Predicting Empathy from Resting Brain Connectivity

Leonardo Christov-Moore[1,2,3,4,*], Nicco Reggente[5], Pamela K. Douglas[2,3,4], Jamie D. Feusner[2,3], Marco Iacoboni[1,2,3]

[1] Ahmanson-Lovelace Brain Mapping Center, UCLA, Los Angeles, CA, USA

[2]Brain Research Institute, UCLA, Los Angeles, CA, USA

[3] Department of Psychiatry and Biobehavioral Sciences, Jane and Terry Semel Institute for Neuroscience and Human Behavior, UCLA, Los Angeles, CA, USA

[4] Institute for Simulation and Training, Orlando, FL, USA

[5]Tiny Blue Dot Foundation, Santa Monica, CA, USA

* Correspondence: lmoore@ist.ucf.edu

Abstract

Recent studies suggest that individual differences in empathic concern may be mediated by continuous interactions between self-other resonance and cognitive control networks. To test this hypothesis, we used machine learning to examine whether *resting fMRI connectivity (*i.e. the degree of synchronous BOLD activity across multiple cortical areas in the absence of task demands) of resonance and control networks could predict trait empathy (n=58). Indeed, resonance and control networks' interconnectivity predicted empathic concern. Empathic concern was also predicted by connectivity within the somatomotor network. In light of numerous reported sex differences in empathy, we controlled for biological sex and also studied separately what aspect of these features could predict participants' sex. Sex was best predicted by the interconnectivity of the visual system with the resonance, somatomotor, and cingulo-opercular network, as well as the somatomotor-control network connectivity. These findings confirm that variation in empathic responses to others reflects characteristic network properties detectable regardless of task demands. Furthermore, network properties of the visual system may be a locus of sex differences previously unaccounted for in empathy research. Finally, these findings suggest that it may be possible to assess empathic predispositions in individuals without needing to perform conventional empathy assessments.

Keywords: empathy, empathic concern, sex, resting state fMRI, machine learning, self-other resonance, control, network, cognitive neuroscience, social neuroscience

Introduction

Empathy is a complex phenomenon that allows us to share in (or *resonate* with) the internal states of others, as well as *infer* their beliefs and intentions (Christov-Moore and Iacoboni, 2016; Decety and Jackson, 2006; Zaki and Ochsner, 2012). It has been suggested that empathy's *purpose*, in both humans and nonhuman animals, can be broadly divided into two categories: First, promoting pro-social, cooperative behavior via empathic concern for others and second, inferring and predicting the internal states, behavior and intentions of others (Davis, 1983; Preston and De Waal, 2002; Smith, 2006).

Evidence suggests that empathy relies in part on our brains' ability to process the observed experiences of others much in the same way we do our own (reviewed in Zaki and Ochsner, 2012), and possibly even those of inferred states of absent or fictional third persons (Christov-Moore et al., 2017b; Clay and Iacoboni, 2011; Davis, 1983;). We tend to mimic each other's behavior, often without our knowledge, and our tendency to do so is closely related to our degree of affiliation, similarity or liking for that person (Chartrand and Bargh, 1999; Lakin and Chartrand, 2003; Meltzoff, 1970; Sperduti et al., 2014). This ability has been theorized to reflect a predictive, generative model continuously minimizing the prediction error between stimuli and external causes at the neural network level (Kilner et al., 2009). We will refer to this reflexive and embodied ability to simulate others as "self-other resonance" (Christov-Moore and Iacoboni, 2016), or *resonance* for short. The most likely neural substrate for resonance appears to be "neural resonance" (Zaki and 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 (Iacoboni, 2009; Keysers and Fadiga, 2008). Not surprisingly, neural resonance has been repeatedly associated with self reported measures of trait empathy (Avenanti et al., 2009; Jabbi et al., 2011; Pfeifer et al., 2008) and is predictive of pro-social behavior (charitable donations: Ma et al., 2011; helping behavior: Hein et al., 2011; Morelli et al., 2014; non-strategic generosity in economic games: Christov-Moore and Iacoboni, 2016), suggesting that our resonance with others may underlie our concern for others.

