The effect of attentional focus on emotional and neural responses to scenes depicting interpersonal aggression

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"The will to overcome an emotion is ultimately only the will of another emotion or of several others"

-Friedrich Nietzsche

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Abstract

Social interactions can induce a variety of affective states in an observer, depending not only on the emotion(s) expressed by the individuals involved but also on the context of their interaction. For example, the same scene of interpersonal aggression can elicit very different emotional responses, depending on whether one focuses attention on the aggressor or the victim. Yet, previous studies aiming at delineating the neural basis of social emotional processing have typically categorized images *a priori* based on an emotion thought to best characterize the scene. Thus, it remains unclear how the differential emotional reactions to identical complex scenes are reflected at the neural level. The goal of this thesis was to directly test whether changing the focus of attention to different individuals, playing opposite roles, in identical social emotional scenes would induce differential emotional reactions associated with differential neural activity and connectivity patterns. Another aim was to investigate the potential influence of relevant personality traits, namely trait anger, trait empathy and trait anxiety, on task-related brain activity and connectivity. To this end, our lab conducted a functional magnetic resonance imaging study, during which twenty-three young, healthy females viewed photographs depicting interpersonal aggression across various contexts and were instructed to pay attention to either the aggressor or the victim and label the emotion felt toward that individual. Our results revealed that the aggressor- and victim-focus conditions were distinguished not only at the behavioural level, the former eliciting anger and the latter inducing sadness or fear in participants, but also at the neural level, reflected by differential activity patterns observed between the conditions in a number of brain areas including the amygdala, ventromedial and lateral parts of the prefrontal cortex, and insula. In addition, subjects' trait empathy scores modulated task-related brain activity in the cuneus, superior temporal gyrus and insula. The results from functional connectivity analyses revealed greater functional coupling of the anterior insula with the temporoparietal junction and cuneus in the aggressor- compared to victim-focus condition while the reverse contrast displayed increased connectivity

between the ventromedial prefrontal cortex and middle frontal gyrus. Furthermore individual difference in dispositional empathy, anger and anxiety influenced task-related connectivity patterns. Taken together, our findings demonstrate that the same social scenes of interpersonal violence can induce different emotional and neural responses depending on the focus of attention, as well as on individual differences in trait empathy, anger and anxiety.

Résumé

Les interactions sociales peuvent induire une variété d'états affectifs chez un observeur, ce qui dépend non seulement des émotions exprimées par les individus impliqués mais aussi du contexte dans lequel elles intéragissent. Par exemple, une même scène d'aggression interpersonnelle peut éliciter différentes réponses émotionnelles, dépendant de si l'attention est portée sur l'aggresseur ou sur la victime. Des études antérieures visant à délimiter la base neuronale du traitement émotionel social ont typiquement déjà catégorisé des images a priori basées sur une émotion pensée caractériser le mieux la scène. Cependant, le fait de savoir comment les différentes réactions émotionnelles pour des scènes complexes identiques sont reflétés au niveau neuronal reste incertain. L'objectif de cette thèse était de tester directement si le fait de changer l'objet de l'attention qui était portée sur différent individus, jouant des rôles opposés, dans des scènes d'émotion sociales identiques induirait des réactions émotionnelles différentes associées avec des activités neuronales différentes et des models de connectivité. Un autre but était d'étudier l'influence potentielle des traits de personnalité relevants, à savoir les traits de colère, d'empathie et d'anxiété sur l'activité du cerveau relié à la tache expérimentale et à la connectivité. A cette fin, notre laboratoire a conduit une étude d'imagerie par resonnance magnétique fonctionnelle durant laquelle vingt-trois jeunes femmes en bonne santé ont vu des photographies représentant des aggressions interpersonnelles à travers divers contexts et où on leur a demandé de porter leur attention soit sur l'aggresseur ou sur la victime et de donner leur émotions ressenties envers cet individu. Nos résultats on révélés que les conditions de focalisation envers l'aggresseur et la victime ont été différentes non seulement au niveau comportemental, le premier élicitant la colère and le suivant induisant la tristesse ou la peur chez les participants, mais aussi au niveau neuronal, reflété par différents patterns d'activité observés entre les conditions dans un certain nombre d'aires cérébrales incluant l'amygdale, les parties ventromédiales et latérales du cortex préfontal et l'insula. De plus, les scores des traits empathiques des sujets ont modulés l'activité

cérébrale reliée à la tâche expérimentale dans le cuneus, le gyrus temporal supérieur et l'insula. Les résultats des analyses de la connectivité fonctionnelle ont révélés de meilleurs couplages fonctionnels de l'insula antérieure avec la jonction temporo-pariétale et le cuneus dans la condition de focalisation d'aggression comparée à la condition de focalisation de la victime alors que le contraire contraste avec l'apparition d'une augmentation de connectivité entre la partie ventromédial du cortex préfontal et du milieu du gyrus frontal. De plus, la différence individuelle dans la disposition de l'empathie, la colère ou l'anxiété ont influencés les patterns de connectivité reliés à la tâche expérimentale. Pris tous ensemble, nos résultats démontrent que les même scènes sociales de violence interpersonnelle peuvent induire des émotions différentes et des réponses neurales dépendant de la focalisation de l'attention ainsi que des différences individuelles dans les traits d'empathie, de colère et d'anxiété.

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List of abbreviations

AI – anterior insula

ACC – anterior cingulate cortex

BA – Brodmann area

BOLD – blood oxygenation level dependent

DLPFC – dorsolateral prefrontal cortex

DMN – default mode network

DMPFC – dorsomedial prefrontal cortex

EEG – electroencephalography

fMRI – functional magnetic resonance imaging

GLM – general linear model

IFG – inferior frontal gyrus

IPL – inferior parietal lobule

MFG – middle frontal gyrus

MNS – mirror neuron system

MRI – magnetic resonance imaging

OFC – orbitofrontal cortex

PET – positron emission tomography

PFC – prefrontal cortex

PPI – psychophysiological interactions

SFG – superior frontal gyrus

SMA – supplementary motor area

SPM – statistical parametric mapping

STG – superior temporal gyrus

STS – superior temporal sulcus

TMS – transcranial magnetic stimulation

ToM – theory of mind

TPJ – temporoparietal junction

TPN – task positive network

VLPFC – ventrolateral prefrontal cortex

VMPFC – ventromedial prefrontal cortex

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Figure 9. Areas displaying association between Trait Anxiety and functional connectivity with the Ventromedial Prefrontal Cortex in the *Aggressor* versus *Victim* contrast

CHAPTER 1
INTRODUCTION AND BACKGROUND

1.1 Overview

For most people, confronting a situation involving interpersonal aggression generates negative feelings. However, the specific emotion elicited by such a scene will not only depend on the emotion(s) expressed by the individuals involved and the context of their interaction, but also on the relation between the observer and the participants. In particular, focusing one's attention on the victim will typically be associated with feelings of sadness or fear for the well-being of that individual; that is, we will most likely show empathic concern for a person who is suffering (Eisenberg & Strayer, 1987). In contrast, focusing on the aggressor may induce anger toward or even fear of the target, which may depend on how self-relevant we perceive the situation to be.

This issue is particularly important when attempting to explore the brain circuitry engaged in the social emotional processing, and the related deficits observed in several psychiatric disorders, such as social anxiety disorder (Freitas-Ferrari et al., 2010), autism (Neuhaus, Beauchaine, & Bernier, 2010; Volkmar, 2011), schizophrenia (Anticevic et al., 2010; Taylor et al., 2012) and psychopathy (Anderson & Kiehl, 2011; Herba et al., 2007). Indeed, a widely used approach in this field has been to study responses to a variety of pictures of emotional social scenes such as those from the International Affective Pictorial System (Lang, Bradley, & Cuthbert, 1997). These scenes have been demonstrated in numerous studies to elicit activity in brain regions such as the amygdala, ventromedial prefrontal cortex (VMPFC) and visual cortices (e.g., Britton, Taylor, Sudheimer, & Liberzon, 2006). While these studies have greatly advanced our understating of the neural correlates underlying the social emotional processing, their research approaches may have prevented a full understanding. Specifically these studies have typically categorized the images based on valence (negative/unpleasant versus positive/pleasant) (e.g., Cacioppo, Norris, Decety, Monteleone, & Nusbaum, 2009; Kim & Hamann, 2007) and/or the predominant emotion that is

displayed in a scene (Britton et al., 2006; Turner et al., 2007). Yet, it has been shown that identical social scenes can elicit a range of feeling states in observers (e.g., Bradley, Codispoti, Sabatinelli, & Lang, 2001; Bradley & Lang, 2007; Mikels et al., 2005). Little is known about how the different emotional reactions to the same social scenes would be reflected at the neural level. This is not a trivial issue considering the evidence that although processing different social emotions may involve overlapping neural networks, some of the key regions may differ (see Britton et al., 2006; Vytal & Hamann, 2010 for reviews). For example, anger across different experimental paradigms and modalities has been shown to be associated with brain regions such as the amygdala, inferior frontal gyrus (IFG), orbitofrontal cortex (OFC), middle and medial frontal gyri, and anterior cingulate cortex (ACC) (Vytal & Hamann, 2010), whereas empathic concern has been linked to activity in the anterior insula (AI) and ACC (Fan, Duncan, de Greck, & Northoff, 2011; Lamm, Decety, & Singer, 2011). Additionally, given that frontal activation to anger-provoking pictures and empathy-related activity in the AI and ACC have been shown to correlate with trait anger (Harmon-Jones, 2007) and trait empathy scores (e.g., Krach et al., 2011; Singer et al., 2004), respectively, both attentional focus and individual differences in relevant personality traits are likely to modulate neural activity during perception of identical social scenes.

Therefore, the goal of our study was to directly test whether focusing on different aspects of complex scenes would yield distinctive patterns of brain activity associated with differential feeling states. To this aim, we used pictures depicting interpersonal aggression across various contexts and observed whole-brain activity with functional magnetic resonance neuroimaging (fMRI), comparing the responses to the exact same images while participants' attention was directed to the aggressor or the victim. Several personality questionnaires were also administered to assess the potential influence of subjects' dispositional empathy, anger and anxiety on task-related brain activity and functional connectivity.

Before investigating our research questions and hypotheses, it is important to first review previous research findings on anger and empathy, as these are the two emotions most likely to be elicited in the study presented in this thesis (placing the focus of attention on the aggressor would evoke anger while attending to the victim would induce empathic concern in participants) and the primary goal of the study was to directly compare them. Thus, in the following section, I will review what psychology and neuroscience have revealed about anger and empathy, with emphasis on their underlying neural mechanisms, and subsequently provide a brief introduction to fMRI, the technique employed to address our research questions.

1.2 Anger

According to Averill (1982), "…most people report becoming mildly to moderately angry anywhere from several times a day to several times a week" (Averill, 1982, p. 1146). Perhaps the prevalence of anger experience, in addition to its importance in social interaction may at least partially explain why this emotion has interested us throughout history. Before anger was rationally scrutinized by ancient philosophers, psychologists and neuroscientists among others, it was frequently read about in myths and tales across different cultures depicting angry gods, spirits and ghosts (see Potegal & Novaco, 2010 for review). Ancient philosophers such as Plato, Aristotle, Seneca and Plutarch considered anger as an intensely negative emotion, which according to Plato had to be controlled by reason (Tavris, 1982). Darwin (1965) thought of anger as a less intense form of rage, which promoted an effort to defend oneself when attacked or threatened and thus evolutionarily adaptive while Freud who established the link between aggression and 'death instinct' stressed the self-destructive nature of anger, which could yield to depression and psychosomatic disorders (Tavris, 1982). Anger has interested the field of medicine given its influence on physical health such as hypertension (Johnson & Spielberger, 1992) and coronary heart disease (Smith, Glazer, Ruiz, & Gallo, 2004)

1.2.1 Defining anger

Despite or perhaps owing to the popularity of anger as a topic of discussion across disciplines, one finds inconsistencies and ambiguities among precise definitions assigned to anger. However, anger is generally considered as "a psychobiological emotional state or condition that varies in intensity and fluctuates over time" (Spielberger & Reheiser, 2010, p. 405). As implied in the definition, anger is a complex state, encompassing many elements including physiological and neurological changes, sensations, feelings, cognition and behaviors (Russell & Fehr, 1994). Although individuals differ in anger control and expression depending on culture, gender and display rules learned in childhood among other factors (Crick, 1997; Fischer, Rodriguez Mosquera, van Vianen, & Manstead, 2004; Maccoby & Jacklin, 1980), "on the face of an angry person there is almost always one or more of the innate components of the natural expression which signals his or her internal state" (Izard, 1977, p. 330). Another characteristic of anger is that it varies in intensity, ranging from frustration/annoyance to rage although some researchers have suggested qualitative differences between anger and its associated words such as annoyance, fury and rage (Lewis, 1993; Russell & Fehr, 1994). Anger is typically invited and/or fueled by "...frustration; threats to autonomy, authority, or reputation; disrespect and insult; norm or rule violation; and a sense of injustice" (Potegal & Stemmler, 2010, p. 3) although there are other factors that can influence anger generation and processing include bodily feedback (e.g., skeletal-muscular movements), genes, social norms and/or predicted costs benefits (Berkowitz & Harmon-Jones, 2004).

1.2.2 Anger involves approach inclinations (EEG studies on anger)

Anger is generally classified as a negative emotion (e.g., Berkowitz & Harmon-Jones, 2004; Watson, Wiese, Vaidya, & Tellegen, 1999). However, unlike other negative emotions such as disgust, fear and sadness that are associated with inhibition and withdrawal (e.g., Buss et al., 2003; Harmon-Jones, Harmon-Jones, Amodio, & Gable, 2011), anger has been suggested to engage

active approach, “movement toward the perceived source of the anger” (Harmon-Jones, Peterson, & Harmon-Jones, 2012, p. 64), which, for instance, is aimed at removing (the source of) the anger-inducing situation (e.g., Berkowitz, 1962; Carver & Harmon-Jones, 2009). Much of Eddie Harmon-Jones’ work has been dedicated to more direct examination of anger as an approach-related emotion, corroborating earlier behavioural and clinical evidence (see Harmon-Jones, Harmon-Jones, Abramson, & Peterson, 2009 for review). His studies using electroencephalography (EEG), for instance, have been able to demonstrate in the brain the link between anger and approach. Specifically, it has been well-documented in animal and human research that left frontal regions subserve appetitive/approach motivation while the right half mediates avoidant/withdrawal motivation (Hamon-Jones, Gable, & Peterson, 2010 for review). For example, depressive feelings are elicited when activity in the left hemisphere is suppressed by amytal injections to the same side, while amytal injection into the right hemisphere induces euphoria (Perria, Rosadini, & Rossi, 1961; Terzian & Gecotto, 1959). In support of anger as an approach-associated emotion, anger triggered by verbal insults (Harmon-Jones & Sigelman, 2001), social rejection (Harmon-Jones, Peterson, & Harris, 2009) and impersonal stressor (Jensen-Campbell, Knack, Waldrip, & Campbell, 2007; Verona, Sadeh, & Curtin, 2009) has shown to increase left frontal activity. Interestingly, such asymmetry in frontal cortical activity was reported to disappear when participants’ approach motivation was reduced or prevented, for example when subjects experienced anger in the supine position (Harmon-Jones & Peterson, 2009). Complementing these findings, the perception or expectation of opportunity to take action in anger-provoking situations versus no such perception produced greater left frontal activity (Harmon-Jones, Lueck, Fearn, & Harmon-Jones, 2006; Harmon-Jones, Sigelman, Bohlig, & Harmon-Jones, 2003). In addition, subjects’ trait anger scores were observed to positively correlate with left frontal activity while negatively correlating with right frontal activity during resting state (Harmon-Jones & Allen, 1998) and to positively correlate with left frontal activity during the perception of anger inducting pictures (Harmon-Jones, 2007). In addition to

these EEG studies, repetitive transcranial magnetic stimulation (TMS) research provides evidence for anger as an approach-related affect. For instance, reducing the right prefrontal activity (i.e., increasing activity of the left prefrontal cortex (PFC)) resulted in more vigilant attention to and memory for angry faces while the opposite behaviour was observed upon inhibition of left prefrontal activity (d'Alfonso, van Honk, Hermans, Postma, & de Haan, 2000; van Honk & Schutter, 2006).

1.2.3 Neural correlates of anger

Extending previous work from philosophy and behavioural, cognitive and social psychology, neuroscientific investigation of anger has provided insight into how anger is mapped in the brain. Owing partly to ethical issues in inducing anger in research participants, the study of anger, especially that of anger experience has made a rather slow progress in the neuroimaging literature. In addition, anger and fear are often placed into one category co-representing 'threat' (e.g., Phan et al., 2008) despite the differences between the two emotions at the neural level (e.g., Pichon, de Gelder, & Grezes, 2009; Whalen et al., 2001). Anger has also been shown to often accompany other (rather positive) feeling states such as pride (Harmon-Jones et al., 2010). Furthermore, although aggression does not always follow anger and vice versa (note that researchers hold different viewpoints on the degree to which aggression and anger are linked (e.g., Kassinove, Sukhodolsky, Tsytsarev, & Solovyoya, 1997; Blair, 2012)), anger researchers and those studying aggression especially in clinical neurological research often rely on each other, making it harder to delineate the brain regions specifically linked to anger (e.g., Potegal & Stemmler, 2010; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012). In spite of all these issues, neuroimaging findings, complemented by results from lesion studies and EEG work examined above have allowed us to postulate several brain regions that may subserve anger.

As previously implied, fMRI and Positron Emission Tomography (PET) studies, which capture brain activity while subjects are in the supine position, may not be able to fully capture an important component of anger, approach

motivation (Harmon-Jones & Peterson, 2009). However, unlike the types of EEG methods employed in the majority of anger studies, fMRI and PET, with their superior spatial resolution, permit delineating specific brain regions associated with anger. Neuroimaging studies have used various types of stimuli and task paradigms to probe anger. The majority of these studies observed brain responses to angry faces (e.g., Adams, Gordon, Baird, Ambady, & Kleck, 2003; Blair, Morris, Frith, Perrett, & Dolan, 1999). Other anger-inducing tasks utilized in neuroimaging research include recalling personal episodes that provoked anger in the past (Damasio et al., 2000; Dougherty et al., 1999; Kimbrell et al., 1999), being insulted (Denson, Pedersen, Ronquillo, & Nandy, 2009; Denson, Ronay, von Hippel, & Schira, 2012) and listening to angry prosody (Grandjean et al., 2005; Mothes-Lasch, Mentzel, Miltner, & Straube, 2011). A recent meta-analysis conducted on 30 PET and fMRI studies on different emotions showed that in healthy individuals, anger across different experimental paradigms consistently activated the amygdala, ACC, OFC (Brodmann Area (BA) 13/47), dorsolateral PFC (DLPFC) (BA9), inferior, medial and middle frontal gyri, parahippocampal gyrus, fusiform gyrus, thalamus, superior temporal gyrus (STG), and cerebellum (Vytal & Hamann, 2010). Comparably, a more recent meta-analysis by Lindquist and colleagues (2012) observed that the AI, lateral OFC (BA 10/11/12/13/47), ventrolateral prefrontal cortex (VLPFC) (BA 10/45/47) and anterior temporal lobe to be consistently activated during anger experience (e.g., recalling anger-provoking events) while the perception of anger (e.g., watching angry facial expressions) was associated with increased activity in the VLPFC, DLPFC (BA 9/46), entorhinal cortex, supplementary motor area (SMA) and some visual areas (Lindquist et al., 2012). Some of these brain regions such as the amygdala, ACC, VMPFC and OFC, all of which are implicated in threat processing (Wager et al., 2009), have been suggested to mediate anger in other types of studies such as animal and human lesion studies, reflecting the crucial role of these regions in the processing of anger (Potegal & Stemmler, 2010; Lindquist et al., 2012).

Amygdala

As a key brain region detecting threat, both social and physical, in the environment (Davis & Whalen, 2001), it comes as no surprise that the amygdala has been demonstrated to mediate anger. Enhanced amygdalar activity has been reported during the perception of faces (e.g., Britton et al., 2006; Loughead, Gur, Elliott, & Gur, 2008; Whalen et al., 2001) and whole-bodies expressing anger (Pichon, de Gelder, & Grezes, 2008, 2009). Surprisingly, despite the evidence that anger signals threat and elicits anxiety (Ohman, 1986; Calder, Ewbank, & Passamonti, 2011), only a few studies have explored and demonstrated the influence of subjects' trait anxiety scores on amygdalar responses specific to angry faces, which, in Carre, Fischer, Manuck and Hariri's study (2012), was modulated by trait anger scores and observed only in men (Carre, Fisher, Manuck, & Hariri, 2012; Ewbank et al., 2009). A high density of neurons in the amygdala contains receptors that are activated by testosterone (Simerly, Chang, Muramatsu, & Swanson, 1990), a hormone associated with behavioural and physiological responses to anger (e.g., Herrero, Gadea, Rodriguez-Alarcon, Espert, & Salvador, 2010; Wirth & Schultheiss, 2007). Interestingly, several fMRI studies have recently observed in both men (Dernti et al., 2009; Stanton, Wirth, Waugh, & Schultheiss, 2009) and women (van Wingen et al., 2009) that the levels of testosterone modulated anger-induced amygdalar activity. Furthermore, the volume of the amygdala has been shown to negative correlate with subjects' scores on dispositional anger (Reuter, Weber, Fiebach, Elger, & Montag, 2009). Clinical research also supports the crucial role of the amygdala in the processing of anger. For instance, amygdalar responses to angry faces or aggressive behaviour are exaggerated in patients exhibiting impulsive aggression such as those with borderline personality disorder (Herpertz et al., 2001; Koenigsberg et al., 2009; New et al., 2009) and intermittent explosive disorder (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). Moreover, some patients with damage to the amygdala display impaired anger recognition in both the auditory and visual domains (Calder et al., 1996; Scott et al., 1997). Finally, several pieces of indirect evidence support the link between anger and the amygdala. For example, in

humans, reduced aggressivity has been associated with amygdalar lesions and documented in patients following amygdalotomy (Lee et al., 1998; Mpakopoulou, Gatos, Brotis, Paterakis, & Fountas, 2008). Moreover, electrical stimulation of the amygdala has been associated with changes in aggression and rage in both animals and humans (Mark, Sweet, & Ervin, 1975; Ursin & Kaada, 1960).

