

Transdiagnostic Prediction of Affective, Cognitive, and Social Function Through Brain Reward Anticipation in Schizophrenia, Bipolar Disorder, Major Depression, and Autism Spectrum Diagnoses

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The relationship between transdiagnostic, dimensional, and categorical approaches to psychiatric nosology is under intense debate. To inform this discussion, we studied neural systems linked to reward anticipation across a range of disorders and behavioral dimensions. We assessed brain responses to reward expectancy in a large sample of 221 participants, including patients with schizophrenia (SZ; $n = 27$), bipolar disorder (BP; $n = 28$), major depressive disorder (MD; $n = 31$), autism spectrum disorder (ASD; $n = 25$), and healthy controls ($n = 110$). We also characterized all subjects with an extensive test battery from which a cognitive, affective, and social functioning factor was constructed. These factors were subsequently related to functional responses in the ventral striatum (vST) and neural networks linked to it. We found that blunted vST responses were present in SZ, BP, and ASD but not in MD. Activation within the vST predicted individual differences in affective, cognitive, and social functioning across diagnostic boundaries. Network alterations extended beyond the reward network to include regions implicated in executive control. We further confirmed the robustness of our results in various control analyses. Our findings suggest that altered brain responses during reward anticipation show transdiagnostic alterations that can be mapped onto dimensional measures of functioning. They also highlight the role of executive control of reward and salience signaling in the disorders we study and show the power of

systems-level neuroscience to account for clinically relevant behaviors.

Key words: dimensional/transdiagnostic/reward anticipation/fMRI/ventral striatum/salience

Introduction

Alterations in reward sensitivity or reinforcement-dependent learning play a key role in psychiatric disorders. Previous research has focused on schizophrenia (SZ) where altered brain responses during the anticipation of reward, in particular in the ventral striatum (vST), are well established.¹ However, a growing number of studies reported network alterations during reward anticipation in other disorders,^{2–4} including major depression (MD),^{5,6} bipolar disorder (BP),⁷ and autism spectrum disorder (ASD),⁸ mirroring the significant overlap between these disorders in symptomatology and genetic risk architecture.⁹ In this sense, reward anticipation is a prime example of the current discussion whether categorical diagnoses should be supplemented, or even supplanted, by dimensional constructs linked to function.

Accordingly, recent studies have associated striatal brain responses during reward anticipation to dimensional concepts like anhedonia, depressive symptom severity, or psychotic symptoms across psychiatric conditions.^{3,4,10,11}

These approaches highlight the potential of neuroimaging biomarkers in explaining brain-behavior relationships in a more dimensional and inclusive way, ie, by means of shared psychological or symptom domains and beyond traditional definitions of health and disease.^{12,13} If established, such markers would allow the investigation of brain-behavior relationships independent of clinical status and diagnostic entity, thereby enhancing our current categorical understanding of mental disorders and their neurobiological representation to a more dimensional framework, from which valuable clues for therapy research may arise.

Building on these recent approaches, we investigated the transdiagnostic relevance of reward signaling in 2 ways. First, while previous studies of this system have usually investigated single behavioral domains in restricted groups of disorders, we performed a broad (neuro)psychological characterization to generate independent, data-driven factors that converge on underlying traits or states in a range of participants with serious mental illness along the moods-psychosis spectrum (SZ, BP, MD, and ASD). While exploratory in nature, these factors were expected to map on cognitive, affective, and social functioning, given our selection of tests and questionnaires. Second, previous research oftentimes studied the vST in isolation, often combined with disorder-specific hypotheses about underlying mechanisms (eg, dopamine hypothesis of SZ¹⁴). However, it is clear that the vST participates in several extended networks or loops linked to a range of cognitive, affective, and social behaviors.^{15,16} Alterations on the circuit-level can be studied using functional connectivity, which examines correlations in activity across regions. To date, several studies have reported alterations in cortico-striatal connectivity in SZ (eg, ¹⁷) and other diagnostic entities (eg, BP,¹⁸ MD,¹⁹ and ASD²⁰). However, their joint interpretation is hampered by methodological differences (eg, resting state vs task-based functional magnetic resonance imaging [fMRI]), and transdiagnostic research on brain-behavior relationships is scarce (eg, ²¹). Accordingly, we aimed to identify reward-related alterations in distributed neural networks linked to the vST between and across diagnostic categories. We expected reward-related functional alterations to involve brain circuits beyond the vST. We also expected a relationship of transdiagnostic alterations with dimensional measures, based on evidence of an association with affective measures,^{3,4} the relevance of cognitive control for the processing of motivationally relevant cues,²² and the inherently motivational salience of social stimuli.²³

In addition, we anticipated experimental challenges that arise in clinical imaging research, in particular when investigating different patient groups in the same study. We, therefore, carefully considered various factors related to clinical characteristics²⁴ (eg, comorbidities and medication) and data quality issues (eg, motion artifacts and test-retest reliability) in several control analyses.

Methods

Sample

This study recruited a prospective new sample of 279 subjects. All individuals provided written informed consent for a study protocol approved by the institutional review board of the Medical Faculty Mannheim. After quality assurance procedures, the final sample included 221 participants (Table 1). Patients were recruited from inpatient and outpatient treatment facilities. Healthy subjects were recruited from the local community by advertisement. Psychiatric diagnoses were confirmed by trained clinical interviewers using the Structured Clinical Interview for DSM-IV interview²⁵ for all patient groups and the Autism Diagnostic Observation Schedule Module 4 (ADOS-G²⁶) for ASD patients. Patients with BP type 2 were excluded. See [Supplementary Material](#) for details.

