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Archival Report

Negative Learning Bias in Depression Revisited: Enhanced Neural Response to Surprising Reward Across Psychiatric Disorders

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ABSTRACT

BACKGROUND: Prior work has proposed that major depressive disorder (MDD) is associated with a specific cognitive bias: patients with depression seem to learn more from punishment than from reward. This learning bias has been associated with blunting of reward-related neural responses in the striatum. A key question is whether negative learning bias is also present in patients with MDD and comorbid disorders and whether this bias is specific to depression or shared across disorders.

METHODS: We employed a transdiagnostic approach assessing a heterogeneous group of (nonpsychotic) psychiatric patients from the MIND-Set (Measuring Integrated Novel Dimensions in Neurodevelopmental and Stress-Related Mental Disorders) cohort with and without MDD but also with anxiety, attention-deficit/hyperactivity disorder, and/or autism (n = 66) and healthy control subjects (n = 24). To investigate reward and punishment learning, we employed a deterministic reversal learning task with functional magnetic resonance imaging.

RESULTS: In contrast to previous studies, patients with MDD did not exhibit impaired reward learning or reduced reward-related neural activity anywhere in the brain. Interestingly, we observed consistently increased neural responses in the bilateral lateral prefrontal cortex of patients when they received a surprising reward. This increase was not specific to MDD, but generalized to anxiety, attention-deficit/hyperactivity disorder, and autism. Critically, increased prefrontal activity to surprising reward scaled with transdiagnostic symptom severity, particularly that associated with concentration and attention, as well as the number of diagnoses; patients with more comorbidities showed a stronger prefrontal response to surprising reward.

CONCLUSIONS: Prefrontal enhancement may reflect compensatory working memory recruitment, possibly to counteract the inability to swiftly update reward expectations. This neural mechanism may provide a candidate transdiagnostic index of psychiatric severity.

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Major depressive disorder (MDD) is a highly debilitating psychiatric disorder with an estimated yearly prevalence of 4.4% worldwide (1). Key symptoms of MDD are persistent negative mood and diminished interest or inability to experience pleasure (also termed anhedonia) (2). These symptoms have been linked to a so-called negative learning bias; patients with MDD are thought to weigh negative events more strongly than positive events in their subsequent decisions. Experimentally, this has been measured as reduced learning from positive feedback (reward) compared with negative feedback (punishment) (3–12). This behavioral bias is often accompanied by blunted reward-related activity in the striatum, a brain region involved in processing reward and reward prediction (10,13,14). For example, Robinson *et al.* (7) observed impaired reward-based learning and blunted neural response in the striatum to surprising rewards in MDD compared with control subjects. This negative learning bias concurs with a larger body of work showing that patients with MDD focus more on negative events than on positive events in other cognitive domains. For example, patients with MDD show automatic and selective preferential processing of negative information over neutral or positive information in attention, interpretation, and memory (2,15,16).

However, two key issues have so far been overlooked, namely the generalizability and specificity of the bias to real-world MDD. Most prior studies have relied on highly selected samples from the (sub)clinically depressed population, with limited age ranges, relatively small sample sizes, and nonclinical control samples with low depressive symptom severity. Patient control groups were often not included. Therefore, it remains unclear whether the bias is specific to MDD or rather is also seen in other disorders without comorbid MDD. In addition, many studies 1) have included only patients with no or few comorbid diagnoses, 2) did not extensively

assess comorbidity, or 3) did not purposefully integrate this factor into the study design (4,7,10,17–20). While these types of studies are informative for understanding potential mechanisms and neurocognitive deficits underlying MDD, this approach does not consider one key observation, namely that up to 70% of psychiatric patients with MDD are diagnosed with at least one comorbid mental disorder, including anxiety disorder, addictive disorder, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) (21–23). It remains unclear whether any negative learning bias is also seen in patients with MDD who have other disorders. To tackle these issues, we adopted a transdiagnostic approach in line with the recommendations of the Research Domain Criteria framework. This approach targets the transdiagnostic mechanisms of psychopathology beyond diagnostic labels (24,25) and allowed us to test 1) its generalizability to real-world comorbid depression and 2) its specificity to MDD compared with other disorders. Critically, we employed the reward/punishment reversal learning paradigm that was also used in a previous study demonstrating a negative learning bias and reduced reward-related activity in the striatum (7). We predicted impaired reward versus punishment learning and reduced reward versus punishment-related brain activity in the striatum in MDD versus other disorders. However, based on work suggesting that negative memory bias may be a transdiagnostic mechanism of psychopathology (26), we also considered the possibility that a negative learning bias across diagnoses may reflect a transdiagnostic index or risk factor of psychiatric severity, rather than MDD severity alone.

To recap, the first aim of the current study was to test the generalizability of the negative learning bias seen in MDD to a comorbid patient sample with MDD but also at least one comorbid disorder, including anxiety, addiction, ADHD, and ASD (other mental disorders, except psychotic disorders, were allowed). This approach attempted to reproduce the high comorbidity levels observed in the larger population for which highly selected samples might not be very representative. The second aim was to investigate the specificity of any observed index of negative learning bias and associated striatal activity to depressive symptoms compared with other disorders. Observed neural and/or behavioral markers may reflect an MDD-specific deficit or, alternatively, a transdiagnostic index of psychiatric severity more generally.

