Data supplement for Sharma et al., Connectome-Wide Analysis Reveals Common Dimensional Reward Deficits Across Mood and Psychotic Disorders. Am J Psychiatry (doi: 10.1176/appi.ajp.2016.16070774)

Supplementary Materials

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Supplementary Methods

Sample construction and exclusionary criteria

Subjects were excluded if they had a history of substance abuse or dependence in the past six months or a positive urine drug screen on the day of the study. Subjects were also excluded if they had absent or invariant responses to BAS questionnaire items (n=5), if resting state data was not acquired (n=1), if clinical data was distant from the day of scan (>12 days, n=2), if they lacked adequate functional image coverage (n=1), or if elevated in-scanner motion during the functional image acquisition was present (defined as mean relative displacement exceeding 0.3 mm, n=10) (1).

The final sample included 32 subjects with a current episode of major depression, 50 subjects with bipolar disorder [75% depressed, 10% hypomanic/manic, 7.5% euthymic, 7.5% mixed], 51 subjects with a psychotic disorder [92% schizophrenia, 6% schizoaffective disorder-depressed type, 2% schizophreniform], 39 subjects with psychosis risk [52% first-degree family members, 48% clinical high risk] and 53 healthy comparators. Clinical high risk status was determined as in our previous studies (2), i.e., a Scale of Prodromal Symptoms rating of 3 or higher on >=1 positive symptom or >=2 negative/disorganized symptoms occurring within the past 6 months.

BIS/BAS Factor Analysis

As prior work documents relevant heterogeneity within the BIS-BAS scale including a BAS Reward subdomain, we conducted an exploratory factor analysis (EFA) of the item-level BIS/BAS data. The rationale for running the EFA was to determine whether the previously generated BIS-BAS factors from a sample of healthy, college-

aged adults could be replicated in a population with diverse psychopathology. The analysis was conducted using the irt.fa() function in the *psych* package (3) in R (4). Because the items were treated as ordinal rather than continuous, the correlation matrix input to the EFA comprised polychoric correlations. The (default) least squares extraction method with oblimin rotation was used. The optimal number of factors to extract was determined by parallel analysis, which compares the scree plot of eigenvalues to the eigenvalues of randomly generated data of the same dimensions (5). The two-, three- and four-factor solutions were also examined for interpretability. Both parallel analysis and interpretability supported the four-factor solution, which composed previously identified BIS-BAS subdomains including: 1) BIS, 2) BAS Drive, 3) BAS Fun and 4) BAS Reward (see **Table S2**).

Assessments with Disorder-Specific Disease Severity Measures

In order to investigate how our findings might relate to disorder-specific disease severity measures; we administered the Beck Depression Inventory (BDI) (6) and the Clinical Assessment Interview for Negative Symptoms (CAINS) (7). These scales were chosen as they have previously been utilized to measure disease severity in depression and schizophrenia respectively. In addition, in order to investigate non-specific effects such as scanning-related anxiety; we administered the state subscale of the State-Trait Anxiety Index (STAI-S) (8).

Image Acquisition

All data were acquired on the same scanner (Siemens Tim Trio 3 Tesla, Erlangen, Germany; 32 channel head coil) using the same imaging sequences. Resting-state blood oxygen level dependent (BOLD) fMRI was acquired using a whole-brain, single-shot, multi-slice, gradient-echo (GE) echoplanar (EPI) sequence with the following parameters: 124 volumes, TR 3000 ms, TE 30 ms, flip angle 85°, FOV 192x192mm, matrix 72X72, slice thickness/gap 3mm/0mm, effective voxel resolution 3.0x3.0x3.0mm. Prior to functional time-series acquisition, a magnetization-prepared, rapid acquisition gradient-echo (MPRAGE) T1-weighted image was acquired to aid spatial normalization to standard atlas space, using the following parameters: TR 1810 ms, TE 3.51 ms, FOV 1192x256mm, matrix 256x192, 160 slices, TI 1100 ms, flip angle 9 degrees, effective voxel resolution of 0.9x0.9x1mm. Additionally, a B0 field map was acquired for application of distortion correction procedures, using a double-echo gradient recall echo (GRE) sequence: TR 1000 ms, TE1 2.69 ms, TE2 5.27 ms, 44 slices, slice thickness 4mm, FOV=240mm, flip angle 60 degrees, effective voxel resolution of 3.8x3.8x4mm.