(Neuro)Psychological Characterization

Testing was performed by trained examiners using a battery of well-established tests for intellectual abilities including reasoning, attention, verbal fluency, episodic memory, and working memory. Affective state and trait measures, questionnaires on personality characteristics and social functioning were acquired by online questionnaires. See [Supplementary Material](#) for details.

Neuroimaging Paradigm

We used an adapted version of the well-established incentive delay task involving monetary^{27,28} and social reward²⁹ during fMRI and 2 conditions (cue win and cue neutral), with fair-to-good reliability of reward-network activation (see [Supplementary Material](#) for detailed information on test-retest reliability). We did not differentiate between reward types based on previous evidence of overlapping neural substrates,³⁰ which we similarly demonstrate in our control analyses (see [Supplementary Material](#)). The analysis of mean reaction times and outcome measures revealed no group differences (all $P > .146$; Table 1), which suggests that all subjects understood and engaged in the task equally well. See [Supplementary Material](#) for details.

MRI Data Acquisition and Preprocessing

Functional images were acquired using an echo-planar imaging sequence on a 3-T scanner (Siemens Trio) and preprocessed using standard routines in SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>). See [Supplementary Material](#) for details.

First-Level Analyses

Functional activation during reward anticipation was assessed as differential response to win cues as compared to neutral cues using first-level general linear model (GLM)

Table 1. Sample description

Group	HC	SZ	BP	MD	ASD	Between-group differences
<i>n</i>	110	27	28	31	25	
Age	30.4 (10.3)	32.4 (10.4)	34.0 (9.6)	35.2 (11.2)	32.1 (9.6)	$F_{(4,216)} = 2.12$, $P = .080$
Sex (m/f)	54/56	18/9	12/16	8/23	14/11	$\chi^2_{(4)} = 10.98$, $P = .027$
Education (years)	12.4 (1.1)	11.1 (1.9)	12.3 (1.2)	11.7 (1.5)	11.9 (1.5)	$F_{(4,216)} = 5.55$, $P \leq .001$
Education father (years)	10.9 (1.7)	10.6 (1.9)	10.3 (2.0)	10.4 (1.7)	11.1 (1.8)	$F_{(4,214)} = 1.36$, $P = .250$
Education mother (years)	10.8 (1.5)	10.5 (1.5)	10.2 (1.9)	10.3 (1.6)	10.6 (1.7)	$F_{(4,214)} = 1.18$, $P = .320$
Framewise displacement	0.2 (0.06)	0.2 (0.06)	0.2 (0.07)	0.2 (0.08)	0.2 (0.06)	$F_{(4,216)} = 1.56$, $P = .185$
Medication value	—	2.8 (2.4)	2.6 (1.3)	1.7 (1.5)	0.4 (0.8)	$F_{(3,107)} = 11.98$, $P \leq .001$
CPZ-e	—	415.0 (45.2)	123.8 (42.7)	16.7 (41.3)	3.3 (47.1)	$F_{(3,102)} = 13.66$, $P < .001$
CGI	—	4.35 (1.2)	3.46 (1.2)	3.75 (1.1)	3.5 (1.1)	$F_{(3,100)} = 3.36$, $P = .022$
Number of months of hospitalization during the last 2 years	0	2.9 (3.2)	1.6 (3.5)	1.5 (1.4)	0.4 (0.8)	$F_{(3,103)} = 4.15$, $P = .008$
PANSS	—	54.6 (16.5)	41.0 (10.2)	46.5 (9.1)	—	$F_{(2,82)} = 8.27$, $P = .001$
HAM-D	—	7.8 (5.5)	8.0 (6.5)	13.2 (6.0)	—	$F_{(2,82)} = 7.64$, $P = .001$
YMRS	—	1.2 (2.4)	2.8 (3.7)	0.6 (1.2)	—	$F_{(2,82)} = 5.37$, $P = .006$
ADOS	—	—	—	—	9.5 (2.8)	
Current MD ^a						
Not depressed	108	11	9	4	16	
Mild	1	11	9	10	5	
Moderate	0	5	6	10	3	
Severe	0	0	4	7	0	
Reaction time (s)	239.9 (27.2)	238.3 (28.5)	242.5 (51.8)	244.9 (28.1)	253.3 (29.9)	$F_{(4,216)} = 1.06$, $P = .146$
Number of win trials (max 15)	10.3 (1.1)	10.3 (1.5)	10.0 (1.3)	10.5 (1.1)	9.8 (1.2)	$F_{(4,216)} = 1.72$, $P = .380$

Note: Displayed are mean values (SD) or numbers (male/female) and statistical between-group comparisons. For nonparametric test, we used the Kruskal–Wallis test ($df = 5$). For parametric tests, analysis of variance was computed. HC, healthy control; SZ, schizophrenia; BP, bipolar disorder; MD, major depression; ASD, autism spectrum disorder; m, male; f, female; CPZ-e, chlorpromazine dose equivalents; CGI, Clinical Global Impression Scale⁵⁷ (1: no mental disorder to 7: extreme mental disorder); PANSS, Positive and Negative Symptom Rating Scale⁵⁸; HAM-D, Hamilton Depression Scale⁵⁹; YMRS, Young Mania Rating Scale⁶⁰; ADOS, Autism Observation Schedule Module 4.²⁶

^aCurrent MD, current depressive state as assessed by the Beck Depression Inventory (BDI-II).⁶¹

contrast images (win cue > neutral cue). Functional connectivity was assessed using a seeded connectivity approach with individual GLMs for the first eigenvariate of the time series extracted from the right vST. See [Supplementary Material](#) for details.

