

Neurobiological Bases of Empathy and Prosocial Behavior

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## ABSTRACT

Prosociality is a complex, multifaceted construct that involves cognitive, affective, regulatory, and motivational processes contributing to helpful and compassionate responses to the needs of others. Prosociality can be studied across different levels of analysis, including behavioral, experiential, psychophysiological, and neural, and researchers from different disciplines have investigated these levels separately. As a result, different fields have developed their own theoretical frameworks of prosociality. Integrations across different facets and levels of analysis, as well as across theoretical frameworks, are missing in the literature. Thus, providing a more complete picture of the underpinnings of prosociality requires multimethod approaches that cut across psychology, psychophysiology, and neuroscience. Few studies of prosociality have adopted this approach, but research that considers the links across different facets and levels of analysis are crucial for providing a richer understanding of prosociality that integrates theory across and within disciplines.

The present research used a multimethod approach across three studies in order to better our understanding of how the human nervous system is wired for prosociality. First, we examined links between resting parasympathetic activity and neural reactivity to emotional faces. We found that resting parasympathetic activity was negatively correlated with regions previously implicated in motor imitation and affective aspects of empathy, including the mirror neuron system, insula, and amygdala. Second, we observed whether transcranial magnetic stimulation (TMS) of the right temporoparietal junction (TPJ) alters emotional experiences and autonomic reactivity to others' emotional suffering. TMS to the right TPJ produced 1) greater annoyance/irritation, 2) less compassion, 3) less parasympathetic flexibility, and 4) less deactivation of sympathetic nervous system activity, in response to a sad film clip. Third, we

examined whether the tendency to use cognitive reappraisal shapes whether reactivity to sad faces in motivation-related brain regions predicts more and less prosociality. We found some evidence for this for adolescent boys who showed increased neural reactivity to sadness introspection, but cognitive reappraisal appeared to be more important for girls who showed neural reactivity when focusing on a physical aspect of others' sad faces. Together, these findings provide progress in terms of informing our understanding of central-autonomic integration, making a causal claim about the role of the right TPJ in regulating affective processes, and considering neurobiological effects as person-dependent. These multimethod studies contribute to our understanding of the multifaceted nature of prosociality, and help to integrate various theoretical perspectives on prosociality that have been developed in isolation of each other in psychology, psychophysiology, and neuroscience.

## CHAPTER 1

### GENERAL INTRODUCTION

Prosociality refers to positive behaviors and emotions that orient us toward the needs of others (e.g., empathy, compassion, helping others), and these play a fundamental role in our everyday social interactions. Behaviors like caring for offspring, maintaining and developing relationships with family, close friends, and strangers, and cooperating within groups, all depend on our abilities to share and understand the feelings of others, experience concern for others, and to act on these emotions to provide others with appropriate assistance. We use the term empathy to refer to sharing or resonating with the feelings of others (Singer & Klimecki, 2014). Empathy is multidimensional, involving an emotional response that is similar to the perceived emotion of another person (affective empathy) and a cognitive capacity to adopt another person's perspective (cognitive empathy) (Decety, 2011). Compassion is defined as feeling concern for the misfortunes of others and a desire to help (Goetz, Keltner, & Simon-Thomas, 2010; Singer & Klimecki, 2014). Prosocial behavior is one potential consequence of feeling empathy and compassion (Davidov, Vaish, Knafo-Noam, & Hastings, 2016; de Wall, 2008), and refers to behaviors meant to benefit others (Eisenberg, Fabes, & Spinrad, 2006). Conversely, individuals can also sometimes feel personally distressed by others' suffering, which can lead to avoidance, or feeling annoyed or irritated by others' suffering, which can lead to hostility (Batson, 2011). Emotion regulation is widely considered to be an important part of prosociality, as it can help to prevent confusion between representations of one's own and another's emotion and facilitate other-oriented responses (Decety & Jackson, 2006; Eisenberg & Eggum, 2009).

Psychologists have been studying the cognitive, affective, and behavioral aspects of prosociality for decades, and neuroscientists are providing complementary and new information

on underlying information-processing mechanisms. Current neurobiological models of prosociality are primarily based on functional magnetic resonance imaging (fMRI) studies of the brain. However, prosocial behaviors and emotions arise from coordinated processes across multiple neurobiological systems (Hastings, Miller, Kahle, & Zahn-Waxler, 2014), and the meaning of activity in these systems can also depend on features of the individual (Bartz, Zaki, Bolger, & Ochsner, 2011; Miller, in press). Thus, trait and state prosociality can be studied at different, interacting levels of analysis, including neural, autonomic, experiential, and behavioral.

Most research on prosociality has focused on single levels of analysis rather than taking a multilevel perspective. As a result, theoretical frameworks have been developed in different disciplines in isolation of each other. Still, there are commonalities across different fields and levels of analysis. For example, psychological research suggests that social cognitive processes like perspective-taking are important for affective processes, like feeling safe rather than emotionally overwhelmed in response to others' suffering (Batson, 2011), and social neuroscience has uncovered some of the neural mechanisms of these processes (Decety & Jackson, 2006). Polyvagal theory (Porges, 2011) provides a guiding psychophysiological framework for understanding the role of the vagus nerve in promoting calm, social engagement important for prosociality. Thus, although there are common themes across these literatures that emphasize perspective-taking and self-regulation in prosociality, studies that tie them together are lacking. In addition, focusing on one level of analysis often ignores the importance of other processes underlying prosociality. For example, polyvagal research emphasizes the vagus nerve in prosociality, but this literature does not speak to how this system is integrated with the functioning of other systems implicated in prosociality like, for example, cortical regions critical for social cognition. Thus, considering how various theoretical frameworks complement each

other has the potential to provide a more complete, integrative picture of the underpinnings of prosociality than any single perspective in isolation.

This set of studies examined the links across these levels to better understand prosociality as a multifaceted construct, and combined measures of subjective experience, self-reported prosocial behavior, autonomic nervous system functioning, fMRI, and transcranial magnetic stimulation (TMS). The current studies advance the science of prosociality in three main ways: 1) Examining the integration of central and autonomic nervous system processes, which has been rare in the literature; 2) Using TMS to provide causal evidence for neural regulation of experiential and autonomic responding to others' emotional suffering; and 3) Consideration of the link between neurobiology and prosociality as dependent on individual differences in emotion regulation.

### **Autonomic Nervous System**

Prosocial behaviors and emotions are embodied processes. Visceral changes underlie basic aspects of empathy, such as orienting and arousal, and mobilization of bodily resources to provide help to others (Hastings & Miller, 2014; Miller, in press). These physiological changes are mediated by the parasympathetic and sympathetic branches of the autonomic nervous system (Berntson, Quigley, & Lozano, 2007). The sympathetic branch prepares the body for fight-or-flight responding (increased heart rate, cardiac output and contractility) whereas increased parasympathetic regulation results in slower heart rate and is involved in restorative processes in the body. Common cardiac indices of parasympathetic and sympathetic nervous system activity are high-frequency heart rate variability (HRV) and pre-ejection period (PEP), respectively. HRV refers to fluctuations in heart rate that correspond with breathing. Heart rate increases during inhalation and decreases during exhalation. This phenomenon is believed to be mainly

under the control of the myelinated vagus nerve, which is the main mechanism of parasympathetic regulation of the heart (Berntson et al., 1997). PEP refers to the time period between the beginning of ventricular depolarization and the opening of the aortic valve (Berntson et al., 2007). Shorter PEP intervals index greater sympathetic nervous system activity.

The polyvagal theory provides a conceptual framework for understanding HRV in relation to prosociality (Hastings & Miller, 2014; Porges, 2007, 2011). According to this perspective, the myelinated vagus evolved in mammals, in part, to support social engagement, orienting, and self-regulation. The myelinated vagus originates in the nucleus ambiguus region of the brain stem and extends to a number of target organs important for emotion and communication, including the heart, larynx, and face and neck muscles. Thus, the myelinated vagus is part of a social engagement system that regulates behaviors like looking, emotional facial expression and vocalization, and head turning (Porges & Furman, 2011). In safe social contexts, increased HRV reflecting greater myelinated vagus influence on the heart can help inhibit sympathetic arousal and defensive responding and perhaps promote compassion (Stellar, Cohen, Oveis, & Keltner, 2015), caregiving (Miller, Kahle, Lopez, & Hastings, 2015), altruism (Miller, Kahle, & Hastings, 2015), and other behaviors aimed at promoting social connectedness (Kok & Frederickson, 2010).

### **Resting HRV and Neural Mechanisms of Increasing Empathic Arousal**

Research has generally focused on two aspects of HRV – resting baseline HRV levels and HRV reactivity in response to emotionally evocative contexts. Higher resting HRV indicates greater autonomic flexibility thought to underlie positive functioning (Porges, 2007, 2011). Baseline HRV has been associated with better emotion regulation (Geisler, Kubiak, Siewert, & Weber, 2013; Vogel, Sorg, Studmann, & Weber, 2010), less negative arousal (Fabes &

Eisenberg, 1997), and more positive emotionality at the trait level (Oveis, Cohen, Gruber, Shiota, Haidt, & Keltner, 2009). At the neural level, resting HRV is associated with prefrontal inhibition of threat-related subcortical circuitry that likely contributes to evaluation of the environment as safe (either consciously or nonconsciously) (Beauchaine & Thayer, 2015; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). Thus, resting HRV is increasingly being regarded as a physiological correlate or marker of effective self-regulation (Beauchaine & Thayer, 2015; Porges, 2011).

Given the posited importance of self-regulation for prosociality (Eisenberg & Eggum, 2009; Padilla-Walker & Christensen, 2011), one might expect higher resting HRV to be associated with greater prosociality. However, the literature on resting HRV and prosociality is quite mixed, with studies finding either positive or negative associations, or failing to find statistically significant links (Hastings & Miller, 2014; Miller in press). One potential explanation of these inconsistencies is that the link between resting HRV and prosociality is curvilinear. Low resting HRV may reflect disinhibition of subcortical activity that contributes to defensive rather than prosocial responding when faced with others in need. Conversely, very high resting HRV may reflect a higher threshold for evoking empathic arousal, or a tendency to effectively inhibit empathic arousal (Hastings, Zahn-Waxler, & McShane, 2006). Thus, moderate to moderately high HRV may be related to greater prosociality. Recent research is starting to provide support for this perspective, as moderate resting HRV predicts greater self- and other-reported prosocial behaviors and emotions, more observed comforting behaviors towards others in pain, and donating more of one's own personal resources to benefit less fortunate others (Clark, Skowron, Guiliano, & Fisher, 2016; Kogan et al., 2014; Miller, Kahle, & Hastings, 2017). One interpretation of these findings is that resting HRV may reflect a threshold

for arousal, including arousal in response to the emotions of others (Hastings et al., 2006; Miller et al., 2017; Miller, in press). Moderate resting HRV may be an “optimal” threshold for supporting prosocial responses to others, relative to either very low or very high resting HRV.

There is a consistent association between moderate resting HRV and multiple levels of prosociality across several methods of assessment, but further support for this perspective could come from examining HRV in relation to neural mechanisms of increasing arousal and engagement with others’ emotions. Neuroscience research suggests that there are a number of different paths to feeling empathy (i.e., vicarious sharing of emotion), but at the most basic level, affective empathy involves appraising the emotion of another as salient and as a result, being affected by it (de Waal, 2008). The mirror neuron system, insula, and amygdala are neural regions implicated in affective aspects of empathy, and likely serve as early starting points for increasing arousal and engagement with the emotions of others (Lamm & Majdandžić, 2015). The pars opercularis or dorsal region of the inferior frontal gyrus (IFG) and adjacent premotor cortex areas are the parts of the mirror neuron system most often implicated in empathy (Horan et al., 2014; Pfeiffer, Iacoboni, Mazziota, & Dapretto, 2008). These brain regions contain mirror neurons that fire during the observation and execution of actions (Iacoboni & Dapretto, 2006), and are thought to be important for mapping the motor actions of others (e.g., facial expressions) onto one’s own sensorimotor system (Iacoboni, 2009; Lamm & Majdandžić, 2015). This facilitates motor imitation, which is one potential precursor to empathy in some contexts (Preston & de Waal, 2002). The insula and amygdala are part of a salience network important for rapid detection, prioritization, and processing of events (Decety, 2015; Menon & Uddin, 2010), including others’ emotional cues (Wicker et al., 2003). Thus, these regions are also implicated in affective aspects of empathy (Decety, 2015; Preckel, Kanske, & Singer, 2017).



If HRV reflects resting states of arousal that constrain engagement with others' emotions (i.e., threshold for arousal), then one would expect HRV to be negatively associated with neural mechanisms that increase engagement. Testing this requires integrating measures of autonomic and central nervous system activity. A growing number of studies are taking this approach (Ahs, Sollers, Furmark, Fredrikson, & Thayer, 2009; Critchley et al., 2003; Lane et al., 2009), but almost no studies have examined the link between resting HRV and neural response to emotional facial expressions, which communicate information about the states of others and are critical for eliciting empathic processing. One fMRI paradigm used in the empathy and mirror neuron literature is imitating and observing emotional facial expressions (Flournoy et al., 2016; Horan et al., 2014; Iacoboni, 2009; Pfeifer et al., 2008). This paradigm is useful because it engages regions important for affective aspects of empathy (e.g., mirror neuron portion of IFG, insula, and amygdala).

### **Neural Mechanisms of Experiential and Autonomic Response to Others' Suffering**

In addition to resting HRV, researchers are also interested in phasic changes in parasympathetic regulation in relation to emotion and behavior. Recently, researchers have started quantifying dynamic patterns of change that capture how HRV unfolds over the course of emotional events (Brooker & Buss, 2010; Burt & Obradovic, 2013; Miller et al., 2013). In our own work with children, we identified a specific pattern of nonlinear and dynamic HRV change characterized by early HRV suppression followed by HRV recovery over the course of an empathy induction video (Miller, Nuselovici, & Hastings, 2016). Furthermore, this dynamic parasympathetic response positively correlated with children's self-reported empathic sadness and longitudinally predicted more prosocial behaviors two years later. Other research on adolescents have found that a similar pattern of dynamic HRV change predicts more prosocial

behavior (Cui et al., 2015). Early HRV suppression may be important for orienting to others' distress and needs as emotionally salient. Subsequent HRV rebound or augmentation may help individuals perceive the social environment as safe, and promote calm, social engagement important for other-oriented emotions like compassion. These findings suggest that a specific pattern of flexible parasympathetic regulation is related to prosociality.

The evidence for sympathetic nervous system involvement in prosociality is more mixed (Hastings et al., 2014; Miller, in press), but some studies suggest that increased sympathetic enervation may contribute to self- rather than other-oriented responses (Fabes et al., 1993; Kalvin, Bierman, & Gatzke-Kopp, 2016). Dynamic measures of sympathetic nervous system activity in relation to prosociality have not yet been examined.

Researchers have argued the need for more empirical studies of central and autonomic nervous system integration (Critchley, Corfield, Chandler, Mathias, & Dolan, 2000), but few studies have examined this integration in response to emotionally laden stimuli. In research on empathy for pain, studies have linked regions implicated in affective aspects of empathy (e.g., anterior insula, anterior cingulate cortex) to sympathetic nervous system activity (Azevedo et al., 2013; Gu et al., 2015). However, studies have not examined neural regulation of parasympathetic activity in response to the emotional suffering of others. This is surprising given that the parasympathetic nervous system is considered to be a key part of a social engagement system (Porges & Furman, 2011). In addition, researchers have yet to incorporate measures of subjective experience in studies of central and autonomic integration.

Taken together, one interpretation of the existing limited literature is that neural regions important for affective empathy are implicated in the control of autonomic responding to others' suffering. As described earlier, empathy is multifaceted, and in addition to affective processes,

also involves more cognitive and volitional processes of representing another person's beliefs, goals, and knowledge (Decety & Jackson, 2006). Research suggests separate circuitry for cognitively imagining other's pain or taking another person's perspective versus the affective component of sharing others' feelings (Preckel et al., 2017; Shamay-Tsoory, 2011). Cognitive aspects of empathy have been related to activity in the medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), posterior superior temporal sulcus (STS), the right temporoparietal junction (TPJ) and temporal poles (Decety & Jackson, 2006; Shamay-Tsoory, 2011). The right TPJ appears to be particularly important for detecting and representing the mental states of others (Saxe & Kanwisher, 2003; Saxe & Powell, 2006, Schurz, Radua, Aichorn, Richlan, & Perner, 2014). The right TPJ is also involved in self-other distinction, important for avoiding overlap of the representations of one's own feelings and the feelings of the other person (Decety & Grezes, 2006).

Neuroscience has emphasized the distinctiveness of the neural circuits underlying affective and cognitive aspects of empathy as well as compassion (Decety & Jackson, 2006; Lamm et al., 2017; Preckel et al., 2017), but psychological models of empathy have long considered these aspects to be deeply interactive (Zaki & Ochsner, 2012). Interestingly, cognitive perspective taking has been linked to experiential and physiological aspects of empathy and feeling concern for others (Batson, Fultz, & Schoenrade, 1987; Buffone et al., 2017). Given the role of the right TPJ in perspective taking with self-other distinction, the functioning of this neural region may have implications for affective empathy and compassion in addition to social cognitive processes, thus blurring the line between neural circuits dedicated to cognitive empathy, affective empathy, and compassion.

Neuroscience models proposing distinct circuitry for cognitive and affective aspects of empathy are largely based on fMRI research. This methodology, however, cannot determine whether activity in the brain regions described above is *causally* necessary for affective or cognitive processes. Transcranial magnetic stimulation (TMS) offers a promising method for addressing this concern (Hetu, Taschereau-Dumouchel, & Jackson, 2012; Lamm & Majdandzic, 2015). TMS is based on Faraday's principle that electric current passed through one coil produces a magnetic field that can induce electric current in a nearby coil. TMS machines rapidly pass electrical current through a coil to produce a magnetic field that can alter cortical electrical activity (Luber, Peterchev, Nguyen, Sporn, & Lisanby, 2007). Thus, TMS is a non-invasive method of stimulating neurons in the cortex resulting in a temporary interference of that region's normal processing. Repetitive stimulation (rTMS) involves applying magnetic pulses at a set frequency to induce a temporary "virtual lesion" in a targeted region of the brain that outlast the application of TMS (Walsh & Cowey, 2000). The frequency of rTMS influences the kind of modulatory effects of rTMS on offline cortical activity. Low frequency stimulation (e.g., 1 Hz) results in temporary inhibition of neuronal excitability (Valero-Cabre, Payne, & Pascual-Leone, 2007) potentially via long-term depression (LTD) of synaptic activity (Dudek & Bear, 1992). One of the current studies used low-frequency rTMS to experimentally test whether the right TPJ is causally involved in affective aspects (experiential and physiological) of responding to others' emotional suffering.

### **Motivation-related Brain Regions, Emotion Regulation, and Prosociality**

Motivational frameworks are important for understanding prosocial behaviors (Davidov et al., 2016). At the neural level, circuitry important for motivational processes, like the nucleus accumbens and ventral tegmental area, are implicated in prosociality. For example, people show

activation in these regions when donating to charities (Harbaugh, Mayr, & Burghart, 2007; Moll et al., 2006) and feeling compassion for others (Kim et al., 2009). However, these regions have also been linked to less empathy at the trait level (Chakrabarti et al., 2006), and have been implicated in emotions and behaviors that are contrary to prosociality, like psychopathy (Decety, Chen, Harenski, & Kiehl, 2013), competition (Hein, Silani, Preuschoff, Batson, & Singer, 2010), and schadenfreude (i.e., deriving pleasure from the pain or misfortunes of others) (Takahashi et al., 2009).