METHODS AND MATERIALS

General Procedure and Participants

The current study is part of MIND-Set (Measuring Integrated Novel Dimensions in Neurodevelopmental and Stress-Related Mental Disorders), a large cohort study run by the Department of Psychiatry at Radboud University Medical Center in Nijmegen, The Netherlands. MIND-Set includes new outpatients (18–65 years of age) with depressive disorder (MDD or dysthymia), anxiety disorder, ADHD, and/or ASD. Disorders were assessed with the use of validated semistructured clinical interviews according to DSM criteria (see Supplement for full procedure). Participants were excluded if they had a current psychotic disorder, an IQ estimation <70, sensorimotor disabilities, or insufficient comprehension of the Dutch language. MIND-Set was approved by the local ethics committee.

The final sample included 66 patients and 24 healthy control participants (HCs) (see Supplemental Methods). Patients were divided into two groups: those with a current depressive disorder (n = 43) and those without one (n = 23). In both groups, patients could also have remitted depressive disorder, anxiety disorder, ADHD, and/or ASD. To classify ASD and/or ADHD, patients were first screened and, in case of a positive screening, were further assessed by interviews (Supplement). Three of the included patients did not receive a final diagnosis of ASD and/or ADHD by the end of the study owing to, for example, dropout during the diagnostic process.

We included 24 healthy participants with no current or lifetime psychiatric disorder assessed with the same measures that were used for the patients. They were matched to the patient sample on age, gender, and education level (Table 1). HCs participated in the same tasks and questionnaires as patients (Table S1). Written informed consent was obtained from all subjects prior to participation.

For all participants, we collected sociodemographic information (age, gender, and level of education), psychiatric symptom severity with different questionnaires, background neuropsychology (verbal IQ and working memory capacity), and medication use (see Supplement for details).

Deterministic Reversal Learning Task

A modified version of an established deterministic reversal learning task was employed to investigate learning biases (27) (Figure 1A). The task was programmed with Presentation version 16.2 (Neurobehavioral Systems, Inc., Berkeley, CA). In this task, participants needed to predict whether a specific picture would be followed by a positive outcome (a reward) or a negative outcome (a punishment). On each trial, two vertically adjacent pictures were displayed in grayscale (Figure 1A): a picture of a body and a picture of a scene. We used 18 different unique exemplars of each category (18 bodies and 18 scenes). The decision to use two categories of pictures (rather than just two pictures) was guided by an interest in examining neural activity in category-specific visual association cortices. Results from this parallel research question will be described elsewhere. The location of the pictures (upper or lower half of the screen) was randomized. One of the pictures was highlighted by a black border. Participants needed to predict whether this highlighted picture would lead to a reward or punishment outcome by pressing either a left or right button on a button box (counterbalanced across subjects). Failure to respond within the time limit (1500 ms) was followed by the message “Too late.” In case of a timely response, the outcome (reward or punishment) was presented with the two pictures still on the screen. The reward outcome was a green happy smiley accompanied by the text “+ €100”; the punishment outcome was a red sad smiley accompanied by the text “− €100.” Note that the outcome did not depend on participants’ responses. The critical manipulation was that one category (bodies or scenes) always led to reward, and the other category always led to punishment. Participants needed to learn these category–outcome associations by trial and error and adapt their predictions and responses accordingly.

Table 1. Sample Characteristics: Demographic Information and Group Comparison Statistics

	MDD Present, n = 43	MDD Absent, n = 23	HC, n = 24	Group Comparisons
Age, Years, Mean (SD)	38.23 (13.19)	36.04 (11.46)	35.46 (13.03)	$F_{2,87} = 0.441$, $p = .645$
Gender, n	M: 22 F: 21	M: 14 F: 9	M: 9 F: 15	$\chi^2_2 = 2.61$, $p = .271$
NART Score, Mean (SD)	101.50 (11.04)	99.14 (9.20)	96.35 (19.81)	$F_{2,81} = 1.05$, $p = .354$
SWM Errors, Mean (SD)	20.30 (18.32)	16.14 (13.03)	20.38 (22.30)	$F_{2,82} = 0.41$, $p = .667$
Level of Education, n				$\chi^2_6 = 5.17$, $p = .522$
(Almost) none	2	0	0	–
Low	5	4	2	–
Middle	16	11	8	–
High	18	8	14	–
IDS Score, Mean (SD)	39.72 (10.92)	25.70 (10.90)	4.42 (3.92)	$F_{2,87} = 104.86$, $p < .001$
Number of Diagnoses				$\chi^2_5 = 8.25$, $p = .143$
0[a]	–	3	–	–
1	7	3	–	–
2	14	9	–	–
3	13	6	–	–
4	5	2	–	–
5	4	–	–	–
Medication				
SSRIs	19	5	–	–
Benzodiazepine	10	2	–	–
Antipsychotics	7	3	–	–
DA	4	3	–	–
Opioids	4	–	–	–
TCA	2	1	–	–
Lithium	1	–	–	–

DA, dopaminergic medication; F, female; HC, healthy control subjects; IDS, Inventory of Depressive Symptomatology–Self-Report version; M, male; MDD absent, patients without a current depressive episode but with a different diagnosis; MDD present, patients with a current depressive episode; NART, National Adult Reading Test; SSRI, selective serotonin reuptake inhibitor; SWM, spatial working memory; TCA, tricyclic antidepressants.

