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Reward Processing in Depression: A Conceptual and Meta-Analytic Review Across fMRI and EEG Studies

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Abstract

Objective: A role for aberrant reward processing in the pathogenesis of depression has long been proposed. However, no review has yet examined its role in depression by integrating conceptual and quantitative findings across functional MRI (fMRI) and EEG methodologies. The authors quantified these effects, with an emphasis on development.

Method: A total of 38 fMRI and 12 EEG studies were entered into fMRI and EEG meta-analyses. fMRI studies primarily examined reward anticipation and reward feedback. These were analyzed using the activation likelihood estimation method. EEG studies involved mainly the feedback-related negativity (FRN) event-related potential, and these studies were analyzed using random-effects meta-analysis of the association between FRN and depression.

Results: Analysis of fMRI studies revealed significantly reduced striatal activation in depressed compared with healthy individuals during reward feedback. When region-of-interest analyses were included, reduced activation was also observed in reward anticipation, an effect that was stronger in individuals under age 18. FRN was also significantly reduced in depression, with pronounced effects in individuals under age 18. In longitudinal studies, reduced striatal activation in fMRI and blunted FRN in EEG were found to precede the onset of depression in adolescents.

Conclusions: Taken together, the findings show consistent neural aberrations during reward processing in depression, namely, reduced striatal signal during feedback and blunted FRN. These aberrations may underlie the pathogenesis of depression and have important implications for development of new treatments.

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Depression has a prevalence of 19% in the U.S. population (1), and over 300 million people suffer from the disorder worldwide (2). However, compared with many other medical conditions, we know little about its pathophysiology. In recent years, reward processing aberrations have been proposed as a candidate mechanism, which has implications for much-needed treatment breakthroughs (3–5). This quantitative review integrates the available evidence relating reward processing to depression.

Previous meta-analyses that included data on reward processing and depression have differed from this work in various aspects, including a focus on selected age groups (for example, excluding patients under 18) or on limited populations or only on patients with severe depression; analysis of region-of-interest-based studies; and use of lenient thresholds; some of these studies are also now outdated (6–10). Similarly, no previous quantitative review has pooled effects of electrophysiological studies exploring the association between reward processing and depression. While EEG's spatial resolution is inferior to that of junctional MRI (fMRI), its superior temporal resolution is particularly relevant to the study of reward processing dynamics. Moreover, feedback-related negativity (FRN; also termed reward positivity) has emerged as a powerful measure of reward processing (11, 12) implicated in depression (13), making it essential to include such studies. Notably, in this meta analysis, we also focused on developmental effects, as both reward processes (14) and depression show developmental moderation (15).

CONCEPTUAL LINKS BETWEEN DEPRESSION AND REWARD PROCESSING

Cardinal presentations of depression (16), most notably an-hedonia, are thought to reflect alterations of the experience of reward (17, 18). The following paragraphs conceptually bridge clinical terminology with the burgeoning science of reward processing.

Rewards have been defined as stimuli that induce behaviors that help the animal organism obtain what is necessary for survival (19). In addition, rewards and punishers facilitate learning through positive or negative reinforcement: a reward (or lack of punishers) following a behavior will make the future occurrence of that behavior more likely, often eliciting feelings of pleasure; the opposite is true for behaviors followed by punishers (or lack of rewards). Reductions in reports of pleasure and approach-related behavior are a prominent feature of depression, and many suggest that they arise from aberrations in reward processing (3, 20).

In Table 1, we have adapted previous models (21, 22) to parse four sets of reward processing events and map their links to clinical phenomena. We term the first stage of reward processing *prediction*: it encompasses recognizing an object as potentially rewarding, a process that involves using existing knowledge about the value of objects. Anticipatory anhedonia, defined as a lack of interest in activities that used to be enjoyable, is the clinical depressive symptom that best maps onto this phase. In translational terms, this phase is typically captured by the reward or loss anticipation/prediction phase of an experiment, when a stimulus induces the subject to expect either a win or a loss. When attempting to

engage prediction-related processes in translational work, the classic task is the monetary incentive delay paradigm (23).