Second-Level Analyses

Categorical Between-Group Analyses. To study reward network (dys)function between diagnostic entities, we conducted categorical analyses using individual contrast images for activation and functional connectivity

and full-factorial designs with diagnostic group (HC, SZ, BP, MD, and ASD) as between-subject factor. As groups were naturally heterogeneous with respect to age, sex, and educational level, we included these variables as covariates of no interest in all analyses. In addition, despite nonsignificant differences in head motion between groups (see [table 1](#)), we included mean framewise displacement³¹ as covariate of no interest across analyses. In case of a significant main effect of group, *F*-tests were followed up by post hoc *t*-tests for group comparisons. Significance was assessed at the voxel-level and defined a priori as $P < .05$, familywise error (FWE) corrected within

a well-established mask of the vST³² (see [Supplementary Material](#)). Outside this mask, voxel-level significance was defined as $P_{\text{FWE}} < .05$, corrected across the whole brain.

Dimensional Analyses. We further investigated whether interindividual differences in behavior can be mapped onto reward network functioning irrespective of diagnostic status. We performed a principal component analysis implemented in SPSS (IBM, SPSS, version 23) to identify independent components or factors reflecting higher-order dimensions of (neuro)psychological functioning. The resulting factors could be mapped onto dimensions of cognitive, affective, and social functioning (see [Supplementary Material](#) for details). To identify associations of factors with functional brain responses, we first included individual factor loadings as covariates of interest in one-sample *t*-tests on brain activation and connectivity along with the above named covariates of no interest, without controlling for group. The same statistical thresholds were applied as outlined above. A second analysis step was performed for our vST region of interest to test whether individual factor loadings were predictive of neural responses beyond the effect of diagnostic category. We extracted peak-voxel estimates within significant activation clusters identified in the previous analysis step and used these measures as dependent variables in post hoc multiple regression analyses. We converted the variable coding for the 5 diagnostic groups into 4 dichotomous dummy variables using the HC group as the reference category. The same was done for the variable coding for the interaction effect (group X dimension). We included the resulting variables together with the dimensional factors and our covariates of no interest as independent variables into the regression model.

Control Analyses and Reliability Study

In order to address the challenges common to clinical imaging, we tested the robustness of the identified reward-related activation and connectivity phenotypes in various control analyses. First, in order to target the potentially confounding effect of medication,^{33,34} we computed

chlorpromazine dose equivalents (CPZ-e). However, as CPZ-e values only cover antipsychotic medication not taking into account other classes of medication, we additionally calculated a standardized composite medication value following an established procedure for clinical studies that deal with different types of medication³⁵ (see [Supplementary Material](#) for details). The resulting composite scores and CPZ-e values ([table 1](#)) were subsequently related to second-level peak voxel estimates using partial correlation analyses in SPSS (IBM, SPSS, version 23). Second, to further ensure the robustness of our results with respect to imaging quality, we carefully balanced our sample for several QC parameters and performed partial correlation analyses to show that results were not related to head motion. Third, in order to investigate the effects of reward type (monetary vs social), we performed additional categorical and dimensional second-level analyses as outlined above using individual contrast images capturing the interaction effect between condition and reward type (contrast: (win [social] > neutral [social]) > (neutral [monetary] > win [monetary])). Fourth, we tested for potential influences of sex and current depressive state. See [Supplementary Material](#) for details, also for additional analyses and results for reward consumption.

Results

Diagnostic Group Differences

Compared to HC, we observed reduced vST activation during reward anticipation in SZ, BP, and ASD ($P_{\text{FWE}} < .05$, small volume correction [SVC]) but not MD ([figure 1](#); [table 2](#)). Beyond the vST, activation analyses revealed group differences in areas that have previously been linked to the executive control network, such as the inferior parietal lobule (IPL) and lateral prefrontal cortex ($P_{\text{FWE}} < .05$, whole-brain corrected; [figure 2A](#); [table 2](#)). Post hoc tests revealed that these effects were most pronounced in BP compared to HC ([table 2](#)). In addition, we detected group differences in vST connectivity with the IPL and cerebellum ($P_{\text{FWE}} < .05$, whole-brain corrected,

Categorical analyses: group differences in vST activation

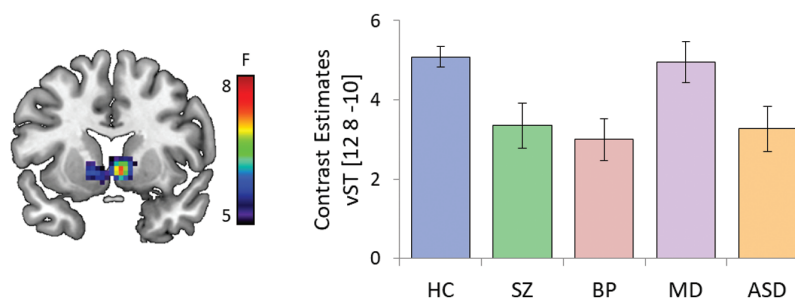


Fig. 1. Categorical group differences in ventral striatum (vST) responses during reward anticipation (cue win vs neutral) and plotted contrast estimates (mean, SE) of the right vST. HC, healthy control; SZ, schizophrenia; BP, bipolar disorder; MD, major depression; ASD, autism spectrum disorder. For illustration, a significance threshold of $P_{\text{uncorr}} < .001$ was applied.

