A Role for Ventromedial Prefrontal Cortex in Facial Emotion Recognition

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Abstract

Facial emotion is a fundamental building block of human communication and impaired emotion recognition is associated with a variety of neurological and psychiatric conditions. Prior work on the neural basis of emotion recognition demonstrated the amygdala's role in guiding fixations to emotionally informative regions of face stimuli. However, this is a complex process that is likely subserved by a number of brain regions. Ventromedial prefrontal cortex (vmPFC) is a candidate for playing a role in facial emotion recognition; vmPFC lesions produce marked social abnormalities, vmPFC exhibits abnormal function in a number of psychiatric disorders, and vmPFC is densely and reciprocally connected with the amygdala. This dissertation tests whether vmPFC is a critical node in a network subserving recognition of emotional facial expressions using behavioral tasks, eye tracking, and magnetic resonance imaging.

Subjects included neurosurgical patients with focal vmPFC lesions, youth with PTSD, and prison inmates. In a facial emotion recognition task, vmPFC lesion patients made fewer fixations to the eyes of faces than comparison subjects. vmPFC lesion patients were also impaired at recognizing moderate intensity expressions of anger, and instructing these patients to fixate on the eyes rescued this impairment. Next, in a study of youth with PTSD, females with PTSD had impaired emotion recognition, and the relationship of vmPFC-amygdala resting state functional connectivity to emotion recognition accuracy was moderated by PTSD diagnosis. Finally, in a study of prison inmates with a range of psychopathy scores, fixations to the eyes during emotion recognition were inversely related to interpersonal and affective traits of psychopathy. Interpersonal and affective traits in a different inmate sample related to uncinate fasciculus microstructural integrity. Together, these studies suggest that vmPFC plays a key role in emotion recognition and vmPFC-amygdala communication is a critical component of normal

emotion recognition and fixations. These studies extend the current understanding of the neural basis of emotion recognition and elucidate the structures that may be affected to perturb emotion recognition across psychiatric diagnoses.

Chapter 1. Introduction and Significance

The fundamental importance of facial emotion expressions for social communication has been recognized for centuries. Darwin wrote at length in 1872 on "the instinctive recognition of expression" and the universality of emotion (Darwin, 2002). Modern studies support Darwin's claims of instinctual face processing with findings that infants less than an hour old show preferential attending to faces versus scrambled face stimuli (Morton & Johnson, 1991). Further evidence for the ubiquity of facial expressions comes from seminal studies that identified six basic emotions (happiness, sadness, fear, anger, disgust, and surprise) commonly recognized across cultures with a wide range of geographic origin and technological development (Ekman & Friesen, 1971; Ekman, Sorenson, & Friesen, 1969). These basic expressions can provide information about the environment; for example, noticing fearful expressions of those around you might increase your alertness for a nearby danger. They can also provide behavioral reinforcement; an expression of disgust from your dinner date may lead you to chew with your mouth closed, while a smile lets you know that he or she enjoys the current conversation. Facial emotion is so fundamental to human communication that the absence of expression in one's audience produces a physiological stress response in most healthy individuals (Kirschbaum, Pirke, & Hellhammer, 1993). It is easy to see, then, that abnormal processing of facial affect can lead to impairments in social functioning that range from simple misunderstandings of intended meaning to anxiety to interpersonal aggression.

Abnormal recognition and processing of facial emotion is present in a range of psychiatric disorders, especially those involving social dysfunction. Studies report emotion recognition impairments in patients with schizophrenia, for example (Brüne, 2005; Larøi,

Fonteneau, Mourad, & Raballo, 2010). Likewise, individuals with autism spectrum disorders, who have profound social impairments, have abnormal visual fixation patterns and neural activity during emotion recognition (Harms, Martin, & Wallace, 2010). Affective face processing can also be biased by experience; maltreated children tend to over-identify anger (Pollak & Kistler, 2002). While facial affect processing abnormalities have been identified in individuals with schizophrenia, autism, and a history of trauma, emotion processing impairments are theorized to play an especially critical role in psychopathy (Blair, Jones, Clark, & Smith, 1997). Several studies have demonstrated emotion recognition impairments in these individuals (Blair et al., 2004; Hastings, Tangney, & Stuewig, 2008), and deficient emotion processing could account for the callous behavior of psychopathic individuals. The fact that facial emotion recognition impairments are present in such a wide array of mental illnesses suggests that there may be a common neural mechanism subserving this function that is likely distributed throughout a number of brain regions affected in these disorders.

A substantial body of research implicates the amygdala, a set of nuclei in the medial temporal lobe, in recognizing emotional content from facial expressions. Results from both non-human primate research (Gothard, Battaglia, Erickson, Spitler, & Amaral, 2007) and human neuroimaging studies (Whalen et al., 2004; Whalen et al., 1998) converge on a role for the amygdala in processing facial expressions. Additionally, human lesion studies indicate that the amygdala contributes to the control of visual fixations during emotion recognition by guiding fixations towards emotionally salient regions of the face, specifically the eyes (Adolphs et al., 2005). However, facial emotion recognition is a complicated task that likely requires coordinated processing across a network of brain regions, including, but not limited to, the amygdala. One region that may play a role alongside the amygdala in emotion recognition is ventromedial

prefrontal cortex (vmPFC). Several studies report emotion recognition impairment in patients with vmPFC lesions (Heberlein, Padon, Gillihan, Farah, & Fellows, 2008; Hornak, Rolls, & Wade, 1996; Tsuchida & Fellows, 2012). Additionally, the amygdala and vmPFC share strong bidirectional projections by way of the uncinate fasciculus (Ghashghaei & Barbas, 2002). Given the apparent involvement of vmPFC in emotion recognition and its anatomical connections with the amygdala, it is possible that vmPFC is another critical node in a network subserving recognition of emotional facial expressions.

Research Strategy

With facial emotion playing such a ubiquitous and critical role in human communication and behavior, a great deal can be learned about human emotion, behavior, and mental illness from a clearer understanding of the neurobiological substrates of emotion recognition. As outlined above, a number of mental illnesses are associated with abnormalities in processing facial affect. The Research Domain Criteria (RDoC) project of the National Institute of Mental Health emphasizes a dimensional approach to psychopathology (Insel et al., 2010). In this framework, categorically different psychiatric disorders may be thought of as different points on a spectrum of function within a given domain. For example, reduced recognition of facial emotion may result in a failure in theory of mind or empathy, while excessive attention to facial cues of threat may result in anxiety. This dissertation research aims to add to the understanding of the neural mechanisms of facial emotion processing by combining behavioral tasks with eye tracking, MRI, the human lesion method, and the study of two clinical samples expected to be at different ends of the emotion processing spectrum: children with posttraumatic stress disorder (PTSD) and prison inmates with psychopathy. Using behavioral tasks and eye tracking in a

group of patients with vmPFC lesions, I first describe a pair of experiments that implicate vmPFC as being critically necessary for facial emotion recognition by influencing the spatial distribution of fixations. Next, I examine the relationship between emotion recognition, eye fixations, and vmPFC structure and function in two psychiatric populations, pediatric PTSD and psychopathy, that both have been reported to have abnormalities relating to facial emotion recognition. This program of research thereby broadens the literature on the neural basis of emotion recognition and elucidates neural mechanisms underlying psychiatric disorders that involve abnormal emotion recognition.

Chapter 2. The Neural Basis for the Modularity of Emotion Recognition

Faces are particularly complex visual stimuli because they convey high-level, but independent, pieces of information such as identity, sex, and emotion (Bruce & Young, 1986). Different categories of emotion are distinguished by different configurations of the facial muscles, eyelids, and mouth. In a simplification of a prominent model of processing in the visual system and related structures, the complexity of information about the stimulus is layered on top of that information which has already been processed: primary visual cortex would process structural features such as contours, while downstream regions such as the fusiform gyrus process features specific to faces, while additional regions in this network process information such as emotion and identity (Goodale & Milner, 1992). While the visual system certainly has a broadly hierarchical structure, the most parsimonious theories also acknowledge the likelihood of multiple parallel pathways and recurrence in this system (Pessoa & Adolphs, 2010).

It is critical to note that emotion recognition is a somewhat modular function, distinct from processes such as identity recognition (Bruce & Young, 1986; Haxby, Hoffman, & Gobbini, 2000). The neural response to identity changes can be distinguished from the neural response to emotion changes in faces (LaBar, Crupain, Voyvodic, & McCarthy, 2003). Additionally, individuals with prosopagnosia, the selective impairment of facial identity recognition, may have intact recognition of facial emotion (Duchaine, Parker, & Nakayama, 2003). Furthermore, unit recordings in nonhuman primates indicate that the responses to expression and identity can be distinguished at the neural level; neurons in the macaque superior temporal sulcus respond to distinct expressions independent of identity (Hasselmo, Rolls, &

Baylis, 1989), while neurons in the inferior temporal gyrus respond to identity (Desimone, 1991). Distinct neurons in basolateral amygdala are also selective for expression and identity, separately (Gothard et al., 2007). It follows that emotion recognition can be selectively impaired in individuals that have no difficulties discerning other information, such as identity or sex, from faces.

Much of current knowledge of selective emotion recognition impairments comes from studies of a rare neurological patient known as SM, who has focal bilateral amygdala damage. In one study, SM was fully capable of identifying familiar faces, but rated faces displaying fear, surprise, and anger as less intense than did brain-damaged comparison subjects (Adolphs, Tranel, Damasio, & Damasio, 1994). SM appeared to specifically fail to recognize fear, as her ratings of fearful faces did not correlate with those ratings made by healthy subjects. In a later study with SM, subjects were asked to identify whether a face was happy or fearful, but on each trial only random portions of the face were visible (Adolphs et al., 2005). SM required more of the face to be revealed to reach accuracy commensurate with that of comparison subjects, suggesting that she uses visual information present in the face less efficiently. Specifically, while healthy subjects used information at the eyes to discern fear from happiness, SM did not use information presented in the eyes. However, SM performed comparably to healthy subjects in a gender discrimination task, and both SM and healthy subjects used information from the eyes to perform this task. When subjects' eye movements during emotion recognition were tracked, SM fixated to the eyes less than did healthy subjects. Finally, when SM was instructed to gaze at the eyes of faces, her recognition accuracy improved. Together these findings indicate that SM is indeed capable of utilizing information from the eyes, that her selective emotion recognition impairment

is due to a failure to automatically fixate to emotionally informative regions of the face, and that the amygdala must be necessary for these processes.

Prompted by the initial finding of SM's emotion recognition impairment and her lesion specificity, a wealth of research has been devoted to understanding the role of the amygdala in facial affect recognition and visual fixations. The amygdala is activated by the presentation of faces in fMRI tasks, especially fearful faces, even when the observer is not consciously aware of their presentation (Whalen et al., 1998). Further, amygdala activation appears to be driven by the eyes, as backward-masked presentation of fearful eye whites activates the amygdala strongly relative to eye whites of happy faces (Whalen et al., 2004). One possibility is that the amygdala generates a signal that prompts one to fixate to emotionally informative regions of the face, perhaps when further information is necessary to discern the emotional expression. One study examined this possibility by making participants initially attend to the eyes or mouth of faces during an fMRI emotion recognition task (Gamer & Buchel, 2009). Amygdala activation was strongest when subjects began a trial fixated on the mouth of a fear face, and the magnitude of this activation in the right lateral amygdala predicted larger gaze shifts towards the eye region of fear faces. Although Whalen et al. (2004) found enhanced amygdala activation when viewing fearful eye whites, these stimuli were presented outside of conscious awareness. Thus, a possible explanation for why the amygdala has enhanced activation to unconsciously attended fearful eyes, but consciously attended fear mouths, is that the amygdala signals for further information in order to correctly categorize the emotion. This proposal is also consistent with findings that SM is particularly unlikely to make her first saccade upon face presentation towards the eyes of the face, and that when a face is blacked out except for the location of current fixation (forcing a

participant to use exhaustive brute force scanning to take in visual information) SM's fear recognition ability is normal (Kennedy & Adolphs, 2010).

Consistent with the proposal above, the amygdala is hypothesized to play a role in detecting salient information and prioritizing attention to goal relevant information (Pessoa & Adolphs, 2010). This model emphasizes the role of the amygdala in an attentional network, but relatively little is known about other structures in this network in comparison to the extent of study that the amygdala has received. Structurally, the amygdala is heavily and reciprocally connected with vmPFC (Ghashghaei & Barbas, 2002), and the two structures similarly have reciprocal connections with medial dorsal thalamus and receive projections from sensory cortices (Barbas, 2000; Krettek & Price, 1974; Xiao, Zikopoulos, & Barbas, 2009). The frontal eye fields, which control the spatial distribution of fixations, receive projections from medial dorsal thalamus, providing a mechanism by which vmPFC and amygdala might affect eye movements during emotion recognition. Given the convergence of anatomical connections between the amygdala and vmPFC, a natural hypothesis is that vmPFC is another node in this amygdala-centric emotion and visual fixation network, and plays a role in the recognition of emotional expressions.

Chapter 3. Functions of Ventromedial Prefrontal Cortex

A key function attributed to vmPFC is value-based decision-making. Clinical descriptions of neurological patients who sustain damage to this region show evidence of decision-making impairments and irrational behavior in addition to the aforementioned abnormal social functioning (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Barrash, Tranel, & Anderson, 2000; Eslinger & Damasio, 1985). However, there is also evidence that vmPFC may be more broadly involved in emotion-related processes.

The seminal laboratory study of decision-making with vmPFC lesion patients employed the Iowa Gambling Task (IGT). In the IGT, subjects pick cards from four decks, with each card indicating a monetary gain or loss, in an attempt to maximize overall profit. The key manipulation of this task is that two decks are "good" in the long-term (modest but consistent gains) whereas two decks are "bad" in the long-term (large initial gains followed by larger subsequent losses). Through their experience with the different decks, healthy subjects eventually learn to avoid "bad" decks, while EVR and other patients with vmPFC lesions persist in selecting from the "bad" decks (Bechara, Damasio, Damasio, & Anderson, 1994). A subsequent study found that as the task progresses, healthy subjects begin to generate anticipatory skin conductance responses (SCRs) before selecting from the "bad" decks, but patients with vmPFC damage develop no such anticipatory SCRs in this task (Bechara, Damasio, Tranel, & Damasio, 1997). Later studies using functional magnetic resonance imaging (fMRI) and the IGT in healthy subjects have offered further confirmation of the pivotal role of vmPFC in emotional decision-making (Fukui, Murai, Fukuyama, Hayashi, & Hanakawa, 2005; Li, Lu, D'Argembeau, Ng, & Bechara, 2010). Consistent with a role for vmPFC in outcome value representation, blood oxygen level-dependent (BOLD) response magnitude in vmPFC is

correlated with the value of appetitive and aversive choices in fMRI tasks (Plassmann, O'Doherty, & Rangel, 2007; Plassmann, O'Doherty, & Rangel, 2010). Studies in nonhuman primates largely support these results by demonstrating that vmPFC neurons are sensitive to a variety of parameters of reward (Grabenhorst & Rolls, 2011; Monosov & Hikosaka, 2012). Building on the IGT findings, a number of more recent studies of human vmPFC lesion patients have demonstrated abnormalities in value-based decision-making, including tasks involving risky gambles (Studer, Manes, Humphreys, Robbins, & Clark, 2015), reinforcement learning (Camille, Tsuchida, & Fellows, 2011; Fellows & Farah, 2003), moral judgment (Koenigs et al., 2007; Young et al., 2010), and item preference (Henri-Bhargava, Simioni, & Fellows, 2012).

Although vmPFC has long been hypothesized to play a role in emotion processing (Damasio, 1996; Harlow, 1868), considerably less is known about its role in this domain, and less still in regards to recognition of facial affect. However, vmPFC responses to affective pictures, including faces, have been observed (Pessoa, McKenna, Gutierrez, & Ungerleider, 2002). A meta-analysis of fMRI tasks employing affective faces as stimuli also strongly suggests a role for vmPFC in processing facial emotion (Fusar-Poli et al., 2009). In a study using unit recordings from depth electrodes placed in right vmPFC and ventrolateral (vl)PFC, vmPFC, but not vlPFC, discriminated fearful from happy faces (Kawasaki et al., 2001). Moreover, this discrimination happened as early as 120 ms post-stimulus onset, a latency that is consistent with vmPFC influencing subsequent fixation deployment. Furthermore, vmPFC deactivation predicts amygdala activation in response to fearful eye whites (Whalen et al., 2004). Thus, there is mounting evidence that vmPFC is involved in facial affect recognition. However, there is a need for a clearer understanding of the context and specificity of vmPFC function during this process, as well as research linking vmPFC function to performance during emotion recognition.

Evidence linking vmPFC function to performance in emotion recognition primarily comes from human lesion studies. The notion that vmPFC plays a role in processing emotional information is supported by behavioral evidence that vmPFC damage results in impairments in recognizing facial emotion, however these results have been equivocal. One study reports no significant overall impairment among patients with vmPFC damage (Hornak et al., 2003). Other studies identified emotion recognition impairments in patients with vmPFC damage, but impairments were also observed in patients with damage in other regions of the frontal lobe (Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Shaw et al., 2005). However, several studies show emotion recognition deficits specifically in patients with vmPFC damage. One early study found that vmPFC damage resulted in impaired emotion recognition, but did not distinguish between types of emotions (Hornak et al., 1996). Other studies have found impaired detection of emotions (Heberlein et al., 2008) and lower recognition accuracy across all emotions in patients with vmPFC damage (Tsuchida & Fellows, 2012). Finally, vmPFC damage has been reported to specifically impair recognition of fear, surprise, and disgust (Vandekerckhove et al., 2014).

There are several possible explanations for null or inconsistent findings of facial emotion recognition impairments in patients with vmPFC damage. One reason may be the lesion characteristics of the vmPFC patients. Each of the previous studies included patients with unilateral vmPFC damage, potentially allowing for complete or partial preservation of function by the intact hemisphere. Varying degrees of unilateral versus bilateral damage in the vmPFC patient samples between studies could potentially account for the mixed results. Notably, in one study that specifically examined the performance of the subset of patients with bilateral vmPFC lesions, it was found that three of the five bilateral cases had significant impairment in facial

emotion recognition (Hornak et al., 2003). A second reason may be the sensitivity of the recognition test. Two of the studies showing deficits in vmPFC patients used tests requiring the detection of subtle differences in facial expressions of emotion (Heberlein et al., 2008; Tsuchida & Fellows, 2012), rather than categorical identification of more exaggerated expressions (Hornak et al., 2003; Hornak et al., 1996; Shamay-Tsoory et al., 2003). Thus, these ostensibly conflicting results could potentially be reconciled by a study that uses expressions with graded emotional intensity to detect more subtle impairments in facial emotion recognition in patients with bilateral damage to vmPFC.

In sum, vmPFC has a clearly established role in value-based decision-making, and there is some evidence that vmPFC may be involved in facial emotion recognition. Studies of the amygdala's role in facial affect processing suggest that the amygdala contributes in part to directing fixations to the eyes of faces (Adolphs et al., 2005; Whalen et al., 2004). It is possible that vmPFC also influences the spatial distribution of fixations during emotion recognition. To examine this possibility, the studies described in **Chapter 7** and **Chapter 8** employ eye tracking and sensitive tests of emotion recognition in patients with vmPFC damage. These studies seek to establish a critical role for vmPFC in facial emotion recognition and guiding fixation patterns. However, this dissertation seeks not only to identify a relationship between vmPFC and emotion recognition, but also to test for the presence of this relationship in populations at different points on an emotion processing spectrum. Several psychiatric disorders associated with vmPFC abnormalities also show abnormal emotion processing. In an attempt to more clearly understand the role of vmPFC in emotion processing and assigning affective value to emotional stimuli, the present research will also consider two psychiatric populations that have disparate symptoms, but abnormal emotion processing; posttraumatic stress disorder (PTSD) and psychopathy.

Chapter 4. Ventromedial Prefrontal Cortex in Posttraumatic Stress Disorder

PTSD is diagnosed as a combination of symptoms present after the experience of a traumatic event that include intrusive re-experiencing of the event, avoidance of stimuli that remind one of the event or emotional numbing, and hyperarousal (APA, 2013). This is a pervasive disorder that affects a broad range of individuals; lifetime prevalence for PTSD is approximately 7.8% (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). A prevailing model of PTSD neuropathology emphasizes hyperactivity in the amygdala and hypoactivity in vmPFC (Rauch, Shin, & Phelps, 2006). Critically, this model attributes specific features of PTSD to vmPFC hypoactivation, including suppressing attentional allocation towards trauma-relevant stimuli. Thus, this model predicts compromised vmPFC function in individuals with PTSD when processing emotional stimuli.

Several studies report abnormal vmPFC function in PTSD patients when viewing trauma-relevant stimuli. In a PET study of women with a history of childhood sexual abuse, half of which had a PTSD diagnosis, PTSD patients had reduced vmPFC activity compared to controls during trauma-related imagery (Shin et al., 1999). In a study of veterans, PTSD symptom severity negatively related to activation in vmPFC during trauma-related imagery (Shin et al., 2004). Additionally, increased activation in vmPFC following exposure-based therapy for PTSD patients relates to PTSD symptom reduction (Felmingham et al., 2007). Finally, meta-analyses of neuroimaging studies on PTSD consistently indicate that vmPFC is hypoactive in this disorder (Etkin & Wager, 2007; Patel, Spreng, Shin, & Girard, 2012). Thus, vmPFC function is consistently perturbed in PTSD during the processing of affectively laden stimuli.

There is also evidence of vmPFC abnormalities related to face viewing in PTSD; two studies have reported diminished vmPFC BOLD response in PTSD when consciously attending to fearful faces (Shin et al., 2005; Williams et al., 2006). However, in a study of adolescents with post-traumatic stress symptoms (PTSS), Garrett et al. (2012) reported increased amygdala and vmPFC activation in PTSS youth relative to healthy non-traumatized youth in response to emotional and neutral faces during an explicit recognition paradigm. Moreover, greater activation in vmPFC during late phases of the response to fear faces predicted both greater total PTSS and greater re-experiencing symptoms. Another study of adolescent sexual assault victims reported an inverse relationship between PTSS and amygdala-vmPFC functional connectivity when viewing fear versus neutral faces (Cisler, Steele, Smitherman, Lenow, & Kilts, 2013). Thus, studies of facial emotion processing in youth with PTSS implicate vmPFC and the amygdala, although the precise nature of the relationship between vmPFC function and facial emotion recognition in PTSD remains poorly understood.

While vmPFC functional abnormality is certainly a feature of PTSD, and seems to be present during face processing, a critical question that remains to be addressed is whether emotion recognition accuracy and fixation patterns are related to vmPFC dysfunction in PTSD. While several studies reviewed above provide evidence that vmPFC abnormalities in PTSD may be related to how individuals with PTSD process emotional stimuli, no study has yet directly measured the spatial deployment of fixations during emotion recognition or directly related emotion recognition abilities to vmPFC function. Furthermore, emotion recognition has not yet been explicitly examined in pediatric PTSD. **Chapter 9** characterizes emotion recognition and fixation patterns in pediatric PTSD, and relates those measures to vmPFC function.

