Prosocial Decision Making: Brain-Behavior Relationships and Neuromodulation

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Prosocial Decision Making:
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ABSTRACT OF THE DISSERTATION

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Brain-Behavior Relationships and Neuromodulation

by

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Doctor of Philosophy in Neuroscience
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Humans and other social animals seem to place a positive reward value on the welfare of others. Many believe that this "prosocial inclination" is driven by empathy for others, though the mechanisms underlying this relationship remain unclear. An important subprocess within empathy is our ability to share in the internal and behavioral states of others, a process we will refer to as self other resonance. Evidence suggests that this ability is heavily driven by neural resonance, a brain mechanism in which the perception of internal states and behavior in others triggers correlated activity in motor, somatosensory and affective brain systems, potentially creating shared information states between individuals. Self-other resonance may foster prosocial inclinations by a simulation mechanism according to which the more we share in others' states, the more we may be inclined to treat them as we would ourselves. Conversely, contextual factors that inhibit or enhance our degree of self-other resonance with others, like their group affiliation,

their social distance, their race or their perceived character, also seem to modulate our prosocial inclinations towards them, suggesting common control mechanisms.

We hypothesize that individual differences in the neural correlates of self–other resonance and its control can predict individual differences in the behavioral correlates of prosociality and its modulation in response to context. We first examined which neural data during self-other resonance tasks was most informative about prosocial behavior in the Dictator Game, a task in which subjects decide how to allocate real money between themselves and 24 players (represented with a neutral-expression headshot, a name and a yearly income) of high and low incomes (Experiment 1, n=20). We then attempted to causally elucidate the relationship between self-other resonance and control by the use of a behavioral intervention (Experiment 2, n=34) and disruptive neuromodulation (Experiment 3, n=58), designed to enhance self-other resonance and disrupt top-down control, respectively. Finally, since all 78 subjects from experiments 1 and 3 underwent identical neuroimaging and behavioral protocols, we investigated gender differences in trait empathy and neural correlates of self-other resonance, including functional connectivity among regions implicated in self-other resonance and its control.

In Experiment 1, we found that individual differences in subjects' vicarious activation in regions associated with self-other resonance (limbic system and somatosensory cortex), and regions associated with top-down control of pain, motor behavior and affect (temporoparietal junction, medial and dorsolateral prefrontal cortex) was correlated with individual differences in subjects' prosocial decisions as well as their tendency to modulate these decisions in response to contextual information. Furthermore, we found evidence for functional connectivity between these self other resonance and top-down control areas, and found that this functional connectivity was also correlated with prosocial decisions. These findings suggest that self other resonance drives greater prosocial inclinations, while top-down control results in inhibition of prosocial inclinations, at least in the experimental setting we adopted. Indeed, disruptive neuromodulation of two putative control areas resulted in reliable increases in prosocial decisions (Experiment 3). The behavioral intervention designed to engage self-other resonance, on the other hand, did not show evidence of increasing prosocial decision-making (Experiment 2), though it did significantly alter the distribution of subjects' offers to low-income players (increased normality and reduced variance). This null finding cannot exclude that more effective or longer interventions may indeed boost prosocial inclinations. Last, in examining gender differences, we found evidence for increased top-down control in males and increased bottom-up perceptual processing in females. This is consistent with previous findings in empathy research suggesting that females are more prone to vicariously respond to the states of others, while males are more prone to engage top-down control of affect and vicarious responding.

These results jointly suggest that self other resonance and control processes may be an important component of prosocial decision-making, by modulating the extent to which we put others' welfare on par with our own, even when social cues typically associated with self other resonance are very limited. An important theoretical question is why self other resonance and its control seem to play such a crucial role in prosocial decision making in these conditions (when social cues are limited). We suggest that the embodied cognition framework provides a plausible functional mechanism that accounts for these findings.

The dissertation of Leonardo Christov Moore is approved

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Dedication

This dissertation is dedicated to my parents, Alice Laetitia Christov and George Mead Moore, for nurturing my curiosity about the world, encouraging empathy and compassion for others, and reminding me of the responsibilities that come with being a researcher in a time when scientific findings and their interpretation form the currency of accepted truth. This is also dedicated to my sister and best friend, Indiana Christov Moore, for inspiring me with her explorative, artistic and kind being, and accompanying me in this strange and beautiful world.

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Introduction

Prosocial Behavior vs. Prosocial Inclination

Prosocial (helpful, cooperative, sympathetic) behavior clearly exists in humans as well as other social animals. However, the reasons for this behavior are less clear, in part because prosocial behavior can have many underlying motivations, such as a) learned cultural norms, b) concern for reputation and reciprocity, and/or c) prosocial inclinations (Penner et al., 2005). This thesis will focus on the last of these, and aims to test whether, as many researchers have proposed, prosocial inclinations arise from experiential forms of empathy.

Evidence from evolutionary biology, anthropology, economics and now neuroscience suggests that humans place a positive reward value on the welfare of others (Fehr & Camerer, 2007, Fehr & Fischbacher, 2003, Moll et al., 2006, Penner et al., 2005, Preston & de Waal, 2002). We are driven to alleviate the suffering of others and increase their well-being, even in situations where we can derive no visible advantage from acting in this way. Why might this be? At the level of ultimate (or evolutionary) causation, there are many mechanisms (group selection, kin selection, reciprocity etc.…) that can explain why one organism would risk its survival (and hence reproductive success) to aid another (Darwin, 1871, Grafen, 1984, Preston & de Waal, 2002, Trivers, 1971). However, the proximate causes (underlying mechanisms) for this prosocial inclination remain unclear.

Prosocial Inclinations and Empathy

Many researchers believe that our prosocial inclinations are linked to experiential forms of empathy that allow us to share in the states of others (De Vignemont & Singer, 2006, Smith, 2006). Traditionally, the concept of experiential (or *affective*, as contrasted with *cognitive,* or *inferential*) empathy has been limited to our sharing in the pain, visceral experiences (like nausea) and emotions of others (Smith, 2006). However, we also share in the motor states of others, via spontaneous or deliberate imitation (Chartrand & Lakin, 2013, Iacoboni, 2009). I will be using the term *self other resonance* (**SR**) as an umbrella term to describe the tendency for our internal *and* behavioral states (experiential empathy and imitation) to become interdependent with those of others. I propose that this "resonance" between self and other in affect, somatosensation and behavior, may also blur the boundaries between the affective reward value or utility (Fehr & Camerer, 2007) given to our and others' welfare in our decision-making. In other words, just as we tend to process the behavior and internal states of others as we would our own, perhaps we also process the *outcomes* of others as if they were our own (Preston & De Waal, 2002, Van Baaren et al., 2004).

Neural Substrates of Self-other Resonance and Their Relation to Prosocial Inclination

The neuroscientific study of our "resonance" with others began with the discovery of mirror neurons, cells in the parietal and frontal lobe that show similar responses whether the subject is performing a motor action or observing actions in another (Di Pellegrino et al., 1992, Keysers &

Fadiga, 2008, Rizolatti & Craighero, 2004,). This cellular phenomenon of perception-action matching (Preston& De Waal, 2002) has since been observed at the systems level for a wide variety of processes. Neuroimaging studies have found that we recruit overlapping areas in inferior parietal and premotor cortex while engaging in purposeful motor actions or observing those same actions (Caspers et al., 2010). Studies using Transcranial Magnetic Stimulation (TMS) have found that when observing actions, the excitability of motor cortex increases in a manner specific to the muscle groups that would be employed in the observed action (Fadiga et al., 1995). fMRI studies have found that subjects activate areas implicated in affective processing (like the anterior insula and amygdala) when observing, executing or imitating emotional facial expressions (Carr et al., 2003, Pfeifer et al., 2006). Similarly, a large body of research has found that subjects activate somatosensory, cingulate and limbic structures associated with pain processing (the "pain matrix") when observing others experiencing painful stimuli, though vicarious activation depends on both intra- and interpersonal factors as well as the properties of the stimulus (reviewed in Lamm & Singer, 2011). A similar pattern of activation has also been observed for the perception and experience of disgust (Jabbi et al., 2011, Wicker et al., 2003). This interdependence between our neural states and those of others is known as neural resonance (Zaki & Ochsner, 2012), and is a likely neural substrate for SR.

A number of studies have demonstrated that our prosocial *inclinations* towards others are correlated with neural resonance for pain (Hein et al., 2010, 2011, Ma et al., 2011). Although behavioral forms of SR such as spontaneous imitation (mimicry) are linked to prosocial behavior (Chartrand et al., 2013), no study prior to the work reported here has examined links between prosocial inclinations and the *neural correlates* of other forms of SR, beyond pain.

Top-down Control of Self-Other Resonance

SR is commonly thought of as a reflexive process, not subject to conscious volition or control. However, this presents a problem: If humans have a reflexive tendency to resonate with the affective states and behavior of others, why don't we mimic the behaviors of others and feel what others feel constantly? Conversely, how is it that we can intensely feel the pain and emotions of those we love and trust, yet remain relatively dispassionate when confronted with the suffering and emotions of those we hate or distrust? In response, we propose that SR as defined here is a prepotent tendency in humans that must be *tonically and contextually inhibited*. Maintaining a stable sense of self requires that we have some tonic control over the extent to which we resonate with others (Decety and Sommerville, 2003, Spengler, et al., 2010). Indeed, TMS-induced transient interference to parietal areas involved in identifying self and other (Uddin et al., 2006) and in imitation (Caspers et al., 2010) has been shown to affect the ability to distinguish between self and other. In neurological patients, lesions to prefrontal cortex (De Renzi et al., 1996, Lhermitte, 1983) have been shown to cause compulsive imitation of others' behavior.

Our affective, somatosensory and behavioral resonance with others is also modulated by individual disposition and inter-personal context, highlighting the importance of control processes for this research subject (for reviews, see Chartrand et al., 2013, Hein & Singer, 2008, Hatfield et al., 1993, Lamm & Singer, 2011). Given the largely reflexive nature of SR, we propose that top-down control mechanisms in the brain exercise a primarily inhibitory, *implicit* control over SR.

Tellingly, the factors that seem to regulate affective, somatosensory and behavioral SR (group affiliation, race, status, personality types, social distance, perceived moral character, etc.) have an analogous effect on prosocial inclinations as manifested in behavior and economic decisions (Engel, 2011, Penner et al., 2005). We propose that the neural mechanisms we use to *control* SR may correspondingly control the extent to which we put others' welfare on par with our own, and *hence our prosocial inclinations towards them*.

Hypotheses

In summary, we propose the following:

A) Prosocial inclinations during decision-making are driven by SR.

B) SR is fairly reflexive yet subject to top-down inhibitory control.

C) Control can be tonic and/or contextual.

D) If A-C, are true, then top-down control also inhibits prosocial inclinations in decision-making.

Project Summary

These hypotheses carry with them a central assumption that is also tested within this project: that there is an overlap or strong link between systems used for SR and its implicit control, and those employed during prosocial decision-making. As we will discuss at greater length in the conclusions, these hypotheses are inspired by the embodied cognition framework, which posits that we ground higher-level concepts on our perceptual and motor experiences (Barsalou, 2008). Simply put, when we make prosocial decisions, we obviously think about other people. If our concepts regarding other people are grounded in the perceptual and motor experiences we have when interacting with them, it is likely that *the way* we interact with others in real-time (showing more or less SR in the form of spontaneous imitation and affective, experiential empathy) shapes the way we think about them and the decisions we make toward them.

In chapter 1, we tested (A-C) by examining correlations between imaging data during SR tasks (perception of pain in others and observation and imitation of facial emotional expressions) and subjects' prosocial inclinations in the Dictator Game, an economic game that measures pure monetary altruism by examining how subjects allocate money between themselves and others. In the modified Dictator Game used here, subjects have no monetary incentive to share (the opposing player cannot reject their offer), they perform the game unsupervised, and their data is kept completely anonymous (to control for effects of supervision and reputation; this control also prevents us from performing brain imaging during the Dictator Game).

We then performed causal tests of (A-D) in the following two chapters. In chapter 2, we examine whether behavioral interventions aimed at stimulating SR in a bottom-up fashion could have an analogous effect on prosocial inclinations. In chapter 3, we apply disruptive neuromodulation to prefrontal areas implicated in top-down control in experiment 1 (dorsomedial and dorsolateral prefrontal cortex) and examine whether this disruption of top-down control increases subjects' prosocial inclinations in the Dictator Game.

In the process of carrying out these studies, we collected a fairly large (n=78) and multidimensional dataset (structural and functional neuroimaging data, trait empathy measures and economic behavior), which we used to investigate a related issue in the social neuroscience of empathy. Gender is increasingly recognized as an important factor within empathy (recently reviewed in Christov-Moore et al., 2014). However, there are only a handful of studies examining gender differences in the neural correlates of SR (neural resonance). In chapter 4, we examine gender differences in trait empathy, then examine gender differences in activation and functional connectivity during two SR tasks after *controlling* for differences in trait empathy.

Innovation

First, while there are several studies relating neural resonance for pain to prosocial behavior, this is the first project to show an analogous relationship with neural resonance during imitation of affective expressions. Second, while there are previous studies in neuroimaging and neuromodulation examining economic behavior, they have focused primarily on the acceptance or rejection of offers in the ultimatum game, a decision which (as we discuss) is more ambiguous in its underlying motivation than the more simple behavior we examine here: offers in an unsupervised, anonymous dictator game. Third, there are no existing studies examining how *connectivity* during neural resonance tasks is related to prosocial behavior, limiting, in our view, the neurobehavioral conclusions that can be drawn from the results. Indeed, while extant models of empathy for pain incorporate affective regulation, none of the cited studies examining neural resonance for pain provide a mechanistic account for why the observed relationship exists. We have employed activation, connectivity and causal tests of our conclusions to attempt to better define a neurobehavioral model that encompasses both neural resonance and prosocial inclinations. Fourth, despite evidence for top-down modulation of SR in response to contextual cues that are also relevant for prosocial inclinations, no study to date has examined how neural correlates of SR *and* its control can predict modulation of prosocial inclinations. Last, this is the first study to date examining the effect of neuromodulation to two prefrontal areas implicated in top-down control on Dictator Game offers.

Chapter 1. Correlating Individual Differences in Neural Resonance with Individual Differences in Prosocial Decision-Making

Embodied Neuroeconomics: Self-Other Resonance and Prosocial Inclinations

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Abstract

Humans seem to place positive reward value on prosocial outcomes such as sharing, comforting behavior, and cooperation. Evidence suggests that this prosocial inclination is driven by our reflexive tendency to share in the observed sensations, emotions and behavior of others, a phenomenon we will refer to as “self-other resonance”. However, contextual factors (e.g., group affiliation, trustworthiness) modulate both self-other resonance and prosocial inclinations, suggesting that both are subject to top-down control. In this study, we examine how individual differences in neural correlates of self-other resonance and its top-down control relate to prosocial decision-making towards individuals of different socioeconomic status (SES) in the Dictator Game.

Subjects performed two tasks previously shown to engage somatosensory and behavioral/affective self-other resonance, while undergoing fMRI: Observation of a human hand pierced by a needle, and observation and imitation of emotional facial expressions. Outside the scanner, we assessed subjects’ prosocial inclinations and their contextual modulation with a modified Dictator Game in which they were asked to allocate $10 per trial between themselves and 24 players of low or high SES (a proxy for perceived need).

Subjects’ costly sharing in the Dictator Game was *positively* correlated with activation in neural systems associated with self-other resonance (such as the amygdala and superior parietal cortex) and *negatively* correlated with activation in systems implicated in the control of pain, affect and imitation (such as the medial and dorsolateral prefrontal cortex). Activity in these latter systems also predicted the degree to which subjects’ sharing diminished towards players of high incomes. Last, functional connectivity between areas involved in self-other resonance and top-down

control of affect (left/right amygdala and anterior cingulate cortex/right dorsolateral prefrontal cortex, respectively) was negatively correlated with costly sharing in the Dictator Game.

This study shows that neural resonance and its implicit control is correlated with the overall amount *and* modulation of costly sharing towards players of different perceived need, even when biological cues associated with self-other resonance are extremely limited. We propose that during decision-making about others' welfare relative to our own, we form embodied models of others (complete with corresponding sensorimotor and affective information) that we "resonate" with. This inner self-other resonance is then modulated in response to context, thus biasing our decisions towards prosocial outcomes in a context-sensitive fashion.

1.1. Introduction

Humans' ability to "resonate" with the internal and behavioral states of others may encourage prosocial behavior towards them. When we observe someone in pain or someone expressing emotion, behavioral, physiological and neural evidence suggests that we process the experience much in the same way we would our own (reviewed in Zaki & Ochsner, 2012). Additionally, we often imitate one another's behaviors (consciously or unconsciously) as a marker of affiliation and rapport (Chartrand & Bargh, 1999, Iacoboni, 2009, Lakin & Chartrand, 2003, Pfeifer et al., 2008, Sperduti et al., 2014). Humans are even able to similarly share in the implied states of fictional characters and absent third persons, suggesting that this ability is not limited to real-world, real-time interactions (Davis, 1983, Clay & Iacoboni, 2011). This ability to share in the internal and behavioral states of others, which we will refer to as "self-other resonance" (SR), is proposed to encourage prosocial motivations towards others (Aron & Aron, 1986, Batson, 1991, Eisenberg & Fabes, 2008, Masten et al., 2011, Smith, 2006). Indeed, neural and physiological correlates of SR with others' pain have been shown to predict prosocial behavior (Hein et al., 2010, 2011, Ma et al., 2011). The reason for this relationship remains unclear, but one possibility is that there are common systems at work. Indeed, recent research suggests that the interaction between motor, somatosensory and affective processing and top-down control are crucial for evaluations of others' beliefs, internal states and intentions (Frith & Singer, 2008, Gallese, 2007, Obhi, 2012, Pineda, 2009, Schulte-Ruther et al., 2007), as well as our conscious decisions about others' welfare (Camerer, 2003, Hewig et al., 2011, Greene et al., 2001, Oullier & Basso, 2010, Van 't Wout et al., 2006).

At the neural level, SR is typically associated with "neural resonance" (Zaki & Ochsner, 2012), the phenomenon of shared neural representations for the perception and experience of disgust

(Jabbi et al., 2011, Wicker et al., 2003), somatosensation (Bufalari et al., 2007, Masten et al., 2011,Singer et al., 2006), emotion (Carr et al., 2003, Pfeifer et al., 2008) and motor behavior (Keysers & Fadiga, 2008). Neural systems showing activity suggesting neural resonance are the frontoparietal human mirror-neuron system, the somatosensory cortex, anterior insula and amygdala (Zaki and Ochsner, 2012).

The blurring between self and other may encourage prosocial inclinations to help and cooperate with others (Aron & Aron, 1986, Batson, 1991, Eisenberg & Fabes, 2008, Masten et al., 2011, Smith, 2006). Perhaps the *less* we distinguish between others and ourselves at a behavioral and neural level, the *more* we are inclined to treat others' welfare as we would our own**.** Individuals who show increased neural resonance in response to others' *pain* tend to give more charitable donations (Ma et al., 2011). Hein et al. (2010, 2011) found that vicarious neural and physiological responses to the pain of in- and out-group members predicted later costly helping towards those same people. Behavioral forms of neural resonance, like spontaneous and deliberate imitation are also linked to prosocial behavior and social competence (Chartrand & Bargh, 1999, Lakin & Chartrand, 2003, Iacoboni, 2009, Pfeifer et al., 2008, Zaki & Ochsner, 2012). These findings suggest that SR and its top-down control may play a role in our evaluations of others' welfare relative to our own during social decision-making.

Economic decision-making is traditionally thought of as a purely rational, self-maximizing process. However, evidence shows that emotions, their physiological components and their regulation have an important role in decision-making, particularly when subjects are aware that their decisions affect *other humans* (Camerer, 2003, Hewig et al., 2011, Greene et al., 2001, Oullier & Basso, 2010, Van 't Wout et al., 2006). Correspondingly, areas implicated in top-down regulation of affect, somatosensation and behavior (dorsolateral prefrontal cortex, dorsal and ventral medial prefrontal cortex, among others) are also associated with economic and moral decision-making (Clark et al., 2008, Hare et al., 2010, Knoch et al., 2006, Volman et al., 2011, Tassy et al., 2012). This suggests that our decisions arise from the *interaction* between bottom-up and top-down processes.