In neurobiological research in general, such mixed findings are quite common. This is likely in part due to the links between neurobiology and prosociality being person-dependent (Miller, in press). That is, there are features of individuals that may change the meaning or interpretation of activity in different neurobiological systems. Emotion regulation strategies like cognitive reappraisal are potentially one such feature. Cognitive reappraisal refers to reinterpreting one's emotional response to modify its intensity, duration, or valence (Gross & John, 2003). Observing others' needs or distress can engage motivation processes, like encoding value, salience detection, and effortful drive (Bromberg-Martin, Matsumoto, & Hikosaka, 2010). How the observer regulates their emotions will influence subsequent behaviors, potentially determining whether motivational processes push one to approach or avoid helping others. Thus, we should expect that activation in motivation-related brain regions in response to others' emotions may underlie both more and less prosocial behavior, depending on ability to effectively regulate emotions. Whether cognitive reappraisal interacts with motivation-related neural circuitry to predict prosocial behavior has not, to our knowledge, been examined.

## Overview of Studies

This dissertation had three main goals. The first goal was to examine the relation between resting HRV and neural reactivity to emotional faces in brain regions important for increasing affective arousal and engagement. The second goal was to test whether the right TPJ, a neural region critical for social cognition, might also be causally necessary for experiential and autonomic response to others' emotional suffering. The third goal was to investigate whether neural reactivity to sad faces in motivation-related regions would predict more and less prosociality depending on the tendency to use cognitive reappraisal.

This dissertation used data from two different projects. The first and second studies were part of a project on the neurobiology of social-emotional responding in adults. Participants initially visited the UC Davis Imaging Research Center in Sacramento to undergo MRI, which included an observation-imitation of emotional faces fMRI paradigm. During a second session on a separate day, participants visited the Center for Mind and Brain in Davis so that we could obtain autonomic data (e.g., resting HRV) and observe potential effects of TMS on experiential and physiological responses to a sadness induction film clip. The goal of Study 1 was to examine the association between resting HRV and neural reactivity to observation and imitation of emotional faces. The hypothesis was that higher resting HRV would negatively correlate with neural reactivity in the mirror neuron system, insula, and amygdala, and that this would be true for observation, but not imitation, of emotional faces. The goal of Study 2 was to use TMS to examine the causal role of the right TPJ on experiential and autonomic aspects of responding to others' suffering. The hypothesis was that TMS to the right TPJ would decrease parasympathetic flexibility and compassion, and increase sympathetic nervous system activity and hostile feelings in response to others' emotional suffering.

Study 3 presents data on adolescents from the California Families Project. Adolescents participated in an fMRI emotional face processing task and reported on their subjective sadness during the task. Adolescents also reported on their own tendencies to use cognitive reappraisal and to engage in prosocial behavior. The goal of this study was to test whether neural response in motivation-related brain regions during emotional face processing interacts with cognitive reappraisal to predict prosocial behavior. The hypothesis was that heightened mesolimbic responding would predict more and less prosocial behavior in participants who use reappraisal more and less often, respectively.

Collectively, this program of work serves to advance our understanding of the neurobiological and psychological processes contributing to prosociality. Adopting a multimethod approach should be valuable for integrating across theoretical frameworks (e.g., polyvagal theory and mirror neuron system perspective of empathy) to test novel hypotheses about the biological organization underlying prosociality. Furthermore, this dissertation aims to provide causal evidence for neurobiological models of prosocial emotions, like empathy and compassion, that are almost completely based on correlational evidence. This is a critical step in progressing our understanding of how humans are wired to feel concern for others' suffering. In addition, despite the arguments for the importance of looking at intersystem processes between the central and autonomic nervous system, little experimental research has been conducted in humans. This project provides novel methodological approaches for experimental and correlational studies of central and autonomic nervous system communication, which could potentially be applied in research areas outside of prosociality as well....

## CHAPTER 2

### STUDY 1: RESTING HEART RATE VARIABILITY NEGATIVELY PREDICTS NEURAL REACTIVITY TO EMOTIONAL FACES

Affective empathy, or the capacity to share in or become emotionally affected by the emotions of others (Decety, Norman, Berntson, & Cacioppo, 2012; Singer & Lamm, 2009), is implemented by a complex network in the brain and body (Decety, 2015; Hastings, Miller, Kahle, & Zahn-Waxler, 2014). For example, neuroscience suggests that neural regions like the insula, anterior cingulate cortex, amygdala, thalamus, and inferior frontal gyrus are activated when perceiving and affectively responding to the emotions of others (Decety, 2015; Lamm, Rütgen, & Wagner, in press). In particular, the mirror neuron system is important for sensorimotor resonance with others' actions (e.g., emotional facial expressions), and the insula and amygdala are part of a salience detection network that is important for increasing arousal (Lamm & Majdandzic, 2015). The processes supported by these neural regions are potential starting points to empathy (Lamm & Majdandzic, 2015), and are also believed to be important for instantiating related visceral processes (Decety & Jackson, 2006; Preston & de Waal, 2002). In addition to phasic changes in the body, autonomic activity at rest, particularly in the vagus nerve system, is thought to be important for prosociality (Hastings et al., 2014; Porges, 2011). Considering that empathy arises from the integration of these brain-body processes, there is a need for more multilevel investigations of neurobiology (Hastings et al., 2014). Although there are conceptual frameworks of empathy that outline how the central nervous system regulates phasic changes in the autonomic nervous system (Preston & de Waal, 2002), few have considered brain-body interactions in the opposite direction. That is, does resting vagus nerve activity predict neural responses to others' emotions?



Resting vagus nerve activity is widely regarded as a physiological correlate or marker of effective self-regulation (Beauchaine & Thayer, 2015; Porges, 2011). Vagal activity may also relate to other functions that are related to self-regulation, potentially including threshold for increasing arousal and engagement with others' emotions (i.e., empathic arousal) (Hastings, Zahn-Waxler, Robinson, Usher, & Bridges, 2000; Miller, Kahle, & Hastings, 2017). Studies of vagal activity in relation to neural mechanisms of social-affective processing could provide further evidence for this perspective. This study aimed to examine the links between resting vagal activity as measured by heart rate variability (HRV) and response to emotional faces in brain regions that play a key role in sensorimotor resonance, detection of salient events, and affective arousal – processes that likely serve as early pathways to empathy (Lamm & Majdandzic, 2015).

### **Resting HRV**

The vagus nerve exerts parasympathetic influence over cardiac activity to provide efficient metabolic regulation in safe contexts (Porges, 2007), and vagus nerve activity can be approximated via HRV (Laborde, Mosley, & Thayer, 2017). The majority of research on HRV is guided by two theoretical perspectives. First, the neurovisceral integration model proposes that HRV is a peripheral marker of prefrontal inhibition of threat-related subcortical activity, and that this mediates individual differences in effective cognitive control and emotional self-regulation (Beauchaine & Thayer, 2015; Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012). In accordance with this perspective, neuroimaging research suggests that HRV is associated with activity and coupling of regions important regulation of emotion, including the medial prefrontal cortex, anterior cingulate cortex, and amygdala (Thayer et al., 2012). Second, polyvagal theory (Porges, 2011) proposes that high HRV indicates high vagal activity that contributes to calm

physiological states important for positive social engagement behaviors (Porges, 2003), including accurate recognition of others' emotions (Quintana, Guastella, Outhred, Hickie, & Kemp, 2012), positive emotional experiences and feelings of social connectedness (Kok & Fredrickson, 2010), and social support seeking (Geisler, Kubiak, Siewert, & Weber, 2013). Taken together, there is a substantial literature linking higher resting HRV to positive social-emotional outcomes. Conversely, individuals with lower resting HRV may be more susceptible to emotion dysregulation and social problems due to hypervigilance in safe contexts (Beauchaine & Thayer, 2015; Porges, 2011).

Resting HRV indicates one's preparedness for responding to different kinds of environments. Thus, resting HRV reflects a tonic state of vigilance versus calm that is prior to the need for active regulation and engagement with social and emotional events. This point is not often explicitly stated in the literature, but has important implications for how we interpret resting HRV. In addition to marking one's capacity to put effective regulation into play when needed, like seeking social support and exerting impulse control when experiencing negative emotions (Geisler et al., 2013; Williams et al., 2015), high HRV may also mark a resting state that is less susceptible to negative emotional reactivity to environmental challenge (i.e., higher threshold for arousal) (Hastings et al., 2000; Porges, 1992). If resting HRV marks the functional integrity of prefrontal-subcortical inhibitory circuits that are important for evaluation of safety, then individuals with higher resting HRV may require stronger environmental cues to capture and hold their attention, including attention to other's displays of emotions. Conversely, individuals with low resting HRV may be more vigilant and have trouble disengaging with others' emotions. In accord with this perspective, higher HRV is associated with inhibition of attention to fearful faces (Park et al., 2012), whereas HRV is associated with faster attentional

engagement and slower disengagement with fearful faces (Park et al., 2013) and stronger fear-potentiated startle (Melzig, Weike, Hamm, & Thayer, 2009).

In addition, we have speculated that considering HRV as a correlate of threshold for increasing arousal could help explain recent findings that moderate to moderately high HRV, rather than low or extremely high values, predicts greater prosociality (Clark, Skowron, Guiliano, & Fisher, 2016; Kogan et al., 2014; Miller et al., 2017). When faced with the needs of others, lower resting HRV may reflect a lack of effective emotion regulation skills and lower threshold for experiencing strong arousal that undermines other-oriented prosocial behavior. Conversely, high resting HRV may reflect a higher threshold for salience detection and arousal, or a tendency to inhibit arousal, to mild or moderate emotional stimuli (Hastings, Zahn-Waxler, & McShane, 2006; Miller, in press; Miller et al., 2017). Thus, from a neurovisceral integration perspective, high HRV may reflect strong prefrontal inhibition of subcortical circuitry that constrains arousal in response to others' emotions.

### **Neural Regions Associated with Affective Aspects of Empathy**

At the biological level, stronger evidence for this perspective could come from measuring neural responses to social-emotional stimuli in brain networks that are key starting points for increasing arousal and attentional engagement. For example, the mirror neuron system in the inferior frontal gyrus, insula, and amygdala are neural regions commonly implicated in affective aspects of empathy and emotional face processing (Decety, 2015; Flourney et al., 2016; Iacoboni, 2009). Mirror neurons are active during observation, execution, and imitation of actions and are primarily contained in the pars opercularis or dorsal section of the inferior frontal gyrus (IFG) and adjacent premotor cortex (PMC) (Carr, Iacoboni, Dubeau, Mazziota, & Lenzi, 2003; Iacoboni, 2009; Rizzolatti & Craighero, 2004; van der Gaag, Minderaa, & Keysers, 2007).

Although activation in these regions in response to emotional faces has been associated with empathy measures (Horan et al., 2014; Pfeiffer, Iacoboni, Mazziota, & Dapretto, 2008), mirror neurons likely do not reflect empathy per se (i.e., understanding and sharing another's emotion), but rather indicate sensorimotor resonance processes (i.e., mapping another's motor actions onto one's own sensorimotor system) that can play a role in facilitating empathic arousal (Lamm & Majdandzic, 2015). The insula and amygdala are part of a salience network in the brain that supports detection and attentional engagement to important events (Adolphs, 2010; Menon & Uddin, 2010), including rapid processing and prioritizing of emotional cues from others (Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2005; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002; Straube & Miltner, 2011). As such, the insula and amygdala have been linked to affective responding to emotional facial expressions and first-hand experiences of emotion (Botvinick et al., 2005; Wicker et al., 2003). Taken together, the mirror neuron system supports sensorimotor resonance, whereas the amygdala and insula are critical for affective responding to others' emotions. Thus, activation in these systems are quick starting points for engaging with the emotions of others (Lamm & Majdandzic, 2015).

Studies that combine resting and task-based measures of HRV with neuroimaging have focused on neural activity across a number of different contexts like social stress (Ahs, Sollers, Furmark, Fredrikson, & Thayer, 2009), effortful cognitive and motor control (Critchely et al., 2003), film and recall based emotion induction (Lane et al., 2009), and functional connectivity at rest (Chang et al., 2013; Sakaki et al., 2016). Overall, however, surprisingly few studies have examined the relation between resting HRV and neural response to the emotional expressions of others. One study found that resting HRV was differentially related to caudate nucleus activity during an emotional face-matching task in social anxiety disorder versus healthy controls

(Gaebler, Daniels, Lamke, Fydrich, & Walter, 2013). Whether resting HRV is linked to neural mechanisms of evoking affective arousal in response to other's emotions has not been studied.

The current study focused on the frontal mirror neuron system, insula, and amygdala response to observing and imitating emotional faces. This observation-imitation paradigm has previously been used to study affective aspects of empathy, and has been shown to engage these regions of interest (Carr et al., 2003; Horan et al., 2014; Pfeifer et al., 2008). This paradigm is particularly useful for identifying mirror neuron regions, as not all IFG and premotor neurons shows mirror neuron properties (Kilner & Lemon, 2013). However, some researchers have argued that passively viewing emotional faces is likely a more appropriate condition than voluntary imitation of facial expressions for assessing affective engagement (Baird, Scheffer, & Wilson, 2011; Leslie, Johnson-Frey, & Grafton, 2004). Automatic imitation during passive observation may play a role in empathy (Jacoboni, 2009). However, voluntary imitation of expressions may have more in common with processes not specific to empathic arousal in response to other's emotions (Baird et al., 2011). In other words, when observing someone expressing sadness (for example), neural responses in the regions previously listed likely support spontaneous increases in affective engagement and arousal important for empathy. Conversely, increased activation in these regions during voluntary imitation may reflect processes related to executing goal-directed actions.

### **Current Study**

The current study examined the relation between resting HRV and frontal mirror neuron system, insula, and amygdala response to emotional faces using a common observation-imitation task (Carr et al., 2003; Horan et al., 2014; Pfeifer et al., 2008). Based on past findings linking these neural regions to sensorimotor and affective aspects of processing emotional expressions in

others, and the putative role of these processes in increasing empathic arousal, we expected higher HRV to be associated with less activity in frontal mirror neuron regions, insula, and amygdala.

## **Methods**

### **Participants**

Forty-one ethnically diverse young adults (11 males; Mean age = 21.47,  $SD = 3.33$ ) between the ages of 18 and 31 were recruited for this study. All participants were healthy, had normal or corrected-to-normal vision, and were right-handed. Participants provided informed consent and were compensated for their participation. Neuroimaging data from 7 participants were omitted from analyses due to excessive movement. One additional participant did not return for the second portion of the study to provide HRV data. As a result, the final sample consisted of 33 participants (8 males; Mean age = 21.29,  $SD = 2.99$ ).

### **Procedure**

Each participant took part in two sessions that were on average 18 days apart ( $SD = 12.79$ ). At the first session, participants underwent structural and functional magnetic resonance imaging (MRI). The fMRI paradigm asked participants to observe and imitate pictures of emotional faces. At the second session, disposable electrodes were attached to the chest to collect electrocardiograph (ECG) data while participants sat quietly by themselves for 5 minutes. This data was used to quantify resting HRV measures.

### **fMRI Task**

The fMRI paradigm was based on tasks previously used in the literature to measure mirror neuron system activity in response to observing and imitating emotional faces (Carr et al., 2003; Horan et al., 2014; Pfeiffer et al., 2008). Face stimuli were projected onto a screen placed

at the foot of the table and participants viewed them using a mirror attached to the head coil. Stimulus pictures were selected from the NimStim set of facial expressions (Tottenham et al., 2009) and included ethnically diverse men and women expressing 4 different emotions (angry, happy, neutral, or sad). Six sets of face stimuli were assembled. Each set included 8 pictures of faces (4 men and 4 women). Within each set, each emotion was presented twice – once by a man and once by a woman. The faces within each set were presented in a fixed order across participants. Each set was presented twice, comprising 12 blocks. Within each block, faces were presented for 4 s each (32 s blocks). Each block was preceded by a 4 s screen instructing participants to either “imitate” or “observe” the expressions on the faces. Each block was followed by a 16 s screen presenting a white fixation cross against a black background. The order of imitation and observation blocks was fixed across participants.

### **fMRI Data Acquisition**

Neuroimaging data were acquired using a Siemens 3T Tim Trio Scanner with a 32-channel head coil. Functional images were acquired using a gradient echo pulse sequence with 2000 ms repetition time (TR), 27 ms echo time (TE), 80 degree flip angle, 3.5 x 3.5 x 3.5 mm voxels, 35 slices, and 224 mm field-of-view (FOV). The first two volumes were discarded to allow for magnet stabilization. A high resolution structural image was obtained using a MPRAGE pulse sequence with a 2500 ms TR, 4.33 ms TE, 7 degree flip angle, 0.9 x 0.9 x 0.9 voxels, 208 slices, and 243 mm FOV.

### **fMRI data processing and analysis**

Analysis of Functional and Neural Images (AFNI) software was used to preprocess and analyze the fMRI data (Cox, 1996). Preprocessing included volume registration to the first volume, spatial smoothing with a 6 mm half-maximum Gaussian kernel, scaling of blood oxygen

level-dependent signal intensity to percentage of signal change, co-registration with the structural images and warping to the Montreal Neurological Institute (MNI) template within AFNI.

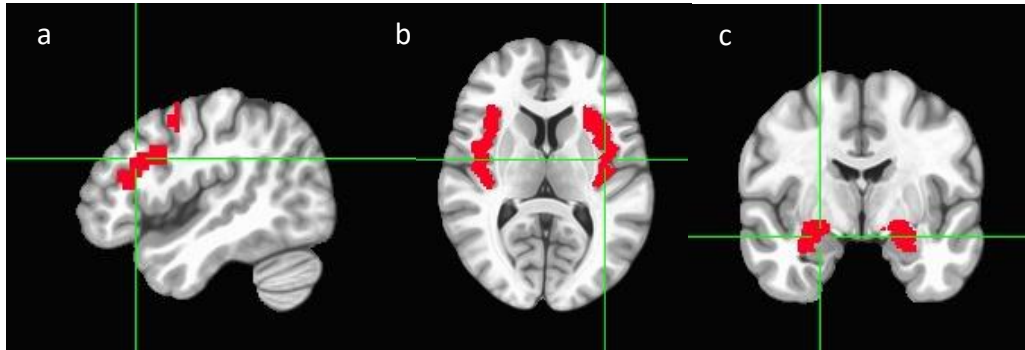
Volumes with head motion greater than 0.3 mm from the previous volume were censored from the data, and 7 participants for whom more than 25% of volumes were censored were excluded from further analyses.