[a]Note that on the number of diagnoses, we included 3 patients who did not finish the diagnostic process and were included without a final diagnosis.

This deterministic link between category and outcome changed after 4 to 6 consecutive correct predictions, so that now the category previously associated with reward (e.g., bodies) would be associated with punishment and vice versa for the other category (defined as a reversal) (Figure 1B). Upon such reversals, an unexpected reward was presented after a picture category was highlighted that was previously followed by a punishment (and vice versa). The participants were required to adapt their predictions accordingly on the following trials (the picture category predicting reward would now be predicting punishment and vice versa). Prediction accuracy on the trials after the unexpected reward or punishment indicated how quickly participants adapted their predictions based on unexpected outcome. Note that a different exemplar from the same category would always be highlighted on the trial after a reversal. This ensured that the need for a response switch was matched between the unexpected reward and unexpected punishment trials (28,29). After 16 consecutive incorrect predictions, the task was terminated, assuming a failure to follow task instructions. If possible and in agreement with the participants, the task would restart. Blocks of trials that were prematurely terminated were excluded from further analysis. We included 3 participants in the analysis (1 HC and 2 patients with MDD) who had one restarted block.

Statistical Analyses

We investigated the effects of expectancy (unexpected > expected), valence (reward > punishment), and the interaction expectancy × valence (unexpected reward − expected reward > unexpected punishment − expected punishment) on the behavioral outcome measures (accuracy and reaction time) and in second-level functional magnetic resonance imaging (fMRI) analyses. We then examined the differences between the groups and as a function of symptom severity, as explained in detail below. For behavior, we used mixed models [R package lme4 (30)], employing generalized mixed models to test trial-by-trial accuracy and used linear mixed models for reaction times. We tested the fixed effects of expectancy, valence, group (HCs, patients with a current depressive episode [MDD present], or patients without a current depressive episode but with a different diagnosis [MDD absent]), and all interactions. The model included a full random-effects structure with random slope and random intercept (31,32). Note that accuracy and reaction time on reversal trials represent data from trials after an unexpected outcome (i.e., a reversal) (Figure 1B).

Imaging was conducted on a Siemens Prisma 3T scanner using a 32-channel head coil. Whole-brain T2*-weighted blood

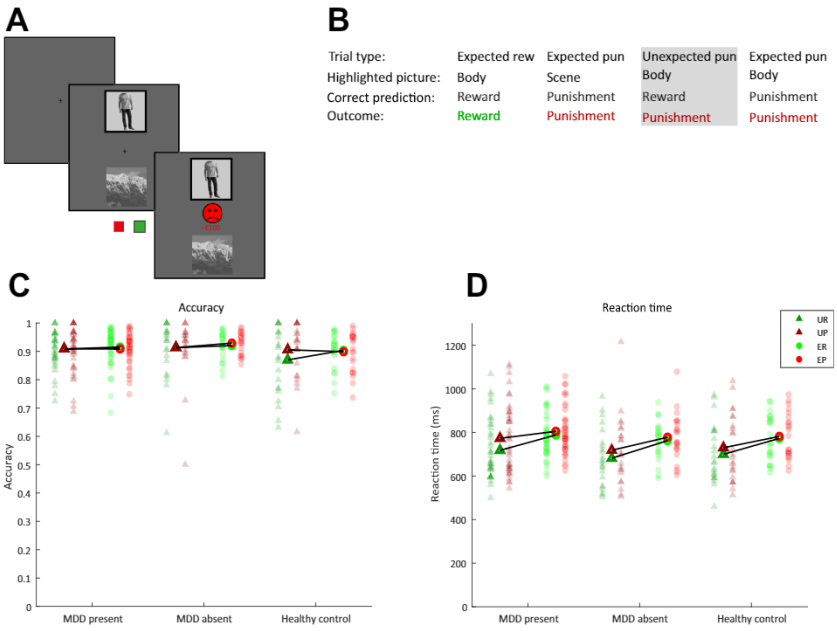

Figure 1. Task and behavioral results. **(A)** Task overview. After a response was given, the outcome was shown for 500 ms after a delay of 1000 ms. There was a jittered intertrial interval of 1500 to 3000 ms, after which two pictures were presented. Here we show an example of an unexpected punishment (UP) trial. First, the body is associated with reward. The body is selected, and therefore the correct prediction is a reward. However, now the outcome reverses unexpectedly, showing an unexpected punishment outcome. In the behavioral analyses, we examined the trials after such an unexpected outcome to assess whether the new category–outcome contingency was learned. For the functional magnetic resonance imaging analyses, we examined outcome-locked activity. Four blocks of the task were performed. Each block consisted of 120 trials and lasted about 10 minutes. Reversals following reward and punishment were randomized across the blocks. Number of reversals per participant depended on performance. **(B)** Example of series of trials before and after the unexpected punishment as presented in **(A)**. **(C)** Accuracy of the 4 trial types for the 3 groups. There were no significant main effects or interactions of the factors expectancy, valence, and group (all $ps > .25$). **(D)** Reaction times on the 4 trial types for the 4 groups. There was a significant interaction between valence and expectancy ($\chi^2_1 = 4.27$, $p = .038$), with the fastest responses being after surprising reward outcomes. There was a significant main effect of valence ($\chi^2_1 = 10.20$, $p = .001$), with faster predictions being for reward compared with punishment, and there was a significant main effect of expectancy ($\chi^2_1 = 37.42$, $p < .001$), with faster predictions after receiving surprising outcomes compared with expected outcomes. No significant interactions with group were observed (all $ps > .39$). EP, expected punishment; ER, expected reward; MDD absent, patients without a current depressive episode but with a different diagnosis; MDD present, patients with a current depressive episode; UR, unexpected reward.

