
		2	0.67	0.239
	Post-therapy	1	0.96	0.403
		2[a]	0.62	0.335

$n = 18$
[a] Denotes significant difference Post-therapy (paired t-test, $p < 0.001$).
Note. '1' and '2' refer to cortisol samples being collected before and after fMRI threat task presentation, respectively.

Table 6
Correlations between Dyadic Adjustment, Pleasantness and Anxiety Ratings, and Cortisol Levels

Variables	Pearson's r Correlation	Significance
Pre DAS/ Post DAS	0.790	0.000
Pre DAS/ Post Pleasantness Alone	-0.509	0.031
Cortisol Pre T1/ Cortisol Pre T2	0.318	0.199
Cortisol Pre T1/Cortisol Post T1	0.663	0.003
Cortisol Post T1/ Cortisol Post T2	0.587	0.010
Cortisol Pre T2/ Cortisol Post T2	0.792	0.000
Pre Pleasantness Alone/ Pre Pleasantness Partner	0.732	0.001
Pre Pleasantness Alone/ Pre Pleasantness Stranger	0.836	0.000
Pre Pleasantness Partner/ Pre Pleasantness Stranger	0.656	0.003
Pre Anxiety Alone/ Pre Anxiety Partner	0.521	0.027
Pre Anxiety Alone / Pre Anxiety Stranger	0.577	0.012
Pre Anxiety Stranger/ Post Anxiety Stranger	0.478	0.045
Post Pleasantness Alone / Post Pleasantness Stranger	0.570	0.014
Post Pleasantness Partner / Post Pleasantness Stranger	0.506	0.032
Post Pleasantness Partner/Post Anxiety Partner	-0.566	0.014
Post Pleasantness Stranger/ Post Anxiety Stranger	-0.479	0.044
Post Anxiety Alone/ Post Anxiety Stranger	0.580	0.012
Pre DAS/ Pre Pleasantness Alone	0.415	0.087
Pre DAS/ Pre Pleasantness Partner	0.424	0.080
Pre DAS/ Pre Pleasantness Stranger	0.317	0.199
Pre DAS/ Pre Anxiety Alone	-0.268	0.282
Pre DAS/ Pre Anxiety Partner	-0.174	0.490
Pre DAS/ Pre Anxiety Stranger	-0.297	0.231
Post DAS/ Post Pleasantness Alone	-.341	0.166
Post DAS/ Post Pleasantness Partner	0.208	0.407
Post DAS/ Post Pleasantness Stranger	-0.030	0.906
Post DAS/ Post Anxiety Alone	0.517	0.028
Post DAS/ Post Anxiety Partner	0.177	0.483
Post DAS/ Post Anxiety Stranger	0.323	0.191
Pre DAS/ Cortisol Pre T1	0.407	0.093
Pre DAS/ Cortisol Pre T2	0.060	0.813
Post DAS/ Cortisol Post T1	-0.074	0.771
Post DAS/ Cortisol Post T2	-0.072	0.777
Pre Pleasantness Alone/Cortisol Pre T2	0.051	0.840
Pre Pleasantness Partner/ Cortisol Pre T2	-0.055	0.829
Pre Pleasantness Stranger/Cortisol Pre T2	0.377	0.123

Pre Anxiety Alone/Cortisol Pre T2	-0.183	0.468
Pre Anxiety Partner /Cortisol Pre T2	0.267	0.285
Pre Anxiety Stranger/Cortisol Pre T2	-0.047	0.853
Post Pleasantness Alone / Cortisol Post T2	-0.066	0.795
Post Pleasantness Partner / Cortisol Post T2	0.237	0.343
Post Pleasantness Stranger/ Cortisol Post T2	0.086	0.734
Post Anxiety Alone/ Cortisol Post T2	0.499	0.035
Post Anxiety Partner/ Cortisol Post T2	0.166	0.510
Post Anxiety Stranger/ Cortisol Post T2	0.189	0.452

Note. 'Pre' and 'Post' refer Pre- and Post-therapy results, respectively.
'T1' and 'T2' refer to cortisol samples being collected before and after fMRI threat task presentation, respectively.
Abbreviation: DAS = Dyadic Adjustment Scale

Table 7
Significant[a] *Fixed Effects ROI Analysis Results for the Alone Handholding Condition Pre- and Post-therapy*

