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Neurophysiological Pathways of Unconscious Emotion Processing in Depression: Insights From a Simultaneous Electroencephalography–Functional Magnetic Resonance Imaging Measurement

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ABSTRACT

BACKGROUND: Major depressive disorder (MDD) is characterized by strong emotional dysregulation. Mechanisms driving the negative affect in depression may be fast processes existing on an unconscious level.

METHODS: A priming task was conducted using simultaneous electroencephalography–functional magnetic resonance imaging measurement involving presentation of facial expressions (happy, sad, and neutral) to examine the neurophysiological pathway of biased unconscious emotion processing in MDD. Priming prior to a target emotion created unconscious (16.7-ms primer) and conscious (150-ms primer) trials. A large sample (N = 126) was recruited, containing healthy control participants (n = 66; 37 women) and participants with MDD (n = 60; 31 women).

RESULTS: The healthy control group showed a shorter reaction time in happy but not in sad or neutral trials compared with the MDD group. N170 amplitudes were lower in trials with unconscious than conscious primer presentation. N170 amplitudes correlated with cortical (right fusiform gyrus, right middle temporal gyrus, right inferior temporal gyrus, left supplementary motor area, right middle frontal gyrus) and subcortical brain regions (right amygdala). The strength of N170 and brain activity correlation increased when the stimulus was consciously presented. Presented emotions did not affect the correlation of N170 values and brain activity.

CONCLUSIONS: Our findings show that MDD may exhibit biased emotion regulation abilities at a behavioral and neurophysiological level. Face-sensitive event-related potentials demonstrate a correlation with heightened brain activity in regions associated with both face recognition (fusiform gyrus) and emotion processing (amygdala). These findings are evident in both MDD and healthy control groups, with lower effect sizes in the MDD group indicating reduced emotion recognition and processing abilities.

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Recent advancements in cognitive neuroscience have shed light on the role of unconscious stimulus processing underlying negative perception and affect. This offers promising approaches for understanding mechanisms underlying major depressive disorder (MDD) (1–3). MDD is associated with an extensive range of cognitive biases, including negative attentional and interpretive biases, memory distortions, and emotional processing abnormalities (4–9). The cognitive model of depression describes 2 mechanisms underlying such dysfunctional processing: 1) a hyperactive response to negative information (bottom-up processing) and 2) an impaired cognitive control (top-down modulation) contributing to the maintenance and exacerbation of depressive symptoms (10). These mechanisms lead to an emotional processing bias and difficulties in evaluating the biased information, respectively (10,11). It remains to be determined whether this mood-congruent bias also operates at an unconscious level.

In MDD, a negative bias is attributed to an impaired cognitive control system, which, under regular conditions, helps disengage from negative stimuli (10). The respective top-down pathway is associated with activity in higher-order cortical brain structures such as the prefrontal cortex (PFC), particularly the dorsolateral PFC (DLPFC) and the anterior cingulate cortex (ACC) (12,13). Several studies using functional magnetic resonance imaging (fMRI) have provided strong support for the role of the PFC and ACC in controlling subcortical processes (14–16). A series of studies have discovered that patients with MDD have difficulty adjusting the involvement of the neural network that supports conflict resolution (17–21). Patients with MDD demonstrate elevated ACC responses to negative but weakened responses to positive

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information, whereas healthy control (HC) participants exhibit the opposite pattern (4,22). Besides an increased negative affect, a decreased level of positive affect is associated with depression. A diminished preference for positive emotions may lead to promoting strategies that enhance reactions toward negative emotions (23). Decreased PFC activation coupled with an increased amygdala response may underlie a greater effort to inhibit an emotional processing bias toward negative stimuli (24), leading to a disruption of efficient cognitive control (10,25).

