Spring 4-17-2017

Functional Neural Connectivity Associated with Moral Processing in Healthy and Antisocial Samples

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BY

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DISSERTATION

Submitted in Partial Fulfilment of the
Requirements for the Degree of
Doctor of Philosophy

Psychology

The University of New Mexico,
Albuquerque, New Mexico

May, 2017

ACKNOWLEDGMENTS

Data used in this thesis were provided by my advisor, Dr. Kent Kiehl, and were collected in part by the laboratory's research assistants. Additionally, I collaborated and consulted with Prashanth Nyalakanti, Vikram Rao, Vaughn Steele, and Keith Harenski on the analyses described within. I would also like to acknowledge Phillip Fansler, who supplemented my programming knowledge in a pinch.

Research described here was supported by the National Institute of Mental Health and National Institute on Drug Abuse under Award Numbers R01MH070539, R01DA026964-03, and R01DA026505-01A1 to Kent A. Kiehl. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

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Abstract

Although research finds that brain abnormalities during moral decisions underlie traits that lead to crime, understanding of these neural dynamics is limited. Here we use two samples to explore the role network engagement and components during moral processing. We used independent component analysis and functional network connectivity analysis to examine hemodynamic response during an fMRI task of moral processing. Eighty-four community and 539 incarcerated adult men and women participated; MANCOVA and machine learning algorithms were used to identify individual and group differences in both samples. We found patterns of neural engagement and connectivity consistent with proposed models of moral cognition and that age, IQ, and sex moderated neural engagement and connectivity during moral cognition in regions including the temporoparietal junction and prefrontal cortex. We also found that incarcerated individuals differed from community controls on functional network connectivity and dynamism during moral processing and that psychopathic traits

were related to network engagement in regions including the temporoparietal junction, cingulate, and temporal poles. These results extend the literature on moral processing to functional network dynamics, as well as highlighting the need to consider individual differences in understanding the neural underpinnings of moral processing. Finally, this study provides evidence that neural connectivity during moral processing may be able to predict criminality, although follow-up research on prospective prediction is necessary.

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Chapter 1

Introduction

Moral Processing in the Brain

The ability to quickly and appropriately make moral decisions is vital for participation in society. Violation of moral rules can result in crime, physical and emotional abuse, unethical professional behavior, and other undesirable outcomes. Estimates of the cost of crime in the United States suggest that almost $200 billion dollars is spent by the government on the justice system and related expenditures (McCollister et al., 2010). The cost of child abuse alone is $124 billion dollars (Fang et al., 2012). Costs associated with white collar crimes may reach up to $1.7 trillion (Helmkamp et al., 1997). In order to understand how to combat moral violations and reduce the overall cost to society, we must understand how moral processing works—specifically, how it goes wrong.

There are several accounts of the biological systems underlying moral processing. The Event-Feature-Emotion complex (EFEC) framework has three main components: structured event knowledge, social perceptual and functional features, and central motive and emotional states. The interactions between these components, in the form of binding mechanisms, give rise to EFECs (Moll et al., 2005). The structured event knowledge component specifies that semi-automatized event sequences are stored in the posterior and medial (m) prefrontal cortex (PFC), and novel or less familiar events are processed by the dorsolateral (dl)PFC. The anterior PFC is involved in making long-term plans and the ventromedial (vm)PFC is implicated in the representation of social and emotional event knowledge. The social perceptual and functional component refers to context-

independent representation of social features, like facial expressions, gestures, and semantic features. The temporoparietal junction (TPJ) stores perceptual representations of facial expression and gestures, and the anterior temporal cortex (ATC) processes semantic representation. These regions interact with the amygdala, a central motive region to integrate these features into social behavior (Moll et al., 2003). Finally, the central motive state component of EFEC covers the emotional aspect of moral processing (Moll et al., 2005). Paralimbic and brainstem regions underlie this process; these are the structures that monitor the key motivational process of homeostasis (i.e., the hypothalamus) and emotionality (e.g., the amygdala). Projections from these paralimbic regions to the PFC, as well as reciprocal inputs, allow for the interactions between central motive states and structured event knowledge.

Another framework, the conflict control account of moral cognition, developed out of complex utilitarian judgment tasks (i.e., the trolley dilemma, as used in Greene et al., 2001). Behavioral studies of these tasks find that allowing someone to die to save the lives of others is permissible while killing someone to save the lives of others is not, despite the identical net gain. The conflict control model explains this difference in terms of moral processing. It merges a rationalist account of moral reasoning (Kohlberg, 1969) and a social-intuitionism account focusing on emotional response (Haidt, 2001), stating that the balance between these two processes reflects the actual dynamics of moral processing. Particularly, it predicts involvement of cognitive control frontal regions, such as the anterior cingulate cortex (ACC) and dlPFC, in rationalist processes needed to override emotional reactions to moral stimuli, located in areas including the mPFC, posterior cingulate (PCC), and TPJ.

The literature on healthy moral processing may support either of the models, as it consistently implicates the mPFC, frontal pole, precuneus, TPJ, PCC, temporal pole, middle temporal gyrus, and left amygdala (see Bzdok et al., 2012 for a meta-analytic review). However, these studies rely primarily on general linear models that examine engagement of specific neural voxels and regions based on model assumptions, rather than agnostic functional connectivity that might explain the interaction between these regions. Moreover, more specific understanding of the network dynamics involved in moral processing may allow us to lend support to one of the neurobiological accounts discussed above others.

Limited work has examined connectivity using Psychophysiological Interactions (PPI). Caceda and colleagues found distinct patterns of functional connectivity in moral processing related to care ethics and justice ethics (2011). Specifically, the authors found that ACC, TPJ, frontal pole, and PCC connectivity were related to moral judgment. Additionally, there is an interaction between the role of intentionality in moral judgment and connectivity between the vmPFC, amygdala, and TPJ (Decety et al., 2012). However, PPI is based on *a priori* seed regions leaving much of the brain unexplored; findings from these studies are better framed in terms of contributions to activations detected in seed regions (Friston et al., 1997). An agnostic functional connectivity analysis is needed to understand the networks underlying moral cognition.

Psychopathy and Criminality

Psychopathy is a clinical condition characterized by deficient emotional reactivity in conjunction with antisocial traits (Hare, 2003). Psychopathic individuals regularly commit moral violations and are responsible for a disproportionate amount of violent and

repetitive crime; psychopaths also constitute approximately 25% of incarcerated populations (Alterman et al., 1993; Hare, 2003). These callous and antisocial behaviors contribute to a high financial burden, estimated to be 30-50% of the $3.2 trillion dollar annual societal cost of crime in the United States (Anderson, 2012; Kiehl, 2014; Kiehl & Hoffman, 2011).

The picture of moral processing in psychopathy is incomplete. Initial observations have confirmed that immoral behaviors are more common among psychopaths than non-psychopaths (Cleckley, 1976). Although psychopaths commit more moral wrongs than others, psychopaths do not differ from non-psychopaths on tasks where they classify stimuli as right or wrong (Aharoni et al., 2012; Cima et al., 2010; Glenn et al., 2009; Harenski et al., 2010; O'Kane et al., 1996; Simon et al., 1951), although conflicting results have been documented (Blair, 1995; Koenigs et al., 2012; Young et al., 2012). However, psychopaths do show different patterns of brain engagement compared to non-psychopaths when processing moral stimuli – even when no behavioral differences exist (Glenn et al., 2009; Harenski et al., 2014; Harenski et al., 2010). Psychopathy-related effects include reduced activation in the amygdala, PCC, and TPJ during processing of moral stimuli. These brain regions play important roles in moral judgment. Specifically, Blair (2007) suggests that the amygdala and vmPFC work through stimulus-reinforcement learning to associate distress with moral transgressions to reduce antisocial behaviors.

Previous work additionally implicates the ACC and dlPFC as having abnormal engagement during moral processing related to psychopathy (Fede, Schaich Borg, et al., 2016). Additionally, that study finds that incarcerated individuals do not differ from

healthy controls in hemodynamic response during performance of a moral decision making task.

Independent component analysis has been applied to psychopathy to a limited extent. Juarez and colleagues found that during an auditory oddball task, psychopathy was correlated with the default mode network, a frontoparietal component, and a visual/posterior cingulate component (2013) . During resting-state, youth with psychopathic traits demonstrate abnormal connectivity in the default mode network and frontoparietal cognitive control network (Cohn et al., 2015). Additionally, seed-based functional connectivity analyses of youth with psychopathic traits have also found less connectivity between the amygdala and the orbital frontal cortex (OFC), temporal cortex, and inferior parietal cortex (Marsh et al., 2011).

Present Study Goals and Hypotheses

The task used in the present study has been previously examined in three different populations using a traditional general linear model (GLM) approach: typically functioning community individuals (Schaich Borg et al., 2011), incarcerated individuals with psychopathy (Fede, Schaich Borg, et al., 2016), and incarcerated stimulant users (Fede, Harenski, et al., 2016). Schaich Borg and colleagues found that moral processing engaged the TPJ/supramarginal gyrus, vmPFC, insula, basal ganglia, temporal pole, brainstem, ACC, amygdala/parahippocampal gyrus, and PCC. Additionally, the author of this dissertation found that in general, incarcerated individuals have a similar pattern of neural engagement during moral processing; however, psychopathic traits were inversely associated with engagement of the ACC, TPJ, and dlPFC. Moreover, use of cocaine and methamphetamine was associated with less amygdala and ACC activity but more vmPFC

activity during moral processing. However, none of these studies have examined differences in whole brain network dynamics.

In the present study, we aimed (1) to better understand the interactions between neural networks during moral processing by (1a) using independent component analysis (ICA) to illustrate functionally connected networks during a moral processing task; (1b) using functional network connectivity (FNC) analyses to explore the connections between these networks; and (1c) exploring whether these moral networks are consistent across individual differences. We also aimed (2) to understand whether differences in neural moral processing were related to traits associated with behavioral moral violations by (2a) using analysis of covariance to investigate differences between incarcerated and community individuals and (2b) differences related to psychopathic traits. We also explored this by (2c) using machine learning to select neural connectivity features and develop models that can predict differences between incarcerated and healthy individuals, and between high and low psychopathy scorers.

Based on the theoretical and empirical accounts of moral cognition, we hypothesized that (1a) moral processing would engage mPFC, dlPFC, frontal pole, insula, hippocampal, amygdala, ACC, PCC, ATC, and TPJ components. Across regions, we anticipated that (1b) limbic components would be highly correlated with temporal and frontal components, since paralimbic regions (such as the amygdala) have reciprocal connections to each of these regions. This would also be consistent with the Moll et al., 2005 study. (1c) We did not anticipate that sex, IQ, or age would have a significant effect on these functional components or functional network connections.

Given the lack of previous evidence finding neural differences between incarcerated individuals in general and community controls, we hypothesized that (2a) the incarcerated sample would not differ significantly from the community sample in functional components or connectivity during moral processing, but that (2b) psychopathy would be related to abnormal paralimbic engagement and connectivity. Given these expected brain differences, we anticipate that (2c) machine learning can be used to develop a brain-based classification model for high/low psychopathy, but not for the incarcerated/community distinction.

Chapter 2

Methodology

Participants

Two samples were collected for this project: a community sample (n = 84) and a sample of incarcerated individuals (referred to as the "forensic sample"; n = 539). All participants were provided written, informed consent and were compensated for their participation. All individuals who participated were required to meet the following criteria: age between 18 and 55, IQ greater than 80, no history of traumatic brain injury with loss of consciousness greater than one hour, and no history of psychosis in self or first degree relative. Additionally, the community sample could not have a history of major substance use or criminal behavior. The forensic sample was recruited from minimum and medium security prisons in New Mexico and Wisconsin; the community sample was recruited in Albuquerque, New Mexico. See Tables 1 and 2 for a description of the samples.

Table 1 .
Descriptive Statistics for Community and Forensic Samples

Variable	**Community (n = 84)**		**Forensic (n = 539)**	
	mean	*sd*	*mean*	*sd*
IQ***	117.18	12.56	97.08	11.55
Age***	27.17	10.29	34.49	8.58
Years of Education***	14.72	1.55	11.75	1.97
PCL-R			20.22	6.85
Substance Use Disorders (number of)			1.75	1.48
Sex (percent)**				
Male		39.3		57.3
Female		60.7		42.7
Race (percent)				
American Indian/ Alaskan Native		7.8		9.8
Asian		5.2		0.4
Black/African American		3.9		12.8
Native Hawaiian/ Pacific Islander		0		0.2
White		68.8		48.7
Other/ Decline to State		14.3		26.9
Ethnicity (percent)**				
Non-Hispanic		75.3		58.3
Hispanic		24.7		41.7
Substance Use Disorders (percent)				
Alcohol				44.5
Sedative/Hypnotic/Anxiolytic				5.3
Cannabis				25.2
Stimulants				36.8
Opiods				21.7
Cocaine				39.3
Hallucinogens				4.1

Notes : Percent refers to the percent of each sample falling into the cateogry indicated. Substance Use Disorder and PCL-R information were only collected for the forensic sample.Astericks next to variable name indicate significant group differences: **p* <.05, ***p* <.01, ****p* <.001

Data Collection Procedure

Assessments

Table 2 .
Associations between individual variables

Community Sample (n = 84)	**IQ**	**Age**	**Years of Education**
IQ	1	-0.086	0.024
Age	-0.086	1	.421**
Years of Education	0.024	.421**	1
Sex Differences			
Males	120.52 (14.11)	26.21 (8.87)	14.69 (1.71)
Females	115.02 (11.05)	27.78 (11.15)	14.75 (1.45)

Forensic Sample (n = 539)	**IQ***	**Age**	**Years of Education**	**PCL-R*** **	**Number of Substance Use Disorders*** **
IQ	1	0.047	.368**	-0.016	-.107*
Age	0.047	1	.167**	-.139**	-.158**
Years of Education	.368**	.167**	1	-0.084	-.103*
PCL-R	-0.016	-.139**	-0.084	1	.200**
Number of Substance Use Disorders	-.107*	-.158**	-.103*	.200**	1
Sex Differences					
Males	98.10 (12.15)	34.82 (9.25)	11.83 (1.82)	21.41 (7.15)	1.48 (1.54)
Females	95.89 (10.70)	34.04 (7.60)	11.67 (2.12)	18.38 (5.98)	2.07 (1.35)

Notes : Continuous variables reported in correlation table form. Sex differences investigated with independent sample t-tests. Values are mean(standard deviation). Significance indicated by astericks as follows: **p* <.05, ***p* <.01, ****p* <.001.