Region of Interest	Pre Therapy - Alone					Post Therapy - Alone				
	Significance	Cluster Size	T score	Z score	x y z coordinates	Significance	Cluster Size	T score	Z score	x y z coordinates
OFC	0.003	128	5.70	5.69	30 58 -4	0.014	80	6.26	6.24	54 20 -6
	0.011	90	5.07	5.06	52 22 -6	0.033	59	4.84	4.83	-52 20 -6
						0.001	153	4.47	4.46	40 52 -8
								4.30	4.29	34 56 -2
								4.01	4.00	46 46 -4
DLPFC	0.000	401	5.74	5.72	28 60 4	0.000	717	5.31	5.30	20 54 26
			4.64	4.63	48 46 12			4.67	4.66	32 60 12
			3.91	3.91	42 52 4			4.21	4.21	26 54 8
DMPFC	n/a	n/a	n/a	n/a	n/a	0.002	165	5.55	5.53	8 52 40
						0.007	121	4.36	4.36	-28 54 18
								3.31	3.31	-20 46 28
IFG	n/a	n/a	n/a	n/a	n/a	0.044	24	4.87	4.87	-54 18 -2
Precentral	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
SMA	n/a	n/a	n/a	n/a	n/a	0.007	61	4.77	4.77	4 22 58
						0.006	64	4.76	4.75	8 -4 68
						0.011	50	4.57	4.56	2 22 58
ACC	n/a	n/a	n/a	n/a	n/a	0.003	114	4.27	4.26	-2 20 36
PCC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Insula	0.014	63	3.81	3.80	36 22 2	n/a	n/a	n/a	n/a	n/a
			3.28	3.28	32 16 6					
Precuneus	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Superior PL	0.049	22	4.54	4.54	40 -60 54	0.049	22	4.54	4.54	40 -60 54
			3.67	3.66	30 -66 54			3.67	3.66	30 -66 54
Superior TG	0.013	50	3.87	3.87	-64 -32 20	0.013	50	3.87	3.87	-64 -32 20
			3.44	3.44	-66 -42 18			3.44	3.44	-66 -42 18
			3.41	3.41	-62 -52 22			3.41	3.41	-62 -52 22
Amygdala	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Hippocampus	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Parahippocampus	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Basal Ganglia	0.000	229	4.98	4.97	24 14 6	n/a	n/a	n/a	n/a	n/a
(caudate,			4.30	4.29	32 -10 -4					
putamen,			3.66	3.66	26 2 -4					
pallidum)										
Thalamus	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

[a] Table shows significant ROI investigation at threshold of $p = 0.001$ (uncorrected), $p_{FWE} = 0.05$ cluster-wise correction, and cluster size>10.

Table 8
Significant[a] *Random Effects Analysis Results for Comparisons of Interest*

Comparison	Region	Area	Significance	Cluster size	x, y, z coordinates	Z score
Pre - Post Alone		n/a	n/a	n/a	n/a	n/a
Post - Pre Alone	Frontal	R SMA	0.000	43	6 24 58	5.90
	Occipital	Lingual Gyrus	0.003	10	0 -74 -2	5.15
	Subcortical	L Cerebellum	0.000	35	-26 -68 -18	5.54
Pre - Post Partner	Parietal	L Postcentral Gyrus	0.000	30	-22 -46 58	5.61
Post – Pre Partner	Frontal	L OFC	0.001	14	-28 28 -12	5.49
Pre – Post Stranger		n/a	n/a	n/a	n/a	n/a
Post – Pre Stranger		n/a	n/a	n/a	n/a	n/a
Pre Partner - Stranger	Frontal	R OFC	0.000	18	52 22 -6	5.75
		L OFC	0.003	10	-4 38 -14	5.23
		R ACC – dorsal	0.000	31	2 -14 50	5.64
		L ACC – rostral	0.005	10	-12 46 10	4.87
		R Insula	0.001	18	36 20 6	5.44
		L IFG	0.002	18	-42 44 2	5.37
		R DLPFC	0.002	11	36 34 42	5.29
		R SMA	0.002	11	6 22 46	5.26
		L DLPFC	0.005	10	-18 52 10	5.20
	Temporal	R Inferior TG	0.000	85	48 -22 -24	5.99
		L Middle TG	0.000	31	-58 -50 -10	5.84
Pre Partner - Alone	Frontal	L IFG	0.000	163	-46 42 -2	7.46
		R Precentral Gyrus	0.000	189	44 2 24	6.78
		L Precentral Gyrus	0.001	17	-36 -20 64	6.05
		R Insula	0.000	189	46 8 6	5.95
		L Insula	0.001	20	-38 12 2	5.82
		R SMA	0.000	268	6 -24 56	6.73