The negative bias in MDD may occur even when the stimuli are processed unconsciously (6,7). Unconsciousness refers to the cognitive and affective evaluation of information occurring outside of conscious awareness. Those with MDD exhibit faster response times to unconscious negative information than HC participants (26), which supports the existence of an emotional processing bias at the unconscious level. On the neuronal level, unconscious presentation of emotional stimuli elicits amygdala responses, a crucial region for detecting emotional stimulus quality (27–32). In response to masked happy emotional faces, HC participants exhibit a greater amygdala response, whereas those with MDD display a greater response to sad faces (33–35). This bottom-up pathway describes a signaling from subcortical structures (amygdala, insula, and ventral striatum) to the ventral ACC, ventromedial PFC, and medial orbitofrontal cortex (36).

Additional support for the neural temporal dynamics associated with unconscious stimulus processing has been revealed via electroencephalography (EEG) research. EEG can be a powerful tool to identify the electrophysiological markers (event-related potentials [ERPs]) of visual attention and awareness (37–39). Typically, amplitude of the N170 component is enhanced between 130 and 200 ms after stimulus onset for facial stimuli (40,41). This ERP reflects rapid neural processing of emotional stimuli prior to conscious awareness (40,42). Furthermore, the N170 component is modulated by conscious recognition. Supraliminal presentation elicits larger N170 amplitudes than subliminal face presentation (37,43). In addition, those with MDD show increased N170 activity in response to masked sad faces compared with HC participants (2).

Based on the predominant role of subcortical regions in unconscious face processing (44), but poor accessibility via EEG alone, we here combine the advantages of EEG and fMRI measures. By simultaneously recording EEG and fMRI, we complement our understanding of the brain's functioning, as EEG records neural activity at high temporal resolution and fMRI provides high spatial resolution of brain activity (45).

We aimed to study whether respective bottom-up and top-down pathways of signal processing are altered in MDD using a backward-mask priming paradigm. The task ensured 2 distinct unconscious and conscious emotional trials. We hypothesized that N170 amplitudes would be higher in conscious than unconscious trials and higher during conscious presentation of sad primers in the MDD group than the HC group and happy primers. We assumed that unconscious presentation would lead to increased activity in subcortical regions (e.g., amygdala), whereas conscious presentation would increase activity in cortical regions (e.g., DLPFC and ACC). Group differences were expected on both unconscious and conscious levels.

METHODS AND MATERIALS

Participants

In total, 126 participants were measured: 66 in the HC group (29 men, 37 women, mean age = 25.89 years, SD = 6.48) and 60 in the MDD group (29 men, 31 women, mean age = 25.90 years, SD = 6.04). Inclusion criteria were an age between 18 and 55 years, fluency in the German language, and right-handedness. Participants had to be free from chronic or acute illness or psychiatric disorders according to the DSM-5 (46) that affect cognitive functions. All participants were screened using the Structured Clinical Interview for DSM-5 (47). Participants with a unilateral diagnosis of depression were included in the MDD group (41 with medication, 18 without, 1 unknown). According to the Declaration of Helsinki, participants gave a written informed consent and were informed about the study before examination. Analyses in the Supplement detail participant exclusion and show no significant effects of MDD medication on behavior, N170, or blood oxygen level–dependent (BOLD) signal.

Neuropsychological and Cognitive Assessment

Participants underwent neuropsychological assessment testing executive functioning [Trail Making Test-A/B (48)], short-term memory [digit span of the Wechsler Memory Scale (49)], and emotion regulation abilities [Difficulties in Emotion Regulation Scale (50) and Cognitive Emotion Regulation Questionnaire (CERQ) (51)]. To test for depressive symptoms, the Beck Depression Inventory-II (BDI-II) (52) and the Hamilton Depression Rating Scale (53) were applied. In addition, symptoms of alexithymia [Bermond-Vorst Alexithymia Questionnaire (54)], anxiety, and negative affectivity [State-Trait Anxiety Inventory 1/2 (55)] were assessed.

Procedure

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was preregistered at the open science framework (https://osf.io/37xd2/). For a detailed description of the procedure, see the Supplement.

Backward-Masked Priming Task

The task provided masked stimulus presentation of emotional and neutral stimuli. Using either unconscious (16.7 ms) or conscious (150 ms) primer presentations, the task provided conflict (primer/target show different facial expressions) or nonconflict (primer/target show same facial expressions) trials. The experimental design created an event-related $2 \times 3 \times 2$ factorial design (2 primer timing conditions, 3 emotion conditions, conflict/nonconflict condition) (Figure S1).