oxygen level–dependent fMRI data were acquired using multiecho echo-planar imaging. Brain images were preprocessed and analyzed using SPM12 (Wellcome Department of Cognitive Neurology, London) and MATLAB R2018a (The MathWorks, Inc., Natick, MA). A first-level general linear model was estimated and included regressors for each of the possible outcomes (specifically unexpected reward, unexpected punishment, correctly predicted expected reward, correctly predicted expected punishment, incorrectly predicted expected outcomes, miss trials, and 6 motion regressors, i.e., 12 regressors in total). Regressors were estimated at the onset of outcome presentation and convolved with a hemodynamic response function.

We calculated individual contrast maps at the first level for expectancy, valence, expectancy × valence, and the reverse contrasts. The individual contrast maps were then included in a second-level random-effects analysis to investigate differences between the groups and as a correlation with the questionnaire scores. A whole-brain voxel-level threshold of $p < .001$ uncorrected was applied with a cluster-level familywise error correction for multiple comparisons of $p < .05$. See the Supplement for a complete description of the behavioral analyses as well as fMRI data acquisition and analyses.

To address our primary aims of assessing generalizability and specificity to MDD, we adopted a multistep procedure in the analyses (Figure S1). First, all brain and behavior analyses were performed using two different stratification approaches of the patient sample: a categorical approach and a dimensional approach. In the categorical approach, we compared 3 groups: HCs, MDD present, and MDD absent. In the dimensional approach, we stratified the sample based on depressive symptom severity, as measured with the Inventory of Depressive Symptomatology–Self-Report version (IDS) (33)]. Second, we repeated this set of analyses (categorical and dimensional) three times for each of the other three diagnoses (anxiety, ADHD, and ASD). In particular, we stratified the sample categorically, based on anxiety, ADHD, or ASD diagnosis (HCs vs. MDD present vs. MDD absent), and dimensionally, using the Anxiety Sensitivity Index (ASI) (34) for anxiety sensitivity, the Conners' Adult ADHD Rating Scale (CAARS) (35) for ADHD, and the Autism Spectrum Quotient (AQ-50) (36) for ASD. This multistep procedure was adopted for the behavioral data (with accuracy and reaction time as dependent variables) as well as for the brain data (whole-brain analyses).

We also assessed whether potential differences in brain activity between patients and control subjects might be accounted for by general psychiatric severity. To this end, first we conducted a random-effect analysis with only the number of diagnoses as a covariate. Second, we added the number of diagnoses as a covariate in the general linear model examining the difference among MDD present, MDD absent, and HCs (categorical approach) to assess whether the effects we found could be accounted for by general psychiatric severity.

We found significant associations between neural activity and total scores on all 4 symptom questionnaires as well as on the number of diagnoses. Therefore, we aimed to explore the nature of this transdiagnostic effect by leveraging all individual item scores across the multiple symptom questionnaires in a

Table 2. Whole-Brain Results

Contrast	Region	MNI Coordinates x	y	z	Cluster Size	*t*	FWE Cluster-Level *p*
MDD Present > HC							
Surprising reward (unexpected reward − expected reward > unexpected punishment − expected punishment)	Left inferior frontal gyrus	−48	35	18	49	4.82	.005
	Right inferior frontal gyrus	46	28	18	31	4.46	.036
MDD Absent > HC							
Surprising reward (unexpected reward − expected reward > unexpected punishment − expected punishment)	Right insula	50	14	−7	133	5.08	<.001
	Left inferior frontal gyrus	−55	18	7	64	4.09	.001
	Right inferior frontal gyrus	43	28	18	36	3.72	.020
IDS							
Surprising reward (unexpected reward − expected reward > unexpected punishment − expected punishment)	Left inferior frontal gyrus	211	−48	38	14	5.24	<.001
	Left inferior temporal gyrus	187	−52	−60	−7	4.86	<.001
	Vermis	98	4	−52	7	4.61	<.001
	Right inferior frontal gyrus (operculum)	111	57	18	4	4.52	<.001
	Right superior frontal gyrus (medial)	52	12	32	38	4.50	.003
	Left middle occipital gyrus	63	−30	−74	32	4.24	.001
	Left inferior parietal	48	−30	−18	28	4.43	.005
	Right angular gyrus	196	43	−46	28	4.40	<.001
	Right calcarine fissure	97	26	−66	10	4.28	<.001
	Right lingual gyrus	65	32	−84	−18	4.24	.001
	Precuneus	196	1	−63	56	4.20	<.001
	Right putamen	37	29	38	14	4.12	.016
	Left middle frontal gyrus	77	−41	4	56	4.06	<.001
	Right inferior frontal gyrus (operculum)	29	46	10	35	3.94	.042
Reward > punishment	Right cerebellum	42	15	−74	−21	4.05	.015

FWE, familywise error; HC, healthy control subjects; IDS, Inventory of Depressive Symptomatology–Self-Report version; MDD absent, patients without a current depressive episode but with a different diagnosis; MDD present, patients with a current depressive episode; MNI, Montreal Neurological Institute.

post hoc analysis. Specifically, a factor analysis (principal component analysis) was conducted comprising all items of the IDS, ASI, CAARS, and AQ-50, resulting in a total of 120 items. This analysis was done on all MIND-Set participants (569 patients and 101 HCs).