		L SMA	0.000	55	-18 -2 64	5.76
		R ACC - dorsal	0.000	268	2 -34 40	5.35
		L DMPFC	0.000	55	-20 8 62	6.58
		R DLPFC	0.000	39	34 50 10	6.29
		R OFC	0.000	48	38 44 -6	6.11
		L OFC	0.001	17	-48 20 -4	5.52
	Temporal	R Temporal Pole	0.000	72	50 14 -34	7.66
		R Fusiform Gyrus	0.000	493	46 -60 -22	7.24
		L Fusiform Gyrus	0.000	68	-24 -72 -16	6.12
		R Middle TG	0.000	122	52 -64 6	6.70
		L Middle TG	0.001	15	-56 -14 -8	5.96
		L Inferior TG	0.000	94	-58 -50 -14	6.37
		R Superior TG	0.000	90	58 -12 0	6.16
	Parietal	R Precuneus	0.000	1342	6 -50 48	Inf
		L Precuneus	0.000	42	-8 -62 40	5.74
		R Supramarginal Gyrus	0.000	255	58 -34 28	7.61
		L Superior PL	0.000	69	-24 -66 52	6.22
		L Inferior PL	0.001	17	-56 -36 38	5.71
		R Inferior PL	0.001	16	36 -50 54	5.41
	Occipital	L Calcarine	0.000	65	-8 -66 10	6.75
		L Lingual Gyrus	0.000	84	-8 -86 -14	6.56
		R Lingual Gyrus	0.000	26	24 -82 -4	5.84
		L Cuneus	0.000	30	-10 -92 26	6.48
		R Cuneus	0.000	22	8 -90 24	5.77
		R Middle OG	0.000	33	34 -72 34	6.12
		L Middle OG	0.003	10	-22 -92 0	5.29
	Subcortical	L Hippocampus	0.000	785	-12 -58 -32	Inf
		R Thalamus	0.000	46	12 -6 -2	6.16
		L Thalamus	0.000	29	-14 -8 4	5.34
		R Amygdala	0.002	11	32 -2 -26	5.50
		R Parahippocampus	0.002	11	32 -10 -28	5.02
		R Cerebellum	0.000	493	28 -58 -26	6.80
		L Cerebellum	0.000	84	-12 -80 -18	5.45
Pre Stranger - Alone	Temporal	R Temporal Pole	0.000	108	50 14 -28	7.02
		R Middle TG	0.000	108	50 2 -26	5.79
	Parietal	L Postcentral Gyrus	0.000	39	-28 -36 50	5.78
		R Precuneus	0.000	71	6 -52 52	6.87

	Occipital	R Lingual Gyrus	0.000	108	22 -84 -6	6.98
	Subcortical	L Hippocampus	0.000	67	-32 -26 -12	6.87
		R Caudate	0.000	46	12 12 16	6.02
		R Cerebellum	0.000	76	48 -54 -36	6.79
		L Cerebellum	0.002	13	-6 -84 -14	5.99
Post Partner - Stranger		n/a	n/a	n/a	n/a	n/a
Post Partner - Alone	Frontal	R Insula	0.000	39	32 22 12	6.28
		L Insula	0.001	19	-40 -2 10	5.26
		L IFG	0.001	19	-38 24 4	5.56
	Temporal	L Middle TG	0.000	459	-42 -66 10	Inf
		L Temporal Pole	0.000	75	-36 14 -36	7.29
		R Inferior TG	0.001	16	50 -58 -12	5.79
		L Inferior TG	0.000	41	-54 -12 -28	5.61
		R Superior TG	0.000	38	56 -18 -2	6.07
Parietal		L Superior PL	0.000	53	-18 -70 44	6.32
	Occipital	L Superior OG	0.000	25	-16 -84 16	6.30
	Subcortical	L Hippocampus	0.000	47	-28 -30 -10	6.34
		R Hippocampus	0.000	39	40 -26 -10	5.63
		R Thalamus	0.002	11	16 -30 4	5.36
		R Cerebellum	0.001	15	24 -52 -42	5.98
Post Stranger – Alone	Frontal	R IFG	0.000	89	38 18 14	6.24
		L IFG	0.000	23	-18 50 8	6.23
		L Insula	0.000	30	-32 12 -8	5.86
		R Insula	0.000	29	38 -2 12	5.67
		L OFC	0.000	26	-36 32 -12	5.59
		R OFC	0.001	19	12 20 -14	5.51
	Temporal	L Temporal Pole	0.000	45	-36 16 -36	Inf
		R Temporal Pole	0.001	20	54 4 -16	6.00
		L Middle TG	0.000	336	-42 -60 10	7.62
		R Middle TG	0.000	95	48 -32 -2	5.58
		R Superior TG	0.000	95	52 -20 -2	6.58
		L Superior TG	0.000	89	-44 -12 10	6.27
		R Inferior TG	0.000	53	50 -58 -12	6.26