Chapter 5. Ventromedial Prefrontal Cortex in Psychopathy

Psychopathy is characterized by traits such as glibness, grandiosity, manipulativeness, impulsivity, irresponsibility, and a parasitic lifestyle. This disorder poses a significant societal cost; while it is approximated that only 1% of the U.S. population meets criteria for psychopathy (Neumann & Hare, 2008), psychopathic individuals constitute an estimated 25% of the prison population (Hare, 1996). Neurobiological accounts of psychopathy place significant emphasis on vmPFC and amygdala dysfunction in giving rise to the notable personality traits characteristic of the disorder (Blair, 2003; Kiehl, 2006). Indeed, early researchers of patients with vmPFC damage referred to such patients as "pseudopsychopaths" based on the pattern of irresponsible and impulsive behavior that vmPFC lesions produce (Blumer & Benson, 1975).

Several vmPFC abnormalities have been reported in psychopathy, including cortical thinning (Yang, Raine, Colletti, Toga, & Narr, 2010) and reduced gray matter volume (Ermer, Cope, Nyalakanti, Calhoun, & Kiehl, 2012). With regards to white matter, several studies have found reduced integrity of the uncinate fasciculus, a major fiber bundle connecting vmPFC and the amygdala, in psychopathic individuals, suggesting impaired connectivity between these two regions (Craig et al., 2009; Motzkin, Newman, Kiehl, & Koenigs, 2011). Moreover, Motzkin and colleagues found that psychopathic inmates also had reduced resting state fMRI functional connectivity between the amygdala and vmPFC. In sum, there is a mounting corpus of findings implicating vmPFC abnormalities in psychopathy.

Although little is known about neural abnormalities in individuals with psychopathy during emotion recognition, several studies have reported emotion recognition impairments in psychopathic individuals. In a task where emotional expressions morphed by intensity from neutral to full intensity of a given emotion, psychopathic inmates required higher intensity

expressions than nonpsychopathic inmates for accurate fear recognition (Blair et al., 2004). In addition to fear recognition impairments, another study of psychopathic inmates reported impaired sadness recognition in psychopathic individuals (Hastings et al., 2008). However, in a forensic sample (averaging subclinical psychopathy scores), Book, Quinsey, and Langford (2007) found that psychopathy scores were not associated with fear recognition accuracy and that psychopathy scores predicted greater accuracy for judging intensity of emotions. These discrepant findings underscore the need to research emotion recognition in inmate samples that have a wider range of psychopathic traits, including more subjects meeting diagnostic criteria for psychopathy. A more definitive answer to whether or not psychopathic criminal offenders have impaired facial emotion recognition can be obtained through a study adhering to the accepted and validated diagnostic criteria of psychopathy in a large inmate sample.

No study has yet investigated the pattern of visual fixations in psychopathic individuals when judging facial affect. Studies have, however, explored fixation patterns during emotion recognition in children with callous and unemotional (CU) traits, which are thought to be developmental precursors to psychopathy (Barry et al., 2000). Boys high in CU traits have poorer fear recognition than boys low in these traits (Dadds et al., 2006). Furthermore, boys with high CU traits show improved fear recognition when instructed to fixate on the eyes of faces. In a follow-up study that used eye tracking, this group found that boys high in CU traits made fewer fixations to the eye regions of faces compared to boys low in CU traits (Dadds, El Masry, Wimalaweera, & Guastella, 2008). Together, these studies indicate that the pattern of fixations during affect recognition in a precursor to psychopathy bears striking resemblance to the pattern of fixations in SM, who has bilateral amygdala damage (Adolphs et al., 2005). However, there is

strong evidence that psychopathy is associated with vmPFC abnormality, a structure that has prominent interactions with the amygdala.

There is a significant gap in the current understanding of emotion recognition and visual fixations in psychopathy, and neuroimaging and neuropsychological studies suggest that these functions may be related to vmPFC and amygdala abnormality in this disorder. To address this gap in the literature, **Chapter 10** presents a pair of studies utilizing inmate samples and adhering to the accepted diagnostic criteria of the PCL-R in order to elucidate the relationship of emotion recognition, visual fixations, and neural circuitry in psychopathy.

Chapter 6. Objectives

While a substantial corpus of research has unequivocally linked the amygdala to emotion recognition, and specifically the pattern of fixations during recognition, less is known about the broader network of brain regions that subserve these psychological processes. Ventromedial PFC may be involved in this broader emotion recognition circuit given its anatomical connections with the amygdala and its activation during emotion recognition tasks. However, questions remain regarding the precise role of vmPFC in facial emotion recognition. It is unclear whether vmPFC's involvement in emotion recognition is to affect the distribution of fixations over a face stimulus. Furthermore, is there a relationship between vmPFC structure or function and emotion recognition in psychiatric patient groups with impairments in processing facial emotion?

This dissertation seeks to elucidate the role of vmPFC in emotion recognition by addressing the questions identified above. In the next four chapters, I describe experiments that implicate vmPFC as being critical for facial emotion recognition by affecting fixations to the eyes of faces, and demonstrate the importance of this brain-behavior relationship in distinct psychiatric patient samples. In **Chapter 7**, I use eye tracking in a sample of neurosurgical patients with circumscribed lesions in vmPFC to examine the extent to which vmPFC damage is associated with reduced fixations to the eyes of emotional faces. In **Chapter 8**, I determine whether vmPFC damage is associated with impaired recognition of relatively low intensity facial expressions, and if effortful fixation to the eyes of emotional faces can ameliorate any observed recognition deficit in these patients. **Chapter 9** examines the relationship of emotion recognition, fixation patterns, and resting state functional connectivity in a pediatric sample of PTSD patients. Finally, **Chapter 10** addresses the relationship of these variables in psychopathic prison inmates.

Chapter 7. Ventromedial Prefrontal Cortex is Critical for Normal Fixations During Facial Emotion Recognition

There is mounting evidence that fixations to the eyes of faces are particularly important for recognition of negative social emotions, such as fear and sadness (Eisenbarth & Alpers, 2011; Smith, Cottrell, Gosselin, & Schyns, 2005). Regarding the neural circuitry subserving this process, the role of the amygdala in fixating to the eyes of faces is best understood and is believed to play a causal role in shaping patterns of fixation during emotion recognition, especially fear (Adolphs et al., 2005; Whalen et al., 2004). However, emotion recognition is a complex process likely to depend on a network of brain regions. Ventromedial PFC shares dense reciprocal connections with the amygdala (Ghashghaei & Barbas, 2002), and the two structures also project to and receive projections from intersecting sets of other brain regions (Barbas, 2000), suggesting that vmPFC may also be a node in a facial emotion recognition network.

There is also evidence directly implicating vmPFC in emotion recognition processes. Patients with lesions in vmPFC exhibit social behavior abnormalities that indicate an emotion processing impairment (Barrash et al., 2000; Damasio, 1996; Eslinger & Damasio, 1985). Additionally, several studies have identified facial emotion recognition impairments in patients with circumscribed vmPFC damage (Heberlein et al., 2008; Hornak et al., 1996; Tsuchida & Fellows, 2012; Vandekerckhove et al., 2014). As of yet, however, no study has investigated the proximate mechanism for putative facial affect recognition impairments associated with vmPFC damage. In this study I will use eye tracking and emotional face stimuli to test whether patterns of fixation to emotional faces differ between patients with vmPFC lesions and comparison subjects. If patients with vmPFC lesions fail to fixate normally to emotionally informative

regions of the face, it may be the case that this disturbed pattern of fixations accounts for previously reported emotion recognition impairments in this population.

Methods

Participants

The target lesion group consisted of three neurosurgical patients with extensive bilateral parenchymal changes, largely confined to the vmPFC, where vmPFC is defined as Brodmann areas 11, 12, 25, 32, and the medial portion of 10 below the level of the genu of the corpus callosum (Figure 7.1). All three patients had large anterior cranial fossa meningiomas with vasogenic edema. Their clinical presentations were subtle or obvious personality changes over at least several months preceding surgery. Each patient underwent gross total tumor resection without any intraoperative or postoperative complications. On post-surgical magnetic resonance imaging (MRI), although vasogenic edema largely resolved, there were persistent circumscribed bilateral vmPFC lesions in each patient.

Ten neurosurgical patients who had focal lesions outside of vmPFC comprised a brain-damaged comparison (BDC) group, which included $n = 8$ patients who had undergone tumor resections and $n = 2$ patients who had undergone surgery for aneurysm clipping following subarachnoid hemorrhage. Lesions in the BDC group involved ventral or lateral anterior temporal cortex ($n = 5$), dorsomedial frontal cortex ($n = 3$), lateral frontal and temporal cortex ($n = 1$), and cerebellum ($n = 1$). All vmPFC and BDC patients' neurosurgeries were performed in adulthood, and all experimental data were collected at least three months after surgery, during the chronic phase of recovery. The inclusion of these BDC patients allows me to rule out the possibility that the pattern of eye fixations observed in the vmPFC lesion group could be due to

anatomically non-specific effects of brain damage or a history of related medical issues (e.g., craniotomy, edema, seizure, past medications, etc.). All neurosurgical patients (vmPFC and BDC) were recruited through a patient registry established by Drs. Koenigs and Baskaya through the University of Wisconsin Department of Neurological Surgery.

Twenty-one neurologically healthy adults also participated as a normal comparison (NC) group. NC participants had no history of brain injury, neurological or psychiatric illness, or current use of psychoactive medication. NC participants were between the ages of 50 and 64 (the age range of vmPFC patients; see Table 7.1 for group demographic and neuropsychological data). One NC participant was excluded as a statistical outlier based on deficient emotion recognition performance (see task description below), and one was excluded due to technical difficulties with eye tracking. This resulted in a final NC group size of $n = 19$. NC participants were recruited through community advertisement. All participants had normal or corrected to normal vision.

	Age	Edu	Sex	IQ	PSI	Pic Comp	Trail A	Trail B-A	BDI	Trait Anx
vmPFC-A	58	12	F	109	100	11	47.0	18.0	3	21
vmPFC-B	50	12	M	88	81	13	32.7	65.9	9	40
vmPFC-C	64	20	M	117	102	8	31.5	40.3	10	42
vmPFC (n = 3)	57.3 (7.0)	14.7 (4.6)	2 M 1 F	104.7 (15.0)	94.3 (11.6)	10.7 (2.52)	37.1 (8.6)	41.4 (24.0)	7.3 (3.8)	34.3 (11.6)
BDC (n = 10)	52.4 (10.8)	14.5* (1.7)	4 M 6 F	102.3* (7.7)	-	-	31.7 (9.3)	31.9 (15.1)	13.1* (8.3)	43.6* (10.6)
NC (n = 19)	58.3 (3.3)	16.6 (2.5)	11 M 8 F	110.2 (6.6)	-	-	-	-	5.1 (5.4)	31.4 (6.4)

Table 7.1. Demographic and neuropsychological data. Age, Age of participant at time of testing, in years; Edu, years of education completed; IQ, intelligence quotient estimated by the Wide Range Achievement Test 4 (Wilkinson & Robertson, 2006b), Blue Reading subtest; PSI, Processing Speed Index from the WAIS (Wechsler, 2008) (standardized mean 100, S.D. 15); Pic Comp, scaled score for subject's age group on the picture completion subtest of the WAIS (standardized mean 10, S.D. 3); Trail A, Trailmaking Test (Reitan & Wolfson, 1985) Part A time to completion, in seconds. (Completion times greater than 78 sec are considered deficient); Trail B-A, Trailmaking Test Part B minus Part A times to completion, in seconds; BDI, Beck Depression Inventory score (Beck, Steer, & Brown, 1996); Trait Anx, score on Trait Anxiety items from the State-Trait Anxiety Inventory (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). For group data, means are presented with standard deviations in parentheses. * indicates significant difference from NC group ($p < 0.05$).

Lesion Segmentation and Image Normalization

Ventromedial PFC patients' lesions were visually identified and manually segmented on a high-resolution (1 mm^3) T1-weighted anatomical MRI image. Lesion boundaries were drawn to include areas with evidence of gross tissue damage or abnormal signal characteristics. A T2*-weighted FLAIR anatomical image was used to identify additional damage surrounding the core lesion area not apparent on the T1-weighted image (tissue with signal characteristics differing from healthy grey or white matter, e.g., hyperintensity). All structural MRI data were obtained at least three months after surgery. T1-weighted anatomical images were preprocessed with the FreeSurfer image analysis suite (http://www.nmr.mgh.harvard.edu/freesurfer) to remove non-

brain tissue, as previously described (Segonne et al., 2004). The resulting skull-stripped anatomical images were diffeomorphically aligned to the Montreal Neurological Institute (MNI) coordinate system using a Symmetric Normalization algorithm (Avants & Gee, 2004) with constrained cost-function masking to prevent warping of tissue within the lesion mask (Brett, Leff, Rorden, & Ashburner, 2001). Computing the sum of lesion masks for all vmPFC subjects in MNI space yielded a lesion overlap map (Figure 7.1).

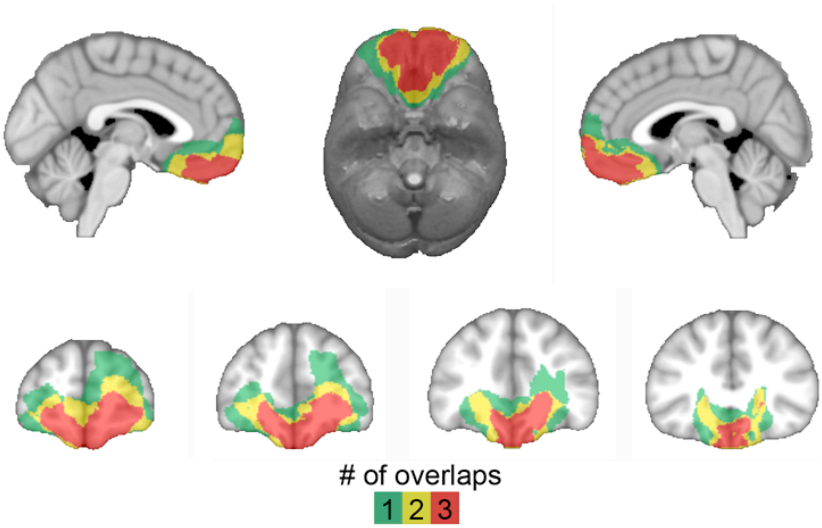

Figure 7.1. Lesion overlap of vmPFC patients. Color indicates the number of overlapping lesions at each voxel.

Facial Emotion Recognition Task

Stimuli were chosen from the Karolinska Directed Emotional Faces set (Lundqvist, Flykt, & Öhman, 1998). Ten male and ten female actors, each depicting two emotions out of happiness, sadness, anger, fear, disgust, and neutral, comprised the stimuli for the recognition task. Face stimuli were converted to gray scale, cropped to remove hair and ears, and matched for size and luminance. Before beginning the task, participants were instructed that on each trial a face would appear onscreen for several seconds, during which time they should try to identify the emotion of

the face. Trials began with presentation of a fixation cross for 4±1 seconds, followed by a 3-second face presentation. Faces were presented such that the tip of the nose appeared at the same point on the screen as the fixation cross. Faces subtended 11.5° visual angle. After viewing the face, participants had unlimited time to use a computer mouse to rate the expression's valence ("How positive or negative was that facial expression?") on a nine-point scale and to identify the emotion from the six possibilities presented. Faces were onscreen during both the valence rating and emotion choice components of the task, to minimize any working memory demands.

Visual Attention Tasks

All vmPFC and BDC patients completed several tests to ensure intact basic elements of visual processing. These tests included a neurological exam, which tests for gross deficits in visual fields, eye movements, and spatial attention; eye tracker calibration, which requires voluntary eye movements to locations spanning the entire stimulus presentation screen (i.e., each corner, each edge, and center); and Trails A, which measures visual search and scanning. All vmPFC and BDC patients exhibited normal performance on each of these tests. Additionally, vmPFC patients completed the Wechsler Adult Intelligence Scale-IV (WAIS) Picture Completion, which measures detailed visual perception and recognition (Wechsler, 2008), and WAIS processing speed index (consisting of Coding and Symbol Search sub-tests), which measures visual perception, scanning speed, and visual working memory. All vmPFC patients exhibited normal performance on these tests (Table 7.1).

Eye Tracking

Participants' eye movements were tracked at 60 Hz with an ASL D6 desk-mounted eye tracker (Applied Science Laboratories, Bedford, MA). Participants were seated approximately 64 cm away from the monitor. All participants underwent a nine-point calibration prior to beginning

the experimental task. Head tracking software was used to account for head movements in real time. Fixations were defined as gaze coordinates remaining inside 1° visual angle for 100ms or greater (Karsh & Breitenbach, 1983; Lambert, Monty, & Hall, 1974), and identified offline using automated software.

Each face stimulus was divided into three areas of interest (AOIs) for analysis. The vertical bounds of the "eye" AOI were just superior of the corrugator muscle and the inferior orbit, and the horizontal bounds were the lateral corners of each eye. The vertical bounds of the "mouth" AOI were the middle of the philtrum and just inferior of the lower lip, and the horizontal bounds were points just beyond the corners of the lips. The "face" AOI was a rectangle the maximum height and width of the face stimulus.

For all analyses performed on eye tracking data, individual trials were excluded if eye tracking failed for greater than 10% of samples (300 milliseconds) during the face presentation. This threshold was set to reduce the impact of eye tracking artifacts introduced by excessive blinking and head movement. 79 out of a total of 1280 trials (6.2%) were excluded on this basis. Groups did not significantly differ with respect to the total number of trials excluded ($p = 0.94$). In order to account for inter-individual variability in overall frequency of visual fixations and to facilitate comparison of data to previous lesion patient research (Adolphs et al., 2005), I used proportion of fixations made to a given AOI (out of the total number fixations during each 3-second face presentation) as my primary dependent measure.

For my main statistical analyses, I performed non-parametric tests due to the small sample size of bilateral vmPFC lesion patients. Specifically, I used a two-tailed Kruskal-Wallis test, followed by between-group comparisons with Mann-Whitney U tests, to test the hypothesis

that, compared to the NC and BDC groups, the vmPFC lesion group would exhibit fewer visual fixations to the eye regions of the faces.

Results

Proportion of Fixations to the Eyes

Overall, there was a significant effect of group on the proportion of fixations to the eye region of faces per trial ($X^2 = 6.07$, $p = 0.048$). Between-group comparisons indicated that the vmPFC group ($M = 13.03\%$, $SD = 4.42$) made a smaller proportion of fixations to the eyes per trial than did the NC group ($M = 28.28\%$, $SD = 15.90$; $U = 7.00$, $p = 0.040$) or BDC group ($M = 37.92\%$, $SD = 21.23$; $U = 2.00$, $p = 0.028$; Figures 7.2A and 7.3A), while there was no significant difference between the NC and BDC groups ($U = 71.00$, $p = 0.27$). This finding supports the main study hypothesis regarding visual fixations.

As a follow-up analysis to this primary result, I examined eye tracking data with respect to individual emotion categories. There was a significant effect of group on the proportion of fixations to the eye region of fear faces ($X^2 = 6.53$, $p = 0.038$; Figure 7.2B). Between-group comparisons indicated that the vmPFC group ($M = 12.40\%$, $SD = 2.64$) made a significantly smaller proportion of fixations to the eyes of fear faces than did the NC group ($M = 31.76\%$, $SD = 18.80$; $U = 7.00$, $p = 0.040$) or BDC group ($M = 42.79\%$, $SD = 22.15$; $U = 1.50$, $p = 0.022$; Figure 7.3A), while there was no significant difference between the NC and BDC groups ($U = 68.00$, $p = 0.22$). For disgust and neutral faces, there were also trends toward group effects on the proportion of fixations made to the eyes (disgust: $X^2 = 5.89$, $p = 0.053$; neutral: $X^2 = 5.86$, $p = 0.053$). No significant group effects were detected for happy, sad, or angry faces (all p's > 0.17).

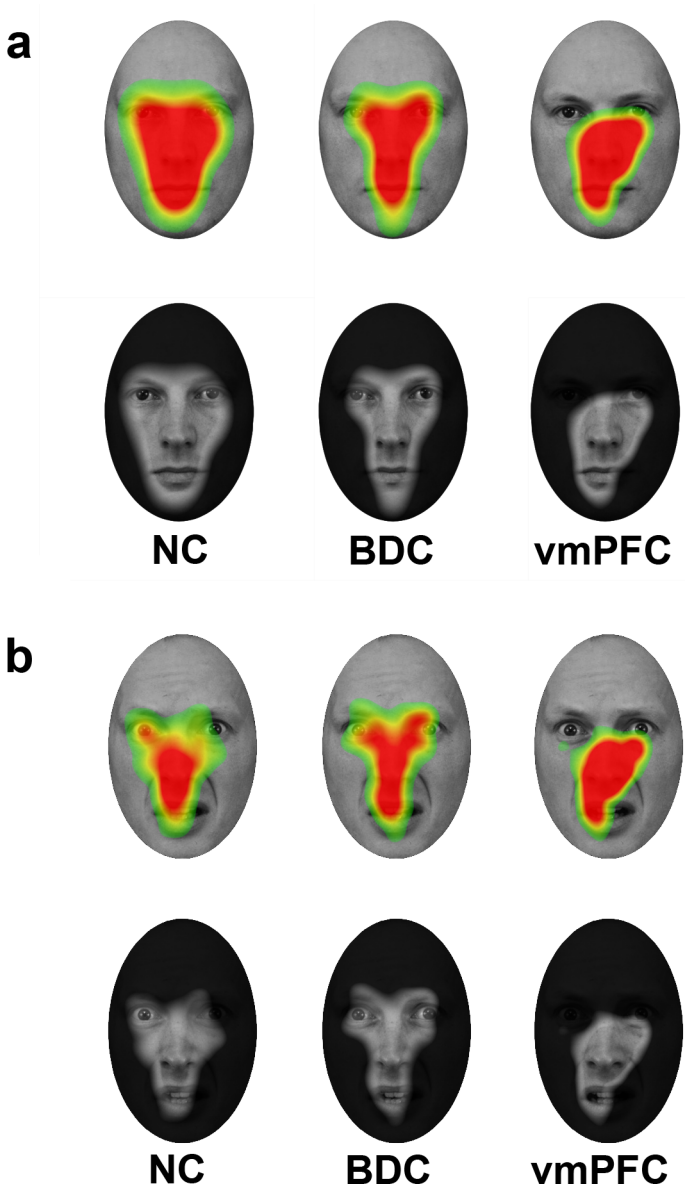

Figure 7.2. Fixation density maps. A) Warmer colors (upper row) and transparent regions (lower row) show where fixation density was greatest across all trials for NC, BDC, and vmPFC groups, respectively, superimposed on one of the neutral face stimuli. All groups made similar rates of fixations to the nose and mouth regions, whereas NC and BDC groups fixated more heavily on the eye region than did the vmPFC group. B) Warmer colors (upper row) and transparent regions (lower row) show where fixation density was greatest when viewing fearful faces for NC, BDC, and vmPFC groups, respectively.