Neuropsychological and Cognitive Questionnaire Analysis

A multivariate analysis of variance was applied using R (version 2023.06.1; RStudio) to identify group differences using Bonferroni correction.

Task Performance Analysis

Mean reaction time (RT) was calculated for each task condition. RT was used as the dependent variable in a general linear mixed model (GLMM) using the lme4 R package (56). The GLMM was designed based on theoretical assumptions targeting differences in emotion processing by time between MDD and HC groups. Main and interacting effects of consciousness (unconscious primer = 16.7 ms, conscious primer = 150 ms), primer emotion, and group were included and an interaction between group × target emotion. Age and sex served as fixed effects. A random intercept for each participant was added. Bonferroni correction was applied for post hoc tests.

$$\text{Model 1} \leftarrow \text{lmer}\,(\text{RT} \sim \text{consciousness} \times \text{primer emotion} \times \text{group} + \text{target emotion} \times \text{group} + \text{age} + \text{sex} + (1 \mid \text{participant})) \quad (1)$$

As an exploratory analysis, all questionnaire scores were included as covariates in a separate model reported in the Supplement and Table S4.

N170 Analysis

Data acquisition and preprocessing steps are described in the Supplement. ERPs were obtained for each participant by averaging segments for each priming condition via EEGLAB version 2022.1 (57) using MATLAB (version 2020b; The MathWorks, Inc.). The data stream was segmented into event-locked epochs ranging from −200 ms before the events to 800 ms afterward. The first 200 ms of each epoch was used for baseline correction. The ERP signals of 4 channels (P7, PO7, P8, and PO8) were clustered creating the mean (Figure S2) based on previous literature (41). EEG impedance levels of the analyzed channels were kept below 10 kΩ.

The period for the N170 component was set between 150 and 200 ms after stimulus onset according to previous literature (41). Individual N170 values were estimated as a negative peak value in this time for every condition (consciousness × emotion). The mean N170 amplitude served as dependent variable in a GLMM. Consciousness, primer emotion, and group were included as main and interacting effects. The individual slope of N170 values across task blocks was included as main and interacting effect (for more details on the slope estimation, see the Supplement). Age and sex served as fixed factors. A random intercept for each participant was included. Bonferroni correction was applied for post hoc tests.

$$\text{Model 2} \leftarrow \text{lmer}\,(\text{N170} \sim \text{consciousness} \times \text{primer emotion} \times \text{group} + \text{slope} \times \text{primer emotion} \times \text{group} + \text{age} + \text{sex} + (1 \mid \text{participant})) \quad (2)$$

fMRI Analysis

Data acquisition and preprocessing steps are described in the Supplement. Individual time series were estimated via a general linear model in SPM12. Primer stimulus onsets and duration defined events for each task condition using the canonical hemodynamic response function implemented in SPM12. A full factorial design was calculated for emotion × consciousness × group.

EEG-Informed fMRI Analysis

Multiple Regression of N170 Values and BOLD Signal. A multiple regression was calculated including the individual N170 values for each condition (emotion × consciousness) as regressor while controlling for age.

Task Effects on Activated Brain Regions. Extracted cluster values were included in a GLMM to determine task-related effects on the correlation of brain activity (BOLD) and the N170 amplitudes (see the Supplement).

$$\text{Model 3} \leftarrow \text{lmer}\,(\text{average cluster activity} \sim \text{consciousness} \times \text{primer emotion} \times \text{group} + \text{sex} + \text{cluster number} + (1 \mid \text{participant})) \quad (3)$$

RESULTS

Neuropsychological and Cognitive Questionnaires

The multivariate analysis of variance analysis revealed significant differences in questionnaire results between groups ($F_{1,26} = 294.03$, $p < .001$) (see descriptive statistics in Table S1 and Figure S3). The MDD group had significantly higher scores in Bermond-Vorst Alexithymia Questionnaire, State-Trait Anxiety Inventory 1, State-Trait Anxiety Inventory 2, all Difficulties in Emotion Regulation Scale scores, BDI-II, CERQ self-blame, CERQ rumination, and CERQ catastrophizing than the HC group. The HC group showed higher scores in CERQ positive reinforcement, CERQ refocus on planning, CERQ positive reappraisal, and CERQ putting into perspective. No significant differences between groups in Wechsler Memory Scale, Trail Making Test-A, Trail Making Test-B, CERQ acceptance, CERQ blaming others, or Digit Span were found (Table 1).