Table 2. Group differences and dimensional association

Region	<i>k</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>F/T</i>	<i>P_{corr}</i>	Significant post hoc group differences
Categorical results							
Activation							
vST R*	69	12	8	-10	7.39	.001	HC > SZ, HC > BP, HC > ASD, MD > BP
vST L*	15	-12	5	-10	5.86	.009	HC > BP, HC > ASD
Inferior parietal lobule L (IPC [PGa])	32	-39	-61	53	9.45	.007	HC > BP
Inferior parietal lobule R (IPC [PGp])	23	33	-73	44	8.88	.017	HC > BP
Lateral frontal gyrus R (Area 45)	10	60	23	8	8.57	.026	HC > BP
vST—connectivity							
Inferior parietal lobule R (SPL [7A])	43	33	-58	53	12.61	<.001	HC > SZ, HC > BP
Fusiform L	34	-24	-70	-16	10.66	.002	HC > BP
Cerebellum R	19	24	-37	-37	9.56	.011	HC > SZ
Dimensional results							
Activation							
Factor 1: affective							
Cerebellum L	40	-21	-76	-34	4.91	.009	
Lateral frontal gyrus R (Area 45)	51	57	20	17	4.91	.010	
Superior medial frontal gyrus	15	3	35	35	4.87	.011	
Superior medial frontal gyrus	12	3	29	53	4.52	.027	
vST R*	49	6	5	-1	4.58	<.001	
vST L*	13	-3	5	-1	3.44	.009	
Factor 2: cognitive							
vST L*	9	-3	8	2	3.15	.020	
vST R*	8	6	8	5	3.11	.022	
Factor 3: social							
vST R*	1	9	11	5	2.81	.049	
vST connectivity							
Factor 1: affective							
Postcentral gyrus L (Area 4a)	74	-30	-31	68	5.78	<.001	
Inferior parietal lobule R (SPL [7A])	60	27	-55	50	5.89	<.001	
Superior parietal cortex L (SPL [7A])	26	-18	-64	62	5.50	.001	
Cuneus L	130	-6	-85	32	5.47	.002	
Insula L (Insula [Id1])	18	-36	-16	-4	5.42	.002	
Superior temporal cortex R (TE 3)	12	66	-22	14	5.39	.002	
Putamen L	15	-27	-4	2	5.18	.006	

Note: Cluster extent *k* is given at $P_{\text{corr}} < .05$, familywise error (FWE) corrected for multiple comparisons within the whole brain for $k > 10$ voxels or within the *ventral striatum (vST) region of interest (ROI) using small volume correction (SVC). *x*-, *y*-, and *z*-coordinates (MNI) and statistical information refer to the peak voxel(s) in the corresponding cluster (voxel-level statistics). In the following, we additionally report cluster-level statistics for vST ROI activation at an initial height threshold of $P_{\text{unorr}} = .001$ and a cluster threshold of $p_{\text{corr}} < .05$, FWE corrected using SVC: categorical—right vST: $k = 67$, $P_{\text{corr}} = .002$, categorical—left vST: $k = 13$, $P_{\text{corr}} = .015$; factor 1—right vST: $k = 35$, $P_{\text{corr}} = .005$, factor 1—left vST: $k = 3$, $P_{\text{corr}} = .016$; factor 2—right vST: $k = 0$, factor 2—left vST: $k = 1$, $P_{\text{corr}} = .019$; factor 3—right vST: $k = 0$, factor 3—left vST: $k = 0$. R, right; L, left.

figure 2B; table 2), which were mainly driven by reduced functional connectivity in SZ and BP compared to HC ($P_{\text{FWE}} < .05$, whole-brain corrected, Table 2). See Supplementary Material for details.

Extraction of Dimensional Measures

The factor-analytical approach revealed 3 uncorrelated factors covering aspects of affective, cognitive, and social functioning (see Supplementary Material and figure 3A). We refer to the first factor as *affective instability* because it is composed of diverse psychological constructs like anxiety, anhedonia, neuroticism, self-control, or impulsivity, all of which converge on difficulties to adequately regulate the affective state. The second factor includes

different measures assessing neurocognitive performance (eg, memory and reasoning) and is referred to as *cognitive functioning*. The third factor specifically covers measures related to social traits and is referred to as *social functioning*. Despite the existence of mean group differences (see Supplementary Material), both within-group variance and cross-group overlap suggest a broad distribution of each factor across disorders (figure 3A).