The second stage, *decision*, involves computing the cost associated with attaining a reward. Depressed patients often report decision-making problems (16, 24), sometimes seen by others as “lack of initiative.” These complaints best map onto this second stage of reward processing and in translational terms correspond to the decision part of an experiment, when a subject chooses between available options, for example, in a gambling task.

The third stage is *action* ,during which effort is expended for a rewarding stimulus to be approached or a punisher to be avoided. Fatigue and low energy, commonly reported in patients with other depressive symptoms (16, 24), map onto this action component. In translational terms, this corresponds to a part of the experiment where a subject performs an action, such as a lever or button press, providing a quantification of task-related effort.

The final stage involves *experience*, which encompasses the consummation of a reward and the feelings that may be associated with it. This phase also entails the consolidation of this experience in memory, which may be accessed for future reward processing. Consummatory anhedonia, the lack of enjoyment from activities that used to be pleasant, best maps onto this phase. Translationally, this corresponds to a subject being faced with either a win or a loss outcome within a task, such as occurs in the monetary incentive delay task. In EEG studies, this is measured in terms of the FRN potential, or its reverse reward positivity (11), which occurs after feedback and is typically recorded at central to frontal-central regions of the scalp. FRN and reward positivity are the contrast of neural response to feedback of loss minus gain, and gain minus loss, respectively.

Reward processing involves many distinct components. One particularly key component of reward processing involves learning, whereby organisms update associated values attributed to objects and actions in their environment. Reward-related learning typically occurs through reward prediction errors, striatal dopamine-encoded signals that indicate the difference between anticipated and experienced reward (19). Such learning influences subsequent decision making and updates anticipation. In that sense, all the phases depicted in the model are part of reward-related learning.

Blunting of reward responses has been observed in major depression in adolescents, but it remains unclear whether the magnitude of this signal reduction varies across development. The sharp increase in depression incidence during adolescence (25) highlights the importance of examining this issue.

METHOD

Data Source and Search Strategy

We searched PubMed, Scopus, PsycINFO, and Web of Science for articles published in English from January 1,2000, to February 1, 2017 (see Figure S1 in the online supplement), using the following terms and their derivatives: depression, anhedonia, reward, motivation, reinforcement, punishment and aversion, prediction error, decision making, and risk taking.

Inclusion and Exclusion Criteria

To be included, studies had to provide a measure of depression or anhedonia in people with major depressive disorder, in people at high risk of depression, or in healthy volunteers. We selected only studies that measured depression or depressive symptoms through questionnaires, structured interviews, or clinical diagnosis. In terms of reward paradigms employed, and following the classification described by Richards et al. (26), we included instrumental- reward tasks and decision-making tasks, which require participants to complete an action correctly in order to obtain a reward, as this action is linked to the reward value at a trial- by-trial level. Hence, reward paradigms in which rewards were presented passively were excluded. Either positive (e.g., winning money) or negative (e.g., losing money) reward manipulations were permitted. No age restrictions were applied.Exclusion criteria are detailed in the online supplement.

To be included in the analysis, fMRI studies had to have used a reward task and have reported on brain coordinates. Connectivity studies were excluded from the analysis.

Among EEG studies, we included studies that reported mean amplitude response to negative/loss and positive/gain feedback on a reward paradigm, either separately or in some combination of these, such as loss minus gain (FRN) or gain minus loss (reward positivity). The corresponding authors of 10 studies that met all but one of the inclusion criteria were contacted to inquire whether a compatible anal-ysis had been conducted, such as mean ampli-tude extraction, rather than a peak approach. Where such analyses had been conducted, the means were requested for inclusion in the meta-analysis (as outlined in greater detail in the online supplement), which resulted in five of these studies being included.

Data Analysis

fMRI meta-analysis.—Of the 66 fMRI studies,38 were included in the fMRI meta-analysis (see Tables 2 and 3 and the online supplement for further information), as they reported consistently the following contrasts: reward anticipation, reward feedback, and loss anticipation plus feedback (these phases were merged to reach a sufficient number ofstudies). For these contrasts of interest, 23 studies reported whole brain analyses, 15 reported region-of-interest analyses, and two reported both types of analysis.