Task Performance Results

The MDD group showed higher mean RT than the HC group ($t_{2183} = 7.80$, $p < .001$; HC mean RT = 0.62 second, SD = 0.15; MDD mean RT = 0.67 second, SD = 0.16) (Table S2). Consciousness, primer/target emotion, group, and sex had significant effects on mean RT (Table 2).

Post hoc analyses showed that the mean RT was lower for trials with neutral than happy or sad primer (neutral vs. happy: $t_{2077} = -2.98$, $p = .008$; neutral vs. sad: $t_{2077} = -3.32$, $p = .003$). No difference was found between happy and sad primer emotions ($t_{2077} = -0.33$, $p > .99$) (Figure 1A). Mean RT was lower in trials with happy than sad or neutral target emotions (happy vs. sad: $t_{130} = -38.55$, $p < .001$; happy vs. neutral: $t_{130} = -22.55$, $p < .001$). Mean RT was higher in trials with sad than neutral target emotions ($t_{130} = 16.01$, $p < .001$) (Figure 1B).

Table 1. Differences Between HC and MDD Groups in Respective Questionnaire Results (MDD > HC)

Questionnaire	*t*	Cohen's *d*	SE	Uncorrected *p*	Adjusted *p*
BVAQ	$t_{95} = 4.565$	0.088	1.781	<.001[a]	<.001[a]
WMS	$t_{116} = -0.705$	−0.035	0.651	.482	>.999
TMT-A	$t_{112} = -1.937$	−0.069	0.900	.055	>.999
TMT-B	$t_{117} = -0.097$	−0.001	3.176	.923	>.999
STAI 1 (Trait)	$t_{96} = 10.564$	0.242	1.486	<.001[a]	<.001[a]
STAI 2 (State)	$t_{114} = 18.296$	0.441	1.353	<.001[a]	<.001[a]
DERS Sum Score	$t_{114} = 13.587$	0.146	3.091	<.001[a]	<.001[a]
DERS Nonacceptance	$t_{110} = 7.28$	0.273	0.886	<.001[a]	<.001[a]
DERS Goals	$t_{118} = 10.664$	0.543	0.657	<.001[a]	<.001[a]
DERS Impulse	$t_{100} = 6.072$	0.265	0.812	<.001[a]	<.001[a]
DERS Awareness	$t_{109} = 4.883$	0.198	0.846	<.001[a]	<.001[a]
DERS Strategies	$t_{115} = 13.396$	0.439	1.005	<.001[a]	<.001[a]
DERS Clarity	$t_{76} = 8.437$	0.433	0.714	<.001[a]	<.001[a]
CERQ Self-Blame	$t_{112} = 5.152$	0.290	0.612	<.001[a]	<.001[a]
CERQ Acceptance	$t_{114} = -0.165$	−0.001	0.559	.869	>.999
CERQ Rumination	$t_{118} = 4.231$	0.259	0.550	<.001[a]	.001[a]
CERQ Positive Reinforcement	$t_{116} = -5.284$	−0.283	0.614	<.001[a]	<.001[a]
CERQ Refocus on Planning	$t_{114} = -4.398$	−0.245	0.619	<.001[a]	.001[a]
CERQ Positive Reappraisal	$t_{119} = -7.451$	−0.382	0.626	<.001[a]	<.001[a]
CERQ Put Into Perspective	$t_{119} = -5.753$	−0.284	0.647	<.001[a]	<.001[a]
CERQ Catastrophizing	$t_{99} = 6.427$	0.446	0.484	<.001[a]	<.001[a]
CERQ Blaming Others	$t_{111} = 2.243$	0.118	0.554	.039	.974
Digit Forward Score	$t_{118} = -0.421$	−0.028	0.460	.675	>.999
Digit Backward Score	$t_{118} = -0.681$	−0.044	0.475	.497	>.999
BDI-II	$t_{63} = 13.56$	0.623	1.650	.000[a]	<.001[a]

Post hoc *t* tests, corrected for multiple comparison with Bonferroni method (adjusted α level for 25 comparisons = 0.002) are presented in the table.