Anterior cingulate cortex

Another brain region that has been implicated in anger and social threat is the ACC. Increased activity in the ACC has been observed while subjects viewed angry faces (Blair et al., 1999), recalled anger-provoking episodes (Damasio et al., 2000; Dougherty et al., 1999), and experienced anger (and potentially other negative affect) upon interpersonal insult (Denson et al., 2009, 2012). Denson and colleagues (2009) were able to further demonstrate a positive correlation between anger-induced ACC activity and self-reported intensity of felt anger. Moreover, subjects' trait anger scores were shown modulate dorsal ACC activity elicited upon experience of social exclusion (although it should be noted that anger does not necessarily follow social exclusion) (Eisenberger, Way, Taylor, Welch, & Lieberman, 2007). The important role the ACC plays in anger is also evident in clinical studies. For instance, patients with tumors in the ACC were reported to exhibit aggressiveness and hostility, which disappeared upon the tumor removal (Angelini, Mazzucchi, Piccioto, Nardocci, & Broggi, 1980; Malamud, 1967; Ward, 1948). Surgically removing the ACC or the cingulum bundle was also observed to lead to diminished tantrum, anger and violence behaviour (Ballantine, Bouchkoms, Thomas, & Giriunas, 1987; Cohen et al., 2001). Finally, as in the case of the amygdala, stimulating the ACC has been shown to induce aggressive behaviour in animals (Siegel & Edinger, 1983).

Ventromedial prefrontal cortex

Although its role in emotion regulation is often pronounced (see Harley & Phelps, 2010 for review), the VMPFC has been suggested to serve a general role in the processing of both positive and negative emotions including anger (Phan, Wager, Taylor, & Liberzon, 2004). Perceiving dynamic actions expressing anger (Pichon et al., 2008) and watching and imitating angry expressions (Damasio et

al., 2000; Lee, Josephs, Dolan, & Critchley, 2006) have been shown to engage the VMPFC. In addition, the levels of endogenous testosterone have been shown to modulate not only amygdalar activity but also the VMPFC responses to angry faces (Stanton et al., 2009). Moreover, individual differences in subjects' trait anger scores influenced VMPFC activation elicited upon imagining aggressive versus non-aggressive behaviour (Strenziok et al., 2011). Clinical research has noted hypoactivity of the VMPFC during anger induction in patients with depression with anger attacks (Dougherty et al., 2004). Finally, individuals with damage to the VMPFC have been reported to score higher on the aggression scale and exhibit aggressive and violence behaviour (Grafman et al., 1996).

Orbitofrontal cortex

With its suggested role in the inhibition of impulses and/or reactive aggression (Hermans, Ramsey, & van Honk, 2008), the OFC, particularly the lateral subdivisions of this structure comprised of BAs 11, 12, 13 and 47, has been most frequently linked to anger (see Linquist et al., 2012; Murphy, Nimmo-Smith, & Lawrence, 2003 for review). This has been confirmed by the meta-analysis conducted by Vytal and Hamann (2010), which showed that activity in this region (BA47) was not only most consistently detected across numerous anger studies employing various anger-inducing paradigms, but it also distinguished anger from other emotions, namely happiness, sadness, fear and disgust. In addition, another meta-analytic study demonstrated the lateral OFC to be the only structure exhibiting consistent activation across all anger studies examined (Murphy et al., 2003). In line with this, a large body of literature has demonstrated a link between the OFC and aggression. For example, greater verbal aggression has been observed in humans following damage to the OFC (Grafman et al., 1996). Abnormalities in this region have been reported in patients with psychopathy, antisocial personality behaviour (see Yang & Raine, 2009 for review), bipolar personality disorder (Goyer, Konicki, & Schulz, 1994; New et al., 2009) and intermittent explosive disorder (Coccaro et al., 2007). Moreover, changes in aggressive behaviour (increase in aggression in the majority of cases) in animals have been associated with OFC lesions (e.g., de Bruin, van Oyen, & Van de Poll,

1983; Machado & Bachevalier, 2006), and consistently, electrical stimulation of this region inhibits aggression in both cats and rats (de Bruin, 1990; Siegel, Edinger, & Dotto, 1975).

Amygdala-cortical connectivity

Interestingly, several studies using functional connectivity or interregional correlation measures have observed anger-associated functional coupling between the above regions (Cremers et al., 2010; Dougherty et al., 2004; Passamonti et al., 2008), corroborating the crucial role of the amygdala and the frontal regions in anger and potentially reflecting the importance of their interaction during the processing of this emotion. These are, however, not surprising findings given the robust and bidirectional anatomical connections between the amygdala and ACC, VMPFC and OFC (e.g., Ghashghaei & Barbas, 2002; Ghashghaei, Hilgetag, & Barbas, 2007). Specifically, Passamonti and colleagues (2008) have demonstrated a (weak) negative functional coupling between the amygdala and VMPFC during the perception of angry faces, which was modulated by subjects' scores on a reward-drive measure. In another study, re-experiencing subjects' past personal events that were anger-provoking elicited an inverse correlation between amygdala and VMPFC activation (Dougherty et al., 2004). Interestingly while this relationship was absent in patients with major depressive disorder, depressed patients with anger attacks displayed a positive correlation between the amygdala and VMPFC. The inverse relationship between the amygdala and prefrontal regions has been demonstrated in studies explicitly probing emotion regulation (e.g., Phan et al., 2005; Urry et al., 2006) and thus the findings above may indicate the presence of some inhibitory processes (automatically induced) during the processing of anger, which is especially likely within the confines of the standard neuroimaging laboratory settings (i.e., lying in the scanner) (Denson et al., 2012).

Other brain regions (e.g., insula, dorsolateral prefrontal cortex, hippocampus)

While the contributions of the amygdala, ACC, VMPFC and OFC and their interaction to anger perception and experience appear highly significant, they are not anger-specific, given that each of these brain regions has been associated

with other emotion(s) (see Lindquist et al., 2012; Vytal & Hamann, 2010 for review). Moreover, the reader should not exclude from consideration other potentially important brain regions for anger such as those that seem to be engaged in general processing of (negative) emotions such as the insula, DLPFC (BA 9/46) and regions of visual cortex. Lindquist and colleagues' meta-analysis (2012) indeed observed that perception of anger compared to that of other emotions was more likely to be associated with increased activity in the DLPFC, which has been suggested to mediate executive functions such as working memory and attention switching (Bledowski, Kaiser, & Rahm, 2010; Wager & Smith, 2003) as well as emotion regulation (see Ochsner & Gross, 2005; Phillips, Ladouceur, & Drevets, 2008 for review). Accordingly, insult-induced anger was associated not only with robust activation in the DLPFC but also with enhanced functional connectivity between the amygdala and prefrontal regions including the DLPFC (Denson et al., 2012). The AI, with its well-established role in interoceptive awareness (Craig, 2009; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004) and involvement during the processing a broad range of aversive stimuli (Hayes & Northoff, 2011; Phan, Wager, Taylor, & Liberzon, 2002), has also been found to be activated preferentially during the experience of anger compared to other emotions including fear, happiness and sadness (Lindquist et al., 2012). Furthermore, modulation of insult-induced insular activation by the levels of testosterone and cortisol has been reported (Denson et al., 2012). However, it is of importance to note Britton and colleagues' meta-analysis (2006), which failed to examine increased insular activity to angry faces, potentially indicating that the insular involvement in anger is preferential or specific to the experience but not to the perception of this emotion. In addition, anger triggers strong cardiovascular arousal and appears to be closely related to stress (Orth & Wieland, 2006; Thomas, 1997). For instance, angry faces compared to happy and neutral ones are perceived stress provoking (Strauss et al., 2005). Therefore, it may be important to note here stress-related brain regions. Interestingly, the two above-mentioned areas implicated in anger, the amygdala and ACC, are also known for their role during stress responses. Another noteworthy stress-related

region is the hippocampus, which is thought to modulate stress reactivity by contributing to the regulation of the hypothalamic-pituitary-adrenal axis (Herman et al., 2003; Herman, Ostrander, Mueller, & Figueiredo, 2005). Indeed, the hippocampus has been shown to activate upon interpersonal insult (Denson et al., 2009) and be involved in sensitization to angry faces (Strauss et al., 2005).

In summary, while anger appears to engage a wide set of brain areas in the frontal and temporal lobes, especially in the left hemisphere (Harmon-Jones et al., 2010; Lindquist et al., 2012; Potegal & Stemmler, 2010), the amygdala, ACC, VMPFC and OFC have been suggested to be particularly important in the processing of this emotion. Moreover, anger-related activity in these regions is influenced by various factors including individual differences in trait anger and trait anxiety.

1.3 Empathy

From psychotherapy and social neuroscience to economics and politics, the importance of empathy has been recognized across disciplines. President Barack Obama, for example, picked empathy as one of the criteria for selecting a Supreme Court nominee (Hook & Parsons, 2009). One's ability to empathize or share emotional states of others has been shown to enhance personal well-being (Batson, Fultz, & Schoenrade, 1987) as well as the quality of interpersonal relationships (Davis & Oathout, 1987). Conversely, poor empathy can have a negative impact on the quality of relationships with others, which can be followed by isolation and feelings of loneliness and subsequently decreased levels of personal well-being (Kalliopuska, 1986).

1.3.1 Defining empathy

The word "einfühlung" ("feeling into", "empathy") was first coined by Robert Vischer in 1873 and used to explain our experience of inanimate objects. Later, Theodor Lipps (1903), regarded as the father of the scientific theory of

empathy, expanded the notion of einfühlung to explain how we grasp other peoples' mental states. Subsequently, einfühlung was translated into "empathy" by an American psychologist, Edward Tichener (1909) who defined the term as a "process of humanizing objects, of reading or feeling ourselves into them" (Titchener, 1924, p. 417). For both Lipps and Titchener, empathy mainly entailed emotional simulation or immersion to the mental states of others. Cognitive aspects of empathy were not acknowledged in the field of psychology until 1929 when Wolfgang Kohler claimed that the key process of empathy was not sharing of another's feelings but understanding them (Kohler, 1929). Such emphasis on the cognitive forms of empathy was shared by Mead (1934) whose work touched upon the involvement of self-other distinction in empathy and role-taking ability in understanding how others view the world and Piaget (1932, 1967) who stressed the importance of one's ability to imagine the roles or situations of others in empathy.

Despite abundant research on empathy during the last century, there still exist disagreements among researchers with regard to the precise nature and concept of this phenomenon. However, the debate over whether empathy is strictly a cognitive process (e.g., Dymond, 1949; Hogan, 1969) or an affective process (e.g., Aderman & Berkowitz, 1970; Mehrabian & Epstein, 1972) has subsided and the current consensus based on behavioural, neuroimaging and clinical evidence is that empathy is a multifaceted phenomenon (e.g., Decety & Jackson, 2004; Shamay-Tsoory, 2011)

1.3.2 Affective and cognitive components of empathy

While subtle differences in what constitutes empathy exist in the literature, most researchers recognize *affect sharing/simulation* and *theory of mind (ToM)* as the components of empathy (e.g., Decety & Jackson, 2004; Schulte-Ruther & Greimel, 2011; Shamay-Tsoory, 2011). According to the perception-action model (Preston & de Waal, 2002), empathy entails the perception of another's emotional state spontaneously generating the same or similar emotion in the observer, which "…results from the fact that the subject's representations of the emotional state

are automatically activated when the subject pays attention to the emotional state of the object" (Preston, 2007, p. 428). Such affective responsiveness or 'mirroring' is already present in a newborn who displays signs of distress in the face of another infant crying (Dondi, Simion, & Caltran, 1999; Martin & Clark, 1987). Interestingly, it has been shown that empathic compared to non-empathic people imitate others' postures, mannerism and facial expressions to a greater extent (Chartrand & Bargh, 1999; Sonnby-Borgstrom, Jonsson, & Svensson, 2003). The mirror neuron system (MNS), a set of neurons in monkeys that jointly fire when executing actions and observing the identical or similar acts performed by others (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti & Craighero, 2004), has been suggested to be the underlying neural mechanisms for such 'shared representations', which is elaborated below (see section *1.3.3.1 Brain regions subserving emotional empathy*). Another component of empathy is ToM, also known as mentalizing or mindreading, which refers to our capacity to represent or imagine others' mental states through which we understand their thoughts, feelings, intentions, and desires (Premack & Woodruff, 1978). ToM can be further divided into affective and cognitive ToM. Affective ToM is the ability to infer others' emotions while cognitive ToM is mentalizing about others' cognitive states including their beliefs (see Shamay-Tsoory, 2011; Walter, 2012 for review). One prerequisite for mentalizing is self-other distinction (Mitchell, 2009). Being aware that the source of experienced sadness is not oneself but the other may be important and even necessary to empathize and behave accordingly (Decety & Lamm, 2006).

Behavioural, neuroimaging and clinical studies have demonstrated that the affective forms of empathy, including emotion simulation and emotional contagion, and cognitive empathy, involving ToM are two dissociable but potentially interdependent systems (e.g., Eisenberg & Eggum, 2009; Decety, 2011; Shamay-Tsoory, 2011). Affective empathy has been suggested to involve automatic, bottom-up processes while cognitive empathy is characterized by voluntary, top-down processes (Decety, 2011). As implied in the above example of an infant being affected by another baby, emotional empathy is present early in

development whereas the cognitive forms of empathy involve higher executive functions mediated by brain regions such as the PFC, which develop later in life (Decety, 2011). The distinction between emotional and cognitive empathy has also been demonstrated in clinical studies. For example, while autism is typically characterized by deficits of cognitive empathy, particularly perspective taking, with intact affective empathy, psychopathy and anti-social behaviour are associated with poor emotional empathy but not with impaired ToM (Decety & Moriguchi, 2007; Jones, Happe, Gilbert, Burnett, & Viding, 2010).

In addition to ToM, several researchers consider *emotion regulation* to be an additional component of cognitive empathy (e.g., Cameron & Payne, 2011; Decety & Jackson, 2004; Decety, 2011). The importance of emotion regulation in empathy had been implied earlier in Hoffmans' work (1977), which suggested that the formation of empathic responses could be hindered should excessive emotional reactions toward another in pain result in personal distress.

These different components have been demonstrated to involve distinctive neural mechanisms, which will be reviewed in the next section.

1.3.3 Neural basis of empathy

Empathy has been of great interest to social cognitive neuroscientists over the last decade. Like anger, many different types of stimuli and task paradigms have been used to probe empathy in the neuroimaging literature. Most neuroimaging studies on empathy have focused on empathy for others in physical pain, also referred to as *vicarious pain* (Jackson, Brunet, Meltzoff, & Decety, 2006; Morrison, Lloyd, Pellegrino, & Roberts, 2004). Subjects in these studies, for instance, were presented with stimuli depicting different body parts in pain through video clips or pictures and instructed to passively watch or explicitly empathize with them. While pain is an inducer of empathy, a reliable and robust one (Bernhardt & Singer, 2012), it is not the only trigger (Duan, 2000). Indeed, brain responses have also been mapped using other target emotions of empathy including disgust (Benuzzi, Lui, Duzzi, Nichelli, & Porro, 2008; Jabbi, Swart, & Keysers, 2007; Wicker et al., 2003), anger (de Greck et al., 2012a, b;

Nummenmaa, Hirvonen, Parkkola, & Hietanen, 2008; Shulte-Ruther, Markowitsch, Fink, & Piefke, 2007), sadness (Harrison, Singer, Rotshtein, Dolan, & Critchley, 2006), fear (Han, Alders, Greening, Neufeld, & Mitchell, 2011; Shulte-Ruther et al., 2007), anxiety (Prehn-Kristensen et al., 2009), pleasure (Jabbi et al., 2007; Mobbs et al., 2009) and social pain (Krach et al., 2011; Masten, Morelli, & Eisenberger, 2011; Meyer et al., 2012). In addition to the neuroimaging literature, studies using lesions to infer functions have allowed us to postulate specific brain areas that may be necessary for normal human empathic experience.

1.3.3.1 Brains regions subserving emotional empathy

In one of the first neuroimaging studies investigating empathy, Wicker and colleagues (2003) observed that smelling disgusting odorants firsthand and observing others smelling them activated the same voxels within the AI and ACC. Likewise, increased activity in these two brain regions was detected in female participants both during firsthand experience of shock-induced pain and the perception of their loved ones receiving electric shocks (Singer et al., 2004). Ever since these studies, increased activity in the AI and ACC has been reported in numerous studies on empathy. As two recent meta-analyses of fMRI studies on empathy confirmed, these were the two brain regions that exhibited the most consistent activation irrespective of the types of stimuli and empathy induction methods, not only across studies probing vicarious pain (Lamm et al., 2011) but also across studies examining empathy for various emotions (e.g., fear, happiness, disgust and anxiety) (Fan et al., 2011). Furthermore, Lamm and colleagues (2011) were able to identify subparts of the AI and the dorsal ACC, which were activated by both feeling and observing pain. Corroborating the crucial involvement of these areas in (emotional) empathy, several studies have shown positive correlations between empathy-related activity in the insula and ACC and subjects' scores on several affective empathy measures such as the emotional contagion scale assessing the degree to which one simulates the feeling states of others and a questionnaire assessing trait emotional empathy (Krach et al., 2011; Lamm,

Batson, & Decety, 2007a; Lamm, Nusbaum, Meltzoff, & Decety, 2007b; Saarela et al., 2007; Singer et al., 2004).

One actively discussed question in the field of empathy is whether or not automatic 'mirror matching' of emotions between self and others underlies empathy-related recruitment of the AI and ACC. Testing the existence of mirror neurons requires single-cell recordings, which have been scarcely performed in humans, only in the motor domain (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010) and thus it remains unknown whether the AI and ACC are indeed part of the MNS. Moreover, it is possible that in the studies described above, felt and observed pain recruited distinctive populations of neurons in each of the AI and ACC (Fabbri-Destro & Rizzolatti, 2008). In support of this, Danzinger, Faillenot and Peyron's study (2009) has shown that patients who have never experienced pain displayed 'normal' increased activity in the AI and anterior midcingulate cortex while observing someone else in pain. Nevertheless, many researchers suggest that these brain structures, especially the AI, with its well-documented role in interoceptive awareness (see Craig, 2009; Critchley et al., 2004 for review), are part of the human emotional mirror system (see Bastiaansen, Thioux, & Keysers, 2009 for review). In support of this view, AI activity during the perception of others experiencing disgust was stronger with greater distress experienced by subjects during the task (Jabbi et al., 2007). Similarly, another study reported that activation strengths of the AI and ACC during the processing of faces depicting pain positively correlated with the intensity ratings of observed pain (Saarela et al., 2007). Finally, strengthening the argument for the AI and ACC as part of the human emotional MNS, Corradi-Dell'Acqua, Hofstetter and Vuilleumier (2011) recently observed similar patterns of activity in the midcingulate cortex and AI during both felt and observed pain. In addition to the neuroimaging studies, lesion studies have found that individuals with damage to the insula are not only impaired in feeling disgust but also in recognizing expressions of disgust in others (Calder, Keane, Manes, Antoun, & Young, 2000; Dal Monte et al., 2012). Abnormalities in the AI have also been reported in disorders marked by impaired recognition of disgust, including Wilson's disease

(Wang, Hoosain, Yang, Meng, & Wang, 2003), Huntington's disease (Gray, Young, Barker, Curtis, & Gibson, 1997; Sprengelmeyer et al., 1996; Wang et al., 2003) and obsessive-compulsive disorder (Breiter & Rauch, 1996; Sprengelmeyer et al., 1997). Taken together, the role of the AI and ACC in empathy may be attributed to their contribution to shared representations, which result in matching emotions between self and others.

Another notable brain region implicated in emotional empathy is the IFG. As mirror neurons were first discovered while monkeys executed and observed actions, the original concept of the MNS was formulated in the field of motor representations (Gallese et al.,1996; Rizzolatti & Craighero, 2004). A substantial number of TMS and fMRI studies have provided indirect evidence for the presence of the motor MNS in humans, which include the IFG (BA 6, 44, 45) and inferior parietal lobule (IPL) (see Fabbri-Destro & Rizzolatti, 2008; Rizzolatti, Fabbri-Destro, & Cattaneo, 2009 for review). For instance, both observing and imitating bodily expressions activate these areas (see Caspers, Zilles, Laird, & Eickhoff, 2010 for review). However, the involvement of the human motor MNS may be beyond simulation of other individuals' bodily actions, as studies have also shown increased activity in the IFG during imitation and observation of emotional as well as neutral facial expressions (e.g., Carr, Iacoboni Dubeau, Mazziotta, & Lenzi, 2003; van der Gaag, Minderaa, & Keysers, 2007). Intriguingly, Lamm and colleagues' meta-analysis of the empathy literature (2011) found that compared to cue-based tasks that require the ability to empathize cognitively (see section *1.3.3.2 Brain regions mediating cognitive empathy*), picture-based tasks (e.g., viewing images depicting body parts in pain), which are assumed to involve automatic mimicry and emotional contagion preferentially activated the IFG and IPL. Moreover, several studies have reported correlations between activation strength in the IFC and subjects' scores on measures of emotional empathy, namely the empathic concern and the personal distress scales (Jabbi et al., 2007; Kaplan & Lacoboni, 2006; Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008; Schulte-Ruther et al., 2007). The link between the IFG and the emotional forms of empathy finds additional support from lesion

studies. Specifically, individuals with IFG lesions compared to healthy controls and patients with damage to the VMPFC or to posterior cortex scored lower on both the empathic concern and the personal distress scales and displayed impaired performance on a task probing emotion recognition (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). It is important to note that patients with IFG lesions score normally on cognitive empathy measures and perform flawlessly on tasks probing ToM, suggesting the specific or preferential involvement of the IFG in the emotional forms of empathy (Stone, Baron-Cohen, & Knight, 1998; Shamay-Tsoory et al., 2009). Finally, some researchers suggest that impaired empathy in individuals with autism may be related to their dysfunctional MNS of which the IFG is part (e.g., see Baird, Scheffer, & Wilson, 2011; Hadjikhani, 2007 for review, but also see Dapretto et al., 2005), although it should be noted that autism has been more consistently characterized by impaired cognitive empathy, specifically ToM, with intact emotional empathy (Decety & Moriguchi, 2007; Jones et al., 2010). With respect to the involvement of the motor MNS in human empathy, some researchers speculate that empathizing and affect sharing require action representation associated with emotions witnessed via the MNS (Carr et al., 2003; Dapretto et al., 2006).