IQ was estimated using the Vocabulary and Matrix Reasoning subtests of the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1997; Ryan et al., 1999) and reading level was assessed with the Wide Range Achievement Test Word Reading subtest (WRAT-3; Wilkinson, 1993). Psychiatric and substance use histories were assessed with the Structured Clinical Interview for DSM-IV disorders (SCID; First et al., 2002).

Psychopathy was assessed using the Hare Psychopathy Checklist- Revised (Hare, 2003). The PCL-R is the most widely used assessment of psychopathy in forensic populations. It is made up of 20 items each scored 0 *doesn't apply*, 1 *applies somewhat*, or 2 *definitely applies*. PCL-R Total score is made up of two factors: Factor 1 is composed of interpersonal and affective traits (e.g., lack of remorse, grandiosity) whereas Factor 2 is made up of lifestyle and antisocial traits (e.g., poor behavioral controls, impulsivity). Trained research assistants, including the author of this dissertation, conducted these semi-structured interviews covering topics including school and employment history, work history, criminal activity, and interpersonal behaviors in addition to reviewing institutional records. Interviews were recorded for reliability

assessment and a randomly selected portion of the sample (approximately 10%) was double rated to insure inter-rater reliability.

Task

Participants were shown words and phrases describing moral acts or concepts (task adapted from Schaich Borg et al., 2011). Fifty stimuli were classified as *noncontroversial* negative (e.g., murder, slavery), fifty were classified as *noncontroversial* positive (e.g., charity, kindness), and fifty were classified as *controversial* (e.g., animal testing, gun control). *Controversial* stimuli required more processing than *noncontroversial* stimuli, confirmed in our study by an increased response time to the stimuli (Fede, Harenski, et al., 2016; Fede, Schaich Borg, et al., 2016). Participants were presented with a stimulus and asked to press one button to indicate that they thought the word or phrase was morally wrong and a different button to indicate that they thought the stimuli was morally not wrong. After the button was pressed, a black jittered screen was shown for 1 to 6 seconds. Three runs of the task were administered, each including 50 stimuli evenly divided among stimulus types.

Participants were scanned during the task using the Mind Research Network's 1.5T Siemens Avanto mobile MRI scanner stationed at the correctional facilities and at the University of New Mexico. The scans were acquired using an EPI gradient-echo pulse sequence (parameters: TR 2000, TE 39 ms, flip angle 75°, FOV 24 x 24 cm, 64 x 64 matrix, 4 mm slice thickness, 27 slices). The task was presented using E-Prime software (Psychological Software Tools, 2012).

Data Analysis Procedure

Image Preprocessing

Imaging data were preprocessed using Statistical Parametric Mapping software (SPM5; Wellcome Department of Cognitive Neurology, 2005). A multistage procedure was used to address the issue of head motion. First, the ArtRepair Toolbox in SPM (Mazaika et al., 2009) was used to identify and remove severe artifacts, defined as time points with greater than 4% signal change from the global mean signal. Next, head motion was estimated using INRIAlign, an algorithm that is insensitive to eye movements and blood oxygenation level dependent (BOLD) activity (Freire et al., 2002). The ArtRepair Toolbox removes severe motion artifacts but does not account for smaller, more distributed effects of motion. INRIAlign software creates parameters that account for remaining motion and include them as a variable in the modeling of hemodynamic response. Images were then spatially normalized to the Montreal Neurological Institute (MNI) template and smoothed with an 8 mm full-width at half-maximum Gaussian smoothing kernel. A high-pass filter removed low-frequency drift at 1/128 HZ.

Independent Component Analysis

ICA was applied to extract network components (ICs). ICA is an agnostic technique for extracting independent sources from fMRI data. Group ICA in GIFT (Calhoun, 2004) was conducted to maximize the independence of 75 components using a PCA based separation algorithm at a single-subject level. This higher model order separation was based on previous studies (e.g., Allen et al., 2011) and in order to detect more specific sub-network effects (Smith et al., 2009). Resulting ICs were then labeled spatially or identified as artefactual by experts based on *the Brain Atlas* (Woolsey et al.,

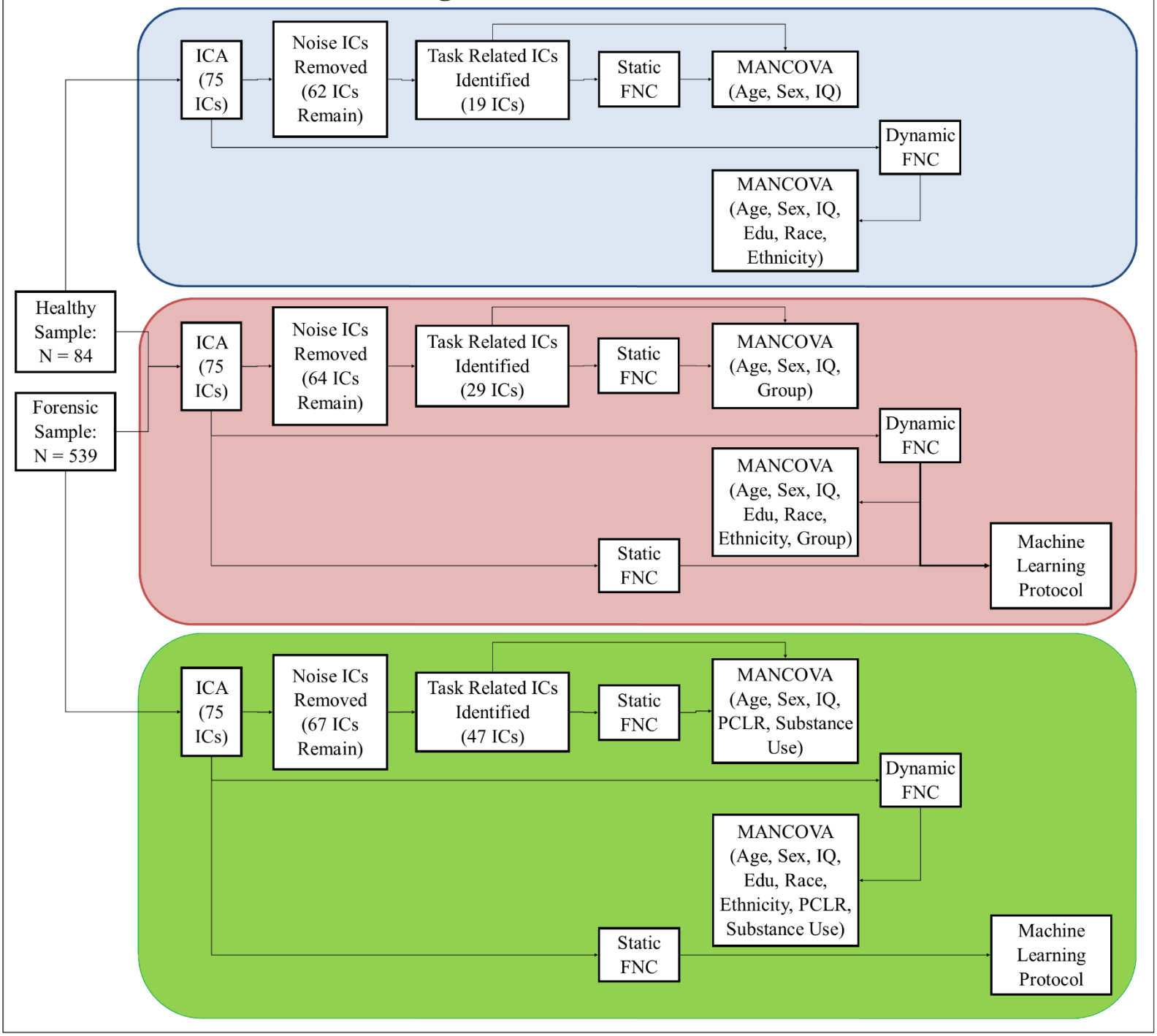
2013) and the Wake Forest University Pick Atlas in SPM (Maldjian et al., 2004; Maldjian et al., 2003). Prior to further analysis, ICs related to artifact or noise were identified and removed from further analyses.

The SPM Statistics utility within GIFT was then used to identify task-event related components by regressing stimuli onsets and comparing stimuli types. Specifically, components were sorted temporally based on the SPM design matrix (stimuli onsets). These parameters were then used to compare *controversial* moral stimuli related component activity (considered moral processing) to *noncontroversial* moral stimuli related activity in a one-way ANOVA design. See Figure 1 for a flowchart of the procedures for the ICA and functional network connectivity analysis.

Functional Network Connectivity

Functional network connectivity (FNC) was examined using the FNC toolbox for GIFT (Jafri et al., 2008; Swanson & Calhoun, 2009). FNC analyses examine the correlations between the time courses of each component extracted in the ICA analysis in order to create a matrix quantifying network connectivity. Two types of FNC analyses were conducted. First, static FNC was used to determine IC connectivity, concatenating across all three runs of the task. Then, dynamic FNC was used to look at changing functional connectivity across the course of the task (Allen et al., 2012). Typical FNC analysis assumes that brain connectivity is stable over time; research using this technique has demonstrated that this is not true during resting state (much less during a more

Figure 1. Procedures Flow Chart



complex task.) The analysis identified distinct patterns of network connectivity along the time course by using sliding tapered windowed FNCs (wFNCs) at intervals of 1 TR. Then, *k*-means clustering on the 2775 functional connection features was used to identify

patterns across these wFNC matrixes for each individual. Several summary variables of this FNC dynamism were extracted for each individuals based on that analysis: number of dynamic states (how many clusters were extracted), number of changes from one state to another state (how often did the individual transition from one pattern cluster extracted to another pattern cluster extracted, and back and so on), the maximal span of the states (the difference between an individual's two maximally different cluster patterns), and the total distance in state space (for every transition between cluster, the difference between the original and the new state, added to each of the other transition differences), following the recommendations in Calhoun et al., 2014. Larger values on these scales indicate greater neural connectivity dynamism; higher levels of dynamism are thought to be adaptive (e.g., mindfulness in children is related to higher dynamic functional network connectivity (Marusak et al., 2017), while lower dynamism may be a biomarker of mental illness, such as schizophrenia (Damaraju et al., 2014; Miller et al., 2014; Miller et al., 2016).

Univariate/Multivariate Analysis of Covariance

In order to investigate if these network components and connections were related to individual differences within our sample, we conducted univariate analyses of covariance (ANCOVA) and multi-way, multivariate analyses of covariance (MANCOVA), modeling variables of interest and the interactions between each. These analyses were conducted using the MANCOVAN toolbox in GIFT (Allen et al., 2011). Additionally, R was used for analysis of summary variables from the dFNC (R Core Team, 2016); specifically, a MANOVA using the Wilks lambda F-test was used, followed by univariate tests to interpret the findings.

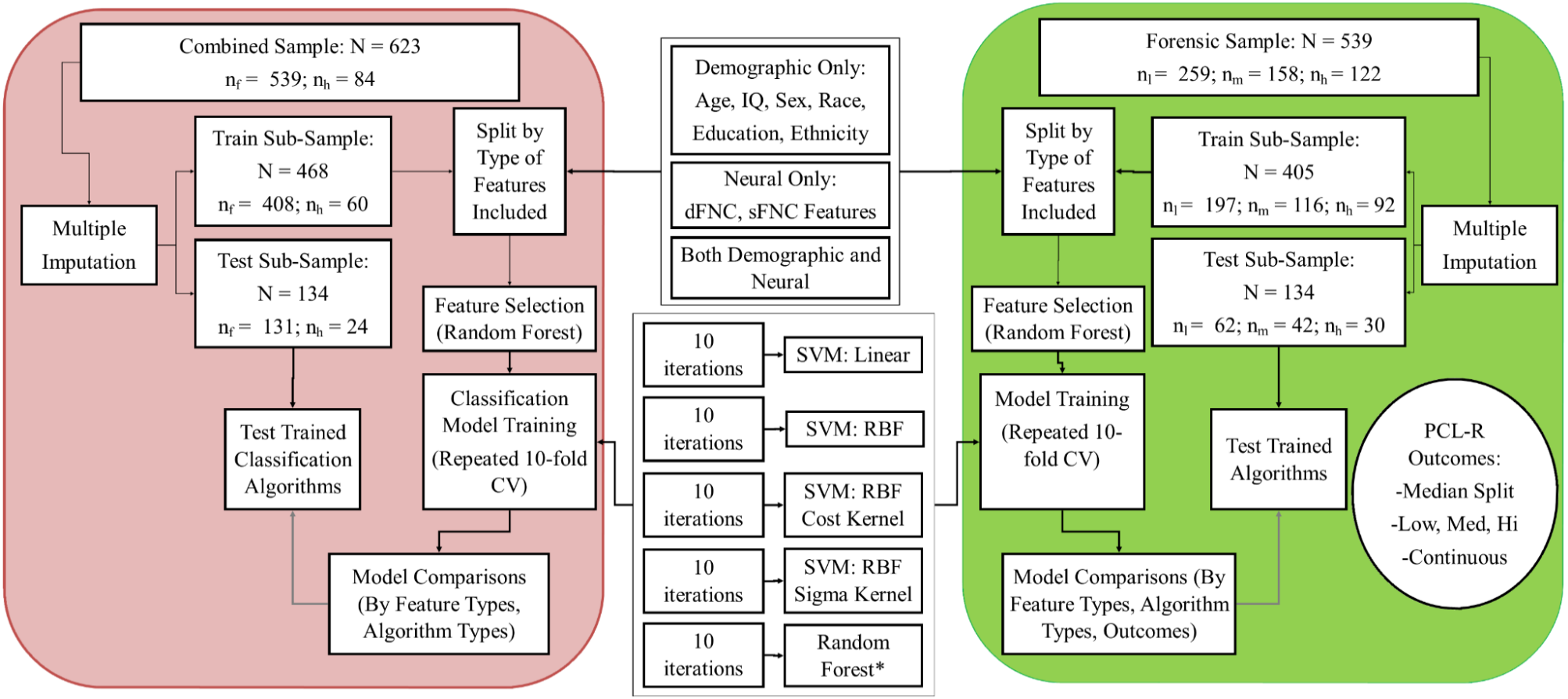
Machine Learning

The data sets were first split into three based on types of features included. The first data set was neural features only, specifically FNC matrix values and dFNC summary values from the analyses described previously. The second set was demographic and behavioral features only, including age, sex, IQ, years of education, race, and ethnicity (as well as number of substance use disorders for the forensic sample). A third data set including both types of features was also analyzed. This allowed us to identify whether or not neural features were useful above and beyond more easily collected demographic variables. See Figure 2 for a flow chart of the machine learning analysis procedure, as well as the details following.

