Functional Connectivity Between Anterior Insula and Key Nodes of Frontoparietal Executive Control and Salience Networks Distinguish Bipolar Depression From Unipolar Depression and Healthy Controls

Supplemental Information

Description of Parent Study Participant Selection

Procedures for all three parent studies were reviewed and approved by The Partners Healthcare Human Research Committee Institutional Review Board. All subjects had decisional capacity and provided informed consent before beginning any study procedures.

Mechanisms of Action of Electroconvulsive Therapy (ECT) Study. This project aims to use functional connectivity MRI (fcMRI) to determine the therapeutic antidepressant mechanism of action of ECT at the circuit level. Patients were recruited through the Massachusetts General Hospital (MGH) and McLean Hospital inpatient and outpatient ECT clinical services. Inclusion criteria were: 1) males and females between the ages of 18-80, 2) DSM-IV diagnosis of Depressive Episode; 3) patients requiring ECT treatment as part of their psychiatric care; 4) right-hand dominance; (5) English speaking. Exclusion criteria were: 1) comorbid DSM-IV primary diagnoses of major depressive disorder with psychotic features, schizoaffective disorder, schizophrenia or dementia; 2) substance use disorder (abuse or dependence) with active use within the last 6 months; 3) severe or unstable medical illness, including medical contraindication to anesthesia or to ECT (i.e. recent myocardial infarction, increased intracranial pressure); 4) MRI contraindications as determined by MGH department of radiology. Comorbid anxiety disorders (generalized anxiety disorder, panic disorder, social anxiety) were allowed as long as they are not the primary diagnosis. Concomitant, ongoing stable doses of antidepressant medications were also allowed.

Mechanisms of Action of Transcranial Magnetic Stimulation (TMS) Study. This project aims to use fcMRI to determine the therapeutic antidepressant mechanism of action of TMS at the circuit level. Patients were recruited through the MGH Transcranial Magnetic Stimulation (TMS) clinical service.

Inclusion criteria were: 1) males and females between the ages of 18-80, 2) DSM-IV diagnosis of Depressive Episode; 3) patients requiring TMS treatment as part of their psychiatric care; 4) right-hand dominance; 5) English speaking. Exclusion criteria were: 1) comorbid DSM-IV primary diagnoses of major depressive disorder with psychotic features, schizoaffective disorder, schizophrenia or dementia; 2) substance use disorder (abuse or dependence) with active use within the last 6 months; 3) history of seizure disorder, unstable medical illness, or any neurological disease; (4) MRI contraindications as determined by MGH department of radiology. Comorbid anxiety disorders (generalized anxiety disorder, panic disorder, social anxiety) were allowed as long as they are not the primary diagnosis. Concomitant, ongoing stable doses of antidepressant medications were also allowed.

Transdiagnostic Cognitive Behavioral Therapy for Bipolar Disorder and Anxiety (CBT) Study. This project aims to investigate the feasibility, acceptability, and preliminary efficacy of a transdiagnostic CBT treatment for bipolar disorder with comorbid anxiety disorders, using fcMRI to identify neural predictors of treatment response. Patients were recruited through the MGH bipolar clinical research program. Inclusion criteria were: 1) males and females between the ages of 18-65; 2) DSM-IV diagnosis of bipolar disorder; 3) DSM-IV diagnosis of at least one anxiety disorder (generalized anxiety disorder, panic disorder, or social phobia); 4) at least 3 months of stability on current dosage(s) of medication(s); 5) English speaking; 6) right hand dominance. Exclusion criteria were: 1) DSM-IV diagnosis of current mania, major depressive disorder, psychotic disorder; schizoaffective disorder, schizophrenia or dementia; 2) current active suicidal ideation; 3) substance use disorder (abuse or dependence) with active use within the last 6 months; 4) history of seizure disorder, unstable medical illness, or any neurological disease; 5) MRI contraindications as determined by MGH department of radiology; 6) ECT within the six months preceding the study.

MRI Studies of Folate-Related Genes, Diet, and Development (GDD) Study. This study aims to examine how blood folate level influences frontoparietal control network (FPCN) structure and function. Healthy subjects were recruited from the community through local advertisements and Partners Healthcare electronic resources. Inclusion criteria were: 1) males and females between the ages of 18-35;

2) right-hand dominance; 3) English speaking. Exclusion criteria were: 1) current or past DSM-IV Axis I psychiatric disorder (as determined by the SCID-NP); 2) current use of psychotropic medications, 3) major medical or neurological condition that in the opinion of the Principal Investigator would potentially influence MRI results, and 4) contraindication to MRI scanning.

Additional Methods

Inclusion and Exclusion Criteria

Patients meeting a diagnosis of unipolar or bipolar depression on a stabilized medication regimen were included. Presence or absence of psychiatric diagnoses were confirmed as part of parent study protocols using the Mini International Neuropsychiatric Interview 6.0 (1) (TMS, ECT studies) or the Structured Clinical Interview for DSM-IV (2) (CBT study, healthy controls) conducted by doctoral-level licensed clinicians, or by certified raters under the supervision of a doctoral-level licensed clinician. Patient samples were further assessed for depression severity using the Hamilton Depression Rating Scale (HAM-D-17) (3). Patients with a comorbid primary diagnosis of schizoaffective disorder, schizophrenia, psychotic disorders, dementia, or substance use disorder with active use in last three months were excluded. Healthy control subjects had no current or lifetime history of psychiatric disorders and were not taking psychoactive medications. Exclusion criteria for all subjects across protocols included history of seizure disorder, unstable medical illness, or any neurological disease, and MRI contraindications.