In order to further minimize motion, subjects were stabilized with the head coil using one foam pad over each ear and a third over the top of the head. During the resting-state scan, a fixation cross was displayed as images were acquired. Participants were instructed to stay awake, keep their eyes open, fixate on the displayed crosshair, and remain still.

Subject-level time series processing

Time series data was processed using a validated confound regression procedure that has been optimized to reduce the influence of subject motion (9). The first 4 volumes of the resting functional time series were removed to allow signal stabilization, leaving 120 volumes for subsequent analysis. The time series were distortion-corrected, slice-time corrected, skull-stripped, realigned, and spatially smoothed at 6mm FWHM. Functional time series were band-pass filtered to retain frequencies between 0.01-0.08 Hz. Functional images were re-aligned using MCFLIRT (10). Mean white matter (WM) and cerebrospinal fluid (CSF) signals were extracted from the filtered time series data using tissue segments generated for each subject. Prior to confound regression, all motion parameters and confound time courses were band-pass filtered in an identical fashion as the time series data itself in order to prevent frequency mismatching and allow the confound parameters to best fit the retained signal frequencies (11). Improved confound regression included 9 standard confound signals (6 motions parameters + global/ WM/ CSF) as well as the temporal derivative, quadratic term, and the temporal derivative of the quadratic (36 parameters total).

Image registration

The T1 image was skull stripped using FSL BET (12), bias corrected using multiplicative intrinsic component optimization (13) and registered to the Montreal Neurological Institute (MNI) template using a highly accurate deformable registration with attribute matching and mutual salience weighting (14). Processed subject-level BOLD images were co-registered to the T1 image using boundary-based registration

(15) with integrated distortion correction as implemented in FSL 5. All registrations were inspected manually and also evaluated for accuracy using spatial correlations. As in Shehzad et al., (2014), for computational feasibility, standard-space voxelwise time series data were down-sampled to 4mm isotropic voxels prior to CWAS.

Connectome-Wide Association Study (CWAS) using MDMR

In the first step, the processed, standard-space 4mm voxelwise subject time series data were used to conduct a seed-based connectivity analysis at each gray matter voxel. This is defined as the temporal Pearson's correlation between each voxel's BOLD time series with that of every other voxel within gray matter (defined by the MNI mask). This analysis produced a correlation matrix of all pairs of gray matter voxels (14,735 voxels x 14,735 voxels) for each subject.

In the second step, the overall multivariate pattern of connectivity for each voxel, represented by the correlation matrix in step 1, was compared between the subjects using a distance metric. The distance metric, which is a function of Pearson's correlation, quantifies the similarity in the pattern of connectivity between each pair of subjects. This produced a matrix of distances (225 x 225) representing all subject-pairs for each voxel. This group-level distance matrix was generated for each of the 14,735 gray matter voxels.

Finally, in the third step, MDMR was used to test how well each phenotypic variable explained the distances between each subject's pattern of seeded connectivity created in step 2. This provided a measure of how the overall pattern of connectivity with that seed voxel was impacted by each group level variable entered into the design

matrix in standard regression format. Our group-level design matrix included the dimensional variable of interest (BAS Reward) as well as covariates including clinical group status (i.e. MDD, BPD, SCZ, PR, NC), age, sex, and in-scanner motion. Motion was summarized for each subject as the mean relative displacement of realignment parameters across the time series.