First, feature selection was used in each data set using the Boguta package for R (Kursa & Rudnicki, 2010). This procedure employs the random forest algorithm, and requires input of classification variables (Liaw & Wiener, 2002). Random forest is an iterative process that generates decision trees based on randomly selected combinations of features. Features that are ranked significantly more important for classification than randomly generated noise features across iterations are identified as important to the model. Since random forest classification procedures do not handle missing data well, missing data, assumed to be missing at random, was imputed prior to feature selection using predictive mean matching multiple imputation generating 5 imputation sets with 50 iterations. This was done using the mice package in R (Buuren & Groothuis-Oudshoorn, 2011).

Two types of classification algorithms were then evaluated: random forest and support vector machine (SVM). These analyses were conducted using the caret package

Figure 2. Machine Learning Procedure Flow Chart



Notes: *Only random forest was used for the continuous PCL-R outcome variable. No SVM kernels were used, since this was not a classification algorithm. Abbreviations: PCL-R: Psychopathy Checklist-Revised; CV: Cross Validation; SVM: Support Vector Machine; RBF: Radial Basis Function; s(d)FNC: static(dynamic) Functional Network Connectivity

in R was then used to train and generate a classification model based on a given kernel specification (Kuhn, 2008). Random forest algorithms, previously described, can be used for both classification and regression, allowing for prediction of a continuous dependent variable. SVM is a supervised learning binary linear classification algorithm that uses kernels to model non-linear binary classes. Several kernels were evaluated here: linear, radial basis function (RBF; a Gaussian function), RB(cost)F, and RB(sigma)F. The RB(cost)F kernel leads the algorithm to favor the cost bias parameter while the RB(sigma)F kernel leads the algorithm to favor the sigma smoothing parameter. Given the relatively low number of features, and the medium number of cases, an RBF kernel was expected to be optimum (Ng, 2017). Additionally, non-binary classification can be done using SVM by employing the all-versus-one technique; the classifier is trained on each class as either belonging to the class or not, across all three classes. The concatenation of these class analyses allows a non-binary classification. All machine learning classifiers were trained with variables consisting of the dfNC, static FNC features, and behavioral and demographic data selected in the previous step. The classifiers were first trained using a random subset of the dataset and then tested on the remaining subjects (naïve to the classifier). 10-fold cross-validation, repeated 10 times, was used for training.

Model fit for random forest and SVM classifiers was evaluated based on accuracy and Cohen's kappa coefficient; accuracy refers to the observed rate of correct classification, while kappa adjusts for the expected accuracy of a random classifier. Regression based algorithms were evaluated based on minimizing Root Mean Squared Error (RMSE) and maximizing R^2, which indicates the variance accounted for by the

model. Models were compared using a *t*-test of the accuracy and kappa coefficients (pooled across resamples), where the null hypothesis was that the models did not differ, corrected for multiple comparisons using a Bonferroni *p*-value adjustment. Notably, regression algorithms could not be compared directly to classification algorithms due to having different metrics.

Chapter 3:

Healthy Moral Processing

Analysis Methods for Healthy Sample

ICA was used as described in Chapter 2. Of the 75 components extracted, 13 were identified as noise components based on a visual inspection of the t-maps and time-courses. An ANOVA was then used to examine the relationship between the remaining 62 components and the task, as previously described. A FNC matrix for each subject and condition was then calculated based on the procedure described in Chapter 2. Only connectivity between task related components, identified above, was examined.

In the MANCOVA, covariates of interest were modeled: age, IQ, and sex. Additionally, the interactions between these variables were modeled. This analysis was applied to the independent components (ICs) and to the FNC matrixes. Dynamic FNC was evaluated by conducting a MANCOVA in R modeling the three previously identified variables as well as years of education, ethnicity, and race as independent variables and the dynamism values as dependent variables in the multivariate model.

Independent Components related to Moral Processing

Nineteen components (ICs) in the frontal cortex, parietal lobe, limbic system, basal ganglia, cerebellum and occipital regions were engaged during moral processing (see Table 3 for a complete list and statistics). Specifically, in the ANOVA comparing *controversial > noncontroversial*, frontal ICs corresponding to the vmPFC (*T = 7.915)*, dlPFC (*T = 3.926)*, and dmPFC (*T = 6.402)* were significant. Additionally, the TPJ (*T = 6.316)*, parahippocampal gyrus (*T = 2.922*), ACC (*T = 7.211)*, PCC (*T = 6.007)*, and caudate (*T = 5.519)* were significant in that analysis.

Functional Network Connectivity during Moral Processing

Of the 19 ICs that were found to be significantly engaged during moral processing, all were significantly functionally connected to at least one of the others. Most notably, the time courses of components corresponding to the Frontal Eye Fields (BA 8) and to Wernicke's area were significantly correlated with all other moral processing component time courses. Additionally, dlPFC, PCC, and somatosensory association area ICs were correlated with 17 out of 18 of the remaining components. Time courses of the component corresponding to the V2 area had the lowest number of significant connections with other moral components (11 out of 18).

Table 3.
Moral task related independent components in the community sample

Region	IC	BA	F	T
Frontal Cortex				
Ventromedial Prefrontal Cortex	63	11	22.965	7.915***
Dorsomedial Prefrontal Cortex	60	10	15.78	6.402***
Dorsolateral Prefrontal Cortex	57	9	3.417	3.043*
Dorsolateral Prefrontal Cortex	7	9	5.597	3.926***
Frontal Eye Field	38	8	10.16	5.171***
Frontal Eye Field	42	8	9.891	4.849***
Supplementary Motor Area	37	6	16.257	6.889***
Parietal Lobe				
Temporoparietal Junction	72	39	16.591	6.316***
Wernicke's	51	22	5.463	3.837**
Somatosensory Association Area	67	7	6.108	3.938***
Limbic/Subcortical/Cingulate				
Parahippocampal Gyrus	34	34	3.264	2.922*
Posterior Cingulate	70	30	8.237	4.59***
Posterior Cingulate	13	23	15.108	6.007***
Anterior Cingulate	65	32	18.858	7.211***
Caudate Head	36	*	10.981	5.519***
Declive	54	*	4.992	3.801*
Brainstem	45	*	6.769	4.368***
Occipital				
V2	74	18	2.719	2.81*
Lingual Gyrus	44	18	5.681	1.435***

Notes : Only components significant in the contrast of task events controversial > non-controversial (representing moral processing) presented here. IC = independent component number; BA = brodmann area; F = test statistic (unstandardized); T = test statistic (standardized). Significance indicated by astericks as follows: *p<.05, **p<.01, ***p<.001.

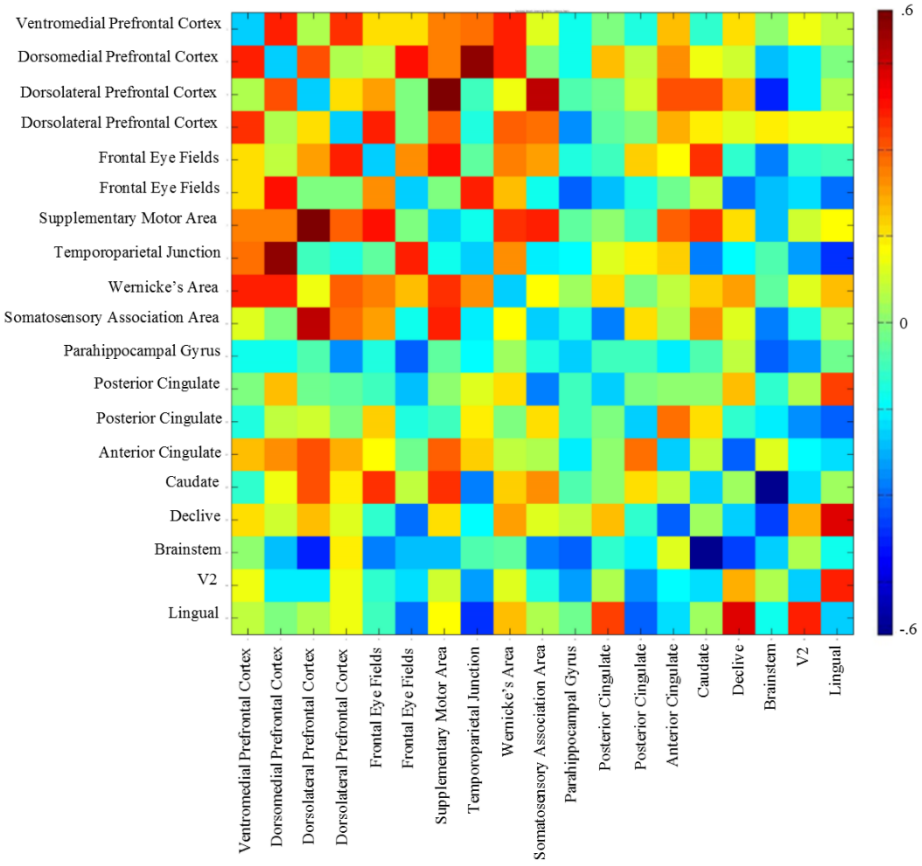
In the FNC, three component time courses were especially correlated with each other: the dlPFC and supplementary motor area ICs (r = .5166, p = <.000001), the TPJ and dmPFC IC s(r = .5014, p = <.000001), and the dlPFC and somatosensory association area ICs (r = .4626, p < .000001). Additionally, the brainstem and caudate ICs were significantly negatively correlated (r = -.2398, p < .000001). The complete connectivity matrix can be seen in Figure 3.

From the dFNC, several summary values were extracted. On average, the community participants occupied 14.00 meta-states during moral processing (sd = 2.86) with 18.00 transitions between states (sd = 3.22). The average maximum state span was 7.55 (sd = 1.28) with the distance on average being 20.71 (sd = 4.17).

Individual Differences in Neural Moral Processing

The MANCOVA modeling individual differences (age, sex, IQ) and their interactions with ICA spatial maps and FNC correlations found several significant effects of individual differences. First, age moderated the engagement of ICs corresponding to the vmPFC, somatosensory association area, and PCC. Age also moderated overall functional network connectivity; specifically, parahippocampal gyrus-TPJ connectivity and dlPFC-frontal eye field connectivity were positively related to age. Meanwhile, connectivity between a frontal eye field IC and ICs in the dmPFC, vmPFC, Wernicke's area, TPJ, and cerebellum, as well as TPJ-caudate connectivity were negatively associated with age. Sex moderated engagement of

Figure 3. Functional network connectivity matrix for community sample



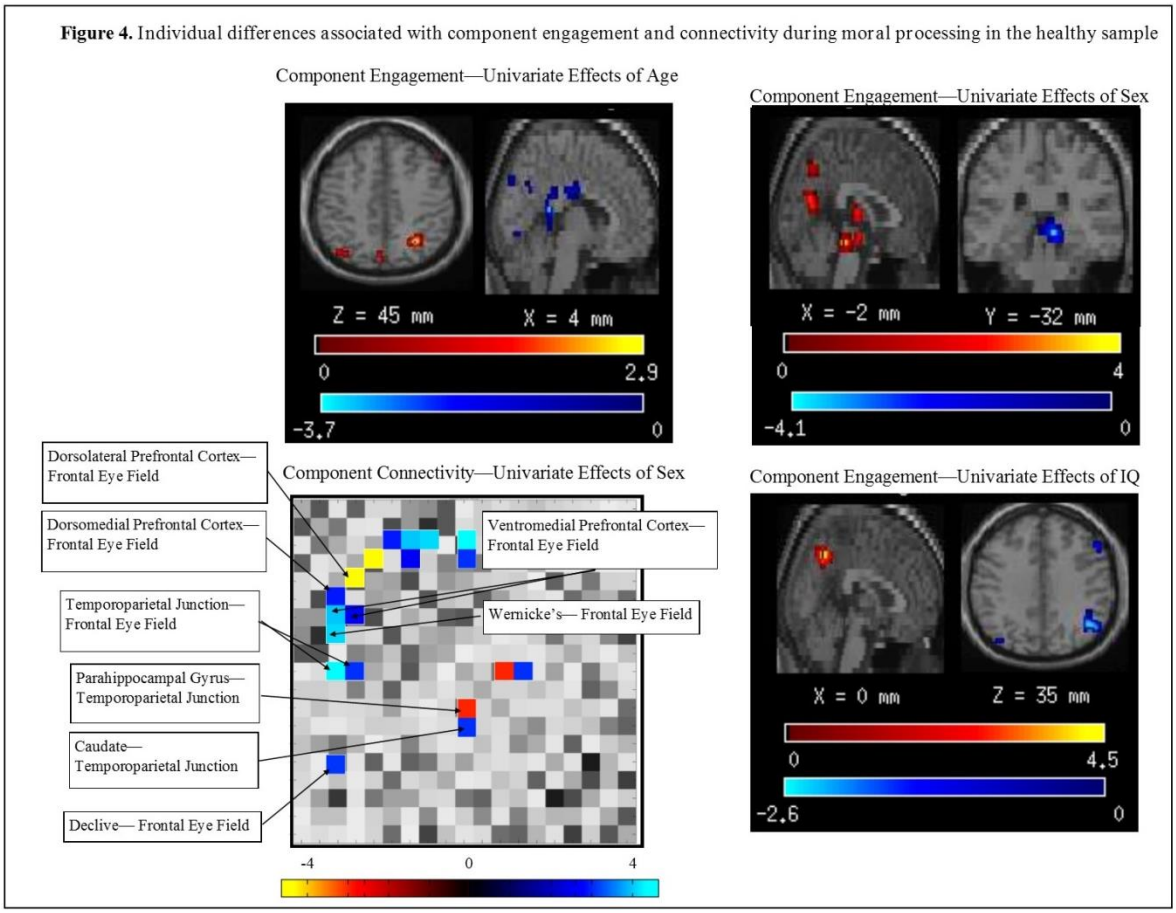


Figure 4. Individual differences associated with component engagement and connectivity during moral processing in the healthy sample

ICs corresponding to the TPJ, PCC, and brainstem, while IQ moderated engagement of TPJ and somatosensory association area components. See Figure 4 for a graphical representation.