Description of Clinical Measures

Mini International Neuropsychiatric Interview (MINI; (1)). The MINI is a structured interview, administered by a trained rater that assesses for current Axis I diagnoses, exploring lifetime diagnoses where clinically relevant (i.e., previous manic episode for a diagnosis of bipolar disorder). Diagnoses can be ruled out by answering no to one or two screening questions. Positive responses to screening questions are followed by further exploration of other diagnostic criteria. The MINI shows good specificity and sensitivity for most psychiatric diagnoses and concordance with other structured diagnostic interviews.

Structured Clinical Interview for DSM-IV (SCID-IV; (2)). The SCID-IV is a semi-structured clinical interview used to diagnose and document the major axis I disorders of adolescents and adults according to DSM-IV criteria set by the APA. It assesses both current and lifetime symptoms, as well as subclinical presentations. The SCID-IV has demonstrated good reliability and validity (2).

Hamilton Depression Rating Scale (HAM-D-17; (3)). The HAM-D-17 is a well-established clinician-rated structured interview designed to assess current symptoms of depression. It exhibits high reliability and validity, recently re-evaluated in a large meta-analysis (4).

Affective Control Scale (ACS; (5)). The ACS is a 42-item self-report measure designed to assess perceived controllability of emotions and fear of loss of control when experiencing strong affective states. ACS subscales expand on the construct of fear of fear, including fear of anxiety, fear of depression, fear of anger, and fear of strong positive affective states. The ACS has demonstrated acceptable internal consistency, test-retest reliability, and concurrent and divergent validity (5, 6).

Behavioral Inhibition System / Behavioral Activation System Scales (BIS/BAS; (7)). The BIS/BAS was developed to measure behavioral inhibition (negative reactivity to aversive events) and behavioral activation (responsiveness to positive incentives and motivation and drive towards reward). It is comprised of 20 items with a 4-point Likert -type scale (1 = quite untrue of you; 4 = quite true of you). Four subscales are derived consisting of Behavioral Inhibition (BIS), Reward Responsiveness (BAS-Reward), Drive (BAS-Drive) and Fun Seeking (BAS-Fun). The BIS/BAS has demonstrated good reliability and convergent validity in clinical samples, and the original factor structure (7) was replicated in patients with anxiety and mood disorders (8).

MRI Acquisition

All subjects included in this study were scanned using a single scanner and identical scanning protocol. Images were collected on a 3-Tesla Siemens Skyra MRI scanner (Siemens Healthcare, Malvern, PA, USA). Structural data was acquired with an anatomical T1-weighted multi-echo magnetization prepared rapid gradient-echo sequence with parameters: Repetition time (TR) = 2530ms, echo time (TE) = 1.69ms,

inversion time (TI) = 1100ms, flip angle = 7.0°, number of excitations = 1, slice thickness = 1mm, field of view (FoV) = 256mm, in-plane resolution = 1.0 x 1.0mm, and a matrix of 256 x 256. Resting-state BOLD data was collected with a whole-brain echoplanar imaging sequence with the following parameters: TR = 3000ms, TE= 30ms, flip angle = 85°, slice thickness = 3.0mm, in-plane resolution = 3.0 x 3.0mm, FoV = 216mm. Subjects were instructed to keep eyes open and try to stay focused passively on a fixation cross displayed behind them during the resting-state scan (white cross on black background).

Data Preprocessing

MRI preprocessing and first level analyses were carried out with a combination of tools from FSL v5.0.4 (FMRIB, Oxford, UK) and SPM2 (Wellcome Department of Cognitive Neurology, London, UK) using in-house scripts as previously described in Van Dijk et al. 2010 (9). The following steps were completed: the first four volumes were dropped to allow for T1 equilibration effects, correction for slice-dependent time shifts was done using SPM2, six degree-of-freedom rigid body translation and rotation were used to correct for head motion using FSL, spatial normalization to the Montreal Neurological Institute (MNI) atlas space, resampling to 2mm isotropic voxels, spatial smoothing using a 6mm full-width at half-maximum (FWHM) Gaussian kernel, and band-pass temporal filtering between 0.01 and 0.08 Hz. Sources of spurious variance and their first temporal derivatives were removed with linear regression: six parameters derived from the rigid-body head motion correction, the signal averaged over the entire brain (global signal), the signal averaged over an area within the deep cerebral white matter, and the signal averaged over the lateral ventricles. The residual BOLD time-courses were retained for functional connectivity analysis.

Insula Seed Region Selection

Anterior insula (AI) seed regions of interest (ROI) were defined using masks from the Kelly et al. (2012)(10) three-cluster solution derived using task-evoked coactivation, intrinsic functional connectivity, and grey matter structural covariance (see Kelly et al., 2012 for details). Clusters included bilateral 2mm

spherical masks from dorsal and ventral mid anterior insula (available for download at http://fcon_1000.projects.nitrc.org).