Furthermore, we examined a selected subsample of patients with MDD without comorbidity to be able to compare the results with findings from previous studies that included only patients with MDD without comorbidity. Finally, based on the study of Robinson *et al.* (7), we performed an additional region of interest analysis specifically targeting neural activity in the striatum. Results of these analyses are presented in the Supplement.

RESULTS

Demographics and Behavioral Results

Patient groups and controls did not differ significantly in terms of age, gender, working memory capacity, verbal IQ, or level of education (Table 1; see Table S1 for a detailed description of the questionnaires and tasks used). Critically, the number of diagnoses did not differ between patients with MDD and patients without MDD. As expected, there was a significant group difference in depressive symptom severity (IDS), with lower ratings in the HC group than the MDD present group ($t_{58.00} = -19.11$, $p < .001$) and MDD absent group ($t_{27.39} = -8.83$, $p < .001$). Depressive symptom ratings of the MDD absent group were lower than those of the MDD present group ($t_{64.00} = -4.98$, $p < .001$).

There were no differences among the groups on accuracy and reaction time; the patients performed the task as well as the HCs (Figure 1C, D). Furthermore, accuracy and reaction time also did not vary with any of the other diagnostic categories (anxiety, ADHD, or ASD), and there were also no significant effects of the IDS, ASI, CAARS, or AQ-50 scores on accuracy or reaction time. See the Supplement for a detailed report.

Whole-Brain fMRI Results

Patients with MDD exhibited enhanced reward prediction error–related blood oxygen level–dependent signals in the bilateral inferior frontal gyrus compared with HCs (Table 2 and Figure 2A) (contrast: unexpected reward − expected reward > unexpected punishment − expected punishment). This enhanced lateral prefrontal cortex (LPFC) response was also observed in patients without MDD compared with HCs (Table 2). Conversely, no group differences were found between the MDD present and MDD absent groups. There were no other effects of group as a function of valence or expectancy.

A breakdown of the interaction demonstrated that the increased activity in the LPFC was driven by an enhanced