Association of Dimensional Measures with Brain Activity and Connectivity

Higher affective instability (factor 1) was associated with reduced vST activation, while higher cognitive and social functioning (factor 2 and 3) were related to higher

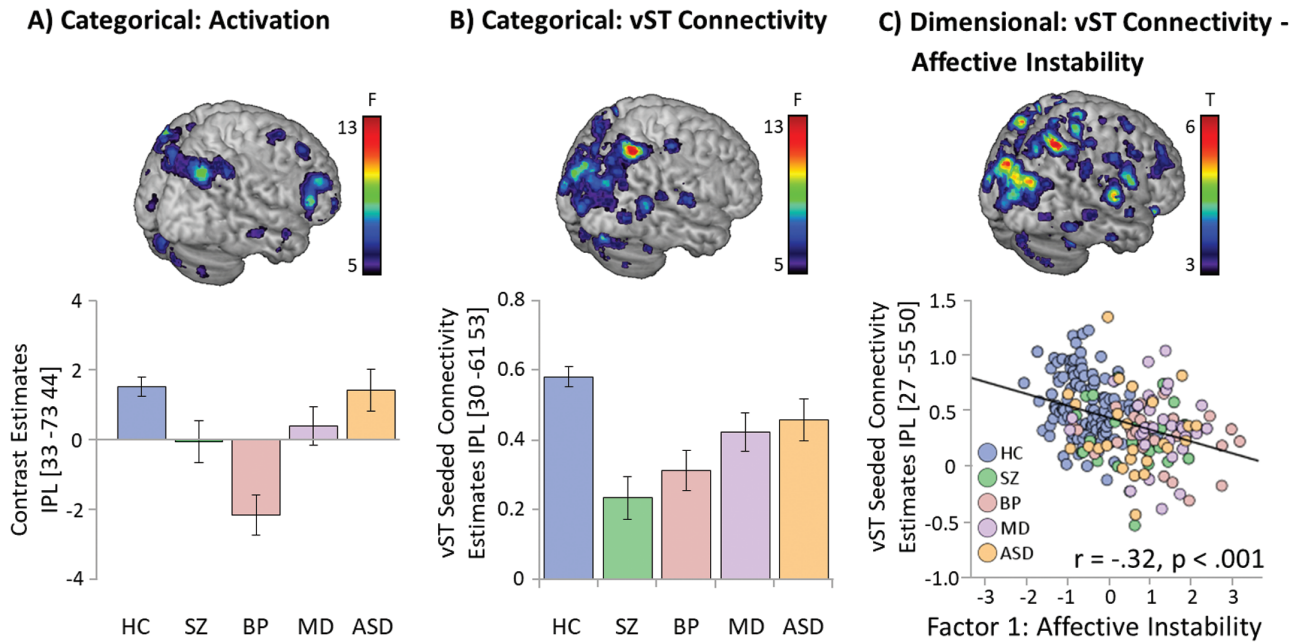


Fig. 2. Whole-brain activation and connectivity results. Main effect of group for activation (A; cue win vs neutral) and ventral striatal (vST) seeded connectivity (B). (C) Negative association between affective instability and vST seeded connectivity with the right inferior parietal lobule (IPL). Bar plots depict respective contrast and seeded connectivity estimates (mean, SE) of the peak voxel in the right IPL. r , Pearson correlation coefficient; HC, healthy control; SZ, schizophrenia; BP, bipolar disorder; MD, major depression; ASD, autism spectrum disorder. For illustration, a significance threshold of $P_{\text{uncorr}} < .001$ (cluster extent > 20) was applied.

vST activation ($P_{\text{FWE}} < .05$, SVC; figure 3B; table 2). On the whole-brain level, higher affective instability (factor 1) was associated with lower activation in lateral and medial frontal areas as well as in the cerebellum ($P_{\text{FWE}} < .05$, whole-brain corrected; table 2). No significant association emerged for factors 2 and 3. In addition, affective instability (factor 1) was associated with reduced vST connectivity with visual and motor areas and in parietal regions, with prominent clusters in the IPL, insula, and putamen (figure 2C; table 2).

Post hoc multiple regression analyses revealed that individual factor loadings predicted vST activation beyond the effect of diagnostic group for affective instability (right vST: beta = -1.687 , $P = .044$) and cognitive functioning (left vST: beta = 1.307 , $P = .022$), while the association with social functioning was trend-level significant (right vST: beta = $.936$, $P = .070$). The interaction effects between diagnostic group and factor loadings did not yield significant results (all $P > .05$). See [Supplementary Material](#) for details.

Control Analyses

Partial correlation analyses showed that overall results were not related to medication load, CPZ-e, or head motion. Furthermore, results were not differentially affected by reward type (monetary vs social), current depressive state (except for the expected association with factor 1), or sex. See [Supplementary Material](#) for details.