Additional Discussion

VLPFC and DMN Findings

In the current study, bipolar disorder patients evidenced weaker right dorsal anterior insula functional connectivity with the right VLPFC relative to healthy controls, although this finding is tentative at uncorrected significance. Multiple studies have shown dysfunctional recruitment of the VLPFC during emotion regulation in bipolar disorder. Neuroimaging studies of individuals with bipolar disorder consistently point to hypoactivation of bilateral VLPFC coupled with hyperactivation of limbic structures in the context of emotion processing, as well as aberrant amygdala-VLPFC functional connectivity (11-18) .

Decreased VLPFC activation and corresponding increased amygdala activation has been demonstrated during emotion regulation using cognitive reappraisal in euthymic BD patients (13). Decreased VLPFC activation, and corresponding increased amygdala activation, has also been demonstrated during performance on emotional Stroop and affect labeling tasks (12, 15, 19, 20). Several studies have shown increased functional connectivity between amygdala and VLPFC during emotion regulation and at rest, suggesting inefficient downregulation of amygdala by VLPFC (16, 17). Our findings (weaker functional connectivity between the right dorsal AI and right VLPFC), although tentative given trend wise significance after correction, suggest bipolar depression may be associated with a functional disruption in a key neural pathway by which the VLPFC exerts regulatory control over amygdala responses. Thus, disrupted functional connectivity between the AI, VLPFC and the broader neurocircuitry supporting emotion regulation may also play a key role in the severe emotion dysregulation seen in bipolar disorder.

Unipolar depression showed significantly stronger left dorsal AI-DMN (bilateral vmPFC) and weaker left dorsal AI-SN (left VLPFC) functional connectivity relative to healthy controls, although these

findings are again tentative at uncorrected significance. Greater recruitment of DMN in depression has been found in several studies, and is associated with increased negative self-rumination and a sense of being "locked-inside" oneself (21-24). Stronger AI-DMN functional connectivity and weaker AI-SN functional connectivity may be associated with deficits in regulating away from internally focused processing and decreased salience processing. Difficulties switching out of default mode processing may occur to the detriment of the external-focused processing necessary for behavioral motivation and activation, contributing to the sense of amotivation and blunted affect seen in depression. Further, reduced AI-SN functional connectivity in unipolar depression may underlie alexithymia or the inability to label current emotional experiences. Specifically, if patients cannot integrate interoceptive somatosensory signals with a sense of self, this may manifest as alexithymia and lead to maladaptive regulation strategies. Given the trend-wise significance of these findings in the current study, further studies of AI-DMN and AI-SN functional connectivity in unipolar depression are needed to replicate or clarify the results reported here.

Dimensional Findings in AI-VLPFC Connectivity

AI-VLPFC functional connectivity was not a significant classifier of bipolar versus unipolar depression. Indeed, no significant differences in AI-VLPFC functional connectivity were found between bipolar and unipolar patients, or unipolar and healthy controls. However, although no significant differences in this signature classified clinical syndromes categorically, differential relationships of this connectivity to psychological dimensions of behavioral inhibition were found. Specifically, bipolar disorder patients showed a negative relationship between right AI-VLPFC connectivity and behavioral inhibition, with weaker connectivity associated with *more* inhibition, whereas unipolar patients showed a positive relationship with weaker connectivity associated with *less* inhibition (Figure 6). These findings suggest the adaptive nature of weak AI-VLPFC connectivity in the right hemisphere: it is associated with *more inhibition in bipolar patients* who suffer from disinhibition, but also with *less inhibition in unipolar patients* who are excessively withdrawn. These findings show that weak right AI-VLPFC connectivity is

not associated with more or less inhibition, but suggest it is linked with the flexible allostatic modulation of these systems, leading to adaptive behaviors different from the rigid "locked in" states (i.e. disinhibition or withdrawal independent of internal or external input) that characterize mood disorders. In line with these findings, a positive relationship between ventral AI-VLPFC functional connectivity and depression symptom severity was found in bipolar patients only, so that stronger connectivity reflected greater depression severity. Future studies examining whole brain connectivity differences may help elucidate disorder-specific functions of this connectivity on a network-wide level. For example, understanding the interaction of the anterior insula, IPL and VLPFC may shed light on these disparities.