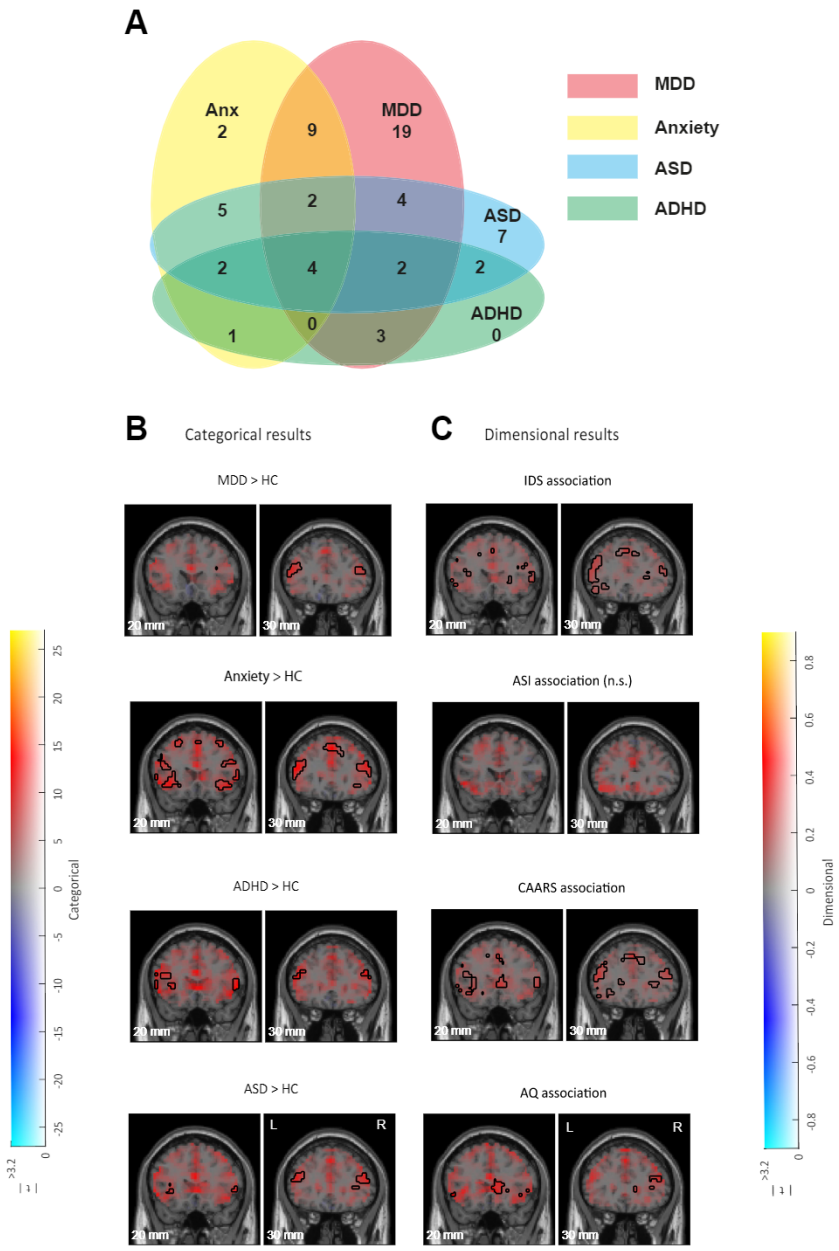

Figure 2. Overlap between patient groups and dual-coded whole-brain maps. **(A)** Number of participants with each disorder. All patients with major depressive disorder (MDD) (marked in red) were in the MDD present group, and all patients without MDD were in the MDD absent group. Note that this figure does not include 3 participants without a final diagnosis and 1 participant who was diagnosed with only remitted MDD. The size of the square does not represent the number of patients. **(B)** Categorical results. **(C)** Dimensional results. Clusters show positive (red) activity for the contrast of the interaction of group × valence × expectancy (unexpected reward − expected reward > unexpected punishment − expected punishment), with the groupwise comparisons in **(B)** and the associated questionnaire scores in **(C)**. The maps are dual coded and display both the contrast estimate (x-axis) and unthresholded *t* values (y-axis). Significant clusters (cluster level corrected, familywise error, $p < .05$) are marked with a black border. These whole-brain maps are displayed using a procedure introduced by Allen *et al.* (63) and implemented by Zandbelt (64). ADHD, attention-deficit/hyperactivity disorder; Anx, anxiety; AQ, Autism Spectrum Quotient; ASD, autism spectrum disorder; ASI, Anxiety Sensitivity Index; CAARS, Conners' Adult ADHD Rating Scale; HC, healthy control subjects; IDS, Inventory of Depressive Symptomatology–Self-Report version; n.s., nonsignificant.

response to unexpected reward. First, we examined the separate contrasts unexpected reward > expected reward and unexpected punishment > expected punishment. For the contrast unexpected punishment > expected punishment, there were no significant clusters in any of the group comparisons. For the contrast unexpected reward > expected reward, in the comparison between the MDD present group and the HC group there was a significant cluster in the LPFC (left inferior frontal gyrus; Montreal Neurological Institute [MNI] coordinates x = −44, y = 28, z = 21; cluster size = 41, $t = 4.37$, corrected $p = .025$), and in the comparison between the MDD absent group and the HC group there were clusters in the anterior cingulate cortex (MNI coordinates x = 4, y = 18, z = 21; cluster size = 40, $t = 4.10$, corrected $p = .027$) and left insula/inferior frontal gyrus (MNI coordinates x = −38, y = 18, z = −10; cluster size = 40, $t = 4.08$, corrected $p = .027$) (Figure S2). There were no significant differences between the MDD present and MDD absent groups. Further breakdown into simple effects (for each event type separately) demonstrated that MDD present group versus HC group exhibited a significantly increased response in the left superior frontal gyrus during unexpected reward (MNI coordinates x = −24, y = 52, z = −7; cluster size = 45, $t = 5.34$, corrected $p = .019$), but there were no differences during expected reward (Figure S3).

Critically, the enhanced response in the LPFC to surprising reward was observed not only when patients with MDD were

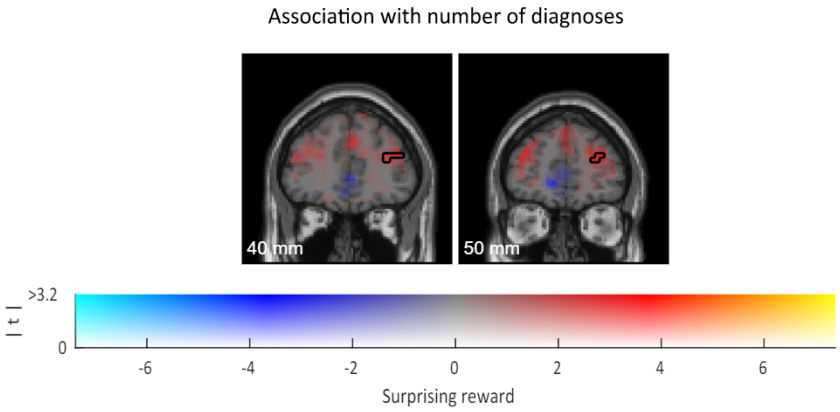

Figure 3. General psychiatric severity. Neural response to surprising reward increases as a function of number of diagnoses. Clusters show positive (red) and negative (blue) activity for the contrast of the interaction of number of diagnoses × valence × expectancy (unexpected reward − expected reward > unexpected punishment − expected punishment).

compared with HCs but also when the sample was stratified by anxiety, ADHD, or ASD. It was present as a function of depressive, ADHD, and ASD symptoms and also as a function of the number of diagnoses (Figure 2B, C; see the Supplement for a full report).