BDI-II, Beck Depression Inventory-II; BVAQ, Bermond-Vorst Alexithymia Questionnaire; CERQ, Cognitive Emotion Regulation Questionnaire; DERS, Difficulties in Emotion Regulation Scale; HC, healthy control; MDD, major depressive disorder; STAI, State-Trait Anxiety Inventory; TMT-A/B, Trail Making Test-A/B; WMS, Wechsler Memory Scale.

[a]$p < .001$.

Mean RT was higher in trials with unconscious than conscious primer presentation ($t_{2077} = 2.13$, $p = .034$) (Figure 1C). Mean RT was higher in the MDD group than the HC group ($t_{119} = 2.34$, $p = .021$) (Figure 1D) and higher in men than women ($t_{119} = 1.99$, $p = .049$) (Figure 1E). There was no difference in mean RT between groups in sad or neutral trials (group × target emotion) (Table S3). The HC group had a lower mean RT in happy target trials than the MDD group (Table S3 and Figure 1F). In both groups, happy elicited lower mean RT than sad or neutral targets (Table S3).

N170 Results

The primer emotion, presentation time, age, and sex had significant effects on the N170 amplitude (Table 3).

Table 2. Effects on Response Time: Type III Analysis of Variance Table With Kenward-Roger's Method (Model 1)

Factor	Sum of Squares	Mean of Squares	*F*	*p*
Primer Emotion	0.08	0.04	$F_{2,2077} = 6.66$	.001[a]
Target Emotion	9.03	4.52	$F_{2,2077} = 750.23$	<.001[a]
Consciousness	0.03	0.03	$F_{1,2077} = 4.52$	.034[b]
Group	0.03	0.03	$F_{1,119} = 5.48$	.021[b]
Sex	0.02	0.02	$F_{1,119} = 3.97$	.049[b]
Age	0.01	0.01	$F_{1,119} = 2.35$	.128
Consciousness × Primer Emotion	0.02	0.01	$F_{2,2077} = 1.39$	.249
Consciousness × Group	0.00	0.00	$F_{1,2077} = 0.71$	.400
Primer Emotion × Group	0.00	0.00	$F_{2,2077} = 0.26$	.775
Target Emotion × Group	0.15	0.08	$F_{2,2077} = 12.74$	<.001[a]
Consciousness × Primer Emotion × Group	0.01	0.00	$F_{2,2077} = 0.82$	.439

[a]$p < .001$.
[b]$p < .05$.

