Research Article

POTENTIATED PROCESSING OF NEGATIVE FEEDBACK IN DEPRESSION IS ATTENUATED BY ANHEDONIA

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Background: *Although cognitive theories of depression have postulated enhanced processing of negatively valenced information, previous EEG studies have shown both increased and reduced sensitivity for negative performance feedback in MDD. To reconcile these paradoxical findings, it has been speculated that sensitivity for negative feedback is potentiated in moderate MDD, but reduced in highly anhedonic subjects. The goal of this study was to test this hypothesis by analyzing the feedback-related negativity (FRN), frontomedial theta power (FMT), and source-localized anterior midcingulate cortex (aMCC) activity after negative feedback.* **Methods:** *Fourteen unmedicated participants with Major Depressive Disorder (MDD) and 15 control participants performed a reinforcement learning task while 128-channel Electroencephalogram (EEG) was recorded. FRN, FMT, and LORETA source-localized aMCC activity after negative and positive feedback were compared between groups.* **Results:** *The MDD group showed higher FRN amplitudes and aMCC activation to negative feedback than controls. Moreover, aMCC activation to negative feedback was inversely related to self-reported anhedonia. In contrast, self-reported anxiety correlated with feedback-evoked frontomedial theta (FMT) within the depression group.* **Conclusions:** *The present findings suggest that, among depressed and anxious individuals, enhanced processing of negative feedback occurs relatively early in the information processing stream. These results extend prior work and indicate that although moderate depression is associated with elevated sensitivity for negative feedback, high levels of anhedonia may attenuate this effect. Depression and Anxiety 32:296–305, 2015.*

Key words: *feedback-related negativity (FRN); action monitoring; theta; error-related negativity; depression; LORETA*

INTRODUCTION

The cognitive triad of depression includes potentiated negative processing of oneself, one's future, and one's external environment.[1] Feedback on own performance is an important external source for the self-concept and hence of particular relevance for depression. Whether depressed individuals process negative feedback more intensely at relatively early stages of the information processing stream is not yet fully understood.

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Early brain responses to feedback can be measured with EEG. In particular, the feedback-related negativity (FRN)[2] is a negative deflection in the event-related potential that peaks at frontomedial electrodes about 250 ms after an external feedback stimulus has been presented and is more negative for negative versus positive feedback. Of relevance, the FRN is generated in or nearby the anterior midcingulate cortex (aMCC) (e.g.[3–5]). The FRN may reflect an affective response to negative feedback[4], is relevant for reinforcement learning[5], and has been linked to dopamine.[6–9] Because abnormal dopamine availability and reward dysfunction have been hypothesized in depression[10,11], a link between depression and FRN is plausible from a biological point of view.

Previous studies on the relationship between FRN and depression reported increased amplitudes in response to negative feedback in moderate[12], subclinical[13], or remitted[14] depression, whereas others have linked depression to reduced FRN amplitudes in adults[15], children[16], and adolescents[17] or reported no associations between FRN to positive versus negative feedback and depression.[18] Analyses within groups of depressed individuals indicate that high levels of symptom severity[12], particularly anhedonia[19], are associated with relatively lower FRN amplitudes to negative versus positive feedback. In addition, the aMCC and surrounding regions are crucially implicated in the pathophysiology of MDD[20,21] and fMRI studies have reported both aMCC hyper-[22] and hypo-activity[23] in response to negative stimuli (including negative feedback) in MDD. This pattern of mixed findings may be due to differences of paradigms and task contexts.[24–26] In addition, findings could be integrated by assuming that moderate, subclinical, or remitted depression is characterized by potentiated processing of negative feedback in the aMCC, whereas very high levels of depression and anhedonia predict normal or even reduced responses to negative feedback.[12,27]

In addition to FRN, the total power of frontomedial oscillations in the theta band (4–8 Hz, FMT) is enhanced after negative versus positive feedback.[28,29] FMT in response to negative versus positive feedback is not correlated with the FRN across individuals[26] and has previously been related to depression in one study[30] but not in another.[13] FMT may reflect cognitive control processes with particular relevance for anxiety .[31] In line with this assumption, we recently showed increased FMT in response to (a) negative feedback in high versus low trait anxious individuals[26] and (b) previously fear-conditioned stimuli in normally anxious individuals.[32] Taken together, FMT and FRN may provide complementary electrophysiological indices of feedback processing. FMT may not be increased in depressed individuals per se, but rather be associated with anxiety, which is generally elevated in depression.