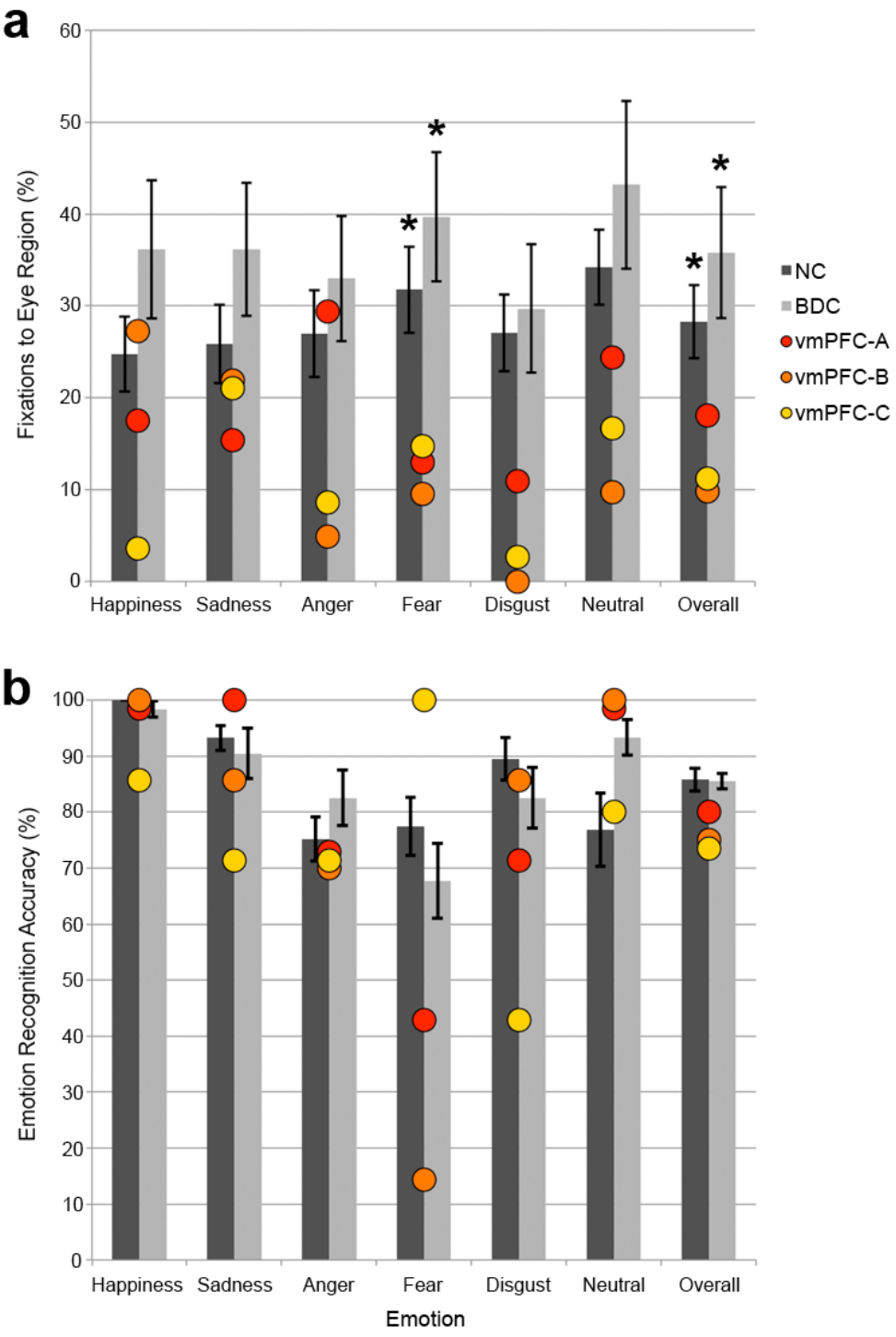

Figure 7.3. Eye tracking and emotion recognition results. A) Percentage of fixations to the eye area of faces, with vmPFC patients plotted individually. Red: vmPFC-A, orange: vmPFC-B, yellow: vmPFC-C. B) Emotion recognition accuracy, with vmPFC patients plotted individually. Error bars indicate standard error of the mean. Differences from vmPFC group: $*p < 0.05$

Proportion of Fixation Time to the Eyes

To confirm that the fixation deficit observed in the vmPFC group was not due to them making fewer, but longer, fixations to the eye region than the comparison groups, I also investigated group differences in the average proportion of total eye fixation time, relative to total fixation time per trial. Consistent with the main fixation analyses, there was a trend towards a group effect of eye fixation time when collapsing across emotion categories ($X^2 = 5.18$, $p = 0.075$). Between-group comparisons indicated that the vmPFC group ($M = 11.96\%$, $SD = 7.57$) spent a smaller proportion of total fixation time looking at the eye region than did the NC group ($M = 26.94\%$, $SD = 16.62$; $U = 11.00$, $p = 0.094$) or BDC group ($M = 38.02\%$, $SD = 22.30$; $U = 3.00$, $p = 0.043$), while the NC and BDC groups did not significantly differ ($U = 67.00$, $p = 0.20$). Also consistent with the main fixation analyses, there was a significant group effect of eye fixation time specific to fear faces ($X^2 = 6.94$, $p = 0.031$). Between-group comparisons indicate that the vmPFC group ($M = 11.35\%$, $SD = 5.20$) spent a smaller proportion of total fixation time looking at the eye region of fear faces than did the NC group ($M = 30.34\%$, $SD = 19.32$; $U = 10.00$, $p = 0.077$) or BDC group ($M = 43.11\%$, $SD = 23.58$; $U = 2.00$, $p = 0.028$). There was also a trend towards the NC group spending less time looking at the eyes than the BDC group ($U = 57.00$, $p = 0.081$). Thus, the pattern of results with respect to time spent looking at the eye region of the face largely complements the pattern observed when analyzing proportion of fixations made to the eye region of the face, and rules out the possibility that vmPFC patients made fewer, but longer, fixations to the eye regions relative to comparison groups.

General Measures of Visual Exploration

To examine whether the deficits observed in the vmPFC group's fixations to the eye region of faces was due to a general lack of visual exploration or eye movement, I tested for

group differences on a variety of visual exploration metrics. The groups did not significantly differ with respect to total number of fixations per trial ($p = 0.51$), nor did the groups significantly differ with respect to proportion of fixations to the mouth per trial ($p = 0.94$). As an indicator of the total distance of eye movements made during a trial, we summed the distances between consecutive fixations within each trial. This value yields a gross measure of total eye movement during the task. Groups did not differ with respect to total distance between fixations across all trials ($p = 0.34$) or for fear trials specifically ($p = 0.30$). To test whether the observed fixation abnormalities were due to the vmPFC patients making multiple fixations near the point of initial fixation (i.e., the nose), we looked for group differences in average distance of participants' furthest fixations from the nose. For each trial, we calculated the length of the longest line segment formed between the nose and the coordinates of each fixation and then averaged across trials. No group differences were detected for average distance of the furthest fixation from the nose across all trials ($p = 0.25$) or within fear trials specifically ($p = 0.12$). Hence, the fixation deficit in the vmPFC group appeared to be specific to the eye region of the face and not attributable to a more general deficit in generating eye movements or exploring stimuli.

Epoch Analysis

In order to further elucidate the time-course of the fixation deficit observed in the vmPFC group, I repeated the analyses of proportion of fixations to the eye region of fear faces after binning each 3-second trial into three 1-second epochs. Within the interval of 0 to 1 second post-stimulus onset, there was a significant group effect with respect to proportion of fixations made to the eyes of fear faces ($X^2 = 7.69$, $p = 0.021$; Figure 7.4). Between-group comparisons indicated that the vmPFC group ($M = 0.00\%$, $SD = 0.00$) made a smaller proportion of fixations to the eyes

of fear faces within this interval than did the NC group (M = 28.08%, SD = 20.85; U = 3.00, p = 0.014) or BDC group (M = 36.67%, SD = 26.49; U = 0.00, p = 0.011), while the NC and BDC groups did not significantly differ (U = 74.50, p = 0.35). Within the interval of 1 to 2 seconds post-stimulus onset, there was no significant group effect with respect to proportion of fixations made to the eyes of fear faces (X^2 = 4.49, p = 0.11). Similarly, within the interval of 2 to 3 seconds post-stimulus onset, there was no significant group effect with respect to proportion of fixations made to the eyes of fear faces (X^2 = 4.17, p = 0.12).

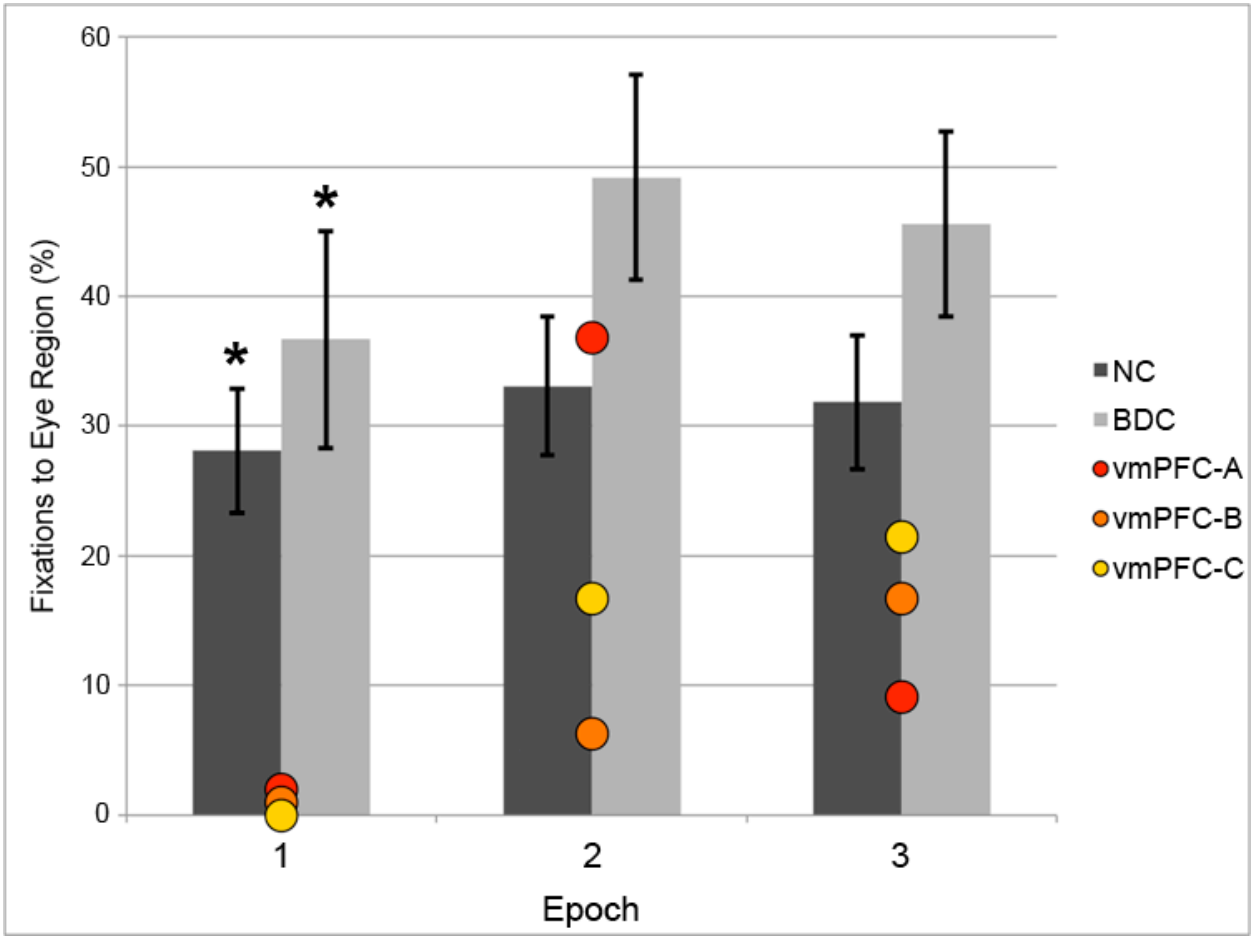

Figure 7.4. Eye tracking results in 1-second time bins. Percentage of fixations to the eye area of fearful faces during each 1-second epoch of the trial, with vmPFC patients plotted individually. Red: vmPFC-A, orange: vmPFC-B, yellow: vmPFC-C. Error bars indicate standard error of the mean. Differences from vmPFC group: *p < 0.05

Facial Emotion Recognition

Although the vmPFC group had lower overall emotion recognition accuracy (M = 76.67%, SD = 2.89) than the NC group (M = 85.79%, SD = 8.82) and BDC group (M = 84.94%, SD = 4.52), these differences were not statistically significant ($X^2 = 4.23$, $p = 0.12$; Figure 7.3B). To determine if the vmPFC group's fixation deficit to the eye region of fear faces was accompanied by a deficit in fear recognition, I tested for group differences in fear recognition. The vmPFC group had lower fear recognition accuracy (M = 52.38%, SD = 43.64) than the NC (M = 77.44%, SD = 22.50) and BDC groups (M = 69.52%, SD = 20.72), however these differences were not statistically significant ($X^2 = 2.02$, $p = 0.36$).

Discussion

These results show that vmPFC damage impairs visual attention during facial emotion recognition. This study is the first to use eye tracking in vmPFC lesion patients to assess spatial deployment of fixations during facial emotion recognition. Previous studies of human neurological lesion patients played an integral role in elucidating the neurocircuitry supporting these processes; building on initial neuropsychological studies that associated amygdala damage with marked deficits in identifying facial expressions of emotion, particularly fear (Adolphs et al., 1994; Adolphs et al., 1999; Young, Hellawell, Van De Wal, & Johnson, 1996), a subsequent eye tracking study demonstrated that the root cause of this amygdala-dependent deficit is the failure to fixate to the eye region of the face during visual inspection (Adolphs et al., 2005). The present results indicate that vmPFC also plays a critical role in guiding visual fixations to the eye region of the face.

Considering the substantial degree of structural and functional interconnection between vmPFC and amygdala (Barbas, 2000; Ghashghaei & Barbas, 2002), these two regions may comprise part of a neural circuit responsible for endogenously controlling fixations to emotionally salient, biologically relevant stimuli (Pessoa & Adolphs, 2010). One possibility is that reciprocal or coincident activity between vmPFC and amygdala may signal the social and emotional salience of the stimulus, and direct subsequent eye movements accordingly. Functional and anatomical studies of these brain regions are consistent with this proposal, separately implicating vmPFC and the amygdala in relatively early stages of emotion processing. Human fMRI data have shown that amygdala activity discriminates between fearful and happy faces, even when the faces are backward-masked and presented for less than 50 milliseconds (Whalen et al., 1998). In addition, single-neuron recordings from vmPFC in humans have shown short-latency (less than 200 milliseconds from stimulus onset) discrimination between fearful and happy faces (Kawasaki et al., 2001). Anatomically, vmPFC and amygdala share robust bidirectional projections with each other; both regions receive projections from high-level visual areas in temporal cortex; and both regions interconnect densely with areas of posterior lateral orbital cortex, which in turn projects to the lateral frontal eye fields that control eye movement (Barbas, 2000; Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000). Given these anatomical connections and the evidence of both vmPFC and the amygdala responding to emotional stimuli relatively early in the processing stream, it is feasible that these two regions contribute to a visual orienting response during emotion recognition.

An early visual orienting function is consistent with previous neuropsychological data showing that bilateral amygdala damage specifically impairs fixation to the eye region of faces for the first fixation following stimulus onset (Kennedy & Adolphs, 2010), as well as my own

follow-up analyses with vmPFC lesion patients demonstrating the most pronounced deficit of eye-fixations during the first second of face viewing. To further explore the putative relationship between vmPFC and amygdala for this function, an important follow-up study in vmPFC patients will be to determine whether instructions to fixate to the eye region of the face rescues deficits in emotion recognition, as was the case for a bilateral amygdala lesion patient (Adolphs et al., 2005). A study involving gaze manipulation would also serve to more clearly establish whether abnormalities in visual fixations are causally linked to emotion recognition performance in vmPFC lesion patients.

Although this study is the first to use eye tracking in vmPFC lesion patients to assess visual attention to emotional faces, a number of previous studies have assessed emotion recognition accuracy in this patient population. The findings of these studies have been somewhat mixed, with several reporting either no significant overall impairment among patients with vmPFC damage (Hornak et al., 2003) or that prefrontal lesions, including but not limited to vmPFC, produce emotion recognition impairments (Shamay-Tsoory et al., 2003; Shaw et al., 2005). Other studies, however, report clear emotion recognition deficits specific to patients with vmPFC lesions (Heberlein et al., 2008; Hornak et al., 1996; Tsuchida & Fellows, 2012). One reason for these divergent emotion recognition results may be the sensitivity of the recognition test. Two of the studies showing deficits in vmPFC patients used tests requiring the detection of subtle differences in facial expressions of emotion (Heberlein et al., 2008; Tsuchida & Fellows, 2012), rather than categorical identification of more exaggerated expressions (Hornak et al., 2003; Hornak et al., 1996; Shamay-Tsoory et al., 2003). The task used here, categorization of exaggerated stereotypical facial expressions of emotion, is well-suited for eye-tracking (Adolphs et al., 2005), but it is not an especially sensitive measure of recognition accuracy. Moreover,

because there were only seven trials for each category of emotion and the response accuracy was dichotomous (correct/incorrect) and near ceiling, there was not a sufficiently variable or continuous distribution of accuracy scores to perform a valid correlation analysis relating eye tracking results to recognition accuracy. Future studies with this patient population could use more sensitive emotion recognition tests.

One aspect of the current study that warrants further discussion is the limited sample size of vmPFC lesion patients ($n = 3$). For this study, I employed extremely stringent selection criteria for the target group; lesions had to involve substantial portions of vmPFC bilaterally, but could not extend significantly outside vmPFC. Limiting the vmPFC lesion patient group to these criteria increases lesion homogeneity and reduces the likelihood of preservation of function by a single hemisphere. This patient selection strategy is distinct from typical vmPFC lesion studies, which often include patients with lesions that are exclusively or primarily unilateral and/or lesions that extend beyond the boundaries of vmPFC (e.g., into adjacent dorsomedial PFC, lateral PFC, or anterior temporal lobe). To our knowledge, no previous vmPFC patient study has limited its sample to bilateral, yet selective, vmPFC lesions. Thus, although this sample size may be small by conventional vmPFC lesion patient standards (which typically feature $n = 5$ to $n = 12$ vmPFC lesion patients), it is unique with respect to the uniformity of selective bilateral vmPFC lesions.

In sum, through a novel application of eye tracking in human lesion patients with bilateral vmPFC damage, this study demonstrates a previously unknown role for vmPFC in affecting visual fixations during the recognition of facial expressions of emotion. These results broaden the understanding of vmPFC function to include not just higher-order cognitive processes like value computation and emotion regulation, but also the relatively lower-level

process of controlling eye movement to the socially or emotionally salient features of the environment. However, a causal link between fixations to the eyes of emotional faces and emotion recognition accuracy has not yet been established amongst patients with vmPFC lesions. In the next chapter, I describe a study that seeks to determine whether vmPFC is necessary for emotion recognition and if so, whether recognition impairments amongst patients with vmPFC lesions are due to the failure to fixate to the eyes of emotional faces, as was observed in this study.

Chapter 8. Emotion Recognition Deficits are Associated with Ventromedial Prefrontal Cortex Damage and Rescued by Gaze Manipulation

It has long been established that patients with lesions in vmPFC exhibit social behavior abnormalities that indicate an emotion processing impairment (Barrash et al., 2000; Damasio, 1996; Eslinger & Damasio, 1985), but the precise nature of the emotional impairment in this population remains unclear. There is one report that patients with vmPFC lesions are unimpaired at recognizing emotional expressions (Hornak et al., 2003), in addition to the lack of an observed recognition impairment in the study described in **Chapter 7**. However, several studies have demonstrated general emotion recognition impairments in patients with vmPFC lesions, relative to either healthy or brain-damaged comparison populations (Heberlein et al., 2008; Hornak et al., 1996; Shamay-Tsoory et al., 2003; Shaw et al., 2005; Tsuchida & Fellows, 2012). One potential explanation for these equivocal findings might be related to the intensity of emotional expressions in the stimuli. Studies reporting null findings have used high intensity, exaggerated facial expressions that lack ecological validity and may introduce a ceiling effect as a result of the ease with which individuals can identify these expressions (**Chapter 7**). In contrast, studies reporting emotion recognition impairments amongst individuals with vmPFC lesions have used less intense morphed emotional expressions, putatively making the recognition task more difficult (Heberlein et al., 2008; Tsuchida & Fellows, 2012). It is possible that use of more ecologically valid, lower intensity expression stimuli is necessary for detecting emotion recognition impairments in vmPFC lesion patients.

The work described in **Chapter 7** established that patients with vmPFC lesions make fewer fixations than comparison subjects to the eyes during emotion recognition, particularly for fearful expressions, similar to the effect of amygdala damage leading to reduced fixations to the eyes of emotional faces (Adolphs et al., 2005). Given that the amygdala and vmPFC share strong reciprocal connections (Ghashghaei & Barbas, 2002), if patients with vmPFC lesions have an emotion recognition impairment, this impairment may be a direct result of patients with vmPFC lesions making fewer fixations to the eyes of emotional faces, as is the case for patients with amygdala damage (Adolphs et al., 2005). It might therefore be expected that effortful fixation to the eyes of emotional faces could rescue any emotion recognition deficit observed in patients with vmPFC lesions.

The present study uses an emotion recognition task with morphed expressions of varying intensities to determine whether or not vmPFC is essential for emotion recognition and if vmPFC contributes to guiding fixations towards emotionally salient regions of the face. First, I test the hypothesis that vmPFC is essential for emotion recognition of low and moderate intensity expressions. Because the study in **Chapter 7** showed that patients with vmPFC lesions fixate to the eyes of fearful faces less than comparison subjects, I specifically hypothesized that patients with vmPFC lesions would have impaired recognition of fear at low and moderate intensities. Second, I test the hypothesis that vmPFC, like the amygdala, contributes to guiding fixations to emotionally salient regions of the face. Specifically, I hypothesized that any emotion recognition impairment in patients with vmPFC lesions would be alleviated by effortful attention to the eyes of emotional faces.

Methods

Participants

The target lesion group consisted of seven neurosurgical patients with extensive parenchymal changes, largely confined to vmPFC, where vmPFC is defined as Brodmann areas 11, 12, 25, 32, and the medial portion of 10 below the level of the genu of the corpus callosum (Figure 8.1). Five vmPFC lesion patients had bilateral damage, while two had damage restricted to the right hemisphere. All bilateral vmPFC lesion patients had large anterior cranial fossa meningiomas that underwent gross total tumor resection. Both unilateral vmPFC lesion patients had right anterior cerebral artery aneurysms treated by surgery for clipping, one following subarachnoid hemorrhage.