		L Inferior TG	0.000	59	-44 0 -32	6.03
	Parietal	L Postcentral Gyrus	0.000	49	-52 -8 34	6.41
		L Inferior PL	0.000	24	-40 -48 40	5.71
	Occipital	L Lingual Gyrus	0.000	26	-6 -80 0	6.20
		L Middle OG	0.000	46	-26 -82 0	6.09
	Subcortical	L Hippocampus	0.000	45	-28 -32 -8	7.13
		R Thalamus	0.001	20	6 -18 8	6.00
		R Cerebellum	0.002	13	24 -54 -42	5.88
Pre Stranger - Partner		n/a	n/a	n/a	n/a	n/a
Pre Alone - Partner	Frontal	R DLPFC	0.000	163	48 44 16	Inf
		L DLPFC	0.000	51	-32 48 24	6.34
		R IFG	0.000	163	56 32 8	6.40
		L IFG	0.000	80	-54 16 20	6.33
		L OFC	0.000	257	-26 32 -6	7.15
		R DMPFC	0.000	108	24 42 38	7.26
		R OFC	0.000	105	8 48 2	6.65
		L OFC	0.000	223	-4 60 8	6.47
		L Precentral Gyrus	0.000	80	-58 8 26	5.71
		L Insula	0.000	81	-38 -6 8	5.71
		L PCC	0.000	46	-4 48 30	6.03
		R ACC - rostral	0.002	12	6 38 28	5.36
	Temporal	L Temporal Pole	0.000	201	-42 16 -24	7.41
		L Superior TG	0.000	230	-50 -28 4	6.95
		L Middle TG	0.000	103	-40 -58 -4	6.52
		R Middle TG	0.002	12	64 -52 14	6.23
	Parietal	L Inferior PL	0.000	23	-42 -50 56	6.90
		L Superior PL	0.000	47	-14 -78 46	6.27
		R Angular Gyrus	0.000	30	56 -62 32	6.26
		R Supramarginal Gyrus	0.000	42	52 -40 40	6.08
		L Postcentral Gyrus	0.002	11	-66 -16 26	5.70
		L Precuneus	0.001	19	-4 -44 10	5.09
	Occipital	R Inferior OG	0.000	99	32 -90 -2	7.08
		R Calcarine	0.000	23	16 -78 16	6.39
		L Calcarine	0.001	15	-22 -58 4	5.73

	Subcortical	L Putamen	0.000	257	-24 14 -6	7.65
		R Thalamus	0.001	19	10 -14 14	5.48
		L Cerebellum	0.001	19	-6 -36 -12	5.44
Pre Alone - Stranger	Frontal	L OFC	0.000	4871	-28 34 -8	Inf
		R OFC	0.000	98	52 24 -4	6.74
		R DMPFC	0.000	4871	26 42 38	Inf
		L IFG	0.000	1041	-52 14 14	Inf
		R IFG	0.000	42	58 12 10	6.09
		R Precentral Gyrus	0.000	254	46 6 36	6.98
		L Precentral Gyrus	0.000	30	-36 -8 58	6.04
		L SMA	0.000	140	-4 14 50	6.19
		L DLPFC	0.000	140	-42 20 44	6.01
		L ACC - dorsal	0.001	116	-8 -32 40	5.86
	Temporal	L Middle TG	0.000	79	-50 -28 -12	7.41
		R Middle TG	0.000	38	64 -52 12	5.84
		L Superior TG	0.000	272	-50 -30 6	6.66
		L Superior TG	0.000	61	-52 -4 -2	6.45
		R Superior TG	0.000	38	68 -40 12	5.24
		L Temporal Pole	0.001	19	-38 20 -34	6.40
		L Inferior TG	0.000	31	-42 -14 -22	5.12
	Parietal	L Postcentral Gyrus	0.000	296	-44 -20 36	Inf
		L Supramarginal Gyrus	0.000	254	-52 -42 30	6.99
		R Supramarginal Gyrus	0.000	37	38 -42 42	6.19
		R Angular Gyrus	0.000	61	52 -64 30	6.38
		L Angular Gyrus	0.002	13	-50 -62 24	5.77
	Occipital	L Lingual Gyrus	0.000	70	-20 -44 -2	7.03
		R Lingual Gyrus	0.000	29	18 -56 2	5.90
		R Middle OG	0.000	61	46 -70 28	5.04
		L Calcarine	0.000	23	-16 -70 14	6.28
	Subcortical	R Putamen	0.000	4871	28 10 0	7.72
		L Putamen	0.000	1041	-22 10 -4	7.30
		L Cerebellum	0.002	13	-24 -36 -30	5.99
Post Stranger – Partner	Frontal	L ACC - dorsal	0.003	10	-2 -10 46	5.37