The MANCOVA of dFNC summary statistics indicated two significant interactions between independent and dependent variables. First, the interaction between age, sex, and years of education was significant in the model ($F(1,39) = 3.3270$, $p = .02036$). Second, the interaction between IQ, age, years of education, and race was significant in the model ($F(1,39) = 4.3074$, $p = .00599$).

Univariate ANCOVA analyses were conducted to see the simple effects. The interaction between age, sex, and years of education was at a trend level in the model of span ($F(1,75) = 3.726$, $p = .0573$). The interaction between IQ, age, years of education,

and race were significant in the models of change states ($F(1,67) = 5.057$, $p = .0278$) and distance ($F(1,67) = 4.234$). More simple effects were not significant.

Discussion

We conducted an ICA and FNC analysis of hemodynamic response during moral processing in a typically functioning community sample. We hypothesized that the ICA would identify network components consistent with previous GLM studies of the neural underpinnings of moral decision making. This was largely confirmed. We found that components corresponding to the mPFC, dlPFC, TPJ, cingulate, and parahippocampal gyrus were significantly task related. Additionally, components corresponding to the basal ganglia, lingual gyrus, somatosensory association area, and supplementary motor area were found to be task related. However, we did not find significant task related components in the insula or temporal regions. The parahippocampal component subsumed the amygdala and the dmPFC component included the frontopolar region. Importantly, this lends support to theories of moral processing that focus not only on frontal cognitive and limbic emotional network processes (e.g., Greene et al., 2004), but also on temporoparietal networks that relate to social context processing (e.g., Moll et al., 2005). Although the basal ganglia and lingual gyrus were not specifically hypothesized as being related to moral processing, they were found to be related in the Schaich Borg et al. (2011) study using this same task.

We expected that the limbic components (cingulate, parahippocampal gyrus) would be highly correlated with temporal (TPJ) and frontal (mPFC, dlPFC) components. This hypothesis was partially supported by the FNC findings. Overall, the moral task-related components were correlated with each other. However, the strongest correlations

were between frontal and temporoparietal components, rather than with limbic component time courses. This may reflect greater engagement of social rules during cognitive phases of moral decision making, rather than the cognitive-affective balance posited by the conflict-control model. However, it may also reflect a temporal offset between rational (i.e., consideration of social mores, action oriented decision making) and affective response. An electrophysiology study of moral cognition found evidence for distinct temporal onset of neural processes, including intention evaluation (62ms), affective processing (122-182ms), and decision making (~300ms; Decety & Cacioppo, 2012). The authors also found that temporoparietal engagement corresponds to early intentionality evaluation rather than to later cognitive processing; thus, additional electrophysiology work examining roles of that region during moral processing may be required to understand the functional connectivity findings in the present study.

We did not anticipate that age, IQ, or sex related variability would be associated with functional components or networks during moral processing. This hypothesis was not supported by our findings. In fact, we found that age was significantly related to overall network connectivity. As age increased, so did connectivity between the parahippocampal gyrus/ amygdala and TPJ. In contrast, basal ganglia-TPJ and frontal eye field-mPFC-parietal connectivity decreased with age. This suggests that FNC during moral processing, particularly in terms of communication between processes, is variable with age. Although this was not the hypothesized outcome, it is consistent with the literature. Older adults with neurodegenerative disorders have less small-world connectivity (Supekar et al., 2008), less specificity in brain networks, and greater/less connectivity in sensorimotor/default mode networks, respectively (Song et al., 2014).

We also found evidence of sex differences in individual component engagement corresponding to the PCC, TPJ, and brainstem. These findings are also consistent with the literature. In a meta-analysis of emotional processing, women were found to have greater brainstem activation and less PCC activation than men (Wager et al., 2003). Additionally, men have been found to have greater left TPJ but less right TPJ engagement during a task of empathy (Schulte-Rüther et al., 2008).

Finally, IQ, as measured by an abbreviated version of the WAIS, was found to be related to component engagement in TPJ and somatosensory association ICs. Some previous literature indicates differences in functional connectivity related to intelligence level, although primarily in occipital and mPFC regions (Haier et al., 2003). Overall gray matter volume (GMV) has also been correlated with IQ, as well as parietal GMV, supramarginal gyrus GMV and white matter volume near the TPJ (Andreasen et al., 1993; Colom et al., 2006; Haier et al., 2004; McDaniel, 2005)

We also conducted an analysis of FNC dynamism. dFNC methodology has primarily been used to identify group differences; there are no published standards on typical resting dynamics and in fact, these reported values are not comparable to other published uses of this technique with different sized state-spaces. However, the dynamism for the community participants was reported here for comparison with the dynamism for the other samples.

There were significant interactions between functional connectivity dynamics and demographic variables. The interaction between age, sex, and years of education was significantly related to maximal distance between dynamic functional connectivity states, although simple effects were not. However, examination of correlations patterns for each

of the variables may indicate the following explanation of the interaction. For males, as years of education increased and age decreased, maximal distance between dynamic functional states increased, suggesting greater neural dynamism during moral processing. For females, maximal distance increased as both years of education and age decreased. The interaction between IQ, age, years of education, and race was significantly related to the number of transitions between dynamic function connectivity states, although simple effects were not. Examination of correlation patterns can partially explain the interaction. For individuals identifying as Caucasian/White, Latin/Other, and African American/ Black, both age and years of education were negatively correlated with number of transitions between states; however, Caucasian/White and African American/Black individuals had a positive correlation between IQ and number of transitions between states while Latin/Other individuals had a negative relationship between IQ and transitions. Additionally, both Asian and American Indian individuals had a positive relationship between age and number of transitions between functional connectivity states, but Asian individuals also had a positive relationship between years of education and transitions, while American Indian individuals had a negative association. This suggests a very complicated relationship between race, age, IQ, years of education and dynamism during moral processing.

Chapter 4:

Forensic Moral Processing

Analysis Methods for Forensic Sample

ICA was used as described in Chapter 2. This analysis was run in two samples: 1) the complete sample of forensic and community participants (n = 623); and 2) the forensic sample only (n = 539). For sample one, 11 of the 75 components were identified as noise components based on a visual inspection of the t-maps and time-courses. A 2 (*controversial; noncontroversial*) x 2 (*community; forensic*) ANOVA was then used to examine the relationship between the remaining 64 components, the task, and the two types of subjects. For sample two, eight ICs were identified as noise. A one-way ANOVA was then used to identify task related components for further analysis.

A FNC matrix for each subject and condition was then calculated based on the procedure described in Chapter 2. Only connectivity between task related components, identified above, was examined. A feature selection was run, and random forest and SVM classifiers were trained to differentiate between forensic and community individuals.

In the MANCOVA, covariates of interest were modeled: age, IQ, and sex. Additionally, the interactions between these variables were modeled. This analysis was applied to the independent components (ICs) and to the FNC matrixes. Dynamic FNC was evaluated by conducting a MANCOVA in R modeling the previously identified variables as well as years of education, ethnicity, and race as independent variables and the dynamism values as dependent variables in the multivariate model. Number of substance use dependencies was also included as a variable in the forensic sample only.

Additional follow-up analyses were done to refine the predictive utility of the brain connectivity features. First, feature selection was used to identify features that were important to the distinction between the forensic and community samples. Then, SVM and random forest classifiers were trained using those selected FNC, dFNC, and behavioral and demographic features to discriminate between the two samples. This procedure was also followed in the forensic sample to classify high and low psychopathy groups with number of substance use disorders also included in the model. The forensic groups were divided by psychopathy in two ways: first, the sample was split at the median (20) into high and low scorers; second, the sample was split into high, medium, and low groups based on thresholds for clinical diagnosis (30 and above, between 20 and 30, and 20 and below, respectively). Additionally, a random forest regression (as opposed to classification) algorithm was used with PCL-R Total score as a continuous dependent variable. Sex was included as a demographic variable in the feature selection, given findings that male and female psychopathy may be meaningfully distinct (Cale & Lilienfeld, 2002).

Moral Processing Differences between Incarcerated and Community Individuals

Twenty-nine ICs in the cingulate cortex, parietal, occipital, and temporal lobes, basal ganglia, and Broca's area that were engaged during moral processing were also significantly different between forensic and community participants (see Table 4 for a complete list and statistics). Specifically, in the ANOVA comparing *community* > *forensic*, cingulate ICs corresponding to the PCC (ventral: T = 4.228; dorsal: T = -3.521*)* and ventral ACC (T = -4.389 for one vACC IC, although also T = 2.422 for another vACC IC*)* were significantly different between groups. Additionally, the TPJ (T =

5.315*)*, parahippocampal gyrus (*T* = -3.423), insula (*T* = -4.119), caudate (tail: *T* = -4.598; body: *T* = 3.847*),* and globus pallidus (*T* = 3.315) were significantly different between groups.

Forty-seven ICs in the frontal cortex, parietal lobe, cingulate, basal ganglia, limbic system, and lingual gyrus were engaged during moral processing in the forensic sample (see Table 5 for a complete list and statistics). Specifically, in the ANOVA comparing *controversial* > *noncontroversial*, ICs corresponding to the TPJ (*T* = 13.273), vmPFC (*T* = 9.768), ACC (*T* = 8.742), PCC (*T* = 14.333), parahippocampal gyrus (*T* = 11.622), and temporal pole (*T* = 6.81) had greater activity in the moral processing condition.

The MANCOVA modeling effect of subject type (forensic and community) and its

Table 4.
Distinct moral task related independent components in the forensic vs. community sample

Region	IC	BA	F	T (Community > Forensic)
Frontal Cortex				
Inferior Frontal Gyrus	66	45	4.606**	-2.009*
Inferior Frontal Gyrus	70	45	59.119***	2.469*
Temporal Lobe				
Insula	1	13	6.714***	-3.473***
Insula	38	13	18.122***	-4.119***
Temporal Pole	24	38	19.25***	5.661***
Superior Temporal Gyrus	49	13	55.813***	-2.211*
Parahippocampal Gyrus	13	35	3.148*	-3.423***
Parietal Lobe				
Temporoparietal Junction	55	39	77.021***	5.315***
Supramarginal Gyrus	58	40	16.999***	2.556*
Cingulate				
Posterior Cingulate	31	23	39.629***	4.228***
Posterior Cingulate	74	29	3.809**	-3.276**
Posterior Cingulate	6	29	109.562***	4.422***
Posterior Cingulate	11	31	17.182***	-3.521***
Posterior Cingulate	52	23	4.566**	2.95**
Anterior Cingulate	23	24	5.835***	2.422*
Anterior Cingulate	41	24	3.682*	-4.389***
Anterior Cingulate	56	24	35.202***	2.132*
Subcortical/ Basal Ganglia				
Caudate	19	*	14.455***	-3.276**
Caudate	22	*	20.782***	-4.539***
Caudate Tail	71	*	2.652*	-4.980***
Caudate Body	68	*	7.484***	3.847***
Caudate Head	53	*	2.614*	-2.088*
Globus Pallidus	42	*	52.944***	3.315***
Thalamus	34	*	17.209***	-6.724***
Sensory				
Fusiform	8	37	3.98**	-3.17**
Fusiform	9	19	20.045***	2.687**
V2	40	18	3.195*	4.191***
Primary Association Area	18	41	12.208***	2.591**
Precuneus	10	7	3.405*	2.699**

Notes : Only components significant in the contrast of task events controversial > non-controversial (representing moral processing) presented here. IC = independent component number; BA = brodmann area; F = test statistic (unstandardized); T = standardized contrast statistic. Significance indicated by astericks as follows: *p<.05, **p<.01, ***p<.001.

interactions with ICA spatial maps and FNC correlations was significant. First, subject type moderated the engagement of ICs corresponding to the parahippocampal gyrus, insula, PCC, caudate, thalamus, precuneus, and primary association area. Overall functional network connectivity also differed by subject type; specifically, community participants had greater connectivity between the inferior frontal gyrus component and caudate body, TPJ, and globus pallidus ICs, between the PCC component and the fusiform gyrus, globus pallidus, and caudate body, as well as between the ACC and TPJ, precuneus, and caudate. Additionally, the community participants had greater insula-primary association area, TPJ-fusiform, and intra-caudate connectivity. Forensic subjects had greater connectivity between caudate components and temporal pole, TPJ, PCC, and primary association area ICs, as well as fusiform gyrus-IFG and globus pallidus-PCC component connectivity. See Figure 5 for a graphical representation.