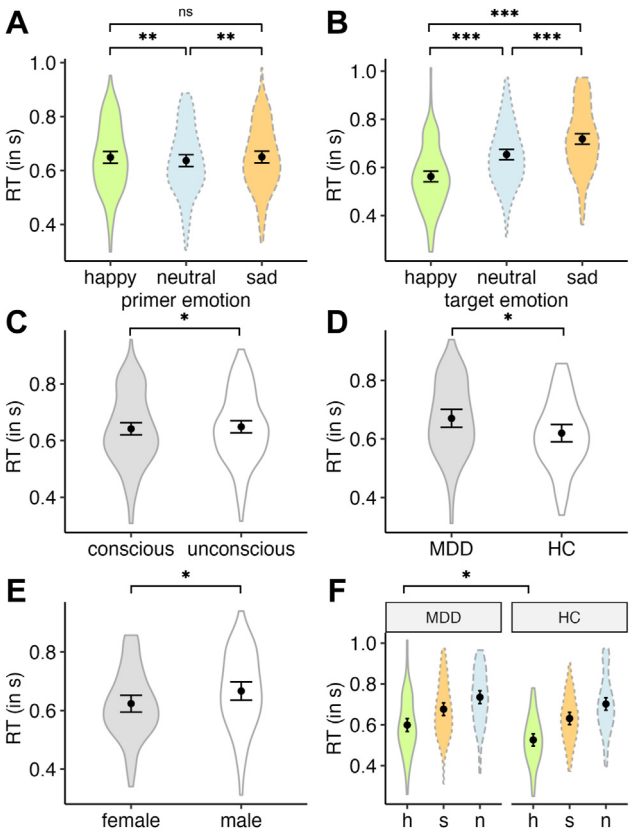

Figure 1. Effect plots of significant factors within the linear mixed model using mean reaction time (RT) values as dependent variable. Significant main effects were **(A, B)** primer/target emotion, **(C)** primer consciousness, **(D)** group, and **(E)** sex. **(F)** A significant interaction of group vs. target emotion was found. *$p < .05$, **$p < .01$, ***$p < .001$. h, happy; HC, healthy control; MDD, major depressive disorder; n, neutral; ns, nonsignificant; s, sad.

N170 values were lower in happy than neutral ($t_{1789} = -4.688$, $p < .001$) but not compared with sad trials ($t_{1789} = -1.171$, $p > .7252$) (Figures S4A and S5). N170 values were significantly lower in sad than neutral trials ($t_{1789} = -3.511$, $p = .001$) (Figures S4A and S5). N170 values were lower during conscious than unconscious presentation ($t_{1789} = -18.414$, $p < .001$) (Figures S4B and S5) in both groups with a higher effect size in the HC group than the MDD group (Table 4). Men showed lower N170 values than women ($t_{103} = 2.834$, $p = .006$) (Figure S4C). With higher age, participants showed higher N170 amplitudes (Spearman's rho = −0.146, $p < .001$) (Figure S4D). The MDD group showed a lower N170 in unconscious trials than the HC group in conscious trials but the HC group did not show a lower N170 in unconscious trials than the MDD group in conscious trials (Table 4 and Figure S4E).

Post hoc calculated interaction effects of group × sex and group × age on N170 values were not significant (see Effect of Demographics on Neurophysiological Data in the Supplement).

fMRI Results

No significant BOLD signal differences between groups remained after familywise error correction (FWE) correction. Interaction effects between consciousness × primer emotion, consciousness × group, group × primer emotion, or group × consciousness × emotion revealed no significant effects after FWE correction.

There was a significant main effect of consciousness in several cortical and subcortical brain regions (conscious vs. unconscious) (Figure 2 and Table S6). The main effect of the primer emotion (happy, sad, neutral) revealed 1 significant cluster after FWE correction (Table S6). Sad primer presentation induced higher brain activity in the left superior frontal gyrus and the left precentral gyrus than neutral primer (Table S6 and Figure 2). All significant clusters (FWE cluster-corrected $p < .05$, $k > 10$) were labeled via the AAL3 toolbox in SPM12 (58).

Effects of behavioral responses on BOLD signal were analyzed in a multiple regression analysis. Slow RT correlated with mainly frontal areas, and fast RT correlated with cortical and subcortical areas (e.g., thalamus, precuneus, and ventromedial PFC) (see Effect of Reaction Time on fMRI Data in the Supplement).

Table 3. Effect on N170 Values: Type III Analysis of Variance Table With Kenward-Roger's Method (Model 2)

Factor	Sum of Squares	Mean of Squares	F	p
Primer Emotion	44.04	22.02	$F_{2,1790} = 10.63$	<.0001[a]
Consciousness	702.28	702.28	$F_{1,1789} = 339.09$	<.0001[a]
Group	1.39	1.39	$F_{1,103} = 0.67$	.414
Sex	16.64	16.64	$F_{1,103} = 8.03$	.006[b]
Age	11.56	11.56	$F_{1,103} = 5.58$	.020[c]
Slope	0.68	0.68	$F_{1,1817} = 0.33$	.567
Consciousness × Primer Emotion	0.36	0.18	$F_{1,1789} = 0.09$	.917
Consciousness × Group	12.61	12.61	$F_{1,1789} = 6.09$	.014[c]
Primer Emotion × Group	2.73	1.37	$F_{2,1790} = 0.66$	.517
Consciousness × Primer Emotion × Group	11.9	5.95	$F_{2,1789} = 2.87$	.057
Slope × Group	0.39	0.39	$F_{1,1820} = 0.19$	.663
Slope × Primer Emotion	1.25	0.63	$F_{2,1796} = 0.30$	.739
Slope × Primer Emotion × Group	6.13	3.07	$F_{2,1796} = 1.48$	.228