Interestingly, several studies have observed enhanced functional coupling between the AI/its adjacent frontal operculum and the IFG during the observation of disgust versus neutral facial expressions (Jabbi, Bastiaansen, & Keyserts, 2008; Jabbi & Keysers, 2008). Jabbi and Keysers (2008) further demonstrated using an effective connectivity technique the unidirectional influence, activity in the IFG causing AI activity during the disgust condition. These findings may imply the influence of motor simulation on emotional perception and simulation and the potentially crucial interaction between the motor MNS and emotional MNS during the experience of empathy.

1.3.3.2 Brain regions mediating cognitive empathy

In line with the fact that nearly all definitions of empathy involve the affective forms of empathy (affect sharing, emotion contagion) (e.g., Batson, Ahmad, Lishner, & Tsang, 2002; Duan, 2000; Eisenberg, 2002), the brain regions

subserving emotional empathy, namely the AI and ACC have been shown to be most consistently activated in numerous empathy studies irrespective of types of stimuli, induction methods and target emotions of empathy (Lamm et al., 2011; Fan et al., 2011). For some researchers, not only the affective forms of empathy but also the cognitive forms co-occur, although not to the same degree, in every empathic response (Baron-Cohen & Wheelwright, 2004; Shamay-Tsoory, 2011). Others, on the other hand, argue that only some situations may additionally engage our ability to empathize cognitively, although the process of self-other distinction should always be present (de Vignemont & Singer, 2006). An experimental task probing the cognitive forms of empathy, for instance, entailed watching abstract symbols in different colours that cued the participant whether he/she or a person sitting next to him/her would receive electrical stimulation and whether or not it would be painful. The cognitive empathy tasks, without explicit displays signalling pain in others, require participants to effortfully represent the mental states of others (i.e., ToM) and thus engage top-down processes (Bernhardt & Singer, 2012; Lamm et al., 2011). A recent review of neuroimaging studies investigating ToM revealed that the majority of studies (93%) reported activation in the medial PFC and about half of the studies detected activation in the temporoparietal junction (TPJ) and superior temporal sulcus (STS) (Carrington & Bailey, 2009). In agreement with this, Lamm and colleagues' meta-analysis (2011) observed that cognitive empathy tasks compared to conventional picture-based paradigms (i.e., tasks using images or video clips that explicitly depict suffering of others) showed preferential activation in the areas subserving ToM including the VMPFC, STG, TPJ and precuneus.

Clinical studies also support these neuroimaging findings. For instance, abnormalities in the STS have been reported in autistic children who are impaired in cognitive but not affective empathy (Boddaert et al., 2004; Schroeder, Desrocher, Bebko, & Cappadocia, 2010). In addition, patients with STS lesions along with those with damage to the VMPFC show poorer performance on a ToM task compared to patients with IFG lesions and healthy controls (Shamay-Tsoory et al., 2009). Patients with VMPFC lesions compared to those with posterior

cortical or IFG lesions and healthy controls were also reported to score lower on the perspective-taking and the fantasy scales, both of which tap into the cognitive forms of empathy (Shamay-Tsoory et al., 2009; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003). It is important to note that emotional empathy is not impaired in patients with VMPFC lesions. As mentioned above (see section *1.3.2 Affective and cognitive components of empathy*), ToM entails both affective and cognitive forms of mentalizing. Indeed, evidence suggests that not all aspects of ToM are affected by damage to the VMPFC. Specifically, several studies comparing these patients' performance on cognitive and affective ToM tasks have shown that their deficits were restricted to the affective aspect of mentalizing (Leopold et al., 2011; Shamay-Tsoory, Tibi-Elhanany, & Aharon-Peretz, 2006). Furthermore, a more specific role of this region has been suggested. While mentalizing-induced VMPFC activation has been demonstrated in many neuroimaging studies (see Carrington & Bailey, 2009 for review), this region has also been ascribed a role in *self-referential processing*, that is, the process of relating stimuli to one's own attributes, traits or values (see Northoff et al., 2006 for review but also see D'Argembeau et al., 2007). The involvement of the VMPFC in both mentalizing and self-relevant processing has indeed been confirmed by recent studies directly comparing the two processes (Saxe, Moran, Scholz, & Gabrieli, 2006; Lombardo et al., 2010). Based on these findings, empathy researchers suggest that the VMPFC is a region subserving self-other distinction (Mitchell, 2009). Specifically, the process of self-reflection enables one to distinguish one's own mental states from others', which is a crucial component of mentalizing and empathy (Mitchell, 2009). In support of this, for instance, autistic individuals who are impaired in ToM exhibit abnormal activity patterns in the VMPFC during self- and other-referential processing (Lombardo et al., 2010).

Another noteworthy brain region implicated in cognitive empathy is the TPJ. Unlike the VMPFC, involvement of the TPJ appears to be more specific to mentalizing about others (Lombardo et al., 2011; Saxe et al., 2006). Increased activity in the TPJ was detected when subjects imagined how others experiencing

pain would feel compared to when imagining themselves in pain (Jackson et al., 2006; Lamm et al., 2007a; Ruby & Decety, 2004). Interestingly, Lawrence and colleagues (2006) observed that the TPJ activity during social perception judgment task was negatively correlated with self-other overlap scores on a trait attribution task. Similarly, a recent study by Cheng, Chen, Lin, Chou and Decety (2010) instructed male participants to imagine themselves, their loved one and a stranger in painful and non-painful situations. Adopting the perspective of a stranger compared to imagining himself and his loved-one in painful situations led to increased activity in the TPJ and medial PFC while the reverse contrast displayed greater activity in the ACC and AI. Interestingly, the TPJ activity to imagining a loved one in painful compared to neutral situations was negatively correlated with the relationship duration, further associating greater TPJ activity with less intimacy or less self-other overlap. Furthermore, the TPJ displayed a negative coupling with the insula and an enhanced connectivity with the superior frontal gyrus (SFG) only when adopting the perspective of a stranger in painful situations. Taken together, the process of mentally differentiating self from another appears to recruit the TPJ and the extent of intimacy may modulate the degree of TPJ involvement in this process.

In some cases, contexts that trigger empathic concern can also be perceived as a threat to the observer, resulting in personal distress. Unless regulated, this distress can deplete one's resources, hindering the execution of appropriate prosocial behaviour and/or even normal functioning (Decety & Lamm, 2009; Muraven & Baumeister, 2000). Indeed, studies have demonstrated a positive association between one's capacity to regulate emotion and the ability to empathize (Rothbart, Ahadi, & Hershey, 1994). Several neuroimaging studies have captured subjects' involvement in emotion regulation during empathic experience reflected by recruitment of the brain areas implicated in emotion regulation such as the ACC, DLPFC, OFC and medial PFC (Cheng et al., 2007; Lamm et al., 2007a,b). For example, Cheng and colleagues (2007) compared physicians' and non-physicians' brain responses to visual displays of body parts being pricked by a needle or a cotton bud. In support of the notion that physicians

may learn to adopt strategies to spontaneously regulate their emotions in the face of patients' suffering, which can exhaust their emotional and cognitive resources (e.g., Butler et al., 2003; Figley, 2002), Cheng et al. (2007) observed that in physicians compared to non-physicians, seeing the pain of others led to reduced activation in the AI and ACC and increased activity in the areas involved in emotion regulation including the DLPFC and medial PFC. Moreover, only in physicians, the 'pain' condition additionally induced a negative functional connectivity between the medial PFC and insula, further demonstrating physicians' suppression of their emotional reactions to the suffering of others. Another fMRI study, which manipulated participants' involvement in emotion regulation during the experience of vicarious pain by providing information about whether or not the perceived body parts in pain are anaesthetized, observed differential involvement of the brain regions subserving emotion regulation including the OFC and medial and superior frontal gyrus (Lamm et al., 2007b).

In summary, the AI and ACC appear to be the core brain regions subserving all forms of empathy, by potentially mediating shared representations, which result in matching emotions between self and others. Affect sharing may be in many instances triggered by motor simulation through the interaction between the emotional MNS (e.g., AI and ACC) and the motor MNS (e.g., IFG, IPL). Cognitive empathy involves higher cognitive processes such as mentalizing and emotion regulation mediated primarily by the medial PFC, OFC, DLPFC, TPJ, and STG. According to Van Overwall and Baeten (2009), given that the MNS and the neural network subserving ToM are rarely simultaneously active, the MNS may provide a rapid input to the metalizing network, potentially via the TPJ that is close to the IPL. Although the few functional connectivity studies examined in this review section may reflect interactions taking place between brain regions involved in emotional empathy and those mediating cognitive empathy, future studies should further test for the potential causal influences between the two (or more) systems mediating empathy using techniques such as effective connectivity measures.

1.4 Anger versus empathy

Over 150 years ago, Phineas Gage, a railroad worker suffered a tragic accident where an iron rod penetrated his brain, damaging the VMPFC among others (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). Following the injury, Gage's personality changes noted by his physician, John Harlow included not only his decreased capacity for empathy but also increased aggressive behaviour (Harlow, 1848, 1868). The relationship between aggression/anger and empathy has been scrutinized in behavioural studies. For example, Strayer and Roberts (2004) found a negative correlation between anger and empathy such that more empathic children displayed less anger. Anger and empathy have also been indirectly compared. For instance, while high levels of testosterone have been associated with anger (Peterson & Harmon-Jones, 2011), impairment in cognitive empathy was reported to follow administration of testosterone (van Honk et al., 2011). Moreover, whereas a large body of EEG work has established a link between anger and left frontal asymmetry (see Harmon-Jones et al., 2010 for review), empathic concern was observed to be associated with right frontal EEG asymmetry in one recent work by Tullett, Harmon-Jones, and Inzlicht (2012). Although anger and empathy appear to be opposite constructs, as reviewed above, they seem to involve many overlapping brain regions including the VMPFC, IFG and ACC. Given that some components of anger and empathy may be shared, this is not a surprising observation. For instance, as noted above, the experience of anger and empathy sometimes engage emotion regulation subserved primarily by the prefrontal regions. Another example is the involvement of the MNS, which has been observed not only during the perception of facial expressions of pain or disgust, which induces empathic concern in the observer (Lamm et al., 2011), but also during the processing of angry faces (Montgomery & Haxby, 2008; Schulte-Ruther et al., 2007). Both empathy and anger, specifically anger perception, may involve the MNS. However, the presence of common and differential neural network recruited during the processing empathy and anger is a speculation based on neuroimaging and lesion studies, which separately examined the two

constructs. One proper way to evaluate whether anger and empathy involve differentiable neural substrates is to compare them concurrently in the same study.

To my knowledge, so far only two studies have directly compared neural responses to anger and empathy. In one study, male and female participants performed a gender-discrimination task while (implicitly) processing facial expression of pain and anger (Simon, Craig, Miltner, & Rainville, 2006). The perception of male faces depicting pain versus anger revealed increased activation in the amygdala, VMPFC, AI, STG, primary and secondary somatosensory cortex and fusiform face area. Only the fusiform face area exhibited increased activity in response to the perception of female faces expressing pain versus anger. One potential issue with this study paradigm would be that it might be comparing empathic *experience* to anger *perception.* Specifically, while observing pain in others is known to be a reliable inducer of empathic concern (Bernhardt & Singer, 2012), in the absence of anger triggers, merely viewing angry faces is not likely to elicit anger in the observer (Takahashi et al., 2004). Another fMRI study compared brain responses to imagining harming oneself ('self-anger'), being harmed by someone else ('other-anger'), harming someone else ('self-guilt'), and someone harming another ('compassion') (Kedia, Berthoz, Wessa, Hilton, & Marinot, 2008). No neural differences were reported between the other-anger and compassion conditions. One weakness the authors mentioned was that due to the nature of the induction paradigm used in the study and methodological limitations of fMRI, subtle neural activity differences may not have been captured.

1.5 Mapping brain activity and connectivity using fMRI

The use of neuroimaging techniques such as EEG, magnetoencephalography, PET and fMRI has greatly furthered our understanding of the neural circuitry underlying emotional processing. PET and fMRI, which detect changes in regional blood flow, thought to reflect neural activity (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Raichle, 1987), are the most widely employed techniques for localizing cognitive and affective processes

in the human brain. As the study presented in this thesis utilized fMRI, here I briefly introduce what fMRI measures, experimental designs used in fMRI studies and how fMRI data is analyzed.

1.5.1 What does fMRI measure?

Human and animal mental processes are believed to depend on brain activity, whose origin is neuronal communication. Information from one neuron can be transmitted to another mainly via electrical transmission in which electrical properties of one neuron directly affect those of another (physically connected) neuron, or through chemical neurotransmission during which neurotransmitters (chemicals) from one neuron dock on the dendrites of its neighbouring cell, which may then fire, transmitting the message in the form of electric signals along its length (see Lovinger, 2008 for review). Neuronal communication requires energy, mainly obtained from oxygen and glucose. It is haemoglobin in the red blood cells that transports oxygen to where neuronal firing is taking place. Thus, an increase in blood flow or volume in a given brain region is likely to reflect the presence of neuronal activity in that area (see Raichle, 2009 for review).

The amount of oxygenated haemoglobin (oxyhemoglobin) delivered to a given region of neuronal activity is more than necessary, which inevitably results in a decrease in deoxygenated haemoglobin (deoxyhemoglobin) in that part of the brain. While oxyhemoglobin is weakly diamagnetic, deoxyhemoglobin is paramagnetic (Pauling & Coryell, 1936), which is attracted by and distorts the nearby magnetic fields. Such changes in the blood oxygenation level can be detected by fMRI.

In the presence of a magnetic field, hydrogen nuclei, abundant in the brain, absorb energy applied at a specific (‘right’) radio frequency. Upon such excitation, these atoms emit energy until they go back to their equilibrium (‘relax’) state. The total radio-frequency energy or signal emitted by hydrogen nuclei is what the magnetic resonance imaging (MRI) scanner measures. One factor that affects the strength of MRI signal is how homogenous the magnetic

field is. Specifically, greater homogeneity results in an increase in the MRI signals (Heeger & Ressi, 2002).

Taken together, when neural activity increases in a specific brain region, there will be decreases in deoxyhemoglobin in that area, which results in greater homogeneity/less distortion in the nearby magnetic field, ultimately increasing the MRI signals. The most commonly utilized fMRI captures such blood oxygenation level dependent (BOLD) signal. One noteworthy property of BOLD fMRI that has an impact on fMRI study designs is the slow temporal dynamics of the hemodynamic response relative to the rapid dynamics of the neural activity. Specially, the hemodynamic response begins to appear only 1-2 seconds after the increase in (experimentally-induced) neural activity in a brain region, rises to its peak 3-4 seconds later and returns to the baseline over a period of about 10-11 seconds (see Amaro & Barker, 2006 for review).

1.5.2 Experimental designs in fMRI

BOLD signal differs from one scan session to another and thus absolute neural activity cannot be assessed by BOLD fMRI. Therefore, experimental designs utilized in fMRI studies should aim to measure relative changes of brain activity. Studies have most commonly employed subtraction approach (i.e., categorical design) where BOLD signals or neural responses are compared between two or more conditions or tasks (Friston et al., 1996; Friston, Zarahn, Josephs, Henson, & Dale, 1999). This approach assumes “pure insertion” (Donders, 1969). In measuring task-specific brain activity, for instance, hemodynamic responses at rest or during performance of a ‘baseline’ task will be subtracted from those recorded while subjects are performing a task probing a cognitive process of interest (Gusnard & Raichle, 2001). However, given the presence of brain/cognitive activity during the resting state (Stark & Squire, 2001), baseline tasks, which are designed to involve identical processes except for the process under investigation, are most frequently used. As a consequence, in fMRI studies, neural responses underlying a cognitive process of research interest will always be described in comparison to those evoked during performance of a

baseline task. There are other experimental designs, which include factorial designs that assume the interdependent nature of cognitive processes, and parametric designs, which allow investigating systematic changes in brain activity depending on psychological, behavioural and cognitive variables (e.g., reaction time, attention load) (Amaro & Barker, 2006; Friston, 1997).

Given the temporal properties of the hemodynamic response noted above (e.g., delayed and sluggish), there are typically two possible types of study designs, namely block- and event-related design (see Amaro & Barker, 2006 for review). In studies using block-designs, one experimental condition lasts for an extended period of time, followed by another 'block' of a different condition or a control/null condition. In studies employing event-related designs, such as the one presented in this thesis, each stimulus is presented for a short period of time, followed by an inter-trial interval during which a black screen is usually presented. In this case, BOLD response to each trial is measured. One advantage of block-design is that as the duration of a block increases, a greater neural response is evoked in each condition, which in turn leads to greater detection power. The optimal duration considering the signal-to-noise ratio is suggested to be the duration of the hemodynamic responses (i.e., about 16 seconds). The downside of block-design experiments, which measure BOLD response to a series of stimuli, is that activation time course of each trial or a particular process cannot be obtained. Another notable disadvantage of block-designs, particularly important for studies investigating emotion or learning, is their susceptibility to potential confounds such as habituation and anticipation. Event-related designs, on the other hand, are less prone to these confounds as they permit manipulating the order of presentation of stimuli. In addition, as BOLD response to each trial can be analyzed separately, a change in signal can be attributed to a particular process/condition in event-related experiments.

1.5.3 fMRI data analysis

Among many tools available for analyzing fMRI data including AFNI (Cox, 1996) and FSL (Smith et al., 2004), Statistical Parametric Mapping (SPM)

(Wellcome Department of Imaging Neuroscience, London, UK) was used in this thesis and hence this section introducing fMRI data analysis will be based on the approach taken by SPM.

1.5.3.1 Preprocessing

The following review is based on the chapter, *Preprocessing of fMRI Data* in the textbook by Huettel, Song and McCarthy (2008, pp. 254-280). Prior to statistical analysis of fMRI data, the data should be preprocessed in order to correct for displacements of the scan images in time and/or space present due to the nature of image acquisition and physiological oscillations among others and to enhance signal detection. The first two steps entail slice acquisition correction and motion correction. Generally speaking, if the image slices are collected in a sequential manner, slice timing correction should follow motion correction or spatial realignment. The order is reversed if the slices are acquired in an interleaved fashion. Despite much effort to minimize head motion (e.g., by placing padding around the head), subjects often move their heads and/or bodies during scanning. Since even subtle movements have devastating impact on the data, spatial realignment is applied to reduce the movement-induced effects. This is usually achieved by realigning the image volumes in the time series to a chosen reference volume, often the first volume acquired. The scanner takes images one slice at a time, resulting in the differences in acquisition time between slices. This is dealt with during the next preprocessing step, slice acquisition time correction. The correction is achieved through temporal interpolation by calculating the amplitude of the BOLD fMRI signal at one chosen time point (e.g., onset of the TR) and it is particularly an important step for high-temporal frequency event-related designs. Following spatial realignment and slice acquisition correction, normalization is performed to control for the variability in the brain morphology across subjects. In essence, this step computationally warps/normalizes each subject's data into a template brain in a standardized space such as the MNI space used in this thesis. This procedure allows for averaging the data across individuals within a study, and for comparing results obtained across different studies using the same coordinate system. The last preprocessing step is spatial smoothing with

a Gaussian kernal. Although smoothing the data reduces spatial resolution, it decreases the number of statistical tests performed during statistical analysis of the data, increasing the validity of the tests and also improves comparisons across participants by reducing/smoothing out anatomical differences between individuals' brains. Low-frequency temporal drifts are also removed by a high pass filter applied to the data.

1.5.3.2 Analysis of regional effects using GLM

For fMRI data analysis, the study presented in this thesis used the commonly implemented technique, univariate approach, during which each voxel is treated and analyzed independently and thus this approach, particularly that using General Linear Model (GLM) will be focused in this section (Friston et al., 1995). However, the reader should keep in mind that there are other techniques that can be implemented to analyze fMRI data such as multivariate techniques (e.g., Partial Least Sqaures (McIntosh. Bookstein, Haxby, & Grady, 1996)).

Following data preprocessing, the GLM needs to be specified with information regarding the onsets and durations of each event type of interest. Since the motion correction step during preprocessing does not fully remove the movement-induced signal artifacts, the six movement parameters obtained from the realignment procedure can be included as nuisance covariates in the single-subject linear model (Aguirre, 2006). For each subject, linear contrasts of parameter estimates for conditions of interest are generated and subsequently submitted to a random-effects analysis where t-tests or ANOVAs are performed.

1.5.3.3 Connectivity analysis using PPI

The above approach provides information on distinct brain area(s) engaged during performance of a specific task. However, it is now widely accepted that no one single brain region subserves a specific function and that it is the interactions between different brain regions that give rise to a cognitive process. With much advancement in fMRI analytic techniques over the past decade, fMRI data can now be processed to reveal brain interactions related to a cognitive process under investigation or those present during a resting state. Broadly speaking, there are two approaches taken by these connectivity analyses.