To increase the power of our analyses, we compared the combined depression and high-risk groups to healthy volunteers, also including the studies that examined the effects of depressive symptoms on reward processing. This dimensional approach to depression is consistent with current nosological approaches to the disorder (27). However, in the online supplement, we describe analyses that include only studies comparing major depression and healthy volunteer groups.

Overall, we conducted 21 activation likelihood estimation (ALE) meta-analyses, a method proposed by Turkeltaub et al. (28) and Laird et al. (29). For our primary analyses, we included only the studies that examined whole brain activation and excluded region-of-interest and small-volume-correction studies; this is standard practice to avoid experimenter-imposed localization bias (6, 30). Hence, no studies with predefined region-of-interest masks

were included. Instead, after whole brain analyses identified the caudate as the area that was significantly different between depressed and nondepressed subjects, region-of-interest studies of that region were added in follow-up analyses focusing on developmental effects. We did not impose specific requirements for the statistical thresholds or correction for multiple comparisons. To estimate the developmental influence of activation changes, studies were split between those with subjects under age 18 and those with subjects age 18 and older and analyzed separately. Then the two ALE images were contrasted to analyze the age-related differences.

The ALE analysis was implemented in GingerALE 2.1.1 (www.brainmap.org/ale). Except as otherwise indicated, all ALE images were family-wise error corrected for multiple comparisons at the whole brain level, using a cluster-level inference correction to a p level of 0.05, with an uncorrected p level of 0.001 (see the online supplement for further details).

EEG meta-analysis.—Of the 32 EEG studies, 12 were included in the EEG meta-analyses (see Tables 2 and 3 and the online supplement for further information). To meta-analyze the EEG studies, all effects were coded to a direction consistent with loss minus gain feedback (i.e., FRN), where more negative values are indicative of a greater differentiation between the neural response to gain and loss feedback. To combine the effect sizes of the studies, correlation coefficients and mean differences were converted to standardized effect sizes (Cohen's d). These were then subjected to a random-effects meta-analysis in Stata across all included studies. We report the variance of effect sizes attributable to heterogeneity using the I^2 statistic, and between-study variance with tau-squared. All procedures of coefficient conversion and subsequent meta-analysis are described in more detail in the online supplement. Because of the small number of longitudinal studies meeting inclusion criteria, a separate meta-analysis on these could not be conducted.

RESULTS

fMRI Meta-Analysis

Overall, the 38 fMRI studies (31–68) examined 428 subjects with major depression, 225 subjects with high risk of depression, and 503 subjects from studies that correlated brain activity with continuous measures of depressive symptoms. (See Tables S2 and S3 in the online supplement for summaries of the study samples' demographic and analytic characteristics.)

Studies examining whole brain activation.

Reward anticipation: —We found 12 whole-brain studies comprising 16 experiments, 84 foci, and 274 subjects. Meta-analysis showed no significant ALE clusters when correcting for multiple comparisons (see the online supplement for uncorrected results at p threshold of 0.001, focused in the caudate head).

Reward feedback:

We found 14 studies comprising 17 experiments, 110 foci, and 306 subjects. Meta-analysis revealed a significant cluster in the right caudate body and head and the left caudate body (Figure 1A; 322 voxels, peak ALE value=0.016), showing a difference between depressed and healthy subjects. No other brain regions emerged as significant. Because ALE results only reflect a significant spatial overlap of reported coordinates, we also present a plot of the direction of effect of each individual study for the striatal findings (Figure 1B). As shown in the figure, 13 of the 14 studies (92.9%) reported decreased activity in depressed subjects. A single study (57) found a small cluster (5 voxels) of increased activation.

Inclusion of region-of-interest studies.

We next included in the analyses the studies that reported region-of-interest findings. This larger study inclusion enabled us to compare results between subjects under age 18 and those 18 and older.

Reward anticipation: We found 24 studies comprising 32 experiments, 119 foci, and 822 subjects. Meta-analysis revealed a significant cluster of decreased activity in depressed subjects, bilaterally at the caudate head as well as at the left putamen (see Table S4 and Figure S3 in online supplement).