The aim of the current study was to investigate FRN, FMT, and source-localized aMCC activity in healthy and depressed individuals with varying degrees of anhedonic symptoms and anxiety. We hypothesized that depressed individuals would be characterized by increased FRN amplitudes and aMCC activity, although reduced sensitivity for negative feedback may be observed in the context of elevated anhedonic symptoms within the MDD group.[12] Moreover, we hypothesized that symptoms of anxiety would correlate with FMT to negative feedback. To test these hypotheses participants performed a probabilistic learning task[33] previously shown to evoke increased FRN amplitudes in individuals with subclinical depression.[13]

MATERIALS AND METHODS

PARTICIPANTS AND PROCEDURE

Twenty-nine individuals participated in this study. Subjects were only included if they were right-handed and reported no significant medical or neurological conditions, current mood disorders (other than MDD for the depressed group), or current or past psychotic symptoms, somatoform disorders, personality disorders, lifetime substance dependence, substance abuse within the past 12 months, seizures, or use of antidepressant medication in the past 2 months (6 weeks for fluoxetine). Presence (MDD group, $n = 14$) and absence (control group, $n = 15$) of depression was confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).[34] Characteristics and demographic information on the sample are provided in Table 1.

PARADIGM

A reinforcement-learning paradigm[35] was used, which is described in more detail elsewhere.[36] The task consists of two to six training blocks (60 trials per block) depending on participants' performance plus a subsequent test phase with a single block. In the training blocks three different stimulus pairs of Snodgrass images (A and B, C and D, and E and F) were randomly presented on a computer screen and participants were instructed to select as quickly and accurately as possible one of the two images that they thought had the highest chance of being correct. Feedback was probabilistic with the following probabilities for positive feedback after A, B, C, D, E, or F selection: 80%, 20%, 70%, 30%, 60%, and 40%. Accordingly, choosing A over B, C over D, and E over F was most often followed by positive feedback, whereas choosing B over A, D over C, and F over E was most often followed by negative feedback. All participants performed at least two blocks and completed up to six blocks until a predefined learning criterion was met.[36] To ensure comparable amount of learning experience across groups, the number of blocks required to reach the learning criteria was analyzed as a behavioral measure of training performance.

Of relevance, favoring A over B can be achieved by learning that stimulus A usually leads to positive feedback ("Choose A" = learning from reward), stimulus B usually leads to negative feedback ("Avoid B" = learning from punishment), or both. To probe which type of learning had primarily occurred within individuals, the test phase consisted of not only the three previously learned or "familiar" pairs (A and B, C and D, and E and F), but also 12 "novel" combinations of all possible stimuli pairs (e.g., A–C, A–D, etc.) and no feedback was given. For the test phase, the number of accurate decisions (= choose A in A-novel and avoid B in B-novel trials) as well as reaction times for A-novel and B-novel trials was analyzed.

EEG RECORDING AND ANALYSIS

EEG was recorded referenced to channel Cz in an electrically and acoustically shielded room using a 128-channel EGI (Electrical

TABLE 1. Demographics and clinical data

	MDD ($n = 14$)	Controls ($n = 15$)	Statistical value	*P*-value
Demographics				
Age, mean (*SD*) (years)	28.3 (8.0)	24.5 (4.0)	$t(28) = 1.58$	.13
Females (no.)	11	13	$\chi^2 = .33$	.65
White (no.)	10	9	$\chi^2 = .42$	.70
Years education, mean (*SD*)	15.14 (2.03)	16.26 (1.83)	$t(28) = 1.57$	.13
Clinical measures				
BDI-II score, mean (*SD*)	25.79 (7.74)	7.67 (9.60)	$t(28) = 5.57$	<.001
MASQ AD score, mean (*SD*)	83.57 (10.81)	45.87 (10.51)	$t(28) = 9.50$	<.001
MASQ AA score, mean (*SD*)	24.93 (5.89)	17.93 (1.10)	$t(28) = 4.37$	<.001
Length MDE, mean (*SD*), (months)	3.9 (2.3)	-		
Past episodes				
1 Prior episode (no.)	2	0		
2 Prior episodes (no.)	2	0		
3–5 Prior episodes (no.)	3	0		
>6 Prior episodes (no.)	4	0		
Chronic condition (no.)	5	0		
Age at first episode, mean (*SD*) (years)	18.9 (7.6)	-		
Distress disorder in family				
Mother (no.)	5	0		
Father (no.)	0	0		

MDE, major depressive episode. Only nonchronic MDD participants are included in the mean.

Geodesics Inc.) hydrocell system with an NA 300 amplifier at a sampling rate of 250 Hz and a 0.1–100 Hz bandpass filter. Impedances were below 85 kOhms.