Top-down control of neural resonance may modulate the extent to which we treat others' states (and outcomes) as if they were our own. We do not "resonate" with all others equally. Indeed, our closeness to others, their group affiliation and their perceived trustworthiness modulate neural resonance (Cheng et al., 2010, Gu & Han, 2007, Guo et al., 2012, Hein & Singer, 2008, Lamm et al., 2007, Loggia et al., 2008, Reynolds-Losin et al., 2013, 2014, in press, Singer et al., 2006). The prereflective nature of neural resonance suggests that this sensitivity to context is the result of *implicit* control. Furthermore, this control seems to be *inhibitory*. Prefrontal cortex lesions associated with compulsive imitative behavior suggest that some control mechanisms are always at play, unless damaged (Lhermitte, 1983, De Renzi et al., 1996). Top-down control of affective, somatosensory and motor processes in behavior and decision-making is subserved by a large set of prefrontal and temporal systems, including the medial and dorsolateral prefrontal cortex and temporoparietal junction (Banks et al., 2007, Brighina et al., 2010, Cho & Strafella, 2009, Decety & Lamm, 2007, Miller & Cohen, 2001, Spengler et al., 2009, 2010, Tassy et al., 2012, Volman et al., 2011, Winecoff et al., 2013). Correspondingly, we are not universally prosocial: individual predispositions and contextual factors like closeness, perceived need and affiliation modulate our willingness to share with others at personal cost in economic games (Engel, 2011) and in daily life (Trivers, 1971). These disparate findings from economics, social psychology and neuroscience suggest a link between our modulation of the perceived affective, somatosensory and behavioral importance of others and the relative reward value we place on their welfare.

Despite these findings, the relationship between SR, top-down control and prosocial decision-making remains unclear. We propose that during economic interactions (allocation or exchange of resources or cooperation) with a human “other” (present or implied), we implicitly assign reward values (or utilities, to use the neuroeconomic term) to the outcomes of our possible decisions (Fehr & Camerer, 2007). In order to assign such values, we must construct an internal model of the “other”, including their intentions, moral character, group affiliation, etc. In addition, this process may evoke perceptual, affective and motor experiences we associate with people from past experience. Indeed, a major proposed subcomponent of empathy is fantasizing (Clay & Iacoboni, 2011, Davis, 1983), our ability to take the perspective of absent or fictional characters and become correspondingly invested in their welfare (our screams to warn the hero onscreen about a monster behind them, or our sadness at their demise). This embodied model of the “other” may evoke SR and its top-down control in response to contextual cues (like perceived moral character, closeness, affiliation, etc.) thus influencing the relative utility of their welfare (Bechara & Damasio, 2005). This framework may explain why individual differences in neural and behavioral markers of SR and its top-down control have been correlated with prosocial inclinations in decision-making. We propose that activation in and connectivity between SR and top-down control systems inform individual differences in prosocial inclination and its contextual modulation.

To test this theory, we recruited subjects to perform two tasks, each examining an important component of SR, inside an MRI scanner. For the first task, subjects passively observed a human hand being prodded with a syringe or a q-tip (the Needle Test or NT). This was taken as a measure of reflexive SR in response to painful stimuli in another. For the second task, subjects either passively observed or actively imitated emotional facial expressions (Emotion imitation and observation or EOI). Vicarious activation of motor and limbic regions during observation of emotional facial expressions has been linked to empathic concern while similar activation during imitation of facial expressions is linked to social competence (Pfeifer et al., 2008). Indeed, imitation has been suggested as a way to *deliberately* engage vicarious emotional responses to the emotions of others (Carr et al., 2003). The needle test should reflect vicarious sensory and affective responses to another's pain and their control. The emotion imitation task, on the other hand, should reflect vicarious emotional processing evoked via deliberate motor imitation (Carr et al., 2003), and *its* respective control. We propose that despite the different contexts of these tasks, analogous patterns of SR- and control-related neural activity should correlate with prosocial decision-making.

However, prosocial decisions in economic games involving sharing are often due to multiple factors, such as strategy (sharing enough that the offer will not be rejected), or social pressure (altruistic behavior enhances reputation). To control for these factors, we employed a modified Dictator game, a task thought to measure altruistic fairness, in which subjects show rich variation in response to context (Aguiar et al., 2008, Benenson et al., 2007, Eckel & Grossman, 1996, Hoffman et al., 1996, Liebe & Tutic, 2010, Weiland et al., 2012). Subjects were tasked with dividing up a sum of money ($10/trial) between themselves and 24 players (represented with photographic profiles) representing people of *high* or *low* income (a proxy for socioeconomic status, or SES). This was done to introduce a contextual variable which could be ascribed to top-down control in the prosocial decision-making process (typically subjects share relatively less money with players of high income/low perceived need)(Engel, 2011). In order to engage subjects in the task, they were truthfully informed that a random subset of the players represented real people in Los Angeles who would *actually receive the money they allotted to them*. To control for social pressure, subjects were truthfully informed that they would perform the task alone and unobserved, that their data was linked to an ID number devoid of identifying information, and that their responses would be scored by a research assistant that did not come into contact with any subjects. This strict maintenance of anonymity and lack of supervision was the primary impetus for having subjects perform the study outside of the scanner. This, to the best of our abilities, allowed us to observe behavioral correlates of prosocial inclination and its modulation in response to the opposing player's perceived need, in absence of other regulating factors such as strategy or concerns about one's own reputation.

We propose that individual differences in SR and its top-down control reflect individual differences in prosocial decisions and their respective modulation during the Dictator Game (DG). Furthermore, we propose that top-down control in both contexts is inhibitory in nature. Accordingly, we hypothesized the following:

1. Brain activity during SR-evoking tasks is correlated with DG offers (a proxy for the relative utility of the players' welfare). The sign of the correlation should also reveal the nature of the processes implemented by the implicated areas, with a positive correlation implying greater SR and a negative correlation implying greater top-down control. In other words, subjects who show greater correlates of SR during scanning should also behave more generously, while subjects who show greater inverse correlations with offers should behave less generously, especially to high SES players.

2. Subjects' tendency to decrease their offers to high SES players (the normalized difference between their offers to high and low SES players) is also correlated with activation in areas typically associated with top-down control.

There are functional interactions between regions associated with SR and top-down control during the tasks and the strength of interaction will be correlated with subjects' offers.

1.2. Methods

1.2.1. Subjects

Subjects were 20 ethnically diverse adults aged 18-35 (9 female). All subjects were recruited from the local community through fliers. Eligibility criteria included: right handed, no prior or concurrent diagnosis of any neurological (e.g., epilepsy, Tourette's syndrome), psychiatric (e.g., schizophrenia), or developmental (e.g., ADHD; dyslexia) disorders, no history of drug or alcohol abuse. All recruitment and experimental procedures were performed under approval of UCLA's institutional review board.

1.2.2. Behavioral task

The Dictator Game (DG): Subjects were instructed to select a portion of a sum of money ($0-10 out of $10) to be given to a player (henceforth referred to as the *player*, to distinguish them from the subject throughout the manuscript), represented by a digital profile presented on a computer screen, for each of 24 trials. In each trial, subjects were presented with 1 of 24 full-color photographs (equalized for luminance) of neutral faces selected from stock photographs and the Nim Stim Face Stimulus Set (Tottenham et al., 2009) coupled with a name and a yearly income in dollars, both presented on the right portion of the screen in black letters with a white background (See figure 1.1). Player profiles had one of two levels of income: Low ($18,000-$30,000/yr) or High ($70,000-$200,000/yr). Income was used as a proxy for socioeconomic status (SES). Both genders were equally represented, while racial composition ((2)Caucasian:(2)Hispanic/Latino:(1)Black:(1)Asian) was derived from census data and matched between genders and income levels. Low and high SES profiles were presented in 1 of 4 different pseudorandomized orders throughout the game. Subjects encountered each player only once. Each player profile was presented for 4 seconds, after which the subjects were given an onscreen prompt to make their offer ("How much $ would you like to offer?"), which appeared in the bottom right corner of the screen. This screen remained for 5 seconds, during which subjects had to make their offer.

Figure 1.1. Four examples of player profiles used in the Dictator Game.

Subjects were truthfully informed that a subset (n=12) of the players in the experiment corresponded to people in Los Angeles (contacted for approval prior to the experiment) who would receive the money allotted to them by each subject. Their photograph and name was changed for confidentiality, though the photograph used was matched to their gender and race, and their actual income was displayed. Genders, races and SES groups were equally represented among the 12 real profiles. Subjects were informed that they would be rewarded for 3 randomly selected trials out of the total 24. Thus, on any given trial, they could be playing with a real person who would actually receive the money allotted to them, and the subjects could receive what they allotted for themselves in that trial. Subjects carried out the task unobserved, in a closed room without cameras. Their responses were saved in association with an ID number, and scored by a different researcher than the experimenter, ensuring subjects' anonymity. Subjects were comprehensively informed about these controls and explicitly instructed prior to and during briefing that the paradigm included *no deception*.

The subjects' 24 offers (1 per player) were averaged and separated by player income (high or low). This resulted in 2 means per subject: low SES and high SES. Additionally, we created a third variable to index contextual modulation of offers, ΔDG, equal to the normalized difference between offers to Low SES and High SES $({}^{\text{LowSES-HighSES}}/_{(\text{LowSES+HighSES})})$.

1.2.3 fMRI Tasks

Emotion Observation and Imitation (EOI): The stimuli were 48 full-color faces comprising an ethnically diverse set of 12 individuals (6 males and 6 females taken from the Nim Stim Face Stimulus Set (Tottenham et al., 2009) expressing 4 different emotions (angry, fearful, happy, or sad). None of the faces used in the DG appeared in this task. Task blocks consisted of 6 stimuli, presented for 4.5s each, with an interstimulus interval (ISI) of 400ms. Prior to each block, subjects were presented for 1.5s with a screen consisting of white letters on a black background, instructing subjects to "imitate the following facial expressions" (Imitation condition), or "look at the following faces" (Observation condition). The run consisted of 8 task blocks lasting 29s each, interleaved with an additional 9 rest blocks consisting of a white fixation cross on a black background, lasting 15s each. Imitation and Observation blocks were presented in alternating order for a total of four per condition.

Needle Test (NT): The stimuli were 27 full-color videos previously used by Bufalari et al. (2007), and used with permission by their research group, depicting a human hand being pierced by a hypodermic syringe (Pain condition) and touched by a wooden q-tip (Touch condition) in varying locations, as well as a static hand without stimulation (Hand condition) for use as a control. The run consisted of 12 trial blocks lasting 26s each, plus 8 alternating rest blocks that lasted either 5s or 10s. Each trial block consisted of 4 videos of a single condition (Pain, Touch, Hand), 5s in duration each, with an interstimulus interval of 400ms. Subjects were simply instructed to watch the video clips. They were assured that the hand in the video clip was a human hand and not a model, but they were not instructed to empathize with the model nor were there any audiovisual cues to indicate pain in the hand's owner.

For each task, two different block orders were used, and controlled to ensure an approximately equal proportion of male and female subjects were exposed to each block order. The order of the fMRI and behavioral task blocks was counterbalanced across subjects, as was the order of the fMRI tasks within the fMRI task block. All tasks were coded within Presentation (created by Neurobehavioral Systems).

1.2.4 Behavioral Assessment

After completing the experiment, subjects were given two questionnaires, which they filled out in a closed room, unobserved.

I) Interpersonal Reactivity Index (IRI): The IRI (Davis, 1983) is widely used (Avenanti et al., 2009, Pfeifer et al., 2008) and validated (Litvack-Miller et al., 1997) questionnaire designed to measure both ''cognitive'' and ''emotional'' components of empathy. It consists of 24 statements that the subject rates on a 5-point scale ranging from 0 (Does not describe me very well) to 5 (Describes me very well). The statements are calculated to test four theorized subdimensions of empathy:

Fantasizing Scale (FS): the tendency to take the perspective of fictional characters.

Empathic Concern (EC): sympathetic reactions to the distress of others.

Perspective Taking (PT): the tendency to take other's perspective

Personal Distress (PD): aversive reactions to the distress of others

Scores were summed for each subdimension (measured by 6 items) to make 4 scores per subject. Cronbach's alpha, a measure of reliability, was assessed for the IRI using SPSS (FS=0.756, EC=0.773, PT=0.807, PD=0.821).

2) Personal Altruism Level (PAL): The PAL is designed to assess the disposition to engage in prosocial behavior such as sharing, comforting and cooperating towards friends and family (subscale I), or strangers (subscale II). It consists of 18 statements that subjects rate their agreement with on a 5-point scale ranging from 0 (highly agree) to 5 (Highly disagree). Scores are summed for each subscale (measured by 9 items) to make 2 scores per subject (I and II).

Behavioral analysis: Subjects' scores on each subscale of the PAL and IRI were correlated with their average offers to Low SES and High SES players, separately.

1.2.5 MR Image Acquisition

fMRI data were acquired on a Siemens Trio 3 Tesla system housed in the Staglin Center for Cognitive Neuroscience at UCLA. One subject's data was collected on an identical scanner housed in the adjacent Ahmanson-Lovelace Brain Mapping Center. Functional images were collected over 36 axial slices covering the whole cerebral volume using an echo planar T2*-weighted gradient echo sequence (TR=2500 ms; TE=25 ms; flip angle=90 degrees; matrix size=64 x 64; FOV 20 cm; in-plane resolution=3 mm x 3 mm; slice thickness=3 mm/1 mm gap). A high-resolution EPI structural volume was also acquired coplanar with the functional images (TR=2500 ms, TE=33 ms, 128 x 128 matrix size, FOV=256 cm). Finally, a high-resolution T1-weighted volume was acquired in each subject (TR=2300 ms, TE=25 ms, TI=100 ms, flip angle=8°, matrix size=192x192, FOV=256 cm, 160 slices), with approximately 1 mm isometric voxels (1.3 x 1.3x 1.0 mm).

1.2.6. Functional MRI Analysis

Analyses were performed in FEAT (FMRI Expert Analysis Tool), part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). After motion correction using MCFLIRT, images were temporally high-pass filtered with a cutoff period of 70 and 90 seconds for NT and EOI, respectively (approximately equal to one rest-task-rest-task period), and smoothed using a 6 mm Gaussian FHWM algorithm in 3 dimensions. Each subjects' functional data was coregistered to standard space (MNI 152 template) via registration of an averaged functional image to the high resolution T1-weighted volume using a six degree-of-freedom linear registration and of the high-resolution T1-weighted volume to the MNI 152 template via 12 degree-of-freedom linear affine registration, implemented in FLIRT.

The BOLD response was modeled using an explanatory variable (EV) consisting of a boxcar function describing the onset and duration of each relevant experimental condition (task conditions, rest, instruction scree) convolved with a double gamma HRF to produce an expected BOLD response. The temporal derivative of each task EV was also included in the model. In addition, each subject's 6 motion parameters were included as additional EVs of no interest, to control for head motion. Functional data were then fitted to the model using FSL's implementation of the general linear model. Higher-level analyses were implemented using DG offers to Low and High SES players as separate explanatory variables. Resultant images were cluster corrected at a z-threshold of 2.3 and p-value cutoff of .05, using FLAME 1+2.

Dictator Game offers were divided into two separate EVs corresponding to the mean offer for each SES group within the player profiles (Low SES and High SES), per subject, and correlated with subjects' BOLD data for each functional contrast of interest, using FSL's implementation of the general linear model. Contrasts were made examining variance unique to either Low SES or High SES offers (1 0 or 0 1) and shared variance (.5 .5). These results will be referred to throughout the manuscript as correlations with *High* or *Low SES* offers, on one hand, or *overall offers,* respectively. A final analysis was carried out using as an EV the difference between subjects' offers to Low SES and High SES profiles normalized to their total offers ($^{\text{LowSES-HighSES}}/_{\text{(LowSES+HighSES)}}$), or ΔDG.

1.2.7. Psychophysiological Interaction analysis (PPI)

To test whether functional interactions *between* SR and top-down control regions exist and are correlated with DG offers, we examined psychophysiological interactions between EOI and NT data and DG offers. In order to remove non-neuronal sources of coherent oscillation in the relevant frequency band (.01-.1Hz), preprocessed data was subjected to probabilistic independent component analysis as implemented in MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) Version 3.10, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Noise components corresponding to head motion, scanner noise, cardiac/respiratory signals were identified by observing their localization, time series and spectral properties and removed using FSL’s regfilt command.

To create the ROI’s, time series were extracted from 6mm diameter seeds created in standard (MNI 152) space centered on voxels showing high correlations with overall DG offers in the principal contrasts reported on here (See Figure 1.5). Center voxel coordinates (in voxels) and contrasts used are as follows. For the EOI gPPI analysis: Right amygdala (x=35, y=61, z=25), right dorsolateral prefrontal cortex (DLPFC)(x=25, y=75, z=55). For the NT gPPI analysis: left superior parietal lobule (SPL)(x=55, y=39, z=69), left DLPFC (x=45, y=68, z=51) and left precentral gyrus (PCG) (x-63, y=67,z=49).

For each analysis, we modeled activity using the following EV’s: *Psychological*, consisting of a boxcar functions modeling the onset and duration of each task condition, convolved with a canonical double-gamma HRF; *physiological*, consisting of the ROI’s time series (one per analysis); and a *psychophysiological interaction* (PPI) for each task condition, modeling the interaction between the expected BOLD response to each condition and the time series of interest. These separate PPI estimates were then contrasted at the group level. This allowed us to test for voxels that display significant *changes* in correlation with the time series of the ROI for any task contrast of interest, an approach known as generalized PPI or gPPI (Mclaren et al., 2012). gPPI analyses of EOI data employed the right amygdala and right DLPFC seeds, while NT data was analyzed with the left SPL, left PCG and left DLPFC seeds. These sets were specifically chosen to test for functional connectivity between areas of positive correlation with DG offers (proposed primary SR areas) for NT and EOI (left SPL and right amygdala, respectively) and corresponding areas of negative correlation with DG offers (proposed control areas) (left DLPFC/left PCG and right DLPFC, respectively). First level analyses were carried out using FEAT. A higher-level analysis was carried out to examine correlations between PPI parameter estimates and DG offers. Resultant images were cluster corrected at a z-threshold of 2.3 and p-value cutoff of .05, using FLAME 1+2.

1.3. Results

1.3.1. Behavior

Subjects offered, on average, \$6.18 (SD = 2.66) to Low SES players, and \$2.63 (SD= 2.81) to High SES players. Subjects' offers to Low and High SES players were significantly correlated (R^2=0.49, p=.0004). Subjects' scores on the Personal Distress (PD) subscale of the IRI were correlated with their offers to high SES profiles (R^2=0.46, p=.0026). Subjects' offers to Low SES profiles were correlated (R^2=0.2, p=.0475) with their scores on the Empathic Concern (EC) subscale. Subjects' scores on the PAL did not show any significant correlation with subjects' offers or imaging data.

1.3.2. Needle Test

We will report here correlations between DG offers and the contrast Pain>Hand. Similar but much weaker correlations were found for the contrast Pain>Touch (see Table 1.1). This suggests an overlap between neural resonance processes recruited during the "pain" and "touch" condition, resulting in the contrast subtracting out much of the relevant signal variance. As in previous studies employing this paradigm (Bufalari et al., 2007), this task contrast activated a broad array of areas including cerebellum, bilateral visual cortex, MT/V5 and somatosensory cortices, ventral premotor cortex, pars opercularis and pars orbitalis, anterolateral prefrontal cortex, anterior and posterior insula, left putamen, right thalamus, and right globus pallidus (Supplementary figure 1.1, 1.3).

Overall offers were positively correlated with BOLD signal changes in a cluster encompassing primary somatosensory cortex, that previous studies have associated with the experience and observation of painful and tactile stimuli (Bufalari et al., 2007, Keysers et al., 2010), and the adjacent superior parietal lobule, an area also associated with the observation and experience of pain (Lamm et al., 2011), as well as aversive objects near one's body (Lloyds & Roberts, 2006). Positive correlations were also found within extrastriate visual cortex (Fig.1.2, a).

As shown in figure 1.2(b), overall offers were negatively correlated with signal changes in areas implicated in control of affect (left dorsomedial prefrontal cortex or DMPFC, left DLPFC, frontal pole)(Miller & Cohen, 2001) and pain (left anterior precentral gyrus or PCG, left DLPFC) (Brighina et al., 2010, Garcia-Lerrea & Peyron, 2007).

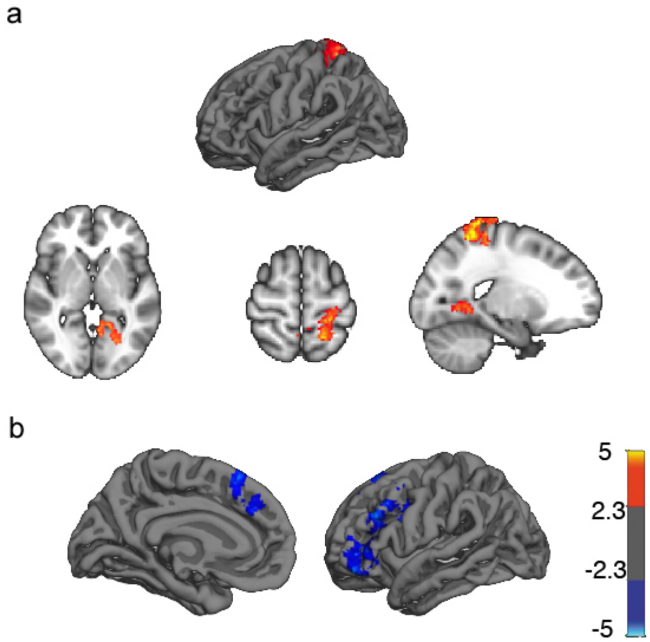


Figure 1.2. Correlations between BOLD signal changes during the Needle Test and Dictator Game behavior. Areas where activation for the contrast Pain>Hand correlates positively (red-yellow) and negatively (blue-dark blue) with subjects' overall offers in the Dictator Game (cluster corrected at z-threshold > 2.3, p<.05). Heat maps reflect z-scores. Slices are displayed in radiological orientation.