When we divided these studies into over and under age 18, we found a stronger blunting of activity in the younger-age studies. (See Table S4 in the online supplement, which describes the cluster in the caudate when contrasting the ALE images of studies between those under age 18 compared with those 18 and older.)

Reward feedback: We found 22 studies comprising 27 experiments, 135 foci, and 572 subjects. Meta-analysis showed a significant cluster of decreased activity in the caudate, the putamen, and the globus pallidus for depressed compared with healthy subjects (see Figure S6A in the online supplement). We found no significant difference between age groups (see Figure S6B-C in the online supplement).

Loss contrast meta-analysis showed no significant difference between depressed and healthy subjects (see the online supplement).

Sensitivity analyses are detailed in the online supplement.

EEG Meta-Analysis

Random-effects meta-analysis across the 12 studies (13, 69–79) yielded a statistically significant effect ($z=2.82$, $p<0.01$, two-tailed) with a pooled effect size (d) of 0.38 (95% CI=0.12, 0.64). There was high heterogeneity across studies ($\chi^2=47.69$, $df=2$, $N=11$, $p<0.001$; $I^2=76.9\%$). Between-study variance, as measured by tau-squared, was 0.15.

In a subsequent analysis, we tested age as a moderator of the relationship between FRN and depression. The analysis replicated the significant effect in studies with participants under age 18, with an effect size of 0.50 (95% CI=0.15, 0.85; $z=2.78$, $p<0.01$, two-tailed). Study heterogeneity in the younger group was moderate ($\chi^2=15.76$, $df=2$, $N=5$, $p<0.05$; $I^2=68.3\%$;

tau-squared=0.12). However, in studies with samples over age 18, the association between FRN and depression was found to be nonsignificant (z=1.23, p=0.22, two-tailed). This result was based on a pooled effect size of 0.26 (95% CI=—0.16, 0.68), with a heterogeneity (χ^2) of 27.77 (df=2, N=5, p<0.05; I^2=82%; tau-squared=0.22). Despite this, the pooled weighted effect sizes within each age group were not significantly different from one another (z=0.62, p=0.54, two-tailed), as calculated according to Borenstein et al. (80). These results are summarized in Figure 2. See the online supplement for sensitivity analyses.

Longitudinal fMRI and EEG Studies

There was an insufficient number of longitudinal studies to conduct a separate meta-analysis (13, 31–34, 69–71, 81–85). These findings are summarized in the online supplement.

Behavioral Findings

No statistics are presented here, as only seven (18%) fMRI studies showed a group difference (40, 57, 58, 60, 63, 65, 68), and only two EEG studies reported behavioral results (72,73).

DISCUSSION

This work links depression to aberrant reward processing. In particular, functional imaging and electrophysiological findings converge to show a blunted neural response to reward, and this effect may be more pronounced in individuals under age 18.

Our meta-analysis of fMRI studies found decreased striatal activity in subjects with depression compared with healthy volunteers during reward feedback. This finding is in keeping with the meta-analysis of Zhang et al. (6), although only 25% of studies included in our meta-analysis overlapped with those of Zhang et al., with the addition of several (N=15) new studies published since then. These findings cannot be attributed to localization bias, as they also occur in non- region-of-interest studies. We also found decreased anticipation activity in depressed subjects when we lowered the statistical threshold or added region-of-interest studies. Reward anticipation and feedback are distinguished conceptually; it has been suggested (86) that dopaminergic neurons are primarily associated with anticipation of reward (87). By contrast, opioid neurons are associated with consummation of reward and therefore the feedback phase. The fMRI measures do not allow distinctions at the neurotransmitter level, and macroscopic anatomical overlap should not be taken to imply mechanistic overlap. There were no significant results for fMRI contrasts of loss. Because of the small number of studies, we combined loss anticipation and feedback (88), and this may have diluted effects.

A previous meta-analysis (10) found no differences overall between healthy and depressed subjects, but that analysis focused on a broad range of emotional and learning-related responses, rather than on strictly defined reward processing, as our study did. Moreover, the authors excluded studies with participants under age 18, whereas our study used a developmental approach including all ages and comparing adolescence with adulthood. Furthermore, we found evidence from longitudinal studies that aberrations in reward processing were predictive of new-onset depression (33) and increased the risk for

depression (81). Interestingly, a recent connectivity study (89) demonstrated that increased connectivity of the ventral striatum predicts depression, in keeping with striatal aberrations in this disorder.