The first is functional connectivity, which is referred to as "temporal correlations between spatially remote neurophysiological events" and methods to model functional connectivity include psychophyiological interactions (PPI) (Friston et al., 1997) and independent component analysis (McKeown et al., 1998). The second approach is effective connectivity, which measures the "influence that one neural system exerts over another" and methods to model effective connectivity include dynamic causal modeling (Friston, Harrison, & Penny, 2003) and structural equation modeling (McIntosh & Gonzalez-Lima, 1994). As PPI was performed in the study presented in this thesis, I will provide a brief introduction of this method, based on the paper by Friston and colleagues (1997).

PPI analysis identifies brain areas whose time-course covaries with the time-course of activity in the predefined 'seed' or 'source' region as a function of experimental task or psychological state. Thus, results from PPI analysis display brain regions that establish stronger functional connection with the chosen seed region during one experimental condition versus another. It is of importance to note that PPI does not provide information about causal relationships among brain regions.

The data processing steps are as follow. The standard preprocessing steps, namely realignment, slice time correction, normalization and spatial smoothing, are applied to the data. The next step entails defining a seed region, which can be done anatomically or functionally. Specifically, a source region can be traced on each subject's data or on a standardized template brain. One can also define a seed region by choosing a coordinate and including a volume of a chosen size (e.g., a certain number of voxels, a specific size of sphere) around that coordinate. Many researchers define a source region functionally, based on task-related activation in that region. A region can be defined in each subject separately based on his/her activation patterns (obtained from the standard GLM analysis). One main benefit of this approach is that it adjusts for the inter-subject differences in brain features/anatomical location of the source region. Another approach is to choose a coordinate from the result of the group-level analysis or prior studies and include a volume around the selected coordinate. Once a source region is defined, the time

series are extracted from the region and deconvolved. The extracted time course is indeed that of BOLD response and it should be deconvolved to represent the time course of the underlying neural activity so that it can be multiplied element-by-element with a vector coding for the differential effect of experimental task or psychological factor. When the product of the task regressor and seed region's time course is reconvovled with a hemodynamic response function, the interaction term, 'PPI' is created. Subsequently, for each subject, 'PPI', the seed region's time series and the psychological variable are entered as regressors in a first level GLM. The resulting individual contrast images are subsequently submitted to a whole-brain second-level random-effects analysis, the results of which display the brain regions whose connectivity with the source region changes as a function of experimental task.

It is important to keep in mind in order to fully understand the neural basis of a given process, neuroimaging findings, which inform us about which brain regions and inter-regional interactions are *associated* with the function, should be complemented by lesion and/or TMS studies that can identify brain structures *necessary* for the process (Baird, Scheffer, & Wilson, 2011).

1.6 Specific goals and hypotheses of the thesis

A social context that induces empathic concern in the observer often contains not only the target of empathy (a victim) but also his/her aggressor. Thus, scenes depicting such complex social situation will induce in the observer different emotional reactions depending on his or her focus of attention. In order to properly characterize the brain responses to social emotional stimuli, it is important to distinguish between the different emotions elicited by a given scene. However, there are no studies as of yet directly addressing the effect of attentional focus on the neural responses to identical complex social scenes.

To fill this gap in the literature, our lab recently conducted a study to dissociate brain responses to the differently experienced social emotions, anger

and empathy in particular, involved in processing complex social information. More specifically, the study used pictures depicting interpersonal aggression across various contexts and observed whole-brain activity with fMRI, comparing the responses to the exact same images while participants' attention was directed to the aggressor or the victim. Precisely comparing brain activity to the exact same scenes controlled for some potential non-specific confounds such as the differences in predominant emotions and personal relevance.

First, I performed contrast analyses to determine the brain regions commonly and differentially engaged in the aggressor- and victim-focus conditions. In order to overcome the paucity of data on the brain's functional network underlying anger and empathy, functional connectivity analyses were additionally conducted to examine how different brain regions involved in emotion interact during the processing of the scenes and how they vary depending on the focus of attention (and thus the emotion elicited). Finally, regression analyses were performed to examine whether the strengths of these connections as well as the task-related brain responses were modulated by individual differences in relevant personality traits, namely trait empathy, trait anger and trait anxiety.

We predicted that participants would feel anger toward aggressors and empathic concern toward victims. Based on previous findings, we hypothesized that viewing images of interpersonal violence, compared to those of neutral or mildly positive social interactions, would engage, regardless of the focus of attention, regions usually associated with the processing of negative emotional pictures, such as the ACC, VMPFC and visual areas (Britton et al., 2006; Vytal & Hamann, 2010). However, activity in some of these regions should be modulated by the focus of attention and the observer's personality characteristics. For instance, focusing on the victim should strongly or differentially engage regions more consistently associated with empathy, such as the AI (Fan et al., 2011; Lamm et al., 2011), whereas the aggressor-focus condition should additionally recruit structures involved in anger and threat processing, including the amygdala and OFC (Blair, 2012; Murphy et al., 2003; Vytal & Hamman, 2010). With respect to functional connectivity, we predicted that due to the involvement of

different key brain regions, the aggressor- and victim-focus conditions might be associated with differential functional connectivity patterns, which will be further modulated by dispositional empathy, anger and/or anxiety scores.

CHAPTER 2
METHODS

2.1 Participants

Twenty-three right-handed women with normal or corrected-to-normal vision, aged between 18 and 28 years (mean age: 21 years, SD=3) were recruited through McGill and other local advertisements to participate in the study. We included only females because of the sex difference between aggressors and victims depicted in our pictorial stimuli (i.e., the majority of aggressors were males while most victims were females) and the reported sex-by-sex (receiver vs. emitter) interactions in emotional processing (e.g., Armony and Sergerie, 2007; Kret, Pichon, Grezes, & de Gelder, 2011). Exclusion criteria constituted any contraindication with MRI and claustrophobia. The MINI International Neuropsychiatric Interview (Sheehan et al., 1998) administered by a clinical psychologist ensured that all participants were free of any psychiatric or neurological illness and substance abuse/dependence and had no current use of any psychotropic drugs and no history of a head injury with loss of consciousness. The study was approved by the Institutional Review Board of the Faculty of Medicine of McGill University. All participants provided written informed consent prior to the experiment and received monetary compensation for their participation.

2.2 Stimuli

The stimulus set consisted of pictures displaying interpersonal physical aggression in various contexts (e.g., a man beating a woman, a man pointing a gun at another bleeding man, a man handing a gun to a child), each of which depicted an aggressor who threatened or violated the well–being of another person, the victim. Control images portraying neutral or mildly happy social interaction (e.g., a couple shopping, friends looking at a map, people playing sports) were chosen to match a specific negative image with respect to background content (e.g., indoor/outdoor) and the number and sex of persons

present. The matching procedure resulted in each individual aggressor and victim having their counterpart in a neutral/happy scene, hereafter referred to as $Control_A$ and $Control_V$, respectively.

The photographs used in the fMRI study were selected from an initial set of 180 pictures (60 negative, 60 matched neutral and 60 matched happy scenes), obtained from the International Affective Pictorial System (Lang et al., 1997), commercial and other online picture databases, news pages and movies. The selection was made from a separate behavioural study during which 49 female participants were instructed to view one image at a time each of the 180 pictures with an arrow pointing to either the aggressor, victim, $control_A$ or $control_V$, and to indicate the predominant emotion they felt toward the pre-selected target by choosing from 'happy', 'neutral', 'fear', 'anger' and 'sadness' labels, and to rate the intensity of each chosen emotion On a continuous visual-analog scale (0: *not intense* to 100: *very inte*nse; no intensity rating was required for images labeled as neutral by the participant). The final set of 60 images used in the fMRI study was chosen among those that elicited the most consistent ratings among participants for each target emotion. The neutral and happy pictures were grouped into one 'control' category (15 of each category) in order to reduce the number of event types during scanning. Finally, modifications of the selected pictures were made to ensure uniformity among pictures in terms of image characteristics (e.g., average contrast value, overall intensity and color composition) and quality.

2.3 Questionnaires

The Balanced Emotional Empathy Scale (BEES) (Mehrabian, 2000) was administered to measure subjects' affective empathy. This 30-item questionnaire uses a nine-point scale ranging from -4 (very strong disagreement) to 4 (very strong agreement) and has high internal consistency (α=0.87). The 10-item trait component of the State Trait- Anger Expression Inventory – 2 (STAXI) (Spielberger, 1999) measured participants' disposition to experience anger. Finally, a measure of both state and trait anxiety, the State and Trait Anxiety Inventory (STAI) (Spielberger, 1983) was administered to quantify subjects'

anxiety levels. This questionnaire asks subjects to evaluate whether each of 20 statements applies to them 'right now' (the state scale) or 'in general' (the trait scale). Only the trait scale (score range: 20-80) was used in the present study, as our focus was on individual differences in (stable) personality traits.

2.4 Experimental procedure

After signing the informed consent form, following a thorough explanation of the study, subjects were asked to fill out the BEES, STAXI and STAI questionnaires.

All participants underwent one fMRI session with two runs with two different sets of images. In each run, 15 negative and the corresponding 15 control images were presented for 5 seconds. An arrow superimposed on each picture instructed subjects to direct their attention to either the aggressor (or their corresponding $control_A$) or the victim (or their corresponding $control_V$). Upon viewing each stimulus, participants indicated their experienced emotion toward the target of attention by choosing one of five emotion labels ('neutral', 'happy', 'fear', 'anger' and 'sad'), which appeared on the screen. Subject's response terminated the trial, which was then followed by an intertrial black screen (with a white fixation cross in the middle) with a jittered interval ranging from 3 to 12 sec (see Figure 1 for an example of a trial). Each image was presented twice, once with the arrow pointing toward the aggressor or $control_A$, and once toward the victim or $control_V$. The order of stimulus presentation was balanced so that there was an equal number of images first presented with the arrow pointing to the aggressor as those that first required attention to the victim (similarly for the control images). Stimuli were presented in a pseudo-random order such that no more than 3 negative or 3 neutral scenes were presented consecutively in order to avoid induction of a negative mood state. To prevent the effect of habituation to the target person's role (i.e., aggressor or victim), no more than 3 negative scenes following in the sequence required attention to the persons in an equivalent position. Finally, no two identical images appeared consecutively.

After completion of the imaging part of the study, a rating task was administered outside the scanner. All stimuli shown during the scan were presented once more and subjects were asked to indicate their experienced emotion toward each target person of attention using the same interface as during the scan, following by a rating of the intensity of the felt emotion on a 0-100 visual analog scale ranging from 'not intense at all' to 'very intense'. Images labeled as "neutral" by the participants did not require intensity ratings, as these would not be meaningful.

2.5 fMRI data acquisition

Imaging was conducted using a 1.5 Tesla Siemens Sonata Scanner with a standard head coil at the Montreal Neurological Institute. Following a T1-wegithed anatomical scan (TR = 22 ms, TE = 9.2 ms, Flip angle=30º, Voxel size = 1 x 1 x 1 mm^3), functional T2*-weighted echoplanar images were acquired parallel to the anterior-posterior commissural plane using blood oxygenation level dependent (BOLD) contrast (2 sessions of 340 to 360 volumes each, 30 axial slices, TR = 2450 ms, TE = 50ms, FOV = 256 mm, voxel size = 4 x 4 x 4 mm^3). E-Prime (Psychology Software Tools, Pittsburgh, PA) running on a PC laptop was used to present stimuli, projected onto a screen in the scanner visible to participants through a mirror system, and to record subjects' responses through a two-button MR-compatible mouse.

2.6 fMRI data analysis

SPM8 software (Wellcome Department of Imaging Neuroscience, London, UK) was used for preprocessing and statistical analysis of the fMRI data. The preprocessing steps included realignment of the images to the first volume, slice-time correction, normalization of the images into the MNI space (final voxel size = 2 x 2 x 2 mm^3) (Evans, Kamber, Collins, & MacDonald, 1994) and spatial smoothing (isotropic Gaussian kernel of 8mm FWHM). A high pass filter with a cut-off of 1/128 s was also applied to remove low frequency temporal drifts. The smoothed images were used in both the subtraction and connectivity analyses.

2.6.1 Analysis of regional effects

The event-related GLM implemented by SPM was used for statistical analysis. Five event types of interest were defined based on the task, the type of image and the focus of attention: (1) *Aggressor* (i.e., aggressor-focus condition), (2) *Victim* (i.e., victim-focus condition), (3) $Control_A$ (i.e., $control_A$-focus condition), (4) $Control_V$ (i.e., $control_V$-focus condition) and (5) *Response*. As indicated above, the first two (*Aggressor* and *Victim*) and the last two ($Control_A$ and $Control_V$) conditions corresponded to the same images, negative and neutral/happy respectively, the difference being the focus of attention. The first four conditions were modeled with a boxcar of 5 seconds starting at the onset of each picture convolved with a standard synthetic hemodynamic response function, whereas the (trial-specific) duration for the last condition was the time between the image offset and the first button press. The six movement parameters obtained from the realignment procedure were also included in the single-subject linear model. For each subject, linear contrasts of parameter estimates for conditions of interest were generated and subsequently submitted to a whole-brain second-level random-effects analysis.

First, to explore the common effects of aggressor- and victim-focus conditions, we conducted a conjunction analysis (null hypothesis; Nichols, Brett, Andersson, Wager, & Poline, 2005) for the negative versus control conditions (i.e., [($Aggressor - Control_A$) ∩ ($Victim - Control_V$)]). Second, we performed one sample t-tests on the [*Aggressor – Victim*] and [*Victim – Aggressor*] contrasts to examine the differential effect of attentional focus. Lastly, to examine the potential influence of participants' personality on brain activity, scores from the trait empathy, anger and anxiety questionnaires were entered separately into a whole-brain regression analysis with the [*Aggressor – Victim*] contrast images.

Given its important role in emotional processing and its relatively small size, in the case of the amygdala we controlled for multiple comparisons within a search space defined by an anatomical mask of this structure (WFU Pickatlas; Maldjian, Laurienti, Kraft, & Burdette, 2003).

To better characterize the observed activations, especially when comparing aggressor and victim-focus conditions, and to discard possible nonspecific effects of sex or age (most aggressors depicted in negative social scenes were adult males while victims were usually women and children), the parameter estimates for the aggressor- and victim-focus conditions were extracted for the peak voxels and plotted relative to those of $control_A$- and $control_V$-focus conditions, respectively (similar results were obtained when using the average cluster values and hence not shown here).

2.6.2 PPI analyses

Based on the results from the subtraction analysis above, the AI, DLPFC and VMPFC were chosen as seed regions for separate PPI analyses, the rationalization for which is detailed below (see section *3.5 Region selection for PPI*). PPI analyses, identical with all three source regions, were performed as follow: a mask was created for each source region identified in the group-level conjunction analysis of negative > control (displayed at $p<0.005$, uncorrected). The voxels in each seed-region mask were not restricted to those activated in the [*Aggressor – Victim*] contrast in order to avoid biasing our results toward detecting task-related connectivity patterns. For each subject, the first eigenvariate time series were extracted from the mask (in the conjunction contrast, thresholded at $p<0.05$ uncorrected). Participants who did not show any activation within each seed region were excluded (AI: N=9, DLPFC: N=6, left VMPFC: N=7, right VMPFC: N=7). For the remaining subjects, the extracted time series were deconvolved, multiplied element-by- element with a vector coding for the differential effect of attentional focus (i.e., aggressor- versus victim-focus condition) and reconvolved with a hemodynamic response function, which produced the interaction term, 'PPI'. Subsequently, for each subject, 'PPI', the seed region's time series and the psychological variable were entered as regressors in a first level GLM. The resulting individual contrast images were subsequently submitted to a whole-brain second-level random-effects analysis, which displayed the brain regions whose connectivity with the source region changed in the aggressor- versus victim-focus condition.

2.6.3. Correlation analyses with trait measures

In order to test whether individual differences in dispositional anger, empathy and anxiety modulated task-related brain regional activity as well as functional connectivity, scores from the trait empathy, anger and anxiety questionnaires were entered separately into a whole-brain regression analysis with the [*Aggressor – Victim*] contrast images obtained from both the subtraction and connectivity analyses.

All statistical maps were thresholded at $p<0.005$ at the voxel level with a minimum cluster size of 190, corresponding to $p<0.05$, corrected for multiple comparisons (Monte Carlo simulations, n=10,000).

CHAPTER 3
RESULTS

3.1 Personality measures

Questionnaire data for two subjects were missing and thus the personality-based analyses were performed using scores collected in the remaining 21 participants. The mean trait empathy (BEES) score was 53.7 (SD=23.5, range: 4-105), comparable to the values reported in similar populations (Mehrabian, 2000). Similarly, values for the STAI-T (M= 35.9, SD=9.1, range: 22-51) and STAXI-T (M=17.1, SD=3.2, range: 10-24) were consistent with the normative data for this age group (Culhane and Morera, 2010; Spielberger, 1999). A positive correlation was found between trait empathy and trait anger scores ($r=0.45$, $p<0.05$). Neither of these scores correlated significantly with trait anxiety scores (anxiety and empathy: $r=0.26$, $p=0.25$, anxiety and anger: $r=0.23$, $p=0.33$).

3.2 Behavioural results

The analysis of the emotion categorization task was conducted in 20 subjects due to missing data (N=3). As illustrated in Figure 2, the results of the emotion categorization task during the scan confirmed that the stimuli reliably elicited the pre-selected target emotions, namely anger toward the aggressor (85%) and sadness or fear for the victim (i.e., empathic concern; 94%). The results of the emotion labeling tasks completed inside and outside the scanner were highly correlated. Post-scan intensity ratings of the experienced emotion toward aggressors and victims were higher than those for their respective controls ($t(19)=12.05$ and $t(19)=10.79$, respectively, p's<0.001) but did not differ significantly from each other ($t(19)=-0.90$, $p=0.38$). Likewise, $control_A$- and $control_V$-focus conditions did not differ significantly from each other in terms of rated intensity levels ($t(19)= 0.74$, $p=0.47$). The intensity ratings of experienced anger toward aggressors positively correlated with those of experienced sadness toward victims ($r=0.74$, $p<0.001$). As well, the intensity ratings of experienced happiness in the $control_A$-focus condition exhibited a positive correlation with

those obtained in the $control_V$-focus condition ($r=0.523$, $p<0.05$). Individuals with low empathy were more likely to select neutral as the emotion felt for aggressors (Low: 5.15%, High: 0.7%; $p<0.01$) while no differences were observed for other images.

3.3 Personality measure and post-scan intensity ratings

Trait scores and post-scan intensity ratings were also analyzed together, which revealed that trait empathy scores positive correlated with the intensity ratings of experienced anger in the aggressor-focus condition ($r=0.54$, $p<0.05$) as well as with the intensity ratings of experienced sadness toward victims ($r=0.54$, $p<0.05$). These correlations remained significant (BEES and experienced anger: $r=0.62$, $p<0.01$, BEES and experienced sadness: $r=0.53$, $p<0.05$) even after controlling for trait anger scores (which correlated significantly with trait empathy scores).

3.4 Regional effects

3.4.1 Main effect of emotion

Table 1 and Figure 3 show the significant activations for the conjunction analysis assessing the common effects of the aggressor- and victim-focus relative to control conditions (i.e., $control_A$- and $control_V$-focus conditions). Both the aggressor- and victim-focus conditions activated the AI, VLPFC, DLPFC, OFC, IFG, lateral visual areas (i.e., lateral occipital cortex and fusiform gyrus), caudate, premotor areas, thalamus, superior parietal lobule, cerebellum and precuneus. On the other hand, the perception of negative (violent) versus neutral scenes decreased BOLD signals in the VMPFC, ACC, temporal gyri and occipital regions (e.g., cuneus and lingual gyrus), IPL and superior and middle frontal gyri.

3.4.2 Differential effect of attentional focus

As listed in Table 1 and illustrated in Figure 4A, the aggressor- compared to victim-focus condition yielded stronger activation in the VMPFC, the mid – posterior aspects of the insula, superior and middle temporal gyri, TPJ, IFG, occipital regions (i.e., cuneus, and calcarine and lingual gyrus), fusiform gyrus

and premotor cortex. Post-hoc analyses showed that the victim-focus condition was mainly responsible for the differences found in this contrast in several of the areas. Specifically, the positive activation in the insula, VMPFC, cuneus and TPJ was produced by greater deactivations, relative to the control images, in the victim-focus condition (see Figure 4A). In the case of the amygdala, we observed a significant deactivation in the [*Victim – Control*$_V$] contrast in the left hemisphere ([-24 -2 -14], z=3.46, 52 voxels; Figure 4B). At a less-stringent threshold of $p<0.05$ (uncorrected), activity in the peak voxel in the amygdala was significantly stronger in the aggressor- than victim-focus condition.

The opposite contrast, [*Victim – Aggressor*], resulted in a much smaller map of the left the DLPFC (BA46), left VLPFC/OFC (BA10) and bilateral caudate (see Table1 and Figure 5).

3.4.3 Relationship between trait measures and brain activation

Regions that correlated significantly with trait empathy scores in the contrast [*Aggressor – Victim*] are shown in Table 2 and Figure 6A. For illustrative purposes and easier interpretation of results, subjects were also assigned to high- and low-empathy score groups by a median split of BEES scores (low: N=11, BEES range: 4-45; high: N=10, BEES range=54-105). Trait empathy scores correlated negatively with this contrast in the right ventral insula (r=-0.75), cuneus (r=-0.68) and bilateral STG (r=-0.66 and r=-0.70), which remained significant even when trait anger scores (which correlated with trait empathy scores) were added as a covariate (p's < 0.01). Post-hoc analyses indicated that these effects were mainly due to differences between the aggressor- and victim-focus conditions in the low-empathy group (see Figure 6B). No regions showed significant correlations with trait anger or anxiety scores.