Discussion

This study aimed to confirm and extend current knowledge about alterations in reward anticipation in severe mental disorders by systematically examining the relation to disorder categories and functional dimensions. Our results show that alterations in vST-related networks constitute transdiagnostic phenotypes that (1) relate to affective, cognitive, and social functioning across diagnoses and (2) are associated with alterations in frontal and parietal regions likely involved in executive control.

vST response alterations between and across nosological boundaries

We replicated the finding of reduced vST activation during reward anticipation in patients with SZ and demonstrated similar alterations in BP and ASD, lending further evidence to the cross-diagnostic relevance of this phenotype.³ In contrast to some previous reports,^{5,6} we did not find reduced vST responses in MD patients. Besides differences in medication and task design, this discrepancy might result from differences in current depressive state, which ranged from fully remitted to currently depressed in our MD sample. State-dependent vST alterations¹¹ might, therefore, be masked, although this was not supported by our control analyses. Interestingly, however, our dimensional approach nonetheless suggests an impact of affective functioning on reward processing, with higher affective instability

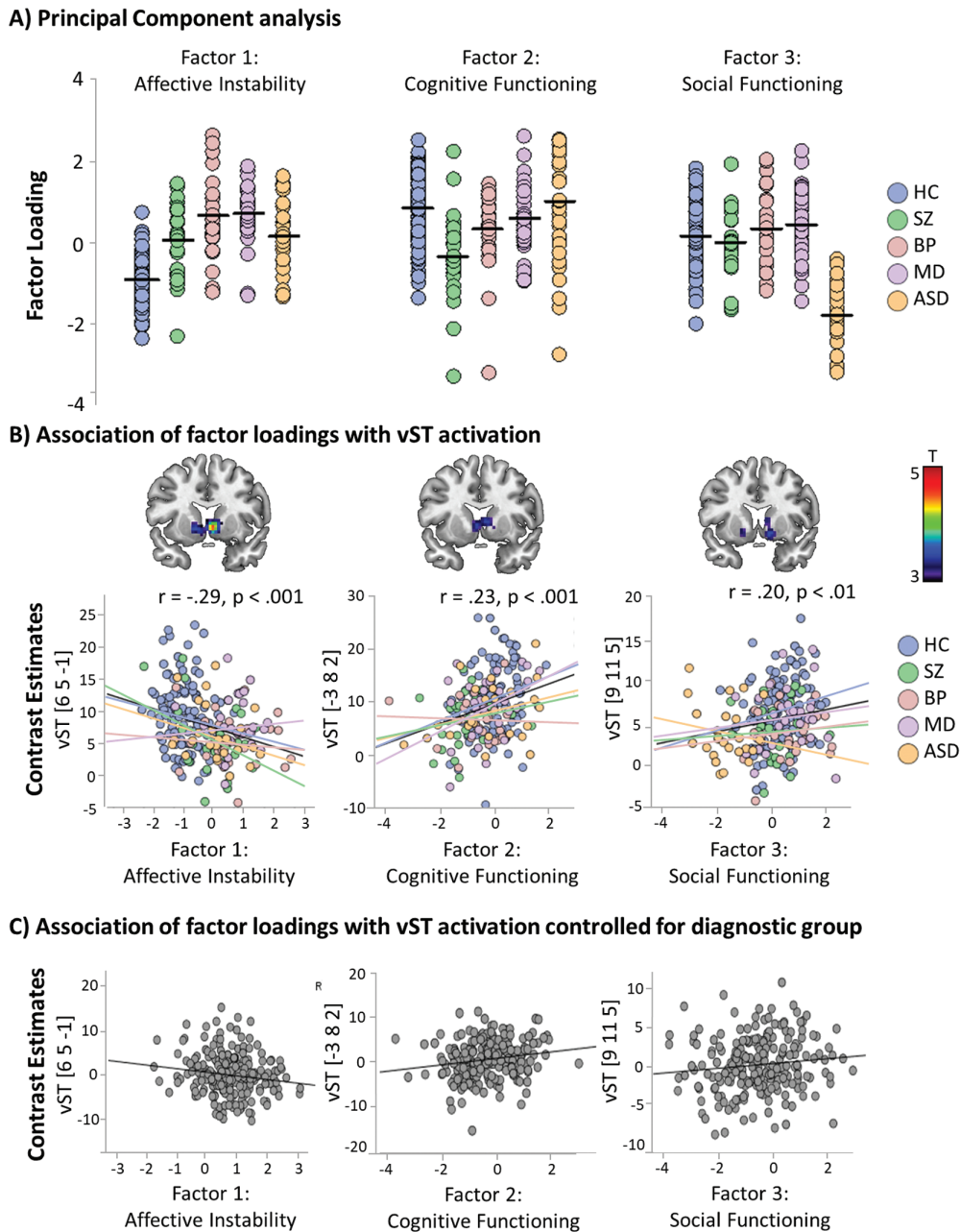


Fig. 3. Dimensional results. (A) Group-specific factor loadings. (B) Scatter plots depict associations between peak voxel contrast estimates in the ventral striatum (vST) and dimensional factors relating to affective instability (left), cognitive functioning (middle), and social functioning (right). Linear fit lines in black color refer to the full sample, while group-specific linear fit lines are depicted in color. (C) Scatter plots display the partial correlation results between each factor and peak voxel contrast estimates in the vST while controlling for diagnostic group, age, sex, and education. r , Pearson correlation coefficient; HC, healthy control; SZ, schizophrenia; BP, bipolar disorder; MD, major depression; ASD, autism spectrum disorder. For illustration, images were masked with the predefined vST mask and a significance threshold of $P_{\text{uncorr}} < .005$ was applied.