However, we do not "resonate" equally with all others. Mimicry and neural resonance are implicitly modulated by others' closeness, status, group affiliation and perceived trustworthiness (Chartrand and Bargh, 1999; Cheng et al., 2010; Gu and Han, 2007; Guo et al., 2012; Hein and Singer, 2008; Lakin and Chartrand, 2003; Lamm et al., 2007; Liew et al., 2007; Loggia et al., 2008; Reynolds-Losin et al., 2013; 2014; Schmälzle et al., 2017; Singer et al., 2006; Sperduti et al., 2014). This is likely due to top-down control processes that integrate contextual information and conscious appraisal with affective, somatosensory and motor processes into behavior and decision-making. Control in this context seems to be subserved by prefrontal and temporal systems including the temporoparietal junction (TPJ) as well as dorsomedial and dorsolateral prefrontal cortex (DMPFC and DLPFC) (Banks et al., 2007; Brighina et al., 2010; Cho and Strafella, 2009; Decety and Lamm, 2007; Miller and Cohen, 2001; Spengler et al., 2010; Tassy et al., 2012; Volman et al., 2011; Winecoff et al., 2013). This control seems to be inhibitory: recent work from our group has found that disruptive neuromodulation of DMPFC and DLPFC caused a decrease in the inhibitory influence of context on prosocial behavior previously associated with resonance (Christov-Moore et al., 2017). Evidence suggests that this top-down control of resonance is also continuously engaged: lesions to prefrontal cortex are associated with compulsive imitative behavior, suggesting that, for

normal behavior to exist, some mechanisms to control resonance are always at play, unless damaged (Lhermitte, 1983; De Renzi et al., 1996). Interestingly, these control systems overlap considerably with those associated with conscious appraisal processes and inferential forms of empathy or mentalizing (Mahy et al., 2014).

Indeed, the neural bases of resonance and control processes may not be cleanly separable. Recent research suggests that somatomotor and affective processing contribute to our evaluations of others' internal states, beliefs, and intentions (Christov-Moore and Iacoboni, 2016; Christov-Moore et al., 2017b; Frith and Singer, 2008; Gallese, 2007; Obhi, 2012; Schulte-Ruther et al., 2007), as well as our decisions about others' welfare (Camerer, 2003; Hewig et al., 2011; Greene et al., 2001; Oullier and Basso, 2010; Van 't Wout et al., 2006). Conversely, top-down control processes are increasingly implicated in the contextual modulation of neural resonance (Cheng et al., 2010; Gu and Han, 2007; Guo et al., 2012; Hein and Singer, 2008; Lamm et al., 2007; Loggia et al., 2008; Reynolds-Losin et al., 2013; 2014; Singer et al., 2006). Many studies have reported concurrent activation of and connectivity between networks associated with resonance and top-down control, such as during passive observation of emotions or pain (Christov-Moore and Iacoboni, 2016), reciprocal imitation (Sperduti et al., 2014), tests of empathic accuracy (Zaki and Ochsner, 2009), and comprehension of others' emotions (Spunt and Lieberman, 2012). Thus, their neural instantiation may rely on systems that may operate like connected clusters in a network, with different modes and configurations of function (Fox and Friston, 2012).

On the basis of this evidence, we propose that individual differences in empathic function (particularly empathic prosocial concern for others) arise in large part from the continuous, characteristic interactions between resonance and control processes at the neural level (Christov-Moore and Iacoboni, 2016; Christov-Moore et al., 2017). This is

compatible with contemporary research showing that individual differences in active, task-relevant network configuration are reflected in intrinsic functional connectivity patterns (Tavor et al., 2016). We propose that in adults, these individual differences in empathic function should be apparent in resting connectivity (i.e. in the absence of empathy-evoking stimuli), much in the way a river carves out a characteristic pattern in bedrock over time. Thus, we approached this current work with specific and general hypotheses: Specifically, we hypothesized, in line with our prior studies on the neural bases of prosociality, that multivariate characteristics of the interaction between resonance and top-down control networks (Christov-Moore and Iacoboni, 2016) would predict subjects' empathic concern for others. In a more exploratory fashion, we hypothesized that resting connectivity patterns within and between other cortical networks are predictive of trait empathy.

Additionally, there is a great deal of evidence for sex differences in empathy across a broad array of measures and associated brain function (Cohn, 1991; Christov-Moore et al., 2014; Eisenberg and Lennon, 1983; Feingold, 1994; Hall, 1978; 1984; Hoffman, 1977; Konrath et al., 2011; Thompson and Voyer, 2014; although, for negative/null results see Lamm et al., 2011). For example, females display greater concern and sympathetic behavior towards others in real and hypothetical scenarios (Christov-Moore et al., 2014; Eisenberg and Lennon 1993; Friesdorf et al., 2015; Mesch et al. 2011). Females also show greater vicarious somatosensory responses to the sight or knowledge of another person in pain or distress (Christov-Moore et al., 2014; Christov-Moore and Iacoboni, 2018; Groen et al., 2013; Singer et al., 2006; Yang et al. 2009), and exhibit greater facial mimicry when viewing emotional facial expressions (Sonnby-Borgström 2002). For this reason, we controlled for sex within the primary analysis predicting trait empathy. We also simultaneously attempted to predict subject sex within

our cohort from resting connectivity features used in our primary analysis (as in Zhang et al., 2018), in order to elucidate the aspects of resting connectivity that were accounted for by sex (and hence partially regressed out of our primary analysis).