1.3.3. Emotion Observation and Imitation

We correlated DG offers with the contrast Imitate>Observe for the following two reasons: first, "rest" is difficult to control as a baseline condition, given the uncertain nature of the cognitive processes occurring therein, *particularly* with regard to prefrontal structures associated with social cognition (Amodio & Frith, 2006). Second, imitation of emotional facial expressions typically activates structures associated with observation, but to a greater extent (Iacoboni, 2009). Indeed, our results show significantly greater activation in all structures activated by the observation task during the imitation condition (see supplemental figures 1.2 and 1.4). This contrast allows us to observe individual differences in vicarious emotional responses produced by simultaneously *executing* and *observing* emotional facial expressions (Carr et al., 2003).

Subjects' overall offers were positively correlated with BOLD signal changes in areas associated with neural resonance (bilateral amygdalae, left anterior insula) and trait empathy (left fusiform cortex) (Carr et al., 2003, Pfeifer et al., 2008). Correlations were also found with signal changes in bilateral hippocampi and parahippocampal gyri (PHG), recently found to contain mirror neurons in humans during single cell recordings while subjects – relevant to these findings - observed and executed facial emotional expressions (Mukamel et al., 2010)(Fig.1.3, a).

Subjects' offers to high SES profiles were negatively correlated with signal changes in areas associated with multiple forms of top-down control: control of imitation (right temporoparietal junction or TPJ)(Spengler et al., 2010), affective regulation (DMPFC, right anterior cingulate cortex or ACC, right frontal pole, left DLPFC)(Medford & Critchley, 2010, Miller & Cohen, 2001) and the right DLPFC, which is *causally implicated* in inhibiting prepotent emotional responses during social decision-making (Knoch et al., 2006, Tassy et al., 2012). Negative correlations were also found with a cluster in the right PHG, centered on different coordinates than the abovementioned positive correlations in bilateral PHG (see Table 1.1).

Significant negative correlations with offers to high SES players were also found in the posterior cingulate (PCC) and precuneus (Fig.1.3, b). These areas have been associated with self-referential processing (Brewer et al., 2013, Cavanna & Trimble, 2006, Johnson et al., 2006, Northoff et al., 2006), perhaps suggesting that this correlation reflects self-other *distinction* rather than self-other *resonance*.

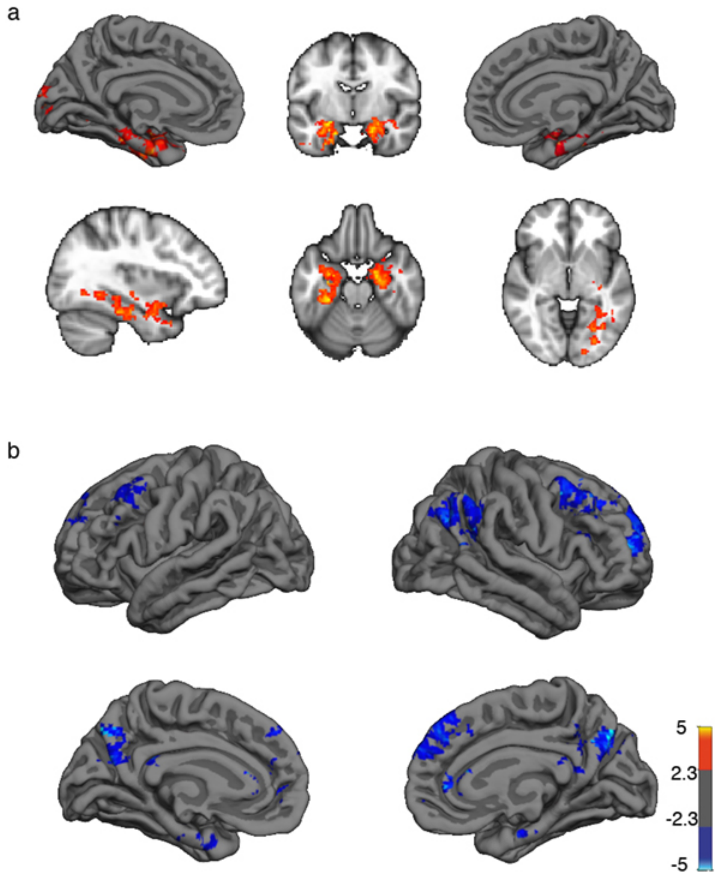


Figure 1.3. Correlations between BOLD signal changes during EOI and Dictator Game behavior. (a) Areas where activation during Imitation > Observation correlates positively with overall offers in the Dictator Game and (**b)** areas where activation during Imitation>Observation correlates negatively with subjects' offers to High SES profiles in the Dictator Game (cluster corrected at z-threshold > 2.3, p<.05). Heat maps reflect z-scores. Slices are displayed in radiological orientation.

1.3.4. ΔDG

The normalized difference between subjects' offers to high and low income players (ΔDG) – which is an obvious behavioral index of contextual regulation - was correlated with signal changes in cortical regions similar to those implicated in top-down control in the NT and EOI.

For the contrast Pain>Hand, ΔDG was correlated with signal changes in bilateral DLPFC, orbitofrontal cortex, DMPFC, superior frontal gyrus or SFG, left TPJ and ventromedial prefrontal cortex VMPFC(Banks et al., 2007, Fehr & Camerer, 2007, Spengler et al., 2010, Volman et al., 2011, Miller & Cohen, 2001)(Fig.1.4, a).

For the contrast Imitate>Observe, ΔDG was correlated with signal changes in a similar set of areas (bilateral DMPFC, ACC, right DLPFC, MPFC, APFC)(Medford & Critchley, 2010, Miller & Cohen, 2001, Spengler et al., 2010), as well as the precuneus (Brewer et al., 2013, Cavanna & Trimble, 2006, Johnson et al., 2006, Northoff et al., 2006) (Fig.1.4, b).

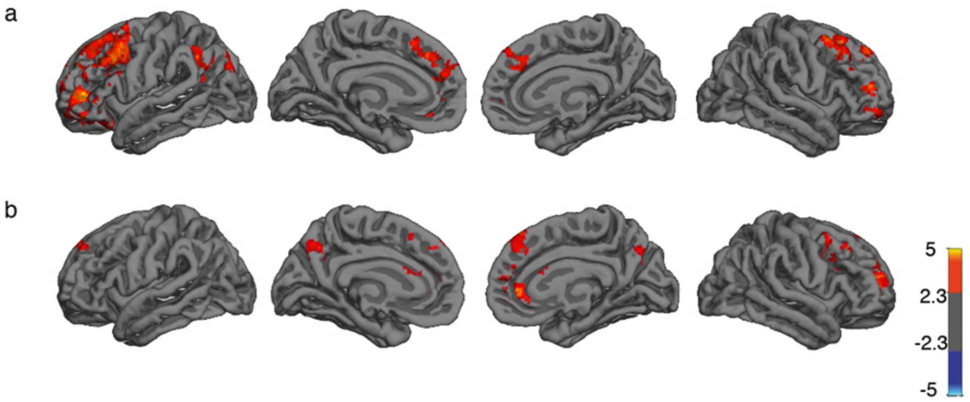


Figure 1.4. Areas where BOLD signal changes for the contrasts Imitate>Observe and Pain>Hand is correlated with the normalized difference between each subjects' offers to High and Low SES players (ΔDG) in the Dictator game. (a) Areas of correlation with ΔDG during Pain>Hand (b) Areas of correlation with ΔDG during Imitate>Observe (cluster corrected at z-threshold > 2.3, p<.05). Heat maps reflect z-scores.

1.3.5. Connectivity

We propose that neural systems supporting top-down control exert a modulatory influence on systems supporting SR during the fMRI tasks. To test this hypothesis we examined task-related changes in connectivity (psychophysiological interaction or PPI) in ROIs implicated in SR and top-down control correlated with behavior in the DG. Correlations between parameter estimates in center voxels of each ROI and DG offers are displayed in figure 1.5.

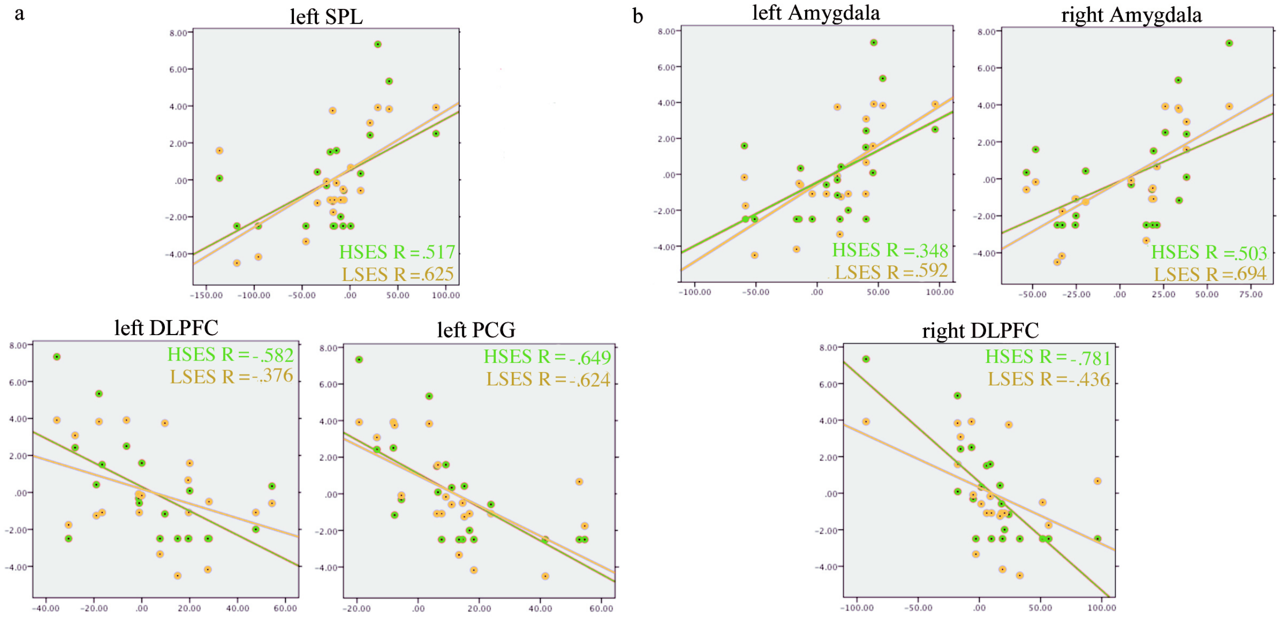


Figure 1.5. Descriptive plots of correlations between DG offers and beta estimates in PPI ROI's. Areas of high correlations between demeaned DG offers (y-axis, in dollars) to low (yellow) and high (green) SES players and parameter estimates (x-axis) in peak voxels for the task(contrast) a)NT(Pain>Hand) and b) EOI(Imitate>Observe). Abbreviations and MNI voxel coordinates are as follows: SPL=superior parietal lobe(x=55, y=39, z=69); Left (x=57, y=58, z=28) and right (x=35, y=61, z=25)Amygdala; Left (x=45, y=68, z=51) and right (x=25, y=75, z=55) DLPFC/dorsolateral prefrontal cortex.; Left PCG/precentral gyrus (x=63, y=67, z=49).

PPI analyses of SPL, PCG and left DLPFC for NT data did not yield any significant result. However, for the contrast Imitation > Observation, right amygdala (Fig.1.6, a) showed increased connectivity with DMPFC and VMPFC, areas associated with affective regulation and decision-making (Hare et al., 2010, Miller and Cohen, 2001, Volman et al., 2011)(Fig.1.6, d). Left amygdala showed increased connectivity with the ACC (Medford & Critchley, 2010, Miller & Cohen, 2001) and right paracingulate gyrus, areas implicated in affective regulation, as well as bilateral basal ganglia and posterior insula; left superior temporal gyrus and hippocampus. The right DLPFC (Fig.1.6, b) showed increased connectivity with a wide range of cortical and subcortical areas involved in motor behavior, affect, motivation and somatosensation (bilateral amygdala, bilateral hippocampus, left anterior insula/frontal operculum, bilateral putamen, bilateral pallidum, bilateral post central gyrus, medial parietal lobe, SPL and the cerebellum)(Fig. 1.6, d).

Crucially, task-related increases in connectivity (PPI) in regions implicated in SR (left and right amygdala) were negatively correlated with overall offers for the contrast Imitate>Observe, that is, higher increases in connectivity resulted in less offers. We found a negative correlation between overall DG offers and PPI between right amygdala (Fig.1.7, a) and several areas involved in top-down control (right APFC, ACC, DLPFC and DMPFC)(Medford & Critchley, 2010, Miller & Cohen, 2001, Spengler et al., 2010); as well as the human mirror neuron system (IFG)(Keysers & Fadiga, 2008); the processing of complex biological stimuli (superior temporal sulcus)(Obhi, 2012, Zaki & Ochsner, 2012) and the basal ganglia, which are broadly implicated in controlling behavior and affect (Fig. 1.7, c). This relationship was also found between left amygdala (Fig.1.7, b) and bilateral ACC (Fig.1.7, d).

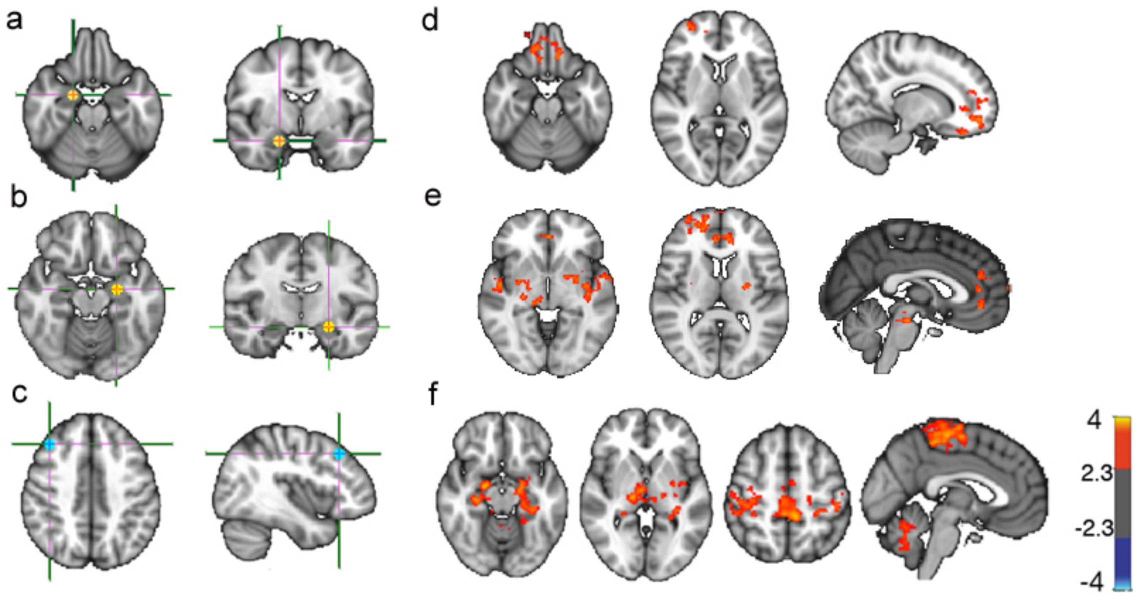


Figure 1.6. Areas showing psychophysiological interaction with seed ROI's. (a-c) Locations of the seed ROI's in (a) right amygdala (x=25, y=75, z=55), (b) left amygdala (x=57, y=58, z=28), (c) dorsolateral prefrontal cortex (x=25, y=75, z=55). (d-f) Areas of increased connectivity during Imitation vs. Observation with (d) right amygdala, (e) left amygdala and (f) right dorsolateral prefrontal cortex (cluster corrected at z-threshold > 2.3, p<.05). Heat maps reflect z-scores. All coordinates reported in voxels in MNI space. All slices are displayed in radiological orientation.

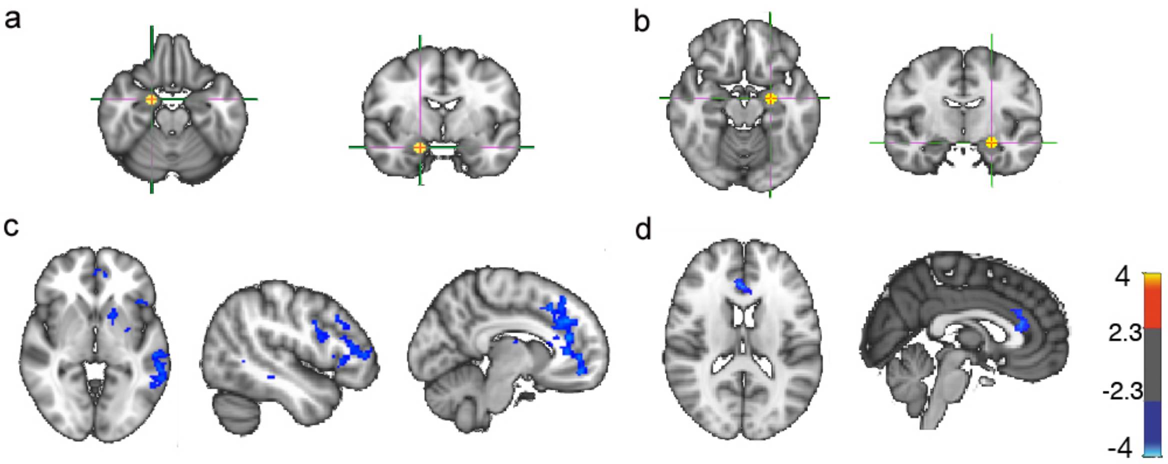


Figure 1.7. Correlation between PPI variable and offers in the Dictator Game. (a,b) Location of the seed ROI in (a) right (x=35, y=61, z=25) and (b) left (x=57, y=58, z=28) amygdala. (c,d) Areas where increased functional connectivity with right (c) and left (d) amygdala during Imitate > Observe correlates negatively with subjects' overall offers in the Dictator Game (cluster corrected at z-threshold > 2.3, p<.05). Heat maps reflect z-scores. All coordinates reported in voxels in MNI space. All slices are displayed in radiological orientation.

Contrast	Correlation	Variable	Area	Coordinates (mm)			Z	Consistent with theory
				x	y	z		
Pain> Hand	Positive	overall offers	Extrastriate visual cortex	-8	-60	0	4.12	unclear
			L SI/Superior parietal lobe	-18	-48	76	4.93	+
			L Superior parietal lobe	-20	-52	62	4.45	+
	Negative	overall offers	L Anterior precentral gyrus	-36	8	24	4.87	+
			L Frontal pole	-34	42	0	4.54	+
			L Dorsolateral prefrontal cortex	-44	20	38	4.08	+
			L Superior frontal gyrus	-16	24	60	4.43	+
			L Dorsomedial prefrontal cortex	-4	22	62	4	+
Imitate> Observe	Positive	overall offers	L Amygdala	-22	-10	-14	6.31	+
			R Amygdala	26	-10	-16	4.38	+
			L Hippocampus	-24	-8	-22	4.89	+
			R Hippocampus	28	-14	-22	4.01	+
			L Parahippocampal gyrus	-26	-28	-20	6.17	unclear
			R Parahippocampal gyrus	20	-8	-24	4.92	+
			L Temporal fusiform cortex	-30	-32	-22	4.85	+
			R Temporal fusiform cortex	40	-22	-26	4.34	+
	Negative	High SES offers	L Dorsolateral prefrontal cortex	-36	6	64	4.16	+
			R Dorsolateral prefrontal cortex	42	24	38	5.35	+
			R Frontal pole	28	56	26	5.58	+
			Medial prefrontal cortex	0	54	6	4.99	+
			R Medial prefrontal cortex	2	52	22	5.07	+
			L Precuneus	-4	-76	40	5.96	+
			R Precuneus	12	-72	34	6.72	+
			R parahippocampal gyrus	16	-8	-30	4.31	unclear
			Dorsomedial prefrontal cortex	0	40	38	5.16	+
			R temporoparietal junction	46	-56	58	5.74	+
			R Dorsomedial prefrontal cortex	2	20	52	4.56	+
Pain> Hand	Positive	**ΔDG**	L Frontal pole	-40	54	-2	4.29	+
			R Frontal pole	44	52	10	4.97	+
			L Dorsolateral prefrontal cortex	-44	16	36	4.87	+
			R Dorsolateral prefrontal cortex	36	4	60	4.38	+
			L Dorsomedial prefrontal cortex	-2	24	44	4.69	+
			L Orbitofrontal cortex	38	44	6	4.68	+
			R Superior Frontal gyrus	20	22	52	4.1	+
			L Temporoparietal junction	-48	-52	38	4.54	+
Imitate> Observe	Positive	**ΔDG**	R Anterior cingulate cortex	6	38	2	4.53	+
			R Dorsomedial prefrontal cortex	6	34	52	4.23	+
			R Frontal pole	24	50	16	5.23	+
			R Medial prefrontal cortex	2	54	20	4.67	+
			L Precuneus	-10	-64	22	3.89	+
			R Precuneus	18	-62	28	3.55	+

Table 1.1. Local maxima of Correlation between BOLD signal changes during Needle Test(NT)/Emotion Observation and Imitation(EOI), and Dictator Game offers. Right most column indicates whether finding is consistent (+) or inconsistent (-) with our hypotheses.