Our fMRI findings fit with predictions from animal work (90) on the centrality of the striatum in reward processing. It is notable that the peak of activity difference between healthy volunteers and depressed subjects is in the caudate, rather than in the nucleus accumbens, a key part of the circuitry associated with reward processing (91). Indeed, there is substantial cytoarchitectural overlap between the accum- bens and ventromedial parts of the caudate andputamen (92), and they are collectively designated as the ventral striatum (92, 93). The striatum receives rich input from various cortical areas, including the ventromedial prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex, as well as the amygdala and hippocampus (93, 94). This input is integrated and then translated into action via neighboring areas in the basal ganglia.

The overall association between FRN and depression yielded a significant effect size of 0.38 in the random-effects analysis. When we stratified our samples into subjects under age 18 and age 18 and older, significance was only found in youth depression but not adult depression, although the moderation statistic was not significant. We also noted evidence that blunted FRN is a predictor of future depression onset (71). Longitudinal effects were observed in adolescents only, as no studies examined this association in adults. Taken together, and in line with the fMRI studies, these results suggest a decreased brain sensitivity to anticipating and consuming rewards in depression. While fMRI studies suggest that this deficit involves the striatum, the source of the FRN is still debated; however, it may partially reflect striatal signals (95, 96) or the indirect influence of striatal signals on other neural regions (97, 98). It is worth speculating about the fact that there was a lower heterogeneity in the younger than the older subsamples. The younger subsamples were more likely to be community based, were narrower in age range, and had lower levels of medication, whereas the older sample was more diverse in terms of demographic variables. Medication was not consistently reported among the studies, and therefore we could not assess its effects on the outcomes. It should also be noted that the younger samples contained more females than did the older samples, which may have influenced the results.

The reward system is known to undergo transition during the adolescent period, with changes indexed by FRN (99,100) and BOLD signal (14). More studies, particularly longitudinal studies of depressed individuals that span adolescence and adulthood, will be needed to understand the interaction between development and depression.

When considering these findings, several conceptual and empirical challenges need to be considered. First, postulating depression to be a generalized inability to anticipate or perceive pleasure (or avoid pain) may be overly simplistic. Depressed individuals can still crave rewards, as evidenced by the increased levels of drug and alcohol dependency in depression (101). Anhedonia is a core feature of depression closely linked to reward processing (102). Unfortunately, few studies have included measures of anhedonia to quantify the degree to which reward system dysfunction is moderated by anhedonia level.

Moreover, depression studies are needed that combine the high temporal precision of EEG or mag- netoencephalography with the spatial precision of fMRI.

Second, few studies have demonstrated aberrations in depression that span the three levels of explanation: brain circuitry, task behavior, and clinical symptoms. Indeed, many of the tasks addressing reward processing, notably the monetary incentive delay task, are less suited to capturing behavioral effects and reward experience (103). Developing tasks to overcome such shortcomings will be important. It will also be important to explore the interplay between reward and cognitions relevant to depression, such as executive control (104).

Third, future studies should go beyond typical case- control designs to include comparisons of reward processing between subjects with depression and other morbid groups. We found very few studies that directly compared reward processing in depression alongside other disorders. Two studies that compared reward processing across alcohol dependence, schizophrenia, depression, or bipolar disorder found that decreased striatal activity was correlated with depressive symptoms (35, 36).

Fourth, there were surprisingly few experimental studies embedded in treatment studies. Deep brain stimulation is the most direct way of testingthis, although it is the most ethically challenging. Promising initial results of deep brain stimulation of the ventral striatum (105, 106) did not replicate in controlled studies (107). While some pharmacological (31, 108,109) or psychological (110) interventions show promise in probing reward signal, they do not yet demonstrate that affecting reward modulates depressive symptoms.