The MDMR procedure yielded a voxelwise pseudo-F statistic map, with permutation-based significance testing using 5,000 permutations. The result of this procedure identified voxels where BAS Reward affected the overall pattern of connectivity. As in Shehzad et al., MDMR type I error was controlled using cluster-correction with a voxel height of z>1.64. Cluster probability was corrected at a *p*-value threshold of 0.01 using 10,000 Monte-Carlo simulations. Cortical projections were displayed using Caret.

Follow up seed-based analyses

Seeds were defined for each cluster returned by MDMR. Specifically, data were extracted from 5mm-radius spheres at the center of gravity of each cluster. A seed map was created for each subject by calculating the Pearson's correlation between the time series of each seed and every other voxel in the brain. Seed maps were Fisher z-transformed to improve normality. The maps were evaluated with a group-level regression to determine the association between reward responsiveness (BAS Reward) and seed-based connectivity. Group status, age, sex and motion were included as covariates in all analyses. For follow-up seed analyses, clusters were considered significant using the same voxelwise cluster-corrected threshold as for MDMR ($Z > 1.64$,

P < 0.01). However, it should be emphasized that the follow-up seed-based analysis subsequent to MDMR does not constitute a unique hypothesis test, as the seeds were identified based on the significance of the MDMR result. Rather, this follow-up seed analysis is a necessary post-hoc test needed to understand the MDMR result.

Network construction and analyses

Follow-up seed based analyses delineated a consistent pattern of altered connectivity among brain regions identified by MDMR. In order to concisely summarize interactions among these regions, we evaluated connections between these regions within a network framework. We constructed a graph of 8 nodes consisting of clusters identified by MDMR. To ensure that differences in cluster size did not influence results, average time series were extracted from 5mm-radius spheres at the center of gravity (COG) of each cluster. Spheres that were at brain boundaries were not used; instead we chose the nearest coordinates that resulted in all voxels within the sphere being placed within gray matter. Pair-wise Pearson's correlations among all nodes were calculated for each subject, and *z*-transformed prior to conducting analyses. This produced a reduced network (size 8 x 8 for each subject) among regions identified by MDMR where connectivity was dimensionally altered in association with BAS Reward.

In order to summarize this network, we next assigned each cortical MDMR node to a network module using community detection techniques. The subcortical NAc node was excluded to delineate cortical modules. This was done in three steps: first, the Louvain modularity detection algorithm (16) was run for each subject (50 iterations). Second, a subject-level consensus procedure (500 iterations) produced a community

assignment for each of the cortical nodes for each subject. Third, group level community structure was determined through a consensus-clustering procedure (5000 iterations) (17). This yielded two cortical modules, which corresponded to elements of the DMN and CON. The Yeo et al. (18) seven-network parcellation was used to assess spatial correspondence of MDMR clusters to known large-scale functional networks. We confirmed network communities by comparing the cortical modules with a null model of permuted networks (1000 iterations) where the consensus partition labels were randomized for each node while keeping the underlying edge weights intact (DMN: $P=1.95 \times 10^{-4}$; CON: $P=2.39 \times 10^{-4}$). Network structure was visualized using a force-directed Kamada-Kawai layout in Gephi (19).

We next examined BAS Reward effects on connectivity measures among the cortical modules and with the NAc using measures of within-network and between-network connectivity (20). Within-network connectivity is defined as the mean strength of all edges within a network community. In contrast, between-network connectivity is defined on a pairwise basis as the mean strength of edges between nodes in a community and those outside the community. The relationship of BAS Reward to these connectivity measures was examined using linear regression with group status, age, sex, and motion used as covariates.

Supplementary Results

Specificity of MDMR Findings

Although this study focused on transdiagnostic phenotypes, we conducted a fully exploratory MDMR analysis evaluating group effects. This analysis revealed significant MDMR clusters for the effect of clinical diagnosis (**Table S4**), which were distinct from the findings related to BAS Reward. Specifically, in contrast to the analysis of BAS Reward, this categorical analysis of diagnostic group did not identify hubs of the reward system such as the nucleus accumbens.