The EEG was re-referenced to the average reference, low-pass filtered with a 50 Hz, 24 Hz/octave cutoff, and manually screened for nonocular artifacts using Brain Vision Analyzer 2 (Brain Products, Gilching, Germany). Eye-movement artifacts (e.g., blinks) were removed using independent component analysis (ICA), and EEG channels with a high number of channel-specific artifacts were removed and topographically interpolated using spline interpolation. The EEG of the training phase was segmented from –500 to 1,000 ms, baseline-corrected (–200 to 0 ms), averaged across all trials in which positive or negative feedback was given, and corrected for a fixed 8-ms delay relative to real time that was caused by the anti-aliasing filter of the EEG recording system. In order to detect the time points with maximal differentiation between positive and negative feedback at channel FCz (E6), a grand average difference wave FRN (negative minus positive feedback) across groups was computed (Fig. 2). Because the difference wave peaked at 252 ms, the FRN was measured as the mean amplitude at 252 ± 50 ms at a cluster of electrodes around channel FCz (E5, E6, E7, E12, E13, E106, E112). To test for the specificity of our hypothesized results with regard to the FRN, we also measured the P300 as the difference wave, which revealed a maximum differentiation of positive versus negative feedback at 392 ms. Accordingly, the P300 was

TABLE 2. Mean electrophysiological responses (±SEM) to feedback and correlations with symptom scales

	MDD ($n = 14$)	Controls ($n = 15$)	*t*-value ($df = 28$)	*P*-value	r_{AD} (MDD/CT)	r_{AA} (MDD/CT)	r_{BDI} (MDD/CT)
FRN							
Positive feedback	3.27(.90)	1.45(.82)	1.49	.15	−.27/.07	−.23/.05	−.05/−.29
Negative feedback	1.50(.78)	.89(.72)	.59	.56	−.25/.14	−.20/.27	−.05/−.24
Difference (positive minus negative)	1.75(.24)	.57(.41)	2.45	.02	−.21/−.11	−.23/−.38	−.02/−.16
aMCC (MNI: -10, 31, 29)							
Positive feedback	−1.06(.11)[a]	−1.22(.07)	1.25	.22	.15/−.25	.24/.07	.29/.32
Negative feedback	−.97(.08)	−1.44(.11)	3.39	.002	**−.64***/−.25	−.44/.11	−.25/−.13
Difference (positive minus negative)	.09(.14)	−.22(.13)	1.59	.12	**−.47§**/ −.07	−.42/.06	−.35/−.29
FMT							
Positive feedback	−.26(.12)	−.24(.10)	.12	ns	.06/.04	−.07/.11	.20/.07
Negative feedback	−.12(.11)	−.12(.12)	.05	ns	.12/−.02	.14/.09	.20/.10
Difference (positive minus negative)	−.13(.04)	−.12(.05)	.17	ns	−.16/.16	**−.61***/.01	.04/−.09

$r_{AD/AA/BDI}$, correlation of variable with the Anhedonic Depression scale of the MASQ, Anxious Arousal scale of the MASQ, or with Beck Depression Inventory score (separate correlations for MDD and Controls are provided). Correlations with *P*-value below .10 are printed in bold.
[a]FMT values are negative due to log-transformation.
*$P < .05$.
§$P < .10$.

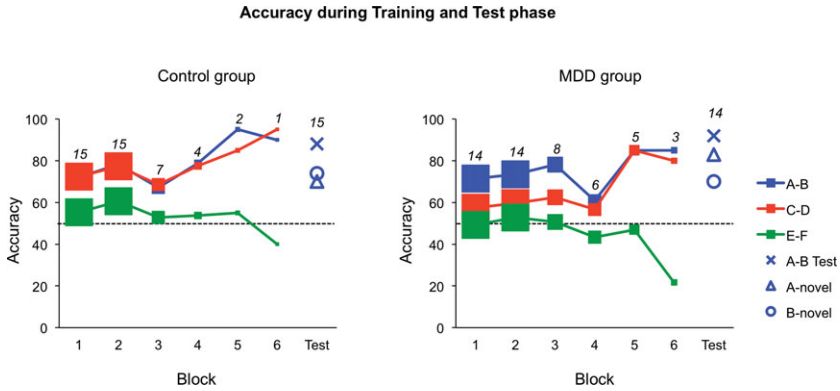

Figure 1. Accuracy for (A and B, blue), (C and D, red), and (E and F, green) trials for each training block and the test phase (*x*-axis) for the control group (left) and MDD group (right). The size of the block indicates the number of subjects in the corresponding block due to not reaching the learning criterion in the previous block. Therefore, decreasing square sizes as a function of training block indicate that more participants reached the learning criterion. Performance during the test phase for (A and B, blue *X*), A-novel (blue triangle), and B-novel (blue circle) trials is also indicated. The dashed black line indicates the chance level. As evident from the figure, both the control and MDD group showed above-chance selection of (A) in A-novel trials and (correct) avoidance of (B) in B-novel trials during the test phase, indicating successful transfer from training to test phase.

measured at 392 ± 80[1] ms at a cluster of electrodes around channel Cz (E7, E10, E31, E55, E80), where the topography of the difference wave was maximal (Fig. 2A and B). To measure FMT, a fast Fourier transform (FFT) was chosen, because it provides a robust aggregate measure of spectral power within a predefined time period that is sensitive to feedback valence.[26] Segments from 0 to 1 s relative to feedback onset were 50% hamming windowed (thereby attenuating the impact of very early and late EEG during the segment) and subjected to FFT analysis.[26] Prior to statistical analyses, power in the theta range (4–8 Hz) was log-transformed. FMT analyses were performed for the same channels as the FRN analyses.