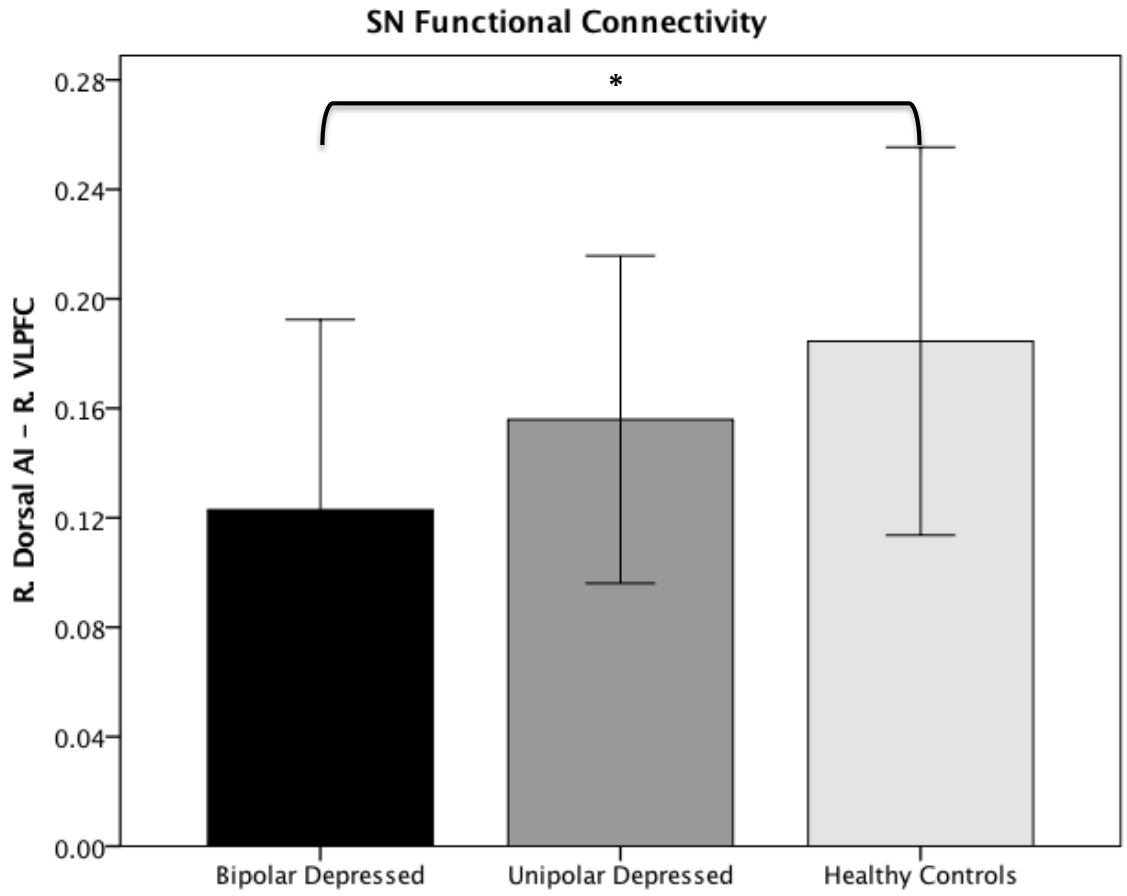
Supplemental Tables and Figures

Table S1. Partial correlations between anterior insula-functional network connectivity and clinical dimensions.