3.5 Region selection for PPI

The results of the subtraction analysis revealed that the victim-focus condition deactivated the amygdala and led to greater activity in the DLPFC compared to the aggressor-focus condition. As elaborated in the discussion chapter (see section *4.1 Task-related brain activity*), automatic emotion

regulation, which has been suggested to occur during tasks like ours (i.e., emotion labeling task) as well as intentional emotion regulation have been repeatedly associated with decreased amygdalar activity and increased activity in the DLPFC (see Lieberman, Inagaki, Tabibnia, & Crockett, 2011; Phillips, Ladouceur, & Drevets, 2008 for review). Furthermore, functional coupling between the amygdala and DLPFC has been linked to emotion regulation in many studies using PPI (e.g., Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Drabant, McRae, Manuck, Hariri, & Gross, 2009). These previous findings led us to speculate that our participants might have engaged in incidental emotion regulation to a greater extent when attending to victims compared to aggressors. Although this suggestion remains speculative, as the current thesis did not directly assess subjects' engagement in emotion regulation, it would be of interest to explore functional connectivity between the amygdala and DLPFC as a function of attentional focus. If, for instance, a PPI analysis reveals that activity in the DLPFC covaried significantly with the amygdala during the victim-focus condition or that the strength of this functional coupling was greater in the victim- compared to aggressor-focus condition, this may provide additional piece of evidence for our emotion regulation speculation. Thus, the DLPFC, specifically BA 9 and 46, was chosen as a seed region for a PPI analysis. Only the left DLPFC was used as a source region given its robust activation.

In addition to the DLPFC, the AI was chosen as another seed region for a separate PPI analysis. As reviewed in the introduction chapter, the AI has been regarded as a key region of empathy while its involvement in the processing of anger is less consistently observed. Surprisingly, the results of the subtraction analysis revealed that activity patterns in the AI did not distinguish the empathy-inducing (i.e., victim-focus) condition from the anger-inducing (i.e., aggressor-focus) condition. By performing a PPI analysis with the AI as a source region, we wanted to explore whether its connectivity patterns differed between the two conditions. Like the DLPFC, time series were extracted from only the left AI, which exhibited robust activation.

Finally, in order to explore our dataset further, the VMPFC, which has been implicated in both anger and empathy, was selected as another seed region.

3.6 PPI results (preliminary)

3.6.1 Task-related functional connectivity

Table 3 lists the brain regions, which displayed increased functional connectivity with each of the seed regions, namely the left AI, left DLPFC and bilateral VMPFC, as a function of attentional focus. We observed enhanced functional connectivity between the left AI and several regions including the right supramarginal gyrus, right TPJ and bilateral cuneus in the aggressor- compared to victim-focus condition (see Figure 7). This indicates that the covariance in activity between the left AI and all of the supramarginal gyrus, TPJ and cuneus during the aggressor-focus condition was significantly greater than that during the victim-focus condition. Subsequent analyses using parameter estimates for each of these regions observed that a significant decoupling of the TPJ activity from the AI activity during the victim-focus condition produced the differential connectivity strength between the two conditions. The same effect was observed for the left cuneus (see Figure 7). The [*Victim – Aggressor*] contrast did not display a significant PPI effect for the AI seed.

While there were no regions showing task-based changes in functional connectivity with the left DLPFC or the right VMPFC, we observed increased functional coupling between the left VMPFC and the middle frontal gyrus (MFG) in the [*Victim - Aggressor*] contrast, which arose from a strong positive functional coupling between the two regions in the victim-focus condition.

3.6.2 Relationship between trait measures and brain connectivity

Left anterior insula as the seed region

The brain areas showing functional connectivity with the AI that was correlated separately with trait empathy and trait anxiety scores in the aggressor- versus victim-focus condition are listed in Table 4. There were no brain regions whose task-related change in functional coupling with the AI was modulated by trait anger scores. Higher trait empathy scores were associated with less

functional coupling between the AI and both the cerebellum (r=-0.90) and the inferior occipital gyrus (r=-0.85) in the [*Aggressor – Victim*] contrast, which remained significant even after trait anger scores were entered as covariate (p's<0.005). These results were produced mainly from the aggressor-focus condition, during which connectivity of the AI with both the inferior occipital gyrus and cerebellum correlated negatively with trait empathy scores (r=-0.57 and r=-0.56 respectively).

Trait anxiety scores also modulated task-related connectivity between the AI and other brain regions. Specifically, higher trait anxiety scores were associated with greater functional connectivity between the AI and the hippocampus, SFG, MFG and IFG in the [*Aggressor – Victim*] contrast (r=0.68, r=0.85, r= 0.83, r=0.79 respectively). Subjects were subsequently assigned to high- and low-anxiety groups by a median split of trait anxiety scores (low: N=7, trait anxiety range: 22-32; high: N=7, trait anxiety range=37-51). Post-hoc analysis revealed that in the case of AI-SFG connectivity, the effects were mainly due to differences between the aggressor- and victim-focus conditions in the high-anxiety group.

Left dorsolateral prefrontal cortex as the seed region

Table 5 lists the brain areas showing task-related functional connectivity with the left DLPFC that was correlated separately with trait empathy, anger and anxiety scores. As illustrated in Figure 8A, higher trait empathy scores were associated with greater functional connectivity between the left LDPFC and all of the insula (r=0.86), supramarginal gyrus (r=0.85), IPL (r=0.75), TPJ (r=0.78), middle and posterior cingulate cortex (r's=0.80), SFG (r=0.79), MFG (r=0.71), SMA (r=0.69) and paracentral lobule (r=0.77) during the aggressor- compared to victim-focus condition. These correlations remained significant even after trait anger scores were added as covariate (p's<0.01). Subjects were subsequently assigned to high- and low-empathy score groups by a median split of BEES scores (low: N=8, BEES range: 4-41; high: N=8, range=45-105). Post-hoc analysis revealed that in the case of both DLPFC-insula and DLPFC-SMA connectivity, the effects were mainly due to differences between the aggressor- and victim-

focus conditions in individuals with high empathy scores (see Figure 8B). Note that the insula detected in this PPI analysis lies more dorsal to the insula whose activation strength in the [*Victim – Aggressor*] contrast was observed to correlate with trait empathy scores.

Higher trait anger scores were shown to be associated with greater functional connectivity between the left DLPFC and a number of brain regions including the MFG (r=0.81), SFG (r=0.79), paracentral lobule (r=0.80), postcentral gyrus (r=0.71), IPL (r=0.68), angular gyrus (r=0.75), middle occipital gyrus (r=0.75) and parietal operculum (r=0.75) in the [*Aggressor – Victim*] contrast. The correlations remained significant even after trait empathy scores were added as covariate (p's<0.01). In the case of the DLPFC-parietal operculum coupling, the observed effects were mainly due to the victim-focus condition, during which higher trait anger scores were associated with less functional connectivity between the DLPFC and parietal operculum (r=-0.60).

Finally, higher trait anxiety scores were associated with greater functional connectivity between the left DLPFC and bilateral DMPFG (right: r=0.81, left: r=0.71) during the aggressor- relative to victim-focus condition.

Left ventromedial prefrontal cortex as the seed region

The brain areas showing functional connectivity with the left VMPFC that was correlated with trait anxiety scores in the aggressor- versus victim-focus condition are listed in Table 6. There were no brain regions whose task-related change in functional coupling with the left VMPFC was modulated by trait empathy or anger scores. Higher trait anxiety scores were associated with less functional connectivity between the left VMPFC and a number of brain regions including the thalamus (r=-0.84), cerebellum (r=-0.83), putamen (r=-0.83) and superior and middle temporal gyri (both r's=-0.79) in the [*Aggressor – Victim*] contrast (see Figure 9A). Subjects were subsequently assigned to high- and low-anxiety score groups by a median split of trait anxiety scores (low: N=8, trait anxiety range: 24-32; high: N=8, BEES range=36-51). In the case of the right thalamus and putamen, the effects were due to differences between aggressor- and victim-focus conditions in the low-anxiety group. In the case of functional

coupling between the VMPFC and both the right thalamus and cerebellum, the effects arose mainly from the aggressor-focus condition, during which greater functional connectivity was associated with lower trait anxiety scores (r=-0.68 for thalamus and r=-0.54 for cerebellum). In the case of the right STG, the effects mainly arose from the victim-focus condition, during which higher trait anxiety scores were associated with greater functional connectivity between the left VMPFC and STG (r=0.62).

Right ventromedial prefrontal cortex as the seed region

Table 7 lists the brain areas showing functional connectivity with the right VMPFC that was correlated separately with trait empathy and trait anxiety scores in the aggressor- versus victim-focus condition. There were no brain regions whose task-related change in functional coupling with the right VMPFC was modulated by trait anger scores. Higher trait empathy scores were associated with greater functional connectivity between the right VMPFC and several brain regions such as the paracentral lobule, postcentral gyrus and SFG in the [*Aggressor – Victim*] contrast (r=0.76, r=0.71, r=0.76 respectively), which remained significant even after trait anger scores were added as covariate (p's<0.005).

Higher trait anxiety scores were associated with less functional connectivity between the right VMPFC and both the right SFG (r=-0.82) and dorsomedial PFC (DMPFC) (r=-0.82) during the aggressor- relative to victim-focus condition (Figure 9A). In the case of coupling between the VMPFC and SFG, the effects mainly arose from the aggressor-focus condition, during which the change in functional connectivity between the right VMPFC and SFG was negatively correlated with trait anxiety scores (r=-0.60). Post-hoc analysis performed after subjects were assigned to high- and low-trait anxiety score groups by a median split of trait anxiety scores (low: N=7, trait anxiety range: 22-32; high: N=8, trait anxiety range=36-51) revealed that in the case of VMPFC-DMPFC coupling, the effects were mainly due to differences between aggressor- and victim-focus conditions in the high trait anxiety group (see Figure 9B).

CHAPTER 4
DISCUSSION

While identical social scenes can induce different emotional responses depending on where a person focuses his or her attention in a scene, previous neuroimaging studies of emotions related to neural activity elicited by social scenes have not accounted for attentional focus. Therefore, it remains unknown how the differential emotional reactions to the same complex scenes are reflected at the neural level. To fill this gap in the literature, this thesis explored whether the same scenes depicting interpersonal aggression would elicit distinct feeling states, associated with differential brain activity and functional connectivity, depending on whether attention was focused on the aggressor or the victim. We further examined whether task-related activation and functional connectivity were modulated by individual differences in trait empathy, trait anger and trait anxiety. It was hypothesized that different emotions would be elicited by the aggressor- and victim-focus conditions (i.e., anger and empathic concern respectively) and that these would be associated with differential brain responses in areas typically involved in anger and empathy processing. We further predicted that task-related brain activity and functional connectivity would be modulated by the observer's trait empathy, trait anger and trait anxiety. In this section, I summarize the key findings of this thesis and offer their potential interpretations. It is important for the reader to keep in mind that our results may only be applicable to women.

Consistent with our hypothesis, attending to aggressors and victims elicited differential emotional states in participants. Anger was felt primarily during the aggressor-focus condition while the victim-focus condition evoked sadness or fear in the viewers (see Figure 2).

4.1 Task-related brain activity

In agreement with our hypothesis, the negative stimulus conditions, regardless of the focus of attention, engaged a large network of brain regions

implicated in emotional processing (see Lindquist et al., 2012; Vytal & Hamann, 2010 for reviews) including the VMPFC, ACC, visual areas, the insula, lateral frontal regions (IFG, VLPFC, DLPFC) and caudate. Although we expected that attending to aggressors would independently recruit the OFC, both the aggressor- and victim-focus conditions produced increased activation in this brain region. However, this is not a surprising finding considering the suggested role of the OFC in valence evaluation (Kringelbach & Rolls, 2004) and the nature of our task that required subjects to rate which emotion they felt in each trial. The OFC involvement during the negative stimulus conditions can also be interpreted to reflect the presence of automatic emotion regulation, which is detailed below. Focusing on the aggressor, compared to the victim, activated several regions previously implicated in the perception of threatening (angry) body expressions, such as the VMPFC, premotor cortex and middle temporal gyrus/superior temporal sulcus (Grosbras & Paus, 2006; Pichon, de Gelder, & Grezes, 2008, 2009, 2011). In contrast to our hypothesis positing that the anger-inducing (i.e., aggressor-focus) condition would additionally engage the amygdala, differential activity patterns observed in this region between the condition arose mainly from the victim-focus condition, which is further discussed below. As predicted based on previous findings that highlight the AI/IFG as a key region in empathy, we observed bilateral activation in this region in the victim-focus condition, although this region was also activated when focusing on the aggressor (see Figure 3A). This anger-induced AI activity may be related to the experience of negativity (Carretie, Albert, Lopez-Martin, & Tapia, 2009; Hayes & Northoff, 2011), and/or unfairness of perceived violence (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003; Tabibnia, Satpute, & Lieberman, 2008). Yet, other, more posterior regions within the insula responded differently to victims than to aggressors, as shown in Figure 4A, and discussed below. The bilateral activation of the caudate in the victim- relative to aggressor-focus condition is consistent with previous studies that reported activation in this region when subjects perceived others in pain (Botvinick et al., 2005; Danziger et al., 2009; Lamm et al., 2007a,b). It also fits with a study by Rankin and colleagues (2006) showing a correlation between

empathy scores and gray matter volume in this structure.

The inclusion of matched control (neutral and mildly happy) images allowed us to better determine the source of the observed differences between aggressor- and victim-focus conditions; that is, we could assess whether the effects were mainly due to a significant activation/deactivation of one of the two conditions, relative to their specific control, or some combination thereof. These analyses revealed that the victim-focus condition deactivated the amygdala and insula, and induced greater activation in the OFC, VLPFC, DLPFC and caudate and stronger deactivation in the VMPFC and cuneus than the aggressor-focus condition. Interestingly, these activity patterns, shown in Figures 3, 4 and 5, seem consistent with the notion that participants may have engaged in spontaneous emotion regulation during the perception of negative scenes in general, and to a greater extent when their attention was allocated to the victim. Although subjects were not instructed to down-regulate their emotional responses to the scenes, there is growing evidence that tasks like the one used in our study automatically induce emotion regulation (Drabant et al., 2009; Lieberman et al., 2007, 2011). Incidental emotion regulation during passive viewing of emotional stimuli has been linked to diminished activity in the amygdala and increased activity in the DLPFC (Drabant et al., 2009), while activation in the VLPFC and deactivation in the amygdala during emotion labeling are suggested to be related to task-induced affect attenuation (Hariri, Bookheimer, & Mazziotta, 2000; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Liebermann et al., 2007, 2011). In addition, signal decreases in the VMPFC, STG, and posterior cingulate cortex/precuneus, part of the *Default Mode Network (DMN)*, have been observed when viewing negative pictures (Grimm et al., 2009, 2011; Sheline et al., 2009; Sreenivas, Boehm, & Linden, 2012). It has been argued that this deactivation may represent not only a change in attentional demands typically associated with the DMN (e.g., McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Tomasi, Ernst, Caparelli, & Chang, 2006), but it may also reflect the modulation of negative emotional experience (Grimm et al., 2009). Furthermore, it has been suggested that the caudate, which has been implicated in pain modulation (see Hagelberg et

al., 2004 for review) and impulse control (e.g., Brown, Manuck, Flory, & Hariri, 2006; Durston et al., 2002), plays an important role in automatic emotion attenuation (Mauss, Bunge, & Gross, 2007). Finally, our finding of the deactivation in the insula for the victim-focus condition further supports the emotion regulation hypothesis, as reduced activity in this areas has been observed in participants employing various emotion regulatory strategies, such as cognitive reappraisal (e.g., Delgado, Nearing, LeDoux, & Phelps, 2008; Harenski & Hamann, 2006; McRae et al., 2010) and attentional distraction (see Ochsner & Gross, 2005 for review; McRae et al., 2010), and shown to positively correlate with the degree to which subjects apply reappraisal strategies in everyday life (Carlson & Mujica-Parodi, 2010; Herwig et al., 2007).

The differences in brain activation between stimuli and attention focus can also be interpreted in the context of another process important for the evaluation of social emotional scenes, namely *self- referential processing,* introduced previously (see Northoff et al., 2006 for review). In particular, the DMN has been extensively investigated in this context. Previous research associates self-related, internal processing with more activation of the DMN, particularly in the cortical midline structures, namely the medial prefrontal cortex (PFC) (including VMPFC and subgenual ACC) and posterior cingulate cortex/precuneus. The insula, which has a well-documented role in interoceptive awareness (Craig, 2009), has also been shown to activate during self-referential processing (see Qin et al., 2012 for review). Thus, decreased BOLD signals in the VMPFC, precuneus and insula in processing negative social scenes may reflect not only incidental emotion regulation but also greater disengagement from self-referential processing in the negative versus neutral stimulus condition. Furthermore, larger deactivation in these areas in the victim- compared to the aggressor-focus condition may suggest even less attention allocated to the self (e.g., the feeling states of the self) when the victim was the target of attention.

Results from the correlation analyses then suggest that individual differences in dispositional empathy may have influenced the degree to which subjects engaged in self-referential processing. Specifically, the low-empathy

group showed significantly greater activity in the right insula, cuneus and STG in the aggressor- compared to the victim-focus condition, while no such difference was found in the high-empathy group. These findings seem to suggest that people with low empathy scores used self-referential processing to a greater extent when attending to aggressors compared to victims. Interestingly, the behavioural part of our study showed that individuals with low empathy scores felt 'neutral' toward aggressors more frequently than those with high empathy scores, even though the two groups did not differ in the frequency of feeling 'sad' toward victims. This latter observation is in line with the positive correlation between the levels of self-reported empathy and anger felt toward another treated unfairly reported by Batson and colleagues (2007). Taken together, our findings could lead us to hypothesize that low empathy people, who are more self-focused, felt anger less frequently because aggression depicted in the scene was not directed toward them. On the other hand, highly empathic individuals, who showed less activity in the areas involved in self-referential processing, may have felt anger toward the aggressor more frequently because of the victim present in the background.

Importantly, the two hypotheses presented to explain our results, based on emotion regulation and self- referential processing, are not mutually exclusive, and it is likely that both contributed to the observed brain activation patterns reported here. In addition, it is possible that other factors also played a role in the differential brain responses observed between the aggressor- and victim-focus conditions. For example, larger deactivations in the DMN regions in the victim- versus aggressor-focus condition may be related to a greater cognitive load in the latter case, due to our natural tendency to detect more quickly and pay more attention to threatening than to sad faces (Mather & Knight, 2006; Ohman, Lundqvist, & Esteves, 2001; Vuilleumier, 2002). In a similar vein, the act of violence may have been a greater peripheral distraction, making focusing attention on the victim more cognitive challenging. This is plausible considering our observation that the victim- compared to the aggressor-focus condition led to greater deactivation in the right TPJ, which has been linked to filtering of distractors (Shulman, Astafiev, McAvoy, d'Avossa, & Corbetta, 2007).

4.2 Task-related functional connectivity

Although the AI has been regarded as a key region of empathy (Fan et al., 2011; Lamm et al., 2011), we did not observe differential activity patterns in this region between the aggressor- and victim-focus conditions. However, our PPI analysis revealed differential functional connectivity patterns of the AI between the conditions. Specifically there was increased functional coupling between the AI and supramarginal gyrus, TPJ and cuneus when subjects attended to aggressors versus victims. In the case of AI-TPJ connectivity, the effects arose mainly from the negative functional coupling between these two regions in the victim-focus condition. These findings may be comparable to those from Cheng and colleagues' study (2009), which observed a negative functional connectivity between the right TPJ and the AI during imagination of a stranger in painful situations while no such connectivity patterns were observed when subjects adopted perspective of self or his loved one. Their results were interpreted as the presence of cognitive inhibitory control over the affective responsiveness to seeing others in pain. As noted above, Van Overwalle and Baetens (2009) speculated that the MNS's interaction with the TPJ might initiate the communication between brain regions subserving emotional empathy with those involved in mentalizing. In light of this, the decoupling of the TPJ from the AI during the victim-focus condition could also reflect less interaction between the neural system subserving affective empathy (e.g., AI) and brain regions subserving mentalizing, which may further support our interpretation of the results of the subtraction analysis that attending to victims compared to aggressors may have involved less self-referential processing (i.e., mentalizing about the self).

Based on the results of the subtraction analysis, which were interpreted to reflect greater involvement of emotion regulation during the victim- compared to aggressor-focus condition, we expected that the DLPFC would engage the amygdala differentially or more strongly in the victim-focus condition. However, there were no brain regions displaying task-related changes in functional connectivity with the DLPFC. These null findings could indicate that our emotion

regulation speculation is wrong. However, as emotion regulation has been linked to functional interaction between the amygdala and other frontal regions such as the VLPFC and medial PFC (Banks et al., 2007), it is possible that emotion regulation induced during our task recruited brain regions other than the DLPFC. The VLPFC is a likely candidate as activation in this region has been repeatedly related to affect attenuation incidentally induced in emotion labeling tasks (see Lieberman et al., 2011 for review). Moreover, the PPI analysis of the right VMPFC seed revealed that there was a strong positive functional coupling between the VMPFC and MFG in the victim-focus condition, distinguishing this condition from the aggressor-focus condition. Given that increased activity in both the VMPFC and MFG has been associated with emotion regulation (e.g., Eippert et al., 2007; Goldin et al., 2008; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008), our connectivity findings may reflect subjects' greater use of emotion regulation when attending to the victim, supporting our emotion regulation speculation.