[a]$p < .001$.
[b]$p < .01$.
[c]$p < .05$.

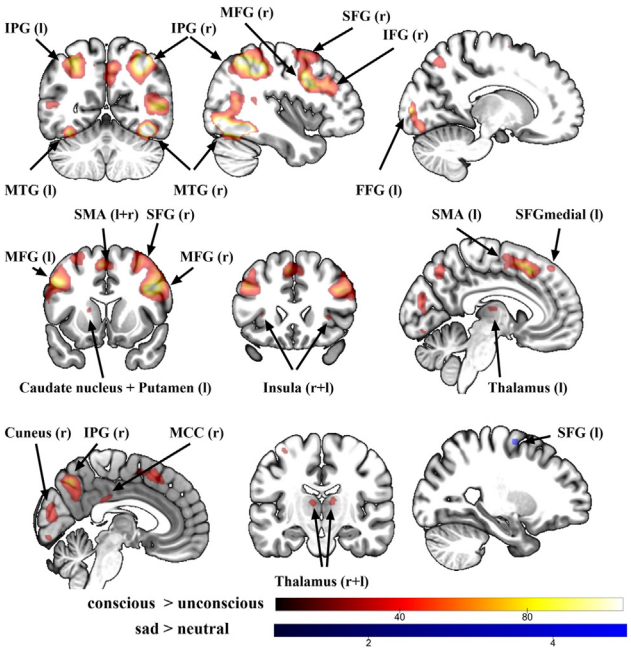

Figure 2. Statistical parametric map showing the main effect of consciousness (conscious primer > unconscious primer) and the effect of sad primer > neutral primer presentation from the full factorial design calculated for each condition (happy/sad/neutral primer × conscious/unconscious × group) including age and sex as covariates ($p < .05$, familywise error cluster corrected). FFG, fusiform gyrus; IFG, inferior frontal gyrus; IPG, inferior parietal gyrus; ITG, inferior temporal gyrus; l, left hemisphere; MCC, middle cingulate and paracingulate gyri; MFG, middle frontal gyrus; MTG, middle temporal gyrus; r, right hemisphere; SFG, superior frontal gyrus; SMA, supplementary motor area.

EEG-Informed fMRI Results

Multiple Regression of N170 Values and BOLD Signal. The higher the N170 amplitude (lower N170 effect), the higher was the BOLD signal in cortical regions, e.g., ACC, middle frontal gyrus, inferior frontal gyrus, precentral gyrus, supramarginal gyrus, or Rolandic operculum (Table 5 and Figure 3).

The higher the N170 amplitude, the higher was the BOLD signal in cortical regions, e.g., fusiform gyrus (FFG), middle temporal gyrus, inferior temporal gyrus, supplementary motor area, middle frontal gyrus, superior frontal gyrus medial, middle cingulate and paracingulate gyri, superior frontal gyrus, and cerebellum. Activity in the right amygdala correlated significantly with higher N170 (Table 6 and Figure 4).

Task Effects on Activated Brain Regions. Conscious primer presentation led to higher BOLD values than unconscious primer presentation (Table 7 and Table S7).

DISCUSSION

The study combined EEG-fMRI indicating that depressive symptoms resulted in an unconscious bias in emotion processing. The MDD group showed slower reactions to happy facial expressions than the HC group, which may support the claimed negative emotional bias in patients with depression (59). We found slower reactions during unconscious stimulus presentation and a robust effect of emotion across groups, with a facilitating effect for happy faces. This was paralleled by the EEG potential, the N170 where MDD shows reduced face recognition and emotion processing abilities.