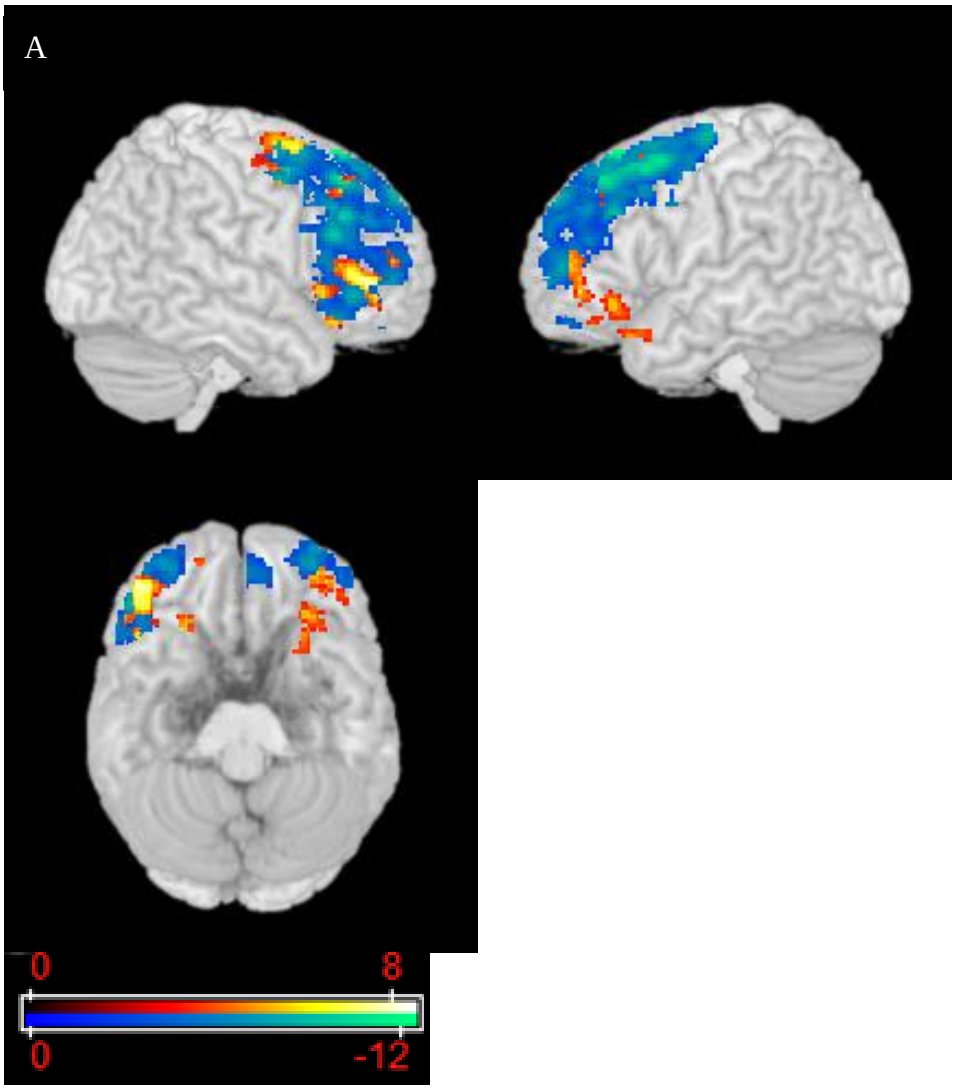
Post Alone - Partner	Frontal	R DMPFC	0.000	6845	10 24 60	Inf
		R Premotor Area	0.000	6845	36 8 56	Inf
		L DLPFC	0.000	495	-34 28 48	Inf
		R IFG	0.000	134	34 58 0	6.48
		L DLPFC	0.000	495	-24 44 40	7.29
		R OFC	0.000	134	30 52 8	6.70
		L Precentral Gyrus	0.000	127	-44 2 52	Inf
		L IFG	0.000	280	-52 26 22	Inf
		R OFC	0.000	535	2 30 -20	6.86
		L OFC	0.000	68	-52 34 -6	7.19
		R ACC – dorsal	0.000	71	12 30 16	6.77
		ACC – dorsal	0.000	23	0 14 36	5.33
	Temporal	L Inferior TG	0.000	458	-44 -46 -26	Inf
		L Superior TG	0.000	116	-66 -16 8	Inf
		R Superior TG	0.000	309	42 -26 10	Inf
		R Middle TG	0.000	635	64 -40 2	Inf
		L Middle TG	0.000	25	-68 -42 0	6.39
		R Fusiform Gyrus	0.000	345	36 -52 -20	Inf
		L Temporal Pole	0.000	139	-56 14 -6	7.78
		R Temporal Pole	0.000	97	52 14 -14	7.16
	Parietal	R Supramarginal Gyrus	0.000	309	66 -16 24	7.25
		L Inferior PL	0.000	75	-56 -30 46	Inf
		R Precuneus	0.000	344	8 -74 38	6.37
		R Superior PL	0.000	46	24 -74 48	6.15
		L Superior PL	0.000	45	-22 -68 54	5.45
		R Angular Gyrus	0.000	46	32 -66 44	5.06
	Occipital	R Lingual Gyrus	0.000	345	18 -62 -12	7.74
		L Lingual Gyrus	0.000	31	-20 -74 2	6.07
		L Cuneus	0.000	344	-4 -80 34	Inf
		R Cuneus	0.000	356	12 -88 22	7.56
		R Calcarine	0.000	356	4 -90 12	Inf
		L Calcarine	0.000	82	-4 -64 8	6.02
		R Inferior OG	0.000	105	44 -84 -4	6.80
		L Inferior OG	0.003	10	-48 -74 -10	5.70
		L Superior OG	0.000	27	-24 -80 42	6.41
		R Middle OG	0.003	10	36 -76 32	5.24
	Subcortical	R Parahippocampus	0.000	111	28 12 -30	7.46
		R Thalamus	0.000	535	12 -12 18	7.32
		R Amygdala	0.000	108	24 -6 -20	5.87
		L Cerebellum	0.000	458	-30 -34 -42	Inf