In addition, we observed that trait empathy, anger and anxiety scores modulated task-related functional connectivity among many brain regions. Some of these findings are particularly noteworthy. First, greater trait anxiety scores were associated with greater functional connectivity between the left VMPFC (seed) and the STG and between the right VMPFC (seed) and both the DMPFC and SFG in the victim- versus aggressor-focus condition (see Figure 9). While the VMPFC, DMPFC and STG have been implicated in both self-related processing and mentalizing (Frith & Singer, 2008; Van Overwalle & Baetens, 2009), D' Argembeau and colleagues' study (2005) has suggested that the medial PFC can be subdivided into several functional areas. Specifically while self-referential processing was associated with enhanced activity in the VMPFC, increased activity in the DMPFC was detected during perspective taking. Although we interpreted differential activity patterns in these DMN regions between the conditions as the involvement of less self-referential processing in the victim- versus aggressor-focus condition, it may be more suitable to discuss the functional connectivity results in terms of the process of mentalizing. Specifically, our

connectivity findings may suggest that individuals who are more prone to anxiety than those with less propensity to anxiety elicit greater interactions among brain regions mediating mentalizing when attending to victims' suffering. Interestingly, Tibi-Elhanany and Shamay-Tsoory (2011) have recently reported that high socially anxious individuals with high anxiety scores compared to low anxious people exhibit greater empathic abilities, indicated by their better performance on an affective ToM task among others. It should however be kept in mind that our subtraction analysis did not reveal a significant association between activation strength in these mentalizing brain regions and subjects' trait anxiety scores.

We also observed that greater trait empathy scores were associated with greater functional coupling between the left DPFC and right mid-insula in the aggressor- compared to the victim-focus condition, which was driven mainly by the high empathy group (see Figure 8). These findings may be comparable to previous studies that demonstrated greater functional coupling between the AI and IFG during observation of disgust versus neutral facial expressions (Jabbi et al., 2008; Jabbi & Keysers, 2008). Their findings were suggested to reflect the close relationship between the motor MNS and affective MNS and more specifically the influence of motor simulation on emotion sharing during perception of emotions of others. In light of such proposal, our DLPFC-insula connectivity results may then indicate that the influence of facial mimicry on sharing of the emotional states of aggressors compared to victims might have been greater in individuals with high empathy scores. This appears to be a plausible interpretation given that empathic compared to non-empathic people have been shown to imitate others' postures, mannerism and facial expressions to a greater extent (Chartrand & Bargh, 1999; Sonnby-Borgstrom et al., 2003). However, given that empathizing or affect sharing is more likely to occur in the face of a victim than an attacker (Duan, 2000), one would expect to have seen greater coupling between the affective MNS and motor MNS in the reverse contrast (i.e., victim- versus aggressor focus condition). However, it could also be that the more dynamic nature of bodily expressions depicted in aggressors compared to those in victims may have been more spontaneous and robust in producing mimicry in the

observer, leading to greater emotional resonance. While this is an interesting interpretation, it is of importance to note a couple of discrepancies between our study and Jabbi and colleagues' (2008). First, the insula detected in our study is more posterior and dorsal to the insula focused on in their studies. Moreover, our PPI analysis of the AI seed did not reveal connectivity patterns in accordance with our interpretation. Second, the IFG scrutinized in Jabbi and colleagues' studies (2008) was restricted to BA 45, the region well-established to be part of the MNS while our DLPFC seed mask consisted of BA9 and 46. There is, however, some evidence that BA9 is also part of the MNS (Haker, Kawohl, Herwig, & Rossler, 2012).

It was not only the insula but also other brain regions including the SMA, IPL and supramarginal gyrus where greater functional connectivity to the left DLPFC during the aggressor- compared to victim-focus condition were associated with higher trait empathy scores (see Figure 8). In the case of the SMA and insula, the effects arose mainly from the high empathy group. Intriguingly, all these brain regions are collectively known as the *Task Positive Network (TPN),* which has been shown to be consistently activated during performance of numerous types of cognitive and attentional tasks (Fox et al., 2005; Fransson, 2005). Unlike the DMN, which is recruited during internally oriented processing (i.e., self-referential processing), the TPN supports more externally oriented processing. Many studies have indeed more directly examined that the TPN acts in opposition to the DMN. For instance, at rest, the time course of the DMN is anti-correlated with that of the TPN (Fox et al., 2005) and the strength of the negative correlation between the two networks involved during a cognitive task has been shown to predict performance (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). Taken together, our findings may then reflect that individuals with higher empathy scores might have been more externally oriented or involved in other-related processing as opposed to self-referential processing to a greater extent while attending to aggressors versus victims. This speculation is indeed congruent with our results of the subtraction analysis, which were interpreted to indicate low empathy individuals' greater involvement in self-referential processing when

attending to aggressors compared to victims. Taken collectively with our behavioural results, while the activation results driven mainly by individuals with low trait empathy scores may imply that low empathy people felt less anger toward aggressors due to their greater self-focused-ness, our connectivity results driven mainly by the high trait empathy group explain the other half of the story by suggesting that highly empathic individuals might have felt anger toward aggressors more frequently due to their greater involvement in other/external (i.e., victim in the background)-oriented processing. Furthermore, our results may provide indirect, further evidence for that the DMN and TPN may operate in opposition.

CHAPTER 5
LIMITATIONS AND FUTURE DIRECTIONS

Although the use of connectivity techniques allows us to explore a very important question, that is how different brain regions interact during performance of a cognitive task or a resting state, interpreting connectivity findings is often a challenge. This was also the case for the study presented in this thesis. As noted above, PPI analysis performed in this study does not provide information about the directional nature of functionally-coupled brain regions. For several connectivity patterns especially for task-related functional coupling observed between the AI and TPJ and that between the DLPFC and insula, information about directionality of these influences would have offered clarifications on our findings and interpretations. Future studies may therefore employ effective connectivity techniques such as dynamic causal modeling or structural equation modeling in order to infer causal relationships. Moreover, without explicit measures assessing the degree to which subjects were involved in the processes that we proposed to have occurred during our task such as automatic emotion regulation and self- and other-referential processing, our interpretations on the results of both subtraction and connectivity analyses remain speculative. Thus, future studies can, for example, administer additional tasks and/or questionnaires that assess participants' daily or habitual use of emotion regulation strategies to more directly test our speculation about the involvement of emotion regulation (Drabant et al., 2009; Gross & John, 2003). The absence of influence of trait anger scores on task-related brain activity might be due to the fact that the type of anger evoked during our task, empathic anger, may not be captured by the questionnaire administered in our study that touches upon one's general tendency to experience anger (Spielberger, 1999). Indeed, a validated questionnaire assessing empathic anger (Vitaglion & Barnett, 2003) is available and should be utilized in future studies. There are some other limitations that need to be considered. Although the results of the emotion labeling task allow us to assume that subjects' attention was allocated to the pre-selected target, inducing the

feeling state accordingly, it remains unconfirmed whether their attention was sustained for the entire presentation period. Moreover, given our interpretations that highly empathic individuals may show attentional preferences to the victim, it would be critical to implement measures such as eye tracking to validate our attention manipulation paradigm. While eye tracking remains an ideal option, there are other ways to validate the paradigm. One such way is to directly ask participants where they paid attention and how long they attended to the corresponding target. In addition to providing directionality of our findings, the introduction of the control conditions allowed us to control for the gender difference between the aggressor- and victim-focus conditions (see *2.2 Stimuli*). To further address this issue regarding the nature of the stimuli, this study included only female individuals. Women are reported to exhibit higher levels of empathy than men (e.g., Lennon & Eisenberg, 1987; Toussaint & Webb, 2005) and sex differences in anger have also been reported (Brody, Lovas, & Hay, 1995; Fischer & Evers, 2010) and thus, our findings are applicable only to women. It would be important to assess the effect of attentional focus on emotional and neural responses to complex scenes in men. Furthermore, future studies should also directly test the impact of gender differences between the targets of attention on brain activity. Specifically, one can test and compare brain responses in both men and women to female victim vs. male aggressor, male victim vs. female aggressor, female victim vs. female aggressor and male victim vs. male aggressor. Despite much evidence for the influence of the menstrual cycle phase on emotional processing at both the behavioural and neural level (e.g., Dentl et al., 2008; Guapo et al., 2009; Protopopescu et al., 2005), this factor was not controlled in this study. Furthermore, the levels of various hormones such as testosterone and cortisol may have influenced our results as they have been shown to modulate emotional and neural responses to affective stimuli (e.g., Denson et al., 2012; Hermans et al., 2008; Urry et al., 2006). Future studies should therefore assess the levels of relevant hormones using saliva and/or blood samples and include these measures as covariates. It is also important to note the possible influence of social desirability, which, as in most studies involving emotional

labeling or judgment, was not controlled for in this study. Concurrent physiological measures (e.g., heart rate or skin conductance) could provide an additional, objective measure of emotional processing. Finally, despite our strong *a priori* hypothesis, we saw overall little activity in the amygdala; it is possible that our simple 5-sec boxcar model may have failed to capture its rapid and transient response to emotional stimuli, particularly in the right hemisphere (Glascher & Adolphs, 2003; see Sergerie, Chochol, & Armony, 2008 for review).

CHAPTER 6
SUMMARY AND CONCLUSION

The present thesis tested and confirmed the hypothesis that the same scenes of interpersonal violence can evoke differential feeling states and neural responses, depending on whether one focuses on the victim or the aggressor. Participants felt anger toward aggressors and fear or sadness toward victims. Visual processing of the violent scenes, regardless of attentional focus recruited a number of brain regions, some of which including the amygdala, insula, VMPFC, lateral PFC, STG and cuneus exhibited differential activity patterns between the aggressor- and victim-focus conditions. The neural differences between the two conditions were shown to mainly arise from the victim-focus condition, which deactivated the amygdala, insula and TPJ, and led to greater deactivation in the VMPFC, STG and cuneus and stronger activation in the DLPFC and VLPFC compared to the aggressor-focus condition. In congruence with that the victim-focus condition was mainly responsible for the neural differences between the conditions, only trait empathy scores influenced task-related brain activity. Specifically, individuals with low empathy scores showed significantly greater activity in the insula, cuneus and STG in the aggressor- compared to victim-focus condition, while no such difference was found in the high-empathy group. Our preliminary results of the functional connectivity analyses revealed enhanced functional coupling of the AI with the TPJ and cuneus in the aggressor- compared to victim-focus condition while the reverse contrast displayed increased connectivity between the VMPFC and MFG. Furthermore, subjects' trait empathy, trait anger and trait anxiety scores modulated task-related functional connectivity among various brain regions. For instance, greater trait empathy scores were associated with greater functional coupling of the DLPFC with many areas including the insula, supramarginal gyrus, IPL and SMA in the aggressor- versus victim-focus condition. In the reverse contrast, greater functional coupling between the VMPFC and areas including the STG and DMPFC was associated with higher trait anxiety scores.

We propose that the neural differences were mainly due to differential involvement of emotion regulation and/or mentalizing processes between the two conditions, although without explicit measures of these processes our interpretations remain speculative. From a methodological point of view, our findings highlight the importance of participants' focus of attention when studying responses to complex social scenes.

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Table 1. Areas commonly and differentially engaged in the aggressor- and victim-focus conditions

Brain region	MNI coordinates			L/R	Z value	Cluster size
	x	y	z			
(Aggressor – Control$_A$) ∩ (Victim – Control$_V$)						
Lateral Occipital Cortex (Extrastriate Body Area)	-52	-62	6	L	>10	10312
Fusiform Gyrus (Fusiform Face/Body Area)	-42	-50	-18	L	6.75	
Middle Occipital Gyrus	-24	-78	35	L	5.66	
Superior Parietal Lobule	-32	-48	58	L	4.77	
Precuneus	-4	-62	40	L	4.05	
Lateral Occipital Cortex (Extrastriate Body Area)	30	-86	-8	R	7.48	8785
Lateral Occipital Cortex (Extrastriate Body Area)	54	-70	2	R	7.26	
Cerebellum	8	-80	-30	R	6.36	
Fusiform Gyrus (Fusiform Face/Body Area)	42	-46	-22	R	5.15	
Premotor Cortex	-40	0	44	L	6.56	5121
Inferior Frontal Gyrus	-44	12	24	L	6.16	
Dorsolateral Prefrontal Cortex	-42	22	22	L	6.10	
Ventrolateral Prefrontal Cortex	-50	34	12	L	5.69	
Orbitofrontal Cortex	-48	32	0	L	5.60	
Anterior Insula/Inferior Frontal Gyrus	-34	28	-4	L	5.05	
	-56	14	10	L	4.15	
Superior Parietal Lobule	26	-52	68	R	6.04	1192
Ventrolateral Prefrontal Cortex	58	34	6	R	4.33	729
Dorsolateral Prefrontal Cortex	46	20	24	R	4.30	
Anterior Insula	34	28	2	R	3.53	
Caudate	-8	4	14	L	3.78	664
Thalamus	-8	-8	8	L	3.45	
Caudate	10	6	8	R	3.40	
Caudate	-10	-20	14	L	3.25	
Thalamus	4	-8	4	R	2.90	
(Control$_A$ – Aggressor) ∩ (Control$_V$ – Victim)						
Lingual Gyrus	-10	-76	-4	L	5.85	5396
Cuneus	-6	-90	22	L	5.57	
Middle Occipital Cortex	-8	-82	2	L	5.34	
Lingual Gyrus	12	-66	7	R	4.49	
Cuneus	6	-88	14	R	4.37	

Middle/Superior Temporal Gyrus	66	-24	-8	R	5.43	1308
Inferior Temporal Gyrus	64	-16	-20	R	5.30	
	56	-12	-32	R	4.10	
Ventromedial Prefrontal Cortex /Anterior Cingulate Cortex	4	32	-14	R	5.23	2352
Ventromedial Prefrontal Cortex	10	46	-4	R	4.86	
Ventromedial Prefrontal Cortex	-4	42	-10	L	4.65	
Inferior Parietal Lobule	54	-50	40	R	4.49	1046
	52	-42	50	R	4.29	
Superior Frontal Gyrus	20	54	30	R	4.32	318
Middle Temporal Gyrus/Superior Temporal Sulcus	-52	-20	0	L	4.17	980
	-66	-28	4	L	3.96	
Inferior Temporal Gyrus	-62	-28	-20	L	3.93	
Middle Frontal Gyrus	38	28	44	R	3.62	547
Superior Frontal Gyrus	24	24	54	R	3.43	
	20	32	40	R	3.05	
Aggressor – Victim						
Middle Occipital Gyrus	-16	-100	10	L	5.26	2745
Cuneus	14	-92	24	R	4.82	
Middle Occipital Gyrus	6	-90	10	R	4.45	
Cuneus	-8	-96	32	L	3.40	
Tempoparietal Junction	48	-28	6	R	4.48	805
Middle Temporal Gyrus/Superior Temporal Sulcus	60	-24	-10	R	4.28	
Posterior Insula	42	-14	18	R	3.05	
Insula	44	10	8	R	3.85	402
Inferior Frontal Gyrus	64	6	10	R	3.55	
Superior Temporal Gyrus	58	0	-2	R	3.08	
Premotor Cortex	-44	-12	52	L	3.76	247
	-38	-12	58	L	3.41	
Ventromedial Prefrontal Cortex	4	46	-10	R	3.62	411
Ventromedial Prefrontal Cortex	0	60	-4		3.22	
Calcarine Gyrus	-22	-58	6	L	3.61	579
Lingual Gyrus	12	-68	-4	R	3.55	469
Calcarine Gyrus	18	-50	0	R	3.23	
Fusiform Gyrus	26	-60	-6	R	3.52	
Middle Temporal Gyrus/Superior Temporal Sulcus	-62	-18	-8	L	3.28	219
Superior Temporal Gyrus	-58	-10	6	L	3.05	
Victim – Aggressor						
Dorsolateral Prefrontal Cortex	-50	30	24	L	4.28	1434
	-44	12	20	L	3.49	

Ventrolateral Prefrontal Cortex /Orbitofrontal Cortex	-44	40	6	L	3.84	
	-44	52	2	L	3.68	
Caudate	-10	18	12	L	3.91	425
Caudate	14	18	14	R	3.67	

Note. Coordinates of local maxima at $p<0.005$ at the voxel level with a minimum cluster size of 190. Abbreviations: MNI, Montreal Neurological Institute; L, left; R, right.

Table 2. Areas in which activity in the *Victim* minus *Aggressor* contrast correlated with Trait Empathy scores

Brain region	MNI coordinates			R/L	Z value	Cluster size
	x	y	z			
Insula	42	8	-10	R	3.91	716
	40	0	0	R	3.51	
Superior Temporal Gyrus	42	-12	-10	R	3.28	
Superior Temporal Gyrus	-26	-18	10	L	3.51	228
	-50	-30	12	L	3.24	
Cuneus	12	-58	18	R	3.41	214
	8	-66	24	R	3.29	

Note. Coordinates of local maxima at $p<0.005$ at the voxel level with a minimum cluster size of 190. Abbreviations: MNI, Montreal Neurological Institute; L, left; R, right.

Table 3. Areas displaying increased functional connectivity as a function of attentional focus

Brain region of coactivation	MNI coordinates			L/R	Z value	Cluster size
	x	y	z			
Task-related PPI analysis of the left Anterior Insula seed						
Aggressor - Victim						
Temporoparietal Junction	50	-46	30	R	3.86	382
Supramarginal Gyrus	52	-36	36	R	3.65	
Temporoparietal Junction	60	-38	26	R	3.43	
Cuneus	-4	-88	34	L	3.71	258
Cuneus	8	-80	24	R	3.48	
Cuneus	-12	-88	30	L	3.47	
Cuneus	4	-68	2	R	3.66	196
Victim - Aggressor						
No significant clusters						
Task-related PPI analysis of left Dorsolateral Prefrontal Cortex seed						
Aggressor - Victim						
No significant clusters						
Victim – Aggressor						
No significant clusters						
Task-related PPI analysis of left Ventromedial Prefrontal Cortex seed						
Aggressor - Victim						
No significant clusters						
Victim - Aggressor						
Middle Frontal Gyrus	32	48	22	R	4.14	211
Middle/Superior Frontal Gyrus	28	58	30	R	2.68	
Task-related PPI analysis of right Ventromedial Prefrontal Cortex seed						
Aggressor - Victim						
No significant clusters						
Victim - Aggressor						
No significant clusters						

Note. Coordinates of local maxima at $p<0.005$ at the voxel level with a minimum cluster size of 190. Abbreviations: MNI, Montreal Neurological Institute; L, left; R, right.

Table 4. Areas displaying task-related functional connectivity with the left Anterior Insula associated with Trait Empathy and Trait Anxiety

Brain region of coactivation	MNI coordinates			L/R	Z value	Cluster size
	x	y	z			
Trait Empathy						
Aggressor - Victim						
No significant clusters						
Victim - Aggressor						
Cerebellum	28	-68	-22	R	4.35	512
	32	-60	-22	R	3.96	
Inferior Occipital Gyrus	-48	-76	-10	L	3.88	284
	-42	-84	-14	L	3.7	
Cerebellum	-42	-70	-18	L	3.32	
Trait Anxiety						
Aggressor - Victim						
White Matter	42	-40	8	R	4.12	374
Hippocampus	32	-26	-8	R	2.69	
Superior Frontal Gyrus	22	50	36	R	3.89	294
Middle Frontal Gyrus	28	50	28	R	3.64	
Inferior Frontal Gyrus	52	18	44	R	3.38	235
Middle Frontal Gyrus	30	38	46	R	3.07	
Victim - Aggressor						
No significant clusters						

Note. Coordinates of local maxima at $p<0.005$ at the voxel level with a minimum cluster size of 190. Abbreviations: MNI, Montreal Neurological Institute; L, left; R, right.

Table 5. Areas displaying task-related functional coupling with the left Dorsolateral Prefrontal Cortex associated with Trait Empathy, Trait Anger and Trait Anxiety

Brain region of coactivation	MNI coordinates			L/R	Z value	Cluster size
	x	y	z			
Trait Empathy						
Aggressor - Victim						
Supplementary Motor Area	12	-20	58	R	4.84	2578
	10	0	52	R	4.34	
	14	-6	72	R	3.49	
Middle Frontal Gyrus	30	-4	62	R	3.85	
Middle Cingulate Cortex	14	6	42	R	3.74	
Superior Frontal Gyrus	18	-12	74	R	3.67	
Paracentral Lobule	-12	-38	62	L	3.50	
Insula	38	10	10	R	4.26	199
Supramarginal Gyrus	64	-28	36	R	4.19	408
Temporoparietal Junction	60	-34	28	R	3.59	
Inferior Parietal Lobule	52	-20	28	R	3.35	
Middle Frontal Gyrus	-30	32	44	L	4.12	362
	-26	22	52	L	3.03	
White Matter	12	38	38	R	4.01	289
Middle Frontal Gyrus	28	30	36	R	3.1	
Posterior Cingulate Cortex	-8	-24	42	L	3.74	292
White Matter	-14	-32	36	L	3.61	
	-20	-34	44	L	3.53	
Victim - Aggressor						
No significant clusters						
Trait Anger						
Aggressor - Victim						
White Matter	20	10	34	R	3.83	820
Middle Frontal Gyrus	34	10	54	R	3.8	
	30	-4	64	R	3	
Superior Frontal Gyrus	18	4	60	R	3.63	
	26	14	48	R	3.39	
	22	22	48	R	3.52	
Paracentral Lobule	6	-34	68	R	3.68	351
	10	-24	58	R	3.02	
	8	-26	62	R	3.12	
Paracentral Lobule	-4	-28	68	L	2.95	
Postcentral Gyrus	-38	-50	50	L	3.58	357

Postcentral Gyrus	-42	-38	48	L	3.11	
	-50	-48	48	L	3.02	
Inferior Parietal Lobule	-52	-50	54	L	2.9	
Angular Gyrus	42	-72	42	R	3.36	258
	34	-64	52	R	3.23	
Middle occipital gyrus	38	-74	42	R	3.34	
Parietal operculum	-36	-16	24	L	3.33	199
	-42	-12	20	L	3.09	
Victim - Aggressor						
No significant clusters						

Trait Anxiety

Aggressor - Victim						
Dorsomedial Prefrontal Cortex	8	46	34	R	3.78	211
Dorsomedial Prefrontal Cortex	-2	42	32	L	3.10	
Victim - Aggressor						
No significant clusters						

Note. Coordinates of local maxima at $p<0.005$ at the voxel level with a minimum cluster size of 190. Abbreviations: MNI, Montreal Neurological Institute; L, left; R, right.