A general linear model was used at the single subject level to identify beta values. For the observation and imitation of emotional faces, we modeled a 32 s boxcar plot convolved with the hemodynamic response function. Fixation was treated as the implicit baseline. AFNI's 3dClustSim (version AFNI\_16.3.05, 2016) was used to identify 39 voxels as the minimum cluster size at a voxel-wise threshold of  $p = .001$  to obtain an overall alpha of  $p < .05$ . We used a priori regions of interest (ROI) to test the relations between measures of HRV and neural activity. We used the CA\_ML\_18\_MNIA atlas in AFNI to create anatomically defined ROIs in the right and left amygdala and insula (see Figure 1). We used a conjunction analysis to reveal areas that showed significant activation in response to both observation and imitation of emotional faces, thus displaying mirror neuron like properties. Areas in the left and right IFG (pars opercularis and pars triangularis), and extending into the right premotor cortex, were defined as ROIs in the conjunction analysis (see Figure 1.1). The contrasts of interest were observation minus baseline (i.e., fixation) and imitation minus baseline (i.e., fixation). Mean percent signal change values (betas) were extracted from each ROI for each contrast for each subject. We tested correlations between these beta values and HRV measures.



Figure 1.1

*Masks of the Regions of Interest*



**Note.** Bilateral (a) inferior frontal gyrus (and right premotor cortex), (b) insula, and (c) amygdala

## HRV data

On a separate day from the MRI visit, ECG data were collected in the laboratory using MindWare Technologies ambulatory monitors (Gahanna, Ohio). These data were collected at a sampling rate of 500 Hz and were wirelessly transmitted to a computer for later inspection and editing of artifacts. Frequency and time domain measures of HRV were quantified from the 5 min baseline period. For the spectral analysis of the ECG data, the high frequency band-pass for HRV was set to range from .12 to .40 Hz. The mean raw power ( $\text{ms}^2$ ) and log-transformed values of high frequency HRV [ $\ln(\text{ms}^2)$ ] were used as frequency domain measures of vagal activity. From here on out, we use the terms HF power to refer to the raw power values and respiratory sinus arrhythmia (RSA) to refer to the log-transformed values of HRV. These measures reflect parasympathetic (vagal) modulation of cardiovascular activity. The standard deviation of interbeat intervals (SDNN) and root mean square of successive differences (RMSSD) were used as time domain measures of vagal activity. RMSSD and short term measurements of SDNN have been used as measures of parasympathetic activity, and these time domain measures of HRV may be less sensitive than frequency domain measures to changes in breathing rate (Penttila et al., 2001). Inspection of the data showed one extreme outlier value for HF power (greater than the mean by 1.5 times the difference between quartile 1 and 3). This value was winsorized to maintain the rank-order of HF power within the sample by bringing it down to the second highest value and adding one.

## Results

Descriptive statistics for the HRV and ROI betas are presented in Table 1.1. In line with previous research (Carr et al., 2003), imitation of emotional faces elicited stronger activity in many of these regions (bilateral IFG and insula) than passive observation (all  $|t| > 3.94$ ,  $p < .001$ ).

Right amygdala activity did not differ between observation and imitation ( $t = .81, p = .419$ ), and there was a trend level difference for greater left amygdala activation during imitation compared to observation ( $t = 1.76, p = .088$ ). As expected, all of the HRV measures were highly correlated with each other ( $r$ 's ranging from .80 to .94, all  $p < .001$ ). All of the ROI beta values for the observation vs fixation contrast were positively correlated with each other ( $r$ 's ranging from .36 to .85, all  $p < .043$ ). The correlations between the ROI beta values for the imitation vs fixation contrast were more mixed and are presented in Table 1.2.

Table 1.1

*Descriptive Statistics*

Variable	Mean	SD
RSA	6.39	1.26
HF power	1045.23	1038.83
SDNN	64.56	25.88
RMSSD	45.64	25.17
Observation R IFG	.23	.23
Observation L IFG	.20	.22
Observation R Insula	-.05	.12
Observation L Insula	-.05	.10
Observation R Amygdala	.11	.16
Observation L Amygdala	.07	.12
Imitation R IFG	.48	.30
Imitation L IFG	.31	.35
Imitation R Insula	.15	.18
Imitation L Insula	.10	.20
Imitation R Amygdala	.17	.32
Imitation L Amygdala	.16	.25

Note. RSA, respiratory sinus arrhythmia [ $\ln(\text{ms}^2)$ ]; HF power, high frequency power ( $\text{ms}^2$ ); SDNN, standard deviation of interbeat intervals; RMSSD, root mean square of successive differences.

Table 1.2

*Correlations Between ROIs for Imitation versus Fixation Contrast*

Variable	1	2	3	4	5
1. Right IFG	1				
2. Left IFG	.74***	1			
3. Right Insula	.61***	.50**	1		
4. Left Insula	.62***	.59***	.90***	1	
5. Right Amygdala	.23	.22	.26	.45**	1
6. Left Amygdala	.19	.29	.55**	.69***	.55**

Note. \*\* $p = .001$ , \*\*\* $p < .001$ .

Bivariate correlations were used to examine the links between parasympathetic measures and neural activation during observation and imitation of emotional faces (see Table 1.3). Of 24 correlations between HRV and activation during observation, 7 were significant ( $p < .05$ ) and 2 approached significance ( $.05 < p < .10$ ), with all correlations showing an inverse association between HRV and neural activation. For the frequency domain measures of HRV, participants with higher resting RSA demonstrated less activation in the right IFG/premotor cortex ( $r = -.36$ ,  $p = .040$ ) and left insula ( $r = -.37$ ,  $p = .035$ ) when observing emotional faces. There were also trends for RSA negatively correlating with left amygdala ( $r = -.30$ ,  $p = .093$ ) and right insula ( $r = -.32$ ,  $p = .073$ ) response to observing emotional faces. Conversely, resting HF power was not associated with neural response to observation of emotional faces (all  $p > .124$ ). For the time domain measures of HRV, there were statistically significant negative associations between resting SDNN and right IFG/premotor cortex ( $r = -.35$ ,  $p = .044$ ), left amygdala ( $r = -.35$ ,  $p = .047$ ), and right ( $r = -.36$ ,  $p = .039$ ) and left insula ( $r = -.44$ ,  $p = .010$ ) in response to observing emotional faces; baseline RMSSD values were negatively associated with left insula ( $r = -.38$ ,  $p = .031$ ). None of the 24 correlations between HRV and neural response to imitation of emotional faces were significant (all  $p > .113$ ).

Table 1.3

*Correlations Between HRV Measures and ROI betas for Observation and Imitation of Emotional**Faces*

	RSA	HF power	SDNN	RMSSD
Observation R IFG	-.36*	-.22	-.35*	-.22
Observation L IFG	-.21	-.15	-.23	-.11
Observation R Insula	-.32 <sup>†</sup>	-.13	-.36*	-.19
Observation L Insula	-.37*	-.28	-.44**	-.38*
Observation R Amygdala	-.14	.01	-.29	-.01
Observation L Amygdala	-.30 <sup>†</sup>	-.14	-.35*	-.20
Imitation R IFG	.07	.07	.00	.04
Imitation L IFG	.28	.22	.14	.18
Imitation R Insula	.15	.07	.21	.08
Imitation L Insula	.12	-.04	.15	-.03
Imitation R Amygdala	-.04	.05	.18	-.04
Imitation L Amygdala	.03	-.02	.16	-.08

Note. <sup>†</sup> $p < .10$ , \*  $p < .05$ , \*\* $p = .01$

## Discussion

Current perspectives suggest that resting HRV is as a physiological measure of capacity for effective emotion regulation (Beauchaine & Thayer, 2015; Porges, 2011), but resting HRV may also reflect threshold for reactive empathic arousal and attentional engagement in response to other's emotional cues (Hastings et al., 2006; Miller, in press; Miller et al., 2017). The current paper tested the hypothesis that higher resting HRV would be associated with less neural response to other's emotional expressions in the mirror neuron system (IFG and premotor cortex), insula, and amygdala. This study extends previous work on the link between HRV and prefrontal inhibition of subcortical circuitry (Ahs et al., 2009; Chang et al., 2013; Critchley et al., 2003; Lane et al., 2009; Sakaki et al., 2016) and is the first to examine the link between resting HRV and mirror neuron system activity in response to emotional faces. High resting HRV was linked to less activation in response to observation, but not imitation, of emotional faces in neural regions implicated in sensorimotor resonance, saliency, and arousal. This pattern of findings provides novel insights into our understanding of resting HRV.

Prior to any need for active regulation and engagement with social or emotionally evocative events, effective prefrontal-subcortical inhibition that contributes to increased vagal regulation at rest creates a calm, soothed physiological state. Conversely, disinhibited subcortical circuitry in safe contexts as indexed by low resting HRV contributes to hypervigilant states (Beauchaine & Thayer, 2015; Thayer et al., 2012). When faced with emotional stimuli, the degree of safety detection versus vigilance at rest may constrain or incline neural mechanisms of engagement. These results are consistent with the possibility that resting HRV is linked to neural sensitivity to other's emotional cues, both in terms of the tendency to (a) automatically map other's emotional facial expressions onto one's own motor system, and (b)



rapidly detect and mark other's emotional facial expressions as salient events for additional processing and increasing arousal. These findings further our understanding of how resting HRV may be a peripheral measure that reflects different kinds of preparedness to attend to and become affected by emotional cues in the social environment.

The present findings contribute to brain-body models of empathic responding. Current models of empathy primarily focus on how neural processes might instantiate visceral processes (Decety, 2015; Preston & de Waal, 2002). However, the present findings suggest that resting autonomic activity can also have implications for neural reactivity in response to others' emotions. In addition, the neurovisceral integration model is one of the dominant perspectives guiding research on resting HRV and emotional functioning. To our knowledge, the current study is the first to consider this model in relation to emotional face processing.

To be clear, we are not interpreting activation across neural regions of interest as direct evidence for empathy (understanding and isomorphic sharing of another's emotion) (Decety et al., 2012; Singer & Lamm, 2009), but rather as neural pathways that can lead to arousal and attentional engagement with the emotions of others. In addition, we do not contend that lower resting HRV and related increased activation in the mirror neuron system, insula, or amygdala are necessarily adaptive or healthy at the state or trait level. Mirror neuron system response to emotional faces is typically associated with positive functioning in the social domain (Dapretto et al., 2006; Pfeifer et al., 2008), and the insula and amygdala are critical brain areas for affective aspects of empathy (Decety, 2015; Singer & Lamm, 2009). However, heightened insula and amygdala response to emotional faces has also often been linked to psychopathology (Beesdo et al., 2009; Monk et al., 2008; Stein, Simmons, Feinstein, & Paulus, 2007), and higher resting HRV has generally been found to be protective (Beauchaine & Thayer, 2015; Chalmers,

Quintana, & Abbot, 2014). In addition, to the degree that lower resting HRV and related activation in sensorimotor resonance and affective engagement pathways contribute to strong empathic arousal, these physiological processes may lead to emotional states characterized by self-oriented personal distress (Batson, 2009). Thus, it is unclear from our study whether heightened neural response reflects appropriate or maladaptive engagement with the emotions of others. Further research is necessary to address whether response to emotional faces in these brain regions might mediate the relation between resting HRV and social-emotional outcomes.

One strength of this study was the inclusion of a range of HRV measures, and there was some variability in the link with neural activity depending on the specific measure of HRV. This was somewhat surprising given the strong correlations among the different HRV measures. RSA and SDNN were correlated either significantly or at the trend level with activation in 4 out of 6 ROIs (Right IFG, bilateral insula, and left amygdala) for observation of emotional faces. Conversely, RMSSD was only associated with left insula activation and HF power was not significantly associated with beta values in any ROI. It is unclear why RSA and SDNN would show stronger relations with neural activation than HF power and RMSSD. Some previous studies that used frequency- and time-domain measures of HRV found significant links between the outcome of interest and one HRV measure but not the other (Garakani et al., 2009; Martens, Nyklicek, Szabo, & Kuper, 2008; Thayer, Friedman, & Borkovec, 1996). However, given that RSA and SDNN are frequency- and time-domain measures, respectively, it is unlikely that differences in the present study are due to the domain of HRV analysis. One potential explanation for the lack of consistency across HRV measures is the limited sample size of this study. The nonsignificant negative correlations between neural activation and HF power and

RMSSD may require greater statistical power. Further research is necessary to determine the contexts in which different HRV measures are more appropriate than others.

In addition to sample size, another limitation of the present study is the reliance on brain activation as evidence for degree of engagement with other's emotions. For example, we interpreted increased activation in mirror neuron regions (as defined by a conjunction analysis) as indication of sensorimotor resonance processes. Behaviorally, these neural processes might be expected to correspond with unconscious mimicry of facial expressions (Baird et al., 2011), but the present study did not include a measure of involuntary facial muscle action (e.g., electromyography). The present study also did not include other measures of attentional engagement (e.g., performance on a spatial cuing task using emotional faces) and arousal (e.g., skin conductance) to complement measures of insula and amygdala activation. HRV research that incorporates other kinds of measures of sensorimotor resonance, attention, and arousal with neuroimaging would provide stronger evidence for our interpretation the present results.

In conclusion, this is the first study to demonstrate an inverse association between resting HRV and activation of the mirror neuron system, insula, and amygdala in response to passive viewing of emotional faces. Activity in these brain regions has been posited as important for increasing arousal and attentional engagement with others' emotions. Thus, the present findings are consistent with the hypothesis that resting HRV may relate to threshold for increasing empathic arousal.

## CHAPTER 3

### STUDY 2: TRANSCRANIAL MAGNETIC STIMULATION OF THE RIGHT TPJ AFFECTS EXPERIENTIAL AND PHYSIOLOGICAL RESPONSES TO OTHERS' EMOTIONAL SUFFERING

Current perspectives suggest that distinct neural circuits underlie cognitive and affective components of responding to the suffering of others (Decety, 2015; Lamm, Rutgen, & Wagner, 2017; Preckel, Kanske, & Singer, 2018; Shamay-Tsoory, 2011). However, social cognitive processes play an important role in bringing about and modulating affective processes, and tasks meant to assess social cognition and emotion often recruit overlapping regions of the brain (Olsson & Ochsner, 2008). The right temporoparietal junction (TPJ), in particular, has consistently been identified as an important neural region for representing the mental states of others and self-other distinction. These aspects of social cognition contribute to how people feel and physiologically respond to others' emotions. However, research on the role of the right TPJ in instantiating affective responses to others' emotional suffering, both at the experiential and physiological level, is lacking. The current study utilized transcranial magnetic stimulation (TMS) to examine right TPJ involvement in subjective feelings and physiological responses to another's emotional suffering.

#### **Experiential Aspects of Responding to Others' Suffering**

Suffering in others can elicit a number of different responses in the observer, including sharing or resonating with the other person's feelings (i.e., empathy) and feelings of concern coupled with a desire to alleviate the other's suffering (i.e., compassion) (Decety, 2015; Goetz, Keltner, & Simon-Thomas, 2010; Singer & Klimecki, 2014). Empathy and compassion are widely believed to facilitate prosocial behaviors meant to help others (Batson, 2011; Davidov,

Vaish, Knafo-Noam, & Hastings, 2016; de Waal, 2008). However, various literatures suggest that others' suffering can also induce feelings of annoyance and aggravation, which can lead to hostility. For example, harsh and abusive parents report being more annoyed and irritated by infant cries than non-abusive parents (Frodi & Lamb, 1980); mental health workers can experience increased irritability toward others' needs as a symptom of work-related stress and burnout (Frigley, 2002); and in research on public attitudes toward mental health problems, some people report emotional reactions of anger and irritation toward depressed individuals, who experience chronic suffering (Angermeyer & Matschinger, 2004).

These reactions to others' suffering could be considered the converse of emotions like compassion. However, it is important to note the possibility that these emotions can, to some degree, simultaneously co-occur, as research suggests that oppositely valenced emotions can be activated at the same time (Berrios, Totterdell, & Kellett, 2015; Larsen & McGraw, 2011). For example, Kreibig and colleagues (2013) found that participants reported both amusement and disgust in response to emotional film clips. Researchers are typically interested in the overall self-reported levels of distinct emotions, but rarely have considered how emotions are experienced relative to each other. Further, to our knowledge, studies that have taken this approach to comparing compassion, empathy, and annoyance or irritation, have not been performed.

### **Autonomic Physiology in Response to Others' Suffering**

In addition to subjective feelings, observation of suffering in others elicits physiological changes in the parasympathetic and sympathetic branches of the autonomic nervous system (Hastings, Miller, Kahle, & Zahn-Waxler, 2014; Miller, in press). The parasympathetic nervous system downregulates physiological arousal to contribute to a calm, soothed state that is

conducive to social engagement (Porges, 2007). The sympathetic nervous system is the activating branch of the autonomic nervous system and is important for preparing the body for defensive responses to stress (Cannon, 1932). In response to emotion induction procedures, a dynamic pattern of parasympathetic activity characterized by initial decreases followed by rebound has been linked with subjective empathy, prosocial development, and control of aggression in children (Miller et al., 2013; Miller, Nuselovici, & Hastings, 2016); prosocial behavior in adolescents (Cui et al., 2015); and positive maternal caregiving (Guiliano, Skowron, & Berkman, 2015). Thus, this specific pattern of parasympathetic flexibility appears to support social engagement across different contexts, as initial decreases in parasympathetic activity might indicate orienting to others' emotions or distress via some arousal, without necessitating sympathetic activation that could motivate defensive responses, and subsequent rebound in parasympathetic activity could underlie calm, social engagement with that distress (Hastings & Miller, 2014; Miller, 2018). Researchers have not examined dynamic patterns of sympathetic nervous system activity in response to empathy induction procedures. However, there is evidence that increased sympathetic reactivity to emotional film clips might contribute to increased negativity and undermine prosocial emotions and behaviors (Fabes et al., 1993; Hastings, Miller, Kahle, & Zahn-Waxler, 2014; Kalvin, Bierman, Gatzke-Kopp, 2016). In addition, anger, which is closely related to annoyance and irritation, is typically associated with increased sympathetic and decreased parasympathetic activity (Kreibig, 2010). Taken together, flexible parasympathetic regulation and decreasing sympathetic influence have typically been associated with more prosociality. Conversely, heightened sympathetic activity coupled with inhibited parasympathetic activity increases physiological arousal and can promote negative emotionality.

## **Neural Mechanisms of Experiential and Autonomic Responding**

At the neural level, recent research has made progress in clarifying the mechanisms of empathic and compassionate responses to the suffering of others. For example, the anterior insula, anterior cingulate cortex, and amygdala are core neural regions in affective aspects of empathy (Decety, 2015), whereas compassion may involve increased recruitment of dopaminergic regions like ventral striatum, ventral tegmental area, and putamen (Preckel et al., 2018). Although less work has been done on the mechanisms of feeling aggravated by others' suffering, research on adult response to infant cry sounds suggests that annoyance and behavioral avoidance tendencies are associated with increased activation in sensorimotor information processing regions, including the posterior insula, calcarine sulcus, and fusiform gyrus (Kim, Ho, Evans, Liberzon, & Swain, 2015). However, we are unaware of any studies that consider neural processes underlying how empathy, compassion, and annoyance are experienced relative to each other.

Compared to neuroscience research on subjective experiences in empathy contexts, the neural processes that modulate autonomic response to others' suffering are less understood. In research on empathy for pain, anterior insula activation in response to images of painful stimulation has been correlated with autonomic arousal as indexed by pupil dilation (Azevedo et al., 2013) and skin conductance (i.e., sympathetic nervous system activity) (Gu et al., 2015). These findings are in line with perspectives that the insula plays an important role in modulation of autonomic reactivity to salient events (Menon & Uddin, 2010), including the distress or pain of others. However, researchers have yet to study central and autonomic processes in conjunction with experiential aspects of empathy-related responding.