Five neurosurgical patients who had focal lesions outside of vmPFC comprised a brain-damaged comparison (BDC) group. Three patients had undergone surgery for aneurysm clipping following subarachnoid hemorrhage in the right anterior temporal lobe. The remaining two BDC patients underwent tumor resection, one in the cerebellum and one in dorsomedial frontal cortex. The inclusion of these BDC patients allows me to rule out the possibility that differences in emotion recognition accuracy observed in the vmPFC lesion group could be due to anatomically non-specific effects of brain damage or a history of related medical issues (e.g., craniotomy, edema, seizure, past medications, etc.).

All vmPFC lesion and BDC patients' surgeries were performed in adulthood and all experimental data were collected at least three months after surgery, during the chronic phase of recovery. All neurosurgical patients were recruited through a patient registry established through the University of Wisconsin Department of Neurological Surgery.

Twenty-five neurologically healthy adults, matched in age and sex to the vmPFC lesion group, participated in the study as a healthy comparison group. The healthy comparison group had no history of brain damage, neurological or psychiatric illness, or current use of psychoactive medication. One healthy comparison participant was excluded as a statistical outlier based on deficient emotion recognition performance during the free viewing block of the experimental task (see emotion recognition task below). This resulted in a final healthy comparison group size of $n = 24$. Healthy comparison subjects were recruited through community advertisement. All participants had normal or corrected to normal vision. All participants provided informed consent.

Lesion segmentation and image normalization

Structural images for vmPFC patients' were obtained at least three months after surgery. For all vmPFC lesion patients, lesions were visually identified and manually segmented. For the five bilateral patients, high-resolution ($1mm^3$) T1-weighted anatomical magnetic resonance images were available. In this case, lesion boundaries were drawn in native space to include areas with evidence of gross tissue damage or signal abnormalities. A T2*-weighted FLAIR anatomical image was used to identify additional damage surrounding the core lesion area not apparent on the T1-weighted image. T1-weighted anatomical images were preprocessed with the FreeSurfer image analysis suite (http://www.nmr.mgh.harvard.edu/freesurfer) to remove non-brain tissue, as previously described (Segonne et al., 2004). The resulting skull-stripped anatomical images were diffeomorphically aligned to the MNI coordinate system using a symmetric normalization algorithm (Avants & Gee, 2004) with constrained cost-function masking to prevent warping of tissue within the lesion mask (Brett et al., 2001). For the two unilateral vmPFC lesion patients, MRI data were not available due to the presence of aneurysm

clips. For these patients, lesions were segmented by inspecting CT images available from medical records and tracing areas with evidence of tissue damage onto an MNI template brain in relation to anatomical landmarks. A lesion overlap map (Figure 8.1) was computed as the sum of lesion masks for all vmPFC lesion patients in MNI space.

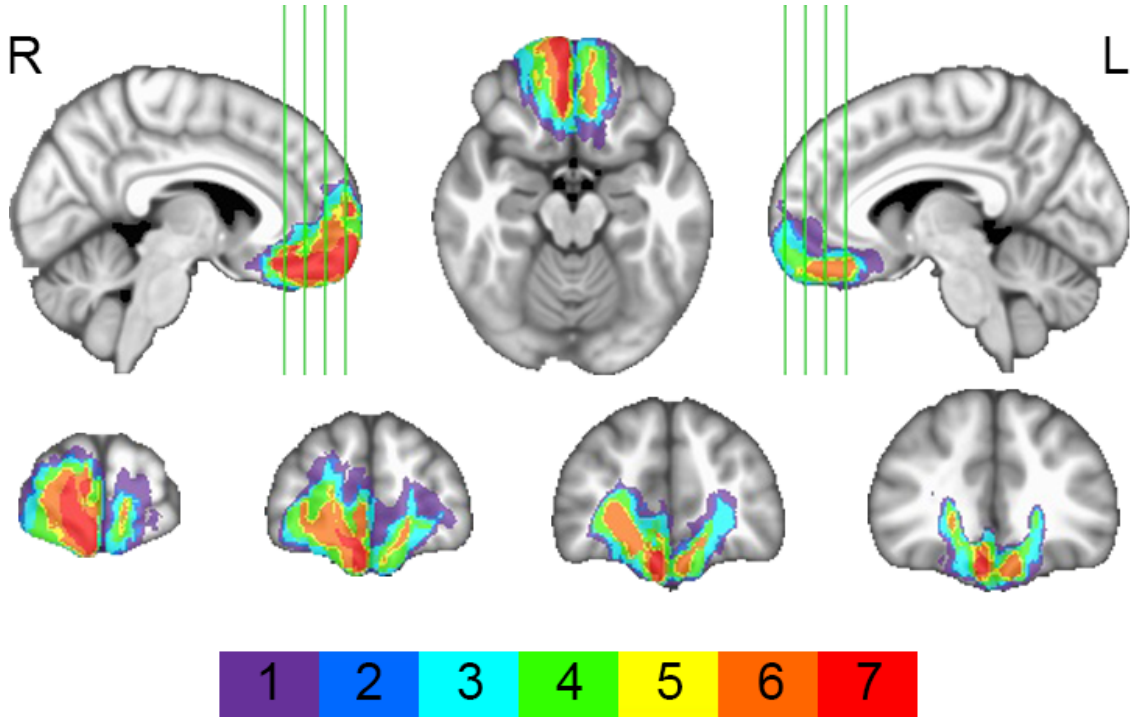

Figure 8.1. Lesion overlap of vmPFC patients.
Color indicates the number of overlapping lesions at each voxel.

Emotion recognition task

The emotion recognition task employed expressions of fear, anger, happiness, sadness, disgust, and surprise from the pictures of facial affect set (Ekman & Friesen, 1976). Morphing a neutral face with a full intensity expression depicted by the same model generated images of varying emotional intensities. Morph intensities were generated in 10% increments ranging from 10% (i.e., 90% neutral) to 100% (Marsh, Yu, Pine, & Blair, 2010). Participants saw a total of

360 static images during the task, where each of the 6 expressions was depicted by each of 6 models (3 male, 3 female) at 10 intensity levels.

The emotion recognition task was broken into 3 blocks. In each block 120 images were randomly selected, without replacement, with the requirement that all intensities of each emotion be displayed once by a male model and once by a female model. All participants completed the three blocks in the same order: free viewing, attend-to-mouth, and attend-to-eyes. The attend-to-eyes condition was always presented last to ensure that participants did not identify focusing on the eyes as an optimal emotion recognition strategy that could be used in other blocks of the experiment. In the free viewing block, participants were instructed to look anywhere on the face to help them determine what expression was on the face, while in the attend-to-mouth and attend-to-eyes blocks participants were instructed focus only on those regions of the face, respectively. Each trial in the free viewing block began with a fixation cross in the center of the screen presented for 1.5 seconds, followed by a face presented for 500 milliseconds such that the tip of the nose was coincident with the previous location of the fixation cross. The course of the trial was identical in the attend-to-mouth and attend-to-eyes conditions, except that the fixation cross was shifted down or up on the screen to appear where the mouth or eyes, respectively, would subsequently appear. After each trial subjects were asked to identify the expression on the face as one of the six basic emotions (fear, anger, happiness, sadness, disgust, or surprise). Subjects provided their responses using a keyboard. The duration of the experimental task was approximately 25 minutes.

Supplementary cognitive tasks

All vmPFC lesion patients completed an abbreviated form of the Wechsler Adult Intelligence Scale-IV (WAIS) (Wechsler, 2008) to estimate IQ and its subcomponents. The mean

WAIS score for vmPFC lesion patients was 99.93 (*SD* = 8.70, range = 91-112), indicating that vmPFC lesion patients were in the normal range of IQ scores. All vmPFC lesion patients and BDC patients completed the Trail Making Test (Reitan & Wolfson, 1985) to test for differences in visual search abilities and working memory. All participants completed the Wide Range Achievement Test 4 Blue Reading subtest (Wilkinson & Robertson, 2006a) as an additional IQ estimate. Results of these neuropsychological measures are presented in Table 8.1.

	Sex	**Age**	**IQ**	**Trails A**	**Trails B-A**
Healthy	12 M 12 F	61.88 (3.88)	111.92* (6.26)	-	-
BDC	2 M 3 F	58.60 (9.15)	102.00 (9.19)	32.95 (7.55)	46.63 (30.56)
vmPFC	4 M 3 F	56.57 (9.61)	102.00 (11.15)	39.93 (11.60)	52.76 (26.22)

Table 8.1. Group demographics. Age = age at time of testing. IQ = estimated IQ based on Wide Range Achievement Test 4 blue reading subtest (Wilkinson & Robertson, 2006a). Trails A = Trail Making Test (Reitan & Wolfson, 1985) Part A time to completion (seconds). Trails B-A = Trail Making Test Part B time to completion (seconds) minus Part A time to completion. Means are presented with SD in parentheses. *Significantly greater than both BDC ($W = 19.5$, $p = 0.020$) and vmPFC patients ($W = 132.5$, $p = 0.023$).

Statistical analyses

All analyses were performed in R. Emotion recognition accuracy was calculated as the number of correct responses divided by the number of trials for a given emotion in a given intensity bin. Intensity was binned as low (10-30%), moderate (40-60%), and high (70-100%). Due to the small sample sizes of patient groups, I performed non-parametric tests to address study hypotheses. For the free viewing block I used a two-tailed Kruskal-Wallis test to detect an emotion recognition accuracy difference amongst groups within a given emotion and intensity level. If this multi-group test was significant, it was followed by between group comparisons

with Mann-Whitney U tests, to address the hypothesis that the vmPFC lesion group would have impaired emotion recognition relative to comparison groups. This manner of "protected" testing helps limit the number of statistical tests performed throughout the analysis. Finally, to address the hypothesis that vmPFC lesion patients' emotion recognition impairments could be rescued by effortful attention to the eyes of emotional faces, for any emotion and intensity in which the vmPFC group had impaired recognition relative to comparison groups, I used a Mann-Whitney U test to determine if the vmPFC group's performance in the attend-to-eyes block was improved relative to the free viewing and attend-to-mouth blocks.

Results

Free viewing

There were no significant group differences in emotion recognition accuracy of any emotion at low intensities (all $p > 0.11$). At moderate intensities, there were no significant group differences in emotion recognition accuracy for fear ($X^2 = 1.15$, $p = 0.56$; Figure 8.2), surprise ($X^2 = 0.80$, $p = 0.67$), disgust ($X^2 = 0.70$, $p = 0.70$), happiness ($X^2 = 2.35$, $p = 0.31$), or sadness ($X^2 = 2.57$, $p = 0.28$). However, there was a significant group difference for anger at moderate intensity ($X^2 = 7.10$, $p = 0.029$; Figure 8.2). Consistent with the hypothesis that the vmPFC lesion group would have impaired recognition of moderate intensity emotion relative to comparison groups, the vmPFC group had lower recognition accuracy of moderate intensity anger than both the healthy comparison group ($W = 136$, $p = 0.012$) and the BDC group ($W = 28$, $p = 0.086$), while the two comparison groups did not significantly differ ($W = 45$, $p = 0.39$). Thus, the only recognition deficit specific to the vmPFC lesion group was for moderate intensity angry faces.

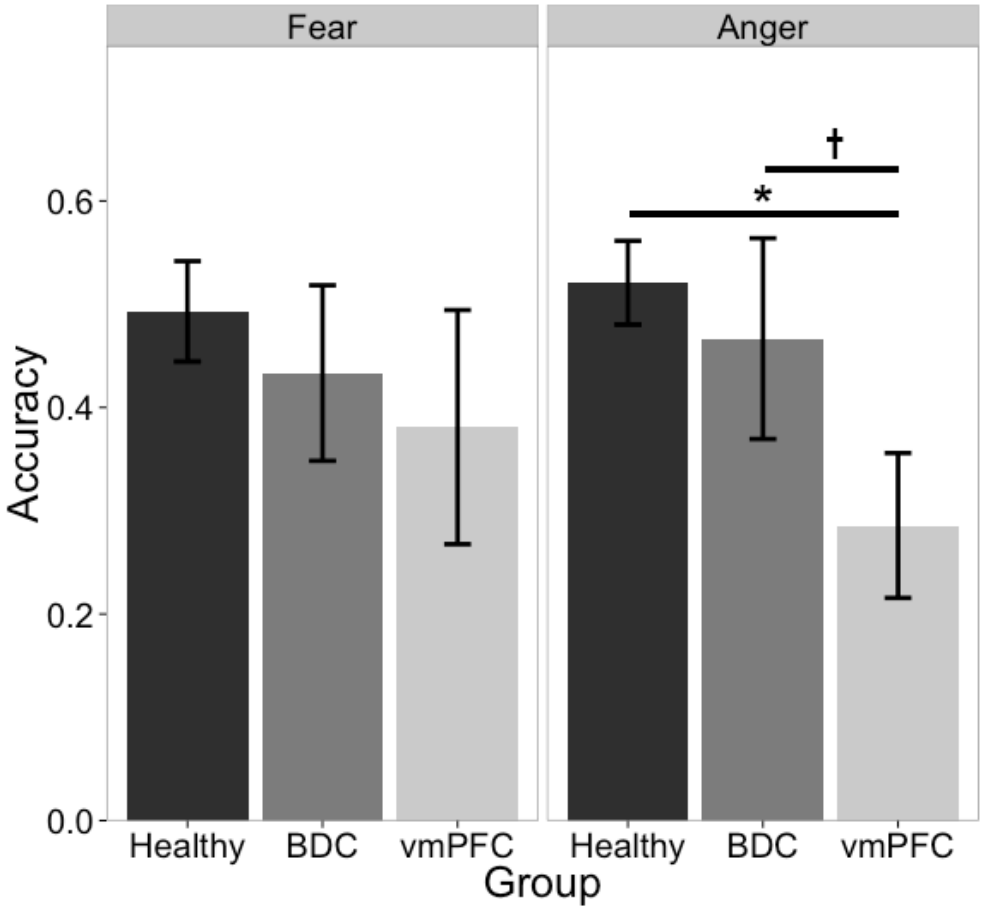

Figure 8.2. Group effects of free viewing moderate intensity fear and anger
Left panel: there were no group differences for recognition of moderate intensity fear in the free viewing condition. Right panel: vmPFC lesion patients had lower recognition accuracy than either comparison group. *$p < 0.05$, †$p < 0.1$.

Gaze manipulation

Consistent with the hypothesis that effortful attention to the eyes of emotional faces would rescue vmPFC lesion patients' emotion recognition impairments, the vmPFC lesion group showed better moderate intensity anger recognition in the attend-to-eyes block relative to the attend-to-mouth block ($W = 40$, $p = 0.049$) and the free viewing block ($W = 45$, $p = 0.0090$) (Figure 8.3). This performance improvement was not observed in either comparison group; the healthy comparison group did not have significantly better moderate intensity anger recognition

accuracy in the attend-to-eyes block relative to the attend-to-mouth block ($W = 287.5$, $p = 0.99$) or to the free viewing block ($W = 287.5$, $p = 0.99$). Likewise, the BDC group also did not have significantly higher moderate intensity anger recognition accuracy in the attend-to-eyes block relative to the attend-to-mouth block ($W = 17$, $p = 0.40$) or to the free viewing block ($W = 17.5$, $p = 0.34$). Finally, the attend-to-eyes instruction raised the vmPFC lesion group's performance to normal; there was no significant difference between groups for moderate intensity anger recognition during the attend-to-eyes block ($X^2 = 3.64$, $p = 0.16$).

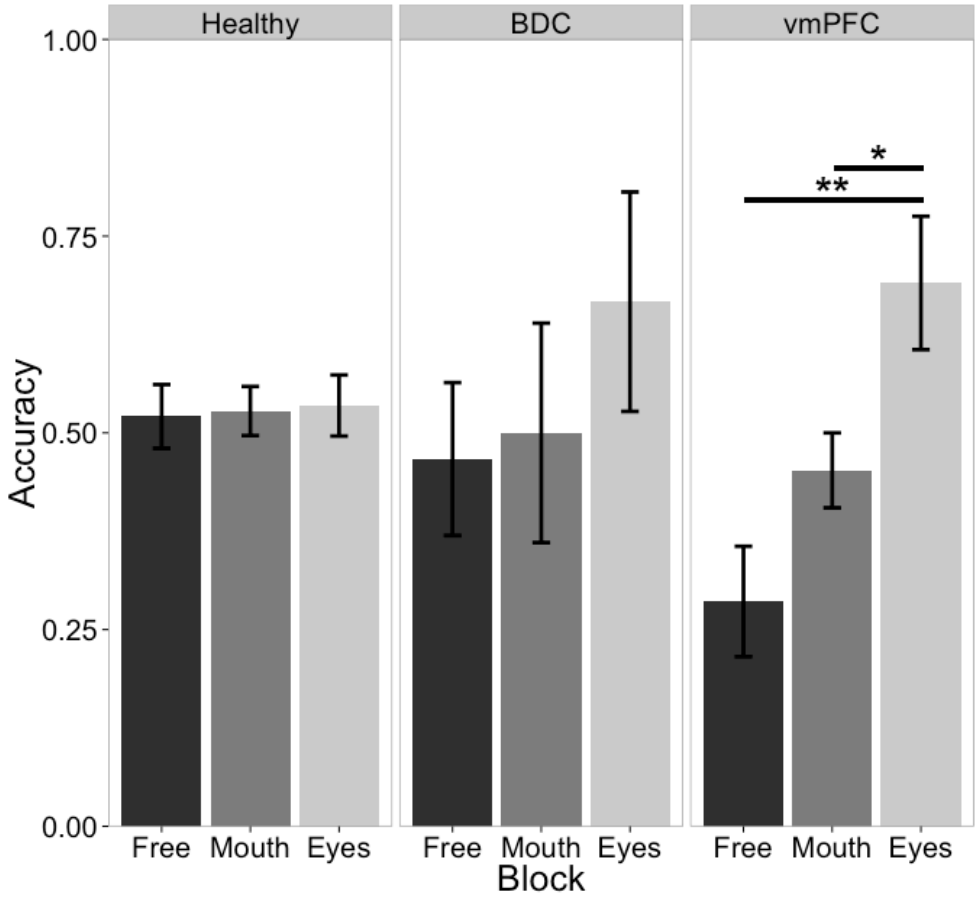

Figure 8.3. Moderate intensity inger recognition across groups and conditions.
There was no moderate intensity anger recognition accuracy improvement in the attend-to-eyes condition relative to the free viewing condition for either healthy comparison subjects (left panel) or brain-damaged comparison patients (middle panel). Ventromedial PFC lesion patients' free viewing moderate intensity anger recognition impairment was rescued to normal in the attend-to-eyes condition. *$p < 0.05$, **$p < 0.01$.

Discussion

This study examined the extent to which vmPFC is necessary for recognition of emotional expressions across different intensities. My specific hypothesis of a low or moderate intensity fear recognition impairment amongst patients with vmPFC lesions was not supported; patients with vmPFC lesions had comparable recognition accuracy of fear relative to comparison subjects across intensities. However, consistent with the notion that vmPFC is critical for emotion recognition, patients with vmPFC lesions were impaired at recognizing moderate intensity anger relative to comparison subjects. Moreover, patients with vmPFC lesions improved to normal levels of recognition accuracy when instructed to fixate to the eyes of moderate intensity anger faces. In addition to broadening the literature on vmPFC's role in emotion recognition, the gaze manipulation results offer novel insight on the precise contributions of vmPFC during the complex process of identifying facial expressions; vmPFC may contribute to the spatial deployment of fixations during emotion recognition.

An important remaining question is the specificity of the emotion recognition impairment in patients with vmPFC damage. Several studies have identified emotion recognition impairments in individuals with vmPFC damage, although the specificity of the impairment differs across studies. Three studies of patients with vmPFC lesions found general emotion recognition impairments across all basic emotions (Heberlein et al., 2008; Hornak et al., 1996; Tsuchida & Fellows, 2012). Similar to the present study, a case study of a patient with a right vmPFC lesion reported an impairment in recognizing anger and disgust (Blair & Cipolotti, 2000). It is thus still unclear whether there is a general emotion recognition impairment related to vmPFC damage, or if this impairment is specific to negative emotions such as anger. Notably, some studies reporting more general impairments in patients with vmPFC damage have

employed a multidimensional emotion rating task (Heberlein et al., 2008; Tsuchida & Fellows, 2012), in which each stimulus is rated for the presence of each of the basic emotions, rather than a forced-choice labeling task like the current study. One possible explanation for the discrepancy in generality of impairment may be that patients with vmPFC lesions are most profoundly impaired at anger recognition, but are also impaired at recognizing other emotions to a lesser degree that is only detectable with a dependent measure more sensitive than forced-choice labeling. The current study supports the view that vmPFC is critical for emotion recognition, at least for anger.

Previous work has implicated fixation to the eyes as a key factor in emotion recognition (Adolphs et al., 2005; Eisenbarth & Alpers, 2011; Smith et al., 2005). In the current study I found that instructed fixation to the eyes of moderate intensity anger faces was sufficient to improve recognition accuracy for patients with vmPFC damage, suggesting that the emotion recognition deficit associated with vmPFC damage is due in part to failing to deploy visual attention to emotionally informative regions of the face. This notion is further supported by the findings reported in **Chapter 7**, showing that patients with vmPFC damage make fewer fixations to the eyes of emotional faces during emotion recognition. High spatial frequency information from the eyes of emotional faces is critical for discriminating fear, sadness, and anger from other emotions (Adolphs et al., 2005; Smith et al., 2005). These findings, together, indicate that vmPFC may play a causal role in guiding visual fixations to emotionally salient regions of the face, such as the eyes.

It is interesting to note that a similar pattern of findings has previously been observed in a patient with bilateral amygdala lesions (Adolphs et al., 2005; Adolphs et al., 1994). This individual is profoundly impaired at recognizing fearful expressions, but exhibits improved

recognition of fear when instructed to fixate to the eyes. Given that this pattern of results has now separately been observed in patients with amygdala lesions (for fear) and patients with vmPFC lesions (for anger), it seems that both of these brain regions are necessary for emotion recognition and contribute to fixating to the eyes during emotion recognition. It is likely that the amygdala and vmPFC actively exchange information during emotion recognition, and one result of this communication is the prototypic pattern of fixations to the eyes (Eisenbarth & Alpers, 2011). Indeed, the amygdala and vmPFC share strong bidirectional projections (Ghashghaei & Barbas, 2002). That these two regions share information during emotion recognition also fits well with current theories of affective visual stimulus processing, which have proposed that the amygdala helps coordinate cortical networks to evaluate the biological significance of visual stimuli (Pessoa & Adolphs, 2010). Additionally, a number of studies implicate vmPFC in affective and value-based decision-making (Bechara et al., 1994; Plassmann et al., 2007; Plassmann et al., 2010), and vmPFC is theorized to generate affective meaning for stimuli (Roy, Shohamy, & Wager, 2012). One possibility within these frameworks is that vmPFC provides affective value information to the amygdala about emotional expressions, and both regions need to be intact for healthy fixation patterns. Future research is necessary to more directly investigate the role of vmPFC during emotional recognition and address the hypothesis that vmPFC signals the affective value of visual stimuli.