Table 6. Areas displaying task-related functional connectivity with the left Ventromedial Prefrontal Cortex associated with Trait Anxiety

Brain region of coactivation	MNI coordinates			L/R	Z value	Cluster size
	x	y	z			
Aggressor - Victim						
No significant clusters						
Victim - Aggressor						
Thalamus	8	-22	6	R	4.09	513
	8	-12	4	R	3.29	
	4	-20	4	R	3.88	
Thalamus	-12	-30	4	L	2.81	
Cerebellum	8	-48	0	R	4	
Putamen	30	0	2	R	3.99	226
	32	4	0	R	3.91	
Superior Temporal Gyrus	48	-46	14	R	3.62	280
Middle Temporal Gyrus	68	-42	-2	R	3.62	
	68	-38	8	R	3.49	

Note. Coordinates of local maxima at $p<0.005$ at the voxel level with a minimum cluster size of 190. Abbreviations: MNI, Montreal Neurological Institute; L, left; R, right.

Table 7. Areas displaying task-related functional connectivity with the right Ventromedial Prefrontal Cortex associated with Trait Empathy and Trait Anxiety

Brain region of coactivation	MNI coordinates			L/R	Z value	Cluster size
	x	y	z			
Trait Empathy						
Aggressor-Victim						
White Matter	-18	-44	62	L	4.12	275
	-10	-30	54	L	3.57	
Paracentral Lobule	-12	-36	52	L	3.28	
Postcentral Gyrus	-36	-38	68	L	2.97	
White Matter	-30	20	40	L	3.76	235
Superior Frontal Gyrus	-18	32	40	L	3.3	
Victim-Aggressor						
No significant clusters						
Trait Anxiety						
Aggressor-Victim						
No significant clusters						
Victim-Aggressor						
Superior Frontal Gyrus	14	56	32	R	3.79	210
	20	50	38	R	3.76	
Dorsomedial Prefrontal Cortex	12	50	26	R	3.78	

Note. Coordinates of local maxima at $p<0.005$ at the voxel level with a minimum cluster size of 190. Abbreviations: MNI, Montreal Neurological Institute; L, left; R, right.

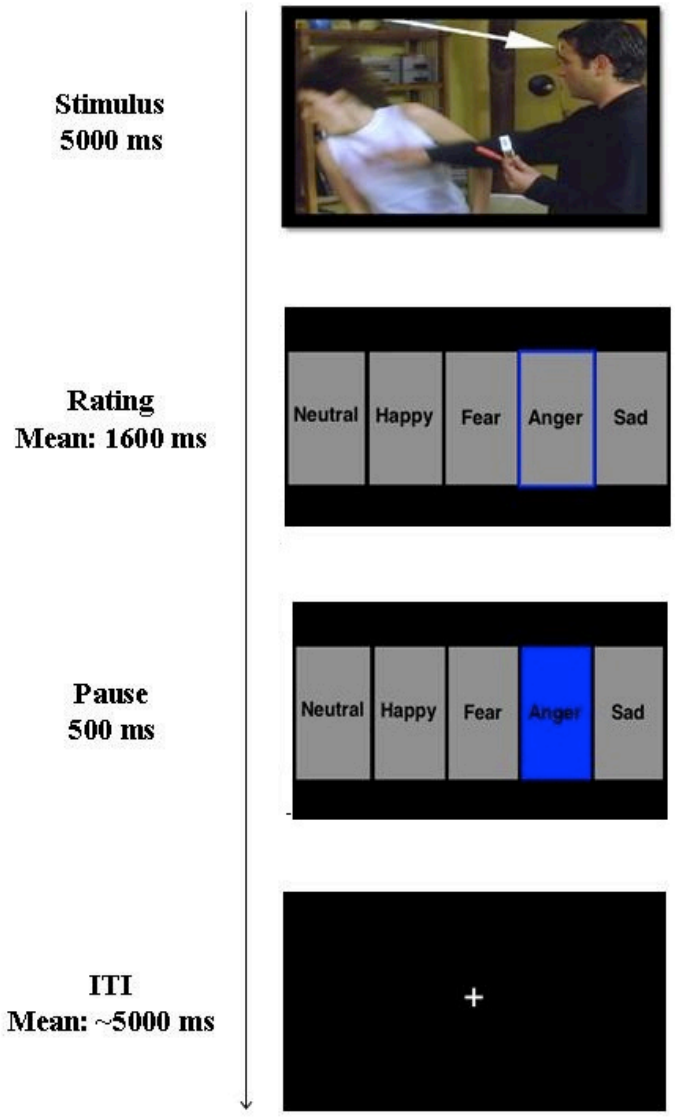


Figure 1. Example of a trial. The image was presented for 5 seconds, with an arrow pointing toward the aggressor or the victim, in the case of negative images, or to $control_A$ or $control_V$, in the case of control (neutral/mildly positive) scenes. The rating slide disappeared 500 ms after the subject made a choice of the emotion elicited by the target person (Neutral/Happy/Fear/Anger/Sad), and was followed by a fixation cross that lasted 3 to 12 seconds (Mean: ~5 seconds).

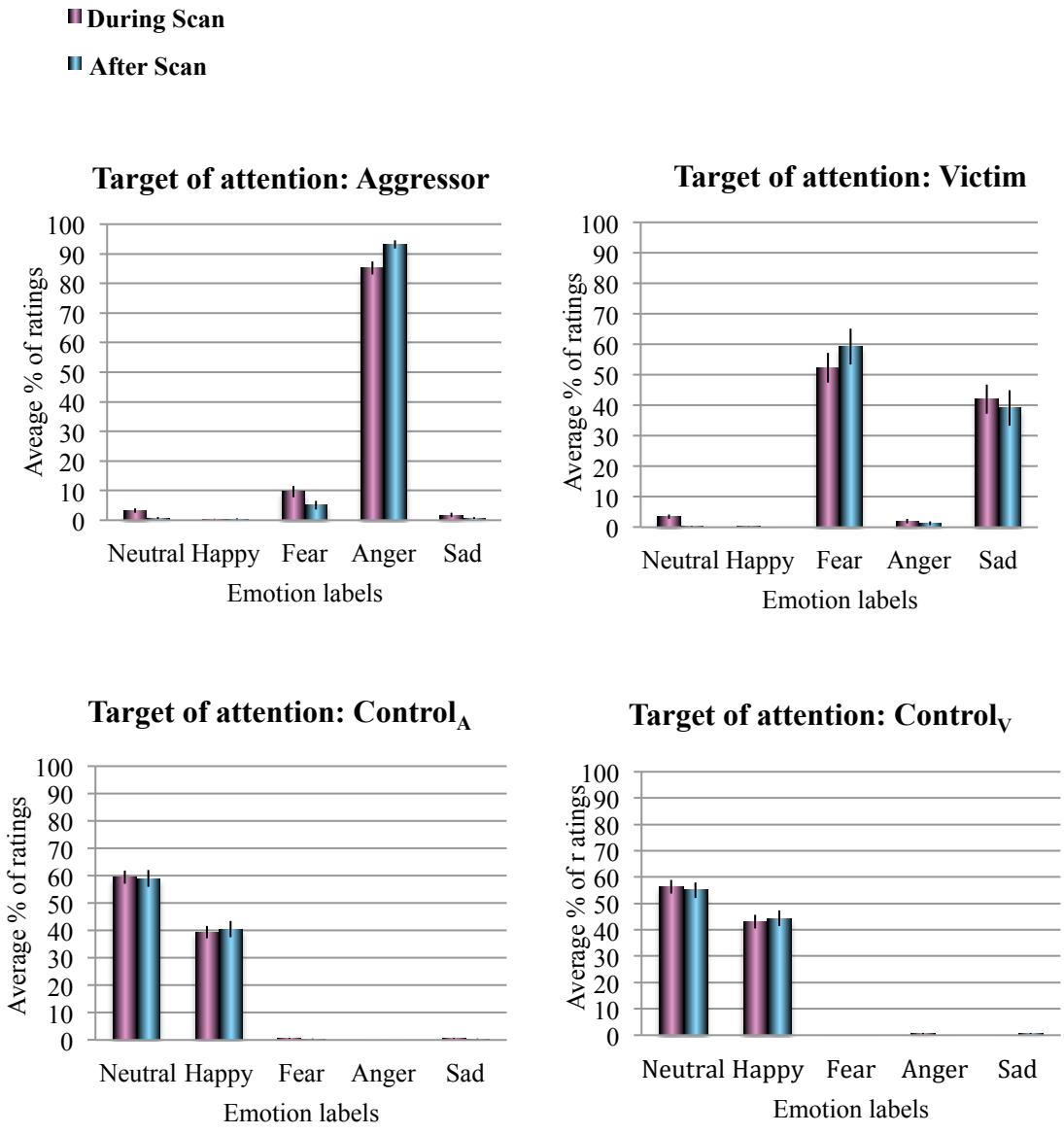
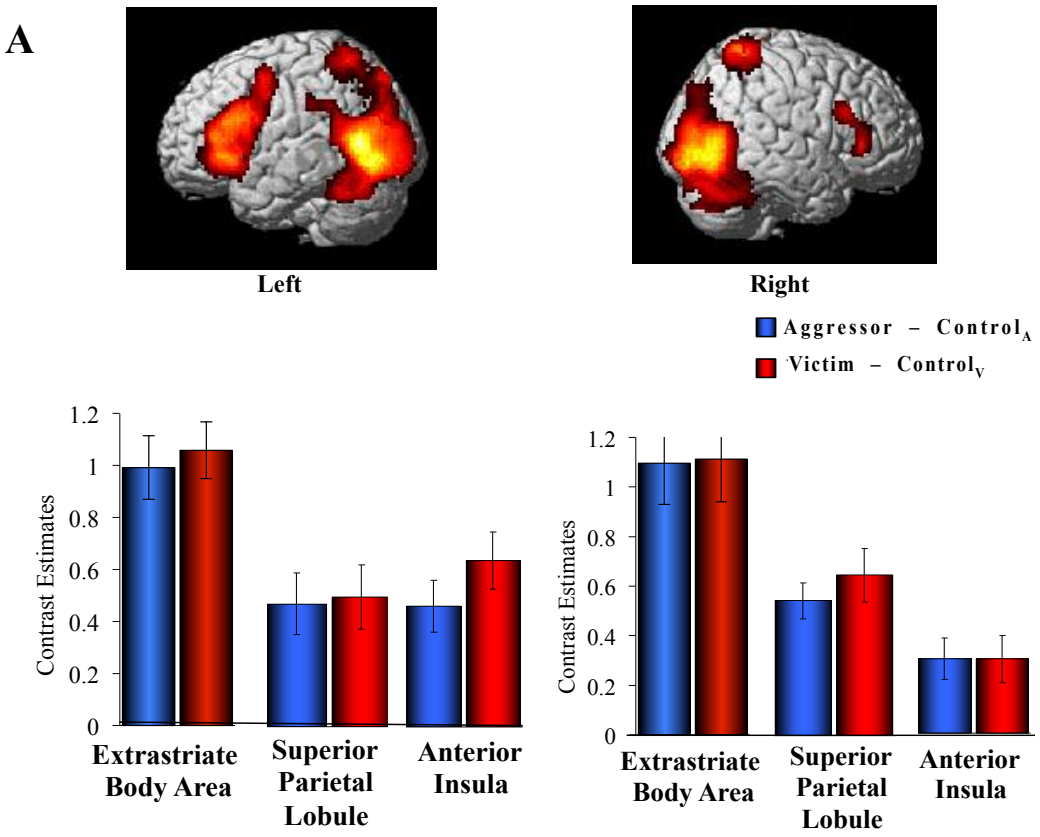


Figure 2. Results of the emotion categorization task during and after the scan. The results confirmed that the stimuli reliably elicited the pre-selected target emotions, namely 'anger' toward the aggressor (85% during scan and 93% after scan), 'sadness' or 'fear' for the victim (i.e., empathic concern; 94% during scan and 98% after scan) and 'happiness' or 'neutral' toward the control$_A$ (98% during scan and 99% after scan) and the control$_V$ (99% during and after scan). Error bars represent the standard error of the mean.


A
Left
Right
Aggressor – Control$_A$
Victim – Control$_V$
Contrast Estimates
1.2
1
0.8
0.6
0.4
0.2
0
Extrastriate Body Area
Superior Parietal Lobule
Anterior Insula
Contrast Estimates
1.2
1
0.8
0.6
0.4
0.2
0
Extrastriate Body Area
Superior Parietal Lobule
Anterior Insula

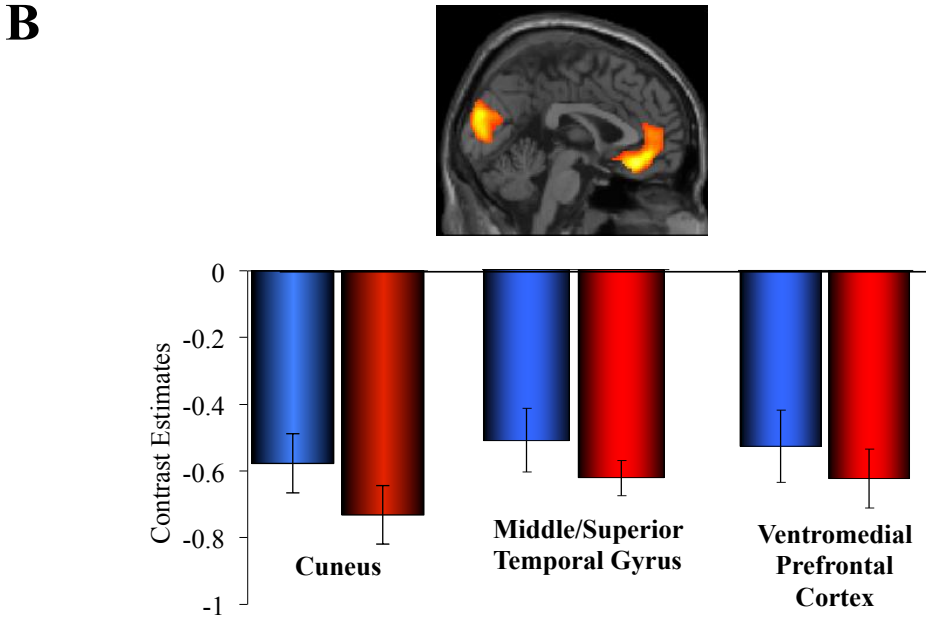

B
Contrast Estimates
0
-0.2
-0.4
-0.6
-0.8
-1
Cuneus
Middle/Superior Temporal Gyrus
Ventromedial Prefrontal Cortex

Figure 3. Areas commonly engaged by the aggressor- and victim-focus conditions. **(A)** *Top:* Regions that responded more strongly to negative than control images, regardless of the focus of attention [(Aggressor – $Control_A$) ∩ (Victim – $Control_V$)], rendered on a canonical brain surface, showing the clusters in the Extrastriate Body Area, Superior Parietal Lobule and Anterior Insula/ Inferior Frontal Gyrus; *Bottom:* the corresponding parameter estimates (in arbitrary units) for the peak voxels of these clusters. **(B)** *Top:* Significant regions obtained in the opposite contrast [($Control_A$ – Aggressor) ∩ ($Control_V$ – Victim)], overlaid on the MNI single-subject brain, showing the clusters in the right Cuneus and Ventromedial Prefrontal Cortex; *Bottom:* the corresponding parameter estimates (in arbitrary units) for the peak voxels of these clusters, as well as of the cluster in the right Medial Temporal Gyrus/Superior Temporal Sulcus. Coordinates of all the significant activations for these contrasts are shown in Table 1.

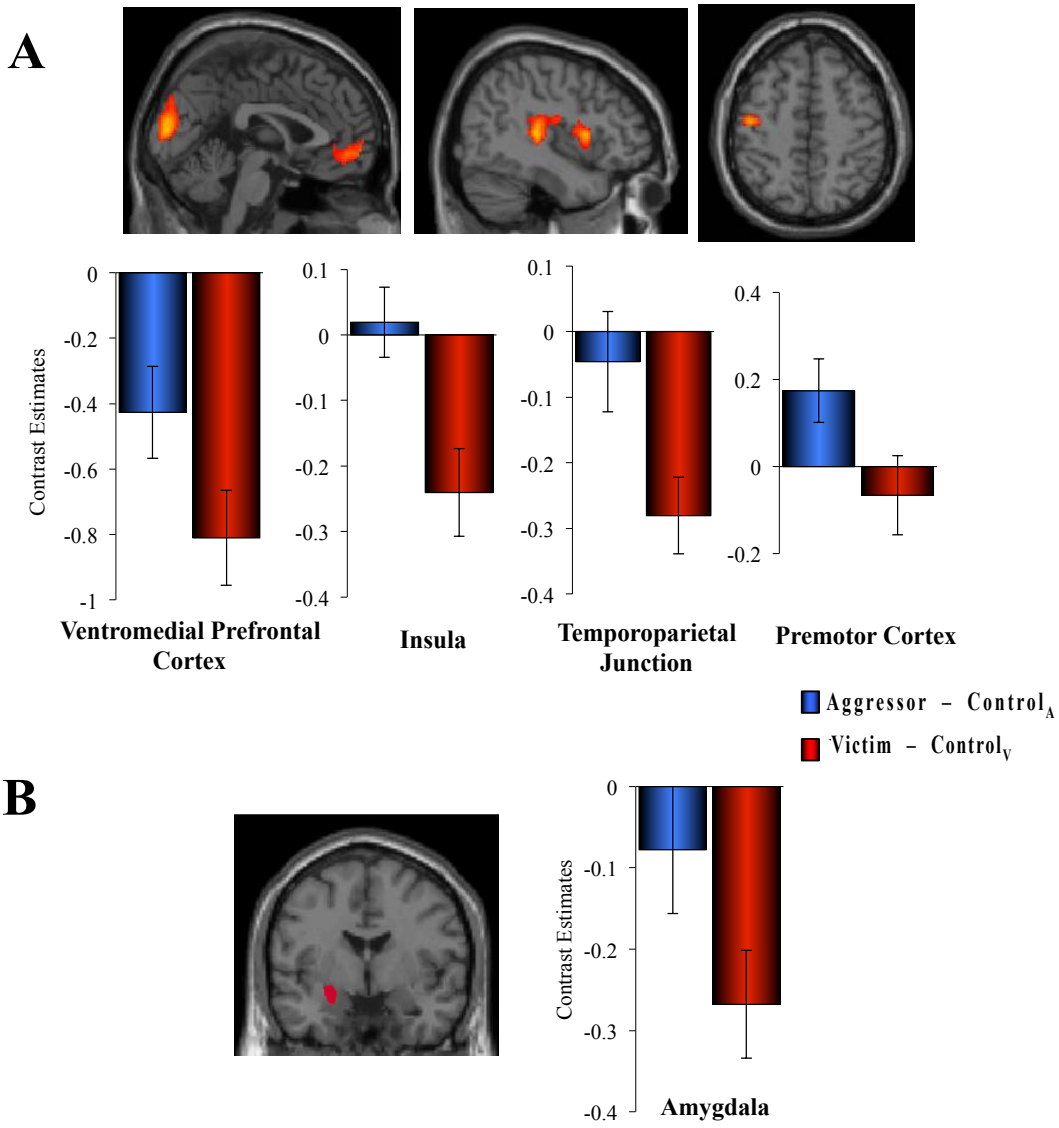


Figure 4. Areas of activation in the *Aggressor* minus *Victim* contrast. **(A)** Statistical Parametric Map of the contrast (Aggressor – Victim), overlaid on the MNI single-subject brain, and the corresponding parameter estimates (in arbitrary units) for the peak voxels of the clusters in the right Cuneus and Ventromedial Prefrontal Cortex, right Tempoparietal Junction, right Insula and left Premotor Cortex (coordinates of all the significant activations for this contrast are shown in Table 1). **(B)** Activation in the left Amygdala ([-24 -2 -14]), and corresponding parameter estimates, for the contrast ($Control_V$ – Victim). The difference between Aggressor and Victim was also significant ($p<0.05$ uncorrected).