## **The Role of Right TPJ and Social Cognition in Emotion**

In addition to emotional responding, top-down cognitive processes can provide understanding of someone else's thoughts, intentions, and emotions. The cognitive process of taking another person's perspective (often examined as an aspect of mentalizing, theory of mind, or cognitive empathy) (Preckel, Kanske, & Singer, 2017) has been shown to be rooted in brain networks that are separate and independent from those that support feeling empathy or compassion (Kanske, Böckler, Trautwein, & Singer, 2015; Preckel et al., 2017; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). In functional neuroimaging research, it has consistently been observed that attributing mental states to others activates a network of brain regions including the medial prefrontal cortex, temporoparietal junction (TPJ), and temporal poles (Frith, 2007; Saxe & Kanwisher, 2003). In particular, the right TPJ shows increased activation during a number of social cognition tasks, including when reading stories that involve the mental states of others (Saxe & Powell, 2006), adopting the perspective of a stranger in a painful situation (Cheng, Chen, Lin, Chou, & Decety, 2010), and attributing emotions to characters in cartoons (Völlm et al., 2006). In addition, inhibiting the right TPJ using transcranial direct current stimulation (tDCS) leads to decreased accuracy on social cognition tasks (Mai et al., 2016), and transcranial magnetic stimulation (TMS) of the right TPJ has been shown to decrease moral judgments that require thinking about the mental states of others (Young, Camprodon, Hauser, Pascual-Leone, & Saxe, 2010). Thus, multiple neuroscience methods suggest that the right TPJ is a critical neural region for inferring and reasoning about others' cognitive and emotional states (Saxe & Kanwisher, 2003; Schurz, Radua, Aichorn, Richlan, & Perner, 2014).

Given the dissociable neural systems underlying cognitive and affective components of empathy-related responding, much of the neuroscience literature has emphasized the distinctiveness of these components rather than the relations between them, whereas



psychological models of empathy and compassion consider these components to be interdependent (Zaki & Ochsner, 2012). For example, psychological research suggests that perspective-taking is one social-cognitive route to feeling empathy and compassion rather than aversive emotions (Batson, Early, & Salvarani, 1997; Vaish, Carpenter, & Tomasello, 2009). Only recently have neuroscience studies started to consider how these cognitive and affective components work together. A meta-analysis of research on empathy for pain suggested that paradigms that used more abstract visual stimuli as cues to empathize tended to elicit co-activation of regions implicated in affective aspects of empathy (e.g., anterior insula and anterior cingulate cortex) and cognitive perspective-taking, including the right TPJ (Lamm, Decety, & Singer, 2011). In addition, complex social stimuli in which people describe personal, emotionally evocative events have been shown to elicit joint activation in neural systems implicated in affective and cognitive aspects of empathy (Zaki, Weber, Bolger, & Ochsner, 2009). However, few studies have considered how these separate processes supported by distinct systems influence each other when responding to others' suffering. One dynamic causal modeling study found support for a model in which anterior insula response to others' distress inhibited left TPJ activity (although not right TPJ) and decreased performance on a theory of mind task (Kanske, Bockler, Trautwein, Lesemann, & Singer, 2016). One interpretation of this finding is that affective processes may downregulate cognitive aspects of empathy in highly emotional situations. However, top-down cognitive processes like perspective taking have also been shown to modulate emotional aspects of empathy-related responding, including facial response, subjective experience, and autonomic physiology (Batson et al., 1997; Buffone et al., 2017; Lamm, Batson, & Decety, 2007; Lamm, Porges, Cacioppo, & Decety, 2008).

Interestingly, the right TPJ has been consistently linked with distinguishing between self and other representations, or knowing that one's own affective state is due to the affective state of another person (Decety & Lamm, 2007; Lamm et al., in press; Steinbeis, 2016). One explanation for right TPJ involvement in perspective taking and self-other distinction is that the two social cognitive processes are interrelated. Self-other distinction is an important part of effectively taking another person's perspective, as empathy and compassion require affective arousal without confusion over whose feelings belong to whom (Batson, Fultz, & Schoenrade, 1987; Decety & Lamm, 2009; de Vignemont & Singer, 2006). Overlap in self-other representations may contribute to contagion of aversive affect (Decety & Lamm, 2009) as well as threat-related autonomic states (Buffone et al., 2017). Thus, perspective taking with self-other distinction is a social cognitive process that inherently regulates affective processes. However, at the neural level, the potential role of the right TPJ in modulating affective responses to others' emotional suffering, both in terms of subjective feelings and physiological regulation, has yet to be examined.

### **Transcranial Magnetic Stimulation**

The overwhelming majority of neuroscience research on empathy-related responding has used non-experimental designs and methods, such as relating brain activity during fMRI to behavioral measures. Scientists have argued for more brain stimulation studies on empathy, which could provide causal evidence to complement evidence from other neuroimaging methods (Hetu, Taschereau-Dumouchel, & Jackson, 2012). Transcranial magnetic stimulation (TMS) could provide causal evidence for the role of the right TPJ in affective processes. In addition, there is a need for more studies of central and autonomic system integration in response to others' suffering (Hastings et al., 2014), and multi-method approaches that consider neural,

autonomic, and experiential aspects of empathy-related responding have been rare. Neural modulation of autonomic reactivity to others' emotional suffering has not yet been examined using TMS.

### **The Current Study**

The current study used a multi-method approach to test whether the right TPJ is causally necessary for instantiating experiential and physiological aspects of responding to others' emotional suffering. To the extent that perspective taking and self-other distinction are (a) psychologically interdependent, (b) dependent on the right TPJ, and (c) important for other-oriented feelings and effective physiological regulation, the functioning of the right TPJ was expected to play a role in promoting feelings of empathic sadness and compassion and parasympathetic flexibility. Disruption of the right TPJ using TMS was expected to increase feelings of annoyance and irritation and decrease compassion in response to others' suffering, decrease parasympathetic flexibility, and potentially increase sympathetic nervous system activity.

### **Methods**

#### **Participants**

This study initially included 41 right-handed young adults with normal or corrected-to-normal vision (11 males; Mean age = 21.47,  $SD = 3.33$ , range = 18-31). Seven participants were dropped from further analyses due to various factors (e.g., refusing TMS, not participating in both sessions). Thus, the final sample included 34 participants (9 males; M age 20.86,  $SD = 2.75$ , range = 18-30). Individuals were screened for contraindication to TMS (Rossi et al., 2009) and were excluded from participating if they met any of the following criteria: metal in the body that could not be removed, fear of small spaces, pregnant, history of neurological disorders or

head trauma, history of seizures, significant visual or hearing impairment, developmental delays or psychiatric disorders, major medical problems, and taking prescription medications. Alcohol use was assessed using the Alcohol Use Disorders Identification Test (Babor, Higgins-Bibble, Saunders, & Monteiro, 2007), and individuals who regularly engaged in heavy/binge drinking were also excluded.

## **Procedure**

Each participant took part in two sessions that were on average 18 days apart ( $SD = 11.43$ ). In the first session participants underwent structural and functional magnetic resonance imaging (MRI). This included a theory of mind task used to localize right TPJ activity for each participant (Dodell-Feder, Koster-Hale, Bedny, & Saxe, 2011). In the second session, electrodes were attached to the chest and back to measure parasympathetic and sympathetic nervous system activity using electrocardiograph (ECG) and impedance cardiograph (ICG) signals. Participants underwent 20 minutes of repetitive TMS over the vertex (control condition) or over the right TPJ. Participants were randomly assigned to condition. After completing the TMS session, participants watched a neutral film clip, then a sadness induction film clip and reported on their subjective emotional experiences. Repetitive TMS leads to disruption of neural activity and behavioral effects that outlast the duration of TMS for roughly 50-200% of the duration of stimulation (Walsh & Cowey, 2000). Thus, the neutral and sadness film clips were presented within a 10-40 min window in which the effects of TMS should have persisted.

## **Neutral film**

To assess whether TMS over the vertex versus right TJP had differential effects on physiology in general (i.e., not specific to the sadness induction), cardiac data were recorded while participants viewed a 2 min instructional film clip mean to be neutral in content. This film

clip has been used in previous studies of emotion as a neutral baseline (Troy, Shallcross, & Mauss, 2013). The neutral film clip was presented on average 10.57 min after administration of TMS ( $SD = 3.66$ ).

### **Emotion induction procedure**

Cardiac data were recorded during a sadness induction procedure that involved watching a 2 min 39 s clip from *The Champ*, which has been used extensively to study physiological and subjective aspects of empathic sadness (Hastings et al., 2009; Marsh, Beauchaine, & Williams, 2008; Seider, Shiota, Whalen, & Levenson, 2011). This film clip presents a boy reacting to the death of his father after a boxing match, first with disbelief and then becoming increasingly sad and distressed. The video was presented on average 13.38 min after administration of TMS ( $SD = 3.54$ ). Following the video, participants were asked to rate on a 7-point likert scale ranging from 1 (Not at all) to 7 (Extremely/a great deal) the degree to which they experienced different emotions during the film clip (afraid/scared, annoyed/irritated, anxious, compassion/sympathy, happy, sad, and warmth/tenderness). The emotion terms were presented in a random order across participants. Given that sadness was the primary emotion depicted in the film clip, we used ratings of sadness as a measure of subjective empathy. To focus on empathic, compassionate, and hostile emotional responding to others' suffering, the current study focused on ratings of sad, compassion/sympathy, and annoyed/irritated.

### **MRI procedure**

At the first session, anatomical and functional MRI (fMRI) data were acquired using a Siemens 3T Tim Trio Scanner with a 32-channel head coil. A high resolution anatomical image was obtained for each participant using a MPRAGE pulse sequence with a 2500 ms repetition time (TR), 4.33 ms echo time (TE), 7 degree flip angle, 0.9 x 0.9 x 0.9 voxels, 208 slices, and

243 mm field-of-view (FOV). Functional images were acquired using a gradient echo pulse sequence with 2000 ms TR, 27 ms TE, 80 degree flip angle, 3.5 x 3.5 x 3.5 mm voxels, 35 slices, and 224 mm FOV.

We used a functional localizer to identify each participant's right TPJ. Participants underwent an fMRI task that presented false-belief stories (i.e., inferences about someone's beliefs) versus stories that required inferences about faulty information in photographs (Dodell-Feder et al., 2011). There were 2 runs of 10 trials including 5 false-belief stories and 5 false-photograph stories. Each trial consisted of a 14 s story and was separated by a 12 s fixation screen.

Each participant's data were preprocessed and analyzed using AFNI (Cox, 1996). Data were motion corrected, registered to the first volume, and smoothed using a 6 mm half-maximum Gaussian kernel. BOLD response for each trial was modeled using a boxcar regressor of 14 s. The fixation cross was treated as the implicit baseline condition. For each participant, the right TPJ was defined based on a single subject whole-brain analysis of the contrast between false-belief stories and false-photograph stories. AFNI's 3dClustSim (version AFNI\_16.3.05, 2016) was used to identify the minimum cluster size for each participant's right TPJ as a voxel-wise threshold of  $p = .001$  to obtain an overall alpha of  $p < .01$ .

### **TMS procedure**

At the second session, we used a Magstim Super Rapid TMS system with a figure-8 shaped coil air-cooled by a vacuum powered fan. Low-frequency (1 Hz) TMS was applied for 20 minutes at 100% of each participant's motor threshold. The motor threshold was determined by examining the minimum stimulator output required to elicit thumb movement for 50% of TMS pulses over the motor cortex (Varnava, Stokes, & Chambers, 2011). We used Brainsight

software (Rogue Industries) to localize TMS to the stimulation site based on each participant's anatomical data or anatomical combined with functional MRI data. For each individual in the control group, the vertex was defined as the meeting point between the left and right postcentral gyri (Ruff et al., 2006). For the right TPJ group, each participant's stimulation site was defined by their functional localizer task data coregistered with their anatomical data in native space. Brainsight was used to monitor accurate coil position during TMS for both conditions. The coil was placed tangentially against the scalp and oriented with the handle pointing posteriorly and approximately 45 degrees to the central sulcus in the right TPJ group.

### **Psychophysiological data**

ECG and ICG data obtained during the emotion induction video were processed using software from MindWare Technologies. Preejection period (PEP) was used as a measure of sympathetic nervous system activity. PEP is the time in milliseconds between cardiac ventricular depolarization and opening of the aortic valve. Ventricular depolarization was defined as the onset of the R-spike in the ECG signal and the aortic valve opening was defined as the B-point in dZ/dt signal (derived impedance signal). Shorter PEP corresponds with greater sympathetic nervous system activity. Due to not providing useable impedance data or technical problems, PEP data were missing for 4 participants in the right TPJ group and 3 participants in the control group.

We used frequency and time-domain measures of heart rate variability (HRV) as measures of parasympathetic nervous system activity. High frequency (HF) power between .12 and .40 Hz was used as a frequency domain measure of HRV. The root mean square of successive differences (RMSSD) was used as a time domain measure of HRV. Due to technical problems, HF power and RMSSD data were missing for 2 participants in the control group.

PEP, HF power, and RMSSD values were computed for the duration of the neutral film clip and in four 40 s segments of the Champ film clip. Inspection of the data showed one participant with extreme outlier values for HF power and RMSSD (greater than the mean by 1.5 times the difference between quartile 1 and 3). This participant's HRV data were winsorized to maintain the rank-order within the sample by bringing their values down to the second highest value and adding one.

### **Analyses**

We used mixed analysis of variance (ANOVA) models to examine the effects of TMS on right TPJ on experiential and physiological response to others' suffering. This included planned comparisons of the effects of TMS on subjective feelings, overall patterns of change in HF power, RMSSD, and PEP (i.e., linear vs quadratic vs cubic change), as well as the epoch to epoch changes in physiology over the course of the film. All participants with available data were used for these analyses. Two analyses were performed to examine the links between physiology and subjective feelings. First, correlations between epoch to epoch changes in physiology and subjective feelings were measured. Second, to test for links between subjective feelings and overall trajectories of physiological change, we modeled latent basis growth curves for HF power, RMSSD, and PEP. Latent basis growth curves can model nonlinear patterns of change and only require fitting an intercept and one slope parameter with two time points assigned factor loadings (Grimm, Ram, & Hamagami, 2011). We used the Tucker-Lewis Index (TLI), comparative fit index (CFI), and root mean square error of approximation (RMSEA) as model fit indices. Good model fit is indicated by TLI and CFI values higher than .95 and RMSEA values lower than .06 (Hu & Bentler, 1999). For models with good fit, the intercept (physiology at the beginning of film) and slope (change in physiology over the course of the



film) were used as predictors of subjective feelings. Maximum likelihood estimation was used to produce model parameters for analyses involving the latent-basis growth curves.

## Results

### Subjective emotional experience

Descriptive data are presented in Table 2.1. Participants who reported feeling more annoyed/irritated in response to the sadness induction reported less compassion/sympathy ( $r = -.60, p < .001$ ) and sadness ( $r = -.45, p = .008$ ). Ratings of compassion/sympathy and sadness were positively correlated ( $r = .56, p = .001$ ). Although the other emotion ratings are not the focus of the current study, it should be noted that they were not correlated with annoyance/irritation, compassion/sympathy, or sadness (all  $p > .150$ ). This could be interpreted as evidence that the other emotion ratings are less tied to empathy-related responding in this task, and justification for focusing on reports of feeling annoyance/irritation, compassion/sympathy, and sadness (empathy).

To analyze the effect of TMS site on subjective emotion, we conducted a 2 (group: right TPJ versus vertex) x 3 (emotion: annoyed/irritated vs compassion/sympathy vs sad) mixed ANOVA. Mauchly's test showed that the assumption of sphericity had been violated ( $\chi^2(2) = 15.27, p < .001$ ). Thus, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ( $\epsilon = .72$ ). There was a significant main effect of emotion,  $F(1.44, 46.08) = 105.00, p < .001$ , partial  $\eta^2 = .77$ . For the whole sample, participants reported more compassion/sympathy and sadness relative to annoyance/irritation (both  $p < .001$ , partial  $\eta^2 = .80$ ), but did not differ in their ratings of compassion/sympathy and sadness,  $F(1, 32) = .59, p = .447$ , partial  $\eta^2 = .02$ .

Table 2.1

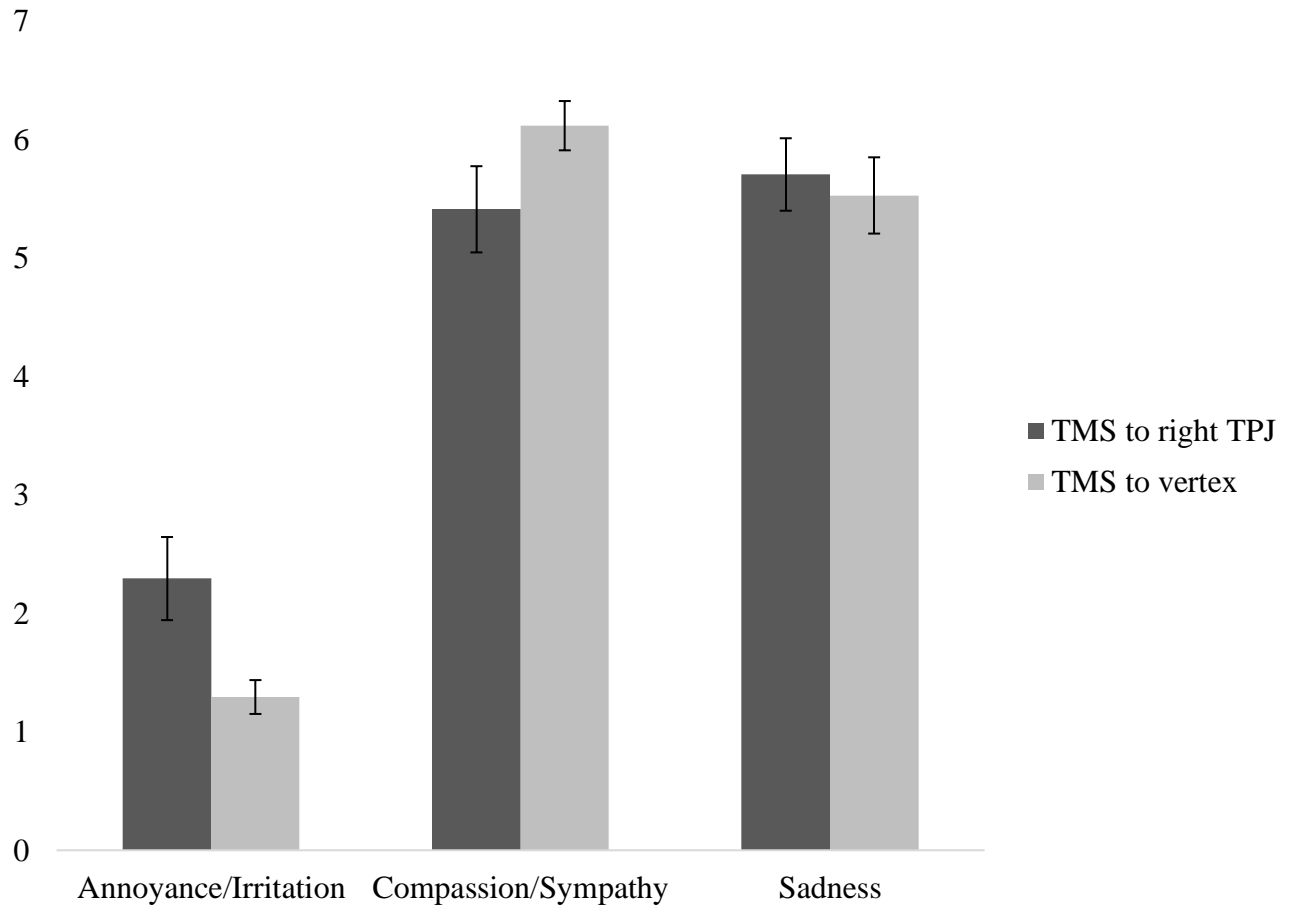
*Descriptive Statistics*

Variable	<i>n</i>	<i>M</i>	<i>SD</i>
Annoyance/Irritation	34	1.79	1.20
Compassion/Sympathy	34	5.76	1.26
Sadness	34	5.62	1.28
HF power neutral video	32	795.13	613.57
RMSSD neutral video	32	49.59	27.53
PEP neutral video	27	102.00	16.39
HF power epoch 1	32	1089.21	1136.56
HF power epoch 2	32	698.54	520.78
HF power epoch 3	32	908.69	870.36
HF power epoch 4	32	738.05	768.66
RMSSD epoch 1	32	49.44	26.59
RMSSD epoch 2	32	45.97	19.51
RMSSD epoch 3	32	45.93	22.10
RMSSD epoch 4	32	44.34	26.29
PEP epoch 1	27	104.22	13.07
PEP epoch 2	27	106.22	12.83
PEP epoch 3	27	106.74	13.30
PEP epoch 4	27	107.33	13.43

There was a statistically significant interaction effect of TMS site on emotion,  $F(1.44, 46.08) = 3.77, p = .044$ , partial  $\eta^2 = .11$  (see Figure 2.1). In response to the sadness induction video, participants who received TMS to the right TPJ reported significantly more annoyance/irritation compared to participants who received TMS to the vertex ( $p = .013$ ). There was a borderline effect for participants in the right TPJ group to report less compassion than participants in the vertex group ( $p = .102$ ). The two groups did not differ in their reports of sadness ( $p = .690$ ).