LORETA

To localize brain sources of putative group differences in the scalp data, we used the LORETA algorithm.[37] The LORETA transformation matrix was computed based on the positions of the hydrocell geodesic sensor net EEG-sensors in Talairach space without oversmoothing. Current source density was then estimated based on the average ERP amplitude from 202 to 302 ms relative to feedback onset (FRN) at all 129 sensors. For each subject and condition, LORETA activity was then normalized to unity and log-transformed.

SYMPTOMS OF ANHEDONIC DEPRESSION AND ANXIETY

To separately assess symptoms of depression and anxiety within individuals with a diagnosis of MDD, all participants completed the Mood and Anxiety Symptom Questionnaire, a reliable instrument that allows dissociating symptoms of depression and anxiety.[38] Anhedonia was measured with the Anhedonic Depression (AD) subscale, whereas anxiety was assessed with the Anxious Arousal (AA) subscale. In support of the two scales probing separate constructs, correlations of the two scales are typically in the medium range (i.e., between .2 and .5[38]) and showed a correlation of .42 in the present MDD sample. Participants also completed the Beck Depression Inventory II,[39] among other questionnaires.

[1]This 80-ms range was chosen in order to also capture the raw-wave P300 peak that occurred earlier than the difference-wave P300 peak. However, results were comparable when the 50-ms range was used instead (i.e., 392 ± 50 ms).

STATISTICAL ANALYSES

Hypotheses on group differences were tested using repeated measures analyses of variance (ANOVAs) with Greenhouse–Geisser corrections were applicable. For FRN and FMT, the between-subjects factor was *Group* (Control vs. MDD) and the within-subjects factors were *Electrode* and *Feedback Valence* (Training phase: positive vs. negative feedback) and the critical *P*-value was set to .05. For source-estimated activity evoked by positive and negative feedback, voxel-wise independent samples *t*-tests were performed with a statistical threshold of .005 and a minimal cluster threshold of five contiguous significant voxels. Within groups, contrasts capturing effects of interest were correlated with different questionnaire measures. To test for differences between dependent correlation coefficients, we used the approach suggested by Meng et al.[40]

RESULTS

BEHAVIORAL RESULTS

Groups did not differ in the number of blocks needed to reach the learning criterion in the training phase (control group: 2.9 ± 1.2 blocks, MDD: 3.6 ± 1.7 blocks; $t(27) = 1.15$, $P > .2$)[2] indicating that for both groups comparable numbers of trials were available for EEG analysis (Fig. 1).

For the test phase the *Group* × *Condition* ("A-novel" vs. "B-novel") ANOVA on accuracy revealed no significant

[2]However, as shown in Fig. 1, a subgroup of $n = 3$ MDD participants failed to reach the learning criterion for EF trials even after the sixth block (as opposed to one participant in the control group). To keep the depression group as large and representative as possible, we decided not to exclude this subgroup of participants. Interestingly, a closer analysis of this subgroup revealed that, relative to the remaining MDD group, these three participants were characterized by elevated BDI-Melancholia subscores (see [54] for BDI items contributing to this subscore), longer reaction times (291 ms longer) and lower income. This suggests that a subgroup of depressed participants with a particularly strong impairment was unable to learn from subtle rewards in the EF condition.

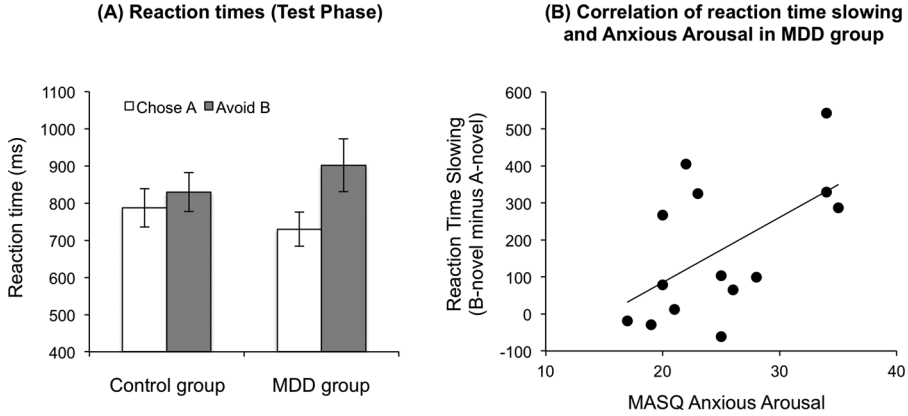

Figure 2. (A) Barplot indicating mean (SEM) reaction times for A-novel (white) and B-novel (gray) trials. A reaction time slowing for B-novel versus A-novel trials can be observed across groups, but is more pronounced in the MDD group. (B) Scatterplot showing the relationship between reaction time slowing (*y*-axis) and MASQ Anxious Arousal (*x*-axis) within the MDD group.