Filth, the extant studies in the literature allowed us to pool results for only two of the four postulated components of reward processing that we outlined above. Clearly, more research is needed to understand the functioning of the other component processes at the neural level in depression. Our review also could not address directly the important issue of reward learning (8), as there were not enough imaging or EEG studies of reward learning in depression that fit our criteria.

Sixth, we found no evidence of publication bias for the EEG studies but cannot exclude the possibility that the non-reporting of null results biased the fMRI findings.

Overall, these findings demonstrate consistent reward processing aberrations in depression, expressed as blunted striatal fMRI and FRN signals, during reward feedback. These aberrations, which potentially underlie the pathogenesis of depression, may have important implications for the development of new treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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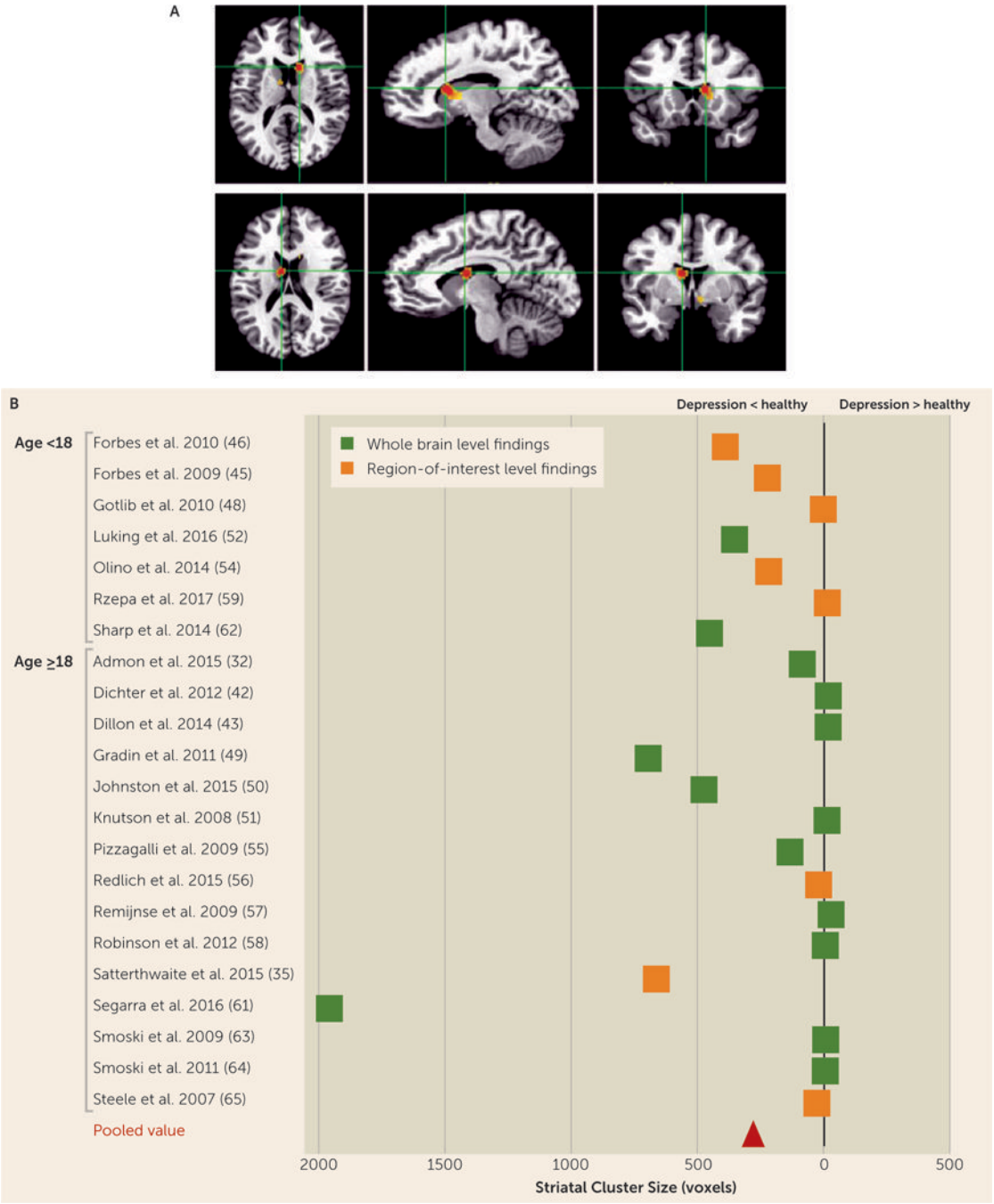