Figure 2.1

*Effect of TMS Site on Reported Feelings*



Note. Error bars represent the standard errors of the means.

There was a statistically significant interaction effect of TMS site on how participants reported experiencing annoyance/irritation relative to compassion/sympathy,  $F(1, 32) = 5.90, p = .021$ , partial  $\eta^2 = .16$ , and compassion/sympathy relative to sadness,  $F(1, 32) = 5.34, p = .027$ , partial  $\eta^2 = .14$ . In response to the sadness induction video, participants who received TMS to the vertex reported more compassion/sympathy relative to annoyance/irritation than participants who received TMS to the right TPJ ( $p = .021$ ). In addition, participants who received TMS to the vertex reported significantly more compassion/sympathy than sadness ( $p = .037$ ), whereas participants who received TMS to the right TPJ reported similar levels of compassion/sympathy and sadness ( $p = .284$ ).

Taken together, participants who received TMS to the right TPJ had a profile of feeling more irritation/annoyance, and tending to feel less compassion/sympathy, than participants in the control group. The right TPJ group reported similar levels of compassion/sympathy and sadness. Conversely, the control group reported greater compassion/sympathy than sadness. Participants in the control group also reported greater compassion/sympathy relative to annoyance/irritation than the participants in the right TPJ group.

### **Physiology during neutral film clip**

Participants in the right TPJ and vertex groups did not differ in terms of HF power, RMSSD, or PEP during the neutral film clip (all  $|t| < 1.61$ , all  $p > .117$ ).

### **Physiology during sad film clip**

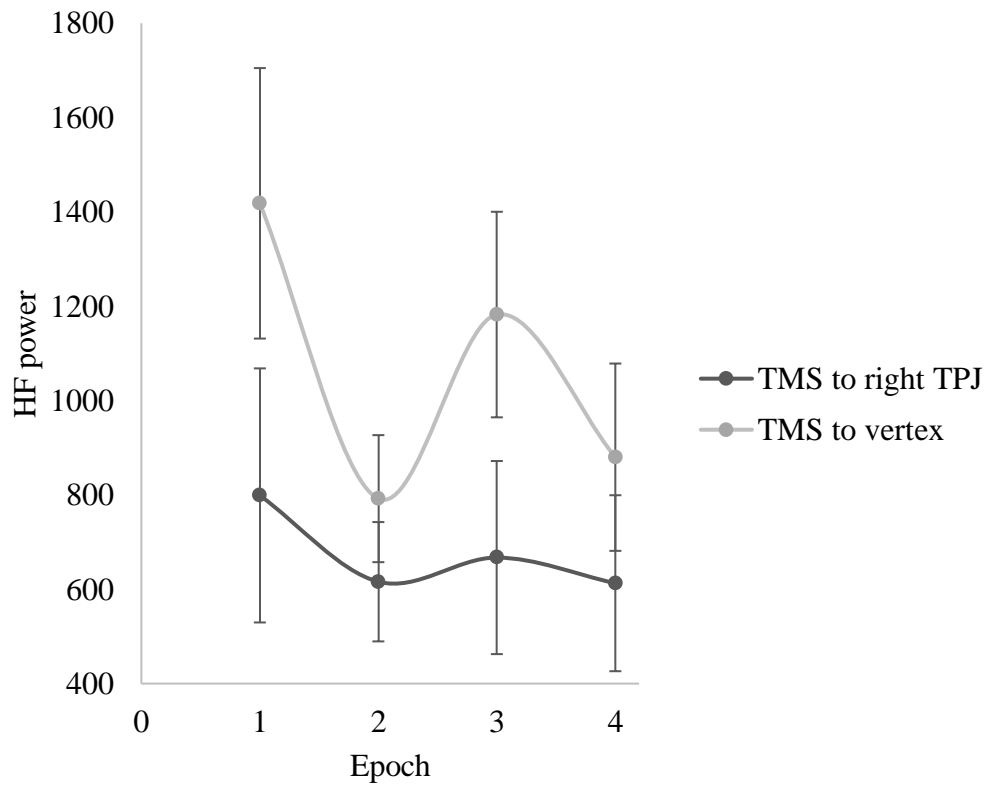
As expected, HF power and RMSSD were highly correlated with each other for each epoch of the sadness induction video ( $r$ 's ranging from .84 to .86,  $p < .001$ ). PEP was not correlated with HF power or RMSSD (all  $p > .422$ ). Table 2.1 presents the descriptive statistics for HF power, RMSSD, and PEP in each epoch of the video.

To analyze the effect of TMS site on parasympathetic and sympathetic nervous system regulation during the sadness induction video, 2 (group: right TPJ versus vertex) x 4 (epoch of champ video) mixed ANOVAs were conducted for HF power, RMSSD, and PEP. Mauchly's test showed that the assumption of sphericity had been violated for HF power ( $\chi^2(5) = 12.86, p = .025$ ), RMSSD ( $\chi^2(5) = 29.02, p < .001$ ), and PEP ( $\chi^2(5) = 32.00, p < .001$ ). Thus, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (HF power  $\epsilon = .75$ , RMSSD  $\epsilon = .66$ , PEP  $\epsilon = .56$ ).

For HF power, there was a significant main effect of epoch,  $F(2.26, 67.83) = 3.98, p = .019$ , partial  $\eta^2 = .12$ . There was trend for participants to show a linear decrease in HF power over the course of the sadness induction video,  $F(1, 30) = 3.96, p = .056$ , partial  $\eta^2 = .12$ , but also a significant cubic pattern of change,  $F(1, 30) = 10.29, p = .003$ , partial  $\eta^2 = .26$ . Overall, participants decreased HF power from epoch 1 to 2 (Mean Difference = -404.52,  $p = .007$ ), showed modest subsequent rebound in HF power from epoch 2 to 3 (Mean Difference = 220.75,  $p = .055$ ), and then maintained this level of HF power from epoch 3 to 4 (Mean Difference = -178.39,  $p = .129$ ). This cubic pattern of change was moderated by TMS site,  $F(1, 30) = 4.60, p = .040$ , partial  $\eta^2 = .13$  (see Figure 2.2). Participants in the right TPJ group did not show significant changes in HF power from epoch to epoch (all  $p > .34$ ). Participants in the vertex group decreased HF power from epoch 1 to 2 (Mean difference = -626.08,  $p = .005$ ), showed some rebound in HF power from epoch 2 to 3 (Mean difference = 390.30,  $p = .022$ ), followed by a modest decrease in HF power from epoch 3 to 4 (Mean difference = -302.41,  $p = .080$ ).

Figure 2.2

*Effect of TMS Site on HF power During the Sadness Induction Video*



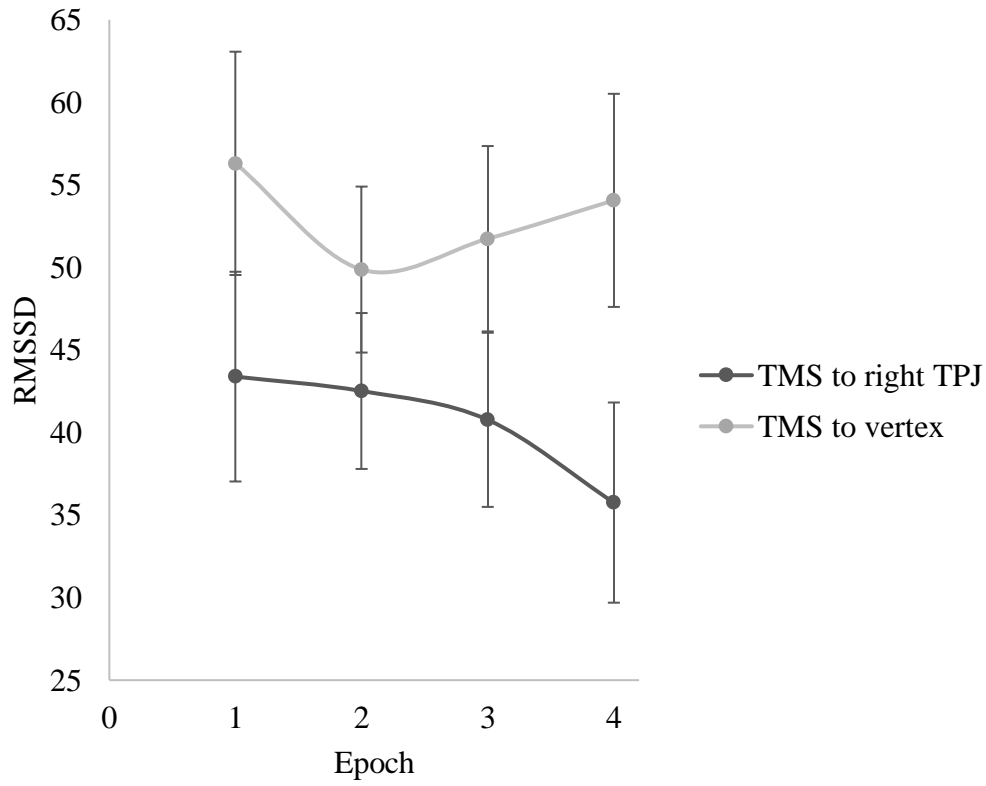
Note. Error bars represent the standard errors of the means.

For RMSSD, there was no significant main effect of epoch,  $F(1.97, 59.03) = 1.78, p = .178$ , partial  $\eta^2 = .06$ . There was a significant interaction effect of site of TMS on quadratic change in RMSSD over the course of the sadness induction video,  $F(1, 30) = 5.98, p = .021$ , partial  $\eta^2 = .17$  (see Figure 2.3). Participants who received TMS to the right TPJ showed a pattern of accelerating decreases in RMSSD as the intensity of the depicted sadness increased over the course of the video. This pattern was characterized by statistically nonsignificant decreases in RMSSD from epochs 1 to 2 (Mean difference =  $-.87, p = .778$ ) and 2 to 3 (Mean difference =  $-1.75, p = .397$ ), and a significant decrease in RMSSD from epochs 3 to 4 (Mean difference =  $-5.01, p = .038$ ). Looking at the overall change, participants who received TMS to the right TPJ decreased RMSSD from the beginning to the end of the sadness induction video (from epoch 1 to 4) at the trend level (Mean difference =  $-7.63, p = .084$ ). Conversely, participants who received TMS to the vertex showed a pattern of initial decrease followed by accelerating rebound in RMSSD over the course of the sadness induction video. This pattern was characterized by a modest decrease in RMSSD from epoch 1 to 2 (Mean difference =  $-6.43, p = .057$ ), followed by statistically nonsignificant increases in RMSSD from epochs 2 to 3 (Mean difference =  $1.87, p = .375$ ) and 3 to 4 (Mean difference =  $2.32, p = .353$ ). RMSSD at the beginning and end of the sadness induction video were not significantly different for participants who received TMS to the vertex (Mean difference =  $-2.24, p = .625$ ).



Figure 2.3

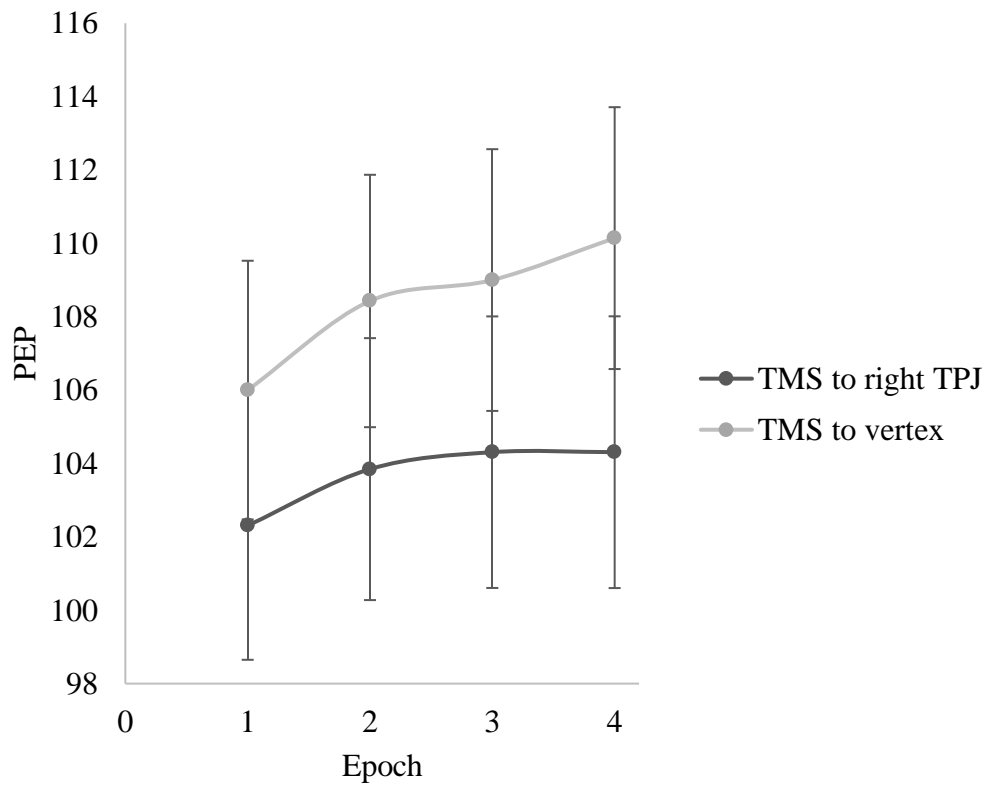
*Effect of TMS Site on RMSSD During the Sadness Induction Video*



For PEP, there was a significant main effect of epoch,  $F(1.69, 42.29) = 9.25, p = .001$ , partial  $\eta^2 = .27$ , but no interaction between epoch and TMS group,  $F(1.69, 42.29) = 1.00, p = .364$ , partial  $\eta^2 = .04$ . For the whole sample, there were significant linear,  $F(1, 25) = 12.39, p = .002$ , partial  $\eta^2 = .33$ , and quadratic changes,  $F(1, 25) = 4.57, p = .042$ , partial  $\eta^2 = .16$  in PEP suggesting a general trend of increasing PEP length (i.e., decreasing sympathetic nervous system activity). Participants increased PEP from epoch 1 to 2 (Mean difference = 1.98,  $p = .004$ ), did not show significant subsequent change from epoch 2 to 3 (Mean difference = .52,  $p = .328$ ), then modestly increased PEP from epoch 3 to 4 (Mean difference = .57,  $p = .054$ ). Looking at the overall change from epoch 1 to 4, PEP was significantly longer by the end of the sadness induction video compared to the beginning (Mean difference = 3.07,  $p = .001$ ), indicating that sympathetic nervous system activity had decreased over the course of the induction. Although non-significant ( $p = .364$ ), group differences in patterns of change in PEP were examined. There were nonsignificant effects of TMS site on PEP change from epochs 1 to 2,  $F(1, 25) = .52, p = .479$ , partial  $\eta^2 = .02$ , and epochs 2 to 3,  $F(1, 25) = .01, p = .916$ , partial  $\eta^2 = .00$ , and a trend for the effect of TMS site on PEP change from epochs 3 to 4,  $F(1, 25) = 4.10, p = .054$ , partial  $\eta^2 = .14$  (see Figure 2.4). Participants who received TMS to the right TPJ showed essentially no change in PEP from epochs 3 to 4 (Mean difference = -.00,  $p = 1.00$ ), whereas participants who received TMS to the vertex showed a significant increase in PEP (Mean difference = 1.14,  $p = .007$ ). The overall change in PEP from epochs 1 to 4 were not different for participants who received TMS to the right TPJ versus the vertex ( $p = .202$ ).

Figure 2.4

*Effect of TMS Site on PEP During the Sadness Induction Video*



Note. Error bars represent standard errors of the means. Higher PEP values reflect less sympathetic nervous system activity.

### **Associations between subjective experience and physiology**

Correlations were computed between subjective ratings of emotions and physiology within each epoch, and physiological changes from epoch to epoch, to examine potential links between experiential and physiological aspects of emotion during the sadness induction video. For HF power, RMSSD, and PEP, values within each epoch were regressed on the values from the previous epoch. The standardized residuals from these regressions were used as epoch to epoch change scores. Subjective experience was not correlated with HF power or PEP in any epoch of the video (all  $p > .149$ ). Participants who reported feeling more compassion/sympathy relative to sadness tended to have higher RMSSD during the first ( $r = .33, p = .064$ ) and third epochs ( $r = .32, p = .073$ ) of the sadness induction video, and had a significantly greater increase in PEP (i.e., stronger decreases in sympathetic nervous system activity) from epochs 3 to 4 ( $r = .44, p = .022$ ). Subjective experience was not correlated with epoch to epoch changes in HF power or RMSSD (all  $p > .136$ ).