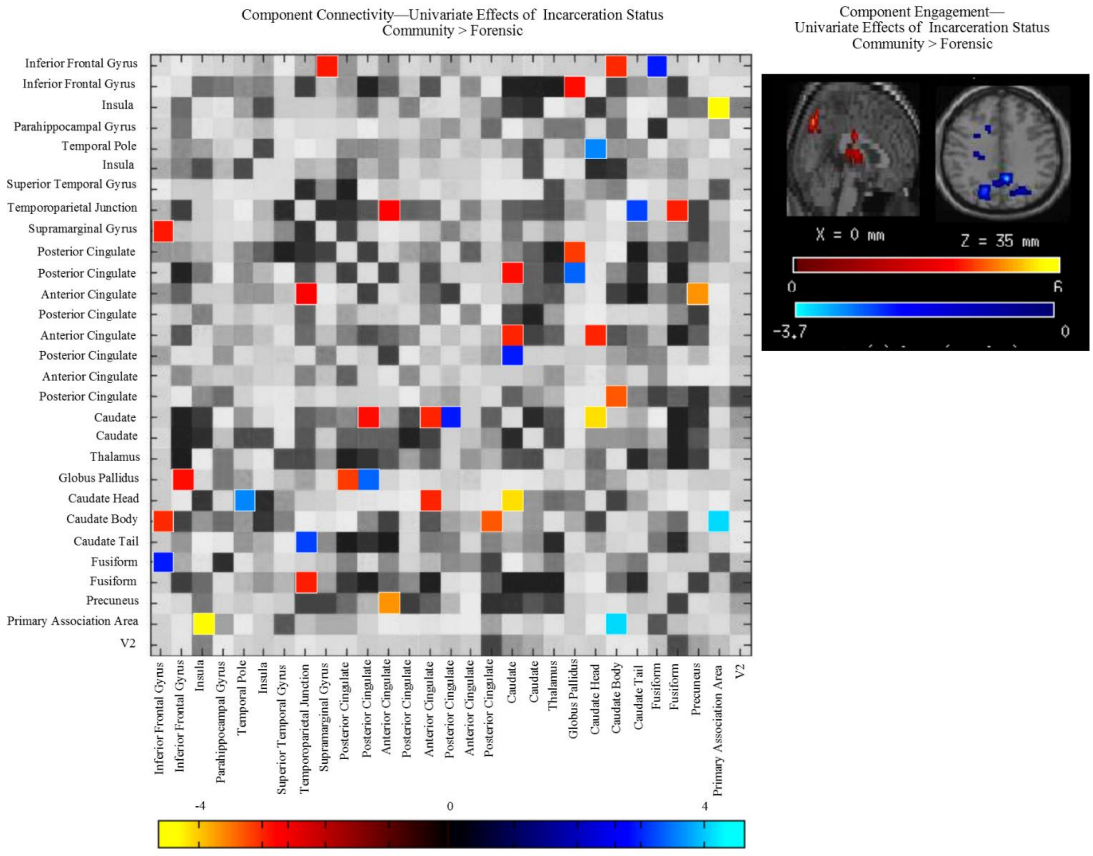
Table 5 .
Moral task related independent components in the forensic sample

Region	**IC**	**BA**	**F**	**T**
Frontal Cortex				
Ventromedial Prefrontal Cortex	46	47	34.812	9.768***
Dorsolateral Prefrontal Cortex	60	46	27.884	8.906***
Frontal Eye Fields	43	8	11.116	5.517***
Premotor	8	6	17.376	6.982***
Premotor	65	6	16.566	-6.123***
Premotor	67	4	8.056	-2.83***
Temporal Lobe				
Insula	4	13	13.186	-5.462***
Insula	14	13	11.466	-5.411***
Inferior Temporal Gyrus	52	20	8.416	4.577***
Superior Temporal Gyrus	70	22	29.833	-9.05***
Temporal Pole	17	38	26.283	-8.529***
Temporal Pole	24	38	17.541	6.81***
Parietal Lobe				
Temporoparietal Junction	58	39	71.549	13.273***
Temporoparietal Junction	55	39	5.778	3.498***
Supramarginal Gyrus	45	40	3.158	3.158*
Supramarginal Gyrus	44	40	50.397	-11.582***
Supramarginal Gyrus	35	40	10.347	4.74***
Superior Parietal Lobule	50	7	21.947	-6.864***
Postcentral Gyrus	29	2	17.648	-7.092***
Postcentral Gyrus	36	1	12.511	-6.009***
Limbic/Subcortical/Cingulate				
Anterior Cingulate	5	24	10.586	-5.094***
Anterior Cingulate	28	24	8.724	-4.78***
Anterior Cingulate	49	25	5.932	-3.886***
Anterior Cingulate	56	24	32.075	8.742***
Posterior Cingulate	3	30	18.936	6.544***
Posterior Cingulate	6	31	9.13	-4.371***
Posterior Cingulate	71	23	3.137	-2.726*
Posterior Cingulate	39	21	87.32	14.333***
Posterior Cingulate	74	29	4.992	3.366**
Precuneus	9	7	18.215	-6.861***
Precuneus	72	7	4.345	-1.845**
Parahippocampal Gyrus	20	34	51.001	11.622***
Globus Pallidus	48	*	7.236	4.495***
Putamen	18	*	4.229	-1.03**
Thalamus	68	*	8.027	4.604***
Thalamus	37	*	6.34	4.272***
Thalamus	16	*	4.414	3.365**
Brainstem	61	*	21.272	7.687***
Cerebellum (Declive)	62	*	7.257	3.856***
Cerebellum (Culmen)	59	*	5.191	3.233**
Cerebellum (Culmen)	57	*	12.843	-5.683***
Cerebellum (Culmen)	47	*	8.632	4.986***
Occipital				
Lingual Gyrus	31	17	4.223	1.418**
Lingual Gyrus	32	18	5.774	-1.192***
Lingual Gyrus	12	18	36.14	-0.095***
V2	73	18	15.662	6.584***
Fusiform	64	19	3.325	-2.645*

Notes : Only components significant in the contrast of task events controversial > non-controversial (representing moral processing) presented here. IC = independent component number; BA = brodmann area; F = test statistic (unstandardized); T = test statistic (standardized). Significance indicated by astericks as follows: *p<.05, **p<.01, ***p<.001.

In the MANCOVA of dFNC summary statistics, the effect of group was significant (F(1,297) = 27.5548, p <2.2E-16). Specifically, groups differed on distance and span dynamics, where typical community individuals compared to incarcerated individuals had greater meta-state distance (community: mean = 23.96863, sd = 3.46243; forensic: 21.2026, sd = 3.978898; F(1,621) = 36.68, p = 2.41e-09) and span (community: mean = 10.96078, sd = 1.189028; forensic: mean = 9.587361, sd = 1.479255; F(1,621) = 66.46, p = 1.98e-15).

Figure 5. Community > Forensic differences associated with component engagement and connectivity during moral processing in the whole sample



Feature selection identified seven features (in the data set that included all features) that discriminated between groups after correction for multiple comparisons. These were IQ, age, years of education, and maximal dynamic state span, as well

asfusiform gyrus- caudate, premotor-STG/insula, and TPJ-lingual gyrus connectivity. Using only these features, the random forest algorithm was best able to discriminate between forensic and community participants in the training (accuracy: 100%, sensitivity: 100%, specificity: 100%, kappa: 1) and in the training set (accuracy: 93.55%, sensitivity: 94.16, specificity: 88.89%, kappa: 0.69.) See Table 6 for results for all classification algorithms. This classifier was significantly better than those with only neural features, and better than a SVM linear classifier. However, it was not significantly different than SVM RBF classifiers in the full feature set or in the behavioral/demographics set only, or than the random forest classifier in the behavioral/demographics set (see Figure 6 for a graphical comparison of classifiers).

Table 6.
Test Results of Machine Learning Algorithms- Community vs. Forensic Samples

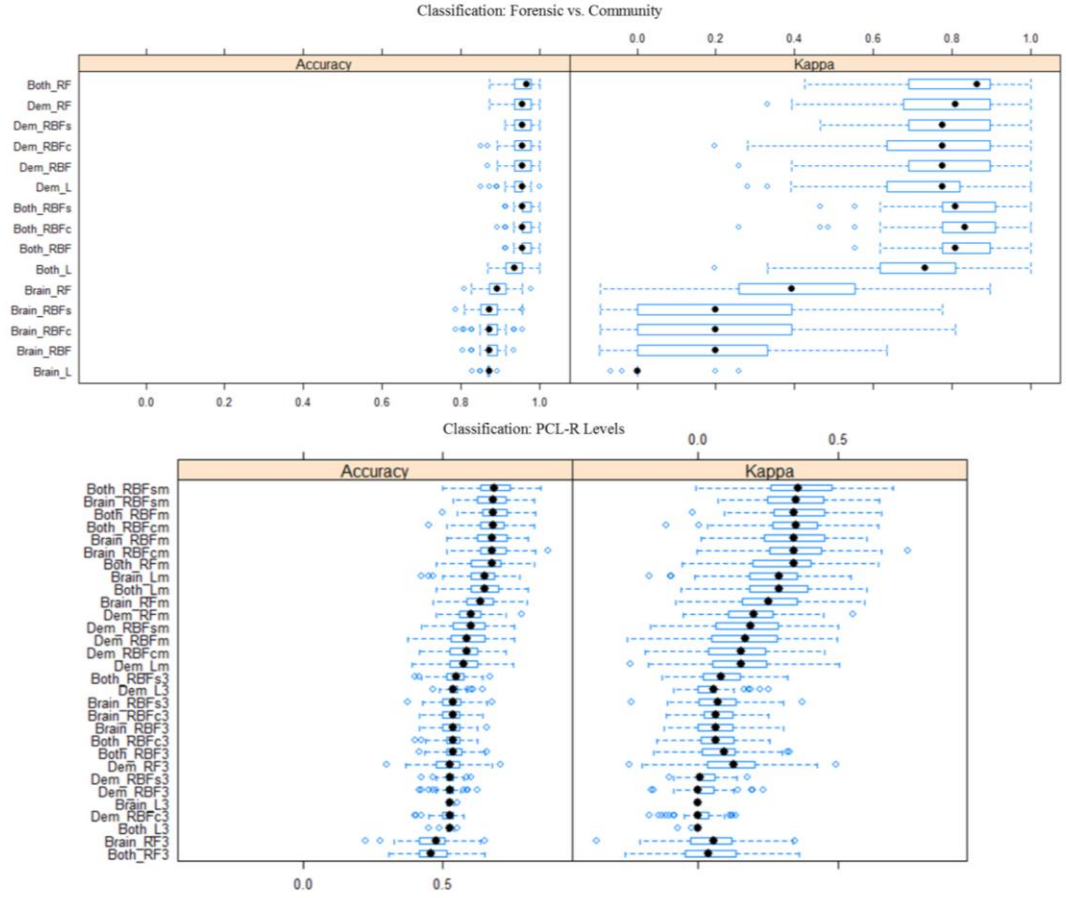
Algorithm	Accuracy	Kappa	Correct "Forensic" Classification	Correct "Community" Classification	p-value	Negative Difference from Best Model- Accuracy (Kappa)
All Selected Features						
SVM- Linear	0.92	0.69	0.95	0.77	0.01	.02* (.10*)
SVM- RBF	0.92	0.68	0.94	0.8	0.03	-.001 (-.01)
SVM- RBF Cost	0.92	0.68	0.94	0.8	0.03	-.001 (-.01)
SVM- RBF Sigma	0.92	0.68	0.94	0.8	0.03	-.004 (.02)
Random Forest	0.94	0.73	0.94	0.89	0.02	**Best**
Selected Neural Features						
SVM- Linear	0.85	0	0.85	NA	1	.09* (.82 *)
SVM- RBF	0.86	0.19	0.86	1	1	.09'* (.63*)
SVM- RBF Cost	0.83	0.11	0.86	0.33	1	.09 (.60*)
SVM- RBF Sigma	0.86	0.18	0.86	0.75	1	.09* (.60*)
Random Forest	0.78	-0.05	0.84	0.08	1	.07* (.42*)
Selected Behavioral/Demographic Features						
SVM- Linear	0.92	0.66	0.93	0.88	0.18	.01 (.08*)
SVM- RBF	0.92	0.59	0.91	1	0.79	.01 (.06)
SVM- RBF Cost	0.92	0.59	0.91	1	0.79	.01 (.06)
SVM- RBF Sigma	0.92	0.64	0.92	0.93	0.35	.01 (.05)
Random Forest	0.93	0.69	0.93	0.88	0.07	.01 (.04)

model column is based on pooled resamples of cross-validated training models and should be interpreted in terms of testing set accuracy and kappa. *p value of difference < .05; SVM: Support Vector Machine; RBF: Radial Basis Function

Moral Processing, Neural Connectivity, and Psychopathy

The MANCOVA modeling PCL-R total score and ICA spatial maps was significant. First, PCL-R total score moderated the engagement of ICs corresponding to the frontal eye fields, TPJ, ACC, precuneus, putamen, cerebellum, lingual gyrus, temporal pole, and V2. Additionally, the interaction between PCL-R total score and number of substance use disorders moderated components corresponding to the supramarginal gryus, superior parietal lobule, PCC, cerebellum, ACC, globus pallidus, insula, and fusiform gyrus. Finally, in the component corresponding to the brainstem, the interaction between PCL-R total score and IQ moderated engagement, while the

Figure 6. Box and Whisker Plot Comparison of Machine Learning Classification Algorithms



Notes: Models ordered from best (top) to worst (bottom). These are based on training setts. Black dots represent median of resamples. Empty circles represent outliers in resamples. Boxes represent lower (25%) and upper (75%) quartiles of resamples. Whiskers represent minimum and maximum values of resamples (excluding outliers). Abbreviations: Brain– Neural feature set only, Dem– Demographic and Behavioral feature set only; Both– Neural, Demographic, and Behavioral feature set. L: Linear support vector machine (SVM) kernel algorithm; RBF: Radial Basis Function SVM kernel; RBFs: RBFsigma kernel; RBFc: RBFcost kernel; RF: random forest; m: Median Split Psychopathy outcome; 3: Low-Median-High Psychopathy outcome. PCL-R: Psychopathy Checklist Revised.

interaction between PCL-R total score and sex moderated the IC corresponding to the inferior temporal gyrus. Overall functional network connectivity was not moderated by PCL-R total score. See Figure 7 for a graphical representation.