ROI	Correlation	Variable	Area	Coordinates (mm)			Z	Consistent with theory
				x	y	z		
R Amygdala	Negative	Overall offers	L Anterior cingulate cortex	-12	38	14	3.27	+
			L Ventromedial prefrontal cortex	-4	50	-10	3.38	+
			L Orbitofrontal cortex	-32	50	22	3.23	+
			L Inferior frontal gyrus/Precentral gyrus	-48	8	22	2.85	unclear
			L Dorsolateral prefrontal cortex	-36	34	18	3.48	+
			L Middle temporal gyrus	-56	-54	2	3.12	+
			L Paracingulate gyrus	-8	34	32	3.23	+
			L Putamen	-16	6	-6	3.3	unclear
			L Superior Temporal gyrus	-56	-26	-4	3.13	unclear
			L Thalamus	-14	-6	8	2.86	unclear
L Amygdala	Negative	Overall offers	L Anterior cingulate cortex	-2	28	26	3	+
			R Anterior cingulate cortex	4	34	14	3.28	+

Table 1.2. Local maxima of Correlation between Pychophysiological Interaction (PPI) term and DG offers. Right most column indicates whether finding is consistent (+) or inconsistent (-) with our hypotheses.

1.4. Discussion

The results reported here largely fit our hypotheses:

1. Brain activity during SR-evoking tasks is correlated with DG offers (a proxy for the relative utility of the players' welfare). The sign of the correlation should also reveal the nature of the processes implemented by the implicated areas (positive for SR and negative for top-down control). In other words, subjects who show greater correlates of SR during scanning should *also behave more generously, while subjects who show greater inverse correlations should behave less generously, especially to high SES players.*

Positive correlations

Positive correlations between DG offers and brain activity during observation of pain were found in the SPL. The SPL is associated with processing aversive stimuli in peripersonal space (Lloyd & Roberts, 2006) and the somatic perception of interactions between external objects and one's own body (Naito et al., 2008). Further, it has been implicated in pain processing (Lamm et al., 2007) and has been proposed as part of the extended human mirror neuron system (Molenberghs et al., 2009). Positive correlations between DG offers and brain activity during imitation were found in the insula and amygdala, two regions associated with SR for emotions (Carr et al., 2003, Volman et al., 2011, Pfeifer et al., 2008). Correlations were also observed with fusiform gyrus, a face processing area whose activation during imitation and observation of emotional facial expressions has been correlated with trait empathy (Pfeifer et al., 2008). These activations are consistent with proposed neural correlates of SR, i.e. the vicarious activation of similar structures for the perception and experience of internal states and behavior.

A complementary pattern emerges within areas whose activation during NT and EOI is negatively correlated with DG offers.

Inverse correlations

We observed negative correlations between DG offers and activation in areas associated with regulation of affect (left DMPFC, left DMPFC, VMPFC)(Banks et al., 2007, Miller & Cohen, 2001). Additionally, there were correlations with activation in ACC, associated with affective regulation (Medford & Critchley, 2010) and the left DLPFC, which is directly relevant to the control of pain processing. Indeed, excitatory repetitive TMS to the left DLPFC has been shown to cause analgesia (Brighina et al., 2010). Also, the DLPFC has been shown to have strong reciprocal connections with the ACC (Cho & Strafella, 2009), an area that is also associated with processing painful stimuli in the self and others (Bufalari et al., 2007, Singer et al., 2004). Negative correlations were also found between offers and activation in left motor cortex (PCG) for the Pain>Hand contrast. Stimulation of motor cortex is effective in treating central and peripheral neuropathic pain, suggesting that it may help regulate the sensory and/or affective aspects of pain (Garcia-Lerrea & Peyron, 2007, Khedr et al., 2005, Velasco et al., 2009, Tsubokawa et al., 1991, among others).

An analogous set of areas showed inverse correlations between activation during EOI and DG offers: The TPJ and the DMPFC have been associated with implicit control of imitation (Spengler et al., 2010). The VMPFC and frontal pole have been associated with the regulation of affect (Banks et al., 2007, Miller and Cohen, 2001, Volman et al., 2011) and decision-making (Tricomi et al., 2010, Winecoff et al., 2013). In addition, the right DLPFC has been implicated as an executive control system during decision-making, particularly in the control of prepotent emotional reactions and the incorporation of moral rules into decision-making (Knoch et al., 2006, Volman et al., 2011, Tassy et al., 2012).

2. Subjects' tendency to decrease their offers to high SES players (the normalized difference between their offers to high and low SES players) is also correlated with activation in areas typically associated with top-down control.

Direct correlations between ΔDG and brain activity during *both tasks* were found in areas consistently associated with top-down control of somatosensation (left DLPFC), affect (ACC, DMPFC, DLPFC), imitation (TPJ) and decision-making (DLPFC, DMPFC). In essence, neural activation consistent with top-down control during SR was correlated with hypothesized *behavioral* indices of top-down control (i.e. inhibitory modulation of offers).

3. There are functional interactions between regions associated with SR and top-down control during the tasks and the strength of interaction will be correlated with subjects' offers.

Areas showing direct correlations with DG offers (indexing SR) and areas showing inverse correlations with DG offers (indexing top-down control), were functionally correlated. In addition, we found that increased functional connectivity between right amygdala (SR), and right DLPFC (top-down control) as well as left amygdala and ACC, was also negatively correlated with DG offers (See Fig. 1.6, 1.7).

1.5. Interpretational Limitations

While we cannot be certain what neural processes were active during the Dictator Game without direct fMRI evidence (which we did not collect to preserve subjects' anonymity and lack of supervision), activation and connectivity of brain areas active in the SR task was correlated with multiple aspects of prosocial decisions in the DG, suggesting an intricate relationship between the two. This leaves us with two possibilities:

1. Brain networks active during the SR tasks and associated control systems are also employed when making conscious decisions about the welfare of others. Individual differences in the way they interact are consistent across different task demands.

2. There are intervening variables responsible for the correlation, such as subjects' engagement in the tasks, as opposed to an actual employment of these networks during the DG. Neural activity during SR in this context is hence informative but some other factor other than SR drives prosocial decisions in the DG.

Let us explore (b). One could postulate that increased attention during the NR tasks might result in increased vicarious affective and somatosensory processing, though it is unclear why this would result in decreased engagement of areas involved in top-down control. Next, it is unclear why *increased* attention to the dictator game would result in higher overall offers, and decreased modulation of offers (ΔDG). One could theorize that increased attention to the Dictator Game results in increased perspective-taking, which could explain increased offers, though it is unclear why this would increase offers towards subjects of high SES (low need). In fact, there is data to suggest the very opposite: a 2014 study by Schulz et al. found that subjects with high cognitive load (intended to *disrupt* high-level cognitive processes) tended to behave *more* generously in the Dictator Game. Hence, making this assumption leaves us with a missing variable, some factor correlated with attention that would drive prosocial inclinations other than SR. This explanation is not entirely implausible, but it does lack parsimony.

As such, we favor (a), for a number of reasons. First, subjects were given ample time (5s) in which to make their offers and showed evidence of having evaluated socioeconomic information about the player in their decisions, making it unlikely that their offers were based simply on quick, reflexive processes like those evoked during the SR tasks. Second, we hypothesized that a) SR drives prosocial inclinations and that b) top-down control of SR is *inhibitory* (at least under the conditions explored here) and *that it occurs in response to context*. In the context of the DG, this follows: the condition in which subjects give less money on average (high SES)(Engel,

2011) show the highest effect of inhibitory control, and vice versa. Hence, we would expect that individual differences in neural correlates of SR would dominate variance in offers to low SES, while individual differences in putative neural correlates of top-down control would dominate variance in offers to high SES. The empirical data fit these predictions: activation in SR areas was most strongly correlated with low SES offers, while activation in areas typically associated with control was most strongly correlated with high SES offers. Additionally, we found that areas showing negative correlations with offers are also implicated in executive control. Third, affective processing and its regulation have already been implicated in decision-making, particularly when subjects are aware that other people are involved (Camerer, 2003, Hewig et al., 2011, Van 't Wout et al., 2006). Last, one could argue that the presence of neutral faces in the DG might somewhat trigger SR, thus biasing behavioral results. Indeed, biological stimuli as sparse as a photograph have been found to increase charitable donations (Genevsky et al., 2013). However, correlations have also been found between SR for pain and charitable donations (Ma et al., 2011) towards anonymous third persons. This suggests that while biological cues may bias us towards SR and enhance prosocial inclinations, they may not be strictly necessary for the engagement of SR processes.

Activation/offer correlations in some areas were not immediately consistent with our hypotheses, such as extrastriate visual cortex. However, there were none that invalidated it – positive correlations were not found in any area typically associated with top-down control (such as the DLPFC, DMPFC or TPJ), nor were negative correlations found in areas typically associated with SR (such as the amygdala or somatosensory cortex). One area, the parahippocampal gyrus (PHG), showed both positive correlations with overall DG offers and negative correlations with DG offers to high SES players, though the two clusters (both in right PHG) are centered on different coordinates (see Table 1.1). Further studies are necessary to clarify whether there are functional subdivisions in PHG that could explain these results.

As mentioned in connectivity results (1.3.5), gPPI analyses of SPL, PCG and left DLPFC for NT data did not yield any significant results. This may be an issue of statistical power: PPI analyses examine significant changes in correlations between conditions of interest, over and above those accounted for by co-activation, thus requiring robust results to reach significance (Friston, 2011). While the EOI and NT are of equivalent durations and TR values, the NT has three conditions compared to the EOI's two, resulting in roughly 2/3 as many data points per condition.

1.6. Conclusions

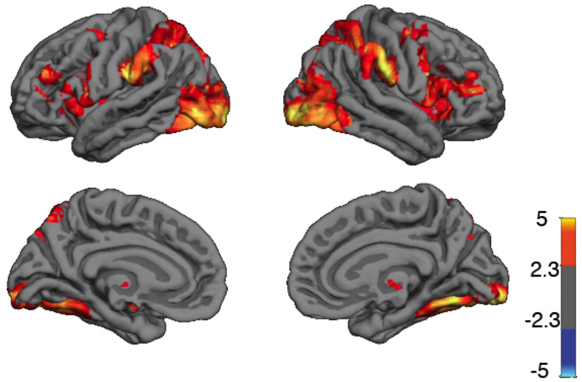
As predicted, we found that subjects who displayed greater neural markers of SR tended to behave more generously, while subjects who displayed greater inverse brain-behavior correlations tended to behave less generously and modulate their costly sharing more in response to the opposing player's income. Additionally, we found that for the EOI, task-related increases in *functional connectivity* between areas associated with vicarious affect and its control were negatively correlated with subjects' costly sharing.

How would neural processes implicated during SR be involved in prosocial decision-making under conditions with impoverished SR cues (only a neutral face)? We suggest that areas associated with SR and its control are employed in different capacities in different contexts: during the SR tasks we use here, somatosensory and limbic systems are vicariously activated, feeding information in a bottom-up fashion and receiving top-down, albeit implicit, modulation. During prosocial decision-making, such as in the Dictator Game, similar activity is implicitly triggered when subjects are thinking about the people represented by the player profiles, thus modulating the perceived utility of their welfare. But why would thinking about the people represented by the player profiles trigger activity associated with SR and its control? We favor the possibility that thinking about people is grounded on the perceptual and motor experiences we have when interacting with people, as suggested by the framework of embodied cognition (Barsalou, 2008, Gallese & Lakoff, 2005).

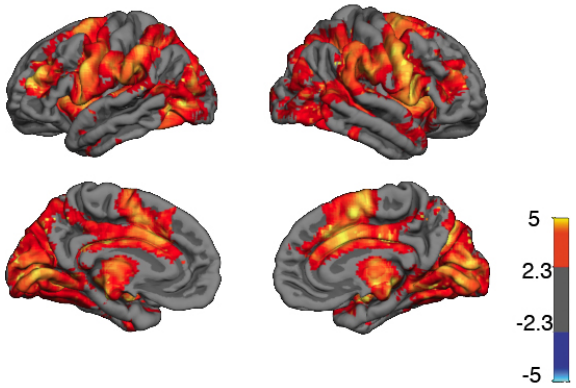
These findings have implications for neuropsychological theory and mental health. While it is intuitive to think of psychological processes as discrete and separate, it is much harder to think of neural systems in the same way. Indeed, neural systems tend to operate much more like connected clusters in a network than separate entities (Mcintosh, 2000). Many studies have reported concurrent activation of and connectivity between areas associated with SR and top-down control, such as during reciprocal imitation (Sperduti et al., 2014), tests of empathic accuracy (Zaki & Ochsner, 2008), and comprehension of others' emotions (Spunt & Lieberman, 2012). In cognitive neuroscience the dominant tendency is to theorize about psychological processes and then investigate the neural correlates of such processes. Perhaps it may be more useful to investigate how psychological processes emerge from brain organization (Fox & Friston, 2012).

With regard to mental health, there is wide consensus that empathy is a fundamental construct for mental health, and yet there is little consensus on how to operationalize such a complex construct (Hasler, 2012). Having metrics that are stable across task demands and predictive of behavior is of great importance for the future of psychiatric research. This study provides a relatively tractable approach to this problem. It also suggests a potential avenue for interventions on deficits and abnormalities in different behavioral and cognitive components of empathy. Perhaps using interventions targeting the interaction between SR and its cognitive control, an approach which has been implemented successfully to enhance social cognition in autism spectrum disorder (ASD) (Ingersoll, 2012) and schizophrenia (Mazza et al., 2012), we can better understand how these processes can positively influence overall social cognition and mental health.

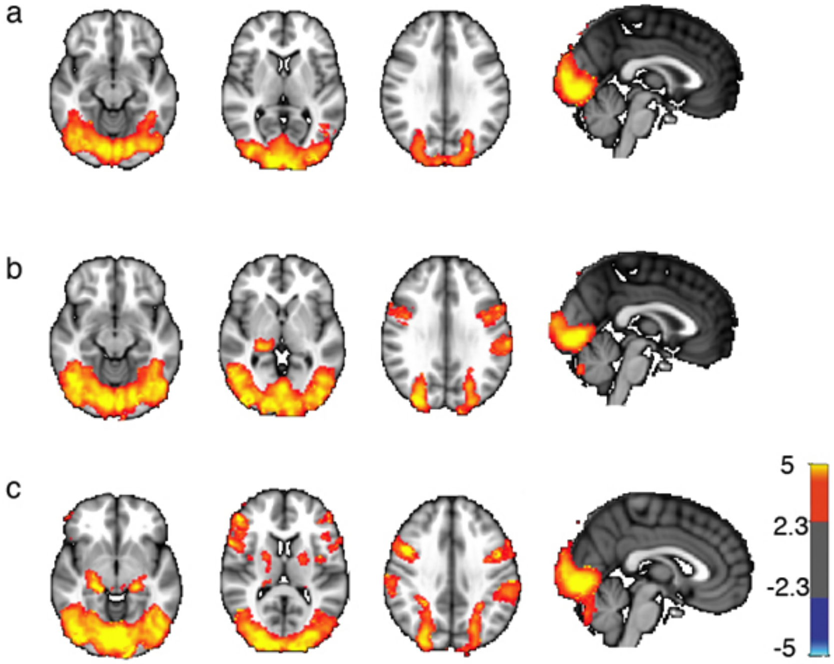
1.7. Supplementary Figures



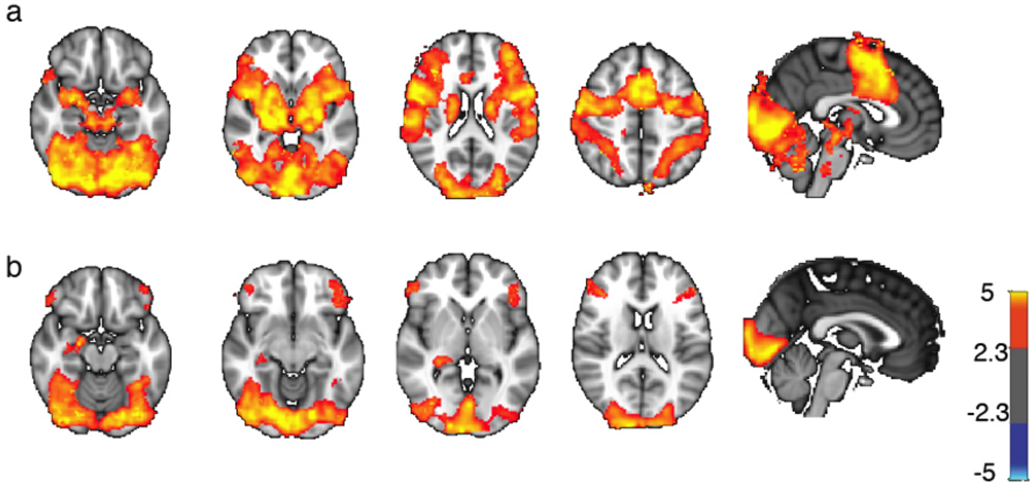
Supplementary figure 1.1.Activation for the contrast Needle>Touch, cluster corrected at z > 2.3, p < .05. Heat maps reflect z-scores.



Supplementary figure 1.2. Activation for the contrast Imitate>Observe, cluster corrected at z > 2.3, p < .05. Heat maps reflect z-scores.



Supplementary figure 1.3 Activation during the (a) Hand, (b) Touch and (c) Needle conditions of the Needle Test, cluster corrected at z > 2.3, p < .05. Heat maps reflect z-scores.



Supplementary figure 1.4 Activation during (a) Imitation and (b) Observation conditions of the Emotion Imitation task, cluster corrected at z > 2.3, p < .05. Heat maps reflect z-scores.

Acknowledgements

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Chapter 2. Can Deliberate Engagement of Self-Other Resonance Increase Prosocial Inclinations?

Examining the Effect of Joint Gaze-following and Imitation on Prosocial Decisions in the Dictator Game

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Abstract

Gaze-following and imitation have been linked to prosocial behavior and social cognition. Indeed, studies have shown that being imitated increases overall prosocial orientations. In this study, we examined whether engaging in a short behavioral intervention consisting of joint gaze-following and imitation of facial expressions and object manipulation could increase subjects' prosocial behavior in the Dictator Game, an economic scenario in which subjects decide how to allocate a sum of money between themselves and other players. 20 subjects performed these three tasks along with a confederate and then played a 24-trial one-shot Dictator Game against players of high and low income. A second group of 20 subjects performed a control task, consisting of cued gaze-direction (using directional arrow cues), non-emotional facial and head movements (prompted by verbal cues) and object manipulation (cued by directional arrow cues), before playing an identical Dictator Game. Test subjects' offers did not differ significantly from controls, though their distribution did show increased normality and reduced variance compared to controls. We discuss possible reasons for these results and make suggestions for future studies examining the relationship between gaze-following, imitation and prosocial orientations.

2.1. Introduction

Humans often deviate from rational self-interest in their economic decisions, suggesting there is a positive reward value associated with prosocial behavior (Fehr and Camerer, 2007, Fehr & Fischbacher, 2003, Moll et al., 2006). Evidence from social psychology and neuroscience suggests that this prosocial inclination in behavior is linked to our tendency to share in the observed internal states and behaviors of others (which we will refer to as "self-other resonance")(Christov-Moore & Iacoboni, under review, Hein et al., 2010, 2011, Ma et al., 2011, Preston & De Waal, 2002, Smith, 2006). Indeed, neural correlates of self-other resonance (SR) have been correlated with prosocial decision-making (Christov-Moore & Iacoboni, under review, Hein et al., 2010,2011, Ma et al., 2011).

Spontaneous imitation (or mimicry), a form of behavioral SR, is linked to empathy, affiliation and prosocial inclinations (Chartrand & Lakin, 2013, Van Baaren et al., 2004). Individuals' tendency to mimic others is correlated with their trait empathy (Chartrand & Bargh, 1999). Not surprisingly, we are more likely to mimic others with whom we desire to affiliate, with whom we have prior rapport, or to whom we feel more similar (for an extensive review of moderating factors in mimicry, see Chartrand & Lakin, 2013). Intriguingly, imitation of others has downstream effects on behavior. Studies have shown that *being* imitated by others increases the sense of trust and rapport with the imitater (reviewed in van Baaren et al., 2009). Additionally, being imitated was shown to increase prosocial orientations in both 18-month old infants (Carpenter et al. 2013) and adults (van Baaren et al., 2004), even towards individuals not involved in the imitation.