In sum, this study adds to a growing literature identifying vmPFC as essential for recognizing emotional facial expressions, and critically expands this literature by demonstrating that emotion recognition impairments present in patients with vmPFC damage causally stem from a failure to fixate to the eye region of the face. Given that vmPFC dysfunction is hypothesized to be involved in the neuropathogenesis of a number of psychiatric disorders (Blair,

2007; Etkin & Wager, 2007; Hamani et al., 2011; Myers-Schulz & Koenigs, 2012), further research into the specific role of vmPFC in emotion recognition and its contribution to visual attention can help yield advances in developing targeted treatments for multiple disorders of social and affective function.

Chapter 9. Pediatric Posttraumatic Stress Disorder is associated with Impaired Emotion Recognition and Altered Prefrontal-Amygdala Connectivity

PTSD is the experience of symptoms such as re-experiencing a trauma, avoidance of stimuli that remind one of the trauma, emotional numbing, and/or hyperarousal following a traumatic event (APA, 2013). Models of the neuropathology of PTSD place heavy emphasis on the role of vmPFC and the amygdala in giving rise to this disorder (Rauch et al., 2006). Consistent with this hypothesis, several studies report abnormal vmPFC activation to face stimuli in PTSD patients relative to comparison groups (Bryant, Kemp, et al., 2008; Herringa, Phillips, Fournier, Kronhaus, & Germain, 2013; Shin et al., 2005; Williams et al., 2006). While these studies looked at the neural response to emotional faces in PTSD, no study has yet investigated emotion recognition accuracy or fixation patterns in pediatric PTSD and related these measures to brain function.

Though few studies have investigated facial emotion recognition in pediatric PTSD, there are preliminary findings from studies of children that have experienced trauma and in youth with PTSS. Children with a history of neglect and/or abuse have difficulty discriminating emotional expressions (Pollak, Cicchetti, Hornung, & Reed, 2000). Additionally, maltreated children show a response bias towards categorizing expressions as angry (Pollak et al., 2000; Pollak & Kistler, 2002). Thus, one could expect children with a history of maltreatment to be impaired at recognizing emotional expressions on average, because they over-attribute expressions to just a subset of the basic emotions.

Using eye tracking in tandem with an emotion recognition task could also clarify the effects of PTSD symptoms on fixation patterns during emotion recognition. No study has yet examined fixation patterns during facial emotion recognition, but there is evidence that PTSD is associated with a bias towards negative images; Kimble, Fleming, Bandy, Kim, and Zambetti (2010) found that Iraq War veterans with greater PTSD symptoms spent more time looking at negative pictures than neutral pictures, relative to veterans reporting low PTSD symptoms. Another study examined PTSD-related fixation bias to threat using word stimuli (Felmingham, Rennie, Manor, & Bryant, 2011). Subjects were presented with four words, one of which was trauma-relevant. This study found that subjects with PTSD more frequently made their initial fixation to the trauma-relevant word, relative to trauma exposed comparison subjects. Together, these studies suggest that PTSD is associated with increased visual fixations to threat cues. However, one study using social stimuli in children with a history of maltreatment found that more severe maltreatment predicted attentional bias away from angry faces (Pine et al., 2005). One possibility is that PTSD is generally associated with bias towards nonsocial threatening stimuli, but away from threatening social stimuli. Importantly, a bias away from social stimuli more generally would be consistent with past findings of misattributing threat to nonthreatening expressions in maltreated samples (Pollak et al., 2000; Pollak & Kistler, 2002).

Several studies have implicated vmPFC and amygdala functional abnormalities in facial emotion processing in PTSD. Two studies have reported diminished vmPFC BOLD response in PTSD when consciously attending to fearful faces (Shin et al., 2005; Williams et al., 2006). However, other studies report increased vmPFC and amygdala activation in PTSD patients when processing fear faces outside of conscious awareness (Bryant, Kemp, et al., 2008). In one study in which subjects with PTSD were shown fearful faces during fMRI collected prior to cognitive

behavioral therapy, pretreatment PTSD symptom severity was positively associated with vmPFC and amygdala response to backwards-masked fear faces (Bryant, Felmingham, et al., 2008). Additionally, PTSS were correlated with greater vmPFC BOLD responses in a study in which angry faces were presented behind translucent task-relevant stimuli (Herringa et al., 2013). In a study of adolescents with PTSS, Garrett et al. (2012) reported increased amygdala and vmPFC activation in PTSS youth to emotional faces during an explicit recognition paradigm. Another study of adolescent sexual assault victims reported an inverse relationship between PTSS and amygdala-vmPFC functional connectivity when viewing fear versus neutral faces (Cisler et al., 2013). Thus, while studies consistently find differences in vmPFC and amygdala function between PTSD patients and comparison groups, the directionality of that difference seems to depend on whether stimuli are consciously and actively attended, as well as the age of the sample. Additionally, while all of these studies provide critical insights about the function of vmPFC and the amygdala in PTSD during emotion processing, none of them directly related emotion recognition accuracy to neural function. It is possible that some ambiguity in the directionality of these results could be resolved by relating neural activity patterns to task performance.

Here I present a study that seeks to directly link vmPFC-amygdala functional connectivity to emotion recognition and eye fixations in pediatric PTSD stemming from traumas that were interpersonal in nature. This study focused on PTSD resulting from interpersonal traumas because, to date, facial emotion recognition impairments identified in pediatric trauma samples has largely involved victims of domestic and sexual abuse (Pollak et al., 2000; Pollak & Kistler, 2002). I hypothesized that youth with PTSD would be impaired at recognizing emotions relative to healthy comparison subjects. Additionally, because youth with trauma history are

more likely to identify facial expressions as threatening (Pollak & Kistler, 2002) and show an attentional bias away from threatening faces (Pine et al., 2005), I hypothesized that youth with PTSD would show decreased fixations to the eyes of emotional faces. Finally, I hypothesized that any differences between PTSD and healthy youth on emotion recognition or eye fixations would relate to vmPFC-amygdala resting state functional connectivity.

Methods

Participants

The present sample consisted of 20 healthy non-traumatized youth and 11 youth with PTSD between the ages of 8 and 19. Healthy comparison participants were recruited through community advertisements, and youth with PTSD were recruited through local outpatient mental health facilities and community advertisements. Exclusion criteria for PTSD youth included active psychosis or suicidality, history of primary psychotic disorder or bipolar disorder, substance abuse/dependence within the past 2 weeks, and use of psychotropic medication in the past 4 weeks (6 weeks for fluoxetine). No youth were taken off medication for the purposes of this study. All youth with PTSD experienced or witnessed domestic abuse, and/or experienced sexual abuse. Healthy youth were required to be free of any history of mental illness and trauma exposure. Exclusion criteria for all participants included history of brain injury, developmental delay, unstable medical condition, MRI contraindication, and possibility of being pregnant. Participant demographic data are provided in Table 9.1. All participants provided written consent, or assent with caregiver consent when applicable. The University of Wisconsin Health Sciences Institutional Review Board approved all procedures.

	Sex	Age	IQ	Pubertal Stage	CAPS Total Score	PTSD Duration, mo.
Healthy (n = 20)	4 M 16 F	14.79 (2.66)	109.55* (10.50)	3.71 (1.16)	-	-
PTSD (n = 11)	4 M 7 F	14.88 (3.11)	94.18 (12.70)	3.30 (2.28)	81.55 (15.59)	49.77 (34.13)

Table 9.1. Group demographics.
*Significantly differs from PTSD group, $t_{(29)} = -3.62$, $p = 0.001$

Assessments

Each participant and a caregiver reporter underwent a psychiatric and trauma screen by a board certified child psychiatrist with the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) (Kaufman et al., 1997). A PTSD diagnosis was determined using DSM-IV criteria by combination of the KSADS and Clinician-Administered PTSD Scale for Children and Adolescents (CAPS) (Nader et al., 1996; Weathers, Keane, & Davidson, 2001). A PTSD diagnosis required at least five DSM-IV symptoms, including at least one from each symptom cluster, following Cohen and colleagues (Cohen, Mannarino, & Iyengar, 2011). Pubertal stage was assessed by self-report using the Tanner picture-based rating scale (Morris & Udry, 1980). IQ was estimated using the Full-Scale IQ-2 component of the Wechsler Abbreviated Scale of Intelligence-II (Wechsler, 2011).

Experimental Tasks

Stimuli were chosen from the Karolinska Directed Emotional Faces set (Lundqvist et al., 1998). Ten male and ten female actors, each depicting two emotions out of happiness, sadness, anger, fear, disgust, and neutral, comprised the stimuli for the recognition task. Face stimuli were converted to gray scale, cropped to remove hair and ears, and matched for size and luminance.

Before beginning the task, participants were instructed that on each trial a face would appear onscreen for several seconds, during which time they should try to identify the emotion of the face. Trials began with presentation of a fixation cross for 4±1 seconds, followed by a 3-second face presentation. Faces were presented such that the tip of the nose appeared at the same point on the screen as the fixation cross. Faces subtended 11.5° visual angle. After viewing the face, participants had unlimited time to use a computer mouse to rate the expression's valence ("How positive or negative was that facial expression?") on a nine-point scale and to identify the emotion from the six possibilities presented.

In addition to the facial emotion recognition task, all participants also completed a gender identification task in order to rule out the possibility that any observed emotion recognition deficits were due to a broader impairment in processing faces. This task was identical to the facial emotion recognition task, except subjects were instructed to try to identify the gender of the face, and then were prompted to identify the face as male or female following presentation of the stimulus. Order of completing the gender identification and facial emotion recognition tasks was counterbalanced across subjects, within each participant group.

Eye Tracking

Participants' eye movements were tracked at 60 Hz with an ASL D6 desk-mounted eye tracker (Applied Science Laboratories, Bedford, MA). Participants were seated approximately 64 cm away from the monitor. All participants underwent a nine-point calibration prior to beginning the experimental task. Head tracking software was used to account for head movements in real time. Fixations were defined as gaze coordinates remaining inside 1° visual angle for 100ms or greater (Karsh & Breitenbach, 1983; Lambert et al., 1974), and identified offline using automated software.

Each face stimulus was divided into three areas of interest (AOIs) for analysis. The vertical bounds of the "eye" AOI were just superior of the corrugator muscle and the inferior orbit, and the horizontal bounds were the lateral corners of each eye. The vertical bounds of the "mouth" AOI were the middle of the philtrum and just inferior of the lower lip, and the horizontal bounds were points just beyond the corners of the lips. The "face" AOI was a rectangle the maximum height and width of the face stimulus.

For all analyses performed on eye tracking data, individual trials were excluded if eye tracking failed for greater than 25% of samples during the face presentation. This threshold was set to reduce the impact of eye tracking artifacts introduced by excessive blinking and head movement. As in previous chapters, I used proportion of fixations made to a given AOI (out of the total number fixations during each 3-second face presentation) as the primary dependent measure.

Behavioral Task and Eye Tracking Statistical Analyses

For the main statistical analyses, I used linear regressions to test the relationship of PTSD diagnosis to emotion recognition and gender identification accuracy, as well as fixations to the eyes of faces in both tasks. Specifically, I used linear regressions to test the hypotheses that youth with PTSD stemming from interpersonal trauma would have reduced emotion recognition accuracy and a smaller proportion of fixations to the eyes of emotional faces. In addition to PTSD diagnosis, each model included sex, age, and their two-way interactions with PTSD diagnosis as covariates. Because the number of males in this sample is relatively small, I also examined group by sex interactions for all tests to determine whether or not any hypothesized effects regarding PTSD diagnosis were present among only one sex.

Resting-State fMRI Data Acquisition

High-resolution T1 and resting state fMRI data were acquired using a 3.0T GE Discovery MR750 scanner with an eight-channel head coil (General Electric Medical Systems, Waukesha, WI). High-resolution T1 images were acquired using a BRAVO pulse sequence (with axial orientation, TE =3.18 ms, TR = 8.16 ms, TI = 450 ms, voxel size = 1 x 1 x 1 mm^3, 156 slices, flip angle = 12 degrees, FOV = 25.6 cm, and matrix size = 256 x 256). Resting state fMRI was acquired using an echo-planar imaging (EPI) pulse sequence (with sagittal orientation, TE = 22 ms, TR = 2150 ms, flip angle = 79 degrees, slice thickness = 3 mm, voxel size = 2 x 2 x 2 mm^3, gap = 0.5 mm, 41 slices, FOV = 224 mm, and matrix size = 64 x 64, number of volumes = 147 [5min16s]). For resting state fMRI, participants were instructed to remain still with their eyes fixated on a cross.

Resting-State fMRI Data Analysis

All data processing was carried out in AFNI (Cox, 1996). Preprocessing steps were completed in the following order: removal of the first three volumes to account for equilibrium effects, despiking of EPI data, slice-timing correction, EPI alignment to T1 anatomical, warp anatomical to standard space, volume registration, blur with a 6mm Gaussian kernel, anatomy segmentation, and nuisance regression. Subject-level nuisance regression included eroded white matter and cerebrospinal fluid masks time series, six motion parameters, and the derivatives of the six motion parameters. During the nuisance regression, a bandpass filter of 0.01Hz to 0.1Hz was applied, and time points were censored if motion exceeded a frame-wise displacement of 0.25mm calculated using the Euclidean norm or if more than 10% of voxels were flagged as outliers in that volume. Participants that failed to complete the scanning protocol or that had greater than 25% of volumes censored were entirely excluded from analyses. This led to a final

sample of $n = 17$ healthy youth and $n = 7$ PTSD youth for imaging analyses.

Amygdala connectivity with medial prefrontal cortex was calculated using a 18010 voxel mask that included vmPFC and the ACC (Pitman et al., 2012). The amygdala was seeded separately for the right (1147 voxels) and the left (1149 voxels) amygdalae using default amygdala masks within AFNI. Connectivity maps were calculated for each subject and seed using AFNI's 3dDeconvolve function. Individual connectivity maps were converted from r to Z using the Fisher-Z transform, accounting for degrees of freedom. Group differences in connectivity's relationship to emotion recognition accuracy were then examined in AFNI with 3dttest++. Covariates for this model included age, sex, overall emotion recognition accuracy, and their interactions with group. Resulting group statistical maps were examined at an uncorrected threshold of $p = 0.005$, and multiple comparisons correction was done using 3dClustSim with a spatial autocorrelation function estimate for a corrected $\alpha = 0.05$ and a voxel-extent threshold of 106 voxels within the *a priori* prefrontal mask (voxel-extent threshold of 264 voxels at whole brain).

Results

Confound Checks

To ensure that any relationship between PTSD diagnosis and eye fixations or emotion recognition accuracy were not driven by general ability to follow task instructions, I regressed the proportion of fixations made to the face stimulus relative to other parts of the stimulus presentation screen on group, as well as age, race, and their two-way interactions with group. For the emotion recognition task, there was a significant effect of PTSD diagnosis on proportion of fixations made to the face stimulus relative to other parts of the stimulus presentation screen ($t_{(22)}$

= -2.27, $p = 0.034$), such that youth with PTSD made fewer fixations to the face stimulus than did healthy subjects. For the gender identification task, there was no significant effect of PTSD diagnosis on proportion of fixations made to the face relative to other parts of the stimulus presentation screen ($t_{(17)} = -1.13$, $p = 0.28$). Additionally, as noted in Table 10.1, PTSD youth had significantly lower IQ scores than did healthy comparison youth ($t_{(29)} = -3.62$, $p = 0.0011$). As a result, for any statistical test reported below in which I found a significant relationship in behavioral data, I reran that test with proportion of fixations to the face and IQ score as covariates to determine whether the significant effect remained.

Task Accuracy

For the emotion recognition task, there was no significant effect of PTSD diagnosis on overall emotion recognition accuracy ($t_{(25)} = -0.99$, $p = 0.33$), although there was a significant group by sex interaction related to overall emotion recognition accuracy ($t_{(25)} = -2.14$, $p = 0.043$). This group by sex interaction remained significant after covarying for proportion of fixations to the face and IQ ($t_{(21)} = -2.15$, $p = 0.044$). Simple effects tests revealed that, consistent with hypotheses, females with PTSD had significantly lower emotion recognition accuracy than healthy females ($t_{(25)} = -2.92$, $p = 0.0073$; Figure 9.1), while males with PTSD did not significantly differ in emotion recognition accuracy compared to healthy males ($t_{(25)} = 0.69$, $p = 0.50$). For the gender identification task, there was no significant effect of PTSD diagnosis on gender identification accuracy ($t_{(23)} = -0.85$, $p = 0.40$), nor was there a group by sex interaction ($t_{(23)} = -0.65$, $p = 0.52$).

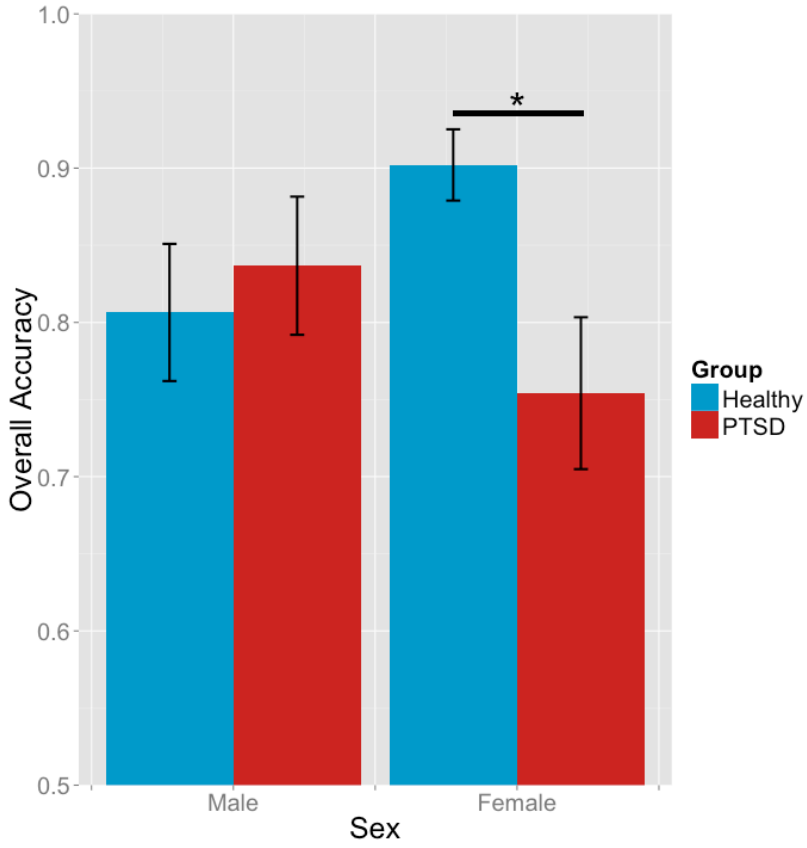

Figure 9.1. Group by sex interaction for emotion recognition accuracy.
Females with PTSD had significantly lower emotion recognition accuracy than healthy females ($t_{(25)}$ = -2.92, p = 0.0073), while males with PTSD did not significantly differ in emotion recognition accuracy compared to healthy males ($t_{(25)}$ = 0.69, p = 0.50). Error bars are ±1 SE.

Eye Tracking

For the emotion recognition task, contrary to my hypothesis, there was no significant effect of PTSD diagnosis on proportion of fixations to the eyes of faces ($t_{(21)}$ = 0.92, p = 0.37), nor was there a group by sex interaction ($t_{(21)}$ = 0.17, p = 0.87). For the gender identification task there was no significant effect of PTSD diagnosis on proportion of fixations to the eyes of faces ($t_{(16)}$ = -0.22, p = 0.83), nor was there a group by sex interaction ($t_{(16)}$ = 0.18, p = 0.86).

Resting-State Functional Connectivity

Seeding the left amygdala, there was a significant group by emotion recognition accuracy interaction in left vmPFC (left subgenual BA 32; Figure 9.2). Specifically, amongst subjects with PTSD, increasing emotion recognition accuracy predicted increasing left amygdala to left vmPFC connectivity, while this relationship was negative amongst healthy subjects. There were no significant clusters identified when seeding the right amygdala. Whole brain results for the left amygdala seed are presented in Table 9.2. No significant clusters were detected at the whole brain level for the right amygdala seed.

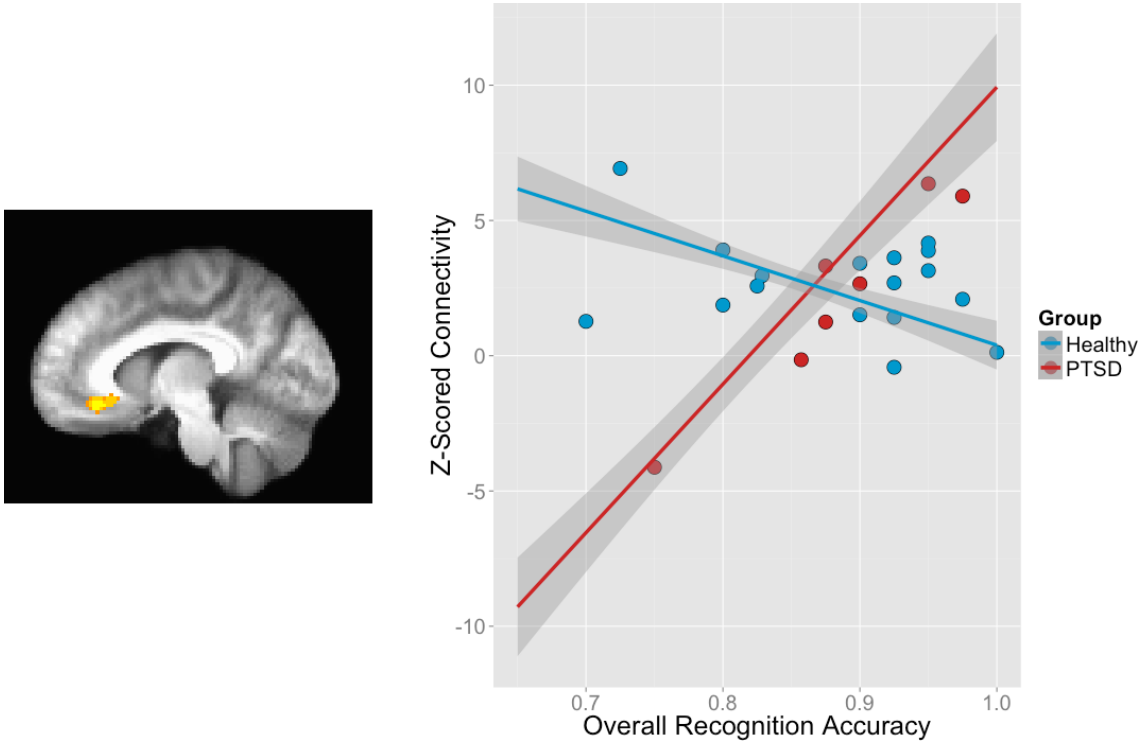

Figure 9.2. Left amygdala to left vmPFC connectivity differentially relates to emotion recognition accuracy by group.
Left, the left vmPFC (BA 32) cluster. Right, the group by emotion recognition interaction in that cluster. For youth with PTSD, increasing emotion recognition accuracy predicted increasing left amygdala to left vmPFC connectivity, while this relationship was inverse in healthy subjects. Scatter plot points are raw data, grey bands are ±1 SE.