To examine whether subjective experience was related to overall patterns of physiological change, we defined latent-basis growth curves to estimate trajectories of change in HF power, RMSSD, and PEP. However, model fit was poor for each physiological variable (all  $TLI < .85$ ,  $CFI < .91$ , and  $RMSEA > .19$ ). Thus, the links between these trajectories and subjective ratings of emotions were not examined for the overall sample. Modeling the trajectories for each TMS group also produced poor model fit for HF power and RMSSD (both  $TLI < .80$ ,  $CFI < .87$ , and  $RMSEA > .21$ ). A multi-group model for PEP fit the data well ( $TLI = .99$ ,  $CFI = .99$ ,  $RMSEA = .05$ ), but the slope factor did not predict any measure of subjective feelings (all  $p > .201$ ).

## Discussion

This study showed that disrupting right TPJ activity with offline TMS affects experiential and physiological response to others' suffering. TMS over the right TPJ appeared to increase feelings of being annoyed and irritated, decrease parasympathetic flexibility, and reduce withdrawal of sympathetic nervous system activity, in response to a sadness induction film clip. Conversely, participants who received TMS to the vertex reported more compassion compared to annoyance and empathic sadness than participants who received TMS to the right TPJ. Participants who received TMS to the vertex also demonstrated stronger parasympathetic flexibility and downregulation of sympathetic activity toward the end of the film clip. The right TPJ is widely considered an important neural region for social cognition, but this is the first study to provide evidence that the right TPJ plays a causal role in affective responses to others' suffering.

Observation of others' emotional suffering can elicit multiple kinds of emotional responses. Right TPJ functioning appears to be important for avoiding feeling aggravated by this suffering. One interpretation of this findings is that social cognitive processes supported by the right TPJ contribute to effective emotion regulation, including inhibition of feelings that can lead to hostility or avoidance of others' distress. Conversely, TMS to the right TPJ did not affect levels of empathic sadness, which is in line with the perspective that dissociable networks are implicated in cognitive and affective aspects of empathy (Shamay-Tsoory, 2011). However, participants who received TMS to the right TPJ experienced similar levels of compassion and empathic sadness, whereas participants in the control group experienced more compassion than empathic sadness. It has been argued that compassion reflects feeling *for* another in need or distress and that empathy reflects feeling *with* or similar to another (Singer & Klimecki, 2014).

The right TPJ has consistently been linked to perspective taking with self-other distinction, and these social cognitive processes may contribute to experiencing compassion above and beyond empathic sadness. Although compassion and empathy are generally both considered emotional mechanisms of prosociality (Batson, 2011; Davidov et al., 2016; de Waal, 2008), it has been argued that compared to empathy, compassion is more predictive of positive social and personal outcomes like prosocial behavior toward others (Jordan, Amir, & Bloom, 2016) and increased positive affect (Klimecki, Leiberg, Lamm, & Singer, 2013). Thus, participants who received TMS to the vertex experienced an emotional profile that is more prosocially oriented and beneficial than the profile of emotions experienced by people who received TMS to the right TPJ. However, whether these observed emotional profiles (a) are due to TMS undermining social cognition, and (b) directly lead to different behavioral outcomes, are still open questions. A number of studies have posited that the link between the right TPJ and prosocial behavior is due to perspective taking skills (Morishima, Schunk, Bruhin, Ruff, & Fehr, 2012; Telzer, Masten, Berkman, Lieberman, & Fuligni, 2011). Future research should test the possibility that downstream effects of right TPJ functioning on affective processing, like experiencing compassion more strongly than empathic sadness and feeling less annoyed and irritated, might mediate the link between social cognition and prosocial behavior.

In addition to subjective feelings, the findings provide evidence that right TPJ functioning plays a role in modulating autonomic reactivity to others' emotional suffering. It is unlikely that these findings are due to differences in overall arousal, as the two TMS groups did not differ in terms of physiological response to a neutral film clip. In response to the sad film clip, TMS to the right TPJ appeared to contribute to a flatter pattern of parasympathetic activity characterized by less change, whereas the control group demonstrated a specific pattern of

parasympathetic flexibility characterized by an initial decrease followed by rebound. Previous studies have associated this pattern of dynamic parasympathetic activity with greater prosociality (Cui et al., 2015; Miller et al., 2016). One interpretation of this pattern of parasympathetic activity is that it reflects a sequence of first orienting to the other's distress via some arousal (decreasing HRV) followed by calm, social engagement with that distress (HRV rebound) (Miller, in press). Participants who received TMS to the vertex decreased sympathetic nervous system activity toward the end of the film induction, whereas participants who received TMS to the right TPJ did not. The parasympathetic nervous system is considered to be a key part of a social engagement system, whereas physiological arousal driven by the sympathetic nervous system can contribute to defensive responding (Porges, 2011). Taken together, TMS to the right TPJ appeared to produce physiological responses previously linked to less concern for others and less prosocial behavior. Conversely, parasympathetic flexibility and deactivation of the sympathetic nervous system may support emotional and behavioral flexibility important for prosociality (Miller, in press). One interpretation of these findings is that the social cognitive processes supported by the right TPJ have downstream consequences for organizing autonomic responses that can either promote or undermine prosociality. These findings inform brain-body models of responding to others' suffering (Hastings et al., 2014).

In addition, greater parasympathetic activity (as measured by RMSSD) during the first and third epochs of the sadness induction were associated at the trend level with experiencing more compassion compared to empathic sadness. These findings fit with the perspective that augmenting parasympathetic activity supports calm, social engagement in safe contexts (Hastings et al., 2008; Porges, 2007) that is important for compassion (Stellar, Cohen, Oveis, & Keltner, 2015). Experiencing more compassion than empathic sadness was also associated with

greater decreases in sympathetic nervous system activity at the end of the film clip (i.e., PEP lengthening). Importantly, participants in the right TPJ group maintained sympathetic activity during this portion of the induction. Increased physiological arousal driven by the sympathetic nervous system may get in the way of experiencing more compassion than empathic sadness. Taken together, right TPJ functioning contributes to patterns of physiological regulation linked to prosocial engagement with the distress of others. Further research is needed to determine the specific neural and psychological paths by which right TPJ activity leads to different physiological responses to others' suffering

There are a number of limitations of this study that should be considered. First, behavioral measures of perspective taking or self-other distinction were not included. Given that these social cognitive processes are rooted in right TPJ functioning, they were presumably altered by disrupting right TPJ activity. However, future research that includes these measures are necessary to confirm whether these social cognitive processes mediate the link between right TPJ functioning and affective response to others' suffering. Second, the between group design and small sample size may have limited our ability to detect some effects of TMS. We had less power than previous studies with larger samples more appropriate for modeling latent trajectories, which likely precluded our ability to fit models to the data and effectively test for links between overall trajectories of physiological activity and subjective feelings. In addition, applying TMS to the right TPJ and a control region within the same participants across multiple sessions, and examining changes in affective responding within participants, would be a strong replication and extension of the present study. Third, the right TPJ may consist of an anterior portion that is more involved in reorienting attention and a posterior portion dedicated to social cognition (Krall et al., 2015). We cannot rule out that TMS in our study did not partially



stimulate the more anterior region of the right TPJ and that this could have contributed to some of the findings. However, we used a theory of mind functional localizer and image-guided TMS to target the specific region of the right TPJ implicated in social cognition for each participant. In addition, the spatial resolution of direct TMS is 3 to 4 mm (Valero-Cabre et al., 2005, 2007), which is a shorter distance than that between the different subregions of the TPJ (Krall et al., 2015), and the modulatory effects of TMS on neural activity are greatest in the target region (Valero-Cabre et al., 2005). Thus, we are confident that the observed effects in this study are more attributable to stimulation of the right TPJ region serving social cognition than direct stimulation of the region serving reorienting of attention. Lastly, although the current study focused on right TPJ functioning, spreading of stimulation to other regions strongly connected to the TPJ likely also occurred (Valero-Cabre et al., 2005). The right TPJ is connected to other regions implicated in social cognitive processes, including the precuneus, posterior cingulate, middle temporal gyrus, temporal pole, and medial prefrontal cortex (Krall et al., 2015; Mars et al., 2012). Although the effects of TMS on neural activity are strongest in the targeted region, indirect activation in other regions connected to the right TPJ could have also contributed to our findings.

There is a large literature which suggests that the right TPJ is important for social cognition, but this is the first study to link right TPJ functioning to multiple components of emotion in an empathy task. We interpret the observed effects of TMS in this study as evidence that the right TPJ is causally implicated in experiential and physiological aspects of responding to others' suffering. The right TPJ is widely considered a core part of a network that is distinct from networks that support empathic sharing of emotion and compassion. At the same time, it is important to keep in mind that social cognitive and affective processes are deeply interactive.

The current findings expand our understanding of right TPJ functioning as being important for affective processes in addition social cognition.

## CHAPTER 4

### STUDY 3: COGNITIVE REAPPRAISAL INTERACTS WITH MESOLIMBIC RESPONSE TO SAD FACES TO PREDICT ADOLESCENT PROSOCIALITY

Prosocial behaviors meant to assist others are important for developing and maintaining healthy social relationships. The mesolimbic dopaminergic system is important for motivational processes and is implicated in prosocial behaviors and sharing or resonating with another person's feelings (i.e., empathy). However, studies have found both positive and negative effects (Harbaugh, Mayr, & Burghart, 2007; Chakrabarti, Bullmore, & Baron-Cohen, 2006), and neurobiological effects can be moderated by personal characteristics (Bartz, Zaki, Bolger, & Ochsner, 2011; Miller, in press). The tendency to use effective emotion regulation strategies like cognitive reappraisal might be one such characteristic. This could be especially true in adolescence, given that this is a period that requires navigating new social and emotional situations, but also heightened mesolimbic response to social and emotional information (Galvan, 2010). Cognitive reappraisal might be important for shaping mesolimbic processing toward prosocial behavior during this period of motivated social engagement. Lastly, Mexican-origin youth represent a rapidly growing segment of the US population, but are underrepresented in psychological research. Thus, the current study examined whether better cognitive reappraisal enhanced the association between mesolimbic response to others' sadness and prosocial behavior in Mexican-origin adolescents.

#### **Mesolimbic System and Prosociality**

The neurotransmitter dopamine plays a crucial role in motivational processes, including detection and response to rewarding stimuli (Bromberg-Martin, Matsumoto, & Hikosaka, 2010). Dopamine is produced by neurons in the midbrain, particularly the ventral tegmental area

(VTA). The VTA projects to the nucleus accumbens (Nacc) in the ventral striatum, which is rich in dopaminergic receptors. Thus, the VTA and Nacc form a mesolimbic pathway that regulates dopaminergic activity. Activation within mesolimbic regions have been linked to prosocial behaviors and emotions. For example, participants show increased activation in the mesolimbic regions when making donations to charity (Harbaugh, Mayr, & Burghart, 2007; Moll et al., 2006), experiencing prosocial emotions like compassion and maternal love (Bartels & Zeki, 2004; Kim et al., 2009), and observing positive outcomes for others (Mobbs et al., 2009). Thus, one common interpretation in the literature is that activation within this system reflects reward processes, which could indicate that there is a reward-seeking or pleasurable component to prosocial behaviors and emotions (Decety, Norman, Berntson, & Cacioppo, 2012; Hastings, Miller, Kahle, & Zahn-Waxler, 2014; Preckel, Kanske, & Singer, 2017; Zaki & Mitchell, 2013). However, the links between mesolimbic functioning and prosocial behaviors and emotions have predominantly been studied in adults rather than adolescents.

The interpretation of activity of the mesolimbic regions reflecting an engagement of reward processing in prosociality has some limitations. First, animal research suggests that some dopaminergic neurons within the VTA and Nacc are sensitive to both rewarding and aversive stimuli (Brischoux, Chakraborty, Brierley, & Unbless, 2009; Matsumoto & Hikosaka, 2009). In human neuroimaging research, VTA and Nacc have been demonstrated to be sensitive to anticipation of both gains and losses in a monetary incentive delay task, perhaps suggesting that these regions are important for motivational relevance (Carter, MacInnes, Huettel, & Adcock, 2009). Emotional face processing research suggests that the VTA is involved in regulating perceived salience of social cues (Groppe et al., 2013). Other researchers have also argued that mesolimbic activation is important for motivational processes beyond just reward or value,

including salience and orienting, exertion of effort, and sustained engagement with stimuli (Bromberg-Martin et al., 2010; Salamone & Correa, 2012). As such, mesolimbic regions are involved in supporting both approach and avoidance actions (Salamone & Correa, 2012), potentially including approach and avoidance of prosociality.

Another concern with the research on mesolimbic functioning is that activity in these areas has been associated both with prosocial behaviors and with characteristics and emotions considered antithetical to them. Adults and adolescents with mental health disorders characterized by deficits in empathy, such as psychopathy and conduct disorder, demonstrate greater ventral striatum activity in empathy for pain tasks (Decety, Chen, Harenski, & Kiehl, 2013; Decety, Michalska, Akitsuki, & Lahey, 2009). Ventral striatum response to sad faces has been negatively associated with individual differences in empathy (Chakrabarti et al., 2006). Participants show increased ventral striatum activation when someone they envy experiences misfortune (Takahashi et al., 2009). Taken together, there is evidence that mesolimbic response to others' suffering is implicated in antisocial traits and states in addition to prosociality.

One explanation for these findings is that neurobiological involvement in prosocial versus antisocial processes depends on features of the context and individual (Bartz et al., 2011; Miller, in press). Person-specific variables, like loneliness (Norman et al., 2011), neuroticism (Fujiwara, Tobler, Taira, Iijima, & Tsutsui, 2008), and social cognitive skills (Bartz et al., 2010), have been shown to moderate effects in other neurobiological systems. However, researchers have not examined whether person-specific variables might moderate whether mesolimbic functioning is associated with more or less prosocial behavior.

### **Cognitive Reappraisal, Motivation, and Prosociality**

One feature of individuals that might moderate mesolimbic effects is the tendency to use effective emotion regulation. Motivational perspectives on prosocial behavior emphasize the importance of emotion regulation for executing motives to approach or avoid others in need (Eisenberg, 2010). Recently, this perspective has re-emerged in the literature on motivational perspectives on empathy (Zaki, 2014). When individuals perceive or experience empathy or helping situations as particularly costly and aversive, they are more motivated to avoid empathy-inducing stimuli (Zaki, 2014). Thus, effective emotion regulation might be important for shaping whether others' emotions elicit approach or avoidance motivation processes, which are likely rooted in mesolimbic functioning. Researchers have yet to provide neurobiological evidence for this model in adolescence.

Cognitive reappraisal is one effective emotion regulation strategy that refers to reframing how one thinks about a stimulus to change its affective impact (Gross, 2002). Although there is evidence that cognitive reappraisal is an effective emotion regulation strategy for youth (Garnefski et al., 2009), it is used less frequently in adolescence than in adulthood (Garnefski et al., 2002). In addition, adults who utilize cognitive reappraisal often are more likely to demonstrate positive social and emotional functioning (Gross & John, 2003), including increased empathic concern for others (Lebowitz & Dovidio, 2015), but these effects have not been tested outside of adulthood.

Adolescence is a period of increased social orientation and emotional reactivity (Casey, Jones, & Hare, 2008; Nelson, Leibenluft, McClure, & Pine, 2005), but also the development of reappraisal ability (McRae et al., 2012). Late adolescence represents a shift from engaging affective systems to utilizing emotion regulation systems when engaging in prosocial behavior (Masten, Morelli, & Eisenberg, 2011). Thus, increased use of cognitive reappraisal could be

interpreted as sign of emotion regulation maturation with implications for adolescent prosocial behavior. However, adolescents also show heightened mesolimbic responsivity to reward compared to adults and children (Galvan et al., 2006; Van Leijenhorst et al., 2010), and this heightened activation has been linked to vulnerabilities for mental health and behavioral problems during this developmental stage (Caouette & Guyer, 2014; Steinberg, 2008). Cognitive reappraisal in adolescence might be particularly important for protecting against neurobiological risk (Ahmed, Bittencourt-Hewitt, & Sebastian, 2015; Garnefski, Kraaij, & van Etten, 2005). Conversely, adolescent mesolimbic functioning has also been related to a number of positive outcomes, like providing money for one's family (Telzer, Masten, Berkman, Lieberman, & Fuligni, 2010), and can buffer against risk in certain contexts (Pfeifer et al., 2011; Telzer, 2016), like in the presence of prosocial peers (Cascio et al., 2014). Taken together, contextual and individual factors can qualify whether adolescent mesolimbic activity is related to positive or negative outcomes, but the implications of these interactions for prosocial outcomes has not been examined. Specifically, more research on the interaction between neurobiology and *intrapersonal* factors, like emotion regulation, are needed (Miller, in press).

### **Gender Differences in Prosociality**

Many studies suggest that females tend to be more prosocial and empathic than males. Compared to males, females self-report, and are often reported by others, as being more empathic and prosocial (Baron-Cohen & Wheelwright, 2004; Eisenberg & Lennon, 1983; Rose & Rudolph, 2006). Females also give more money and volunteer more time to charity (Willer, Wimer, & Owens, 2015), and more strongly prefer egalitarian outcomes in economic exchange games (Guth, Schmidt, & Sutter, 2007). Interestingly, gender differences in prosociality increase during adolescence (Fabes, Carlo, Kupanoff, & Laible, 1999; Lam, Solmeyer, & McHale, 2012),

as males temporarily decline in empathic concern and prosocial behaviors whereas females show stable levels across adolescence (Carlo, Crockett, Randall, & Roesch, 2007; Van der Graaf et al., 2014). At the neural level, there is evidence that females recruit networks associated with affective aspects of empathy more strongly than males (Derntl et al., 2010; Schulte-Ruther, Markowitsch, Shah, Fink, & Piefke, 2008). Taken together, there may be gender differences in the substrates underlying prosociality. However, we are unaware of any study that has examined or found evidence for different neural systems predicting individual differences in prosocial behavior in adolescent boys versus girls. Females and males do not differ in their use of cognitive reappraisal (Gross & John, 2003; Haga, Kraft, & Corby, 2009), but we are unaware of any work investigating gender differences in the associations of cognitive reappraisal and mesolimbic functioning with prosocial outcomes.

### **Emotion Introspection**

Facial expressions communicate information about others' experiences, and emotional face processing tasks have been widely used to study empathy (Chakrabarti et al., 2006; Horan et al., 2014; Jabbi, Swart, & Keysers, 2007; Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008). Emotion introspection, or reflecting on how one feels in response to the emotion of another, is considered one form of perspective taking (Weissman et al., in press). Many studies have considered the role of taking another person's perspective in prosocial behavior, but researchers have yet to examine the importance of emotion introspection. This is surprising given that neural response during emotion introspection processes are implicated in empathy (Schulte-Rüther et al., 2008), which is one of the primary motivational forces for prosocial behavior (Davidov et al., 2016). Further, because empathy-related responses are often evoked by another person's sadness or distress, sadness introspection could be particularly relevant to prosocial behavior. Thus, the



present study focused on mesolimbic functioning during sadness introspection in response to sad faces.

### **Current Study**

The current study aimed to investigate a potential interaction between cognitive reappraisal and mesolimbic response during introspection in response to sad faces in predicting individual differences in prosocial behavior. To the degree that motivation-related processes are rooted in mesolimbic functioning, including processes that drive avoidance and approach motives in empathy contexts, we expected heightened mesolimbic responsivity to be linked with both more and less prosocial behavior. In the context of more frequent use of cognitive reappraisal, indicating effective emotion regulation, we expected heightened mesolimbic responding during sadness introspection to be linked with more prosocial behavior. Conversely, we expected heightened mesolimbic responding during sadness introspection to be linked with less prosocial behavior when participants reported less use of cognitive reappraisal (i.e., less effective emotion regulation). Given the well documented gender differences in prosocial behavior and empathy (Carlo et al., 2007; Derntl et al., 2010; Fabes et al., 1999), we explored whether the interaction between cognitive reappraisal and mesolimbic responsivity might differ for boys and girls.