However, no study has probed whether deliberately *engaging* in coordinated imitation and behavior can cause a lasting increase in overall prosocial inclinations. We tested whether a behavioral intervention designed to stimulate SR via joint facial and gesture imitation and gaze-following could increase subjects' prosocial inclinations, relative to controls. To assess subjects' prosocial inclinations, we used a modified Dictator Game, a widely used economic game in which subjects decide how to allocate money between themselves and others, in this case 24 "players", represented by virtual profiles (consisting of a neutral-expression headshot, a name, and a yearly income. In this version of the game, half of the player profiles are of high socioeconomic status or SES (incomes between $70,000-$200,000/yr) and half are of low SES (incomes between $18,000-$35,000/yr). A subset of the 24 players represent actual people who receive the money allocated to them by the subject, and the subject receives the money they keep for themselves. In addition, the subject performs the task unobserved, and their data is kept anonymous. The subject is comprehensively informed about all of these details. These manipulations are designed to engage naturalistic social cognitive processes (since the subject's decisions can affect real people), and control for strategic and reputation-based influences on the subjects' behavior (since they are anonymous and unobserved, and there is no monetary incentive to share). The SES manipulation furthermore allows us to examine the differential roles of SR and top-down control: prior studies of the Dictator Game have found that subjects consistently share less money with players of low perceived need. In the framework we test here (proposed in Christov-Moore & Iacoboni, under review, Christov-Moore et al., under review), SR drives prosocial inclinations in a reflexive, bottom-up fashion that must be inhibited by both tonic and context-sensitive top-down control. Thus, we theorize that variance in offers to high SES players reflects the influence of SR with contextual and tonic top-down control, while variance in offers to low SES primarily reflects the influence of SR with tonic top-down control.

We hypothesized that engaging in behavioral SR alongside another individual would prime SR mechanisms in a bottom-up fashion, increasing their prosocial inclinations, resulting in significantly higher offers to both high and low SES players in the Dictator Game, relative to controls.

2.2. Methods

2.2.1. Subjects

A total of 34 subjects participated in this experiment (8 males, 26 females, mean age = 22 years, age range: 19-31 years). Subjects were all right-handed, with no history of drug and alcohol abuse and no prior or concurrent diagnosis of any neurological, psychiatric or developmental disorders. Participants were compensated $25 per hour and received additional compensation ($0-30) depending on their performance on the DG. Subjects were randomly assigned to the test (15 females and 3 males) or control (11 females and 5 males) group. The UCLA Institutional Review Board previously approved all aspects of this experiment.

2.2.2. Behavioral Intervention

Intervention

Subjects were seated facing a computer screen, while a confederate was seated next to them, also facing the screen (subject and confederate were placed at approximately 45 degrees from each other). Subjects were instructed that the other subject was a research assistant who was there to do the task with them and help them if they had any difficulty. This was true, though the confederate was additionally tasked with observing the subject to ensure that they were performing the intervention. If asked directly who they were, confederates were to respond: "I am a research assistant who was asked to help with the experiment". If asked whether the confederates were observing them, confederates were to respond: "Yes, I am supposed to make sure you're not having any trouble doing the task and help if necessary". The intervention itself consisted of three tasks, each approximately 4 minutes in length:

Gaze following: In each trial (for a total of 40 trials), subjects were presented with a human face for 4 seconds, looking forward, flanked by two objects of a similar category (fruit, tools, furniture, vehicles, etc.). After 4 seconds, the face's eyes would shift towards one of the two objects, and the face's expression would change from neutral to happy/sad. Subject and confederate were instructed to say aloud which object the face looked at. This required them to implicitly follow the face's gaze and process their subsequent emotional state, a manipulation designed to engage SR in the subjects.

Manual imitation: In each trial, subjects were shown clips of a human hand squeezing a balloon between the thumb and index finger in 1 of 3 different orientations, with the remaining fingers outspread or closed. Subject and confederate were given balloons of approximately identical size and color and asked to imitate the observed actions as closely as possible.

Facial imitation: In a similar fashion, subjects were shown photographs of faces making emotional facial expression, and subject and confederate were instructed to imitate the facial expressions as closely as possible.

After every 6 trials, a "rest" screen appeared for 3 seconds instructing subjects to "take a deep breath and relax".

Control Task

In this version of the task, a confederate was also present, though they were instructed to simply work on a computer in the same room as the subject. The subject was informed that they could consult them in case they had any problems performing the task. The tasks themselves replicated the test intervention absent the biological stimuli and emotional content:

Gaze following: The timing and instructions for this task were identical, only instead of a human face directing its gaze, the guiding stimuli were black arrows of different sizes and shapes.

Gesture Imitation: For this task subjects performed similar squeezing motions, only the guiding stimuli, instead of video clips of hands, were arrows pointing up, left, right or down, indicating the direction in which subjects had to direct their hand while squeezing.

Facial Imitation: Instead of facial expressions, subjects were given verbal prompts to perform non-emotional head movements and gestures, such as opening and closing their eyes, looking upwards or nodding their head.

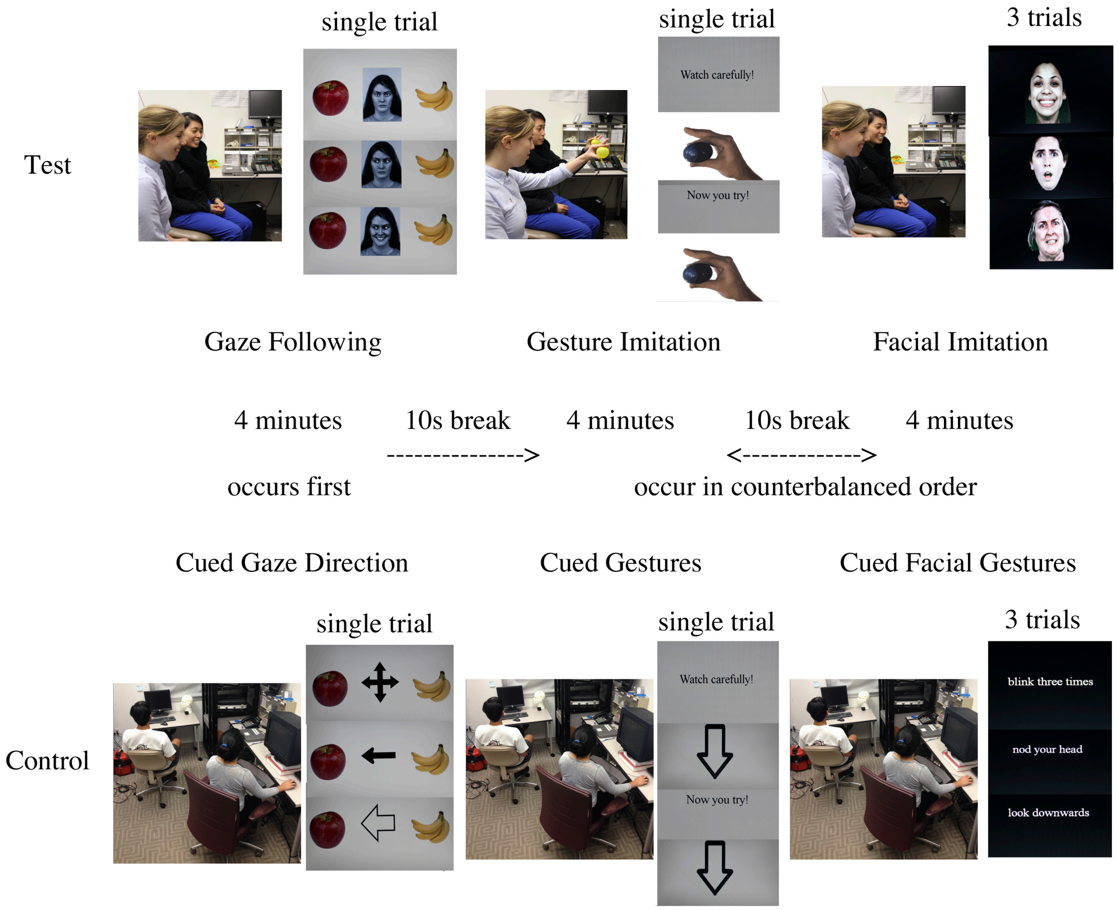

Figure 2.1. Test and control intervention design.

Follow up reporting

Immediately following the intervention, confederates left the room and filled out a short report detailing whether subjects complied with each of the three tasks' instructions. All subjects complied with the intervention and control tasks.

2.2.3. Dictator Game

The Dictator Game (DG): Subjects were instructed to select a portion of a sum of money ($0-10 out of $10) to be given to a player (henceforth referred to as the *player*, to distinguish them from the subject throughout the manuscript), represented by a digital profile presented on a computer screen, for each of 24 trials. In each trial, subjects were presented with 1 of 24 full-color photographs (equalized for luminance) of neutral faces selected from stock photographs and the Nim Stim Face Stimulus Set (Tottenham et al., 2009) coupled with a name and a yearly income in dollars, both presented on the right portion of the screen in black letters with a white background. Player profiles had one of two levels of income: Low ($18,000-$30,000/yr) or High ($70,000-$200,000/yr). Income was used as a proxy for socioeconomic status (SES). Both genders were equally represented, while racial composition ((2)Caucasian:(2)Hispanic/Latino:(1)Black:(1)Asian) was derived from census data and matched between genders and income levels. Low and high SES profiles were presented in 1 of 4 different pseudorandomized orders throughout the game. Subjects encountered each player only once. Each player profile was presented for 4 seconds, after which the subjects were given an onscreen prompt to make their offer ("How much $ would you like to offer?"), which appeared in the bottom right corner of the screen. This screen remained for 5 seconds, during which subjects had to make their offer.

Subjects were truthfully informed that a subset (n=12) of the players in the experiment corresponded to people in Los Angeles (contacted for approval prior to the experiment) who would receive the money allotted to them by each subject. Their photograph and name was changed for confidentiality, though the photograph used was matched to their gender and race, and their actual income was displayed. Genders, races and SES groups were equally represented among the 12 real profiles. Subjects were informed that they would be rewarded for 3 randomly selected trials out of the total 24. Thus, on any given trial, they could be playing with a real person who would actually receive the money allotted to them, and the subjects could receive what they allotted for themselves in that trial. Subjects carried out the task unobserved, in a closed room without cameras. Their responses were saved in association with an ID number, and scored by a different researcher than the experimenter, ensuring subjects' anonymity. Subjects were comprehensively informed about these controls and explicitly instructed prior to and during briefing that the paradigm included *no deception*.

The subjects' 24 offers (1 per player) were averaged and separated by player income (high or low). This resulted in 2 means per subject: low SES and high SES. Additionally, we created a third variable to index contextual modulation of offers, ΔDG, equal to the normalized difference between offers to Low SES and High SES $({}^{\text{LowSES-HighSES}}/_{(\text{LowSES+HighSES})})$.

2.3. Results

Before performing comparisons between the test and control groups, we examined the normality of the data (via a Shapiro-Wilks test). Control subjects' offers violated the assumption of normality (high SES p<.0001, low SES p=.007). Test subjects, on the other hand, showed approximately normally distributed offers (high SES p=.086, low SES p=.381).

Condition	Control		Test	
	$\bar{x}$ (95%CI)	$\sigma_{\bar{x}}$	$\bar{x}$(95%CI)	$\sigma_{\bar{x}}$
Low SES	4.33(2.97,5.69)	3.92	5.4(3.95,6.84)	1.94
High SES	2.3(0.94,3.66)	3.331	1.37(0,2.81)	1.19

Table 2.1. Means with 95% CI's and standard deviations for each group by condition.

We then performed a comparison of offers between groups with a linear mixed model. While there was no significant effect of intervention ($F_{1,32}$=.007, p=.934), we found a significant effect of player SES ($F_{1,32}$=38.94, p<.0001) and a significant group x player SES interaction ($F_{1,32}$=4.232, p=.045). This interaction is likely due to the opposing trends in the data per condition: in the low SES condition, the test group has a higher mean, while in the high SES condition, the test group has a lower mean (see Table 2.1). However, as there was no significant effect of the intervention, this is the most we can extrapolate from these results. Interestingly, although there was no evidence for significant differences between the central descriptors of each group, the Kolgorov-Smirnov test comparing the distributions of control and test subjects within each condition (low SES or high SES) found that the distribution of offers to low SES differed significantly between test and control subjects (D=0.5, p=.029, see Figure 2.3).

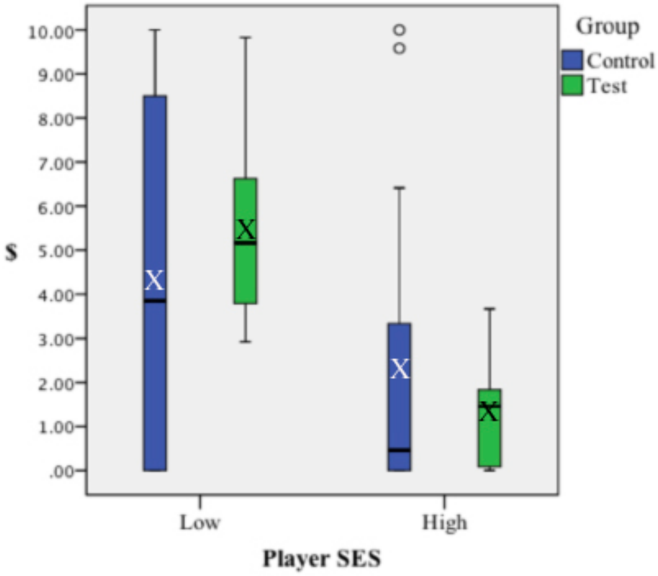

Figure 2.2. Boxplots of mean offers by group and condition. Edges of box indicate 1st and 3rd quantiles. Dots and stars indicate significant outliers. Means are indicated by (X), while medians are indicated by black horizontal line (-). There does not appear to be a significant difference between groups.

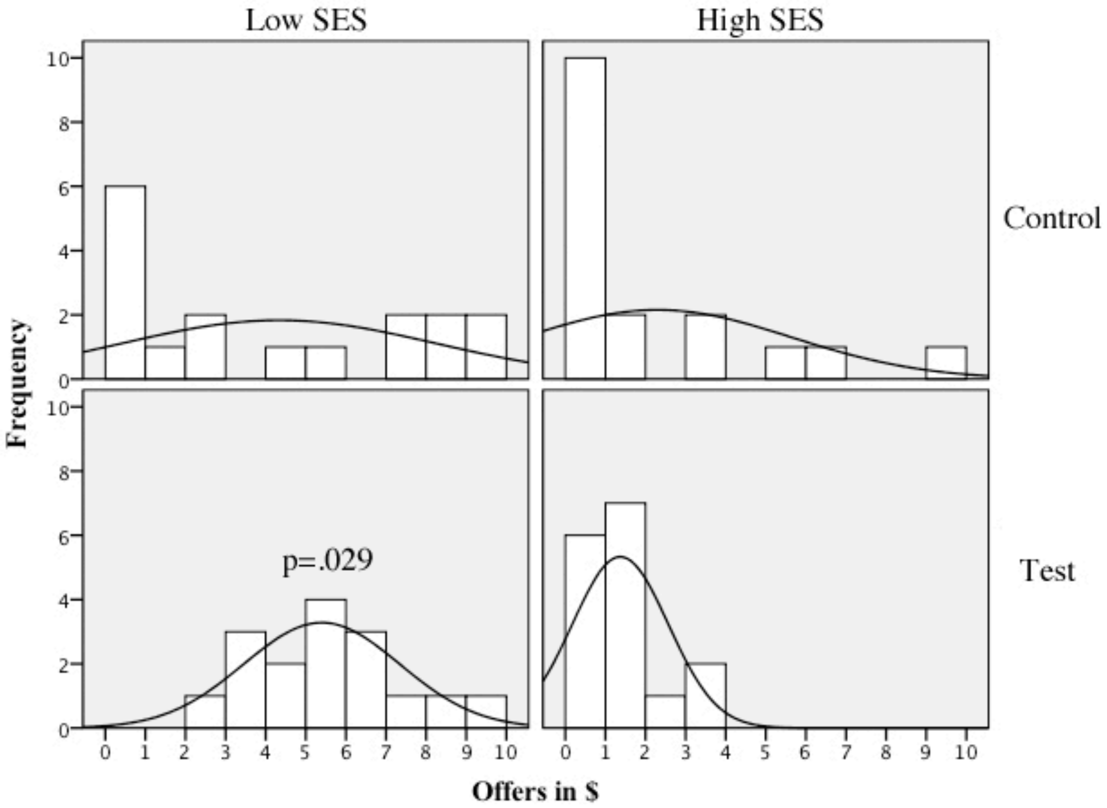

Figure 2.3. Frequency histograms of subjects' offers in the Dictator Game. Test subjects' offers were approximately normally distributed, while control subjects' offers deviated from normality. The distributions of test and control subjects' offers to Low SES players were significantly different (D=0.5, p=.029).

2.4. Conclusions

Contrary to our hypothesis, test subjects did not show increased offers (in either condition) in the Dictator Game relative to controls. This primarily suggests that contrary to the effect of *being imitated,* deliberate engagement in gaze following and imitation of facial expressions and object manipulation does not cause an overall increase in prosocial inclination. It is possible that the absence of a real, human *object* of imitation may have impeded the engagement of the same neural mechanisms. Second, the effects of an intervention targeted solely at bottom-up mechanisms may have been too short-lived to affect subsequent economic behavior. Third, imitation-based behavioral interventions of this kind (e.g. Ingersoll, 2012) typically require long and repeated sessions to achieve robust effects. A single, short intervention with sparse stimuli may not have been sufficient to affect subjects' economic behavior. Last, the sample size for this study was relative small (16-18 subjects per group), increasing the uncertainty inherent in our measurements of the central tendency and spread of the data (as evidenced by the large 95% confidence intervals)(Table 2.1).

This study does suggest that in order to examine the feasibility of such an intervention in the future, it may be necessary to carry out sustained, repeated interventions using real-life interactions. The intervention itself was based on behavioral interventions that have been shown to improve outcomes in social competence and social cognition in children with Autism Spectrum Disorder (ASD) (Ingersoll, 2012) and adults with schizophrenia (Mazza et al., 2009), thus it is possible that the main reason for the lack of a visible effect is its short duration.

One interesting result was the increased normality and reduced spread in the distributions of mean offers in the test group. Of particular interest is the fact that test subjects' offers to low SES subjects were centered around 50/50 (fair) divisions of money, and, unlike control subjects, not one subject showed offers to low SES subjects under 3$. We speculate that this may be due to a) increased engagement of social equity norms (a tendency towards fair offers) following the intervention. Another simple explanation is that the control intervention was simply less engaging and/or entertaining than the test intervention, thus inducing subjects to seek greater compensation for their time spent.

Acknowledgements

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3. **Can Disruptive Neuromodulation of Putative Top-Down Control Areas Increase Prosocial Inclinations? *Article under review**

The Role of Dorsolateral and Dorsomedial Prefrontal Cortex in Prosocial Decision Making: Tonic and Contextual Control

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Abstract

Are humans inherently selfish? Research using economic games shows that, on the contrary, humans often cooperate and share with one another in a manner contrary to rational self-interest. Neuroscientific research additionally suggests that we assign subjective reward value to the welfare of others (prosocial inclination). This may be fostered by neural mechanisms that favor "self-other resonance", a tendency to process the pain, emotions and behavior of others *as if they were our own*. However, prosocial inclinations and neural activity and behavior consistent with self-other resonance vary between individuals, and are selectively inhibited in response to context, due to top-down control. We used continuous Theta Burst Stimulation (cTBS) to transiently disrupt activity in two areas implicated in top-down control, the right dorsolateral prefrontal cortex (DLPFC) and dorsomedial prefrontal cortex (DMPFC), as well as a control cortical area (right MT/V5) in three groups of healthy subjects (1 area per group). We then tested subjects' prosocial inclinations with an unsupervised Dictator Game in which they allocated real money anonymously between themselves and low and high socioeconomic status (SES) players. Subjects stimulated in DLPFC and DMPFC shared more money than the MT/V5 group, though this effect showed a significant interaction with the SES (high or low) of the players. Relative to controls, transient disruption of DLPFC increased offers to high SES players, while disruption of DMPFC caused increased offers to low SES players. These data suggest that DLPFC and MPFC *inhibit* prosocial inclinations during costly sharing, though they may do so in different ways. DLPFC may implement contextual control (in this study due to varying perceived need of the players), while DMPFC may implement a more tonic form of control of prosocial inclinations.

3.1. Introduction

Are people essentially good or bad? This question is best exemplified by Rousseau and Hobbes' debate over the "state of nature", i.e. humanity's "natural", precivilized state. Hobbes considered human nature to be an inherently nasty, brutish thing that is saved and improved by civilization. Rousseau, in contrast, thought that humankind began as "noble savages", which have become warped into beasts by civilization. Whether we apply this debate to individual socialization or to our species' evolution, the central question remains the same: Are we essentially selfish or selfless? To rephrase the question more specifically, is our primary impulse in social interactions to self-maximize and compete, or to share and cooperate? Correspondingly, does socialization constrain our selfishness or warp our altruism?