			Bipolar Depressed			Unipolar Depressed			All Depressed		
Measure	**Fx Network**	**Target ROI**	***r***	***p***	**95% C.I.[a] Lower, Upper**	***r***	***p***	**95% C.I.[a] Lower, Upper**	***r***	***p***	**95% C.I.[a] Lower, Upper**
ACS											
	ECN	**L. IPL**	0.41	0.41	-0.84, 0.80	**-0.37***	**0.05**	**-0.68, -0.02**	**-0.34**	**0.02**	**-0.59, -0.01**
		R. IPL	0.14	0.57	-0.58, 0.71	-0.18	0.37	-0.57, 0.25	-0.08	0.58	-0.35, 0.19
		L. DLPFC	0.07	0.77	-0.55, 0.60	0.07	0.71	-0.39, 0.53	-0.01	0.96	-0.24, 0.22
		R. DLPFC	-0.13	0.60	-0.64, 0.40	0.45	0.02	0.08, 0.72	0.06	0.70	-0.23, 0.31
	SN	L. VLPFC	0.16	0.52	-0.42, 0.61	0.31	0.11	-0.04, 0.59	0.16	0.25	-0.07, 0.39
		R. VLPFC	-0.04	0.87	-0.50, 0.36	**0.39***	**0.04**	**0.04, 0.64**	0.14	0.32	-0.10, 0.36
		L. dACC	0.28	0.25	-0.37, 0.66	0.09	0.64	-0.28, 0.51	0.18	0.19	-0.11, 0.43
		R. dACC	0.08	0.74	-0.52, 0.51	0.15	0.44	-0.22, 0.51	0.11	0.46	-0.19, 0.38
	DMN	L. PCC	-0.24	0.32	-0.67, 0.24	-0.24	0.22	-0.73, 0.43	-0.05	0.70	-0.30, 0.23
		R.PCC	-0.24	0.32	-0.66, 0.28	-0.06	0.78	-0.56, 0.43	-0.04	0.79	-0.31, 0.26
		L. vmPFC	-0.15	0.55	-0.62, 0.42	-0.30	0.13	-0.71, 0.37	-0.19	0.18	-0.48, 0.13
		R. vmPFC	-0.16	0.51	-0.63, 0.43	-0.25	0.21	-0.69, 0.38	-0.18	0.19	-0.47, 0.13
BIS											
	ECN	L. IPL	0.03	0.91	-0.46, 0.70	-0.05	0.82	-0.36, 0.40	-0.14	0.33	-0.36, 0.09
		R. IPL	-0.02	0.94	-0.50, 0.71	0.30	0.12	-0.32, 0.66	0.07	0.61	-0.19, 0.34
		L. DLPFC	-0.16	0.52	-0.61, 0.53	0.38	0.05	-0.15, 0.70	-0.01	0.93	-0.32, 0.32
		R. DLPFC	-0.39	0.10	-0.82, 0.35	0.30	0.12	-0.25, 0.67	-0.13	0.37	-0.43, 0.27
	SN	**L. VLPFC**	-0.05	0.84	-0.59, 0.66	**0.50***	**0.01**	**0.75, 0.55**	0.13	0.35	-0.14, 0.44
		R. VLPFC	**-0.56***	**0.01**	**-0.85, -0.02**	**0.55****	**0.002**	**0.01, 0.81**	-0.09	0.53	-0.49, 0.42
		L. dACC	-0.58	0.01	-0.86, 0.06	0.05	0.81	-0.29, 0.39	-0.22	0.12	-0.54, 0.21
		R. dACC	**-0.62****	**0.004**	**-0.86, -0.12**	0.25	0.20	-0.07, 0.59	-0.19	0.17	-0.51, 0.24
	DMN	**L. PCC**	**0.53***	**0.02**	**0.04, 0.88**	-0.06	0.77	-0.45, 0.29	**0.35***	**0.01**	**0.09, 0.52**
		R.PCC	0.39	0.10	-0.19, 0.91	-0.08	0.70	-0.44, 0.25	0.26	0.07	0.032, 0.43
		L. vmPFC	0.27	0.27	-0.11, 0.68	0.08	0.69	-0.37, 0.42	0.19	0.17	-0.07, 0.40
		R. vmPFC	0.31	0.19	-0.07, 0.72	0.11	0.57	-0.37, 0.46	0.21	0.14	-0.05, 0.41
BAS Reward											
	ECN	**L. IPL**	0.09	0.72	-0.41, 0.44	**-0.45***	**0.02**	**-0.73, -0.03**	**-0.43****	**0.001**	**-0.63, -0.19**
		R. IPL	-0.17	0.50	-0.65, 0.43	-0.22	0.26	-0.65, 0.28	-0.29	0.04	-0.60, 0.11
		L. DLPFC	-0.29	0.22	-0.74, 0.40	0.19	0.33	-0.24, 0.55	-0.06	0.69	-0.34, 0.19
		R. DLPFC	0.16	0.52	-0.40, 0.66	-0.13	0.50	-0.45, 0.22	-0.11	0.42	-0.37, 0.17
	SN	L. VLPFC	-0.27	0.27	-0.70, 0.32	0.13	0.51	-0.27, 0.47	0.00	0.98	-0.29, 0.26
		R. VLPFC	-0.22	0.37	-0.73, 0.37	-0.10	0.60	-0.54, 0.31	-0.22	0.12	-0.52, 0.07
		L. dACC	0.06	0.82	-0.52, 0.69	-0.25	0.21	-0.58, 0.05	-0.01	0.94	-0.33, 0.28
		R. dACC	0.10	0.68	-0.46, 0.66	-0.20	0.32	-0.53, 0.08	-0.01	0.97	-0.29, 0.28
	DMN	L. PCC	-0.14	0.58	-0.51, 0.24	0.09	0.63	-0.34, 0.55	0.00	0.99	-0.28, 0.31
		R.PCC	-0.05	0.83	-0.52, 0.36	-0.15	0.46	-0.55, 0.36	-0.01	0.97	-0.28, 0.24
		L. vmPFC	-0.24	0.33	-0.59, 0.13	0.07	0.73	-0.36, 0.46	-0.13	0.34	-0.44, 0.20
		R. vmPFC	-0.21	0.39	-0.56, 0.17	0.08	0.70	-0.38, 0.50	-0.01	0.95	-0.30, 0.25

Note: [a]Bias-corrected accelerated CIs using iterative bootstrap methods (resample and replace). ACS = Affective Control Scale, a measure of perceived control over emotional experiences; BIS = Behavioral Inhibition Scale which measures inhibition and avoidance; BAS Reward = Behavioral Activation – Reward scale, a measure of responsivity to reward.

a)


SN Functional Connectivity
*
R. Dorsal AI – R. VLPFC
0.28
0.24
0.20
0.16
0.12
0.08
0.04
0.00
Bipolar Depressed
Unipolar Depressed
Healthy Controls

b)