To summarize, we observed enhanced LPFC response to surprising reward in MDD present group versus HC group as well as in MDD absent group versus HC group. This enhanced LPFC response was also observed as a function of depressive, ADHD, and ASD symptom severity and the number of diagnoses (Figure 3). Thus, enhanced LPFC response to surprising reward reflects a transdiagnostic characteristic that is not restricted to one of the four studied disorders.

Next, we explored the nature of this transdiagnostic effect using a post hoc factor analysis on all individual item scores across the multiple symptom questionnaires (see Supplement for the scree plot and table with factor loadings: Figure S6 and Table S7). Four factors were identified based on the scree plot (explained variance: 35.28%). These factors were labeled interest, social interaction, attention and concentration, and physical distress. We explored the selective contribution of each of these factors to brain activity in the LPFC cluster from the surprising reward contrast in the comparison of patients versus HCs. We illustrate the results of this exploratory analysis of the four factor scores but do not perform statistics or report p values (to avoid circular inference). The signal in the LPFC cluster varied with factor 3 scores (attention and concentration) but not with any of the other factor scores (Figure 4). We also performed whole-brain analyses with each of the factors as a covariate in the model. The significant LPFC clusters with each factor are presented in Table S8. A voxel-level threshold of $p < .001$ uncorrected was applied, with a cluster-level familywise error correction for multiple comparisons of $p < .05$. There were significant clusters in the surprising reward contrast for factors 2, 3, and 4.

DISCUSSION

This study investigated the generalizability and specificity of negative learning bias in patients with MDD with psychiatric comorbidities. Contrary to previous reports, we did not replicate previous findings of reduced learning from reward, nor did we find evidence of blunted reward activity in the striatum (in comorbid MDD or in any of the other patient groups). Rather, patients with MDD exhibited markedly enhanced neural response to surprising rewards in the bilateral LPFC, specifically the inferior frontal gyrus. Moreover, this effect was not specific to MDD but rather generalized to patients with anxiety, ADHD, and/or ASD. In fact, this enhanced neural response was accounted for by the number of diagnoses, indicating an effect of general psychiatric severity irrespective of diagnosis.

Increased LPFC response in patients concurs with previous findings from two meta-analyses that found enhanced PFC activity in MDD during reward outcome (37,38). It was proposed that this increase in prefrontal activity might be associated with the previously observed reduction in striatal

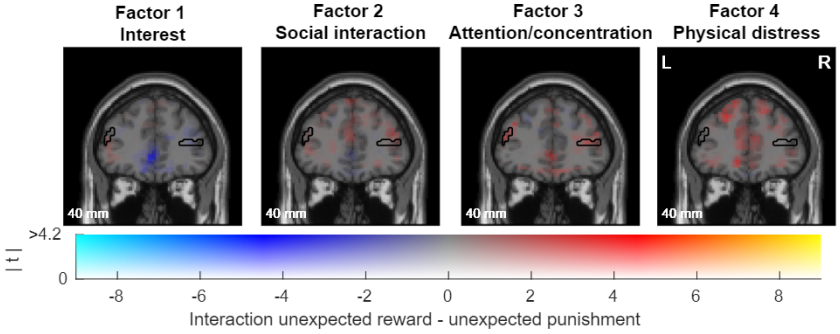

Figure 4. Association between brain responses to surprising reward and factor scores resulting from our factor analysis across all participants. We specifically examined activity within the lateral prefrontal cortex cluster from the surprising reward contrast in the comparison of patients (Figure 2A) vs. healthy control subjects (left: x = −48, y = 35, z = 18, k = 45; right: x = 46, y = 28, z = 18, k = 102). This lateral prefrontal cortex cluster is marked with a black border. Activation in the lateral prefrontal cortex cluster varied only with factor 3.

response in MDD during reward processing (38). However, the current lack of a blunted striatal reward response is not consistent with this account. More targeted region-of-interest analyses even revealed similarly increased reward-related signal in the striatum (see Supplement).

Enhanced neural response to surprising reward in psychiatric patients may reflect one of various underlying mechanisms. The stronger LPFC response might reflect a compensatory response corresponding to the recruitment of a working memory strategy to compensate for a putative underlying striatal reward learning deficit. We argue that the current learning task is particularly sensitive to the recruitment of such cortical rule-based strategies for two reasons. First, the outcome contingencies were deterministic, rendering the use of a working memory strategy more optimal than an incremental reinforcement learning strategy, which benefits learning more in the context of probabilistic contingencies (39,40). Previous literature has indeed observed increased activation in the LPFC in participants with depression during working memory tasks where performance in the patients was also similar to that in the HCs (41–43). Given that performance on both the reversal task and spatial working memory task (see Supplement) did not vary with symptom severity, we speculate that this increase in LPFC response reflects compensatory upregulation. Future studies might test the hypothesis that patients with MDD rely more readily on an LPFC working memory strategy than on a reinforcement learning strategy using paradigms that are explicitly developed to investigate biases in the interaction between working memory and reinforcement learning strategies (39,40). Second, the task required the learning and updating of associations between outcomes and stimulus categories (e.g., bodies) rather than stimulus exemplars, akin to the type of extradimensional set shifting measured, for example, using the classic Wisconsin Card Sorting Task (44). Extradimensional set shifting is well known to be associated with the LPFC (45–47), and patients with MDD have been shown to exhibit enhanced LPFC activity during extradimensional set shifting (48).