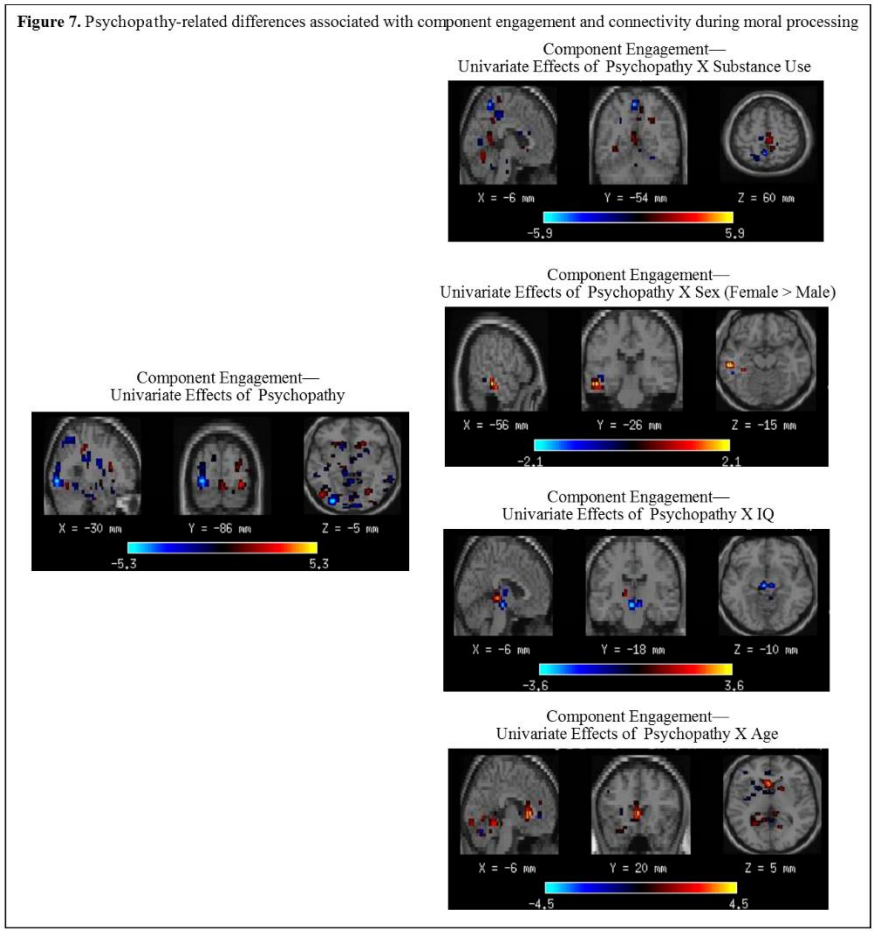


Figure 7. Psychopathy-related differences associated with component engagement and connectivity during moral processing

In the MANCOVA modeling dFNC summary variables, the effect of PCL-R Total score was not significant (F (1,14) = .6644, p = .629695). However, the interactions between PCL-R Total and several other factors were significant. First, the interaction between PCL-R Total and number of substance use disorders was significant (F(1,14) = 11.4688, p = .000647). Second, the interaction between PCL-R Total, sex, and IQ was significant (F(10,14) = 1.7451, p = .036949). Finally, the interaction between PCL-R Total, race, years of education, and IQ was significant (F(2,14) = 3.4743, p = .009698). Univariate ANCOVA analyses were conducted to see the simple effects. The interaction between PCL-R Total, sex, and IQ was significant in the models of meta-state distance (F(16,389)=1.804, p = .0288), transitions between meta-states (F(16,389) = 1.831, p = .0257), and number of meta-states occupied (F (16,389) = 1.803, p = .0289). The

interactions between PCL-R Total, race, years of education, and IQ and between PCL-R Total and the number of substance use disorders were not significant in the simple effect models.

Feature selection identified two features out of the neural and demographic/ behavioral data set that discriminated between high, medium, and low PCL-R groups after correction for multiple comparisons. These were connectivity between the 1) IFG/ Broca's area and insula; and 2) temporal pole and ACC. This feature selection was replicated in the just neural data set; feature selection applied to the demographic variables only identified age and sex as important to distinguishing between levels of psychopathy. On the other hand, feature selection discriminating between high and low psychopathy (based on a median split) identified four additional features in addition to the two identified with the Low Medium High outcome: brainstem-ACC, PCC-brainstem, caudate-V2, and TPJ- STG/ Wernicke's Area connectivity. Feature selection within demographic variables replicated selection of age and sex as important to differentiating levels of psychopathy. Feature selection based on PCL-R Total score identified several of the same features (Sex, IFG/ Broca's area- insula and temporal pole – ACC connectivity) as well as cerebellum-TPJ and thalamus-somatosensory association cortex connectivity.

The best classifier was a SVM with a radial basis sigma function kernel (sigma = .045, C = 32) trained on the six neural features identified in the previous step to discriminate between high and low (median-split) psychopathic levels. This algorithm classified in the training set (accuracy: 76.79%, sensitivity: 74.49%, specificity: 80.38%, kappa: .53); however, in the test set, the SVM did not perform significantly better than

Table 7.
Test Results of Machine Learning Algorithms- Psychopathy

Algorithm	PCLR Outcome	Accuracy	Kappa	Correct "Low" Classification	Correct "Medium" Classification	Correct "High" Classification	p-value	Negative Difference from Best Model- Accuracy (Kappa)
All Selected Features								
SVM- Linear	Median Split	0.49	-0.02	0.51	-	0.46	0.99	4.04 E -02
	LMH	0.49	0	0.49 / NA	NA / 0.6	NA / .89	1	1.64 E -01*
SVM- RBF	Median Split	0.46	-0.09	0.49	-	0.42	1	1.45 E -03
	LMH	0.48	-0.01	.49 /.50	.38 / .60	NA / .89	1	1.47 E -01*
SVM- RBF Cost	Median Split	0.46	-0.09	0.49	-	0.42	1	9.34 E -03
	LMH	0.47	-0.02	.49 / .47	.33 / .60	NA / .89	1	1.52 E -01*
SVM- RBF Sigma	Median Split	0.46	-0.1	0.48	-	0.41	1	**Best**
	LMH	0.49	0.01	.50 / .53	.41 / .61	NA / .89	1	1.47 E -01*
Random Forest	Median Split	0.44	-0.13	0.47	-	0.4	1	2.65 E -02
	LMH	0.42	-0.05	.47 / .47	.38 / .59	0 / .88	1	2.25 E -01*
		R^2	**RMSE**					
	Continuous (Train)	0.15	6.27					**Best**
	Continuous (Test)	0.03	6.39					-

		Accuracy	Kappa	Correct "Low" Classification	Correct "Medium" Classification	Correct "High" Classification	p-value	Negative Difference from Best Model- Accuracy (Kappa)
*Selected Neural Features***								
SVM- Linear	Median Split	0.52	0.04	0.54	-	0.5	0.99	4.66 E -02*
	LMH	-	-	-	-	-	-	-
SVM- RBF	Median Split	0.5	-0.01	0.52	-	0.47	1	1.04 E -02
	LMH	-	-	-	-	-	-	-
SVM- RBF Cost	Median Split	0.52	0.03	0.54	-	0.5	0.99	8.76 E -03
	LMH	-	-	-	-	-	-	-
SVM- RBF Sigma	Median Split	0.52	0.03	0.54	-	0.5	0.99	6.01 E -03
	LMH	-	-	-	-	-	-	-
Random Forest	Median Split	0.53	0.05	0.54	-	0.51	0.98	5.18 E -02*
	LMH	-	-	-	-	-	-	-
		R^2	**RMSE**					
	Continuous (Train)	0.12	6.4					.03* (-.14)
	Continuous (Test)	0.01	6.56					-

		Accuracy	Kappa	Correct "Low" Classification	Correct "Medium" Classification	Correct "High" Classification	p-value	Negative Difference from Best Model- Accuracy (Kappa)
Selected Behavioral/Demographic Features								
SVM- Linear	Median Split	0.56	0.13	0.6	-	0.53	0.87	1.12 E -01*
	LMH	0.51	0.05	.50 / 1	1 / .62	NA / .89	1	1.43 E -01*
SVM- RBF	Median Split	0.55	0.1	0.57	-	0.53	0.67	9.53 E -02*
	LMH	0.49	0	.49 / NA	NA / .60	NA / .89	1	1.64 E -01*
SVM- RBF Cost	Median Split	0.54	0.07	0.55	-	0.52	0.67	1.07 E -01*
	LMH	0.49	0	.49 / NA	NA / .60	NA / .89	1	1.69 E -01*
SVM- RBF Sigma	Median Split	0.56	0.11	0.56	-	0.55	0.98	8.67 E -02*
	LMH	0.5	0.03	.50 / .63	.50 / .61	NA / .89	1	1.51 E -01*
Random Forest	Median Split	0.57	0.13	0.58	-	0.55	0.4	8.11 E -02*
	LMH	0.51	0.12	.56 / .63	.46 / .63	.14 / .89	1	1.63 E -01*
		R^2	**RMSE**					
	Continuous (Train)	0.05	33.49					.10* (-27.22*)
	Continuous (Test)	0.01	37.69					-

Notes : Reported accuracy through p-value columns refer to classification in the test sample. Comparison to model column is based on pooled resamples of cross-validated training models and should be interpreted in terms of testing set accuracy and kappa. *p value of difference < .05; SVM: Support Vector Machine; RBF: Radial Basis Function

chance (accuracy: 45.52%, sensitivity: 48.19%, specificity: 41.18%, kappa: -.10). We also used a random forest regression algorithm to predict PCL-R Total score. The optimum model explained 14.61% of the variance in PCL-R Total score for the training set (RMSE: 6.27), although only 2.56% of the variance for the test set (RMSE: 6.39). See

Table 7 for results for all machine learning algorithms used and Figure 6 for a graphical comparison of classifiers.

The analysis was further broken down into male and female subsets with the complete set of features to evaluate whether a better model could be fit within each respective subset. Classification in these sets was not improved (Male: Random Forest- RMSE: 6.85, R^2: .0004; SVM RB(sigma)F- accuracy: 43.37%, sensitivity: 37.93%, specificity: 46.30%, kappa: -.145. Female subset: Random Forest- RMSE: 5.91, R^2: .0003; SVM RB(sigma)F- accuracy: 47.06%, sensitivity: 53.33%, specificity: 00.00%, kappa: -.224).

Discussion

We conducted an ICA and FNC analysis of hemodynamic response during moral processing in a sample of incarcerated men and women. The purpose of this analysis was two-fold: first, we aimed to understand whether incarcerated individuals differed in functional network engagement and connectivity during moral processing compared to a community sample; second, we investigated how psychopathy may influence these patterns. Based on GLM analyses comparing forensic and community samples on neural engagement during moral processing, we did not anticipate significant differences between the groups on component engagement or functional network connectivity related to the moral task. However, the findings contradicted that prediction.

Using a supervised-learning classification algorithm, we were able to discriminate between community and forensic samples based on patterns of functional neural connectivity related to moral processing at a rate above 90%. In particular, the rate of cases falsely identified as incarcerated was only 11.11% in the testing set; cases falsely

identified as community was at a rate of 5.84%. This was based on features identified through a random-forest based feature selection analysis. Specifically, connectivity between visual components and basal ganglia/TPJ components, as well as between premotor and insula components were identified as important to distinguish between forensic and community participants. Additionally, demographic features (age, IQ, years of education) and network connectivity dynamism distinguished between these groups. Community individuals had greater distance (maximal and overall) between dynamic functional connectivity states than incarcerated individuals, suggesting that incarceration or criminality is associated with lower neural dynamism during moral processing.

Although differentiation based on neural features was not the hypothesized outcome, it is consistent with a previous study that used an SVM classifier to discriminate between male adolescents who had committed homicides versus those who had committed non-violent crimes based on gray matter volume (Cope et al., 2014). In particular, these groups differed on basal ganglia and insula (as well as OFC and ACC) volumes, consistent with the findings seen here. In addition to replicating that analysis, the current study expands the scope of the effect by 1) differentiating offenders and non-offenders, 2) applying it to male and female adults, 3) improving classification accuracy, and 4) applying it to fMRI data and functional network connectivity features. The overall improvement in classification may be due to the particular applicability of moral processing to the context of criminal offending; it may also be due to greater differentiation in FNC features than in GMV or due to a larger sample size in the current analysis.

Additional group differences indicated in the MANCOVA may be important for understanding atypical moral processing in incarcerated individuals. Community and forensic individuals differed in parahippocampal gyrus/amygdala and thalamus component engagement. The parahippocampal gyrus/amygdala region is considered a key part of emotional/affective engagement in moral decision making and connects with the vmPFC to integrate that information into decisions (Moll et al., 2005). Although the thalamus is not a typical region discussed in the context of moral judgment, it may be related to processing moral and non-moral unpleasant, emotionally salient stimuli (Moll et al., 2002). In fact, damage to the thalamus has been related to deficiencies in processing emotional stimuli (Fukatsu et al., 1997). Abnormalities in the engagement of components corresponding to these regions may then reflect atypical use of emotions during moral cognition in incarcerated individuals.

There were several FNC features where community and forensic individuals differed. In particular, the groups differed in connectivity between several hub regions: PCC/precuneus, basal ganglia, and TPJ components. In the basal ganglia, both the caudate, a sub-region that receives inputs from other brain regions, and the globus pallidus, which receive inputs from the caudate/striatum and ultimately communicates to other neural regions, including the limbic system, may be a key to differences in moral decision making. Abnormalities within this system may reflect distinct patterns of reward processes engaged during emotional and social decision making (Hong & Hikosaka, 2008).

The PCC and the TPJ have roles in emotional and social processes. The PCC is involved in integrating memory and emotional experiences as well as evaluating “self” in

relation to sensory information (Maddock et al., 2003; Vogt et al., 1992). On the other hand, the TPJ is hypothesized to be a nexus for social rules, semantic language processing, and memory (Carter & Huettel, 2013). Based on these functions, one possible explanation for this pattern of connectivity results is that abnormalities in basal ganglia connections lead to atypical reward/punishment learning in emotionally salient conditions (Yin et al., 2008), which may in turn affect the tendency for emotional response versus social rule memory retrieval when confronting a moral dilemma.

Forensic and community individuals differed on some measures of dynamism during moral processing. Specifically, community participants had greater maximum divergence between meta-states (span) and greater changes between meta-states (distance) than did forensic participants. This indicated less overall dynamism during moral processing in these incarcerated individuals, and may suggest less ability to flexibly integrate information across the brain as the task demands required.

Another element that we investigated was how variability in levels of psychopathic traits within the incarcerated population related to network component engagement and connectivity during moral processing. Notably, psychopathy moderated activity in components corresponding to the TPJ, cingulate, basal ganglia, and temporal poles. Several of these regions (the ACC, PCC, and temporal poles) are part of the paralimbic dysfunction theory of psychopathy (Kiehl, 2006), and are consistent with our hypothesis.