Effect	Region	BA	Voxels	X	Y	Z	Peak t
Group X Sex	Right Lentiform Nucleus	-	438	22	-10	-8	-6.33
	Left Inferior Frontal Gyrus	47	382	-32	12	-16	-5.58
Group X Age	Right Precentral Gyrus	4	369	10	-34	68	-4.98
	Right Precentral Gyrus	4	277	54	-12	40	-5.59
Group X Accuracy	Right Precentral Gyrus	4	848	10	-34	68	6.21
	Left Insula	16	374	-38	-18	0	6.00

Table 9.2. Whole brain left amygdala functional connectivity results.
Peak coordinates (X, Y, Z) are in MNI space, LPI orientation. No significant clusters were detected with the right amygdala seed.

Discussion

This study examined the extent to which the relationship identified in prior chapters between emotion recognition, fixations to the eyes of faces, and vmPFC function was detectable in PTSD, a disorder commonly associated with vmPFC and amygdala abnormalities (Pitman et al., 2012). Consistent with my hypothesis, girls with PTSD stemming from interpersonal traumas were less accurate in recognizing emotional facial expressions than were healthy girls, and emotion recognition accuracy differentially related to vmPFC-amygdala resting state functional connectivity in PTSD and healthy youth. However, contrary to my hypotheses, there was no PTSD-related difference in fixations to eyes of emotional faces, and PTSD-related emotion recognition differences were limited to female participants. It should be acknowledged that this study is a preliminary analysis of a relatively small sample. However, it provides the first

evidence that interpersonal traumas resulting in PTSD are associated with impaired emotion recognition that relates to vmPFC-amygdala functional connectivity.

The present study found that girls with PTSD from interpersonal traumas were impaired at recognizing facial emotion relative to healthy girls. This is consistent with work showing that childhood maltreatment is associated with the over-attribution of anger (Pollak et al., 2000; Pollak & Kistler, 2002); if one emotion category is being over-identified, overall average accuracy will decrease. One possible explanation for the differences in emotion recognition amongst female subjects is that life experiences, such as growing up in an angry household, lead to a response bias. Alternatively, life experience could alter neural circuitry, like the presently observed group differences in vmPFC-amygdala functional connectivity relating to emotion recognition accuracy, to causally affect emotion recognition abilities. Due to the present study's correlational nature, however, it is impossible to determine the direction of causality between emotion recognition and vmPFC-amygdala resting state functional connectivity, or if the relationship of these variables is mediated by a third variable.

An attribution bias could also explain the lack of a difference between groups in eye fixations. As **Chapters 7** and **8** demonstrated, fixations to the eyes can play a causal role in accuracy of facial emotion recognition. It is likely the case, however, that visual processing of face stimuli only partly influences emotion recognition. The frequency with which different emotions are encountered in daily life could also play a significant role in biasing decisions towards a specific emotional category. Indeed, it is hypothesized that people are generally more accurate at recognizing happiness due to happy expressions being encountered more often throughout the course of a day (Bond & Siddle, 1996). Thus, while an emotion recognition difference was observed between groups amongst females in the present sample, this difference

may be driven by differences in life experience rather than by differences in visual processing.

This study, although preliminary, is the first to link emotion recognition accuracy and neural activity patterns in PTSD. Several studies have identified abnormal vmPFC and amygdala function during facial emotion processing in PTSD, although the precise nature of these abnormalities remains unclear (Bryant, Felmingham, et al., 2008; Bryant, Kemp, et al., 2008; Garrett et al., 2012; Herringa et al., 2013; Shin et al., 2005; Williams et al., 2006). The present study found that emotion recognition accuracy was associated with increasing left vmPFC-amygdala functional connectivity amongst youth with PTSD, but decreasing connectivity amongst healthy youth. Only one previous study has examined vmPFC-amygdala functional connectivity in association with PTSS (Cisler et al., 2013). This group found that PTSS were negatively related to vmPFC-amygdala functional connectivity when processing fear versus neutral faces. One possibility for the discrepancy of this finding with the present results is that these authors examined task-based connectivity during an implicit emotion processing task in which subjects did not have to actively recognize emotional expressions. Given that conscious awareness and task relevance produce different results in activation studies (Bryant, Felmingham, et al., 2008; Bryant, Kemp, et al., 2008; Herringa et al., 2013; Shin et al., 2005), it is possible that functional connectivity of these brain regions change direction in PTSD depending on whether a task requires implicit face processing or active emotion recognition. Further research employing a larger sample and fMRI during an active emotion recognition task will be necessary to shed light on these discrepant findings.

This is a preliminary study, and as such, there are several important limitations that should be considered. One issue is the suboptimal sample size and demographics. The sample of PTSD youth is relatively small and inadequately matched to healthy youth in terms of IQ;

although follow-up tests showed that the observed group by sex interaction for emotion recognition accuracy was still present when covarying for IQ differences. However, the small sample size for PTSD youth, coupled with the small number of males in the entire sample, may have hindered my ability to detect a true difference in emotion recognition ability in PTSD, regardless of sex. Conversely, the PTSD-related emotion recognition impairment observed herein may be specific to females, and may be related to increased susceptibility to PTSD in females (Stein, Walker, & Forde, 2000). Finally, the lack of an emotion recognition accuracy difference in boys may be due to developmental differences. Indeed, PFC actively matures throughout childhood, and females reach peak frontal gray matter volumes at an earlier age than do males (Giedd et al., 1999). It is possible, then, that an emotion recognition difference might be detectable specifically in boys later in adolescence. Another aspect of this study warranting consideration is the specificity of the index trauma in the PTSD sample. Presently, it is unclear whether PTSD, exposure to any trauma, or exposure to interpersonal trauma is associated with impaired emotion recognition. Consistent with the RDoC approach (Insel, 2014), an important consideration is the possibility that different types of traumas differentially affect specific neural circuitry and lead to differing behavioral outcomes. Understanding the relationship between trauma type and pathology will be essential in developing translational research to aid treatment of PTSD. Future research will need to include trauma-exposed subjects that lack full PTSD pathology, as well as subjects exposed to traumas that were not interpersonal in nature, in order to more completely understand the relationship of trauma and emotion recognition impairments.

This study provides a critical first step in identifying the neural correlates of emotion recognition impairments associated with PTSD. Additionally, and relevant to the present dissertation, it suggests that the relationship between vmPFC function and emotion recognition

ability is present in PTSD. If vmPFC plays a causal role in emotion recognition, the relationship of vmPFC function and emotion recognition ability should be observable consistently in populations that have abnormal emotion processing; this study provides preliminary evidence for such a relationship in PTSD.

Chapter 10. Affective and Interpersonal Traits of Psychopathy are Associated with Reduced Eye Fixations and Reduced Uncinate Fasciculus Integrity

Psychopathy is a personality disorder involving a set of behavioral, affective, and interpersonal abnormalities that include impulsivity, lack of empathy and remorse, and the callous manipulation of others (Hare, 1996, 2003). Current theories of the neuropathogenesis of this disorder emphasize a role for the amygdala and vmPFC in underlying the unique set of personality traits observed in psychopathic individuals (Blair, 2003; Kiehl, 2006). There are also notable similarities between the behavior of individuals with acquired vmPFC damage and psychopathic individuals, suggesting that vmPFC function is compromised in psychopathy (Blumer & Benson, 1975). The lack of consideration for others' feelings exhibited by psychopaths may be related to an emotion recognition impairment, and several studies report impaired recognition of facial affect in psychopathic samples (Blair et al., 2004; Hastings et al., 2008). However, psychopathy is a heterogeneous syndrome that consists of two clusters, or "factors" of traits: an interpersonal-affective factor (Factor 1), which includes traits such as manipulation, shallow affect, and callousness, and a lifestyle-antisocial factor (Factor 2), which includes traits such as impulsivity, irresponsibility, and poor behavioral control (Table 10.1). Because psychopathy is a complex and heterogeneous disorder, it is important to consider the possibility that emotion recognition impairments in psychopathy may be only related to a subset of psychopathic traits. Additionally, no study has yet linked vmPFC and amygdala structure or function to emotion recognition performance in psychopathic individuals, nor has any study investigated the pattern of fixations in psychopathic individuals.

Total PCL-R				
Factor 1 Interpersonal-Affective		Factor 2 Lifestyle-Antisocial		Neither Factor
Glibness/ superficial charm	Lack of remorse or guilt	Need for stimulation/ proneness to boredom	Poor behavioral controls	Many short-term marital relationships
Grandiose sense of self-worth	Shallow affect	Parasitic lifestyle	Early behavioral problems	Promiscuous sexual behavior
Pathological lying	Callous/ lack of empathy	Lack of realistic long-term goals	Juvenile delinquency	
Conning/ manipulative	Failure to accept responsibility for own actions	Impulsivity	Revocation of conditional release	
		Irresponsibility	Criminal versatility	

Table 10.1. Factors of psychopathic traits.
The 20 items comprising the Psychopathy Checklist-Revised (PCL-R), and their factor loadings.

Fixation patterns during emotion recognition have not been investigated in adult psychopathy, but a set of studies have investigated these phenomena in children with callous and unemotional (CU) traits. CU traits are thought to be a precursor to adult psychopathy (Barry et al., 2000) and correspond to interpersonal-affective traits; items from the Inventory of Callous-Unemotional Traits bear close resemblance to questions assessing interpersonal-affective traits of psychopathy (e.g., “The feelings of others are unimportant to me”) (Kimonis et al., 2008). In the first of a pair of studies, Dadds and colleagues found that boys high in CU traits had lower recognition of fear compared to boys low in CU traits, but the high CU boys had improved fear recognition when instructed to fixate on the eyes of faces (Dadds et al., 2006). In a follow-up study that used eye tracking, boys high in CU traits made fewer fixations to the eye regions of faces compared to boys low in CU traits (Dadds et al., 2008). These results suggest that, in adult psychopathy, Factor 1 scores may be expected to negatively relate to emotion recognition

accuracy and eye fixations. Thus, a study of emotion recognition that uses eye tracking in a sample of adults with a broad range of Factor 1 scores would fill a critical gap in the literature.

In addition to evidence of emotion recognition impairments in psychopathy, there is also evidence of abnormalities in vmPFC and amygdala in this disorder (Blair, 2003, 2007, 2008). One reliably reported neuroimaging result is an association between psychopathy and reduced microstructural integrity of the right uncinate fasciculus (UF; the major white matter pathway connecting ventral frontal and anterior temporal cortices). The UF is believed to play a critical role in social-affective function and decision-making (Olson, McCoy, Klobusicky, & Ross, 2013; Von Der Heide, Skipper, Klobusicky, & Olson, 2013). Four different diffusion tensor imaging (DTI) studies have found reduced fractional anisotropy (FA) of the right UF in psychopathic and/or antisocial offenders, relative to non-psychopathic individuals (Craig et al., 2009; Hoppenbrouwers et al., 2013; Motzkin et al., 2011; Sundram et al., 2012). However, these studies of UF integrity in psychopathy only looked at overall psychopathy severity, rather than specific clusters of psychopathic traits that could relate more closely to emotion recognition performance. It is possible that UF integrity is related not to psychopathy score, per se, but rather to a specific factor of psychopathy. Given that the previous chapters of this dissertation have established a link between emotion recognition and vmPFC, it is possible that, if Factor 1 scores were related to emotion recognition, UF integrity would also specifically relate to Factor 1 scores.

Here, I present two studies that address the relationship of emotion recognition, eye fixations, and UF structural integrity to Factor 1 scores in psychopathy. Both studies involve criminal offenders with a broad range of Factor 1 scores. The first study examines emotion recognition accuracy. Additionally, study 1 employs eye tracking to determine the extent to

which Factor 1 scores relate to reduced fixations to the eyes of emotional faces. In this study I hypothesize that higher Factor 1 scores will be associated with decreased emotion recognition accuracy and reduced fixations to the eyes of emotional faces. The second study uses DTI to examine the relationship between psychopathic traits and uncinate fasciculus integrity. In this study I hypothesize that higher Factor 1 scores will be associated with decreased uncinate fasciculus white matter integrity.

Study 1: Methods

Participants

Participants were adult male inmates at a medium-security Wisconsin correctional facility. Inmates were eligible if they met the following criteria: 18 to 45 years of age, IQ > 70, free of psychotropic medication use, no history of loss of consciousness lasting longer than 30 minutes, no history of psychosis or bipolar disorder, and normal or corrected to normal vision that was compatible with eye tracking (e.g., contacts or non-bifocal glasses). Sixty-eight subjects participated in study 1. The final sample included $N = 58$ individuals, after excluding 10 subjects for issues with eye tracking or missing data. Participant characteristics for the current study are presented in Table 10.2. All participants provided oral and written informed consent.

	Non-psychopathic (n = 17)	**Intermediate** (n = 19)	**Psychopathic** (n = 22)
Age	34.47 (8.84)	30.84 (7.65)	31.95 (8.34)
Race (Cauc/Af Am)	12/5	16/3	12/10
Years Education	10.94 (1.43)	10.53 (1.98)	10.45 (1.57)
IQ	102.65 (10.49)	100.47 (12.24)	100.14 (11.44)
Anxiety	11.24 (9.92)	16.37 (8.66)	11.27 (9.02)
Digit Span	6.76 (2.05)	6.32 (1.67)	6.14 (2.17)
Substance Use Disorder	8/17	14/19	14/22
PCL-R Total Score	14.10 (3.53)	23.68 (2.07)	31.95 (2.17)
Factor 1	6.24 (1.92)	8.53 (1.74)	12.41 (2.02)
Factor 2	5.63 (2.90)	13.34 (1.73)	16.36 (1.94)

Table 10.2. Study 1 participant characteristics.

Assessments

Psychopathy was assessed by trained research staff using the Psychopathy Checklist-Revised (PCL-R) (Hare, 2003). The PCL-R is a clinical measure of psychopathy, completed based on a 60-90 minute clinical interview and review of institutional files used to assess the presence of 20 psychopathy-related traits (Table 10.1), assigning a score of 0, 1, or 2 for each item. Factor scores were calculated according to published guidelines (Hare & Neumann, 2005; Harpur, Hare, & Hakstian, 1989). Scores for Factors 1 and 2 were moderately correlated (r = 0.64). Participants were identified as psychopathic if they scored 30 or greater on the PCL-R (n = 22), non-psychopathic if they scored 20 or lower (n = 17), and intermediate if they scored between 20 and 30 (n = 19) (Hare, 2003).

Substance use disorder was assessed using the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 2012). A composite variable was calculated for substance use; participants who met criteria for abuse or dependence on any substance (alcohol, cannabis, cocaine, opioids, stimulants, sedatives or hallucinogens) earned a substance use disorder score of "Present," and all other participants were scored as "Absent." IQ was estimated using the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 2008). Working memory was

assessed using the digit span backwards subtest from the WAIS. Trait negative affect was assessed using the Welsh Anxiety Scale (WAS) (Welsh, 1956).

Experimental Tasks

Stimuli were chosen from the Karolinska Directed Emotional Faces set (Lundqvist et al., 1998). Ten male and ten female actors, each depicting two emotions out of happiness, sadness, anger, fear, disgust, and neutral, comprised the stimuli for the recognition task. Face stimuli were converted to gray scale, cropped to remove hair and ears, and matched for size and luminance. Before beginning the task, participants were instructed that on each trial a face would appear onscreen for several seconds, during which time they should try to identify the emotion of the face. Trials began with presentation of a fixation cross for 4±1 seconds, followed by a 3-second face presentation. Faces were presented such that the tip of the nose appeared at the same point on the screen as the fixation cross. Faces subtended 11.5° visual angle. After viewing the face, participants had unlimited time to use a computer mouse to rate the expression's valence ("How positive or negative was that facial expression?") on a nine-point scale and to identify the emotion from the six possibilities presented. Faces were not presented onscreen during the response screens.

In addition to the facial emotion recognition task, all participants also completed a gender identification task in order to rule out the possibility that any observed emotion recognition deficits were due to a broader impairment in processing faces. This task was identical to the facial emotion recognition task, except subjects were instructed to try to identify the gender of the face, and then were prompted to identify the face as male or female following presentation of the stimulus. Order of completing the gender identification and facial emotion recognition tasks was counterbalanced across subjects, within each participant group.

Eye Tracking

Participants' eye movements were tracked at 60 Hz with an ASL D6 desk-mounted eye tracker (Applied Science Laboratories, Bedford, MA). Participants were seated approximately 64 cm away from the monitor. All participants underwent a nine-point calibration prior to beginning the experimental task. Head tracking software was used to account for head movements in real time. Fixations were defined as gaze coordinates remaining inside 1° visual angle for 100ms or greater (Karsh & Breitenbach, 1983; Lambert et al., 1974), and identified offline using automated software.

Each face stimulus was divided into three areas of interest (AOIs) for analysis. The vertical bounds of the "eye" AOI were just superior of the corrugator muscle and the inferior orbit, and the horizontal bounds were the lateral corners of each eye. The vertical bounds of the "mouth" AOI were the middle of the philtrum and just inferior of the lower lip, and the horizontal bounds were points just beyond the corners of the lips. The "face" AOI was a rectangle the maximum height and width of the face stimulus.

For all analyses performed on eye tracking data, individual trials were excluded if eye tracking failed for greater than 25% of samples during the face presentation. This threshold was set to reduce the impact of eye tracking artifacts introduced by excessive blinking and head movement. As in previous chapters, I used proportion of fixations made to a given AOI (out of the total number fixations during each 3-second face presentation) as the primary dependent measure.

Statistical Analyses

For the main statistical analyses, I used linear regressions to test the relationship of PCL-R factor scores to emotion recognition and gender identification accuracy, as well as fixations to

the eyes of faces in both tasks. Specifically, I used linear regressions to test the hypotheses that higher Factor 1 scores would be associated with reduced emotion recognition accuracy and a lower proportion of fixations to the eyes of emotional faces. In addition to psychopathy factor scores, each model included race, age, working memory, and their two-way interactions with psychopathy as covariates. Working memory (i.e., digit span backwards score) was included as a covariate in this analysis because the face stimulus was no longer presented onscreen during the response screens.

To assure accuracy of regressions, I performed model case analysis. This consisted of plotting a histogram of Cook's distances for each model (Cook, 1977), identifying and excluding individuals that had values that were discontinuous with the rest of the distribution (i.e., had disproportionately large influence on the model), and re-running the model. This exclusion criterion was adopted as a means to minimize the error in regressions, which is inflated by influential cases that are outliers with substantial leverage. Based on this criterion, $n = 2$ to 8 subjects were excluded from each analysis.

Study 1: Results

Confound Checks

To ensure that any relationship between factor scores and eye fixations or emotion recognition accuracy were not driven by general ability to follow task instructions, I regressed the proportion of fixations made to the face stimulus relative to other parts of the stimulus presentation screen on factor scores, as well as age, race, working memory, and their two-way interactions with factor scores. There was no significant effect of Factor 1 scores on proportion of fixations made to the face stimulus in the emotion recognition task ($t_{(47)} = -0.40$, $p = 0.69$) or

in the gender identification task ($t_{(46)} = -0.32$, $p = 0.75$). Likewise, there was no significant effect of Factor 2 scores on proportion of fixations made to the face stimulus in the emotion recognition task ($t_{(40)} = -1.43$, $p = 0.16$) or in the gender identification task ($t_{(38)} = 0.52$, $p = 0.61$).

Task Accuracy

For the emotion recognition trials, there was no significant effect of Factor 1 scores on emotion recognition accuracy ($t_{(46)} = 1.26$, $p = 0.22$). There was a trend towards a negative relationship between Factor 2 scores and emotion recognition accuracy ($t_{(38)} = -1.90$, $p = 0.066$). For the gender identification task, there was no significant effect of either Factor 1 scores or Factor 2 scores on gender identification accuracy (Factor 1: $t_{(46)} = -0.30$, $p = 0.76$; Factor 2: $t_{(40)} = 0.82$, $p = 0.42$).

Proportion of Fixations to the Eyes

For the emotion recognition task, consistent with study hypotheses, there was a significant effect of Factor 1 scores on proportion of fixations made to the eyes during emotion recognition trials ($t_{(45)} = -2.20$, $p = 0.033$; Figure 10.1), such that greater Factor 1 scores predicted lower proportions of fixations to the eyes. There was no significant effect of Factor 2 scores on proportion of fixations made to the eyes during emotion recognition trials ($t_{(40)} = 1.04$, $p = 0.31$). For the gender identification trials, there was no significant effect of either Factor 1 scores or Factor 2 scores on the proportion of fixations made to the eyes (Factor 1: $t_{(46)} = -0.69$, $p = 0.49$; Factor 2: $t_{(38)} = 1.50$, $p = 0.14$).

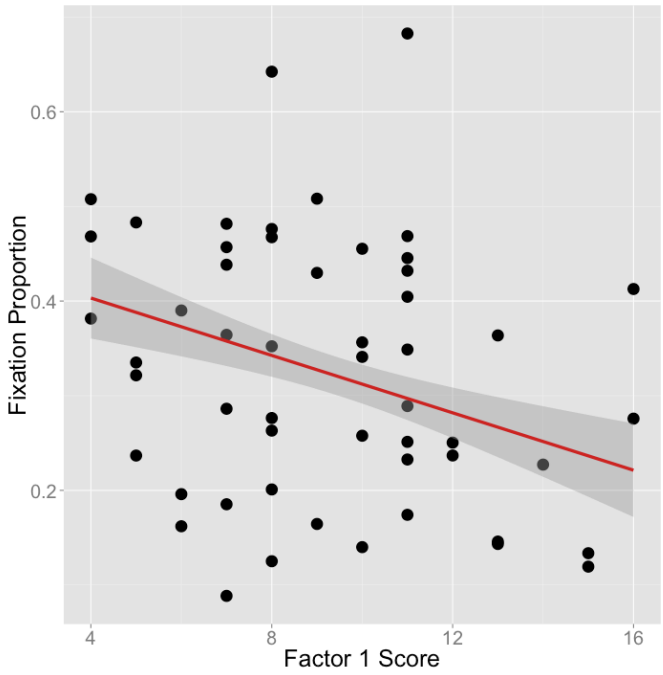

Figure 10.1. Interpersonal-Affective traits predict reduced fixations to eyes. Inverse relationship between proportion of fixations to the eyes during emotion recognition and Factor 1 scores (p = 0.033). Scatter plot points are raw data. Grey band indicates ±1 standard error.