FIGURE 1. Alterations in Brain Activity During Reward Feedback, in Depressed Compared With Healthy Subjects: Meta-Analysis of fMRI Studies[a]

[a] Panel A depicts results across whole brain studies, presented as activation likelihood estimation maps, showing significantly decreased activation in the right caudate head and body (x=+12, y=+14, z=+14). Panel B lists the studies included in the meta-analyses of reward feedback contrast, broken down by age and type, along with the striatal cluster extent and direction of effect (increased versus decreased in depression). (The cluster value in the Johnston et al. study [50] was reported as 10,871 voxels combining several regions, and this is not reflected in its position in the graph because of space concerns.)

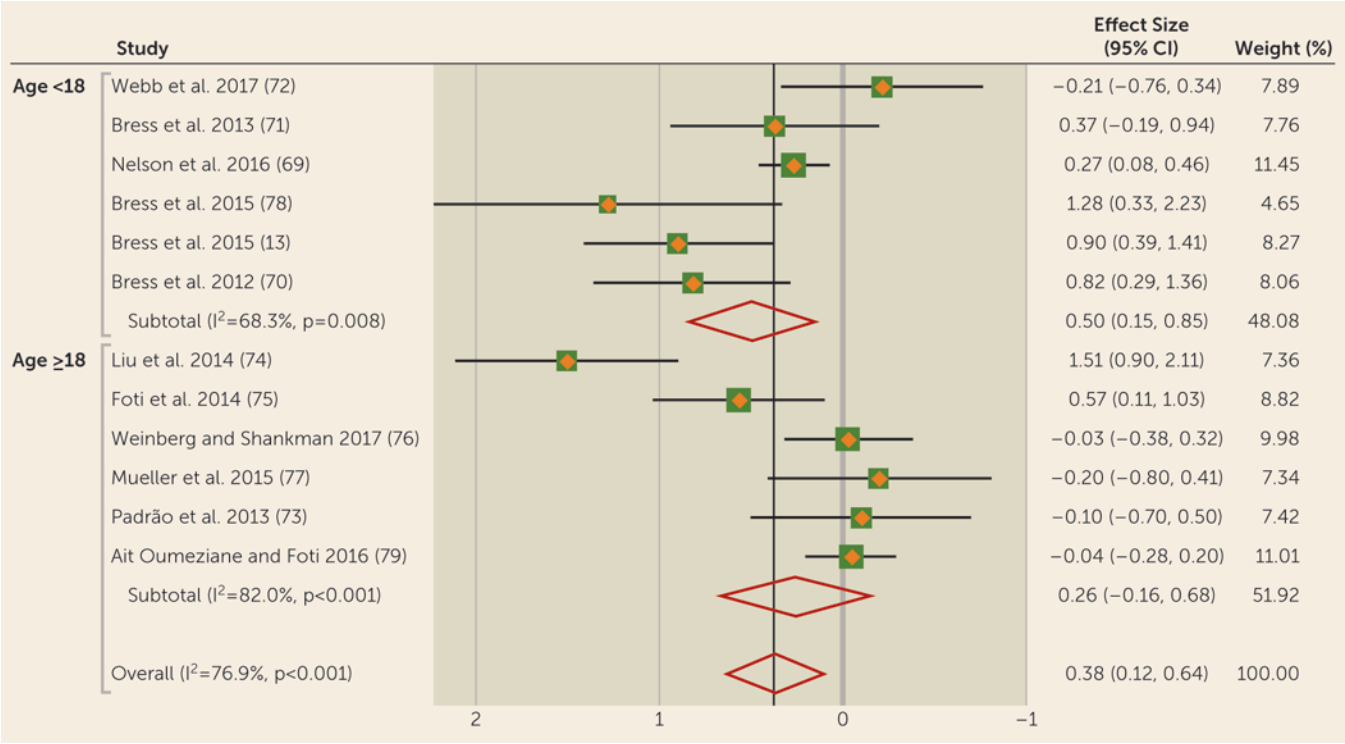

FIGURE 2. Effect Sizes for the Association Between Depression and Feedback-Related Negativity (FRN) in a Meta-Analysis of EEG Studies[a]