effects (all *P*s > .09). The *Group* × *Condition* ANOVA on reaction time revealed delayed responses during B-novel vs. A-novel trials (main effect *Condition*: $F(1,27) = 16.01$, $P < .001$). The reaction time difference for B-novel versus A-novel trials was larger in MDD versus control participants (*Group* × *Condition* interaction: $F(1,27) = 5.80$, $P < .025$; Fig. 2A) and correlated with the MASQ AA ($r = .56$, $P < .04$; Fig. 2B) but not AD scale ($r = .02$, ns; comparison of correlations: $Z = 1.78$, $P < .04$, one-tailed) within the MDD group, suggesting that more anxious depressed individuals responded slower when previously punished stimuli were presented.

ELECTROPHYSIOLOGICAL RESULTS

FRN (252 ± 50 ms). As expected, the *Group* × *Feedback* × *Electrode* ANOVA on the mean FRN amplitude revealed a significant main effect of *Feedback* ($F(1,27) = 22.84$, $P < .0001$) indicating more negative amplitudes for negative versus positive feedback. Importantly, there was a significant *Group* × *Feedback* interaction ($F(1,27) = 5.99$, $P < .025$), which was due to increased differentiation between positive and negative feedback in the MDD ($F(1,14) = 51.35$, $P = .0001$) versus control ($F(1,14) = 1.91$, $P = .19$) group (Figs. 3C and D, Table 2). Finally, there was a *Group* × *Feedback* × *Electrode* interaction ($F(1,27) = 2.43$, $P > .05$) indicating that the *Group* × *Feedback* interaction was most pronounced at centromedial electrode E13 ($F(1,27) = 10.33$, $P < .003$).

The positive versus negative feedback difference-FRN averaged across electrodes was not correlated with the MASQ AD or MASQ AA scales within the depression group (both *P*s > .3).

LORETA (252 ± 50 ms). As shown in Fig. 4A, whole-brain group comparisons revealed that MDD participants displayed more rostral aMCC activation to negative feedback than control participants ($P < .005$), while there were no significant group differences in the aMCC or surrounding regions after positive feedback (see also Fig. 4C). Of particular relevance, after negative feedback, the LORETA-estimated activity in the aMCC-region with the maximum group difference (Montreal Neurological Institute coordinates: *X*: –10, *Y*: 31, *Z*: 29) was *negatively* correlated with the MASQ AD scale ($r = –0.64$, $P < .015$; Fig. 3D). The AA scale ($r = –0.44$, $P > .1$) and the Beck Depression Inventory (BDI; $r = –0.25$, $P > .3$) were not significantly correlated with aMCC activity to negative feedback. Directly comparing these three correlation coefficients yielded a significant difference for AD-aMCC versus BDI-aMCC correlations ($Z = 2.34$, $P < .01$)[40] but not AA-aMCC versus AD-aMCC correlations ($P > .2$) suggesting that anhedonia symptoms (rather than general depression severity) related to blunted responses to negative feedback in depression. Within the control group, the MASQ AD ($r = –.25$) and AA ($r = .11$) scale and the BDI ($r = –.12$) were not significantly correlated with aMCC activity to negative feedback (*P*s > .3).

P300 (392 ± 80 ms). The *Group* × *Feedback* × *Electrode* ANOVA on the mean P300 amplitude revealed increased P300 amplitudes for negative versus positive feedback (main effect of *Feedback*, $F(1,27) = 20.80$, $P < .001$), but no significant main effects or interactions involving *Group* (*P*s > .4), thereby supporting the specificity of the FRN-related findings reported above (see also Fig. 3C).

Feedback-Evoked Theta. The *Group* × *Feedback* × *Electrode* ANOVA on theta power revealed increased theta power to negative versus positive feedback, irrespective of group (main effect *Feedback:* ($F(1,29) = 17.93$, $P < .0001$; *Feedback* × *Group* interaction: $P > .5$). The difference of negative versus positive feedback-evoked theta power and the difference-FRN were not correlated ($r = .11$, $P > .5$) and theta was also not correlated with the difference P300 ($r = .11$, $P > .5$), indicating that all three measures capture different aspects of individual differences in feedback processing.[26]

Importantly, among the MDD participants, FMT for negative minus positive feedback showed a positive correlation with MASQ AA ($r = –0.61$, $P < .025$;