The notion that we are inherently selfish has dominated theory in politics, economics, and social psychology for a long time. However, lower animals as well as primates exhibit apparently altruistic behavior, often risking their lives to protect others within the group (Preston & De Waal, 2002). Children and toddlers also demonstrate spontaneous sympathetic and prosocial behavior in response to the distress of others (Eisenberg & Fabes, 1990). Economic games such as the Prisoner's Dilemma or the Dictator Game show outcomes inconsistent with a self-maximizing drive (Camerer & Thaler, 1995, Engel, 2001, Liebe & Tutic, 2010), leading some to conclude that prosocial outcomes may have a subjective reward value or *utility* during decision-making (Fehr & Camerer, 2007, Fehr & Fischbacher, 2003). Indeed, a 2006 study on neural correlates of charitable donations found that the mesolimbic reward system is engaged by donations in the same way as when monetary rewards are obtained (Moll et al., 2006). A crucial, unanswered question is what is the mechanism that may provide subjective reward value to prosocial decisions.

Prosocial inclinations may originate from our tendency to share in the internal states and behavior of others, a contagion-like process we will refer to as “self-other resonance”. A likely neural mechanism for self-other resonance is *neural resonance*, the tendency to recruit similar neural systems for the pain, emotions and behavior of the self and other people (Zaki & Ochsner, 2012). Neural resonance has been correlated with prosocial behavior (Christov-Moore & Iacoboni, under review, Hein et al., 2010, 2011, Ma et al., 2011, Singer et al., 2006), suggesting that our ability to share in the experiences of others may compel us to include the welfare of others in our decisions (Preston & De Waal, 2002, Smith, 2006). However, contagion-like processes supported by neural resonance are transient and short-lived. How could they influence our prosocial decision making? This puzzling association of previous empirical studies needs more direct testing of causal relationships between neural resonance, its control and prosocial decision-making.

The varying degree to which we process the states of others as if they were our own may determine our inclination to treat them as we would ourselves. Indeed, both neural resonance and prosocial behavior covary with contextual factors like affiliation, race, gender, perceived need and social distance (Camerer & Thaler, 1995, Cheng et al., 2010, Hogeveen et al., 2014, Gu & Han, 2007, Guo et al., 2012, Lamm et al., 2007, Liebe & Tutic, 2010, Loggia et al., 2008, Reynolds-Losin et al., 2013, 2014, in press, Singer et al., 2006). Context sensitivity may result from mechanisms of inhibitory control via prefrontal systems, influencing the relative utility of others’ outcomes in our decisions. Indeed, in line with this hypothesis, research examining the effect of cognitive load (a paradigm used to diminish the role of cognitive control) on Dictator

Game behavior found that subjects with high cognitive load tended to behave more generously, (Schulz et al., 2014). However, the underlying mechanisms for this result are still unclear.

The dorsolateral prefrontal cortex (DLPFC) and dorsomedial prefrontal cortex (DMPFC) may be instrumental in modulating the distinction between self and other during social interactions and decision-making (Camerer & Thaler, 1995, Christov-Moore & Iacoboni, under review, Knoch et al., 2006, Miller & Cohen, 2001, Spengler et al., 2010, Taylor et al., 2012). We have shown that activity of both areas during perception and imitation of others' affective and somatosensory states was negatively correlated with subjects' prosocial decision making (Christov-Moore & Iacoboni, under review). The DMPFC is important for manipulating self and other perspectives (Amodio & Frith, 2006), as well as the tonic control of spontaneous imitation (mimicry) (Cross et al., 2013, Lhermitte, 1999, Spengler et al., 2011). Furthermore, disruptive Theta-Burst stimulation to DMPFC reduced bias towards out-group members and diminished social conformity (Klucharev et al., 2011). The right DLPFC is thought to integrate affective and cognitive information into decision-making (Fehr & Camerer, 2007). Indeed, it has been causally implicated in the inhibition of prereflective affect during social decision-making. Two recent TMS studies found that subjects playing as responders in the Ultimatum Game (in which subjects must accept or reject divisions of money) accepted more unfair offers following disruption of the right DLPFC by low-frequency Transcranial Magnetic Stimulation (TMS) (Knoch et al., 2006, van't Wout et al., 2005). The authors interpreted these data as disinhibition of the self-maximizing impulse, and a disruption of a "default" strategy to reject unfair offers. However, those results could also be interpreted as the manifestation of disinhibition of prosocial impulses. After all, accepting an unfair offer also results in a larger payoff for the opposing player. Perceived need in other people may lead to decisions on accepting unfair offers that are either driven by self-maximization, or by concerns for other people's welfare. To address this ambiguity, we examined *offering behavior* in the Dictator game (DG), which is a more direct measure of subjects' prosocial inclinations, as opposing players cannot reject the subject's offers.

We propose that our prereflective impulse in costly sharing paradigms is towards prosocial decisions, fostered by reflexive forms of empathy that are tonically and contextually inhibited by prefrontal systems involved in top-down control. Prior evidence suggests that DLPFC and DMPFC may be instrumental in this inhibition. In order to test this notion, we transiently disrupted the activity of both DLPFC and DMPFC, and investigated how the influence of these two frontal areas on prosocial decision making varied in response to the perceived need of the opposing player.

3.2. **Methods**

3.2.1. **Subjects**

A total of 58 subjects participated in this experiment (30 women, 28 men, mean age = 21.31 years, age range: 18-35 years). Subjects were all right-handed, with no history of drug and alcohol abuse and no prior or concurrent diagnosis of any neurological, psychiatric or developmental disorders. Participants were compensated $25 per hour and received additional compensation ($0-30) depending on their performance on the DG. Subjects were randomly assigned to stimulation in either the right hemisphere DLPFC (9 females and 10 males), DMPFC (10 females and 9 males) or MT/V5 areas (11 females, 9 males). Subjects underwent continuous theta burst stimulation (cTBS), which has inhibitory effects lasting up to an hour (Huang et al., 2005), to either right DLPFC, DMPFC or MT/V5 before playing the DG. All subjects underwent two experimental sessions. All aspects of this experiment were previously approved by the UCLA Institutional Review Board.

3.2.2. Magnetic Resonance Imaging

The first experimental session, identical for all subjects, consisted of a high-resolution T1-weighted structural scan (TR=1900 ms, TE=2.26 ms, TI=100 ms, flip angle=9°, matrix size=192x192, FOV=250 mm, 176 slices, 1.0 x 1.0 x 1.0 mm voxels). These imaging data were collected to guide the location of the stimulation site. Subjects also performed two tasks of pain perception and facial emotion observation and imitation. Since these two tasks and their results are not relevant to this non invasive neuromodulation study, we will not describe them in detail here.

3.2.3. Transcranial Magnetic Stimulation

Subjects' cTBS session occurred approximately a week after their MRI session. The right DLPFC and DMPFC regions-of-interest (ROI) were constructed in standard space (MNI 152 template) using 10mm diameter spheres centered on voxels in right DLPFC (x = 40mm, y = 24mm, z = 38mm) and right DMPFC (x = 8mm, y = 24mm, z = 54mm). These ROI's were centered on coordinates where activation during affective and somatosensory neural resonance tasks showed the highest correlation with subjects' modulation of DG offers in response to players' SES in a prior experiment (Christov-Moore & Iacoboni, submitted). That is, these areas were correlated with the tendency to share less money with high SES players, compared to low SES players. The rationale behind this experimental design choice is that these coordinates should represent areas of maximal control during the DG that we aim to disrupt with cTBS. The control ROI was constructed in an identical fashion around an area of no a priori interest in MT/V5 (x = 48mm, y = -74mm, z = 0mm), centered on a peak of activation from the same experiment (obtained while subjects viewed a video clip displaying an object in motion) (Fig. 3.1). ROI's were registered to each subject's native space using MCFLIRT (Jenkinson et al., 2002), and used to accurately target the TMS coil using frameless stereotaxy as implemented in Brainsight (Rogue Research).

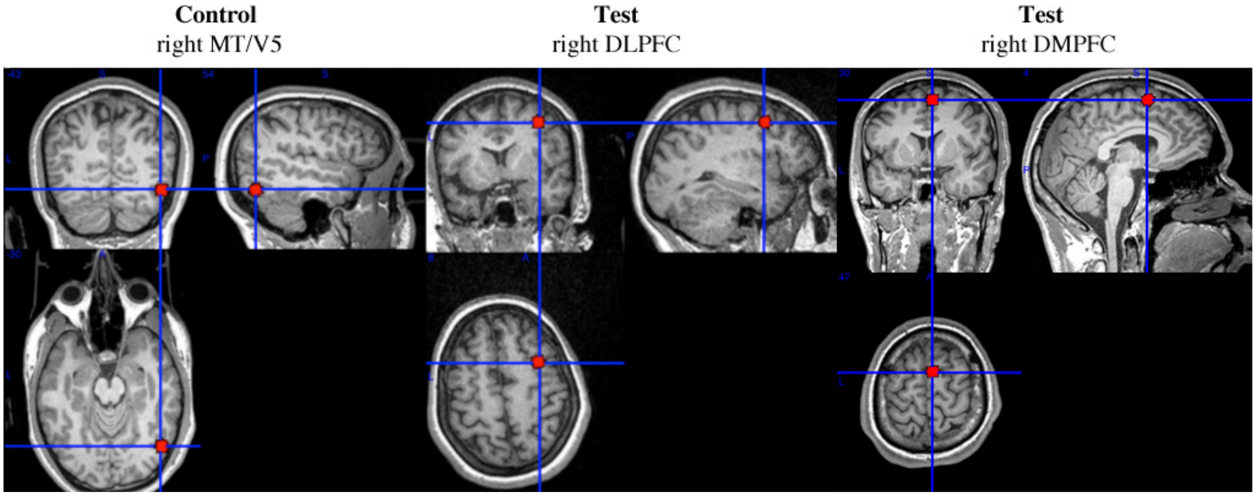

Figure 3.1. Stimulation sites. Control site: area MT/V5 (x = 48mm, y = -74mm, z = 0mm). Test sites: DLPFC (x = 40mm, y = 24mm, z = 38mm) and DMPFC (x = 8mm, y = 24mm, z = 54mm). ROI's are displayed on a single-subject high-resolution T1-weighted images in neurological orientation.

In accordance with previous studies (Klucharev et al., 2011, Knoch et al., 2006), active motor threshold (AMT) was measured in the left first dorsal interosseous for DLPFC and MT/V5, and in the anterior tibialis for DMPFC. AMT was defined as the minimum intensity that produced MEPs of ≥200 uV in 5 of out 10 consecutive stimulations, while subjects concurrently flexed the recorded muscle. Then, cTBS was delivered to the right DLPFC or DMPFC in the test groups and to the right MT/V5 in the control group. cTBS consists of triplets of TMS pulses at 50 Hz, delivered at 5 Hz for a total of 600 pulses over 40 seconds, with intensity set at 80% AMT, using a second-generation Magstim Rapid stimulator. Stimulation was delivered to MT/V5 and right DLPFC using a flat figure-eight coil, while stimulation to right DMPFC was delivered using an angled coil (commonly used to reach deeper stimulation sites, such as DMPFC). Subjects were unaware of their group affiliation (test or control). After cTBS, subjects waited for 5-7 minutes, during which time they were briefed on the DG. Before and during briefing, they were comprehensively informed that the study protocol involved *no deception*.

3.2.4. Dictator Game

For the DG, subjects were asked to divide a sum of money ($10) with another player as they saw fit. The DG consisted of 24 trials with 24 different digital profiles of various ages and race. Each profile contained a name, a headshot from the NimStim facial stimulus set (Tottenham et al., 2009) and a yearly income(SES), which was either low ($18,000-$30,000/yr) or high ($70,000-200,000/yr). This allowed us to test how people's apparently altruistic generosity (a proxy for the relative utility of the player's welfare) varied as a function of the opposing player's SES. SES (a proxy for perceived need) is a contextual factor which previous studies have shown to *inhibit* generosity – people give less money to players with lower perceived need (Engel, 2011, Liebe and Tutic, 2010). In each trial, subjects were shown a profile displayed on a computer screen. They had 5 seconds to observe the profile, after which an onscreen prompt ("How much $ would you like to offer?") appeared in the lower right corner of the profile. Subjects then had 5 seconds to make an offer by pressing a number key (0-10) on a standard keyboard. Subjects interacted with each player only once. The design of the Dictator Game allowed us to isolate the relative utility of subjects' and players' welfare separate from strategic concerns, as the subjects' compensation was dependent only on their allocation of funds. This is distinct from the Ultimatum game, in which players' can reject subjects' offers, which adds a personal strategic value to prosocial decisions.

The DG was designed such that half of the profiles (n=12) represented *real people in Los Angeles (contacted prior to the study) who would actually receive the money subjects offered in the DG*. In order to maintain the profiles' anonymity, we created false names and used NimStim headshots matched for age, gender, and race. Subjects and virtual players were compensated for three randomly selected trials (list randomizer, www.random.org) so that, in any given trial, a subject's decision might affect the welfare of a real person and themselves. This was done to encourage engagement of naturalistic social cognitive processes; previous studies have shown that different behavior and neural activation ensues if subjects believe they are playing the game with a computer (van t'Wout et al., 2006). In order to reduce the possible effect of concerns for reputation and experimenter observation, subjects played the DG alone in a closed room, unobserved and unrecorded. To ensure their anonymity, a research assistant with whom subjects did not interact in the experiment was assigned to process their deidentified data. Subjects were comprehensively informed about all of these controls and questioned to assure that they understood the task parameters and controls.

Four subjects who voluntarily expressed disbelief in the controls following the Dictator Game were excluded from the study (and do not figure in the 58 subjects reported above).

3.2.5. Self Reported Empathy

Following the DG, subjects filled out the *Interpersonal Reactivity Index (IRI)*. The IRI (Davis, 1983) is a widely used (Avenanti et al., 2009, Pfeifer et al., 2008) and previously validated (Litvack-Miller et al., 1997) questionnaire designed to measure both cognitive and affective components of empathy. It consists of 24 statements that the subject rates on a 5-point scale ranging from 0 (Does not describe me very well) to 5 (Describes me very well). The statements are calculated to test four theorized subdimensions of empathy: *Fantasizing Scale (FS)* measures the tendency to take the perspective of fictional characters; *Empathic Concern (EC)* measures sympathetic reactions to the distress of others; *Perspective Taking (PT)* measures the tendency to take others' perspective and *Personal Distress (PD),* which measures aversive reactions to the distress of others. Scores were summed for each sub-dimension (measured by 6 items) to make 4 scores per subject. We included the PT, PD, FS and EC subscales as covariates in our analyses of DG behavior.

3.3. Results

We assessed whether stimulation had a significant effect on offers. We first examined the normality of offers using a Shapiro-Wilk test and found that offers to low SES players were approximately normally distributed (MT/V5 p=.354, DLPFC p=.522), except for the DMPFC group (p=.005). Offers to high SES players violated the assumption of normality, likely due to a floor effect (MT/V5 p=.048, DLPFC p=.04, DMPFC p=.029). In addition, a Levene test of homogeneity of error variance within each SES condition between groups found that offers to high SES players additionally violated the assumption of homogeneity ($F_{2,55}$=8.89, p<.0001), while offers to low SES players did not ($F_{2,55}$=.236, p=.791).

To accommodate non-normality and heteroscedasticity between groups, we employed a repeated-measures linear mixed model with robust standard errors, including gender and the PT, PD, FS and EC IRI subscales as covariates (to control for possible effects of gender and individual differences in trait empathy). We found a trending effect of group on overall offers ($F_{2,107}$=2.589, p=.08), a highly significant effect of player SES on offers ($F_{1,107}$=153.175, p<.0001), and a significant group x player SES interaction ($F_{2,107}$=3.976, p =.022). We did not find a significant effect of trait empathy or gender on offers.

Post-hoc tests of simple effects (t-tests with robust standard error) were conducted to test our hypothesis that offers were *higher* in the DLPFC and DMPFC groups relative to controls. Accordingly, alpha level was set at .05, one tailed. We found a highly significant increase in mean offers to high SES players between the DLPFC (M=2.998, SD=2.63) and MT/V5 (M=1.217, SD=1.09) group; t_{107}=2.777, p=.003. There was also a significant increase in mean offers to low SES players between the DMPFC(M=6.882, SD=2.46) and MT/V5 (M=5.29, SD=2.9) group; t_{107} =1.818, p=.036. For all means and standard deviations see Table 3.1. All analyses were carried out using SPSS (V.21, SPSS Inc., Chicago, Illinois, USA).

Group		Low SES offers		High SES offers	
	n	$\bar{x}$ (95%CI)	σ	$\bar{x}$ (95%CI)	σ
MT/V5	20	5.29 (4.00, 6.58)	0.649	1.22 (0.73, 1.70)	0.244
DMPFC	19	6.88 (5.76, 8.00)	0.566	1.98 (1.09, 2.87)	0.449
DLPFC	19	5.85 (4.78, 6.92)	0.54	3.00 (1.80, 4.20)	0.605

Table 3.1. Means with 95% Confidence Interval (CI) and robust estimated standard errors of dictator game offers (in $) by group and condition.

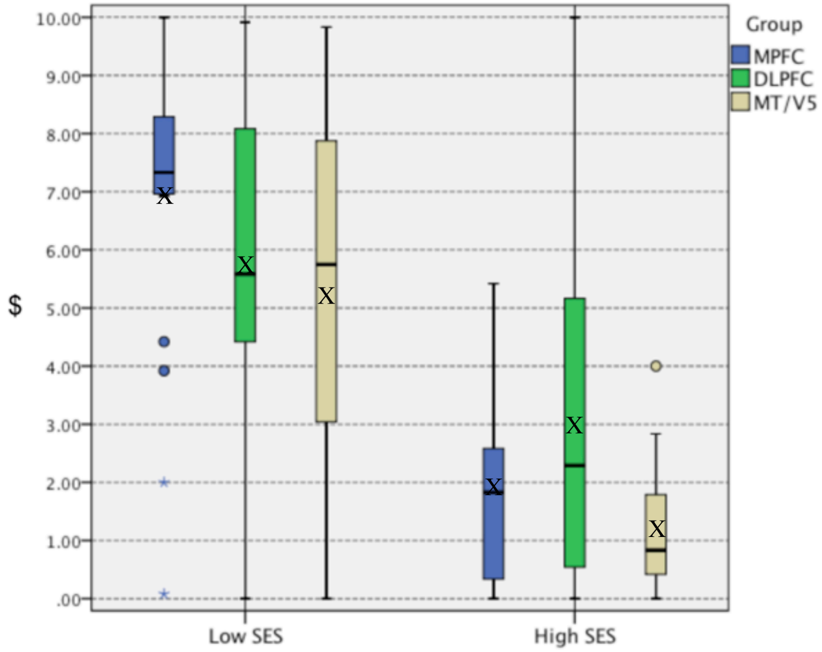

Figure 3.2. Boxplots of average offers to high and low income/SES players by stimulation site. Edges of box indicate 1st and 3rd quantiles. Dots and stars indicate significant outliers. Means are indicated by (X), while medians are indicated by black horizontal line (-). There is a highly significant effect of player SES on offers ($F_{1,107}$=153.175, p <.0001), a significant effect of DLPFC stimulation on High SES offers (t_{107}=2.777, p=.003) and a significant effect of DMPFC stimulation on Low SES offers (t_{107} =1.818, p =.036).

3.4. Discussion

These results demonstrate that a) disruptive stimulation to right DLPFC and DMPFC increased subjects' offers, and that b) these frontal systems control prosocial decision making differently. Player SES was found to have a strong inhibitory effect on prosocial decisions, suggesting that the high SES condition evokes top-down contextual control to a greater extent than the low SES condition. Transient disruption of both prefrontal areas increased offers (in a condition-specific manner), suggesting that top-down control is inhibitory in nature. Thus, transient disruption of the DLPFC reduced the inhibitory effect of contextual cues (offers to high SES players), while transient disruption of DMPFC seemed to reduce context-independent control (offers to low SES players).

These data suggest that DLPFC may implement a form of context-sensitive inhibition, consistent with its proposed role in integrating cognition and emotional responses during decision-making (Fehr & Camerer, 2007, Knoch et al., 2006). DLPFC stimulation had the greatest effect on offers to high SES players, where contextual inhibition is most likely to play a role relative to tonic inhibition. DMPFC may implement tonic control (consistent with its possible role in the tonic control of automatic imitation, Lhermitte, 1983, Spengler et al., 2010), as its effect is most pronounced on offers to low SES players, a condition in which contextual inhibition plays a smaller role.

We theorize that when we make costly decisions about others' welfare in the Dictator Game, we implicitly assess the relative utility of their welfare versus our own. Neuroeconomics research suggests that in order to do this, we automatically form models of the people we are dealing with (Krueger et al., 2008), which may evoke the sensory, affective and motor imagery we associate with other people. This imagery, much like real-time biological stimuli, may drive self-other resonance (and its inhibitory control), thus increasing the respective utility of the other person's welfare. Indeed, there is evidence that affective/motivational structures implicated in neural resonance and empathy (like the amygdala and anterior insula) interact with systems involved in cognitive control (like the DLPFC and ventromedial prefrontal cortex) during social decision-making (Bechara et al., 1999, Camerer, 2003, Hare et al., 2010, Sanfey, 2003).