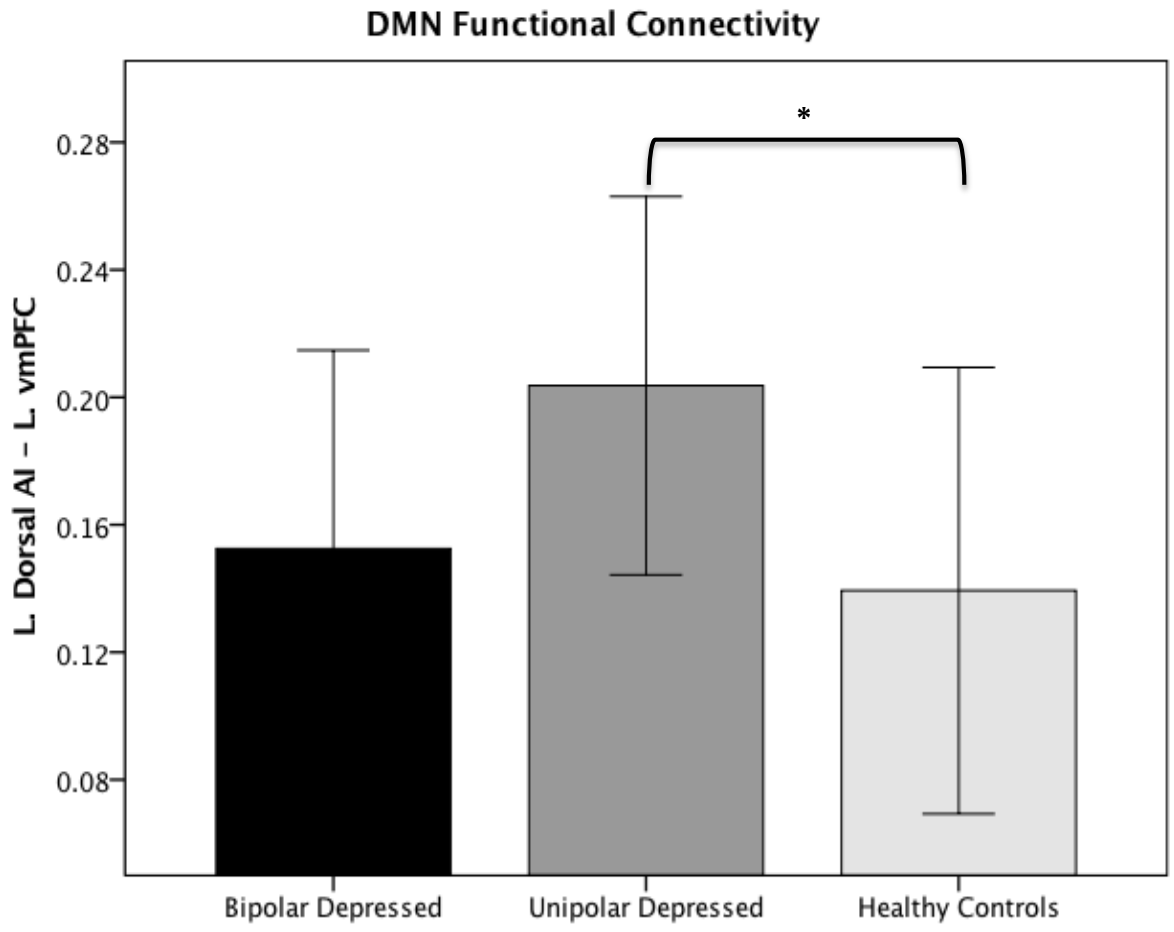


Figure S1. Functional connectivity differences between (a) right dorsal anterior insula and right VLPFC of the SN; (b) left dorsal anterior insula and left vmPFC ROI of the DMN. *p<.05 uncorrected.