		R Cerebellum	0.000	345	30 -58 -22	7.03
Post Alone-Stranger	Frontal	R Precentral Gyrus	0.000	187	48 -10 50	Inf
		L Precentral Gyrus	0.000	26	-44 0 52	6.47
		R IFG	0.000	136	56 26 28	7.67
		L IFG	0.001	19	-42 12 26	5.83
		R IFG	0.001	14	62 14 10	5.72
		R SMA	0.000	174	8 18 56	7.23
		R DMPFC	0.000	174	8 30 58	5.26
		L Premotor Area	0.000	255	-26 12 58	7.09
		L DLPFC	0.000	255	-28 2 60	6.58
		R DLPFC	0.000	322	32 36 44	6.94
		R DMPFC	0.000	322	24 10 62	6.84
		L DMPFC	0.000	76	-22 32 30	5.68
		R DLPFC	0.000	45	18 46 30	6.03
		L DMPFC	0.000	36	-10 32 54	6.58
		L OFC	0.000	52	-2 44 -12	6.10
		R OFC	0.000	78	12 60 -2	5.57
		L ACC - rostral	0.001	17	-2 28 26	5.44
		R ACC - rostral	0.002	12	6 42 20	5.34
		R PCC	0.000	26	4 -44 32	5.68
		L PCC	0.000	21	-2 -34 28	5.42
	Temporal	L Inferior TG	0.000	832	-48 -46 -26	Inf
		L Superior TG	0.000	209	-64 -50 14	7.69
		R Superior TG	0.000	150	44 -28 10	7.15
		R Fusiform Gyrus	0.000	70	38 -52 -18	6.99
		R Middle TG	0.000	83	68 -36 -8	6.63
		L Middle TG	0.000	60	-66 -32 -2	6.41
		R Temporal Pole	0.000	28	44 8 -24	5.46
	Parietal	R Supramarginal Gyrus	0.000	487	62 -42 36	7.35
		R Angular Gyrus	0.000	35	52 -66 34	6.41
		L Inferior PL	0.000	31	-58 -30 46	7.25
		R Superior PL	0.000	354	20 -54 64	7.24
		L Superior PL	0.000	60	-26 -42 64	6.43
		L Precuneus	0.000	354	-6 -54 64	7.24
		R Precuneus	0.000	62	8 -78 44	7.04
		L Postcentral Gyrus	0.000	37	-18 -32 70	7.20
	Occipital	R Calcarine	0.000	307	2 -92 10	Inf
		R Cuneus	0.000	307	12-82 22	5.34
		L Cuneus	0.000	90	-2 -84 34	6.20

	R Inferior OG	0.000	49	28 -92 -12	5.65
	R Lingual Gyrus	0.000	99	20 -68 -14	6.67
	L Lingual Gyrus	0.002	12	-18 -50 -4	5.47
Subcortical	R Parahippocampus	0.000	27	28 12 -30	6.01
	R Hippocampus	0.001	20	28 -8 -22	5.59
	R Putamen	0.002	12	34 -10 -4	5.37
	L Cerebellum	0.000	832	-28 -64 -26	Inf
	R Cerebellum	0.000	208	30 -36 -44	6.20