It is important to note that prosocial decision-making often occurs in circumstances in which the biological stimuli typically associated with neural resonance (Zaki & Ochsner, 2012) are relatively sparse. Indeed, in the Dictator Game employed here, the only biological stimuli associated with players are headshots with neutral facial expressions. However, neural resonance is correlated with prosocial behavior in circumstances involving similarly sparse biological stimuli (Christov-Moore & Iacoboni, under review, Hein et al., 2010, 2011, Ma et al., 2011, Singer et al., 2006). The relative presence of biological stimuli likely has an effect on our prosocial inclinations. Indeed, biological stimuli as sparse as a photograph have been found to increase charitable donations (Genevsky et al., 2013). Further research is needed to comprehensively assess the importance of biological stimuli for prosocial inclinations.

Manipulations designed to diminish the role of top-down control in decision-making (increased cognitive load) have been shown to increase fair offers in the Dictator Game (Schulz et al., 2014). However, to our knowledge, this is the first evidence for a successful effect of neuromodulation on costly sharing. Indeed, in agreement with our hypothesis, these data provide causal evidence that *right DLPFC and DMPFC are important for exerting an inhibitory influence on prereflective prosocial inclinations*. This finding represents a step towards a proximate explanation for humans' tendency to deviate from rational self-interest. Indeed, this suggests that our primary drive in non-strategic social transactions may in fact be to behave prosocially, perhaps due to reflexive forms of empathy that blur the boundaries between individuals. The social brain may, in fact, be Rousseauian.

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Chapter 4. Are There Gender Differences in Neural Resonance and Trait Empathy?

Gender Differences in Neural Resonance and Trait Empathy

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Abstract

There is ample evidence that males and females differ in neural and behavioral correlates of empathy. Numerous studies have found that females score higher on self-reported measures of trait empathy. Previous studies also suggest that females show relatively greater vicarious responses to the pain and emotions of others, while males show greater evidence of top-down control of vicarious responding. However, few studies to date have examined gender differences in neural resonance after controlling for differences in self-reported trait empathy. In this study, we examined self-reported trait empathy as well as activation and functional connectivity during two neural resonance tasks (observation of a human hand receiving painful stimuli, and observation and imitation of emotional facial expressions) in 39 males and 39 females. Females showed significantly increased trait empathy relative to males. After controlling for differences in trait empathy, males showed neural evidence of increased recruitment of top-down control mechanisms, while females showed evidence of increased recruitment of mechanisms involved in perceptual processing. This is consistent with prior neural and behavioral findings showing increased cognitive control of affect in males, and increased sensitivity to others' pain and emotion in females.

4.1. Introduction

It is a commonly held belief that females are more empathic than males. Studies have found that females consistently score higher on measures of trait empathy (Eisienberg & Lennon, 1983, Mestre et al., 2009, Tello et al., 2013, Wheelwright et al., 2006). Starting at a young age, females also seem to evince greater concern and display more sympathetic, prosocial behavior towards others (Hoffman, 1977, Mesch et al., 2011). Many researchers think that empathic concern towards others is driven by our vicarious responses to others' states (Aron & Aron, 1986, Batson, 1991, Eisenberg & Fabes, 2008, Masten et al., 2011). Thus, it is not surprising that females seem to show increased markers of "resonance" with the behavioral, affective and somatosensory states of others (which we will collectively term self-other resonance or SR), while males show greater evidence of top-down control over their vicarious responses to others. This difference is widely thought to originate in an increased emphasis on nurturing behavior in females in human evolution (reviewed in Christov-Moore et al., 2014, Eisenberg & Lennon, 1983).

A recent fMRI study on empathy has revealed gender differences in the inferior frontal cortex, suggesting that these gender differences may be due to differences in the mirror neuron system (Schulte-Rüther et al., 2008). Indeed, automatic imitation or mimicry is a well-documented behavioral correlate of SR that is associated with empathy and the human mirror neuron system (Chartrand & Lakin, 2013, Iacoboni, 2009). Females exhibit greater facial mimicry when viewing emotional facial expressions (Dimberg and Lundquist, 1990; Lundqvist, 1995; Sonnby-Borgström et al., 2003). Females also show increased neural correlates of behavioral SR: Both MEG and EEG demonstrate oscillatory activity in the 10-20 Hz range at rest in central sensory-motor regions that desynchronizes during action performance and observation (the mu rhythm, Muthukumaraswamy et al., 2004b). This pattern of neural activity is interpreted as representing a marker of SR at the level of neuronal ensembles (attributed to the human mirror neuron system), because desynchronization during both action execution and action observation is typically framed in terms of 'motor activation' (Hari et al., 1998). Two groups have reported increased mu suppression in female subjects, compared to males, thus supporting the hypothesis of higher "resonance" with motor behavior in females (Cheng et al., 2008, Yang et al., 2009). In addition, studies of event-related potentials (ERP) in response to simple purposeful behaviors found that females preferentially recruited limbic and cingulate areas, while males preferentially recruited orbital/frontal areas (Proverbio et al., 2010).

Females also seem to be more responsive to the emotions and pain of others. In one study, females, compared to males, reported greater susceptibility to contagion and displayed more overt signs of contagion in a semi-naturalistic setting, for both positive and negative emotions (Doherty et al., 1995). Subjects were asked to focus on either their own feelings when seeing facial emotional expressions or the feelings of the other person. In both the 'self' and 'other' oriented attentional focus, females activated more the inferior frontal cortex, compared to males. In addition, a number of ERP studies have found that females show increased amplitudes of somatosensory processing-related ERP waveforms in response to humans' suffering (Groen et al., 2013, Han et al., 2008, Proverbio et al., 2009a). An fMRI study of neural responses to compassion-inducing images found that females, relative to males, showed increased activation in areas involved in emotional and empathic processes (Mercadillo, 2011).

Conversely, males seem more prone to regulate their emotional responses than females: two studies examining BOLD responses to negative emotion induction found that males showed increased recruitment of regulatory cortical areas like the dorsolateral prefontal, orbitofrontal and anterior cingulate gyrus (Koch et al., 2007, Domes et al., 2010). A study examining induction of negative *and* positive emotional states showed analogous results (Mak et al., 2009).

A handful of studies have also reported empathy-related gender differences in brain structure. Females have larger grey matter volumes in both posterior inferior frontal and anterior inferior parietal cortex(Cheng et al., 2009), two areas typically associated with the human mirror neuron system in the fMRI literature (Caspers et al., 2010, Rizzolatti & Craighero, 2004). Furthermore, empathic predisposition in females correlated with grey matter volume in the inferior frontal cortex, providing additional evidence in favor of gender differences in prereflective forms of empathy (Cheng et al., 2009).

Neural resonance, the recruitment of overlapping brain areas for the perception and experience of affect, somatosensation and behavior (Zaki and Ocshner, 2012), is considered a substrate of self-other resonance (SR). In a study on the modulatory role of social reputation on neural resonance for pain, subjects first played an economic game with cooperative and non-cooperative confederates and then watched the confederates inflicted with pain (Singer et al., 2006). While both males and females demonstrated similar activation of pain-associated neural systems while watching cooperative players, males had reduced activation of pain-associated neural systems while watching non-cooperative players inflicted with pain. Furthermore, males actually showed activation in reward-related structures (nucleus accumbens) when watching non-cooperative players inflicted with pain. This suggests that males are more prone than females to contextual modulation of neural resonance, and conversely more capable of modulating their prosocial inclinations (reward-related processing in response to the pain of another strongly suggests diminished prosocial inclinations towards them).

Neural resonance has also been observed for the imitation of emotional facial expressions – recruitment of affective structures used in experiencing self-emotion (like the anterior insula and amygdala) when imitating the emotional expressions of others (Carr et al., 2003). However, no study to date has examined gender differences in the neural correlates of imitation of affective states. Furthermore, there is evidence that neural resonance for pain and during imitation is correlated with trait empathy (Avenanti et al., 2009, Pfeifer et al., 2008). Thus, in examining gender differences it seems pertinent to control for the mediating effect of trait empathy.

No study to date has examined whether gender differences in neural activation and connectivity during neural resonance tasks persist after controlling for gender differences in trait empathy. Over the course of two prior studies (Christov-Moore & Iacoboni, Christov-Moore et al., under review) we collected a fairly large (n=78) data set of functional neuroimaging data on two neural resonance tasks (observation of a human hand receiving painful stimuli, and observation and imitation of emotional facial expressions) and also trait empathy as measured on the Interpersonal Reactivity Index(Davis, 1983). In this study, we examined gender differences in activation *and* task-dependent functional connectivity (Psychophysiological Interaction, Friston, 2011) after including subjects' trait empathy scores as covariates.

On the basis of the extant literature, we hypothesize that females should show higher trait empathy scores. Furthermore, we hypothesized that after controlling for trait empathy, males should show greater evidence of top-down cognitive control (top down), while females should show greater evidence of bottom-up processing of perceptual stimuli reflecting emotional and somatosensory states in others.

4.2. Methods

This study aggregates identically-collected neuroimaging and behavioral data from two previous experiments (Christov-Moore & Iacoboni, Christov-Moore et al., under review), for a total of 78 subjects. The first experiment (Table 1.1) examined correlations between brain activity during two neural resonance tasks and offers in Dictator Game (Christov-Moore & Iacoboni, under review). The second experiment examined the effect on Dictator Game offers of disruptive neuromodulation (Theta-Burst Stimulation) to right dorsolateral prefrontal cortex (Table 3.1, DLPFC), right dorsomedial prefrontal cortex (Table 3.1, DMPFC) and a control site in right MT/V5 (Table 3.1, MT/V5)(Christov-Moore et al., under review).

	Males	Females
	n	n
Exp.1	11	9
MT/V5	8	10
DLPFC	10	10
DMPFC	9	10

Table 4.1. Numbers of Males and Females by dataset.

4.2.1. Subjects

Subjects were 78 ethnically diverse adults aged 18-35 (39 female, 39 male). All subjects were recruited from the local community through fliers. Eligibility criteria included: right handed, no prior or concurrent diagnosis of any neurological (e.g., epilepsy, Tourette's syndrome), psychiatric (e.g., schizophrenia), or developmental (e.g., ADHD; dyslexia) disorders, no history of drug or alcohol abuse. All recruitment and experimental procedures were performed under approval of UCLA's institutional review board.

4.2.2. Functional MRI Tasks

Emotion Observation and Imitation (EOI): The stimuli were 48 full-color faces comprising an ethnically diverse set of 12 individuals (6 males and 6 females taken from the Nim Stim Face Stimulus Set (Tottenham et al., 2009) expressing 4 different emotions (angry, fearful, happy, or sad). None of the faces used in the DG appeared in this task. Task blocks consisted of 6 stimuli, presented for 4.5s each, with an interstimulus interval (ISI) of 400ms. Prior to each block, subjects were presented for 1.5s with a screen consisting of white letters on a black background, instructing subjects to "imitate the following facial expressions" (Imitation condition), or "look at the following faces" (Observation condition). The run consisted of 8 task blocks lasting 29s each, interleaved with an additional 9 rest blocks consisting of a white fixation cross on a black background, lasting 15s each. Imitation and Observation blocks were presented in alternating order for a total of four per condition.

Needle Test (NT): The stimuli were 27 full-color videos previously used by Bufalari et al. (2007), and used with permission by their research group, depicting a human hand being pierced by a hypodermic syringe (Pain condition) and touched by a wooden q-tip (Touch condition) in varying locations, as well as a static hand without stimulation (Hand condition) for use as a control. The run consisted of 12 trial blocks lasting 26s each, plus 8 alternating rest blocks that lasted either 5s or 10s. Each trial block consisted of 4 videos of a single condition (Pain, Touch, Hand), approximately 5s in duration each, with an interstimulus interval of 400ms. Subjects were simply instructed to watch the video clips. They were assured that the hand in the video clip was a human hand and not a model, but they were not instructed to empathize with the model nor were there any audiovisual cues to indicate pain in the model.

For each task, two different block orders were used, and controlled to ensure an approximately equal proportion of male and female subjects were exposed to each block order. The order of the fMRI and behavioral task blocks was counterbalanced across subjects, as was the order of the fMRI tasks within the fMRI task block. All tasks were coded within Presentation (created by Neurobehavioral Systems).

4.**2.3. Trait Empathy Assessment**

Interpersonal Reactivity Index (IRI): The IRI (Davis, 1983) is widely used (Avenanti et al., 2009, Pfeifer et al., 2008) and validated (Litvack-Miller et al., 1997) questionnaire designed to measure both ‘‘cognitive’’ and ‘‘emotional’’ components of empathy. It consists of 24 statements that the subject rates on a 5-point scale ranging from 0 (Does not describe me very well) to 5 (Describes me very well). The statements are calculated to test four theorized subdimensions of empathy:

Fantasizing Scale (FS): the tendency to take the perspective of fictional characters.

Empathic Concern (EC): sympathetic reactions to the distress of others.

Perspective Taking (PT): the tendency to take other’s perspective

Personal Distress (PD): aversive reactions to the distress of others

Subjects filled out the IRI at the end of each experimental session in a closed room, unobserved. Their scores were summed for each subdimension (measured by 6 items) to make 4 scores per subject. Cronbach's alpha, a measure of reliability, was assessed for the IRI using SPSS (FS=0.752, EC=0.792, PT=0.816, PD=0.839).

4.2.5. MR Image Acquisition

All neuroimaging data was acquired via a series of MRI scans conducted in a Siemens Trio 3T scanner housed in either the Staglin center for Cognitive Neuroscience (n=20) or the adjacent Ahmanson-Lovelace Brain Mapping Center (n=58) at UCLA, for a total of 78 imaging datasets (1 per subject). Functional images were collected over 36 axial slices covering the whole cerebral volume using an echo planar T2*-weighted gradient echo sequence (TR=2500 ms; TE=25 ms; flip angle=90 degrees; matrix size=64 x 64; FOV 20 cm; in-plane resolution=3 mm x 3 mm; slice thickness=3 mm/1 mm gap). A high-resolution EPI structural volume was also acquired coplanar with the functional images (TR=2500 ms, TE=33 ms, 128 x 128 matrix size, FOV=256 cm). Finally, a high-resolution T1-weighted volume was acquired in each subject (TR=2300 ms, TE=25 ms, TI=100 ms, flip angle=8°, matrix size=192x192, FOV=256 cm, 160 slices), with approximately 1 mm isometric voxels (1.3 x 1.3x 1.0 mm).

4.2.6. Functional MRI Analysis

Analyses were performed in FEAT (FMRI Expert Analysis Tool), part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). After motion correction using MCFLIRT, images were temporally high-pass filtered with a cutoff period of 70 and 90 seconds for NT and EOI, respectively (approximately equal to one rest-task-rest-task period), and smoothed using a 6 mm Gaussian FHWM algorithm in 3 dimensions. Each subjects' functional data was coregistered to standard space (MNI 152 template) via registration of an averaged functional image to the high resolution T1-weighted volume using a six degree-of-freedom linear registration and of the high-resolution T1-weighted volume to the MNI 152 template via nonlinear registration, implemented in FNIRT.

The BOLD response was modeled using an explanatory variable (EV) consisting of a boxcar function describing the onset and duration of each relevant experimental condition (task conditions, rest, instruction scree) convolved with a double gamma HRF to produce an expected BOLD response. The temporal derivative of each task EV was also included in the model. In addition, each subject's 6 motion parameters were included as additional EVs of no interest, to control for head motion. Functional data were then fitted to the model using FSL's implementation of the general linear model. A higher-level analysis was carried out to examine correlations between parameter estimates, IRI subscales and gender. Each IRI subscale (FS, EC, PT, PD) was included as a separate explanatory variable, as was gender. Resultant images were cluster corrected at a z-threshold of 2.3 and p-value cutoff of .05, using FLAME 1+2 with automatic outlier deweighting.

4.2.7. Psychophysiological Interaction

Whole-brain Psychophysiological interaction analysis (PPI) examines how functional connectivity changes between a seed ROI and the rest of the brain after controlling for common task-related activation (Friston, 2011).

For each analysis, we modeled activity using the following EV's: *Psychological*, consisting of a boxcar functions modeling the onset and duration of each task condition, convolved with a canonical double-gamma HRF; *physiological*, consisting of the time series in a single region-of-interest (ROI) (one per analysis); and a *psychophysiological interaction* (PPI) for each task condition, modeling the interaction between the expected BOLD response to each condition and the time series of interest. These separate PPI estimates were then contrasted at the group level. This allowed us to test for voxels that display significant *changes* in correlation with the time series of the ROI for any task contrast of interest, an approach known as generalized PPI or gPPI (Mclaren et al., 2012). To create the ROI's, time series were extracted from 8mm diameter seeds created in standard (MNI 152) space centered on regions showing high correlations with overall DG offers in a previous study examining correlations between brain activity and DG behavior (Christov-Moore & Iacoboni, under review). Center voxel coordinates (in voxels) and contrasts used are as follows. For the EOI gPPI analysis: Right amygdala (x=35, y=61, z=25), right dorsolateral prefrontal cortex (DLPFC)(x=25, y=75, z=55), all using the Imitate>Observe contrast. For the NT gPPI analysis: left superior parietal lobule (SPL)(x=55, y=39, z=69), left DLPFC (x=45, y=68, z=51) and left precentral gyrus (PCG) (x-63, y=67,z=49), all using the Pain>Hand contrast. First level analyses were carried out using FEAT. A higher-level analysis was carried out to examine correlations between PPI parameter estimates, each IRI subscale and gender. Resultant images were cluster corrected at a z-threshold of 2.3 and p-value cutoff of .05, using FLAME 1+2 with automatic outlier deweighting.

4.3. Results

4.3.1. IRI

We tested IRI subscale scores across all subjects for normality (Shapiro-Wilks test) and homogeneity of variance (Levene test). Empathic Concern (EC) and Perspective Taking (PT) scores deviated significantly from normality, while Personal Distress (PD) and Fantasizing (FS) subscales did not. No subscale showed significant heterogeneity of variance. We then performed two-tailed parametric (Unpaired t-tests, PD and FS subscales) and non-parametric (Mann-Whitney U tests, EC and PT subscales) analyses accordingly comparing trait empathy scores between genders.

	Male		Female	
	$\bar{x}$ (95%CI)	$\sigma_{\bar{x}}$	$\bar{x}$(95%CI)	$\sigma_{\bar{x}}$
FS	18.95(17.32,20.58)	4.96	21.55(19.98,23.12)	4.9
EC	22.26(20.85,23.67)	4.29	24.2(22.65,25.74)	4.82
PT	21.08(19.5,22.66)	4.8	20.42(18.82,22.02)	5.01
PD	11.45(9.69,13.21)	5.35	15.3(13.56,17.04)	5.45

Table 4.2. Means (with 95% confidence intervals) and standard deviations for each IRI subscale by gender.

Females scored significantly higher than males on the Empathic Concern subscale (Z=2.065, p=.039). There was no significant difference between genders on the Perspective-Taking subscale (Z=1.129, p=.259). Females scored significantly higher than males on both the Personal Distress (t=3.148, p=.002) and Fantasizing (t=2.330, p=.022) subscales.

4.3.2. Activation

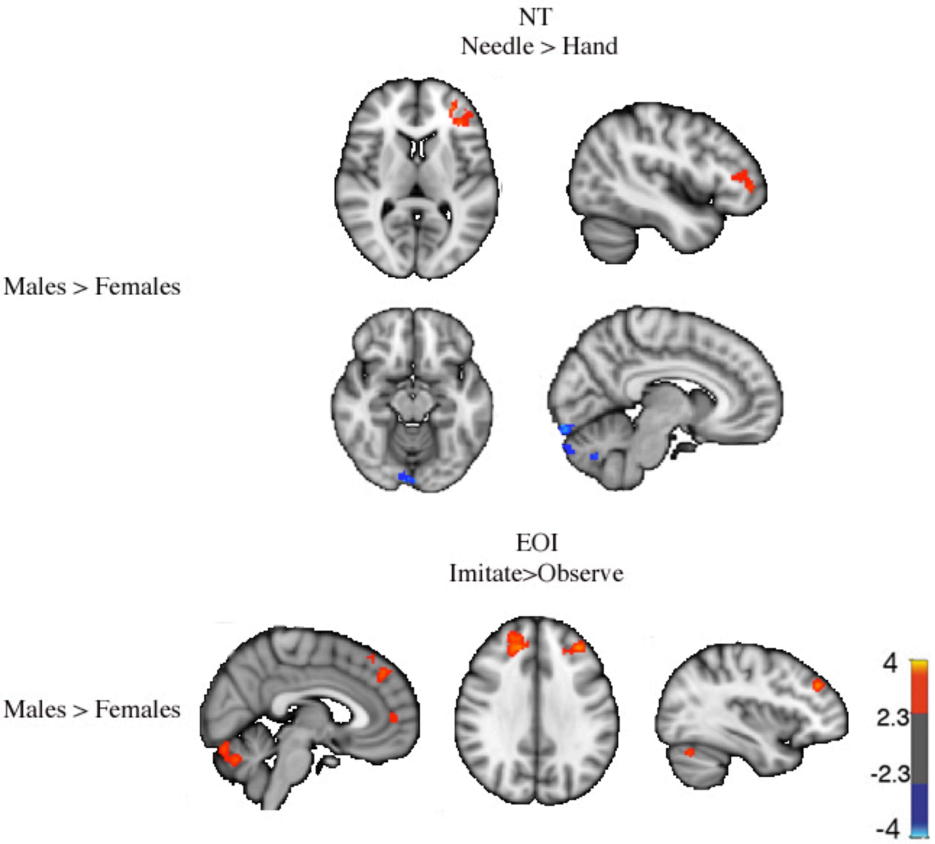


Figure 4.1. Gender differences in activation during neural resonance. NT=Needle Test, EOI=Emotion Observation and Imitation). Heat map values reflect z-scores. Negative z-scores (light blue-blue) correspond to the Females > Males contrast. All slices displayed in radiological orientation.