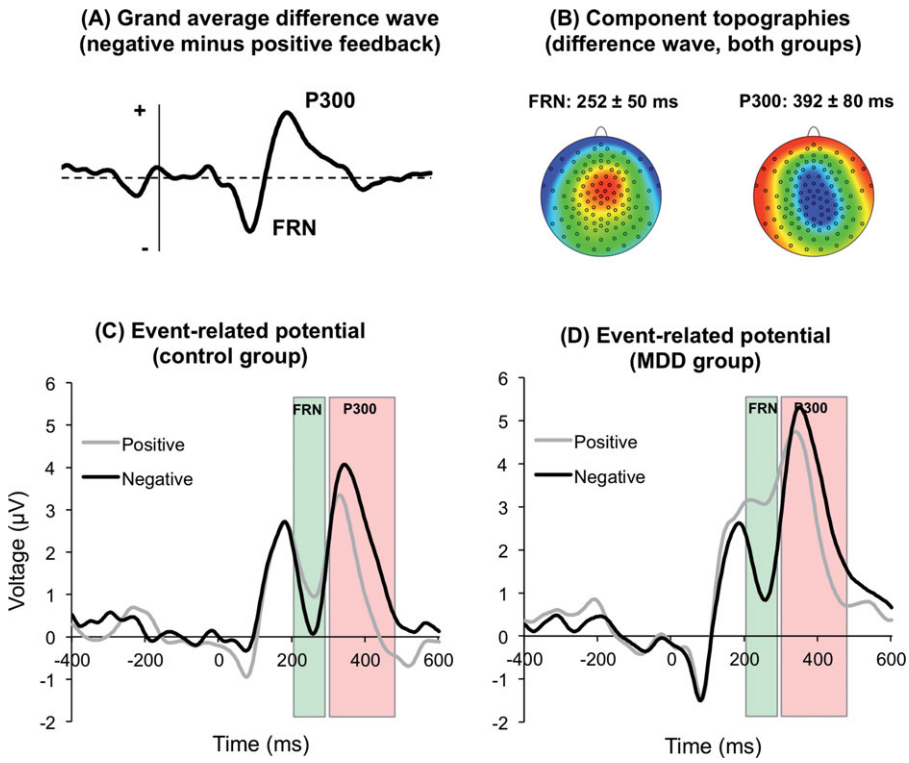

Figure 3. (A) Grand average difference wave for positive minus negative feedback-evoked event-related potentials at channel FCz and a cluster of surrounding electrodes. This difference wave across all participants was used for identifying the time window for the FRN (252 ms ± 50 ms) and for the P300 (392 ± 80 ms) based on maximum differentiation between positive and negative feedback independent of group. (B) Topographies of the positive minus negative feedback contrast during the FRN and P300 time window. (C and D) Event-related potentials at channel FCz and a cluster of surrounding electrodes for positive (gray line) and negative (black line) feedback, separately for the control (C) and MDD (D) group. The measurement windows for FRN (light blue) and P300 (light red) are also indicated.

Fig. 5B) but not AD or BDI scores ($P > .5$), indicating a specific association of FMT and anxiety symptoms within the MDD group (comparison of correlation coefficients: AA-FMT vs. AD-FMT: $Z = 1.57$, $P = .058$, and AA-FMT vs. BDI-FMT: $Z = 2.2$, $P < .02$.[40]

DISCUSSION

The aim of the current study was to investigate the processing of negative feedback in depression. Based on prior work, it was hypothesized that depression would be characterized by increased frontomedial brain responses to negative feedback. Within depressed individuals however, previous findings led us to assume that high levels of anhedonia and/or general depression severity would be associated with reduced rather than enhanced neural sensitivity for negative feedback. Finally, we expected that theta evoked by negative feedback would relate to high levels of anxiety rather than anhedonia or general depression symptoms. Using FRN, FMT, and source localization of feedback-evoked brain activity our hypotheses were largely confirmed. Relative to controls, unmedicated depressed participants showed increased FRN amplitudes and increased aMCC activity to negative (vs. positive) feedback. Moreover, within the MDD group, high anhedonia predicted reduced aMCC activity to negative feedback. Anxiety, in contrast, predicted not only enhanced theta responses to negative feedback, but also prolonged reaction times to stimuli previously associated with negative feedback (i.e., B-stimuli). Together, these findings replicate, integrate and refine a number of earlier findings on feedback processing in depression.

In general, individuals with MDD showed significantly larger FRN to negative versus positive feedback. Source analyses further showed that aMCC activity in the same time window was stronger in depressed versus control participants after negative (but not positive) feedback. These findings are consistent with prior studies on the FRN and similar components (i.e., error-related negativity[41]) showing increased amplitudes in depressed versus control participants[12,42,43] and with studies that localized these components in or in proximity to the aMCC.[4,44,45] Consistent with accounts that emphasize potentiated processing of negatively valenced information in depression, these findings suggest that depressed individuals show an increased sensitivity for negative feedback at relatively early stages of information processing (i.e. ≤ 250 ms after stimulus presentation).