[a] Table shows significant results at threshold of $p = 0.05$ (FWE corrected), and cluster size>10.
Abbreviations: SMA=Supplementary Motor Area, TG = Temporal Gyrus, OG = Occipital Gyrus, PL = Parietal Lobe, DLPFC = Dorsolateral Prefrontal Cortex, DM = Dorsomedial Prefrontal Cortex, IFG = Inferior Frontal Gyrus, OFC = Orbitofrontal Cortex, ACC= Anterior Cingulate Cortex, MCC = Middle Cingulate Cortex, PCC=Posterior Cingulate Cortex.
(R = Right Hemisphere, L= Left Hemisphere; Pre = Pre-therapy, Post = Post-therapy).

Figure 2. Neural threat attenuation for Partner handholding condition compared to Alone (significant results at threshold of $p = 0.05$ (FWE corrected), and cluster size>10). Red spectrum denotes pre-therapy increases in neural activity, and blue spectrum denotes post-therapy attenuation. A) Shows differences in PFC areas, namely the DLPFC, DMPFC, IFG and OFC. B) Shows differences in limbic areas, namely the ACC and amygdala.


A
0
8
0
-12


B
0
7
0
-8

Table 9
Significant[a] *Random Effects ROI Analysis Results for Main Comparisons within Conditions*

Region	Significance	Cluster Size	Z score	x y z coordinates	Significance	Cluster Size	Z score	x y z coordinates
	Post – Pre Partner				Pre – Post Partner			
Hippocampus	0.006	70	4.44	-24 -28 -10	n/a	n/a	n/a	n/a
			3.66	-26 -36 -6				
			3.62	-30 -40 0				
	0.016	47	4.35	-28 -12 -16				
Parahippocampus	0.007	69	4.88	-24 -30 -12	n/a	n/a	n/a	n/a
			3.74	-34 -44 -6				
Amygdala	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
OFC	0.009	95	5.49	-28 28 -12	n/a	n/a	n/a	n/a
ACC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
PCC	0.018	26	4.48	12 -44 18	0.025	20	3.70	4 -40 26
Thalamus	0.024	35	4.87	16 -32 4	n/a	n/a	n/a	n/a
DLPFC	n/a	n/a	n/a	n/a	0.000	423	5.42	36 20 54
							4.66	30 24 36
							4.28	40 36 36
Insula	0.044	37	4.66	-28 16 -8	0.038	40	4.06	48 0 2
			4.10	-28 26 -8				
	Post – Pre Stranger				Pre – Post Stranger			
Hippocampus	0.046	24	3.91	-26 -36 -6	n/a	n/a	n/a	n/a
Parahippocampus	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Amygdala	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
OFC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
ACC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
PCC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Thalamus	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
DLPFC	0.003	154	4.35	-28 50 20	n/a	n/a	n/a	n/a
Insula	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

	Post – Pre Alone				Pre – Post Alone			
Hippocampus	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Parahippocampus	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Amygdala	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
OFC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
ACC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
PCC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Thalamus	0.041	24	3.70	12 -12 18	n/a	n/a	n/a	n/a
			3.45	12 -22 18				
DLPFC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Insula	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

[a] Table shows significant ROI investigation at threshold of $p = 0.001$ (uncorrected), $p_{FWE} = 0.05$ cluster-wise correction, and cluster size>10.

Figure 3. Significant differences in neural activity for the Partner handholding condition following therapy (at threshold of $p = 0.001$ (uncorrected), $p_{FWE} = 0.05$ cluster-wise correction, and cluster size>10). Red spectrum shows increases in activity following therapy, whereas the blue spectrum shows decreases in activity. A) Shows differences in PFC areas, namely the DLPFC, and OFC. B) Shows differences in limbic areas, namely hippocampus and parahippocampus as well as OFC.