Study 2: Methods

Participants

Participants in study 2 were adult male inmates at a medium-security Wisconsin correctional facility. Inmates were eligible if they met the following criteria: 18 to 45 years of age, IQ > 70, free of psychotropic medication use, no history of loss of consciousness lasting longer than 30 minutes, and no history of psychosis or bipolar disorder. The final sample (N = 147) included 22 inmates (n = 13 psychopathic and n = 9 non-psychopathic) who participated in a previous DTI study from our group in which we reported group differences in right UF integrity between relatively small groups of psychopathic and non-psychopathic inmates (Motzkin et al., 2011); however, these individuals were rescanned for the present study.

Participant characteristics for the current study are presented in Table 10.3. All participants provided oral and written informed consent.

	Non-psychopathic (n = 50)	**Intermediate** (n = 47)	**Psychopathic** (n = 50)
Age	31.26 (6.82)	30.94 (6.83)	29.84 (7.48)
Race (Cauc/Af Am)	36/14	19/28	33/17
Years Education	10.96 (1.23)	10.60 (1.23)	10.00 (1.78)
IQ	99.30 (12.64)	96.16 (12.41)	100.86 (10.82)
Anxiety	11.14 (8.43)	10.43 (5.53)	17.06 (8.73)
Violent Offenses	3.63 (3.68)	5.35 (7.28)	6.14 (4.89)
Substance Use Disorder	18/50	39/47	41/50
PCL-R Total Score	14.41 (3.50)	25.54 (2.42)	31.90 (1.57)
Factor 1	5.11 (2.24)	9.43 (2.07)	12.10 (1.84)
Factor 2	7.83 (2.76)	14.11 (1.88)	17.00 (1.52)

Table 10.3. Study 2 participant characteristics.

Assessments

Psychopathy was assessed by trained research staff using the Psychopathy Checklist-Revised (PCL-R) (Hare, 2003). Inter-rater reliability ratings were available for 13 participants and yielded a high intra-class correlation (r = .99) for PCL-R total scores. Factor scores were calculated according to published guidelines (Hare & Neumann, 2005; Harpur et al., 1989). Scores for Factors 1 and 2 were moderately correlated (r = 0.66). For categorical analyses participants were identified as psychopathic if they scored 30 or greater on the PCL-R (n = 50), non-psychopathic if they scored 20 or lower (n = 50), and intermediate if they scored between 20 and 30 (n = 47) (Hare, 2003).

Substance use disorder was assessed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2012). A composite variable was calculated for substance use; participants who met criteria for abuse or dependence on any substance (alcohol, cannabis, cocaine, opioids,

stimulants, sedatives or hallucinogens) earned a substance use disorder score of "Present," and all other participants were scored as "Absent." IQ was estimated using the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 2008). Trait negative affect was assessed using the Welsh Anxiety Scale (WAS) (Welsh, 1956). Finally, the number of violent offenses for each participant was quantified as the count of charges for murder, assault, robbery, sexual assault, weapon-related offenses, and kidnapping.

MRI Data Acquisition

Diffusion-weighted echo-planar MRI was acquired on correctional facility grounds using the Mind Research Network's Siemens 1.5 T Avanto Mobile MRI System equipped with a 12-element head coil. Diffusion sensitizing gradients were applied along 30 non-collinear directions (b value = 800 s/mm^2). Five interleaved non-diffusion-weighted (b value = 0 s/mm^2) volumes were collected during each run to enable corrections for motion and eddy current distortions. Images were collected with the following parameters: repetition time (TR) = 9200 ms, echo time (TE) = 84 ms, field of view (FOV) = 256 mm x 256 mm, matrix size = 128 x 128, slice thickness = 2 mm, no gap, voxel size = 2 mm x 2 mm x 2 mm, 70 slices. The sequence was repeated twice and the data combined to improve signal-to-noise ratio. Head motion was limited using padding and restraint.

DTI data were processed using FSL (Smith et al., 2006; Smith et al., 2004) and Camino (Cook et al., 2006). Eddy current and subject motion were corrected via affine registration to the first non-diffusion-weighted (i.e., b0) volume. Brain extraction to remove non-brain tissue was performed on the b0 image. Masks were eroded and quality checked before being applied to the remainder of non-diffusion-weighted volumes. The resultant images were used for nonlinear diffusion tensor estimation (Alexander & Barker, 2005). Extreme outlier voxels were then

identified and masked. Finally, voxels that led to tensors that were not symmetric positive-definite were identified and forced to meet this criterion (Barmpoutis & Vemuri, 2010) before FA maps were calculated.

FA maps were nonlinearly registered to the MNI152 FA template and resampled to 1 mm^3 using FSL's tract-based spatial statistics workflow (Smith et al., 2006). Alignment quality was visually confirmed for all subjects. A grand mean FA image was used to calculate a white matter skeleton, which was used for all subsequent analyses to minimize the partial volume effect. Tract average FA was computed across voxels in the intersection of the white matter skeleton and Johns Hopkins University white matter atlas labels (Mori, Wakana, Van Zijl, & Nagae-Poetscher, 2005).

Statistical Analysis

Average FA within a given tract was the primary dependent measure for linear regressions performed in R (R Development Core Team, 2014). All statistical models included participant age, race, and presence of substance use disorder as covariates. Left and right UF were selected as *a priori* tracts of interest, while comparison tracts were selected based on either proximity to the UF or on previous studies identifying psychopathy-related abnormalities in these tracts (Hoppenbrouwers et al., 2013; Raine et al., 2003). To determine the relationship between specific psychopathic traits and UF integrity, FA values were regressed on PCL-R factor scores. In some cases, items for specific factors are omitted during the PCL-R interview because the individual's life history is not conducive to accurate assessment (e.g., no history of conditional release, thus revocation of such is not possible); a total of 10 subjects with such omitted items were excluded from Factor 2 analyses. Because PCL-R factor scores are correlated, these analyses were conducted by first running separate models for each individual

factor, and then including both factors in a single model to assess the unique relationship between FA and each factor.

To assure accuracy of regressions, I performed model case analysis. This consisted of plotting a histogram of Cook's distances for each model (Cook, 1977), identifying and excluding individuals that had values that were discontinuous with the rest of the distribution (i.e., had disproportionately large influence on the model), and re-running the model. This exclusion criterion was adopted as a means to minimize the error in regressions, which is inflated by influential cases that are outliers with substantial leverage. Based on this criterion, n = 7 to 9 subjects were excluded from each analysis.

Study 2: Results

Relationship of PCL-R Factor Scores and Right Uncinate Fasciculus Fractional Anisotropy

To determine whether right UF integrity was specifically related to one of the two factors of psychopathy, I regressed FA in this area on Factor 1 (Interpersonal-Affective) and Factor 2 (Antisocial-Lifestyle) scores, with the aforementioned covariates, in separate models. Factor 1 scores were inversely related to right UF FA ($t_{(133)}$ = -2.35, p = 0.021, partial η^2 = 0.040). There was also a trend towards a negative relationship between Factor 2 scores and right UF FA ($t_{(123)}$ = -1.79, p = 0.076, partial η^2 = 0.025).

To determine the unique relationship between each factor score and right UF integrity, I regressed FA in this area in a single model that included Factor 1 scores, Factor 2 scores, their two-way interaction, and aforementioned covariates. Factor 1 scores were inversely related to right UF FA ($t_{(121)}$ = -2.07, p = 0.040, partial η^2 = 0.034; Figure 10.2), while the unique

contributions of Factor 2 scores and the interaction of the two factor scores were unrelated to right UF integrity (both $p > 0.46$).

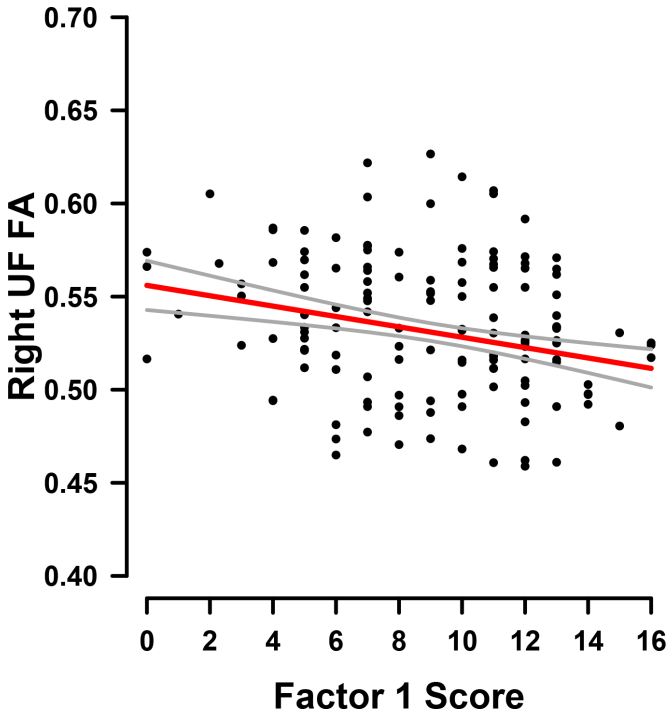

Figure 10.2. Right UF FA relationship to Factor 1 score. Inverse relationship between right UF FA and Factor 1 scores ($p = 0.040$). Scatter plot points are raw data. Grey lines indicate ±1 standard error.

Follow-Up Analyses

Factor 1 scores were unrelated to FA of comparison tracts (cingulum bundle, anterior internal capsule, thalamic radiation, or genu or body of the corpus callosum; all $p > 0.3$). Further, Factor 1 scores were unrelated to whole-brain FA ($p = 0.62$), suggesting that the effect observed in the right UF was not driven by a general relationship between Factor 1 scores and overall white matter integrity. As expected, the presence of substance use disorder was positively correlated with PCL-R total scores ($r_{(145)} = 0.46$, $p < 0.0001$). However, in the models reported above for the relationship between Factor 1 scores and right UF integrity, there was no

significant relationship between presence of substance use disorder and right UF integrity (all $p > 0.42$).

Discussion

Consistent with my hypotheses, these studies found Factor 1 scores to be related to both reduced fixations to the eyes of faces during emotion recognition and reduced right UF integrity. However, contrary to my hypothesis, I did not find a significant relationship between Factor 1 scores and emotion recognition accuracy. Here I will discuss each of these findings.

Past work by Adolphs et al. (2005), as well as data presented in **Chapters 7** and **8** of this dissertation, established that fixations to the eyes play a causal role in recognizing emotion; individuals with emotion recognition impairments can improve by intentionally fixating to the eyes of emotional faces. Thus, it may at first seem counter-intuitive that interpersonal-affective traits are associated with reduced eye fixations but unrelated to emotion recognition accuracy, but considering the nature of these traits may clarify this result. Interpersonal traits include items such as being conning/manipulative and superficial charm and affective traits include items such as being callous and lacking remorse (Hare, 2003). Manipulating people may actually require expert knowledge of human emotion coupled with an emotion processing abnormality that leads to callousness or a shallow emotional experience. Consistent with this concept, one study has reported a positive association between accuracy of judging emotional intensity and psychopathy scores (Book et al., 2007). It is possible that individuals high in interpersonal-affective traits are unimpaired at recognizing emotion, but due to reduced eye fixations or compromised UF integrity, have a shallow emotional experience that enables them to respond inappropriately to emotional stimuli.

These findings support a multi-dimensional model of psychopathy, in which specific components of the disorder are underpinned by distinct neurobiological substrates and associated with unique behavioral abnormalities. Only one previous study has investigated the relationship of psychopathy factor scores with emotion recognition ability; Hastings et al. (2008) found a negative relationship between PCL-R total scores and recognition accuracy for sad and happy faces, but no significant relationship between any factor score and task performance. It should be noted, however, that these authors used the PCL Screening Version, which may have critically limited variability of the factor scores in their sample. More consistently, a fear recognition impairment has been associated with psychopathy (Blair et al., 2004; Dadds et al., 2006). Consistent with these past results, the present study found that lifestyle-antisocial traits were inversely related to fear recognition. Interestingly, in the present study eye fixations were inversely related to interpersonal-affective traits and unrelated to lifestyle-antisocial traits, suggesting that the two factors separately relate to fixation patterns and emotion recognition.

The finding of an inverse relationship between Factor 1 scores and right UF FA across the entire sample of study 2 extends previous findings based on group comparisons with smaller samples, which showed lower FA in right UF in psychopathic offenders versus non-psychopathic individuals (Craig et al., 2009; Hoppenbrouwers et al., 2013; Motzkin et al., 2011; Sundram et al., 2012). My analyses provide novel insight in this regard; reduced right UF integrity was specifically related to the interpersonal-affective traits of psychopathy. Taken together, these results not only corroborate previous reports of right UF abnormalities in psychopathy, but also preliminarily suggest that abnormal fixation patterns are associated with interpersonal-affective traits and that right UF integrity may play a role in fixation patterns.

A critical contribution of the present studies is that they begin to link eye fixations to right UF microstructural integrity. Although I was unable directly test the relationship between eye fixations and right UF integrity due to insufficient neuroimaging data in the eye tracking sample, these two measures were linked to a common variable; interpersonal-affective traits were separately inversely related to both eye fixations during emotion recognition and to right UF FA. Although several studies have reported right UF FA reductions in psychopathy (Craig et al., 2009; Hoppenbrouwers et al., 2013; Motzkin et al., 2011; Sundram et al., 2012), the present studies begin to link this phenomenon to reduced fixations to the eyes. The UF is the major fiber tract linking vmPFC and the amygdala (Ghashghaei & Barbas, 2002), and normal structural integrity of the UF may be necessary for normal levels of fixation to the eyes. This notion is consistent with the idea that vmPFC and the amygdala exchange information during emotion recognition and influence visual processing of affect (Pessoa & Adolphs, 2010).

Although these studies extend the literature on the neural basis of emotion recognition and its relationship to psychopathic traits, there are several caveats to the interpretation of these data. One caveat is that the observed relationships interpersonal-affective traits have to eye fixations and right UF FA are strictly correlational; at present it is unclear whether reduced eye fixations and right UF FA are causes or consequences of psychopathic behavior. Secondly, although the shared relationship of eye fixations and right UF FA to interpersonal-affective traits suggests that eye fixations and right UF FA may be directly related, these relationships were presently observed in separate samples. Future work will need to replicate the present eye tracking results in individuals for which neuroimaging data exist in order to directly observe a relationship between these two measures.

Together, these studies represent preliminary evidence that right UF integrity, and putatively vmPFC-amygdala communication, relates to eye fixations during emotion recognition in individuals with psychopathic traits. If the brain-behavior relationship identified here reflects a distinct etiopathological mechanism for a specific cluster of psychopathic traits, then the development of interventions may benefit from targeting these traits separately. Furthermore, treatments aimed at increasing eye fixations or improving vmPFC-amygdala signaling may improve prognosis for this disorder. Additionally, this study demonstrates that eye fixations are related to right UF integrity in a disorder characterized by symptoms distinct from those that characterize PTSD. Thus, these data suggest that vmPFC relates to eye fixations and emotion recognition at multiple points on the emotion processing spectrum.

Chapter 11. General Discussion

Together, the results described in this dissertation implicate vmPFC in recognizing emotional facial expressions and directing visual fixations to the eyes of faces during emotion recognition. Previous work has implicated the amygdala in these processes (Adolphs et al., 2005; Adolphs et al., 1994; Whalen et al., 2004; Whalen et al., 1998), thus these results begin to outline nodes of a network subserving emotion recognition that includes the amygdala and vmPFC. This expands the current understanding of the neural basis of emotion recognition not only by implicating vmPFC in this process, but also by beginning to map specific functions to this circuitry; vmPFC and the amygdala both appear to be involved in recognizing emotion in facial expressions and directing fixations to the eyes of faces. Additionally, the results described herein indicate that this circuitry is related to emotion recognition impairments and eye fixation abnormalities in pediatric PTSD and psychopathy, respectively. Identifying the relationship of vmPFC-amygdala circuitry and behavioral abnormalities related to emotion recognition in psychiatric samples both lends credence to the proposal that vmPFC is a key node in an emotion recognition network (Pessoa & Adolphs, 2010), and also suggests novel targets for treatment interventions in these disorders. Finally, from a translational science perspective, the present results have important implications for the relationship of emotion recognition and eye fixations.

In **Chapter 7**, I asked if vmPFC is necessary for making fixations to the eyes of faces during emotion recognition. Consistent with the known role of the amygdala in guiding fixations to the eyes of faces (Adolphs et al., 2005) and the fact that the amygdala and vmPFC are densely connected (Ghashghaei & Barbas, 2002), I found that patients with vmPFC lesions made fewer fixations to the eyes of faces, and specifically fear faces, relative to brain-damaged comparison and healthy comparison subjects. This novel finding demonstrates a role for vmPFC in

contributing to the spatial distribution of visual fixations. However, inconsistent with the notion that fixations to the eyes are critical for recognizing emotional expressions (Adolphs et al., 2005; Smith et al., 2005), I found no group differences in emotion recognition accuracy for this study. This inconsistency may be related to a ceiling effect introduced by easily recognized, stereotyped stimuli that are well-suited to eye tracking, but poorly suited to exposing subtle differences in emotion recognition abilities; a notion I addressed in **Chapter 8**.

In **Chapter 8**, I used facial emotion stimuli that varied in intensity in order to test the possibility that patients with vmPFC damage had an emotion recognition impairment that stemmed from an impairment in fixating to the eyes of faces. Consistent with previous reports that vmPFC is necessary for the accurate recognition of emotion (Heberlein et al., 2008; Hornak et al., 1996; Tsuchida & Fellows, 2012), I found that patients with vmPFC lesions had lower recognition accuracy for moderate intensity anger compared to healthy and brain-damaged comparison groups. Furthermore, supporting the notion that the observed anger recognition impairment was related to a failure to fixate to the eyes of angry faces, vmPFC patients' anger recognition accuracies improved to normal levels when they were instructed to fixate on the eyes of angry faces. Considered in tandem with the study presented in **Chapter 7**, this study supports previous reports that information present in the eyes plays a causal role in distinguishing certain emotions, including anger (Adolphs et al., 2005; Smith et al., 2005). Importantly, this study also suggests that vmPFC contributes to the spatial deployment of fixations during emotion recognition, which, when performed abnormally, can lead to impaired emotion recognition. The findings of this study are consistent with reports of the behavior of individuals with acquired vmPFC lesions indicating that vmPFC is necessary for normal processing of social emotions (Barrash et al., 2000; Blair & Cipolotti, 2000; Damasio, 1996; Eslinger & Damasio, 1985), and

suggests that a mechanism underlying the abnormal social behavior of these individuals is perturbed visual processing of emotional stimuli. When considered alongside reports of the amygdala being necessary for guiding visual fixations to emotionally salient regions of the face, these two studies suggest that, not only is vmPFC involved in this function, but also that an exchange of information between vmPFC and the amygdala may contribute to the spatial pattern of fixations during emotion recognition.

In **Chapter 9**, I examined the extent to which emotion recognition and eye fixations related to vmPFC-amygdala functional connectivity in youth with PTSD relating to interpersonal traumas. In this preliminary sample, I found that amongst females, youth with PTSD had lower overall emotion recognition accuracy than did healthy youth, although there were no group differences in fixations to the eyes of faces. This finding is consistent with previous reports of emotion recognition impairments in trauma-exposed youth (Pollak & Kistler, 2002). Moreover, emotion recognition accuracy was associated with increasing vmPFC-amygdala functional connectivity amongst youth with PTSD, but decreasing vmPFC-amygdala functional connectivity amongst healthy youth. If vmPFC and the amygdala subserve emotion recognition, this brain-behavior relationship should be apparent in a range of populations with different emotion recognition impairments. This study provides evidence that the relationship between emotion recognition and vmPFC-amygdala function is present in a psychiatric population with social-affective deficits, namely pediatric PTSD. Importantly, through resting-state functional connectivity, this study also provides evidence that communication between vmPFC and the amygdala is related to emotion recognition ability, rather than these regions playing independent roles.

Finally, in **Chapter 10**, I examined the extent to which particular psychopathic traits related to emotion recognition, eye fixations, and UF white matter integrity in inmates with a wide range of psychopathy severity. Here I found that interpersonal and affective traits were negatively related to fixations to the eyes of emotional faces during emotion recognition, although I found no relationship between interpersonal and affective traits and emotion recognition ability. Additionally, in a separate sample, I found that interpersonal and affective traits negatively related to right UF white matter integrity, raising the possibility that right UF integrity mediates the relationship between interpersonal and affective traits and eye fixations. The eye tracking results of this study are consistent with previous work demonstrating that boys with high levels of callous and unemotional traits make fewer fixations to the eyes of fearful faces than boys low in these traits (Dadds et al., 2008). While several studies have examined emotion recognition in relation to overall psychopathy severity (Blair et al., 2004; Book et al., 2007; Hastings et al., 2008), this study is the first to identify a relationship between eye fixations and a particular cluster of psychopathic traits. Additionally, with both eye fixations and right UF integrity relating to interpersonal and affective traits, this study suggests that vmPFC-amygdala communication may relate to eye fixations.

In sum, these studies provide evidence for vmPFC being necessary for facial emotion recognition and guiding fixations to the eyes of faces, and that this relationship is present in psychiatric disorders in which emotion processing is perturbed. These findings integrate readily with extant knowledge of the neural basis of emotion recognition; the amygdala is known to be necessary for recognizing facial expressions and guiding fixations to the eyes of faces (Adolphs et al., 2005; Adolphs et al., 1994), and recent theoretical frameworks of emotion processing have placed greater emphasis on considering the role of the amygdala in a broader network (Pessoa &

Adolphs, 2010). Considering the dense connections between vmPFC and the amygdala (Ghashghaei & Barbas, 2002), the findings of the human lesion studies presented in **Chapters 7** and **8** suggest that vmPFC is another node, alongside the amygdala, in an emotion processing network. This claim is further supported by the results of **Chapter 9,** which found that emotion recognition ability was related to connectivity of the amygdala and vmPFC, as well as the results of **Chapter 10**, which suggest that eye fixations may be related to structural integrity of the major fiber tract linking vmPFC and the amygdala. Additionally, the results presented in this dissertation raise several possibilities that warrant further consideration and research. One question that remains is the extent to which emotion recognition and eye fixations are dissociable phenomena; while the lesion work presented here suggests that emotion recognition causally depends on eye fixations, the studies of psychiatric populations suggests that these two processes can be differentially affected. Also, it is worth considering the utility of emotion recognition accuracy, eye fixations, and vmPFC-amygdala connectivity as units of analysis for distinguishing between psychiatric disorders, in a manner similar to the present approach applied to pediatric PTSD and psychopathic traits.