In summary, we sought to test three families of hypotheses: I) our primary, theory-driven hypothesis that Resonance and Control interconnectivity at rest predicts Empathic Concern, II) our exploratory, theory-consistent but broader hypothesis that trait empathy can be predicted from resting intra- and inter-connectivity of brain networks, and III) our secondary exploratory hypothesis that participants' sex can be predicted by the connectivity features employed in I and II.

Methods

Subjects

Participants were 58 ethnically diverse adults aged 18-35 (30 female, 28 males) recruited from the local community through fliers. All recruitment and experimental procedures were performed under approval of UCLA's institutional review board.

Eligibility criteria for subjects included: right handed, no prior or concurrent diagnosis of any neurological, psychiatric, or developmental disorders, and no history of drug or alcohol abuse. These were all assessed during preliminary screening interviews conducted by phone at the time of recruitment.

Trait Empathy Assessment

Participants filled out the *Interpersonal Reactivity Index (*IRI) at the end of each experimental session in a closed room, unobserved. The IRI (Davis, 1983) is a 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 participant 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

Participants' scores were summed for each sub-dimension (measured by 6 items) to make 4 scores per participant. 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).

Functional MRI Data Collection

All neuroimaging data was acquired via a series of MRI scans conducted in a Siemens Trio 3T scanner housed in the Ahmanson-Lovelace Brain Mapping Center at UCLA. Resting data were collected while participants passively observed a white fixation cross on a black screen. They were instructed only to "Look at the fixation cross and just let your mind wander". Resting-state functional images were acquired over 36 axial slices covering the whole cerebral volume using an echo planar T2*-weighted gradient echo sequence (6 minutes; 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 T1-weighted volume was also acquired in each participant (TR=2300 ms, TE=25 ms, TI=100 ms, flip angle=8°, matrix size=192x192, FOV=256 cm, 160 slices, voxel size 1.3 x 1.3x 1.0 mm).

Functional MRI Preprocessing

Functional MRI preprocessing was 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 100 seconds (equivalent to .01Hz) and smoothed using a 6 mm Gaussian FHWM algorithm in 3 dimensions. Our protocol stipulated that participants showing absolute or relative head motion exceeding 1mm were excluded from further analyses, though no

participants exceeded this threshold. 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 (as per Kelly et al., 2010) and removed using FSL's regfilt command. Each participants' 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.

Designation of Regions of Interest

For the machine learning analyses, 5mm spherical, network-defined regions of interest (ROIs) were derived from Power et al. (2011) for the Visual, Fronto Parietal, Somatosensory, Motor, and Default Mode Networks and set in MNI_152 standard space. An additional two theory-driven networks (Resonance and Control, see figure 1) were created based on selecting ROIs from Power et al. (2011) that overlapped with trait-empathy activation maps from Christov-Moore and Iacoboni (2016). An additional pair of 5mm ROI's centered on left (x=-22mm, y=-6mm, z=-14mm) and right (x=22mm, y=-6mm, z=-14mm) amygdala were added to the resonance network, due to their relevance for emotional forms of self-other resonance (e.g. Carr et al., 2003, Christov-Moore and Iacoboni, 2016, Pfeifer et al., 2006). For "between-network" analyses, ROIs constituting each previously defined network were concatenated into a single network,

allowing for pairwise connectivity across all composite ROIs.

Statistical Analysis

Machine Learning Analyses

Mean BOLD time-courses were extracted from the average activity across voxels within each ROI. Matrices of pairwise Pearson correlation coefficients were created for each participant by correlating each ROI's BOLD time-course with every other ROI within each network, creating a set of features (non redundant functional connectivity values) for each participant and network. To account for potential covariation, subject sex was iteratively regressed out of each feature and the residuals were subsequently used as the functional connectivity features. We implemented a leave-ten-subjects-out cross validation to assess the predictive power of network-specific feature sets. Specifically, we leveraged a least absolute shrinkage and selection operator (LASSO) regression model built on N-10 participants' feature sets for each IRI subscale.The model's intercept term and outcome beta values were then used as coefficients for each left-out subject's feature set—obtaining a predicted subscale measure for that individual. After N folds, whereby each set of 10 participants was left out exactly once, we correlated the array of predicted values ($\hat{Y}$) with the actual values (Y), yielding Pearson's R– a measure of our model's feature-dependent ability to capture the behavioral variance across participants.