### **Methods**

#### **Participants**

This study included 227 Mexican-origin adolescents (M age = 17.16 years, SD = .44; 110 females) recruited from the California Families Project (CFP), a larger, 10-year longitudinal study of 674 families. Most participants (73.8%) in the current study were born in the United States (56.3% first generation; 17.5% second-generation), and 26.2% were born in Mexico. The

current study was designed to examine the neurobiological mechanisms of the development of depression, and included adolescents with elevated depressive symptoms based on self-report measures in Grade 9 (age 14), including the Diagnostic Interview for Children-IV (Shaffer, Fishe, Lucas, Dulcan, & Schwab-Stone, 2000) and the Anhedonic Depression and General Distress subscales of the Mood and Anxiety Symptom Questionnaire (Watson & Clark, 1991). Adolescents whose symptom scores were above the median on at least one measure of depression made up the majority of the sample, but adolescents who were at or below the median on all 3 measures were also included (N = 54) to ensure variability in symptoms.

### **Questionnaire Measures**

***Cognitive reappraisal.*** Adolescents reported on their tendency to use cognitive reappraisal using the Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). Six items were averaged together to form an index of cognitive reappraisal (e.g., “When I want to feel more positive emotion, I change the way I’m thinking about the situation,” “When I’m faced with a stressful situation, I make myself think about it in a way that helps me stay calm”),  $\alpha = .80$ . Adolescents rated items on a scale ranging from 1 (strongly disagree) to 7 (strongly agree). All 227 participants reported on their use of cognitive reappraisal.

***Prosocial behavior.*** Adolescents reported on their prosocial behaviors using the Strengths and Difficulties Questionnaire (SDQ; Goodman, Meltzer, & Bailey, 1998). Five items were averaged together to form an index of adolescent’s tendencies to engage in prosocial behaviors (e.g., “I often offer to help others,” “I usually share with others”),  $\alpha = .63$ . Adolescents rated items on a scale ranging from 1 (not true) to 3 (certainly true). One participant did not report on their prosocial behavior.

### **fMRI Task**

An emotional face processing task was used to examine neural response in an emotion introspection context (Guyer, Choate, Grimm, Pine, & Keanan, 2011). The fMRI task consisted of 48 emotional faces (12 sad, 12 angry, 12 happy, 12 neutral) presented for 3 s each. There were 3 runs of four 10-trial blocks containing 8 faces and 2 fixation crosses presented in a pseudorandom order. For this paper, only responses to the presentations of sad faces were analyzed. Throughout the task, participants were exposed to two conditions. In the introspection condition, participants were asked to focus on how sad the faces made them feel (“How sad does this person make you feel?”). In the contrast condition, participants were asked to focus on the width of the nose (“How wide is the nose?”). While viewing each picture, participants provided ratings ranging from 1 (“not at all”) to 5 (“very much so”). Due to time constraints, excessive head motion, and some participants not responding during the task, there were 182 participants with useable fMRI data for analysis.

### **fMRI acquisition**

Neuroimaging data were acquired using a Siemens 3T Tim Trio Scanner with a 32-channel head coil. Functional images were acquired using a gradient echo pulse sequence with 2000 ms repetition time (TR), 27 ms echo time (TE), 80 degree flip angle, 3.5 x 3.5 x 3.5 mm voxels, 35 slices, and 224 mm field-of-view (FOV). The first two volumes were discarded to allow for magnet stabilization. A high resolution structural image was obtained using a MPRAGE pulse sequence with a 2500 ms TR, 4.33 ms TE, 7 degree flip angle, 0.9 x 0.9 x 0.9 voxels, 208 slices, and 243 mm FOV.

### **fMRI data processing**

The two-stage registration method in FMRIB Software Library (FSL) was used to co-register each participant’s functional and structural data, and normalization of images to

Montreal Neurological Institute (MNI) space. Alignment for each participant was visually confirmed. AFNI was used to carry out the rest of preprocessing, which included slice timing correction, rigid body motion correction with six degrees of freedom, spatial smoothing with a 6 mm half-maximum Gaussian kernel, scaling of blood oxygen level-dependent signal intensity to percentage of signal change, and censoring volumes that contained motion greater than 1 mm from the previous volume.

### **Data analysis**

Group-level analyses were conducted using a region of interest (ROI) approach. Based on the TT\_Daemon atlas provided in AFNI, 8 mm ROIs were created centered at MNI coordinates  $x = 12, y = 8, z = 8$  (right NAcc) and  $x = -12, y = 8, z = 8$  (left NAcc). Based on prior work (Katsyri, Hari, Ravaja, & Nummenma, 2013), an ROI was created at the VTA centered at MNI coordinates  $x = 0, y = -22, z = 18$ . Signal intensities (beta values) for these ROIs were extracted for each participant for the contrast comparing the “how sad...” condition minus the “how wide...” condition for presentation of sad faces only. The correlations between each ROI ranged from  $r = .57$  to  $r = .88$  (all  $p < .001$ ). Given that we were interested in mesolimbic functioning in general, we created an ROI mask that represented the mean signal intensity across the bilateral NAcc and VTA.

The extracted values from this ROI mask were included in a path analysis model with adolescent prosocial behavior as the outcome variable and gender, reappraisal, mesolimbic activity, and 2-way and 3-way interactions between gender, reappraisal, and mesolimbic response, as predictor variables. All predictor variables were allowed to covary with each other. Interaction terms were based on centered variables and were formed according to guidelines outlined by Aiken and West (1991). The model was run in Amos version 24 and maximum

likelihood estimation was used to account for missing data and estimate model parameters using the full sample.

## Results

### Descriptive Statistics

The descriptive statistics and zero-order correlations for gender, cognitive reappraisal, prosocial behavior, and mesolimbic activation betas are presented in Table 3.1. Girls reported more prosocial behaviors than boys. Participants who reported using more cognitive reappraisal also reported more prosocial behavior.

Mesolimbic activation did not differ significantly for the conditions of rating sadness versus rating nose width ( $p = .364$ ). However, there was significant variability in the contrast of these conditions ( $p < .001$ ), suggesting that there were substantial individual differences in mesolimbic activation associated with sadness introspection.

Table 3.1

*Descriptive Statistics and Correlations*

Variable	1	2	3	4
1. Gender	1			
2. Cognitive Reappraisal	-.02	1		
3. Prosocial Behavior	.22**	.23***	1	
4. Mesolimbic Response	.03	.06	-.03	1
<i>M</i>		4.87	2.48	.01
<i>SD</i>		1.09	.38	.20

Note. \*\* $p = .001$ , \*\*\* $p < .001$ . For Gender variable, boys = 1 and girls = 2. Positive Mesolimbic Response values represent greater activity during the “how sad...” condition. Negative Mesolimbic Response values represent greater activity during the “how wide...” condition.

## Predicting Prosocial Behavior

The estimates for the model predicting self-reported prosocial behavior are presented in Table 3.2. Girls reported more prosocial behavior than boys ( $\beta = .25, p < .001$ ). Adolescents who reported using cognitive reappraisal also reported more prosocial behaviors ( $\beta = .21, p = .001$ ). However, a significant interaction was found between cognitive reappraisal, mesolimbic activity, and gender ( $\beta = -.21, p = .006-.28$ ). Boys who showed a greater mesolimbic response to the “how sad...” condition tended to be less prosocial when they reported less reappraisal ( $\beta = -.28, p = .070$ ). Mesolimbic response did not predict prosocial behavior when boys reported high reappraisal ( $\beta = .08, p = .524$ ) (see Figure 3.1). Conversely, girls who showed greater mesolimbic response to the “how wide...” condition tended to be more prosocial when they reported more reappraisal ( $\beta = -.30, p = .055$ ). Mesolimbic response did not predict prosocial behavior for girls who reported low reappraisal ( $\beta = .18, p = .232$ ) (see Figure 3.2).

Table 3.2

*Regression Model Predicting Prosocial Behavior*

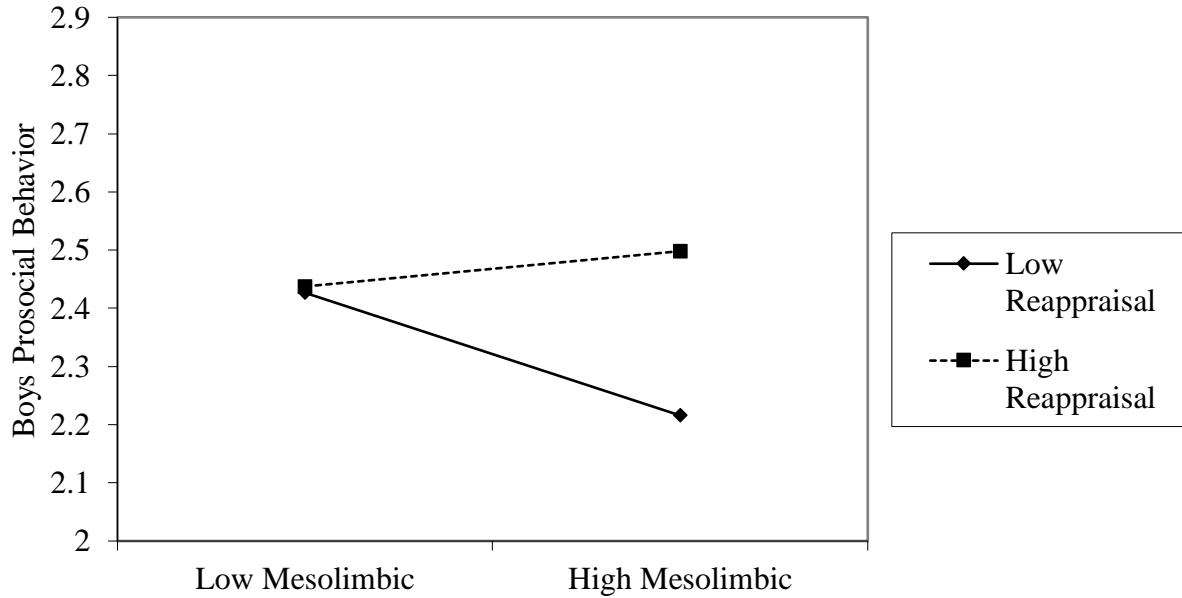
Variable	SDQ Prosocial Behavior			
	B	$\beta$	CR	<i>p</i>
Gender	.19	.25	3.92	<.001
Cognitive Reappraisal	.07	.21	3.27	.001
Mesolimbic Response (ML)	-.17	-.09	1.23	.218
Reappraisal x ML	-.02	-.01	.13	.893
Gender x ML	.10	.03	.38	.702
Gender x Reappraisal	.00	.01	.10	.922
Gender x ML x Reappraisal	-.70	-.21	2.74	.006

Note. For Gender variable, boys = 1 and girls = 2. Critical ratios (CR) represent the unstandardized estimate over the standard error. Critical ratios > 1.96 are significant at the .05 level or better.



Figure 3.1

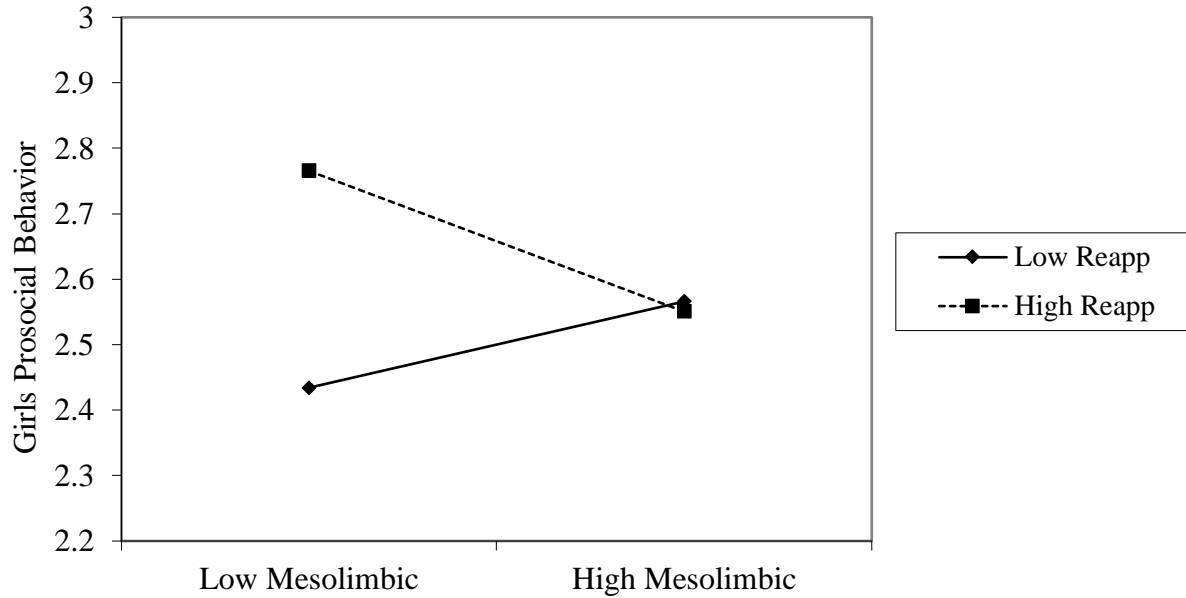
*Reappraisal x Mesolimbic Response Predicting Prosocial Behavior for Boys*



Note. Low Mesolimbic = greater mesolimbic reactivity to the “how wide...” condition compared to the “how sad...” condition. High Mesolimbic = greater mesolimbic reactivity to the “how sad...” condition compared to the “how wide...” condition.

Figure 3.2

*Reappraisal x Mesolimbic Response Predicting Prosocial Behavior for Girls*



Note. Low Mesolimbic = greater mesolimbic reactivity to the “how wide...” condition compared to the “how sad...” condition. High Mesolimbic = greater mesolimbic reactivity to the “how sad...” condition compared to the “how wide...” condition.

## Discussion

This study provided partial evidence that cognitive reappraisal may promote prosociality in adolescents with heightened mesolimbic responsivity, but the nature of this interaction was different for boys and girls. When engaging in sadness introspection, boys who showed greater mesolimbic response reported less prosocial behaviors when they reported low cognitive reappraisal. This link between mesolimbic response and less prosocial behavior was broken for boys who reported more cognitive reappraisal. For boys who show increased response in motivation-related brain regions when introspecting on their empathic sadness, the tendency to use reappraisal might be particularly important for shaping motivational processes (e.g., salience, orienting, exertion of effort) into prosocial engagement. In the absence of effective emotion regulation, increased mesolimbic responsivity during affective engagement with others' sadness may reflect motivational processes that drive adolescent boys to distance themselves and show less prosocial behavior. For these boys who do not use reappraisal, sadness introspection may be evaluated as an aversive or costly experience that should be avoided. In other words, increased mesolimbic responsivity during affective processing of others' sadness may reflect avoidance motivation depending in part on emotion regulation. Cognitive reappraisal might be an effective emotion regulation strategy that provides a path toward approaching prosocial engagement for adolescent boys who might otherwise be considered at risk due to their neural functioning.

However, the interaction between mesolimbic functioning and cognitive reappraisal predicted prosocial behavior differently for girls. Surprisingly, girls who showed greater mesolimbic response to the "how wide..." condition were more prosocial when they reported more cognitive reappraisal. These findings are harder to explain from the perspective that cognitive reappraisal moderates whether mesolimbic reactivity to sadness introspection reflects

risk or propensity for prosociality. Why would reappraisal be more important for girls who showed increased mesolimbic response to the “how wide...” condition compared to the “how sad...” condition? There is fairly consistent evidence that adolescent girls tend to be more empathic and prosocial than adolescent boys (Carlo et al., 2007; Fabes et al., 1999; Lam et al., 2012; Van der Graaf et al., 2014). This was supported in our data as girls reported more prosocial behaviors. One possible interpretation of this gender difference is that girls may be more prone to affective engagement with the emotions of others (Derntl et al., 2010), and thus prosocial behavior and empathy are more natural or automatic for adolescent girls than boys. Indeed, some research suggests that women are more susceptible to automatic contagion and mimicry of others’ emotions than men (Dimberg & Lundquist, 1990; Magen & Konasewich, 2011), and that prosocial behavior is more intuitive for women than men (Rand, Brescoll, Everett, Capraro, & Barcelo, 2016). In our sample, girls who demonstrated increased mesolimbic reactivity to the “how wide...” condition may have experienced increased motivational engagement in this context compared to the affective context, which would be a profile that does not align with the view that girls are more drawn or susceptible to affectively engage with the emotions of others. For these girls, reappraisal might be particularly important for helping to orient to the sadness of others.

Previous research has primarily focused on the social contexts in which adolescent neurobiology, including mesolimbic functioning, might reflect strength or risk for problems (Telzer, 2016). The current study expands on this work by focusing on how person-specific features might qualify the meaning of adolescent mesolimbic functioning, and is in line with calls for more research that considers how neurobiological effects are constrained by individual difference factors (Bartz et al., 2011; Miller, in press). The current study highlights the

importance of cognitive reappraisal (a trait level variable) for qualifying the effects of mesolimbic activity on adolescent prosociality, although differently for boys and girls. In addition, the overwhelming majority of past research on mesolimbic functioning and prosociality interpreted activation in mesolimbic regions as reflecting reward processing. However, this interpretation does not take into account other aspects of motivation supported by mesolimbic regions, like salience or effort, or that mesolimbic regions are involved in non-rewarding experiences, like aversive events (Bromberg-Martin et al., 2010). In our study, we interpret mesolimbic activity as potentially reflecting motivational processes, but more broadly defined than just focusing on value or reward. Thus, the current study was guided by theoretical frameworks that differ from previous studies on mesolimbic functioning and prosociality. Taking an interactionist approach, and considering mesolimbic functioning beyond reward processes, may help to explain past inconsistencies that mesolimbic activity can be linked to both more and less prosociality.

This study has several limitations that should be considered. Our emotional face processing task required awareness and conscious assessment of one's own sadness. Subjective feelings are an important aspect of empathy (Miller, Nuselovici, & Hastings, 2016), but the process of conscious introspection may alter other aspects of emotion. For example, Kassam and Mendes (2013) found that subjectively reporting on emotion altered physiological response to emotionally evocative stimuli. Thus, it is possible that the act of reflecting and reporting on one's own emotional state may change or interrupt how the brain responds to social cues like emotional faces in everyday life. Future research should examine interactions between cognitive reappraisal and mesolimbic activity in response to other kinds of tasks with different emotional demands. In addition, it should be noted that this study used a high-risk sample of Mexican-

origin adolescents. We consider this a strength, as this population is rapidly growing in the United States but is also understudied. Research suggests that there are cultural differences in reappraisal (Haga et al., 2009), prosocial behavior (Knight & Kagan, 1977), and empathy (Trommsdorff, Friedlmeier, & Mayer, 2007), and Latino and white youth differ in the neural processes that underlie prosocial decisions in some contexts (Telzer et al., 2010). Thus, it is possible that some of the findings of the current study are specific to Mexican-origin youth. Research that uses diverse samples would allow for testing of cultural differences in underpinnings of prosociality. Lastly, some mesolimbic dopamine neurons appear to be more involved in assigning motivational value, whereas others are more involved in motivational salience (Bromberg-Martin et al., 2010). Our analysis did not allow for differentiation of mesolimbic regions involved in these different components of motivation. A functional localizer task, like a monetary incentive delay task, may allow for identification of subregions of the mesolimbic system that are more specific to different dimensions of motivation. Deriving ROIs from this kind of task would potentially provide greater specificity regarding the kinds of motivational processes in our emotional face processing task that interacted with reappraisal to predict prosociality.