The Dissociation of Recognition and Fixation: Network Function Implications

Past work in amygdala lesion patients and children with callous and unemotional traits suggests that fixations to the eyes of emotional faces causally impact emotion recognition accuracy (Adolphs et al., 2005; Dadds et al., 2008), and the results of the vmPFC lesion studies in **Chapters 7** and **8** agree with this notion. However, **Chapter 9** describes the selective impairment of emotion recognition accuracy in pediatric PTSD with no corresponding fixation abnormalities, and **Chapter 10** describes the relationship of interpersonal and affective traits in

psychopathy to eye fixations without a corresponding emotion recognition relationship. To further complicate this discrepancy, the results presented in this dissertation suggest that both emotion recognition accuracy and eye fixations are related to measures of vmPFC-amygdala communication. This begs the questions: are emotion recognition and eye fixations dissociable processes, and how can abnormality in a single structure (vmPFC) lead to different impairments?

There are several possible explanations for the seemingly conflicting findings regarding the relationship of emotion recognition and eye fixations, and their shared relationship to vmPFC. One explanation for this pattern of results comes from considering the direction of inference inherent to study design. The lesion work in **Chapters 7** and **8** started by identifying a neural abnormality (focal vmPFC damage) and then identified an associated behavioral deficit. By contrast, the work in **Chapters 9** and **10** began by identifying a behavioral deficit related to a psychiatric condition, and then identified an associated neural abnormality. Table 11.1 summarizes the direction of inference and findings for each study. It is possible that mapping a deficit to a particular structure is inherently less precise than mapping a structure to a deficit, particularly when these psychological abnormalities are not irreducible functions (and thus likely to rely on a distributed set of structures) (Damasio, Adolphs, & Damasio, 2003). Additionally, the lesion studies in this dissertation addressed the relationship of vmPFC to emotion recognition accuracy and fixations, while the work in psychiatric samples identified potential relationships between vmPFC-amygdala communication and emotion recognition accuracy *or* fixations (but not both simultaneously). In the psychiatric cases in which emotion recognition or eye fixations were selectively abnormal, these processes were related to a network of structures, rather than a single structure, which mitigates the discrepancy between these data and the claim that vmPFC is necessary for fixations to the eyes and emotion recognition. It is also worth noting that vmPFC

lesions represent severely compromised function of a structure, while the abnormalities presently identified in pediatric PTSD and psychopathy do not suggest a gross loss of function in any neural circuitry. It is thus possible, regarding interpersonal and affective traits for example, that diminished right UF integrity is sufficient to induce a difference in eye fixations during emotion recognition, but the magnitude of this effect on eye fixations is not sufficient to impact emotion recognition ability. Finally, it is possible that different nodes in a broader emotion recognition network differentially contribute to emotion recognition and the spatial pattern of fixations, leading to cases in which the two processes appear inseparable and cases in which they are divorced.

Chapter	Sample	Direction of Inference	Accuracy	Fixations
7	vmPFC Lesion	Structure ➔ deficit	-	↓ fixations to eyes for overall and fear
8	vmPFC Lesion	Structure ➔ deficit	↓ anger accuracy	↑ Anger accuracy when fixating on eyes
9	Pediatric PTSD	Deficit ➔ circuit	↓ overall accuracy	-
10	Criminal Psychopathy	Deficit ➔ structure	-	↓ overall eye fixations

Table 11.1. Summary of study behavioral results.

The notion that vmPFC and the amygdala are specialized nodes in a network giving rise to the complex process of emotion recognition is consistent with extant literature differentiating the functions of these two brain regions. There is a body of evidence that vmPFC is pivotal in encoding valence of stimuli and value-based decision making (Bechara et al., 1994; Bechara et al., 1997; Kawasaki et al., 2001; Plassmann et al., 2007; Plassmann et al., 2010). Recent theories regarding the function of the gross amygdala in regards to processing emotional visual

information posit that these nuclei coordinate cortical processing of ambiguous, salient, and biologically significant stimuli by prioritizing feature processing via modulation of more specialized regions (Pessoa & Adolphs, 2010). Thus, it is possible that vmPFC is critical for representing affective valence of face stimuli, or signaling uncertainty regarding stimulus valence, while the amygdala is predominantly involved in coordinating neural resources to facilitate determination of affective value, and this likely involves affecting the spatial distribution of fixations.

Ventromedial PFC has long been held to play a role in value-based decision making and valence encoding (Bechara et al., 1997; Kawasaki et al., 2001; Plassmann et al., 2010), and thus is most likely prominently involved in representing the affective valence that is a critical input for assigning an emotional label to a face stimulus. In support of this, one recent study found that monetary and social rewards engaged the same region of vmPFC (Lin, Adolphs, & Rangel, 2012), suggesting that valence of different classes of stimuli (e.g., social and non-social) share a common encoding. Even in the absence of reward contingencies, vmPFC has been shown to encode affective valence in both fMRI (Grimm et al., 2006) and unit recordings (Kawasaki et al., 2001). Thus, damage to vmPFC would be expected to disrupt affect recognition, as was observed in **Chapter 8**. However, the findings presented here regarding pediatric PTSD suggest that communication between vmPFC and amygdala is also important for emotion recognition. One possibility is that, in the absence of a certain value representation for a face stimulus, vmPFC sends an uncertainty signal to the amygdala. There is some evidence that vmPFC is important for affecting behavior in the face of highly ambiguous outcomes (Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009). Patients with vmPFC lesions show reduced activity in the insula, a region involved in processing uncertainty, relative to healthy subjects in response to ambiguous cues of

emotional valence (Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2014). Ventromedial PFC has also been shown to be active during ambiguity related to emotional stimuli, rather than anticipation; in a study in which names of expressions (e.g., "fear" and "happy") were displayed over faces depicting semantically congruent or incongruent expressions, vmPFC was more active when incongruent information was high conflict versus low conflict (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). Moreover, the extent to which this activation was negatively coupled with the amygdala predicted conflict resolution success. It is possible that in the absence of an uncertainty signal from vmPFC, a decision about the affective value of stimuli is made prematurely. In sum, there is evidence that vmPFC has a special role in representing affective value of stimuli, and signaling to the amygdala when that representation has a degree of uncertainty. Relevant to the current dissertation, this is consistent with vmPFC being critical for emotion recognition and the amygdala exerting relatively greater influence over spatial patterns of fixation, but with vmPFC's input to the amygdala potentially affecting fixations as well.

While vmPFC may be specialized for encoding the valence of a stimulus, the amygdala likely plays a role in coordinating stimulus processing efforts, which may impact the spatial distribution of fixations (Pessoa & Adolphs, 2010). Consistent with this, anatomical and functional studies reveal the amygdala to be a highly connected group of nuclei; the basolateral nucleus of the amygdala receives overlapping input from vmPFC and visual association areas in the anterior temporal lobe (Ghashghaei & Barbas, 2002). A brain-wide connectivity analysis identified the amygdala as part of a "core network," suggesting that the amygdala may have a wide-reaching neuromodulatory role (Modha & Singh, 2010). Supporting a claim that the amygdala modulates sensory inputs, healthy subjects show increased fusiform and occipital activation to fearful faces, but individuals with amygdala lesions lack a modulated response in

these sensory regions (Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). But the amygdala also appears to affect the spatial distribution of fixations. Intranasal oxytocin administration, which affects the pattern of fixation deployment to face stimuli, increases functional connectivity between the amygdala and the superior colliculus (Gamer, Zurowski, & Buchel, 2010), a midbrain region critical for generating saccades (Sparks, 1988). It is likely that the amygdala does not directly produce saccades, but rather indirectly acts on structures such as the superior colliculus and/or frontal eye fields (Barbas & Mesulam, 1981) to affect fixation distribution. The magnitude of amygdala response during fear face viewing also predicts gaze shifting from the mouth to the eyes (Gamer & Buchel, 2009). Additionally, amygdala lesions have been demonstrated to critically affect eye fixations during emotion recognition in both humans (Adolphs et al., 2005) and monkeys (Dal Monte, Costa, Noble, Murray, & Averbeck, 2015). Thus, while vmPFC seems critical for representing the affective value of stimuli, the amygdala may integrate that affective value information with sensory inputs to modulate the weights of those inputs, a byproduct of which might be to signal to other structures to affect fixation location. It is worth acknowledging here that the amygdala is a heterogeneous set of structures, and future work will benefit from investigating the distinct roles of amygdala sub-nuclei in these processes.

With this model of the relative roles of the amygdala and vmPFC in a visual emotion processing network, there are clearer interpretations of the results presented in this dissertation. Beginning with the lesion research, it is possible that vmPFC lesion patients make fewer fixations to the eyes of faces because their vmPFC damage leads to a failure to signal uncertainty to the amygdala, resulting in the amygdala not redirecting fixations to emotionally informative regions of the face. When a stimulus is sufficiently ambiguous, such as moderate intensity anger

faces, this failure to redirect fixations can impair recognition. In the case of pediatric PTSD, the emotion recognition impairment may be related more to the interpretation of the valence of sensory signals. In youth exposed to trauma, vmPFC may be biased towards negative valence decisions (Pollak et al., 2000; Pollak & Kistler, 2002). So while there is normal fixation deployment in these individuals, high-level processing of visual information may be abnormal due to abnormal processing in vmPFC or the amygdala failing to provide vmPFC with adequate visual information (presumably forwarded from ventral stream areas). Finally, with regards to interpersonal and affective traits of psychopathy, this model interprets the eye fixation deficit related to these traits as deficient amygdala signaling to redirect fixations to emotionally salient regions of the face. This may be a result of compromised communication between vmPFC and the amygdala, as indexed by UF integrity; uncertainty signals from vmPFC may fail to spur the amygdala to redistribute fixations in individuals high in interpersonal and affective traits. Cognitive recognition of the emotional value of stimuli, mediated to a degree by vmPFC, may be intact in these individuals, but abnormal visual processing could lead to a shallow affective experience that enables callous behavior in spite of cognitive awareness of affective content of the stimulus.

While this model fits with extant data and explains the current findings, it requires further testing to move forward. A critical hypothesis generated by this model is that ambiguity signals in vmPFC induce fixation shifts, a possibility that no study has yet tested. In line with the current research, stimuli for such an experiment might be low to high intensity facial expressions. During simultaneous fMRI and eye tracking, one would expect that expression intensity would negatively correlate with both vmPFC activation and the number of fixations made to emotionally discriminative regions of the face. Additionally, this model predicts that the

amygdala's role in modulating signals regarding specific stimulus features represented in the ventral visual stream will directly affect the valence representation in vmPFC. There is already evidence that amygdala activation modulates earlier visual areas during emotion viewing (Morris et al., 1998; Vuilleumier et al., 2004), but it remains to be demonstrated that this sensory modulation relates to valence representations in vmPFC. Future studies might relate the degree of this amygdala modulation of visual processing areas to valence signals in vmPFC during emotion recognition.

In sum, the results presented in this dissertation shed light on the modular and network level functioning of vmPFC, the amygdala, and structures supporting visual processing and fixation distribution. Building on a pre-existing model of visual emotion processing (Pessoa & Adolphs, 2010), this work begins to generate more specific hypotheses about information flow and functions attributable to distinct regions in a visual emotion processing network. While substantial work remains to clearly test hypotheses, there is preliminary evidence that vmPFC plays a role in representing valence and generating uncertainty signals that cue the amygdala to modulate sensory inputs, and that the amygdala can boost processing of decision-relevant stimulus features, as well as affect fixation patterns through connections with regions involved in generating saccades.

Relevance to Research Domain Criteria

These findings highlight the importance of interrogating RDoC systems and units of analysis in multiple samples with a comparable methodological approach. Integrating findings across samples yields valuable information about the relationship between emotion recognition and visual fixations, as well as their relationship to vmPFC-amygdala communication. By

investigating these units of analysis in samples that lay on disparate ends of the spectrum of emotion processing, one gains a more nuanced understanding of these systems that would be missed by a more traditional approach that focuses on single psychiatric samples (Insel et al., 2010). In addition to demonstrating the inferential power of the RDoC approach, considering this work within the framework of RDoC yields broadly generalizable insights about the neural basis of emotion recognition that may facilitate understanding of impairments in a variety of psychiatric syndromes.

The present findings indicate that emotion processing in pediatric PTSD and psychopathy may be differentiated on the basis of emotion recognition performance and fixation patterns, which suggests that these measures may help elucidate the nature of social emotion impairments across a range of disorders. Much as the present results suggest that emotion recognition impairments in pediatric PTSD may be related to abnormal valence representation in vmPFC, one can consider the position of multiple populations on this emotion processing spectrum to generate testable hypotheses about the neural substrates of psychiatric syndromes and identify commonly impaired domains that cut across diagnostic categories (Figure 11.1). For example, one study found that patients with schizophrenia were impaired at recognizing facial expressions, regardless of intensity level, and were more likely to identify neutral expressions as negatively valenced (Kohler et al., 2003). Considered in the context of the present results, the recognition deficit across intensity levels suggests that this impairment may be more related to valence representation in vmPFC than to fixation distribution; the data presented in **Chapters 7**, **8**, and **10** suggest that fixation abnormalities do not necessarily produce recognition deficits for high intensity stimuli, while the results of **Chapter 9** indicate that abnormal valence representations may produce biases towards recognizing stimuli as a particular valence. Working in the model

presented above, a valence representation bias in schizophrenia could potentially implicate vmPFC dysfunction in the emotion recognition impairments of these patients. Consistent with this possibility, studies have reported vmPFC hypoactivation (Kühn & Gallinat, 2011) and linked reduced vmPFC gray matter volume to theory of mind deficits in schizophrenia (Hooker, Bruce, Lincoln, Fisher, & Vinogradov, 2011). Thus, considering this corpus of results in the context of RDoC, and comparing across psychiatric diagnoses can facilitate the identification of discrete domains of impairment that will also generate testable hypotheses regarding biological substrates of disorders that may be useful treatment targets.

Considering emotion recognition and visual fixations as dimensions of emotion processing may not only help to identify impairments that cut across different diagnoses, but may also facilitate differentiation of heterogeneous etiologies with comparable clinical presentations. A useful example here is anxiety disorders, which may present similarly and share common symptoms (APA, 2013), despite different diagnoses having different treatment implications (Deacon & Abramowitz, 2004). For instance, social phobia and generalized anxiety disorder may be distinguished by emotion recognition performance and fixations; there is evidence that individuals with social phobia have impaired emotion recognition accuracy (Simonian, Beidel, Turner, Berkes, & Long, 2001), while individuals with high trait anxiety (related to generalized anxiety) may have attentional biases towards threat (Bradley, Mogg, White, Groom, & de Bono, 1999) and show enhanced recognition of threat-related facial emotions (Surcinelli, Codispoti, Montebarocci, Rossi, & Baldaro, 2006). This might suggest that social phobia involves a disturbance in valence representation mediated by vmPFC, while generalized anxiety might have accompanying amygdala-mediated fixation biases (Figure 11.1).

These differences in neural underpinnings and behavior would have different treatment implications for the two disorders.

In sum, the cross-diagnostic approach to interrogating emotion processing employed by this dissertation facilitates the development and application of models that are tailored to domains of function, rather than specific psychiatric conditions. As such, models generated in this manner readily generalize to a diverse set of diagnoses, potentially expediting the inferential process. The present data have demonstrable utility; not only in elucidating the neural mechanisms of facial affect recognition, but also in generating hypotheses about the nature of impairment and the neural substrates of that impairment.

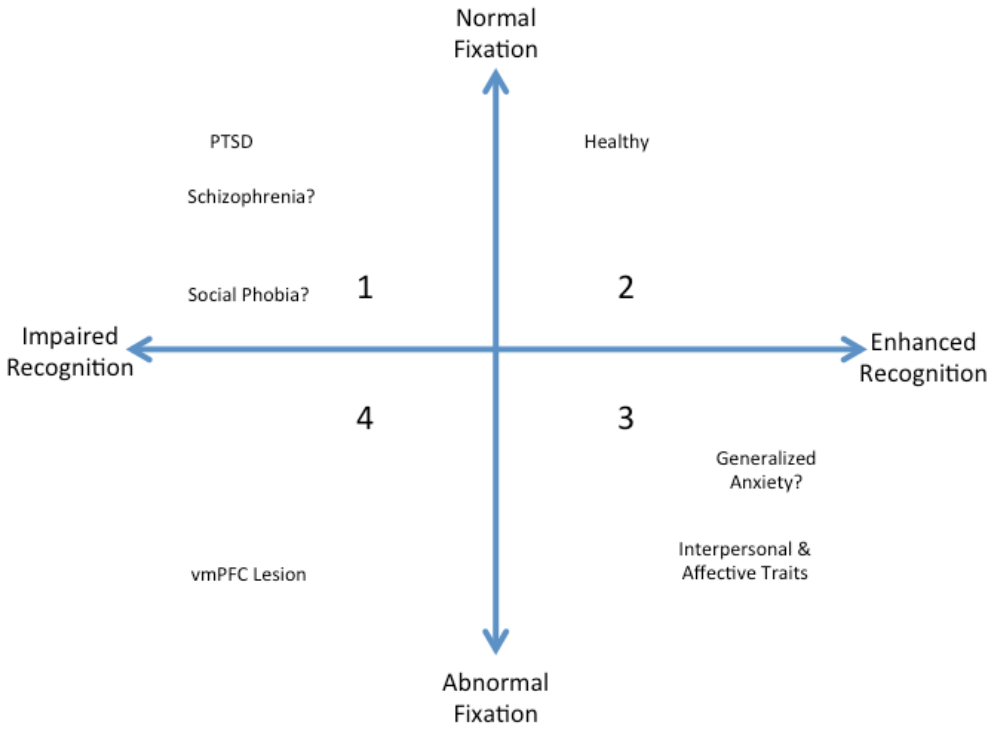

Figure 11.1. Dimensional representation of emotion processing domains. Hypothetical dimensions of emotion processing and where psychiatric samples may exist on this spectrum. 1) Normal fixation and impaired recognition may indicate abnormal valence representation mediated by vmPFC. 2) Normal fixation and recognition indicates healthy vmPFC-amygdala circuitry. 3) Normal to enhanced recognition and reduced fixation may indicate abnormal amygdala function. 4) Impaired recognition and fixation indicates more diffuse network abnormalities or may be primarily driven by one axis (such as fixation driving recognition deficits in vmPFC lesion and amygdala lesion patients). These axes can help differentiate similar clinical presentations, such as anxiety disorders, or could be used to distinguish heterogeneous subtypes within a disorder.

General Limitations

Although the research presented in this dissertation broadens the understanding of the neural basis of facial emotion recognition, there are several caveats that influence the interpretation of the corpus of results presented here. One important factor to consider is that this work considered the influence of visual fixations on emotion recognition, but did not examine the potentially confounding factor of group differences in the spatial deployment of covert

attention during emotion recognition. Additionally, these studies required participants to identify stimuli as belonging to one of six basic emotions (Ekman, 1992), rather than rating emotional expressions dimensionally. Here I will consider these assumptions and their impact on interpreting the present results.

Covert attention refers to the phenomenon by which attention is shifted to a particular spatial location without also shifting eye gaze to that location (Posner, 1980). In relating eye tracking results to emotion recognition accuracy, this work inherently assumes that overt visual attention (e.g., fixation location) plays a significant role in emotion recognition. However, covert attention can impact the neuronal representation of stimuli via signal enhancement (Yeshurun & Carrasco, 1998) and has been shown to modulate face-related activity of the fusiform gyrus (Wojciulik, Kanwisher, & Driver, 1998). It is possible that the findings of this dissertation are influenced by differences in covert attention. For example, individuals higher in interpersonal and affective traits may make fewer fixations to the eyes of faces, but pay greater attention to the eyes covertly. Similarly, youth with PTSD might fixate to faces normally in an effort to appear cooperative with task instructions, but covertly shift attention away from face stimuli if these stimuli cause increases in anxiety, and this might lead to impaired emotion recognition. With regards to the lesion studies, however, the fact that overt attention to the eyes rescued the anger recognition impairment in vmPFC lesion patients suggests that covert attention alone cannot account for recognition impairments in these patients, or the lack of a recognition impairment in **Chapter 7**. Future work might include control conditions with attentional probes at various locations on the face that subjects must detect in order to determine the spatial distribution of covert attention during emotion recognition.

Another factor to consider in interpreting these results is the use of emotion labeling tasks that rely on the basic emotion model (Ekman, 1992), rather than allowing for more dimensional ratings of emotion. Briefly, the basic emotion model posits that fear, anger, happiness, sadness, disgust, and surprise are uniquely identifiable, fundamental to human experience (Ekman & Friesen, 1971), and have unique biological purposes (e.g., disgust expressions serve to close airways, possibly limiting the entrance of noxious pathogens into the organism). Operating within this model, all of my tasks required participants to make forced alternative choices between emotions on each trial, rather than rating stimuli for the presence of each emotion. It is likely that requiring subjects to rate each face for the presence of each emotion, rather than singularly labeling each stimulus, would have better allowed me to interrogate the extent to which this circuitry is engaged by specific emotions. Interestingly, studies using multidimensional scaling of emotion ratings, in which the presence of each emotion is rated for each stimulus, have found that amygdala lesions produce deficits relatively specific to fear (Adolphs et al., 1994), while vmPFC lesion patients appear to have relatively general emotion recognition impairments (Heberlein et al., 2008; Tsuchida & Fellows, 2012). In addition to methodologically allowing for more expressive response options by rating stimuli for multiple emotions, the present work could benefit from leaning on alternative models in addition to the basic emotion model. One well-supported model of emotion emphasizes that emotional stimuli vary along axes of valence and arousal (Bradley, Codispoti, Cuthbert, & Lang, 2001), and these dimensions differentially relate to behavioral measures such as memory for stimuli (Bradley, Greenwald, Petry, & Lang, 1992), as well as prefrontal function during fMRI (Dolcos, LaBar, & Cabeza, 2004). It is possible that the circuitry described above might differentially process valence and arousal, and that these dimensions could differentially affect fixation patterns. Thus,

while the present work extends current models of emotion processing by implicating vmPFC and generating hypotheses, future work may employ more sophisticated behavioral paradigms and modify the methodological approach to allow for testing complementary models of emotion.

Conclusion

In summary, the findings presented in this dissertation clearly outline a role for vmPFC in facial emotion recognition and the spatial distribution of fixations. The lesion studies presented here suggest that vmPFC is necessary for emotion recognition and affecting fixations, and a relationship between vmPFC-amygdala communication, emotion recognition, and eye fixations is preliminarily apparent in psychiatric populations at disparate ends of an emotion processing spectrum, pediatric PTSD and psychopathy. This work clearly implicates vmPFC in a wider circuit for visual emotion processing that centers around the amygdala (Pessoa & Adolphs, 2010). Importantly, this work builds upon this model and generates hypotheses regarding functional specializations within this network; drawing on extant literature, vmPFC may be important for representing stimulus valence and signaling uncertainty to the amygdala, while the amygdala may exert a neuromodulatory influence on visual processing regions and more proximally affect fixations. Finally, these results highlight the utility of considering a corpus of research that uses comparable methods across multiple populations to yield generalizable insights and evaluate the parsimony of models within diverse populations. This work has the potential to advance both the basic understanding of visual emotion processing circuitry, while also identifying novel treatment targets for difficult to treat psychiatric conditions.

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