Resultant r-values from the N-10 cross-validation were submitted to a significance test of the correlation coefficient ($t = \frac{r}{\sqrt{\frac{1-r^2}{N-2}}}$) . Matrices of p-values within each family were

conducted using a Benjamini-Hochberg approach(Benjamini and Hochberg, 1995) in R (p.adjust; method="BH"; R Core Team, 2013) and corrected p-values were considered significant at the 5% positive-tail (i.e. $p<0.05$), as negative R values, indicating poor prediction accuracy (i.e. predicting a negative subscale score when the actual value is positive), are less interpretable.

In our second analysis, in order to examine how resting connectivity predicts subject sex, we used the original functional connectivity feature sets (e.g. prior to regressing out sex) to train a linear nu-SVC support-vector-machine (SVM) classifier (c=1; Chih-Chung, 2011). In order to control for structural properties related to sex that might bias functional connectivity, we conducted a linear mixed model in SPSS (IBM Corp, 2017) which found that gray matter volume across all regions (assessed using Freesurfer) differed significantly ($p=.002$) but the structure*sex interaction was not ($p=.991$). As a result, we regressed out average gray matter volume from each feature and considered the residuals as the feature set prior to the analysis. We leveraged the SVM within a leave-10-subjects out cross-validation scheme (across 50 balanced iterations) to predict participant sex. Significance was determined by comparing the observed accuracy to an accuracy threshold denoting the top 5% of a binomial cumulative distribution function centered around chance (50%), which was determined to be 60% and above. To correct for multiple comparisons, the accuracy threshold was changed to reflect a p-value cutoff at .0038 (.05 / 13) of the binomial cumulative distribution to reflect the number of comparisons conducted within each family of tests (within network and across networks).

Correction for Multiple Comparisons

In order to correct for multiple comparisons, we applied three family-wise corrections, for each set of hypotheses: I) our main, theory-driven hypothesis that Resonance and

Control interconnectivity predict Empathic Concern), II) our exploratory, broad hypothesis that trait empathy can be predicted from resting intra- and inter-connectivity of canonical and theory-driven intrinsic networks, and III) our secondary hypothesis that participants' sex can be predicted by the features employed in I and II.

Results

For the machine learning analyses, we examined 5mm spherical regions of interest set in MNI_152 space for canonical Visual, Fronto Parietal, Somatosensory, Motor, and Default Mode Networks (derived from Power et al.,2011) as well as two theory-driven networks (Resonance and Control, see figure 1) created based on networks proposed in Christov-Moore and Iacoboni (2016).

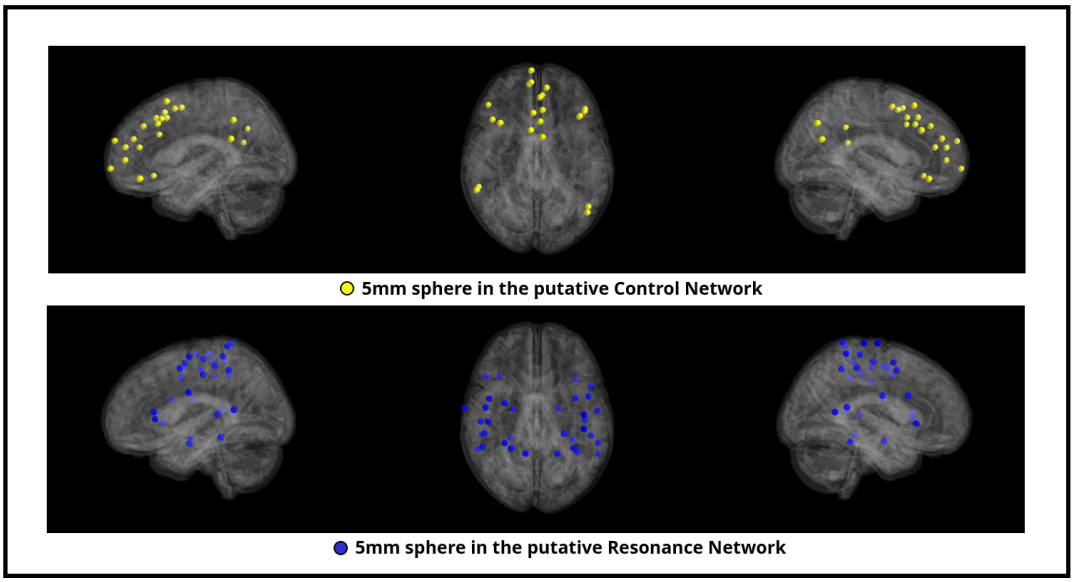

Figure 1. Regions of Interest for the Resonance and Control Networks. 5mm regions of interest superimposed on a standard brain from the Montreal Neurological institute (MNI; Evans et al.,1992) .