[a] Effect sizes have been flipped for illustrative purposes, such that positive effect sizes, indicative of a blunting of FRN in depression, are located to the left of the null line. Weights are from random-effects analysis.

TABLE 1.

The Identified Phases of Reward Processing, Mapped Onto Their Associated Clinical and Translational Terminologies

Reward Phase	Associated Symptom	Translational Term	Example Experimental Task
Prediction	Anticipatory anhedonia	Reward/loss anticipation	Monetary incentive delay task
Decision	Impaired decision making	Choice	Iowa gambling task
Action	Low energy	Effort expenditure	Effort expenditure for rewards task
Experience	Consummatory anhedonia	Reward/loss feedback	Monetary incentive delay task

TABLE 2.

Summary of the Studies Included in the Meta-Analyses of fMRI and EEG Studies of Reward Processing in Depression

Characteristic	Overall	Subjects Under Age 18	Subjects Age 18 and Older
fMRI studies (N=38)			
Sample composition			
Depressed subjects compared with healthy volunteers			
Whole brain only	15	1	14
Whole brain and region of interest	24	4	20
Subjects at high risk of depression compared with healthy volunteers			
Whole brain only	6	2	4
Whole brain and region of interest	10	5	5
Depression on continuum			
Whole brain only	3	0	3
Whole brain and region of interest	8	3	5
Overall			
Whole brain only[a]	23	3	20
Region of interest only	15	7	8
Reward types			
Monetary	32	9	23
Primary	2	1	1
Affective	3		3
Accuracy	2		2
Tasks used			
Monetary incentive delay task	13	2	11
Affective incentive delay task	1		1
Decision making	1		1
Wheel of fortune	4		4
Card guessing	7	6	1
Reward learning	4		4
Pavlovian prediction	1		1
Effort expenditure for rewards task	1		1
Modified reward task	3		3
Primary reward task	1	1	
Reward guessing task	1	1	
Gambling task	1		1
EEG studies (N = 12)			

Characteristic	Overall	Subjects Under Age 18	Subjects Age 18 and Older
Sample composition			
Depressed subjects compared with healthy volunteers	5	2	3
Subjects with high risk of depression compared with healthy volunteers	2	1	1
Depression on continuum	5	3	2
Reward types			
Monetary	11	5	6
Points	1	1	
Tasks used			
Doors guessing task	7	4	3
A gambling task	3		3
A reward guessing task	2	2	

[a]Significant difference between groups, $p<0.001$.

TABLE 3.

Gender Distribution and Medication Status in the Samples Included in the Meta-Analyses of fMRI and EEG Studies of Reward Processing in Depression[a]

	Overall			Subjects Under Age 18			Subjects Age 18 and Older		
Characteristic	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
fMRI studies (N=38)									
Age[b] (years)	29.2	7.5	8–65	13.5	1.6	8–17	34.4	9.5	17–65
Percent female[c]	58.3	21.3	16–100	77.7	17.2	50–100	51.8	19.9	16–79
Percent medicated	16.4	30.4	0–100	0.8	1.5	0–4.5	21.7	33.5	0–100
EEG studies (N=12)									
Age[d] (years)	19.9	7.2	8–65	13.9	2.5	8–17	26.0	4.4	18–65
Percent female	70.2	32.2	48–100	87.0	26.0	48–100	70.8	17.4	55–100
Percent medicated	18.7	16.7	0–41	15.8	15.9	4.5–27	20.6	20.5	0–41

[a] Some studies did not report these characteristics.

[b] Significant difference between groups in mean age, $p<0.001$.

[c] Significant difference between groups in percent female, $p<0.01$.

[d] Significant difference between groups in mean age, $p<0.01$.

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