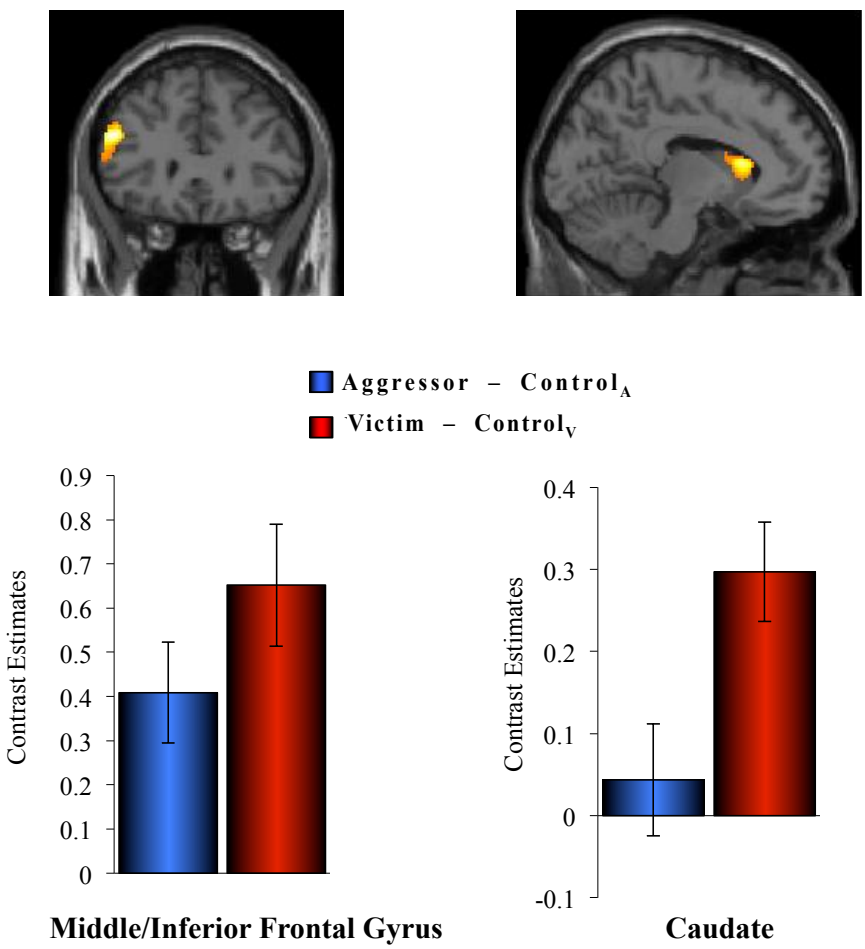
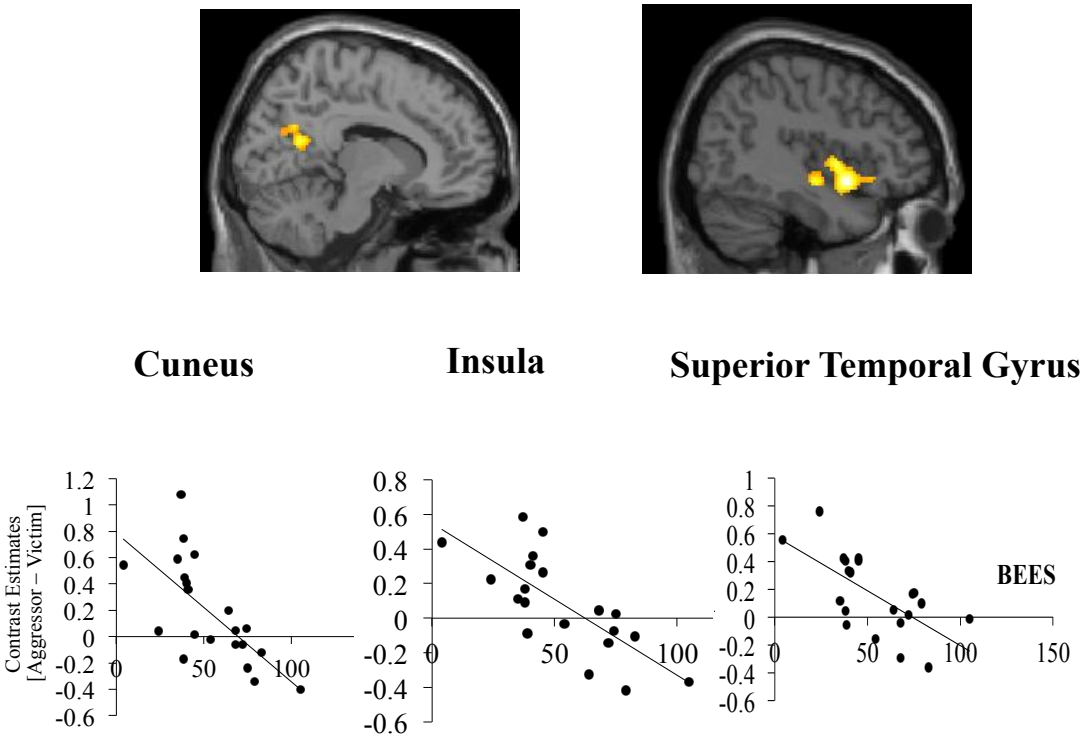


Figure 5. Areas of activation in the *Victim* minus *Aggressor* contrast. *Top:* Statistical Parametric Map of the contrast (Victim – Aggressor), overlaid on a single-subject brain, showing the clusters in the left Middle/Inferior Frontal Gyrus and Caudate; *Bottom:* the corresponding parameter estimates (arbitrary units) for the peak voxels of these clusters. Coordinates of all the significant activations for this contrast are shown in Table 1.

A


Cuneus
Insula
Superior Temporal Gyrus
Contrast Estimates [Aggressor – Victim]
BEES

B

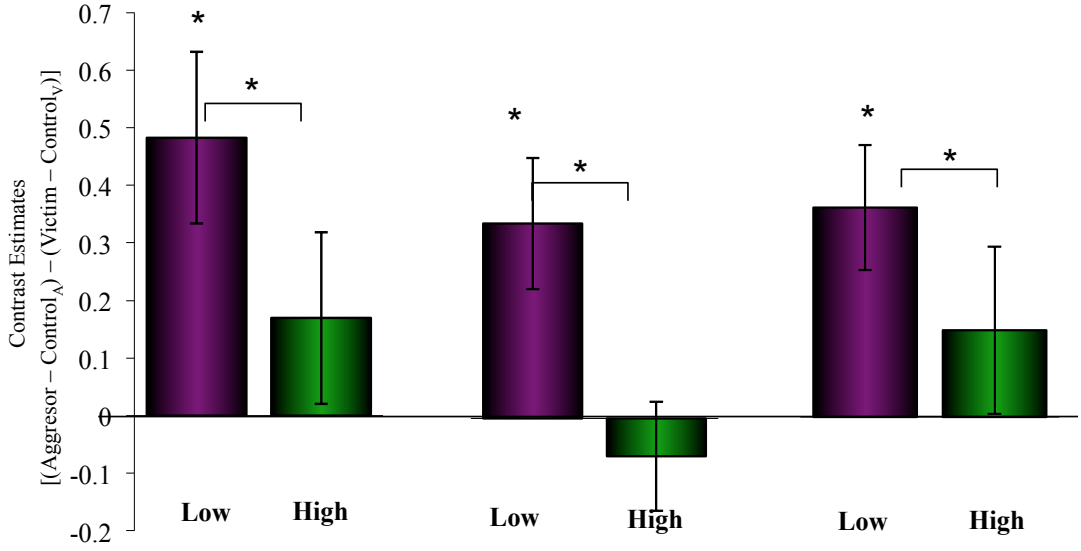

Contrast Estimates [(Aggresor – Control$_A$) – (Victim – Control$_V$)]
Low
High
Low
High
Low
High

Figure 6. Areas displaying association between Trait Empathy and brain activation in the *Aggressor* minus *Victim* contrast. **(A)** *Top:* Results of the regression analysis of the contrast (Aggressor – Victim) with subjects' Empathy Scores (BEES), overlaid on the MNI single-subject brain, showing the clusters in the right Cuneus, Insula and Superior Temporal Gyrus; *Bottom:* the corresponding correlations for the peak voxels of these clusters. Coordinates of all the significant activations for this analysis are shown in Table 2. **(B)** Parameter estimates for the interaction [(Aggresor – $Control_A$) – (Victim – $Control_V$)] for these three regions for the Low-Empathy Group (N=11) and High-Empathy Group (N=10). Asterisks indicate significant differences relative to zero (above bar) or between groups (above bracket) ($p<0.05$, Bonferroni corrected for multiple tests).

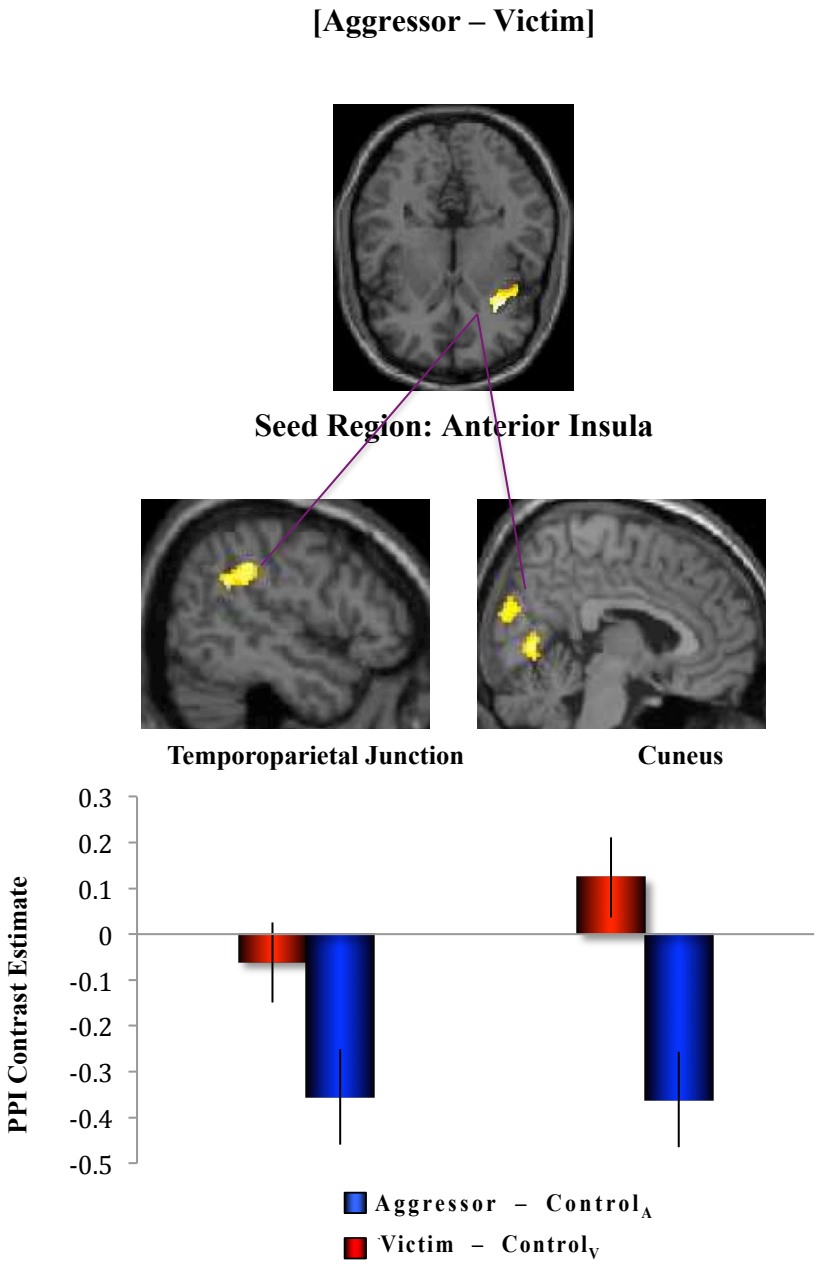


Figure 7. Areas displaying enhanced functional connectivity with the left Anterior Insula in the *Aggressor* versus *Victim* contrast. *Top:* The Anterior Insula seed mask and the Statistical Parametric Map of the contrast (Aggressor – Victim), overlaid on the MNI single-subject brain, showing the clusters in the Anterior Insula (seed) and Temporoparietal Junction and Cuneus; *Bottom:* the corresponding PPI parameter estimates (arbitrary units) for the peak voxels of the clusters in the Temporoparietal Junction and Cuneus. Coordinates of all the significant coactivations for this analysis are shown in Table 3.

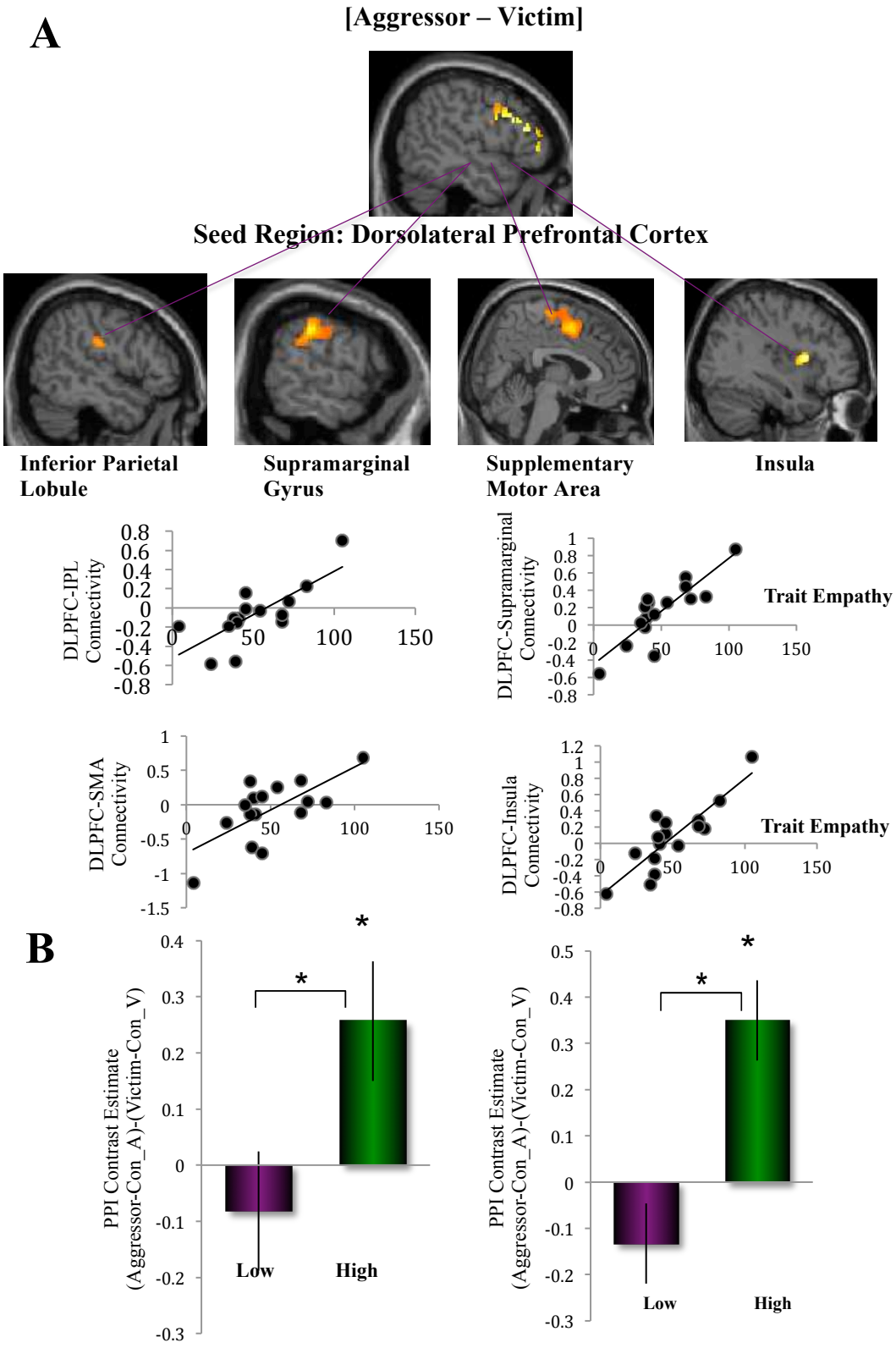

A
[Aggressor – Victim]
Seed Region: Dorsolateral Prefrontal Cortex
Inferior Parietal Lobule
Supramarginal Gyrus
Supplementary Motor Area
Insula
DLPFC-IPL Connectivity
DLPFC-Supramarginal Connectivity
Trait Empathy
DLPFC-SMA Connectivity
DLPFC-Insula Connectivity
Trait Empathy
B
PPI Contrast Estimate (Aggressor-Con_A)-(Victim-Con_V)
Low
High
PPI Contrast Estimate (Aggressor-Con_A)-(Victim-Con_V)
Low
High

Figure 8. Areas displaying association between Trait Empathy and functional coupling with the Dorsolateral Prefrontal Cortex in the *Aggressor* minus *Victim* contrast. **(A)** *Top:* The Dorsolateral Prefrontal Cortex seed mask and the results of the regression analysis of the contrast (Aggressor – Victim) with subjects' Trait Empathy scores, overlaid on the MNI single-subject brain, showing the clusters in the Inferior Parietal Lobule, Supramarginal Gyrus, Supplementary Motor Area and Insula; *Bottom:* the corresponding correlations for the peak voxels of these clusters. Coordinates of all the significant PPI effects for this analysis are shown in Table 5. **(B)** PPI parameter estimates for the interaction [(Aggresor – $Control_A$) – (Victim – $Control_V$)] for the Supplementary Motor Area and Insula for the Low-Empathy Group (N=8) and High-Empathy Group (N=8). Asterisks indicate significant differences relative to zero (above bar) or between groups (above bracket) ($p<0.05$).

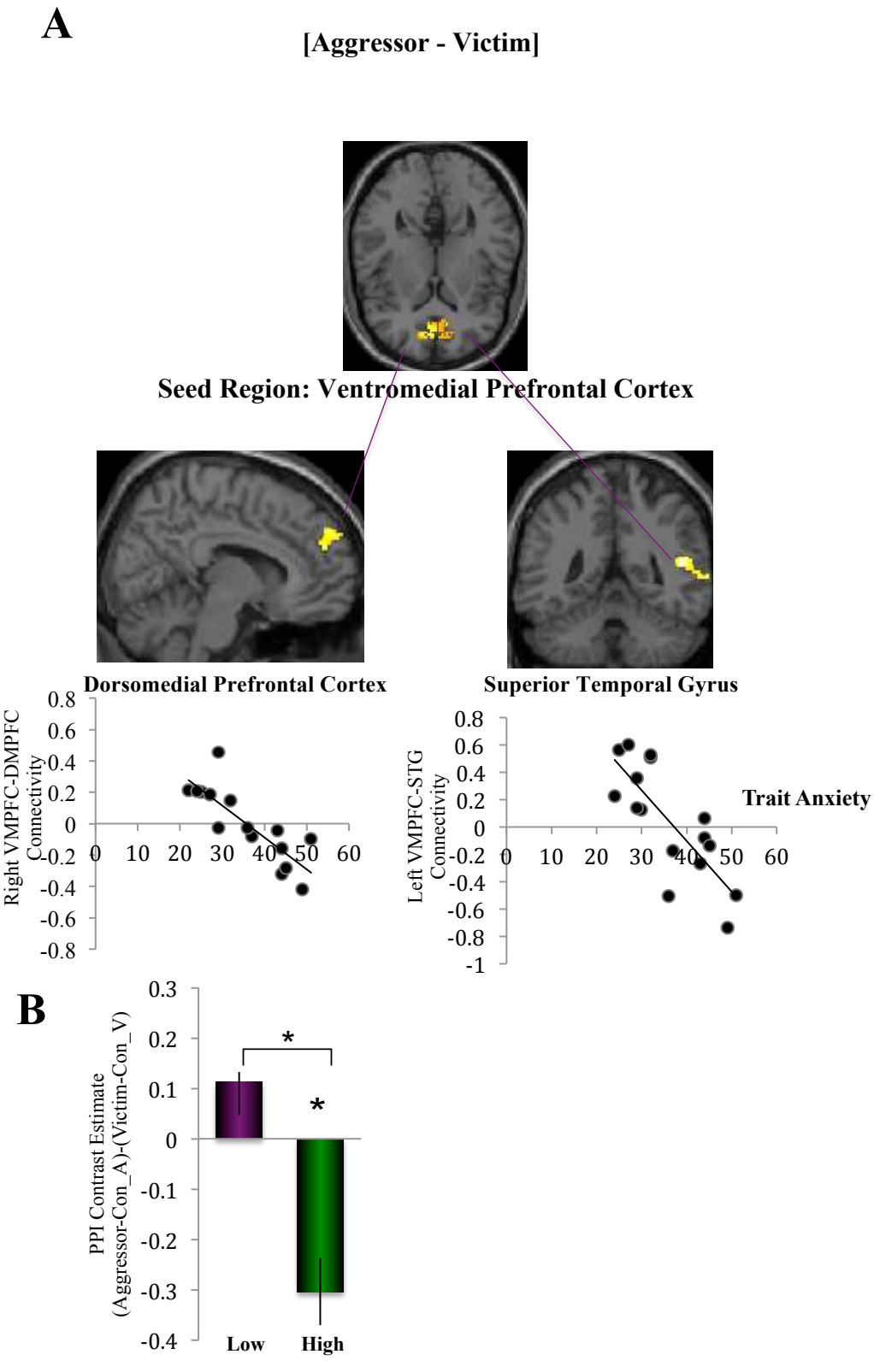

A
[Aggressor - Victim]
Seed Region: Ventromedial Prefrontal Cortex
Dorsomedial Prefrontal Cortex
Superior Temporal Gyrus
Right VMPFC-DMPFC Connectivity
Left VMPFC-STG Connectivity
Trait Anxiety
B
PPI Contrast Estimate (Aggressor-Con_A)-(Victim-Con_V)
Low
High

Figure 9. Areas displaying association between Trait Anxiety and functional connectivity with the Ventromedial Prefrontal Cortex in the *Aggressor* versus *Victim* contrast. **(A)** *Top:* The bilateral Ventromedial Prefrontal Cortex seed masks and the results of the regression analysis of the contrast (Aggressor – Victim) with subjects' Trait Anxiety scores, overlaid on the MNI single-subject brain, showing the clusters in the Dorsomedial Prefrontal Cortex and Superior Temporal Gyrus; *Bottom:* the correlations for the peak voxels of these clusters. Coordinates of all the significant PPI effects for these analyses are shown in Table 6 and 7. **(B)** PPI parameter estimates for the interaction [(Aggresor – $Control_A$) – (Victim – $Control_V$)] for the Dorsomedial Prefrontal Cortex for the Low-Anxiety Group (N=7) and High-Anxiety Group (N=8). Asterisks indicate significant differences relative to zero (above bar) or between groups (above bracket) ($p<0.005$).