Within-Network Resting Connectivity Predicts Trait Empathy

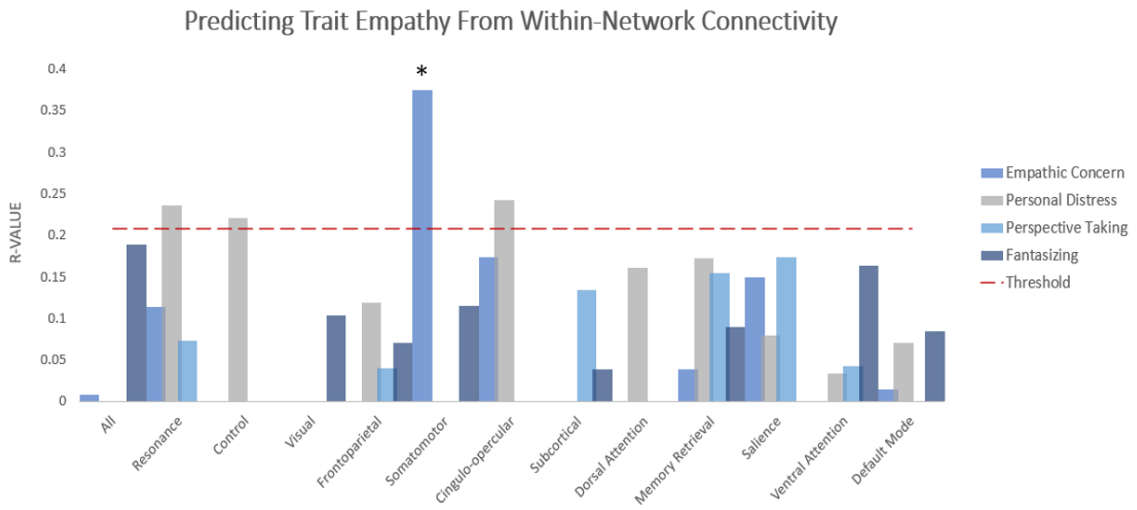

Figure 2. Within-Network Somatomotor Resting Connectivity Predicts Empathic Concern. Y-axis depicts average partial correlations between values predicted from model trained on n-10 cross-validation set and remaining 10 subjects over multiple iterations. Red dashed bar indicates threshold for $p<0.05$, uncorrected. * p-value <0.05 FDR corrected.

When examining the predictive power of connectivity weights *within* the selected intrinsic networks (Figure 2), empathic concern was significantly predicted by the somatomotor network ($R=0.374$, $p=0.022$, Benjamini-Hochberg false discovery rate – FDR – corrected). Personal distress was predicted above threshold by resonance ($R=0.236$, $p=0.037$, uncorrected), control ($R=0.22$, $p=0.048$, uncorrected) and cingulo-opercular networks ($R=0.242$, $p=0.033$, uncorrected), however these did not survive FDR correction for multiple comparisons.