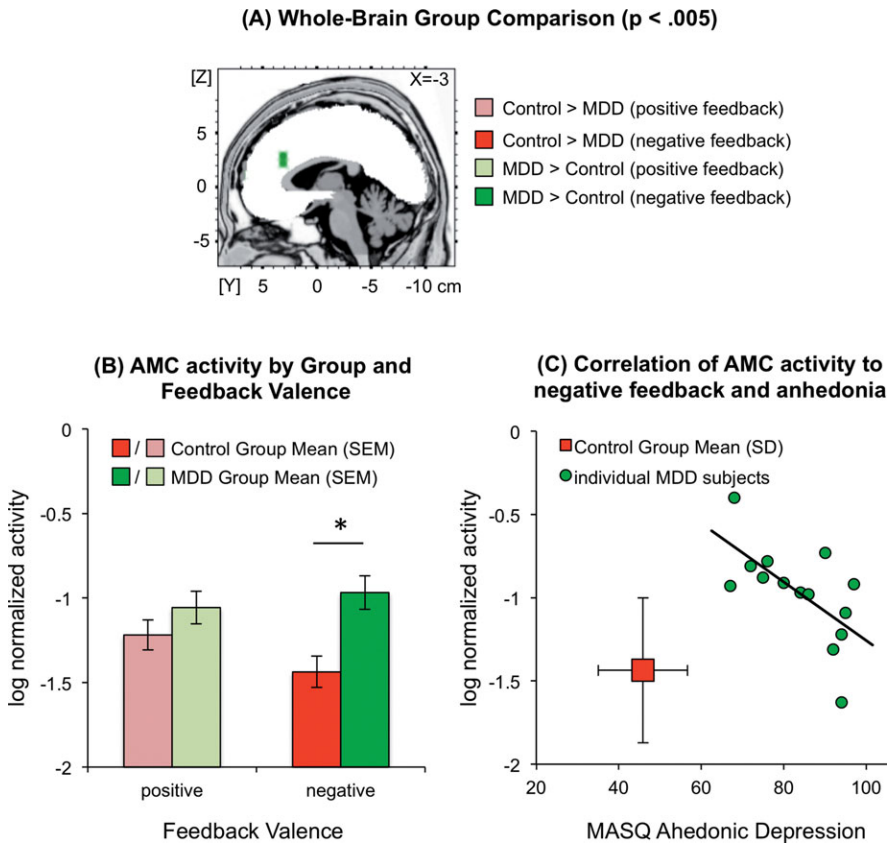

Figure 4. (A) Whole brain analyses of significant group differences ($P < .005$) 224 ± 50 ms after positive (light colors) or negative (dark colors) feedback presentation. Red indicates greater current source density for control versus MDD participants, green indicates greater current source density for MDD versus control participants. (B) Barplot indicating mean (±SEM) log-transformed normalized activity in the anterior midcingulate cortex region shown in (A), separately for group (control group: red; MDD group: green) and feedback (positive: light colors; negative: dark colors). (C) Scatterplot of Anhedonia symptoms (x-axis) and log-transformed normalized activity in the anterior midcingulate cortex region shown in B ($r = –0.64$, $P < .015$). The mean (red square) and *SD* (error bars) of the control group for both variables are also shown.

Of further relevance, aMCC activity to negative feedback correlated negatively with anhedonia severity. Thus, increasing levels of anhedonia were associated with relative blunted neural response to negative feedback. This result converges with prior work showing that severe depression[12,46,47] and anhedonia[19] are characterized by normative or even reduced processing of negative feedback and mistakes. Collectively, these findings suggest an inverted U-shaped association between depression severity and ERN/FRN amplitudes similar to what has been reported for the relationship between FRN[8] or ERN[48] amplitudes and the neuromodulator dopamine. Because dopamine has been linked to depression[10] and particularly reward processing dysfunction[11] and anhedonia[11,49], a shared underlying mechanism is plausible. Of particular practical relevance, such curvilinear relationships would indicate that enhanced sensitivity for negative feedback is only a sensitive marker for moderate MDD without high levels of anhedonia.

Like the FRN, theta power at frontal midline electrodes was sensitive to the feedback valence. Although the FRN can be described as a phase-locked frontomedial response in the theta range, FMT as measured in the present study was based on a longer time period (i.e., 1 s) and also captures non phase-locked theta power. Accordingly, the effect of feedback on FMT was uncorrelated with the effect of feedback on the FRN (see also [26]). Because this result suggests that FRN and FMT do not capture identical brain responses, future studies should attempt to parse the underlying functions of FRN and FMT (e.g. affective responses and/or adaptations in response to negative feedback). This goal is of particular relevance given that, in contrast to FRN, FMT was not significantly enhanced in depressed individuals in the present study and has even been found to be reduced in depression with moderate levels of anhedonia.[30] Although there was no association between depression and FMT, self-reported anxiety symptoms within depressed individuals were positively