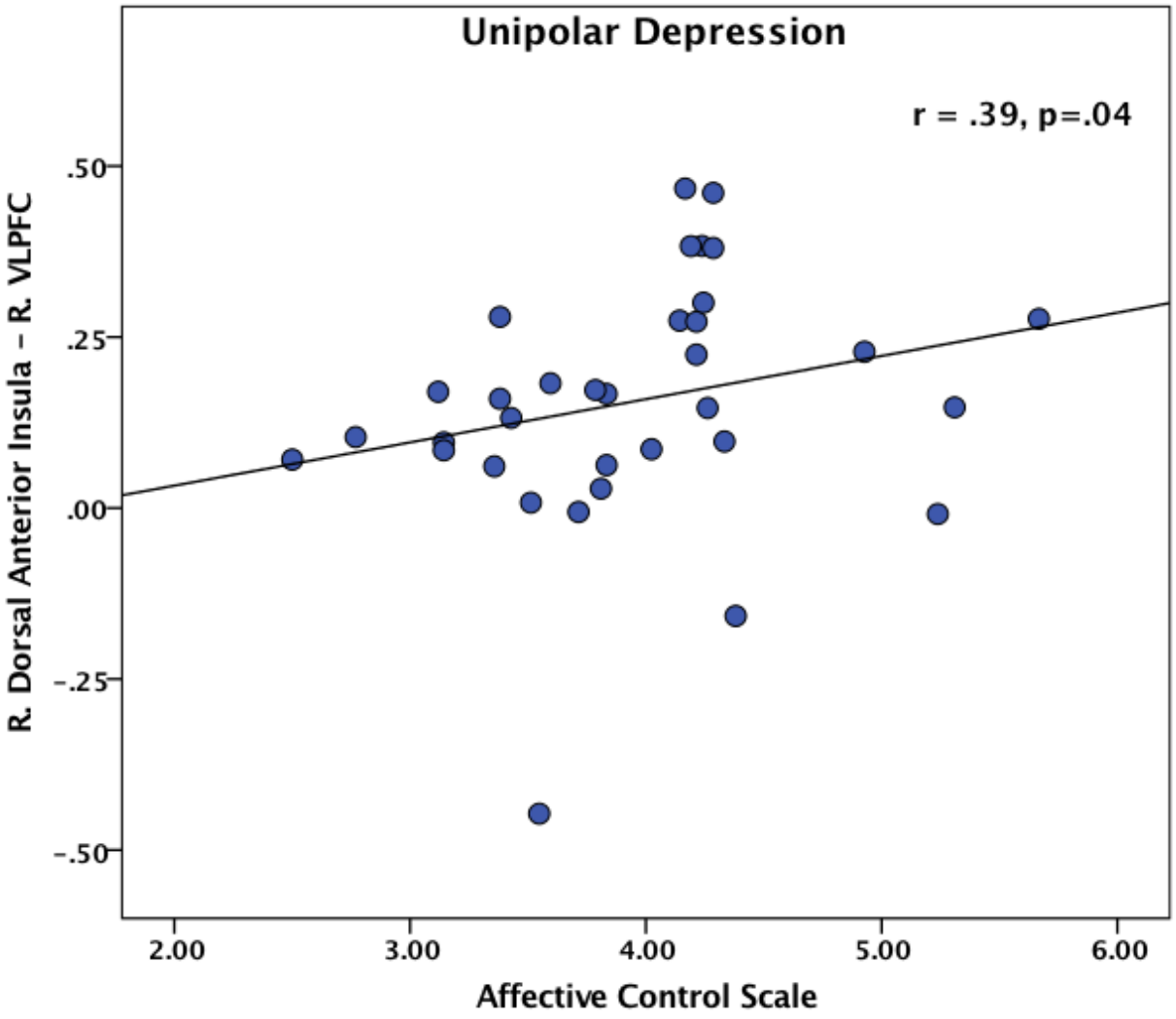
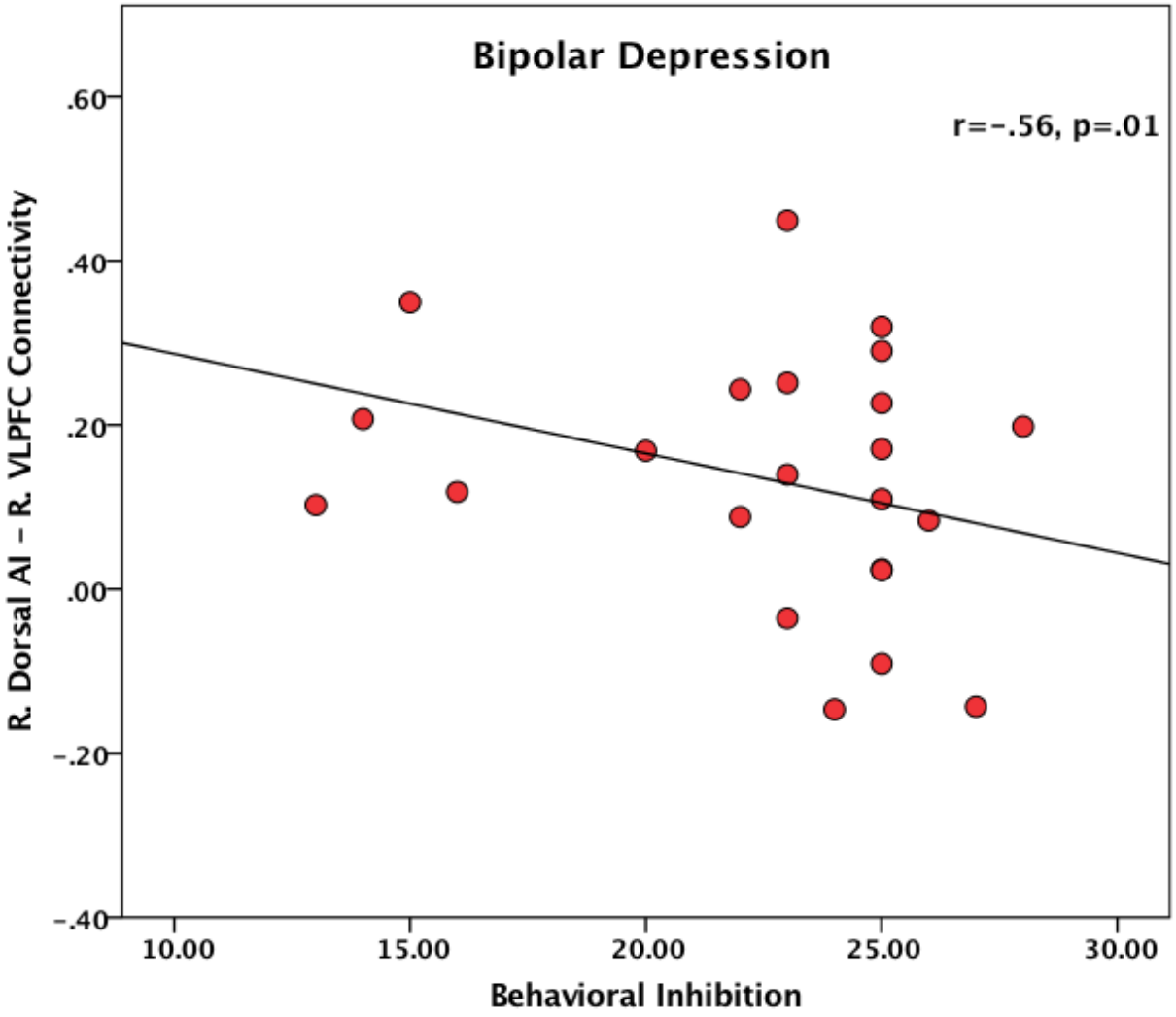