In summary, the current findings provide a complicated picture of adolescent mesolimbic activity as a neural factor that can serve as a risk or strength. Whether or not mesolimbic activity during sadness introspection undermines or supports prosociality may depend on adolescents' tendencies to use effective emotion regulation strategies like cognitive reappraisal. For boys, reappraisal may play an important role in shaping whether motivation-related neural engagement during sadness introspection contributes to approach or avoidance of prosociality. Conversely, reappraisal may be more important for prosociality in girls who experience sadness introspection

as less motivationally relevant. These findings inform our understanding of which adolescents stand to benefit from using effective emotion regulation strategies when it comes to prosociality.

## CHAPTER 5

### GENERAL DISCUSSION

Social cognitive, affective, regulatory, and motivational processes contribute to prosociality. Further, researchers have used diverse methodologies to study prosociality at different levels of analysis. This dissertation focused on integrating different methodologies in an attempt to understand the links between facets of prosociality. This chapter presents the significance of this program of work and potential future directions.

#### **Linking Autonomic and Central Nervous System Processes**

One of the goals of this research was to understand how neural and visceral processes are integrated, and the implications of this integration for understanding the neurobiological bases of prosociality. Some models of empathy provide a conceptual framework that links autonomic with central nervous system processing. For example, the perception-action model of empathy (Preston & de Waal, 2002) proposes that the perception of someone else's emotional state activates mirrored representations in the observer, which then activates similar somatic and autonomic responses while also helping to facilitate cognitive understanding of the target person's emotional state. Further, research on empathy for pain, which dominates the social neuroscience literature, emphasizes the role of the insula and anterior cingulate cortex in generating and coding autonomic states (Singer, Critchley, & Preuschoff, 2009). However, very few studies have empirically studied the interrelations between central and autonomic processes, and the studies that have been done have focused on empathy for pain rather than others' emotional suffering (Azevedo et al., 2013; Gu et al., 2015).

In the psychophysiology literature, autonomic regulation is typically measured in two contexts – at rest and in response to stimuli. This dissertation assessed links between autonomic



regulation in both contexts with neural functioning. In Study 1, parasympathetic influence at rest was inversely associated with neural response to emotional faces in the mirror neuron system, insula, and amygdala. In Study 2, right temporoparietal junction (TPJ) functioning was observed to be critical for instantiating autonomic responses to others' emotional suffering. These studies are the first attempts to link central and autonomic nervous system processes in the context of responding to others' emotions.

Importantly, heart rate variability (HRV) at rest reflects parasympathetic activity that would be expected to be manifest before exposure to emotional faces, and consequent neural activity, began. The vagus nerve is the main mechanism of parasympathetic nervous system activity and provides bidirectional communication between the brain and body. Efferent vagus nerve activity primarily originates in the nucleus ambiguus (NA), whereas afferent and efferent fibers meet in the nucleus of the solitary tract (NTS) (Thayer, Loerbroks, & Sternberg, 2011). Importantly, the NTS and NA regions of the brain stem are directly connected via interneurons (Bennarroch, 1993; Thayer & Lane, 2009). Although HRV reflects efferent effects of the vagus nerve on the heart (i.e., vagal outflow from the brain) (Malik & Camm, 1993), this vagal activity is also indirectly a function of input from the NTS which integrates efferent and afferent vagal regulation and has ascending pathways to brain areas important for cognition and affect (Thayer et al., 2011). Thus, in interpreting the Study 1 findings, resting HRV may not reflect only top-down (i.e., information from central to autonomic nervous system) or bottom-up (i.e., information from autonomic to central nervous system) regulation of neural reactivity to emotional faces, but rather states of bidirectional central-autonomic integration that underlie perceptions of safety and shape how the brain responds in emotional contexts (Thayer et al., 2012). From this interpretation, lower HRV may indicate a state of resting central-autonomic

integration underlying greater resting vigilance for threats or other challenges. This resting state, in turn, may facilitate the activation of neural pathways that evoke empathic arousal and reactivity when faced with others' emotions. Whether this supports or impedes prosocial behavior and compassion is unclear, but researchers have long proposed that too much arousal can lead to self-oriented responding (Batson, 2011). Thus, one might expect low resting HRV to be associated with less prosociality, and a number of studies have found this to be the case (Miller et al., 2017; Taylor, Eisenberg, & Spinrad, 2015). Consistent with this research, the current observation that individuals with lower resting HRV evidenced greater activity in regions of the social brain associated with negative emotional reactivity suggests a lower threshold for threat-related empathic arousal that might interfere with other-oriented responding.

In addition to resting autonomic activity, this dissertation examined central nervous system regulation of autonomic *reactivity*. In Study 2, transcranial magnetic stimulation (TMS) of the right TPJ decreased parasympathetic flexibility and decreased withdrawal of sympathetic nervous system activity in response to a sad film clip, and also elicited more hostile and less compassionate subjective emotional responses. The right TPJ is critical for perspective taking and self-other distinction (Lamm et al., in press), which can influence physiological processes (Buffone et al., 2017), but the role of the right TPJ in influencing autonomic reactivity had not previously been investigated. The right TPJ is not directly connected to regions that control autonomic outflow (e.g., nucleus ambiguus), but is functionally connected to the medial PFC during social emotion tasks (Burnett & Blakemore, 2009). The medial PFC is also involved in social cognition (Frith, 2007), and is a critical hub in the neurovisceral integration model of neural control of cardiac autonomic activity (Thayer et al., 2009). More specially, the medial PFC inhibits subcortical circuitry (e.g., amygdala, hypothalamus, subregions of brain stem)

important for upregulating autonomic activity (Thayer et al., 2009). One interpretation of the Study 2 findings is that the right TPJ is a critical node within a network important for social cognition, and disrupting its functioning has downstream consequences for autonomic responses in the body by way of connectivity with the medial PFC. This could be one functional pathway linking the right TPJ and related social cognitive processing with autonomic aspects of affectively responding to others' suffering. This interpretation is speculative, and research that integrates measures of functional connectivity with autonomic activity in an empathy context will be necessary to more fully test this possibility.

Taken together, Studies 1 and 2 contribute to brain-body models of empathy-related responding in two ways: 1) examining how neurovisceral integration at rest constrains neural response in an emotional context, and 2) examining how a cortical region implicated in social cognition is important for autonomic reactivity in an emotional context. The findings speak to brain-body model that consider the implications of neurovisceral integration and top-down regulation (central nervous system regulating autonomic nervous system) for prosociality.

### **Expanding Our Interpretation of Neurobiological Measures**

One implication of these multilevel studies is that they help to expand and clarify our interpretation of neurobiological measures. The Study 1 findings broaden our understanding of how we should interpret parasympathetic activity at rest in terms of social-emotional responding. There is a growing sentiment in the literature that resting parasympathetic activity as measured by HRV marks the functional integrity of prefrontal-subcortical inhibitory circuits that underlies individual differences in emotion regulation and social competence (Beauchaine & Thayer, 2015; Porges, 2011). However, resting parasympathetic activity likely has other functions too, potentially including threshold for arousal in response to the emotions of others (i.e., empathic

arousal) (Hastings et al., 2000). In Study 1, the observed negative association between resting HRV and mirror neuron, insula, and amygdala reactivity to emotional faces provides evidence at the neural level that parasympathetic activity can constrain reactivity and arousal in response to others' emotional cues (Miller et al., 2017). These findings complement previous research examining HRV in relation to self- and other-report measures of empathy and compassion and behavioral measures of prosocial behavior (Kogan et al., 2014; Miller et al., 2017).

The Study 2 findings highlight the importance of the right TPJ in affective processes, thus blurring the distinction between circuitry specific to social cognition versus affective empathy. This finding builds and expands on the extant social neuroscience literature, which considers the right TPJ to be specialized and critical for social cognition (Frith, 2007; Saxe & Kanwisher, 2003), and emphasizes the distinctiveness of separate brain regions for cognitive and affective aspects of responding to others' suffering (Preckel et al., 2018; Shamay-Tsoory, 2011). However, this "specialization" focus ignores the potential interactions between cognitive and affective processes, which has been emphasized in the psychology literature on empathy (Zaki & Ochsner, 2012). Study 2 suggests that although the right TPJ might be critical for social cognition, its functioning also contributes to experiential and physiological aspects of empathy. Thus, when responding to others' emotional suffering, the distinction between circuitry for cognitive versus affective processes may not be as clear as is often proposed by traditional social neuroscience models of empathy.

In the social neuroscience literature, mesolimbic regions are often referred to as the brain's "reward centers" or "reward system". This emphasis on reward ignores research on mesolimbic involvement in other motivational processes, like salience and effort (Bromberg-Martin et al., 2010), and does not fit with some of the mixed findings in the literature linking

mesolimbic activity to both more and less prosociality. Further, the interpretation of neurobiological measures is often dependent on other features of an individual (Bartz et al., 2011). In accord with this perspective, Study 3 suggests that the effects of mesolimbic functioning during emotion introspection are moderated by cognitive reappraisal differently for boys and girls. This emphasizes a broader interpretation of mesolimbic activity as important for processes beyond reward, and mesolimbic effects as dependent on individual difference moderators.

### **Integration of Theories**

This dissertation project utilized a multilevel analysis in an effort to better our understanding of prosociality as a complex construct. This approach allowed for integration across different theoretical frameworks developed in psychology, psychophysiology, and neuroscience.

Studies 1 and 2 help to integrate theories developed in psychophysiology (i.e., Polyvagal Theory; Porges, 2011) with social neuroscience models of empathy, compassion, and social cognition. Polyvagal theory provides a theoretical framework for the essential role of the autonomic nervous system, and the vagus nerve in particular, in prosociality (Hastings & Miller, 2014). The myelinated vagus originates from the NA region of the brain stem and exerts parasympathetic regulation of the sinoatrial node, effectively slowing heart rate (Porges, 2011). Thus, polyvagal theory posits that resting vagus nerve activity, as measured by HRV, indicates effective cardiac regulation underlying calm states (Porges, 2011). Similarly, the neurovisceral model emphasizes vagal regulation of cardiac activity as indicative of evaluation of environmental safety (Thayer et al., 2012). Other branches of the vagus nerve also originate in the NA and extend out to target muscles in the head, face, and neck important for orienting and

expression of emotion (Porges, 2011). Thus, the polyvagal theory posits that the vagus nerve is one part of a social engagement system. In accordance with this perspective, maintaining or upregulating vagal activity when witnessing someone in distress supports one's preparedness to respond prosocially (Hastings & Miller, 2014; Stellar et al., 2015), whereas sympathetic nervous system activation may contribute to avoidance or defensive responding (Brown, Brown, & Preston, 2011). In addition, recent work highlights the importance of vagal flexibility (i.e., the capacity to down and upregulate vagal activity as conditions change) in prosocial responding (Miller, Kahle, & Hastings, 2015; Miller et al., 2016). On the other hand, neuroimaging research has focused on brain regions implicated in social-emotional processes which, together, are sometimes referred to as the "social brain" (Adolphs, 2009; Blakemore, 2008). This research has implicated regions like the mirror neuron system, insula, and amygdala in affective and sensorimotor aspects of empathy (Lamm & Majdandžić, 2015; Shamay-Tsoory, 2011), and the right TPJ in cognitive aspects of empathy (Preckel et al., 2017). Some of these regions, like the insula and amygdala are known to be important for autonomic regulation (Menon & Uddin, 2010; Thayer et al., 2009), but have not explicitly been tied to vagal nerve functioning and polyvagal theory.

Taken together, the psychophysiology and social neuroscience literatures have developed separate neurobiological models of prosociality that focus on the autonomic and central nervous systems, respectively. Considering these theoretical frameworks in isolation ignores important components of prosociality and the potential links between them. This dissertation provides novel information about the nature of prosociality by integrating these frameworks. Study 1 integrates polyvagal and neurovisceral models with the empathy and mirror neuron system literatures. The findings suggest that resting neurovisceral states underlying perception of

environmental safety (either consciously or nonconsciously), which have been outlined in the psychophysiology literature, constrains neural mechanisms underlying sensorimotor resonance (i.e., mirror neuron system) and empathic arousal (i.e., insula and amygdala), which have been identified in social neuroscience. Together, these findings lend support to the perspective that resting HRV may correlate with threshold for arousal (Hastings et al., 2000; Miller et al., 2017), but also provide novel information about the links between resting HRV and neural systems implicated in empathic arousal. In Study 2, the right TPJ was identified as critical for instantiating vagal flexibility and deactivation of the sympathetic nervous system. Previous research highlights these aspects of autonomic reactivity as important for prosocial responding (Hastings & Miller, 2014; Miller, in press), but these studies have not considered the potential contributions of social cognition systems. Likewise, previous research on the right TPJ has not considered its potential importance for experiential and physiological aspects of responding to others' suffering. One interpretation of Study 2 is that effectively taking another person's perspective, which is dependent on the right TPJ, activates feelings and autonomic states that support orienting to others and prosocial action. The link between right TPJ and experience and autonomic nervous system functioning could not have been identified by studying these levels of analysis in isolation.

Study 3 integrates motivation, emotion regulation and introspection, and gender difference perspectives on prosocial behavior. Few studies have considered the role of emotion introspection processes in prosocial behavior, which is surprising given that reflecting on how someone else's emotion makes you feel is another form of mentalizing or perspective taking (Weissman et al., in press). Conversely, previous research in psychology and neuroscience has considered the main effects of cognitive reappraisal (Lebowitz & Dovidio, 2015) and activity in

motivation-related brain regions (Moll et al., 2006) on prosocial behavior, but not their interaction. Study 3 showed that activation in motivation-related regions in an emotion introspection context predicted more and less prosocial behaviors for youth who reported more and less cognitive reappraisal, respectively. This finding fits with traditional psychology models suggesting that emotion regulation is important for shaping motivational drive to approach or avoid others in distress (Eisenberg, 2010). However, the nature of this interaction differed for boys and girls. Study 3 adds to a literature suggesting that boys and girls rely on divergent processing when engaging with the emotions of others (Derntl et al., 2010). Emotion introspection might be an important context for assessing how boys and girls rely on different strategies when assessing their own emotions in empathic face-to-face contexts.

### **Clinical Implications**

From a clinical perspective, elucidating the neural regions that are causally necessary for feeling compassion and avoiding hostility has implications for understanding and treating a broad range of disorders characterized by social deficits. For example, a lack of concern for others' well-being is one of the hallmark characteristics of psychopathy (Hare, 2003), and parents who engage in child abuse experience their children's distress as more irritating than other parents (Frodi & Lamb, 1985). In addition, some research suggests that ineffective control of aggression and harsh parenting are linked to decreased parasympathetic flexibility (Guliano et al., 2015; Miller et al., 2013) and heightened sympathetic activation (Hubbard et al., 2002; Joosen, Mesman, Bakermans-Kranenburg, & van Ijzendoorn, 2013). Study 2 used low-frequency repetitive TMS to, presumably, *inhibit* right TPJ functioning and alter these aspects of participants' feelings and autonomic physiology. However, there are other brain stimulation protocols that can increase cortical excitability, like high-frequency repetitive TMS and anodal



transcranial direct current stimulation (tDCS) (Hallett, 2007; Nitsche & Paulus, 2000). Whether excitatory stimulation of the right TPJ can enhance experiential and physiological aspects of prosociality in psychiatric populations is an open question. The findings from Study 2 could be useful for guiding future investigations of the utility of TMS for treating social disorders in ways similar to current TMS treatment for mood disorders like depression and bipolar disorder.

This dissertation research also has clinical implications for interpretation of resting HRV, which is increasingly being treated as a transdiagnostic marker of mental illness (Beauchaine, 2015). This perspective posits that HRV reflects prefrontal inhibition of subcortical threat-related circuitry that underlies individual differences in emotion regulation versus dysregulation, with lower resting HRV contributing to greater emotion dysregulation and risk for psychopathology (Beauchaine & Thayer, 2015). To the extent that these processes are important for prosociality, and that prosociality is an important component of healthy social-emotional functioning, then one would expect greater HRV to be linked with greater prosociality. However, some research has found the opposite (Eisenberg et al., 1996) or that moderate levels of resting HRV are linked to greater prosociality (Miller et al., 2017). Some disorders characterized by deficits in empathy, including psychopathy, are associated with lower resting heart rate and higher HRV (Hansen, Johnson, Thornton, Waage, & Thayer, 2007; Raine, 1997). The Study 1 findings complement this literature by showing that higher resting HRV is negatively associated with neural mechanisms of increasing empathic arousal in a community sample. This finding should be replicated in clinical populations, but it calls into question the generalizability of HRV as biomarker of mental illness.

Study 1 and 2 used community samples, whereas Study 3 used a sample of Mexican-origin adolescents at elevated risk for depression-related problems. Latino adolescents generally

face more disadvantage than white adolescents and thus are at greater risk for mental health problems (Conger et al., 2012; Folwer, Tompsett, Braciszweksi, Jacques-Tiura, & Baltes, 2009). Recent research with this population suggests that reduced neural reactivity during emotion introspection in response to faces has implications for the development of externalizing problems (Weissman et al., in press). However, Study 3 suggests that cognitive reappraisal might moderate neural reactivity during emotion introspection to predict prosocial behaviors, which are typically negatively linked with externalizing problems (Flouri & Sarmadi, 2016). Prosocial behaviors might be especially protective for at-risk latino adolescents, as some research suggests that helping others might serve as a compensatory pathway to health for populations that might otherwise be considered at-risk (Miller et al., 2015). Study 3 supports the idea that cognitive reappraisal in adolescence is an important target for intervention (Garnefski et al., 2005), but it may be more important for specific groups of boys and girls. This may inform more targeted interventions for fostering adolescent prosocial behavior.

## **Conclusions**

This program of work represents a significant step forward in multilevel neurobiological analysis of prosociality. The brain and body do not function independently of each other, and this dissertation provides empirical evidence that speaks to how processes in the central and autonomic nervous system interact to promote or constrain empathic arousal and compassion. This dissertation also integrated multiple theoretical frameworks, and the findings offer novel hypotheses about the neurobiological organization underlying trait and state differences in empathy-related responding. Furthermore, this work provides causal testing of neurobiological models of responding to others' emotional suffering that are almost completely based on correlational evidence. This is a critical step in progressing our understanding of how humans

are wired to respond to the emotions of others. Beyond basic science, this research has clinical implications for understanding and treating disorders characterized by deficits in prosociality. These findings may help to guide future work on the utility of TMS for treatment of antisocial disorders, and on the utility of HRV as a biomarker of mental health, as well as help to inform research on targeted interventions for fostering prosocial behavior in adolescence.

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