An alternative explanation is that patients cannot update their reward expectation based on positive feedback as well as HCs. If predictions are generally more negative in patients, then surprisingly good outcomes are relatively more surprising than surprisingly bad outcomes. The concept of a reward prediction deficit in MDD is in line with recent work proposing that negative bias in MDD reflects a pessimistic view of the world and beliefs about the future (49–52). The authors of this work argue that patients with MDD have more difficulties in updating their negative expectation about their own performance after surprising positive feedback. Note that these studies used performance-contingent feedback, thereby reflecting a pessimistic prediction about the outcome of one's actions (49,50,53). In contrast, our study tested participants' prediction about noncontingent outcomes (independent of their performance). Nonetheless, both lines of evidence would support a reward prediction deficit account; if rewards are less expected in general, unexpected rewards will be more surprising.

This account concurs with previous work on prediction (violation) in healthy people, demonstrating LPFC and medial PFC responses to surprising rewards (prediction errors) (54,55). Indeed, the inability to accurately predict rewards has been proposed as a candidate mechanism for anhedonia in depression (56). This pessimistic expectation account might be reconciled with the prefrontal compensatory account if patients rely more on working memory specifically when inhibiting a prior punishment prediction and boosting a novel reward association.

To compare our results with those of Robinson *et al.* (7), we also examined a selected subsample of patients with MDD without comorbidity (see Supplement) who, however, also did not exhibit blunted reward activity. In fact, there was no evidence of reward-related striatal activity in HCs either. A critical difference between the task used in Robinson *et al.* (7) and the current study was the requirement to link outcomes to a category rather than to an exemplar. Moreover, the fact that feedback in the current task was not performance dependent might have further contributed to pushing striatal blood oxygen level–dependent signals below our detection threshold (57). Together with the deterministic nature of the contingencies, these aspects might have led learning to rely more strongly on prefrontal mechanisms than was the case in Robinson *et al.* (7) and other studies using probabilistic tasks (58). Thus, the lack of a striatal reward learning deficit in the current task might not generalize to other reward learning tasks that do implicate the striatum (40,59).

An important aim of the current study was to test the specificity of neural changes to MDD. Enhanced response to surprising reward was observed in all disorders and was also associated with symptom severity in MDD, ASD, and ADHD, arguing against specificity. Intriguingly, activity in the LPFC was positively associated with the number of diagnoses, and when the number of diagnoses was added as a regressor of interest, the group difference was no longer observed. In addition, the number of diagnoses was associated with all symptom-level scores (as measured with the IDS, ASI, CAARS, and AQ-50) (Table S6) and did not differ between the MDD present and MDD absent groups.

The next question we asked was whether this transdiagnostic effect might reflect a disproportionate contribution of a specific subset of transdiagnostic symptoms. Factor analysis of the items from the 4 questionnaires measuring symptom severity of depression, anxiety sensitivity, ADHD, and ASD across participants revealed the four factors: interest, social interaction, attention and concentration, and physical distress. Although all the symptoms of social interaction, attention and concentration, and physical distress were involved, there was some qualitative indication that impaired attention may play a bigger role than the others (yet this remains an exploratory result). However, it might be noted that this analysis will reveal only those factors that are measured using our questionnaires. The current finding does not speak to the exclusion of other (unmeasured) symptom dimensions such as motor action planning and visual perception. Taken together, these findings likely indicate enhanced LPFC response to surprising reward as a candidate transdiagnostic marker of psychiatric conditions, possibly reflecting impaired attention and concentration. Previous work has suggested that comorbidity between different psychiatric disorders could indicate that these disorders at least partially share underlying mechanisms (60). Recent work suggests that negative memory

bias could be an example of a transdiagnostic mechanism of psychopathology (26). The current results suggest that the neural response to surprising reward in the LPFC may be a novel candidate mechanism that could provide a transdiagnostic index of psychiatric severity.

A limitation of this study was the use of psychotropic medication. Many of the patients used not only selective serotonin reuptake inhibitors but also benzodiazepines, antipsychotics, or opioids. These can have a considerable effect on both behavioral and neural responses (61,62). We assessed the effect of selective serotonin reuptake inhibitor use by comparing patients using at least one selective serotonin reuptake inhibitor with patients using no medication or other medication and did not find a difference in LPFC response among these different groups. However, we cannot exclude the possible role of other medications (e.g., benzodiazepines, antipsychotics, psychostimulants). Future studies should include larger samples of patients using different types of psychotropic medications so that the effects of these medications can be investigated in more detail.

To conclude, we investigated negative learning bias in patients with depression with comorbid (nonpsychotic) psychiatric disorders and observed no evidence of reduced reward learning or of blunted reward processing. Conversely, we observed enhanced neural response to surprising reward in the LPFC in patients. This effect was not specific to MDD but rather was generalized to other diagnoses and also scaled with symptom severity. Importantly, it was also associated with the number of diagnoses—a surface measure of comorbidity severity—and the severity of impairments of attention and concentration, as measured with a dimensional approach. Enhanced response to surprising reward in the LPFC thus provides a candidate neural index of psychiatric severity.

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