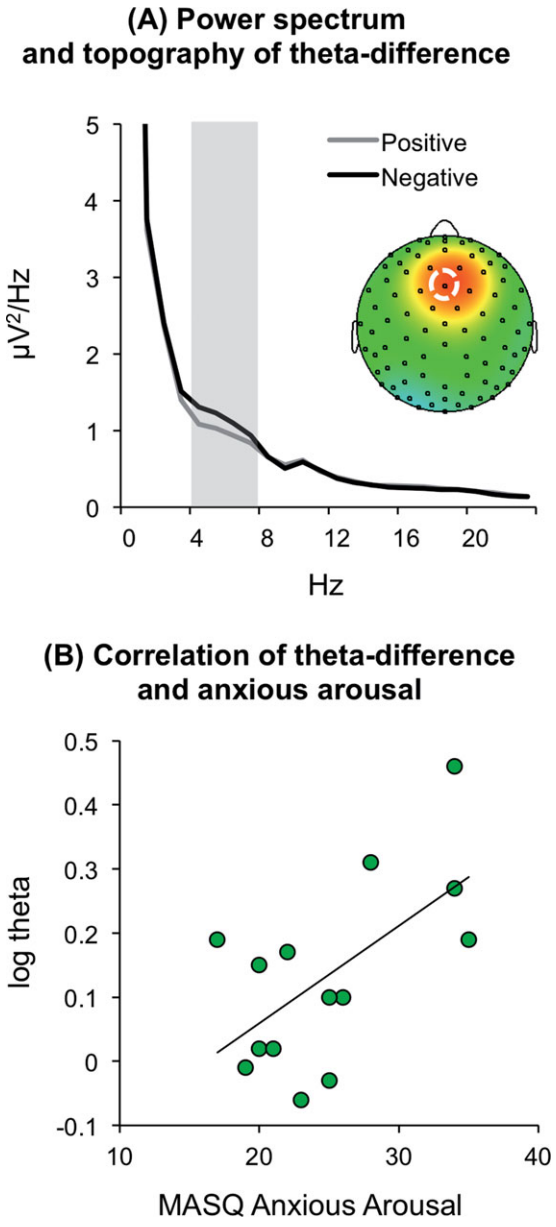

Figure 5. (A) Topography map of differences in theta power for negative versus positive feedback. (B) Scatterplot showing the differences in theta power for negative versus positive feedback (*y*-axis) as a function of anxiety (*x*-axis) within the MDD group.

correlated with FMT responses to negative versus positive feedback. This latter finding converges with earlier work showing that FMT responses to negative versus positive feedback correlate with trait anxiety in healthy participants.[26]

Longer reaction times were observed whenever B-stimuli (previously associated with negative feedback) rather than A-stimuli (previously associated with positive feedback) were presented. This effect was observed across all individuals, but was significantly stronger in the MDD versus control group and was particularly strong in MDD subjects with high anxiety. Under the assumption that these prolonged reactions to B-stimuli are due to inhibitory processes, this result may reflect anxiety-related behavioral inhibition to previously punished stimuli.[50] Taken together, anxious depressed individuals thus show increased FMT responses to negative feedback and also increased behavioral adaptation to negative feedback associated stimuli. These patterns are consistent with the hypothesis by Cavanagh and Shackman[31], which states that frontal midline theta reflects cognitive control processes with particular relevance for anxiety. Whether anxiety disorders are characterized by elevated FMT is a relevant question for future research.

An important limitation of the present study is its relatively small sample size, particularly for correlation analyses within groups. As a result, it is difficult to know whether nonsignificant results reflect an absence of effects in the population or should instead be ascribed to low power. For example, we cannot rule out that FRN in response to *negative* feedback may also have correlated with anxiety symptoms[51–53] or that FRN in response to *positive* feedback may also have correlated with anhedonia in a larger sample.[19] Moreover, the likelihood that spurious correlations reach significance is enhanced in small samples. Future studies with larger samples are warranted to replicate and extend the present findings in order to draw firm conclusions.

CONCLUSION

In conclusion, the present study replicated and integrated prior studies on feedback processing in MDD. We found that increased FRN and aMCC activity to negative feedback characterize depression, whereas high levels of anhedonia seem to counteract this depression-related enhancement of negative feedback processing. Together with previous work, these findings suggest early and automatic information processing biases in moderate depression with altered processing of negative feedback. However, future studies in larger samples and implementing multiple tasks are needed to clarify how task characteristics and context may further affect feedback processing in depression.

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Conflict of interest. Over the past 3 years, Dr. Pizzagalli has received honoraria/consulting fees from Advanced Neuro Technology North America, Otsuka Pharmaceutical, Pfizer, and Servier for activities unrelated to this project. All other authors report no biomedical financial interests to disclose.

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