Specificity of Network Findings

To determine how BAS Reward relates to measures of illness severity, we looked at its relationship with the BDI and the CAINS, illness severity measures normally applied within single disorders (depression and schizophrenia respectively). In our sample, the association of BAS Reward with both BDI severity (r = -0.24) and the Clinical Assessment Interview for Negative Symptoms (CAINS) (r= -0.28) suggested a modest relationship to measures of illness severity.

The BDI and CAINS were not significantly related to the network-level summary measures associated with BAS Reward (**Table S9**). This demonstrates that while BAS Reward is related as expected to measures of illness severity, the results we observed were not explained by severity of depression or negative symptoms domains, and were better captured by the more psychologically-specific and transdiagnostic measure of reward sensitivity.

To further assess for specificity, we also re-evaluated our results using two additional constructs, the fatigue item from the Beck Depression Inventory ($BDI_{fatigue}$) and the State Anxiety score from the State-Trait Anxiety Index (STAI). We examined these measures, as they are likely to provide concise summary measures of two potentially non-specific effects: fatigue and scanning-related anxiety. In our sample, these measures are only modestly correlated with BAS Reward ($BDI_{fatigue}$: r = -0.15; STAI: r = -0.27). Furthermore, neither of these measures were found to significantly associate with the network-level associations (**Table S9**).

Supplementary Tables

TABLE S1. Number of subjects taking each medication class, by clinical group

Class	MDD	BPD	SCZ	PR
Antidepressants	19	13	22	2
Benzodiazepines	6	11	12	2
Antipsychotics	0	24	44	0
Stimulants	1	6	5	4
Mood Stabilizers	3	34	4	0

TABLE S2. BIS/BAS Factor Analysis: Four Factor Solution

Item	Content	F1	F2	F3	F4
13	I feel pretty worried or upset when I think or know somebody is angry at me	0.78			
8	Criticism or scolding hurts me quite a bit	0.70			
24	I worry about making mistakes	0.70			
16	If I think something unpleasant is going to happen I usually get pretty "worked up"	0.67			
19	I feel worried when I think I have done po orly at something important	0.64			
2	Even if something bad is about to happen to me, I rarely experience fear or nervous ness	-0.56			
22	I have very few fears compared to my friends	-0.49			
9	When I want something I usually go all-out to get it		0.78		
3	I go out of my way to get things I want		0.75		
21	When I go after something I use a "no holds barred" approach		0.53		
12	If I see a chance to get something I want I move on it right away		0.52		
4	When I'm doing well at something I love to keep at it		0.46		0.45
20	I crave excitement and new sensations			0.80	
15	I often act on the spur of the moment			0.65	
10	I will often do things for no other reason than that they might be fun			0.40	
23	It would excite me to win a contest				0.63
7	When I get something I want, I feel excited and energized				0.51
14	When I see an opportunity for something I like I get excited right away				0.47
5	I'm always willing to try something new if I think it will be fun			0.30	0.38
18	When good things happen to me, it affects me strongly				0.32

Factor analysis of BIS/BAS generates four factors (F1-F4) corresponding to previously identified BIS-BAS subdomains. Original BIS/BAS items superimposed for BIS (purple), BAS Drive (yellow), BAS Fun (blue) and BAS Reward (green).