Between-Network Resting Connectivity Predicts Trait Empathy

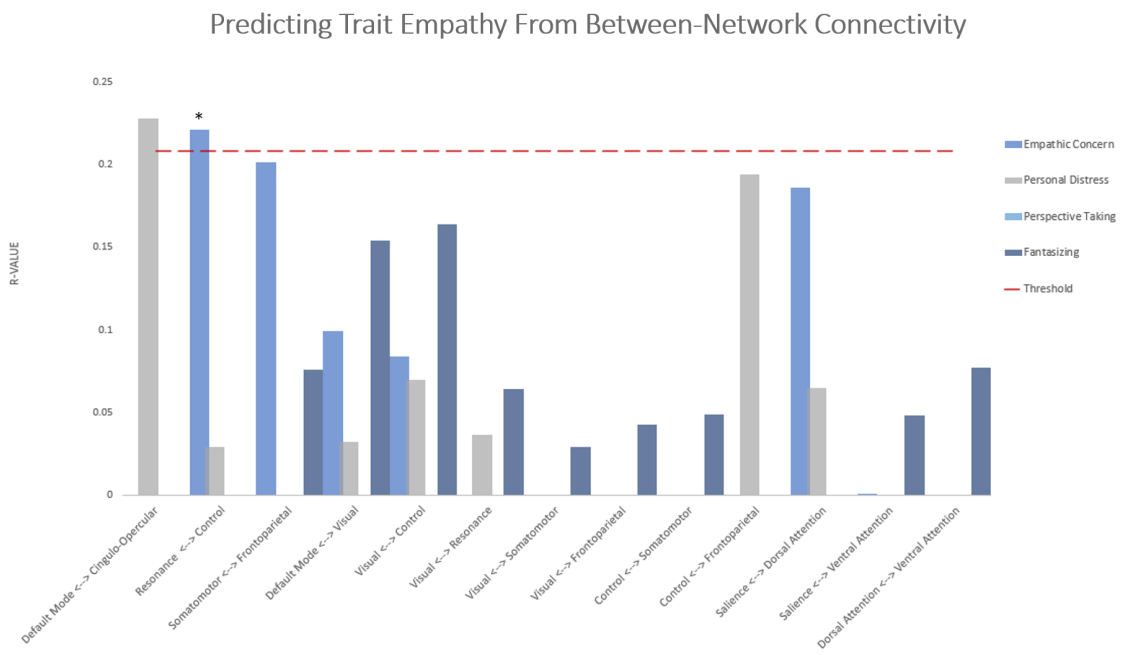

Figure 3. Between-Network Resting Connectivity of Resonance and Control Networks Predicts Empathic Concern. Y-axis depicts average partial correlations between values predicted from model trained on n-10 cross-validation set and remaining 10 subjects over multiple iterations. Red dashed bar indicates threshold for $p<0.05$, uncorrected. * p-value <0.05 FDR corrected.

As outlined in our primary hypothesis, empathic concern was predicted by the interaction between the a priori resonance and control networks ($R=0.221$, $p=0.0475$).

When testing our second family of hypotheses, we examined three types of between-network complexes: bottom-up resonance (visual/somatomotor, visual/frontoparietal, somatomotor/frontoparietal), a priori and classical resonance and control (control/frontoparietal, control/visual, control/somatomotor, cingulo-opercular/default mode), and links of no a priori interest as a comparison (dorsal/ventral attention, salience/dorsal attention), selected to test whether empathic function could be predicted

by differences in attentional networks (Figure 3). None of these survived FDR correction for multiple comparisons

Within-Network Resting Connectivity Predicts Subject Sex

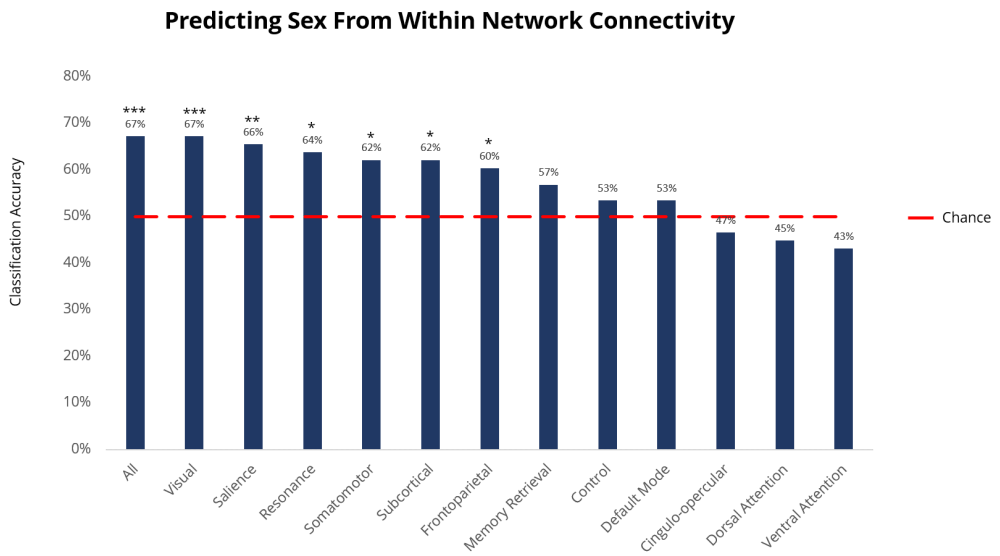

Figure 4. Within-Network Resting Connectivity Predicts Subject Sex. Y-axis depicts prediction accuracy of support vector machine trained on multiple n-10 cross validation sets. *=p<0.05; **=p<0.01, ***=p<.05 Bonferroni Corrected.

Participants' sex was most significantly predicted by resting connectivity within the visual network and by global network connectivity (p<0.05; Bonferroni corrected). It was also significantly predicted by within-network connectivity of the salience (p<0.01 uncorrected), resonance, somatomotor and subcortical networks (p<0.05 uncorrected, figure 4) however these did not survive Bonferroni correction for multiple comparisons.