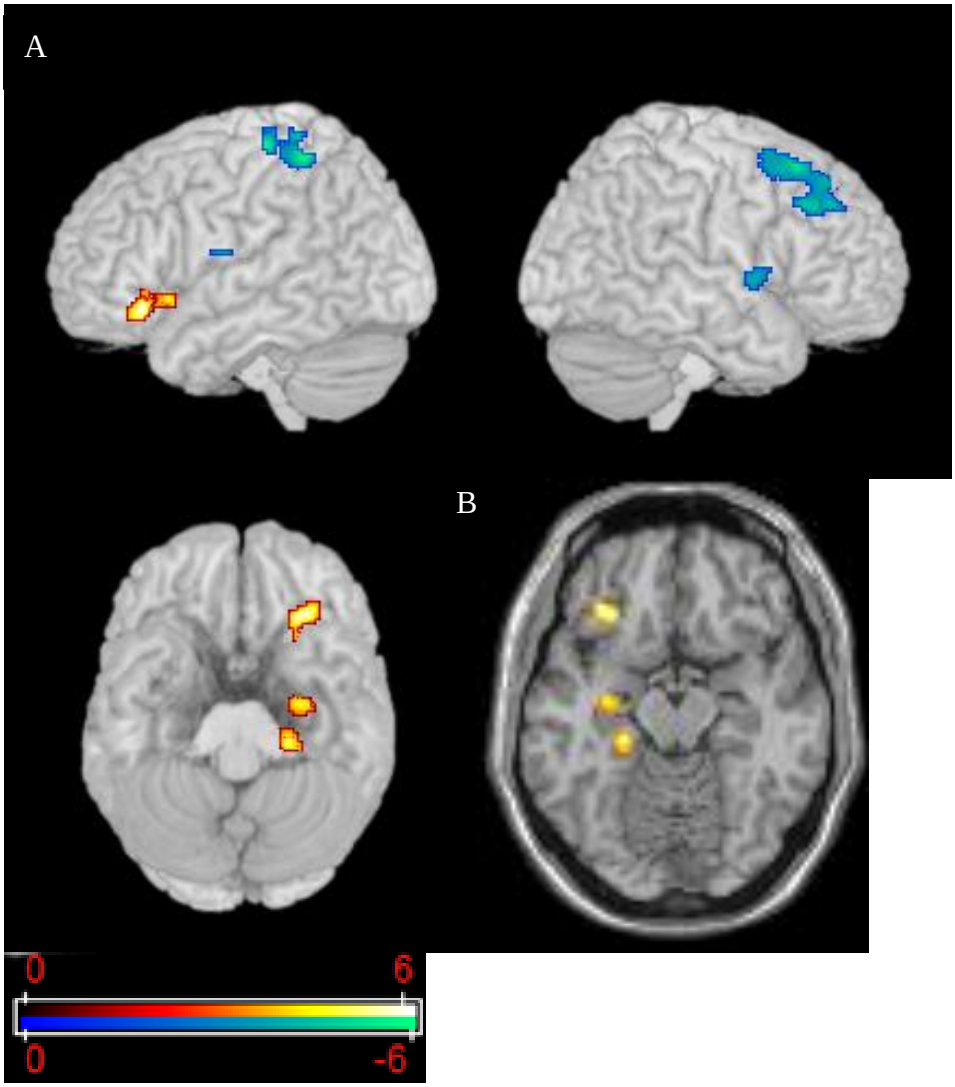
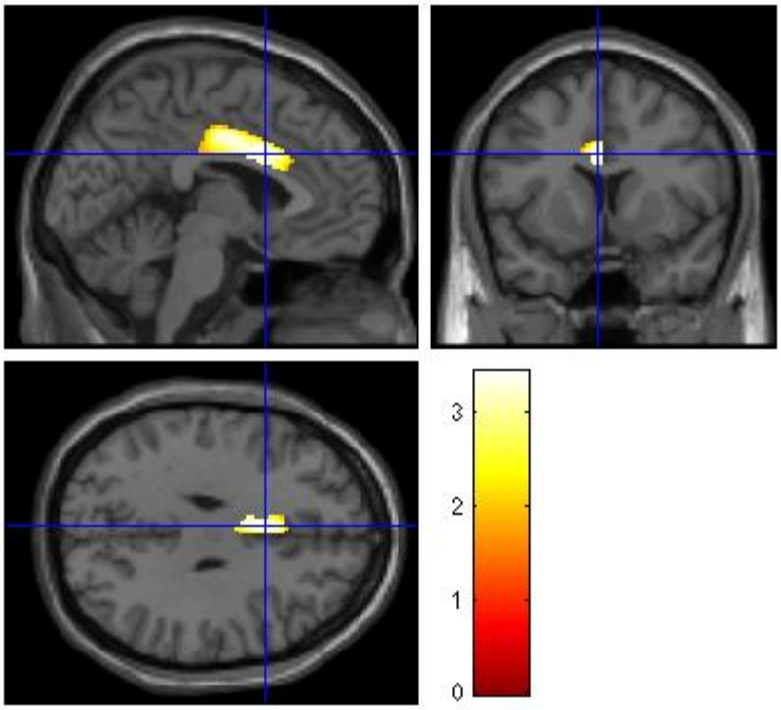

A
B
0
6
0
-6

Figure 4. Structural differences in WM observed post-therapy in the dorsal ACC (at threshold of $p = 0.05$ (uncorrected), $p_{FWE} = 0.05$ cluster-wise correction, and cluster size>10).


3
2
1
0