TABLE S3. MDMR Clusters (BAS Reward)

Region	MNI Coordinates (COG)	Cluster Size (4mm voxels)
Right Inferior Temporal Cortex	58, -18, -24	95
Right Temporoparietal Junction	54, -50, 40	87
Dorsomedial Frontal	-6, -10, 52	79
Left Superior Temporal Cortex	-58, -22, 0	77
Nucleus Accumbens	10, 10, -4	76
Right Insular Cortex	42, 10, 0	67
Left Temporoparietal Junction	-42, -66, 36	58
Left Orbitofrontal Cortex	-46, 30, -4	36

TABLE S4. MDMR Clusters (Clinical Diagnosis)

Region	MNI Coordinates (COG)	Cluster Size (4mm voxels)
Right Central Opercular Cortex/ Right Superior Temporal Cortex	46, -6, 8	748
Dorsomedial Frontal	-2, -6, 52	650
Left Central Opercular Cortex/ Left Insular Cortex	-42, -10, 8	421
Left Frontal Pole	-26, 42, 24	220
Thalamus	-2, -14, 4	189
Cuneal Cortex	10, -70, 36	172
Right Frontal Pole	26, 30, 44	122
Left Lingual Gyrus	-18, -70, -8	86
Left Temporoparietal Junction	-42, -50, 48	58

TABLE S5. BAS Reward Partial Correlations by Group

Group	Within DMN	Between DMN and CON	Between NAc and DMN	Between NAc and CON
Full sample	-0.25	0.32	0.13	-0.14
Psychopathology-only sample (exclusion of controls)	-0.30	0.37	0.19	-0.16
MDD	-0.34	0.35	0.20	-0.10
BPD (depressed)	-0.42	0.39	0.50	-0.19
BPD (non-depressed)	-0.12	0.36	0.35	-0.41
SCZ	-0.22	0.31	0.10	-0.18
PR (clinical risk)	-0.57	0.53	0.15	-0.27
PR (family members)	-0.40	0.71	0.20	-0.43
NC	-0.04	0.18	-0.18	-0.09

TABLE S6. Between Group Comparisons

Measure	ANOVA	Comparison
BAS Reward	$p<0.05$	NC - MDD (t=2.9, $p<0.01$) PR - MDD (t=2.4, $p<0.05$)
BAS Drive	$p<0.05$	NC - MDD (t=3.9, p<0.001) NC - BPD (t=2.5, p<0.05) PR - MDD (t=2.4, p<0.05) SCZ - MDD (t=2.3, p<0.05)
BAS Fun	$p<0.05$	NC - MDD (t=2.7, p<0.01) PR - MDD (t=2.3, p<0.05)
BIS	$p<0.05$	BPD - NC (t=5.5, p<0.0001) MDD - NC (t=5.3, p<0.0001) MDD - PR (t=3.3, p<0.01) MDD - SCZ (t=3.2, p<0.01) BPD - PR (t=3.1, p<0.01) BPD - SCZ (t=2.8, p<0.01) SCZ - NC (t=2.6, p<0.05)
Composite medication index (psychopathology sample)	$p<0.05$	SCZ - PR (t=9.2, $p<0.001$) BPD - PR (t=8.4, $p<0.001$) SCZ - MDD (t=5.5, $p<0.001$) BPD - MDD (t=4.8, $p<0.001$) MDD - PR (t=2.9, $p<0.05$)

TABLE S7. Sensitivity analysis

Condition	Within DMN	Between DMN and CON	Between NAc and DMN	Between NAc and CON
Full sample	-0.25	0.32	0.13	-0.14
Smoking status	-0.26	0.33	0.13	-0.15
Composite medication load	-0.24	0.33	0.11	-0.13

TABLE S8. Comparison of BAS Subscales

BAS Scale	Within DMN	Between DMN and CON	Between NAc and DMN	Between NAc and CON
BAS Reward	-0.25	0.32	0.13	-0.14
BAS Drive	-0.19	0.23	0.08	-0.10
BAS Fun	-0.17	0.23	0.05	-0.08

TABLE S9. Specificity Analysis

Scale	Within DMN	Between DMN and CON	Between NAc and DMN	Between NAc and CON
BDI	-0.01	-0.05	0.00	0.04
$BDI_{fatigue}$	-0.03	-0.02	-0.05	0.08
CAINS	0.07	-0.10	-0.01	0.06
STAI	-0.03	-0.05	0.06	0.00

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