(factor 1) relating to lower responses in the vST across diagnostic entities including MD. While this adds to recent transdiagnostic evidence,^{3,4,11} we additionally show that this association is valid for a broad definition of affective functioning based on a comprehensive collection of clinical measures representing diverse psychological constructs associated with a general risk for psychiatric disorders.³⁶ These observations suggest that

a dysfunctional regulation of affective symptoms relates to vST alterations across the psychiatric spectrum, likely reflecting blunted attribution of motivational salience to rewarding stimuli.³

We also observed an association with a dimensional measure of cognitive functioning (factor 2) where stronger vST responses related to better performance in neurocognitive tests. This suggests that cognitive deficits,

such as deficits in working memory or cognitive flexibility, are relevant to reward anticipation in the context of incentive delay tasks, which require a certain level of task comprehension and working memory capacity. Indeed, deficits in the ability to actively represent and maintain information about the task and the anticipated rewards have been suggested to contribute to blunted reward experience and anhedonia in SZ.³⁷ Here, we show that the relationship between striatal activation and cognitive functioning is not specific to SZ but rather relates to the degree of cognitive impairment independent of diagnostic category.

Regarding social functioning (factor 3), higher scores related to higher vST responses, which was, however, not independent from diagnostic group. In fact, factor 3 was strongly driven by the ASD group. While a role of reward processing in ASD is well established,³⁸ our dimensional analyses tentatively point to a transdiagnostic relationship between social functioning and vST response to reward anticipation.

In sum, our categorical approach suggests that vST functional alterations are present across several diagnostic categories. Moreover, our factor-analytical approach points to distinct brain-behavior relationships that exist across nosological boundaries. Supplemental analyses confirmed that the observed dimensional effects were not (factors 1 and 2) or only to a small extent (factor 3) explained by diagnostic category, emphasizing the higher sensitivity of our dimensional approach. This challenges more disorder-specific mechanistic theories of vST dysfunction (eg, aberrant salience processing in SZ³⁹; anhedonia in MD⁵; alterations in the behavioral activation system in BP⁴⁰; and social motivation deficits in ASD²³) and points to shared underlying neural mechanisms that could, eg, relate to the participation of the vST in separable processing loops.¹⁵ As the limited spatial resolution prevents a more fine-grained structural characterization of the activation pattern associated with each factor, future studies should investigate whether the localization of peak voxels might reflect the well-established pattern of a dorsal-cognitive to ventral-affective gradient in the striatum.¹⁵ Similarly, our supplemental finding of potential transdiagnostic alterations in the vST during reward receipt should be followed up using optimized task designs, eg, jittered target-receipt intervals and a higher number of trials allowing for the comparison of successful and unsuccessful win trials.

Neural Networks Linked to Reward Processing

Beyond the vST, we adopted a brain-wide perspective to explore the distributed networks relevant for dimensional or categorical effects of reward processing which converged on regions related to the frontoparietal network (FPN), specifically on the IPL and prefrontal areas: Categorical whole-brain analyses revealed reduced

brain responses in these regions, most prominently in BP for activation and in SZ and BP for vST connectivity. Dimensional analyses suggest higher affective instability (factor 1) to relate to lower responses in lateral prefrontal regions, as well as to reduced vST connectivity with the IPL.

Our observation of altered functional responses in regions involved in executive control, in particular in BP and SZ patients, aligns with previous findings.^{41–48} In line with our results, a recent study showed that higher genetic risk for psychotic disorders was associated with aberrant integration of information across networks for attention (including the FPN) and the striatum,⁴⁸ suggesting a disrupted cross talk between the executive control and reward network. Our dimensional approach additionally suggests that alterations in executive control areas constitute a shared phenotype across nosological boundaries and relate to affective regulation deficits.

The importance of a tight interaction between the executive control and reward networks is well described.^{49,50} Reward cues facilitate the allocation of processing resources toward behaviorally important stimuli,⁵¹ which is reflected by increased FPN activation^{52–54} and connectivity with the reward network.⁵⁵ The observed association of control network function with affective instability might reflect reduced processing capacities across psychiatric conditions as a result of affective symptom load. This interpretation follows a recent, transdiagnostic theory of psychiatric dysfunction²² which postulates that the experience and regulation of symptoms, such as depressed mood or paranoid ideation, consumes cognitive resources and results in limited flexibility of large-scale control networks.

Strengths and Limitations

This study faced several challenges common to clinical imaging.²⁴ We controlled for basic demographic variables and showed that neither CPZ-e nor total medication were related to striatal responses. We carefully balanced our sample for several quality parameters, showed that results were not related to motion, and demonstrated fair-to-good reliability of task effects in an independent test–retest sample. Our PCA approach comes with the limitation that resulting components depended on the specific test battery, which we addressed by a broad coverage of domains and assessments. Conversely, this approach offers several advantages for dimensional analyses: (1) the resulting components are maximally independent, (2) do not rely on single, often disorder-specific clinical measures with low variance in healthy subjects, (3) do not focus on single psychopathological processes not considering other psychological variables, and (4) reduce the selection bias of single measures out of a large questionnaire and test battery, ie, usually acquired in clinical studies.²⁴

Despite these efforts, we acknowledge that we cannot rule out the possibility of unaddressed influences of some confounders, in particular potential interaction effects of medication. This issue needs to be addressed in larger-scale studies that allow for the comparison of medicated and unmedicated patients, favorably within and across diagnostic groups. In addition, the inclusion of other diagnostic groups known to show alterations in reward processing (eg, obsessive-compulsive disorder), the systematic consideration of current disease state (eg, current episode vs remission states in MD) and comorbidities (eg, type, number, lifetime vs concurrent), and a better matching of groups on demographic characteristics (eg, sex, age, and education) would have been desirable but were beyond the feasible scope of the present study. Finally, we did not correct for the number of tests resulting from this complex research question in order to maximize sensitivity. Also, we acknowledge that our results might to some degree be influenced by the choice of analytical methods, such as preprocessing strategies, statistical models, and the choice of significance assessment (eg, voxel-level vs cluster-level significance).