The interaction between psychopathy and substance use also influenced engagement in these regions (through distinct components) as well as moderating engagement of an insular component, while psychopathy's interactions with IQ and sex

moderated engagement in brainstem and inferior temporal gyrus component engagement, respectively. Although research has already identified a potential relationship between substance use and neural activity during moral processing (Caldwell et al., 2015; Fede, Harenski, et al., 2016), and a relationship between psychopathy and substance use (Hemphill et al., 1994), the interaction between these features in moral processing components may indicate that understanding the combined influence of psychopathic traits and substance use is essential to explaining abnormalities in the brain processes underlying moral decision making. Sex and IQ interactions tended to correspond to individual difference effects seen in the community sample and discussed in Chapter 3.

As previously discussed, TPJ, PCC, and basal ganglia activity may reflect abnormal social/semantic processing, emotional-self memory retrieval, and reward learning. The ACC is involved in affective attention and error monitoring (Margulies et al., 2007), and the temporal pole is involved in integration of sensory features (e.g., face recognition) into theory of mind and emotion processes (Olson et al., 2007). Abnormalities in these systems correspond to the general differences between incarcerated and community individuals; overall differences in level of psychopathic traits between the two groups may explain those findings. The average level of psychopathic traits in our incarcerated sample was 20.22; we did not assess psychopathy in our community sample due to the low base rate in typical adults. In a large community sample, the average score on psychopathic traits was equivalent to a 4.45 on the scale used in the present study; two-thirds of the sample had a score of 3.3 or less (Neumann & Hare, 2008).

Overall static FNC was not moderated by psychopathic traits in the MANCOVA, or the interaction between those traits and other measured variables. We further investigated this through our planned machine learning analysis. A feature selection identified FNC features that were important for distinguishing between high and low scorers on psychopathy. These were between the IFG and insula, between the cingulate and temporal pole / brainstem, between the basal ganglia and V2, and between the TPJ and superior temporal gyrus.

However, classification using these features was less successful. Although classification accuracy was significant in the training set, in the test set, accuracy was not significantly above chance. There are several plausible explanations for this finding. First, the algorithm may be overfitting the training set, meaning that the classifier may be trained to classify based on traits unique to that set, rather than to intrinsic differences between high and low psychopathy. Second, given a lack of overall FNC moderation by psychopathic traits, FNC during moral processing may not be the optimal set of features to discriminate between the two groups. Some potential additions to the model could be component engagement, spectra information, and GLM-ROI based voxel weights. Third, psychopathy may not be a unitary construct across males and females. We ran the SVM classification within each sex, but this did not improve the accuracy of in the test sample. In fact, classification dropped to approximately chance in each test set. However, this may be due to a reduction in sample size in both the testing and training sets. Finally, median-split assignment to high/low psychopathy groups may not be the optimal group assignment. However, we did also run algorithms with two other types of psychopathy outcome variables: 1) traditional low-medium-high diagnostic categories; and 2) PCL-R

Total score as a continuous outcome variable. Classification for the traditional categories was worse than for median split psychopathy categories. A continuous random forest algorithm was able to explain some variance; however, the 2.5% variance explained in the test sample is unlikely to be clinically useful.

Psychopathy significantly moderated dynamic functional network connectivity when considering interactions with sex and IQ; substance use; and education levels, race, and IQ. The latter two interactions were significant in the overall model of FNC dynamism, but not any specific dynamism feature. In contrast, the interactions between psychopathy, sex, and IQ were related to the number of distinct dynamic states occupied during moral processing, how many times an individual switched between these dynamic states, and the size of the changes between those states. Male forensic participants had a small increase in dynamism as PCL-R and IQ increased; female participants had a small to negligible decrease in dynamism as PCL-R and IQ increased. This suggests a complicated interaction between individual traits and dynamic FNC states.

Chapter 5:

Synthesis

Summary of Findings

We aimed to better understand the interactions between neural networks during moral processing by examining task related neural components and the correlations between those component time courses. We also examined how traits including age, IQ, sex, criminality, and psychopathy moderated these functional network dynamics. Finally, we evaluated the utility of these neural features for classifying based on traits associated with commission of crimes.

We predicted that frontal, limbic, and temporal neural components, indicated by neurobiological theory of moral processing, would be identified through ICA and would be functionally connected to each other. We did not anticipate that individual differences or incarceration status would moderate engagement or connectivity of those components, but rather that psychopathy would moderate neural dynamics in paralimbic regions during moral processing. Finally, we expected to be able to classify individuals as high or low in psychopathic traits based on these neural features, but to be unable to classify between individuals that were incarcerated and those that were not.

Several of these hypotheses were supporting by our findings. We found that frontal, limbic, and temporoparietal components were engaged during moral processing, and that these components were largely functionally connected to each other. This lends support to neurobiological theories of moral processing that propose involvement of all three neural networks, such as the Event Feature Emotion Complex theory (Moll et al., 2005). Additionally, we found that secondary visual processing regions were engaged

during moral processing. Although not hypothesized, this may reflect amygdala activity expanding to occipital regions, as has been demonstrated previously in emotion processing (Krolak-Salmon et al., 2004). We replicated these results in the main effects of the forensic sample.

We found that psychopathy moderated engagement of component activity during moral processing. However, in addition to psychopathy effects in predicted paralimbic regions (i.e., ACC, temporal pole, PCC, and insula), we identified an association between psychopathy and component engagement in the TPJ, lingual gyrus, and basal ganglia, and V2/fusiform gyrus regions. This suggests that during moral processing, individuals high in psychopathy have atypical engagement not only in limbic regions, but in social rule/ motivation regions implicated in classical models of moral cognition. Importantly, we could train a SVM to classify high and low psychopathy based on FNC features; however, these algorithms were not useful in a naïve sample.

There are still several important things to take away from the results. First, a non-linear classification algorithm was significantly better than an SVM employing a traditional linear kernel at identifying levels of psychopathy. This may explain inconsistent findings across psychopathy based fMRI analyses using a traditional GLM model; if the maximal neural differences in high and low scorers on psychopathic traits fall in a non-linear pattern, than the assumption of linearity implicit in the GLM model may not be met. Second, machine learning on a median split PCL-R outcome was better than on a low-median-high classification. Although some differences in power may explain this finding, it may also be that in our sample, neural correlates of high and medium psychopathy are not meaningfully different.

There were several unanticipated findings. Across samples, age, IQ, and sex moderated component engagement and connectivity, particularly in the TPJ; additionally, inclusion of these variables improved classification in the SVM. Age, IQ, and sex were also related to dynamism in network connectivity. Although these results were not hypothesized, they were consistent with the literature, as discussed in Chapter 3. These findings emphasize the importance of considering individual differences in functional neuroimaging, including studies investigating moral processing, regardless of whether specific hypotheses predict effects of these traits.

We also did not anticipate the pronounced differences between community and forensic individuals in our sample. Previous work did not indicate differences between an incarcerated sample and previously published community samples when using this task of moral cognition (Fede, Schaich Borg, et al., 2016). One possible explanation is that differences only emerge when examining higher level network dynamics, such as functional network connectivity and dynamism. However, the present analysis differed significantly in other ways. First, the sample sizes of both groups were notably larger. Additionally, the forensic sample in the current study included both male and female individuals, rather than only males. Finally, our analysis quantitatively compared the two samples using statistical testing, rather than by simply using ROIs based on coordinates reported in the original study (Schaich Borg et al., 2011).

Regardless of the failure to hypothesize this result, there are important implications of the finding that network dynamics can classify individuals in a naïve sample based on incarceration status with above 90% accuracy. If there are neural differences in processing of moral stimuli in individuals who are incarcerated, it may be

possible to use these differences as a biomarker of criminality. This would allow us to identify at-risk individuals and intervene before serious or repeated criminal activity.

There are other potential explanations for these findings. It may be possible incarceration leads to changes in neural engagement and connectivity during moral processing. This would provide unique implications about the potential negative impact of incarceration as a solution to crime. In fact, both explanations could compound to account for these findings. Alternatively, it may be that there are additional differences between the samples that were not accounted for in these analyses. Community and forensic individuals did differ on age, IQ, and years of education. We did run machine learning algorithms looking only at neural and only at behavioral features. The algorithms including both types of features performed the best, although not significantly differently from comparable demographic/ behavioral only analysis.

Discussion of Overall Findings

This is the first study to employ ICA and examine functional network connectivity during moral processing in any population or to use machine learning based on neural activity during moral processing. Understanding the connectivity of neural processes during moral cognition may allow for a more sophisticated model of moral cognition in the brain. Additionally, understanding functional network connectivity related specifically to psychopathy may begin to explain discrepancies in findings in traditional GLM analyses of moral processing and psychopathy, since abnormalities may be more complex than simple deficiencies in particular neural regions.

Limitations of the Study

When using supervised learning to classify individuals as criminals or non-criminal community members, there are several potential pitfalls. First, we cannot know whether these neural features reflect pre-existing brain characteristics that could predict future criminality or whether they are incidental to criminality. Longitudinal studies prior to adulthood would be a necessary next step to understand the directionality of these effects; use of the current findings in a legal setting would be premature. Additionally, since these results are specific to adults, we cannot generalize these findings to adolescent populations, where risk assessment would be the most potentially useful, but false labeling would be the most detrimental.

Another limitation is the discrepancy in sample sizes between the community and forensic samples. This imbalance may influence the power to detect differences, and may bias the results. However, we addressed this imbalance in the SVM by adjusting the cost specification while training the classifier to more greatly punish false positives.

There may also have been individual differences that were not controlled for or investigated in the analyses. For example, there may be differences in socioeconomic status and incarceration, in types of crimes committed, and in sentencing. Although we did include a substance use disorder variable in the analysis of the incarcerated population, we did not account for the severity of individual disorders, for sub-dependence use, or for the unique mechanisms of different substances. Additionally, criminal and substance use histories in the community population were self-reported; this may potentially lead to a lower signal-to-noise ratio if individuals misrepresented those features.

Another important consideration is that this study does not identify a specific relationship between atypical processing of moral stimuli and deficiencies in moral behavior or choices, much less identify a mechanism for intervention. Although it is presumed that criminals, and particularly psychopaths, commit moral violations, these individuals do not consistently perform worse on laboratory tasks of moral decision making (i.e., Aharoni et al., 2012). Therefore, it is not clear if the network engagement and connectivity differences reported here correspond to real-world moral decision making.

Conclusions

This study is a first step in understanding network dynamics during moral processing, both in typically functioning adults and in individuals with criminal histories and psychopathic traits. We found support for a three process neurobiological account of moral processing (i.e., fronto-cognitive, limbic-emotive, and temporoparietal – social contextual). We provided the first evidence that incarcerated individuals differ from community members on functional network connectivity and dynamism, and that psychopathy may be related to abnormal limbic, temporal, and basal ganglia network engagement during moral processing. By building on this study through longitudinal research and replication, we may be able to use functional network connectivity during moral processing as a biomarker for risk of criminality and target interventions to the relevant circuits.

References

Aharoni, Sinnott-Armstrong, W., & Kiehl, K. A. (2012). Can psychopathic offenders discern moral wrongs? A new look at the moral/conventional distinction. *J Abnorm Psychol, 121*(2), 484-497. doi: 10.1037/a0024796

Allen, Elena A, Damaraju, Eswar, Plis, Sergey M, Erhardt, Erik B, Eichele, Tom, & Calhoun, Vince D. (2012). Tracking whole-brain connectivity dynamics in the resting state. *Cerebral cortex*, bhs352.

Allen, Elena A, Erhardt, Erik B, Damaraju, Eswar, Gruner, William, Segall, Judith M, Silva, Rogers F, . . . Kalyanam, Ravi. (2011). A baseline for the multivariate comparison of resting-state networks. *Frontiers in systems neuroscience, 5*, 2.

Alterman, A.A., Cacciola, J.S., & Rutherford, M.J. (1993). Reliability of the revised psychopathy checklist in substance abuse patients. *Psychological Assessment, 5*, 442-448.

Anderson, David A. (2012). The Cost of Crime. *Foundations and Trends (R) in Microeconomics, 7*(3), 209-265.

Andreasen, Nancy C, Flaum, Michael, Swayze 2nd, V, O'Leary, Daniel S, Alliger, Randall, Cohen, Gregg, . . . Yuh, William T. (1993). Intelligence and brain structure in normal individuals. *The American journal of psychiatry, 150*(1), 130.

Blair, R. J. R. (1995). A Cognitive Developmental-Approach to Morality - Investigating the Psychopath. *Cognition, 57*(1), 1-29. doi: 10.1016/0010-0277(95)00676-P

Blair, R. J. R. (2007). The amygdala and ventromedial prefrontal cortex in morality and psychopathy. *Trends in cognitive sciences, 11*(9), 387-392. doi: 10.1016/j.tics.2007.07.003

Buuren, Stef, & Groothuis-Oudshoorn, Karin. (2011). mice: Multivariate imputation by chained equations in R. *Journal of statistical software, 45*(3).

Caceda, R., James, G. A., Ely, T. D., Snarey, J., & Kilts, C. D. (2011). Mode of effective connectivity within a putative neural network differentiates moral cognitions related to care and justice ethics. *PLoS One, 6*(2), e14730. doi: 10.1371/journal.pone.0014730

Caldwell, Brendan M, Harenski, Carla L, Harenski, Keith A, Fede, Samantha J, Steele, Vaughn R, Koenigs, Michael R, & Kiehl, Kent A. (2015). Abnormal frontostriatal activity in recently abstinent cocaine users during implicit moral processing. *Frontiers in human neuroscience, 9*.

Cale, Ellison M, & Lilienfeld, Scott O. (2002). Sex differences in psychopathy and antisocial personality disorder: A review and integration. *Clinical psychology review, 22*(8), 1179-1207.

Calhoun, VD. (2004). Group ICA of fMRI toolbox (GIFT). *Online at http://icatb. sourceforge. net*.

Calhoun, Vince D, Miller, Robyn, Pearlson, Godfrey, & Adalı, Tulay. (2014). The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. *Neuron, 84*(2), 262-274.

Carter, R McKell, & Huettel, Scott A. (2013). A nexus model of the temporal–parietal junction. *Trends in cognitive sciences, 17*(7), 328-336.

Cima, M., Tonnaer, F., & Hauser, M. D. (2010). Psychopaths know right from wrong but don't care. *Social cognitive and affective neuroscience, 5*(1), 59-67. doi: 10.1093/scan/nsp051

Cleckley, Hervey M. (1976). The mask of sanity: An attempt to clarify some issues about the so-called psychopathic personality: Mosby (St. Louis).