Between-Network Resting Connectivity Predicts Subject Sex

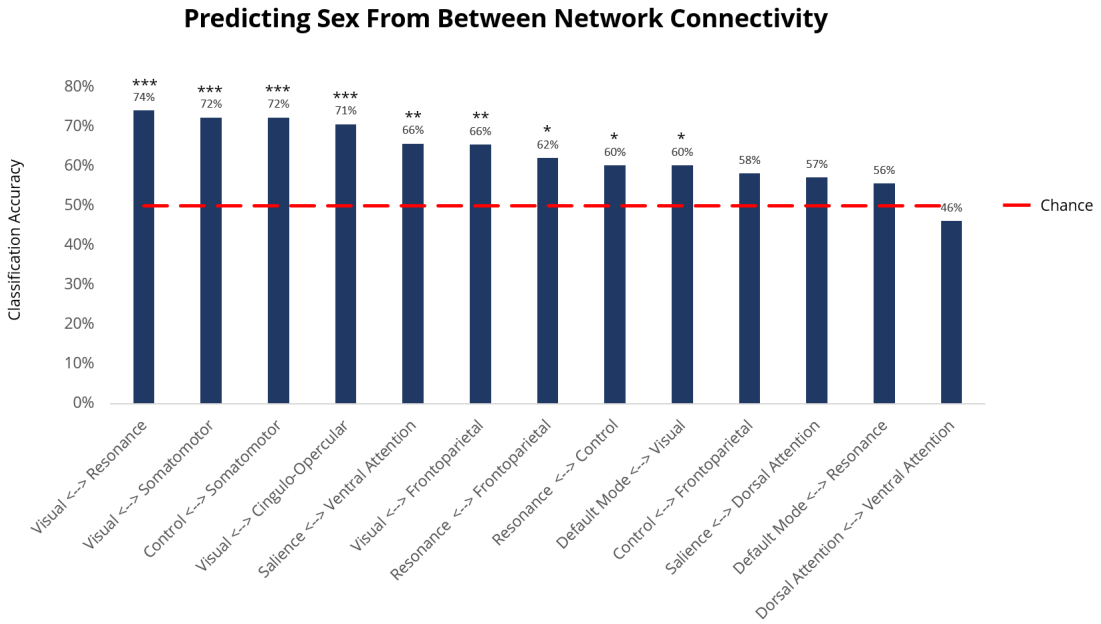

Figure 5. Between-Network Resting Connectivity Predicts Subject Sex. Y-axis depicts prediction accuracy of support vector machine trained on multiple n-10 cross validation sets. *=p<0.05; **=p<0.01, ***=p<.05 Bonferroni Corrected.

We also examined a set of between-network connections, calculated by treating both networks as one (Figure 5). Between-network connectivity of the visual system with the resonance, somatomotor, cingulo-opercular networks, as well as between the control and somatomotor networks (p<0.05, Bonferroni corrected), predicted participants' sex. Sex was also significantly predicted by the between-network connectivity of the visual and frontoparietal, salience and ventral attention networks (p<0.01 uncorrected) as well as between the resonance and control, resonance and frontoparietal, and the visual and default mode networks (p<0.05 uncorrected), however these did not survive Bonferroni correction for multiple comparisons.

Discussion

In this study, we tested three hypotheses:

I) We hypothesized that empathic concern for others would be predicted by the connectivity between our theory-based and empirically-determined *resonance* and *control* networks.

II) We also hypothesized that we could predict participants' *trait empathy* from the within- and between-network resting connectivity of both *resonance/control* and canonical intrinsic networks.

III) In an ancillary analysis, we examined the predictive power of these same features to determine participants' sex, in order to better understand what aspects of connectivity were being accounted for (and hence regressed out of the main analysis).

As hypothesized in (I), participants' levels of empathic concern were predicted by patterns of interconnectivity between the resonance and control networks, supporting the hypothesis (put forth in Christov-Moore and Iacoboni, 2016) that these systems a) continuously interact in a stable, characteristic fashion even in the absence of pertinent task demands, and b) this interaction is a likely neural substrate of empathic concern and pro-social inclinations.

As for (II), empathic concern was predicted by within-network connectivity of the somatomotor network. Vicarious somatosensory activation is associated with multiple forms of prosocial behavior (non-strategic generosity in economic games: Christov-Moore and Iacoboni, 2016; charitable donations: Ma et al., 2011; helping behavior: Hein et al., 2011; Morelli et al., 2014). Thus, this result further supports an embodied, sensorimotor foundation for our concern for others, in line also with our recent finding

that premotor activation during observation of pain in others was predictive of subjects' later tendency to avoid inflicting harm in hypothetical moral dilemmas (Christov-Moore et al., 2017).

There is wide consensus that empathy is fundamental to healthy interpersonal interactions and relationships as well as overall social functioning, yet there is little consensus on how to operationalize such a complex construct in brain and behavior (Hasler, 2012). Although numerous studies have related activation during active empathy tasks to trait empathy, these provide limited mechanistic insight into the problem, as they are invariably domain-specific and typically univariate. Indeed, it is common within cognitive neuroscience to theorize first about psychological processes and then investigate the neural correlates of such processes. Perhaps it would be useful to additionally investigate how psychological processes *emerge* from brain organization (Fox and Friston, 2012). By employing machine learning methods that make few a priori assumptions about the patterns of intrinsic connectivity underlying individual differences, we may achieve a more comprehensive multivariate view of the possible network-level patterns of neural interaction that give rise to individual differences in empathic function.