However, while methodologically very challenging, our approach of jointly investigating different patient groups in the same study comes with the valuable advantage of ruling out methodological differences when comparing results between different diagnoses. Prospectively, there will be a need to conduct large-scale, preregistered, multisite and multidagnosis research to overcome the heterogeneity of findings generated by smaller-sized studies.

Conclusion

The present study demonstrates reward-processing alterations in a range of psychiatric disorders. Using dimensional, behaviorally meaningful measures covering affective, cognitive, and social functioning, we further demonstrate that independent psychological domains relate to altered vST activation across the psychiatric spectrum, thereby informing current disorder-specific mechanistic theories of vST dysfunction. Beyond the vST, our results tentatively point to transdiagnostic alterations in the interaction between the reward and executive control network, suggesting that the symptom-induced reduction of cognitive control capacities might constitute a superordinate transdiagnostic factor mediating domain specific differences such as blunted striatal functioning. Our results can inform the development of therapeutic interventions targeting specifically the enhancement of cognitive control abilities in mental disorders (eg, attentional training techniques included in the metacognitive therapy⁵⁶) and provide a biological account of the underlying pathophysiological landscape of mental illness that can inform both categorical and domain-related accounts of psychiatric nosology. Furthermore, our data indicate good reliability and robustness against common clinical

confounders, indicating that similar measures may usefully contribute to biomarkers in the clinic and, thus, be useful in precision medicine approaches in psychiatry.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

Acknowledgments

We thank Axel Schäfer, Michael Schneider, Dagmar Gass, Birgül Sarun, Claudia Stief, Natalie Hess, and Mirjam Melzer for research assistance. This study was performed at Central Institute of Mental Health.

Funding

This work was supported by the Bundesministerium für Bildung und Forschung (01ZX1314G, 01ZX1311B, and 01GQ1102), the Seventh Framework Programme of the European Community (115300, Project EU-AIMS; 602805, Project EU-AGGRESSOTYPE; 602450, Project EU-IMAGEMEND), and the Deutsche Forschungsgemeinschaft (5485966 and 539/3-1). A.M.-L. further acknowledges grant support by the Deutsche Forschungsgemeinschaft (Collaborative Research Center SFB 1158 subproject B09, Collaborative Research Center TRR 265 subproject S02, Clinical Research Unit KFO 256 subproject IP3, grant ME 1591/4-1) and Bundesministerium für Bildung und Forschung (grants 01EF1803A, 01ZX1314G, 01GQ1003B) and HEALTH-F2-2010-241909, Innovative Medicines Initiative Joint Undertaking (grant 115008) and Ministerium für Wissenschaft, Forschung und Kunst Baden-Württemberg (grant 42-04HV.MED(16)/16/1). H.T. further acknowledges grant support by the Deutsche Forschungsgemeinschaft (Collaborative Research Center SFB 1158 subproject B04, Collaborative Research Center TRR 265 subproject A04, Research Training Group GRK2350/1 subproject B02) and Bundesministerium für Bildung und Forschung (grants 01EF1803A project WP3, 01GQ1102). C.M. is a recipient of the Olympia-Morata grant of the University Heidelberg.

Conflict of Interest statement

K.S., C.M., J.S., S.B., M.P., C.W., S.E., H.W., and H.T. have nothing to declare. D.B. serves as an unpaid scientific consultant for an EU-funded neurofeedback trial. T.B. served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Lundbeck, Medice, Neurim Pharmaceuticals, Novartis, and Shire. He received conference support or speaker's fee by Lilly, Medice, Novartis, and Shire. He has been involved in clinical trials conducted by Shire & Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien,

Oxford University Press. The present work is unrelated to the above grants and relationships. A.M.-L. has received consultant fees from Boehringer Ingelheim, Elsevier, Walt Disney Pictures, Brainsway, Lundbeck Int. Neuroscience Foundation, Sumitomo Dainippon Pharma Co., Academic Medical Center of the University of Amsterdam, Synapsis Foundation-Alzheimer Research Switzerland, IBS Center for Synaptic Brain Dysfunction, Blueprint Partnership, University of Cambridge, Dt. Zentrum für Neurodegenerative Erkrankungen, Universität Zürich, L.E.K. Consulting, ICARE Schizophrenia, Science Advances, and has received fees for lectures, interviews and travels from Lundbeck International Foundation, Paul-Martini-Stiftung, Lilly Deutschland, Atheneum, Fama Public Relations, Institut d'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Jansen-Cilag, Hertie Stiftung, Bodelschwingh-Klinik, Pfizer, Atheneum, Universität Freiburg, Schizophrenia Academy, Hong Kong Society of Biological Psychiatry, Fama Public Relations, Spanish Society of Psychiatry, Reunions I Ciencia S.L., Brain Center Rudolf Magnus UMC Utrecht.

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