NT

For the contrast Needle>Hand, while female showed greater activation in primary visual cortex, males showed greater activation in left ventrolateral prefrontal cortex (Fig.4.1). This is consistent with greater primary processing of the observed painful stimuli in females, and greater cognitive control in males.

EOI

For the contrast Imitate Observe, males showed greater activation in dorsomedial and medial prefrontal cortex, left dorsolateral prefrontal cortex and right frontal pole, consistent with increased top-down control of affect in males.

Contrast		Area	Coordinates (mm)			Z
			x	y	z	
Imitate>Observe	Males>Females	R Superior Frontal Gyrus	10	44	52	3.48
		L Dorsolateral Prefrontal Cortex	-36	38	32	3.21
		L Medial Prefrontal Cortex	-10	50	-8	2.89
		Paracingulate Cortex	0	52	2	2.68
		R Cerebellum	24	-68	-32	3.31
Needle>Hand	Males>Females	L Frontal Pole	-30	46	10	3.81
		L Frontal Pole	-42	46	2	2.77
	Females>Males	Lingual gyrus	4	-88	-16	3.44
		Cerebellum	-4	-86	34	4.32

Table 4.3. Gender Differences in Activation. The contrast Imitate>Observe pertains to the EOI task, while Needle>Hand pertains the NT task. Coordinates (MNI_152 space) are given of local maxima (Z-score) in each cluster.

4.3.3. Psychophysiological Connectivity

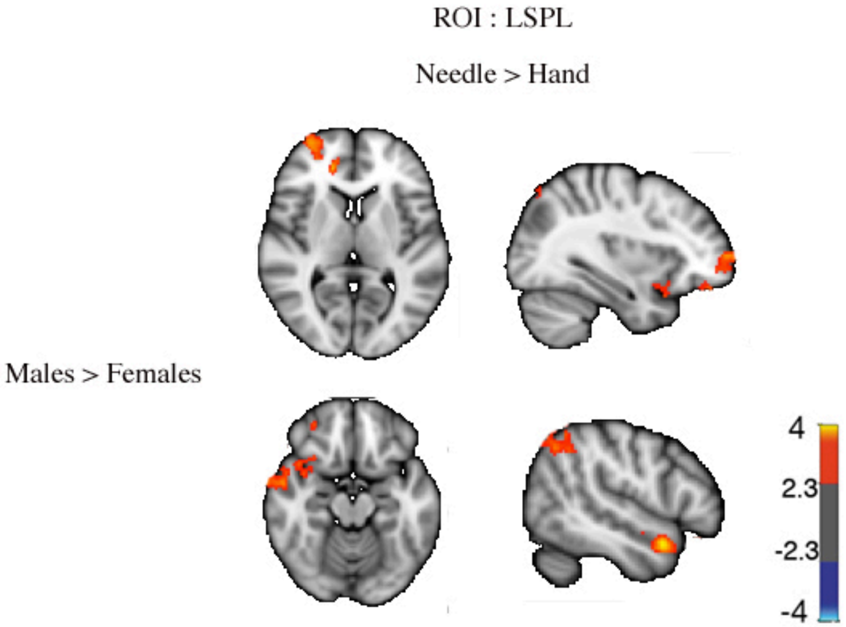


Figure 4.2. Gender differences in task-related increases in connectivity with the left superior parietal lobule (LSPL) during the Needle Test task. Heat map colors reflect z-scores. All slices displayed in radiological orientation.

NT

Left SPL showed greater connectivity in males with regions important for self-other processing and control (right temporoparietal junction), cognitive control and affective regulation (ventrolateral prefrontal cortex and medial prefrontal cortex), binding of high-level perceptual inputs with affective responses (right temporal pole), and the processing visceral and affective stimuli (anterior insula). This is consistent with greater control of vicarious sensorimotor processes in males.

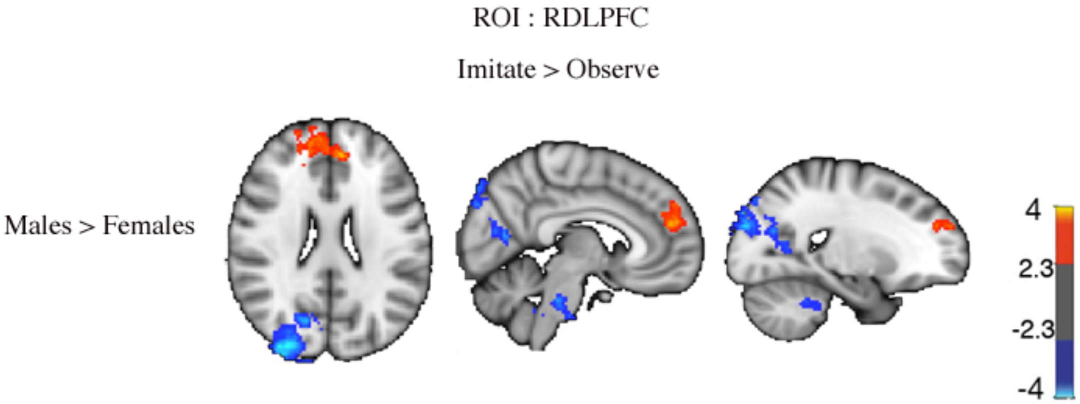
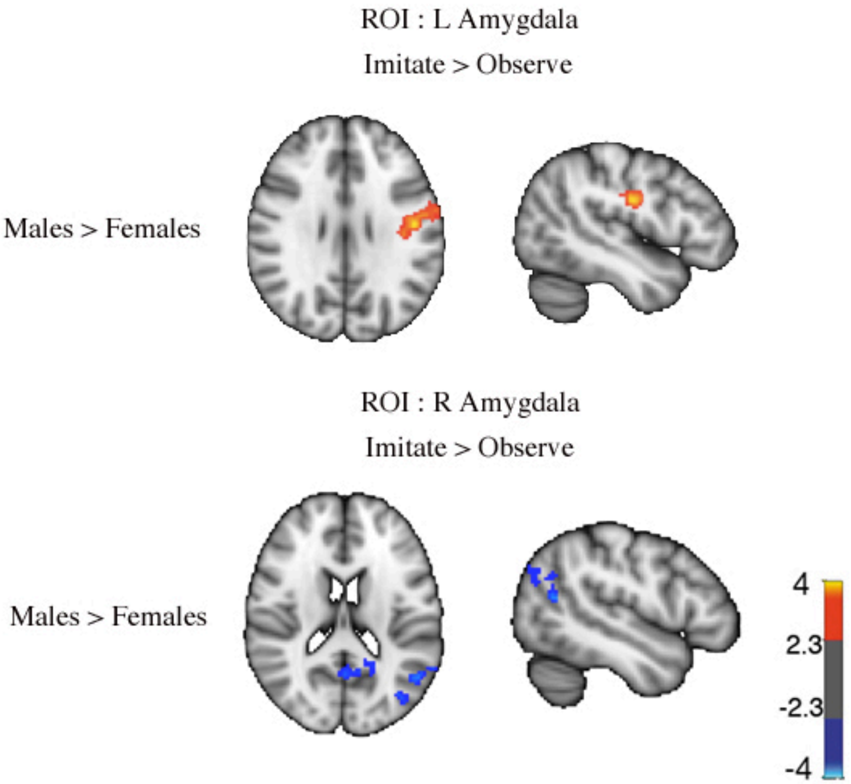


Figure 4.3. Gender differences in task-related increases in connectivity with right dorsolateral prefrontal cortex (RDLPFC) during the Emotion Observation and Imitation task. Heat map colors reflect z-scores. Negative z-scores (light blue-blue) correspond to the Females > Males contrast. All slices displayed in radiological orientation.

EOI

In females, RDLPFC showed increased connectivity with several areas of visual cortex and cerebellum. This may be due to increased regulation of incoming visual input in females (Fig. 4.3).

In males, RDLPFC showed increased connectivity with medial prefrontal cortex. This is consistent with greater recruitment of top-down control regions in males (Fig. 4.3).



ROI : L Amygdala

Imitate > Observe

ROI : R Amygdala

Imitate > Observe

Figure 4.4. Gender differences in task-related increases in connectivity with right dorsolateral prefrontal cortex (RDLPFC) during the Emotion Observation and Imitation task. Heat maps reflect z-scores. Negative z-scores represent Females > Males. All slices displayed in radiological orientation.

Relative to males, females showed increased connectivity between right amygdala and the precuneus, extrastriate visual cortex and lateral occipital cortex, suggesting a greater bottom up processing of affective components of the visual stimuli.

Relative to females, males showed increased connectivity between left amygdala and an area in the ventral portion of the central sulcus. The significance of this is unclear.

Contrast	ROI		Area	Coordinates (mm)			
				x	y	z	Z
Imitate>Observe	R Dorsolateral Prefrontal Cortex	Males>Females	L Paracingulate/Medial prefrontal cortex	-8	42	24	3.57
			R Paracingulate/MPFC	6	50	20	3.5
			R Frontal Pole	22	58	26	3.02
		Females> Males	R Lat. Occipital Cortex	28	-88	26	4.34
			R Cuneus/Precuneus	16	-72	30	3.6
	L Amygdala	Males>Females	L Central Sulcus	-48	-12	30	3.5
		Females>Males	R Lat.Occipital Cortex	28	-88	26	4.34
			R. Cuneus/Precuneus	16	-72	30	3.6
	R Amygdala	Females>Males	L. Lat.Occipital Cortex	-38	-74	18	2.89
			L. Parietooccipital region	-50	-60	16	3.4
			L. Precuneus	-16	-60	22	3.53
			Precuneus	0	-58	20	3.21
Needle>Hand	L Superior Parietal Lobe	Males>Females	R Frontal Pole	28	56	2	3.99
			R Temporal Pole	40	6	-16	3.93
			R Lat. Occipital Cortex	44	-72	44	3.4
			R Ventrolateral Prefrontal Cortex	32	48	-18	3.16
			R Anterior Cingulate Cortex	14	44	8	3.05
			R Insula/Temporal Pole	40	6	-16	2.9

Table 4.4. Gender differences in functional connectivity. The contrast Imitate>Observe pertains to the EOI task, while Needle>Hand pertains to the NT task. Coordinates (MNI_152 space) are given of local maxima (Z-score) in each cluster.

4.4. Discussion

As in previous studies, females reported higher trait empathy, specifically in subscales corresponding to aversive reactions to others' distress (Personal Distress), sympathetic reactions to the plight of others (Empathic Concern) and the tendency to take the perspective of fictional characters (Fantasizing)(Table 4.2). What remained to be seen, however, was whether differences in neural responses to others' emotions and pain would persist after controlling for these differences.

Indeed, a pattern of differences emerged after controlling for trait empathy, broadly consistent with the notion that males show greater evidence of top-down control during neural resonance tasks, while females showed evidence of increased bottom-up processing of pertinent incoming stimuli. For the EOI task, we examined the contrast Imitate>Observe, which allows us to examine vicarious emotional processing evoked by imitating the observed facial expressions (Carr et al., 2003) and top-down control of these vicarious responses. For this contrast, males showed increased recruitment of an array of prefrontal areas implicated in cognitive control of affective responses, including the dorsolateral prefrontal cortex, superior frontal gyrus and medial prefrontal cortex (Medford & Critchley, 2010, Miller & Cohen, 2001). In the NT task, we examined the contrast Needle>Hand, in order to isolate signal variance pertinent to the processing of painful stimuli delivered to another. For this contrast, males showed increased activation in the frontal pole, a prefrontal area also associated with top-down control (Miller & Cohen, 2001). In contrast, females showed increased activation in primary visual cortex and the cerebellum, which suggests increased processing of the incoming visual stimuli.

A similar pattern of results emerged when we examined task-dependent connectivity of areas implicated in neural resonance and its control. When we examined the connectivity of right DLPFC, an area that has been implicated in the top-down control of affect (Knoch et al., 2006, Miller & Cohen, 2001, Tassy et al., 2012), we found that males increased their connectivity with other prefrontal areas, including the paracingulate/MPFC and frontal pole. Females, on the other hand, showed increased connectivity with visual cortex and the cuneus/precuneus. This may suggest that females actually upregulate their perceptual processing of empathy eliciting stimuli. When we examined ROI's in the left and right amygdala, we found that in both cases, females showed increased connectivity with visual areas and the precuneus. These results suggest that females' increased sensitivity to emotional states in others may be due to increased perceptual processing subsequently driving affective processing, akin to a bottom-up pre-amplification process.

Curiously, when we examined the connectivity of the left PCG and left DLPFC, no significant gender differences emerged. However, the superior parietal lobe, which has been implicated in the processing of aversive stimuli around one's own body, showed increased connectivity with a broad array of occipital, temporal and prefrontal areas in males relative to females. These include the high level associative areas like the temporal pole, and areas involved in the top-down control of affect (frontal pole, VLPFC, ACC) as well as pain processing (ACC). This suggests that males, relative to females, may engage a broad network involved in high-level processing and control of the observed painful stimuli.

In summary, these data support the extant empirical consensus that females show greater sensitivity to the emotional and somatosensory states of others, while males seem more prone to regulate their vicarious responses to others' states.

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Conclusion

The findings presented here support the notion that reflexive self-other resonance (SR) and its inhibitory control are key components of the relationship between reflexive, experiential forms of empathy and prosocial behavior.

The results of our first study support our hypothesis (via correlation) that individual differences in SR and its control at the level of simple, stimulus-driven tasks is linked to individual differences in proposed prosocial correlates of SR: decisions reflecting the utility of DG players' welfare relative to subjects' own. Our thesis was supported by three aspects of these findings: a) the sign of the correlations with prosocial decisions (positive for SR, negative for top-down control); b) the relationship between *modulation* of prosocial decisions with neural correlates of top-down control; and c) the functional connectivity between areas associated with SR and top-down control, and the correlation between the degree of connectivity and prosocial decisions in key areas implicated in SR and top-down control (bilateral amygdala and right DLPFC/ACC, respectively).

Based on these findings, we performed two subsequent experiments causally testing our central thesis: In the first, we examined whether a short behavioral intervention (employing imitation and gaze-following) aimed at evoking sensorimotor and affective SR could increase generosity at the DG. This was motivated primarily by previous findings suggesting that being imitated by others increases prosocial inclinations. The behavioral intervention did not have the hypothesized effect on subjects' offers: there was no significant difference between subjects' offers in the DG. This may be due to a number of factors: a) the intervention may not have been of sufficient duration to achieve the same effect size provided by direct neuromodulation; b) deliberate engagement of SR with computer-based biological stimuli (as opposed to a real, present partner) may not have engaged SR processes sufficiently to achieve an effect. However, this also leaves open the possibility that deliberate engagement of imitation with another may not have a comparable effect to being the *subject* of imitation.

We also examined the effect of disruptive neuromodulation of two putative top-down control areas (right DLPFC and right DMPFC) on proposed behavioral correlates of SR, namely prosocial decisions. We hypothesized that top-down control is inhibitory and that there may be both contextual and tonic forms of control. Indeed, prior evidence suggests that tonic control of SR is necessary to control automatic imitation and conserve a coherent sense of self (Decety & Sommerville, 2008, Lhermitte, 1983), while contextual inhibition allows our SR and resultant prosocial inclinations to be modulated in a flexible manner (Christov-Moore & Iacoboni, under review, Hein et al., 2010,2011, Singer et al., 2006). Our data and past studies strongly suggest that high SES causes a context-based inhibition of offers relative to low SES (Engel, 2011, Liebe & Tutic, 2011). Within the theoretical framework of this project, this suggests that variance in high SES offers reflects differing contextual control of prosocial inclinations, while variance in low SES offers primarily reflects tonic control, as context-based inhibition is low. Hence, disruption of contextual control should cause increases primarily in the high SES condition, and disruption of tonic control should cause increases primarily in the low SES conditions.

TBS to right DLPFC caused increased offers to high SES players, while TBS to right DMPFC caused increased offers to low SES players. These findings support the notion that prosocial inclinations are driven by reflexive processes that must be inhibited, and additionally suggested that right DLPFC and right DMPFC may implement different forms of control (contextual and tonic, respectively).

A dominant paradox in this field of research is that on the face of it, the task conditions we associate empirically with the behavioral and neural correlates of SR are not the same as those we associate with prosocial decision-making. It may be intuitive to think that in face-to-face interactions, my real-time engagement in your internal states may drive my engagement in your welfare. However, correlations have been found between neural resonance for pain and charitable donations towards faceless entities (Ma et al., 2011)! Indeed, while most social transactions in our evolutionary history likely occur face-to-face, we are able to empathize with and feel impelled to aid absent, abstract or even fictional "others" (Clay & Iacoboni, 2011). In the experiments reported here, subjects are informed that their decisions affect real people, but those people are represented by photographic profiles, with neutral expressions. This is hardly a fertile source for dynamic, biological information of the kind typically thought to engage SR. Nonetheless, individual differences in SR do seem to correlate with individual differences in proposed prosocial correlates of SR, even in such abstracted scenarios. Why might this be?

We think that the answer lies in the emerging theory of embodied cognition, the notion that even our high-level concepts are grounded in sensorimotor and perceptual processes (Barsalou, 2008, Gallese & Lakoff, 2005). When we think of the concept "lemon", what comes to mind first is not a list of facts, but rather the sensorimotor properties we associate with lemons, their smell, their feel, their acidity, color, the texture of their skin and pulp, etc.… And this comes often without any specification of what kind, age, size, etc.… of lemon under consideration (though that information can refine and change the concept and associated imagery). Now, imagine the exponentially more complex array of information that accompanies the concept of another "person", another "agent". Not only do we incorporate the physical characteristics of a person, but also our own experience of being a person and interacting with a person, their weight, their bodily movements. Add on top of that their internal states, their expressions, their beliefs, intentions, emotions and their moral character. There is evidence that we use many of the same mechanisms to process the concepts of things that we use to process those things in real time. And we seemingly do not require complex stimuli to do so. Let's say I begin a story by saying "there was once a man named Joe". Already, before I've said anything about Joe, you begin to form a concept, perhaps even beginning to make a first impression of this character. And successive information, like Joe's history, his actions, his appearance, not all of which is necessarily biological, shapes this concept. What is to stop us from becoming invested in this person's welfare, even if they are fictional or absent?

Now, imagine you are told that a person, for whom you have a photograph and a name and yearly income, actually exists, and you will actually decide how much money they will receive (as in the Dictator Game employed here). They may not exist in real time, not being in front of you, but in order to make the decision at all you must form a concept of this person. What is to stop you from becoming invested in their welfare, from resonating with the concept you form of them, modulated in response to contextual information much the way it would in real-time? If we resonate with third persons in a similar fashion as we do during prosocial decision-making about others, that disposition should be observable in both types of contexts. Indeed, this is the central notion we tested here. Our findings are in line with this embodied view of prosocial decision-making.

The large, gender-balanced dataset provided by experiments 1 and 3 allowed us to perform a large-scale analysis of gender *differences* in activation and connectivity during the SR tasks. This analysis showed results suggesting differences along the bottom up/top down processing continuum in empathy. Male subjects showed evidence of increased top-down control relative to females, while females showed evidence of increased bottom-up processing of incoming stimuli. In light of our framework, which relates differences in bottom-up processing and top-down control to prosocial inclinations and their modulation, these data are consistent with findings from behavioral psychology and economics suggesting that females are, on the whole, more prosocial, while males show an increased tendency to modulate their prosocial behavior in response to context (reviewed in Christov-Moore et al., 2014).

Despite excellent work on the relationship between neural correlates of SR and prosocial inclinations in decision-making, few studies have proposed mechanisms supporting this relationship. This work adds to our understanding of SR and prosocial decision-making via an embodied model of SR in prosocial decision-making. This work represents a step forward in elaborating on current models of empathy for pain and prosocial inclinations, by including imitation and affect. It furthermore sheds light on just what is meant by control and regulation in the social cognitive context at the level of brain systems, by proposing and testing dissociations in control systems, that can guide high level functional connectivity- and dynamic causal modeling-based analyses of top-down control and its relation to bottom-up sensorimotor processes in empathy.

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