Figure S2. Partial correlation between perceived emotion control (ACS) and right dorsal AI – right VLPFC (SN) functional connectivity strength in unipolar depressed patients. Higher scores on the ACS reflect greater impairment in emotion control.

(a)


Bipolar Depression
r=-.56, p=.01
R. Dorsal AI – R. VLPFC Connectivity
.60
.40
.20
.00
-.20
-.40
10.00
15.00
20.00
25.00
30.00
Behavioral Inhibition

(b)

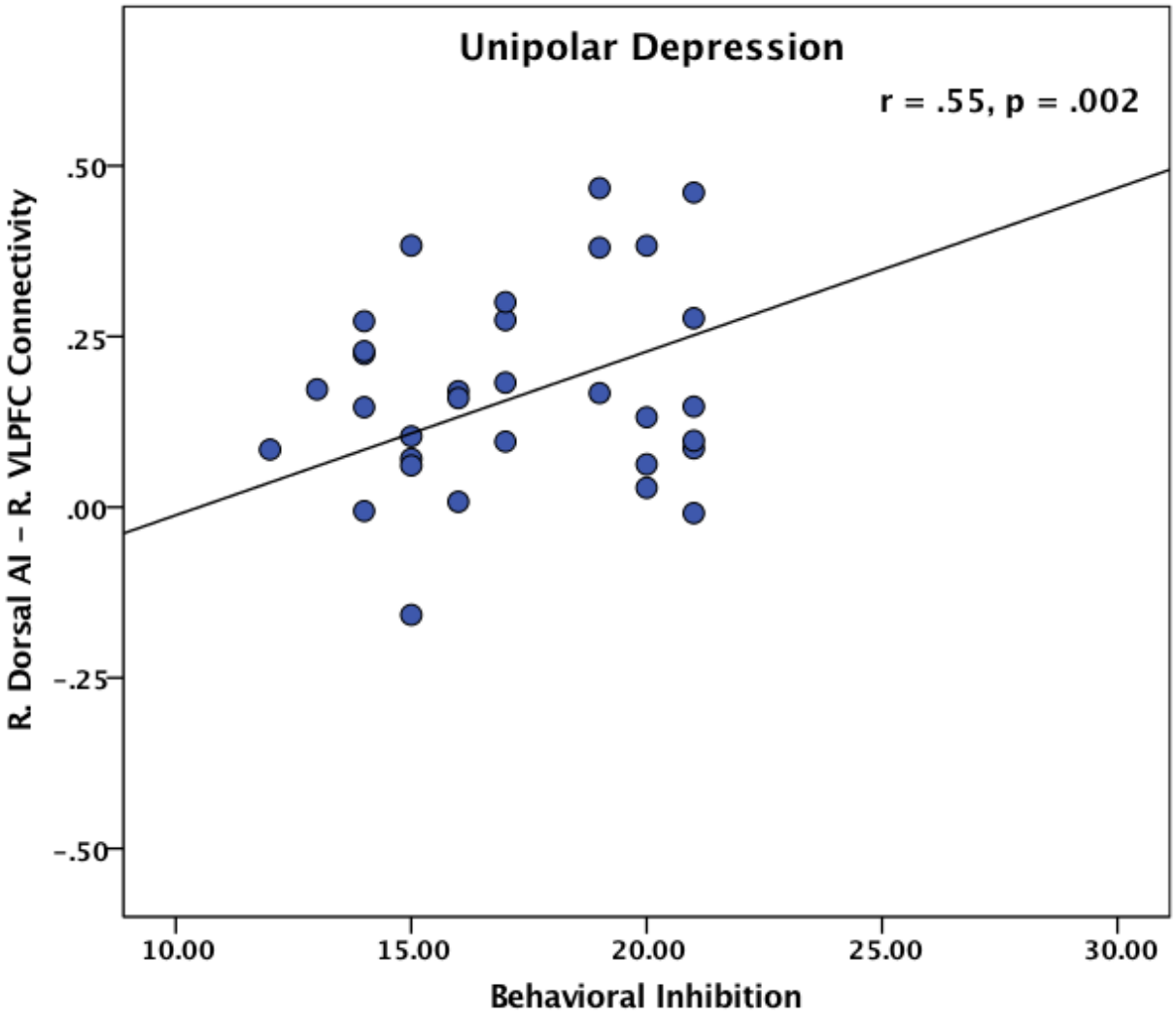


Figure S3. Differential partial correlation between right dorsal AI – right VLPFC and levels of behavioral inhibition in (a) bipolar depression versus (b) unipolar depression.

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