Cohn, Moran D., Pape, Louise E., Schmaal, Lianne, van den Brink, Wim, van Wingen, Guido, Vermeiren, Robert R. J. M., . . . Popma, Arne. (2015). Differential relations between juvenile psychopathic traits and resting state network connectivity. *Human Brain Mapping, 36*(6), 2396-2405. doi: 10.1002/hbm.22779

Colom, Roberto, Jung, Rex E., & Haier, Richard J. (2006). Distributed brain sites for the g-factor of intelligence. *NeuroImage, 31*(3), 1359-1365. doi: http://dx.doi.org/10.1016/j.neuroimage.2006.01.006

Cope, L. M., Ermer, E., Gaudet, L. M., Steele, V. R., Eckhardt, A. L., Arbabshirani, M. R., . . . Kiehl, K. A. (2014). Abnormal brain structure in youth who commit homicide. *Neuroimage Clin, 4*, 800-807. doi: 10.1016/j.nicl.2014.05.002

Damaraju, E, Allen, EA, Belger, A, Ford, JM, McEwen, S, Mathalon, DH, . . . Preda, A. (2014). Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia. *NeuroImage: Clinical, 5*, 298-308.

Decety, J., Michalska, K. J., & Kinzler, K. D. (2012). The contribution of emotion and cognition to moral sensitivity: a neurodevelopmental study. *Cereb Cortex, 22*(1), 209-220. doi: 10.1093/cercor/bhr111

Decety, Jean, & Cacioppo, Stephanie. (2012). The speed of morality: a high-density electrical neuroimaging study. *Journal of neurophysiology*, *108*(11), 3068-3072.

Fang, Xiangming, Brown, Derek S., Florence, Curtis S., & Mercy, James A. (2012). The economic burden of child maltreatment in the United States and implications for prevention. *Child Abuse & Neglect*, *36*(2), 156-165. doi: http://dx.doi.org/10.1016/j.chiabu.2011.10.006

Fede, Samantha J, Harenski, Carla L, Borg, Jana Schaich, Sinnott-Armstrong, Walter, Rao, Vikram, Caldwell, Brendan M, . . . Calhoun, Vince D. (2016). Abnormal fronto-limbic engagement in incarcerated stimulant users during moral processing. *Psychopharmacology*, *233*(17), 3077-3087.

Fede, Samantha J, Schaich Borg, Jana, Nyalakanti, Prashanth K, Harenski, Carla L, Cope, Lora M, Sinnott-Armstrong, Walter, . . . Kiehl, Kent A. (2016). Distinct neuronal patterns of positive and negative moral processing in psychopathy. *Cognitive, Affective, & Behavioral Neuroscience*, 1-12.

Freire, Luis, Roche, Alexis, & Mangin, J-F. (2002). What is the best similarity measure for motion correction in fMRI time series? *Medical Imaging, IEEE Transactions on*, *21*(5), 470-484.

Fukatsu, R, Fujii, T, Yamadori, A, Nagasawa, H, & Sakurai, Y. (1997). Persisting childish behavior after bilateral thalamic infarcts. *European neurology*, *37*(4), 230-235.

Glenn, A. L., Raine, A., & Schug, R. A. (2009). The neural correlates of moral decision-making in psychopathy. *Molecular psychiatry*, *14*(1), 5-6. doi: 10.1038/mp.2008.104

Greene, J. D., Nystrom, L. E., Engell, A. D., Darley, J. M., & Cohen, J. D. (2004). The neural bases of cognitive conflict and control in moral judgment. *Neuron*, *44*(2), 389-400. doi: 10.1016/j.neuron.2004.09.027

Haidt, Jonathan. (2001). The emotional dog and its rational tail: a social intuitionist approach to moral judgment. *Psychological review*, *108*(4), 814.

Haier, Richard J, Jung, Rex E, Yeo, Ronald A, Head, Kevin, & Alkire, Michael T. (2004). Structural brain variation and general intelligence. *Neuroimage*, *23*(1), 425-433.

Haier, Richard J, White, Nathan S, & Alkire, Michael T. (2003). Individual differences in general intelligence correlate with brain function during nonreasoning tasks. *Intelligence*, *31*(5), 429-441.

Hare, R.D. (2003). *Manual for the Hare Psychopathy Checklist-Revised* (2nd ed.). Toronto, CA: Multi-Health Systems.

Harenski, Edwards, Bethany G, Harenski, Keith A, & Kiehl, Kent A. (2014). Neural correlates of moral and non-moral emotion in female psychopathy. *Frontiers in human neuroscience, 8*.

Harenski, Harenski, K. A., Shane, M. S., & Kiehl, K. A. (2010). Aberrant neural processing of moral violations in criminal psychopaths. *Journal of abnormal psychology, 119*(4), 863-874. doi: 10.1037/a0020979

Helmkamp, James C, Townsend, Kitty J, & Sundra, Jenny A. (1997). How Much Does White Collar Crime Cost?

Hemphill, James F, Hart, Stephen D, & D. Hare, Robert. (1994). Psychopathy and substance use. *Journal of Personality Disorders, 8*(3), 169-180.

Hong, Simon, & Hikosaka, Okihide. (2008). The globus pallidus sends reward-related signals to the lateral habenula. *Neuron, 60*(4), 720-729.

Jafri, Madiha J, Pearlson, Godfrey D, Stevens, Michael, & Calhoun, Vince D. (2008). A method for functional network connectivity among spatially independent resting-state components in schizophrenia. *Neuroimage, 39*(4), 1666-1681.

Juárez, Michelle, Kiehl, Kent A, & Calhoun, Vince D. (2013). Intrinsic limbic and paralimbic networks are associated with criminal psychopathy. *Human brain mapping, 34*(8), 1921-1930.

Kiehl, K. A. (2006). A cognitive neuroscience perspective on psychopathy: Evidence for paralimbic system dysfunction. *Psychiatry research, 142*(2-3), 107-128. doi: 10.1016/j.psychres.2005.09.013

Kiehl, K.A. (2014). *The Psychopath Whisperer: The Science of Those Without Conscience*. United States of America: Crown.

Kiehl, K.A., & Hoffman, M.B. (2011). The criminal psychopath: history, neuroscience, treatment, and economics. *Section of Science & Technology Law: American Bar Association.*

Koenigs, Michael, Kruepke, Michael, Zeier, Joshua, & Newman, Joseph P. (2012). Utilitarian moral judgment in psychopathy. *Social Cognitive and Affective Neuroscience, 7*(6), 708-714. doi: 10.1093/scan/nsr048

Kohlberg, Lawrence. (1969). *Stage and sequence: The cognitive-developmental approach to socialization*: publisher not identified.

Krolak-Salmon, P., Henaff, M. A., Vighetto, A., Bertrand, O., & Mauguiere, F. (2004). Early amygdala reaction to fear spreading in occipital, temporal, and frontal cortex: a depth electrode ERP study in human. *Neuron, 42*(4), 665-676.

Kuhn, Max. (2008). Caret package. *Journal of Statistical Software, 28*(5), 1-26.

Kursa, Miron B, & Rudnicki, Witold R. (2010). Feature selection with the Boruta package: Journal.

Liaw, Andy, & Wiener, Matthew. (2002). Classification and regression by randomForest. *R news, 2*(3), 18-22.

Maddock, Richard J, Garrett, Amy S, & Buonocore, Michael H. (2003). Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. *Human brain mapping, 18*(1), 30-41.

Maldjian, J. A., Laurienti, P. J., & Burdette, J. H. (2004). Precentral gyrus discrepancy in electronic versions of the Talairach atlas. *Neuroimage, 21*(1), 450-455.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage, 19*(3), 1233-1239. doi: Doi 10.1016/S1053-8119(03)00169-1

Margulies, Daniel S, Kelly, AM Clare, Uddin, Lucina Q, Biswal, Bharat B, Castellanos, F Xavier, & Milham, Michael P. (2007). Mapping the functional connectivity of anterior cingulate cortex. *Neuroimage, 37*(2), 579-588.

Marsh, A. A., Finger, E. C., Fowler, K. A., Jurkowitz, I. T., Schechter, J. C., Yu, H. H., . . . Blair, R. J. (2011). Reduced amygdala-orbitofrontal connectivity during moral judgments in youths with disruptive behavior disorders and psychopathic traits. *Psychiatry Res, 194*(3), 279-286. doi: 10.1016/j.pscychresns.2011.07.008

Marusak, Hilary A, Thomason, Moriah E, Elrahal, Farrah, Peters, Craig A, Kundu, Prantik, Lombardo, Michael V, . . . Rabinak, Christine A. (2017). Mindfulness and dynamic functional neural connectivity in children and adolescents. *bioRxiv*. doi: 10.1101/106021

Mazaika, Paul K, Hoeft, Fumiko, Glover, GH, & Reiss, Allan L. (2009). Methods and software for fMRI analysis of clinical subjects. *NeuroImage, 47*, S58.

McCollister, Kathryn E., French, Michael T., & Fang, Hai. (2010). The Cost of Crime to Society: New Crime-Specific Estimates for Policy and Program Evaluation. *Drug and alcohol dependence, 108*(1-2), 98-109. doi: 10.1016/j.drugalcdep.2009.12.002

McDaniel, Michael A. (2005). Big-brained people are smarter: A meta-analysis of the relationship between in vivo brain volume and intelligence. *Intelligence, 33*(4), 337-346. doi: http://dx.doi.org/10.1016/j.intell.2004.11.005

Miller, Robyn L, Yaesoubi, Maziar, & Calhoun, Vince D. (2014). *Higher dimensional analysis shows reduced dynamism of time-varying network connectivity in schizophrenia patients.* Paper presented at the Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE.

Miller, Robyn L, Yaesoubi, Maziar, Turner, Jessica A, Mathalon, Daniel, Preda, Adrian, Pearlson, Godfrey, . . . Calhoun, Vince D. (2016). Higher dimensional meta-state analysis reveals reduced resting fMRI connectivity dynamism in schizophrenia patients. *PloS one, 11*(3), e0149849.

Moll, J., de Oliveira-Souza, R., & Eslinger, P. J. (2003). Morals and the human brain: a working model. *Neuroreport, 14*(3), 299-305. doi: 10.1097/01.wnr.0000057866.05120.28

Moll, J., de Oliveira-Souza, R., Eslinger, P. J., Bramati, I. E., Mourao-Miranda, J., Andreiuolo, P. A., & Pessoa, L. (2002). The neural correlates of moral sensitivity: a functional magnetic resonance imaging investigation of basic and moral emotions. *J Neurosci, 22*(7), 2730-2736. doi: 20026214

Moll, Jorge, Zahn, Roland, de Oliveira-Souza, Ricardo, Krueger, Frank, & Grafman, Jordan. (2005). The neural basis of human moral cognition. *Nature Reviews Neuroscience, 6*(10), 799-809.

Neumann, Craig S, & Hare, Robert D. (2008). Psychopathic traits in a large community sample: Links to violence, alcohol use, and intelligence. *Journal of consulting and clinical psychology, 76*(5), 893.

Ng, Andrew. (2017). Machine Learning: Week 7.

O'Kane, Aisling, Fawcett, Diane, & Blackburn, Ronald. (1996). Psychopathy and moral reasoning: Comparison of two classifications. *Personality and Individual Differences, 20*(4), 505-514.

Olson, Ingrid R, Plotzker, Alan, & Ezzyat, Youssef. (2007). The enigmatic temporal pole: a review of findings on social and emotional processing. *Brain, 130*(7), 1718-1731.

Psychological Software Tools. (2012). E-Prime (Version 2.0). Pittsburgh, PA: Psychological Software Tools.

R Core Team. (2016). R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from https://www.R-project.org

Schaich Borg, J., Sinnott-Armstrong, W., Calhoun, V. D., & Kiehl, K. A. (2011). Neural basis of moral verdict and moral deliberation. *Social neuroscience*, *6*(4), 398-413. doi: 10.1080/17470919.2011.559363

Schulte-Rüther, Martin, Markowitsch, Hans J, Shah, N Jon, Fink, Gereon R, & Piefke, Martina. (2008). Gender differences in brain networks supporting empathy. *Neuroimage*, *42*(1), 393-403.

Simon, B., Holzberg, J. D., & Unger, J. F. (1951). A study of judgment in the psychopathic personality. *The Psychiatric quarterly*, *25*(1), 132-150.

Smith, Stephen M., Fox, Peter T., Miller, Karla L., Glahn, David C., Fox, P. Mickle, Mackay, Clare E., . . . Beckmann, Christian F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences*, *106*(31), 13040-13045. doi: 10.1073/pnas.0905267106

Song, Jie, Birn, Rasmus M, Boly, Mélanie, Meier, Timothy B, Nair, Veena A, Meyerand, Mary E, & Prabhakaran, Vivek. (2014). Age-related reorganizational changes in modularity and functional connectivity of human brain networks. *Brain connectivity*, *4*(9), 662-676.

Supekar, Kaustubh, Menon, Vinod, Rubin, Daniel, Musen, Mark, & Greicius, Michael D. (2008). Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Comput Biol*, *4*(6), e1000100.

Swanson, N., & Calhoun, V. (2009). FNC Toolbox.

Vogt, Brent A, Finch, David M, & Olson, Carl R. (1992). Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cerebral cortex*, *2*(6), 435-443.

Wager, Tor D, Phan, K Luan, Liberzon, Israel, & Taylor, Stephan F. (2003). Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. *Neuroimage*, *19*(3), 513-531.

Woolsey, Thomas A, Hanaway, Joseph, & Gado, Mokhtar H. (2013). *The brain atlas: a visual guide to the human central nervous system*: John Wiley & Sons.

Yin, Henry H, Ostlund, Sean B, & Balleine, Bernard W. (2008). Reward-guided learning beyond dopamine in the nucleus accumbens: The integrative functions of cortico-basal ganglia networks. *European Journal of Neuroscience, 28*(8), 1437-1448.

Young, Liane, Koenigs, Michael, Kruepke, Michael, & Newman, Joseph P. (2012). Psychopathy increases perceived moral permissibility of accidents. *Journal of Abnormal Psychology, 121*(3), 659-667. doi: 10.1037/a0027489