Having metrics that are stable, relatively context-invariant, and predictive of behavior is of great importance for the future of psychiatric research. Along these lines, finding markers of empathic functioning that are visible at rest may be of great potential prognostic and therapeutic utility, and could shed light on mechanisms underlying both healthy and abnormal empathic functioning. Indeed, a clinical avenue suggested by this study is the potential ability to predict empathic functioning in populations that might have difficulty performing empathy tasks or filling out questionnaires, either due to being less cooperative or less cognitively able, e.g., in populations such as those with schizophrenia, low functioning autism, intellectual disabilities, or traumatic brain injury.

Individuals in these groups might have, in principle, intact inherent capability for normal-range empathy that could be impeded by other limitations such as verbal or nonverbal communication (autism) or disorganized thought processes (schizophrenia); thus it would help us know what reasonable outcomes in terms of social and interpersonal functioning could be expected to result from therapies that help with training to rehabilitate or improve empathy with the aim of enhancing social competence and social cognition. Indeed, it may be pertinent to include measures of empathic function along with standardized, multisite resting state scan protocols (like the Human Connectome Project), paving the way for a massive data-driven approach to produce models that can predict empathic function from the resting brain in many different populations.

From the perspective of basic science, these findings (along with the previous work that prompted this study) support a dynamic, integrated view of empathic function, one that can partially account, at a neural systems level, for the paradoxical nature of self-other resonance: a process that is simultaneously reflexive and unconscious yet heavily influenced by contextual factors and the products of conscious inference and appraisal. More broadly, these results add an important piece to a growing body of work demonstrating links between resting and task-positive brain function, suggesting that the two may not be as cleanly separable as is often implicitly assumed. Perhaps a theory-driven method like that employed here, combined with large datasets, could be applied to predict many aspects of cognition and behavior from resting brain activity.

Regarding our ancillary analysis (III), we were interested in seeing what predictive aspects of resting connectivity were most related to sex, as this was controlled for in the principal analysis. We found that biological sex was best predicted by the connectivity of the visual system with resonance, somatomotor and cingulo-opercular networks as well as the between-network connectivity of the control and somatomotor networks. This

finding may shed light onto the underpinnings of previously observed sex differences in empathic functioning (Christov-Moore et al., 2014; Christov-Moore & Iacoboni, 2018). Specifically, it is interesting that the principal predictors seem to reflect bottom-up perceptual streams (although we cannot be certain of directionality), as well as top-down control of somatomotor networks, perhaps explaining why ours and other studies have found sex differences in vicarious responsivity to the pain and distress of others as well as the ability to modulate this vicarious response (e.g. Singer et al., 2006, reviewed in Christov-Moore et al., 2014). Furthermore, this highlights the utility of a multivariate approach to examining group differences that may be highly complex. Our most recent study on sex differences in empathy (Christov-Moore & Iacoboni, 2018), which looked at group differences in activation and ROI-based whole-brain connectivity while subjects observed a video clip of a human hand receiving a painful stimulus, found sex differences in vicarious somatomotor activation, yet was unable to find differences in connectivity that might elucidate the reason for this finding. The multivariate approach used here, able to simultaneously process patterns of connectivity (negative and positive) between many ROI's, may be more nuanced and effective in this endeavor. A recent study in a large cohort derived from the Human Connectome Project (n=820) found that resting functional connectivity of default mode, sensorimotor and fronto-parietal networks was predictive of participants' sex (Zhang et al., 2018). However, to the best of our knowledge, sex differences in the between- and within-network connectivity of the visual system have never been previously reported. This suggests a potential target system of interest for interpreting future findings in the area of sex differences in neural function and behavior as well as incorporating sex differences into parameters of neuromodulatory interventions.

This study has several important limitations that can propel future studies:

First, while we have focused primarily on networks underlying empathic concern, future work could test putative networks underlying other sub facets of empathy (such as mentalizing) and social cognition.

Second, while we have shown that network properties, i.e. the aggregate of connectivity weights, can be used meaningfully as features to predict trait empathy, the nature of this multivariate approach cannot provide simple conclusions about *what aspects of these networks* are predictive and in which direction. We cannot, for example, say: “increased interconnectivity predicts personal distress”.

Last, this study only examines “standard” connectivity, i.e. BOLD time-series correlation. Effective connectivity or mutual information analyses may shed light on more complex or nonlinear interactions that might underlie the more dynamic, cognitive aspects of empathy (such as mentalizing or perspective-taking). Additionally, graph theoretical analyses may allow for complementary mechanistic insights into the properties of whole networks, and parts of networks, that can predict trait empathy.

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