Bias in Patients With Depression

Previous research showed that MDD exhibits impaired recognition of facial emotional expressions (5,17,60), bias toward perceiving faces as sad (5,32,33,59,61), and mood-congruent processing biases (4,7,26,34,62). Previous studies demonstrated lower N170 components in masked sad trials in MDD (2,3) using standalone EEG. This suggested impaired emotional response inhibition in MDD under conscious and unconscious conditions. However, our study did not replicate these findings, as no main group difference was displayed in the emotion-specific face-sensitive N170 component. Notably, the greater effect size observed in the HC group within the emotion and consciousness conditions suggests that the effects specific to emotion and consciousness are less marked in the MDD group compared with the HC group. In addition, the similarity in N170 responses in conscious conditions in the MDD group and unconscious conditions in the HC group implies a generally diminished capacity for emotion processing in MDD. Although age and sex have an effect on N170 (higher values in women and with higher age), these demographic influences did not interact with group differences. Behaviorally, slower reaction in MDD in happy target trials could support the idea of a biased emotion processing in MDD as proposed within the cognitive model of depression (10).

Table 4. Post Hoc Interaction Effect of Group and Consciousness on N170 Values (Model 2)

Group × Consciousness Contrast	Estimate	SE	t	p
Conscious MDD/Unconscious MDD	−1.05	0.0943	$t_{1789} = -11.137$	<.0001[a]
Conscious HC/Unconscious HC	−1.375	0.0919	$t_{1789} = -14.955$	<.0001[a]
Conscious HC/Conscious MDD	−0.553	0.4919	$t_{107} = -1.125$	>.999
Conscious HC/Unconscious MDD	−1.603	0.4919	$t_{107} = -3.26$	.009[b]
Unconscious HC/Conscious MDD	0.822	0.4919	$t_{107} = 1.671$	.5862
Unconscious HC/Unconscious MDD	−0.228	0.4919	$t_{107} = -0.464$	>.999

Bonferroni-adjusted p values.
HC, healthy control; MDD, major depressive disorder.
[a]$p < .001$.
[b]$p < .01$.

Table 5. Brain Regions With Significant Positive Correlation of Brain Activity and N170 Amplitudes

Label	Cluster	Maximum	% Cluster	*k*	MNI x	MNI y	MNI z
Middle Cingulate and Paracingulate Gyri (R)	1	1	15.15%	33	16	20	30
Anterior Cingulate Cortex, Subgenual (R)		2	12.12%				
Lobule IV, V of Cerebellar Hemisphere	2	1	27.27%	33	10	−56	−24
Lobule IV, V of Vermis		2	18.18%				
Middle Frontal Gyrus (L)	3	1	61.54%	26	−34	32	18
Inferior Frontal Gyrus, Triangular Part (L)		2	38.46%				
Inferior Frontal Gyrus, Triangular Part (R)	4	1	61.90%	21	34	16	26
Inferior Frontal Gyrus, Opercular Part (R)		2	38.10%				
Postcentral Gyrus (R)	5	1	64.71%	17	52	−22	32
Supramarginal Gyrus (R)		2	35.29%				
Rolandic Operculum (R)	6	1	100%	16	50	2	10

Familywise error–corrected cluster-level $p < .05$. *k* refers to the number of voxels. Clusters were labeled with AAL3 toolbox in SPM12. Clusters labeled with "outside" or smaller than $k < 10$ are not reported.

L, left; MNI, Montreal Neurological Institute; R, right.

Our results partly align with earlier investigations that elaborated unconscious emotional biases in depression revealing a slower RT in patients during unconscious happy facial expression presentation than the HC participants. These studies, in contrast to our results, also found group differences in unconscious sad stimulus presentation (2).

Prior investigations observed that happy stimuli are known for their propensity to elicit an elevated discriminative capacity when contrasted with neutral expressions (63) and that HC exhibit faster response to identifying happy facial expressions (64). In our sample, participants with higher BDI-II scores showed slower responses. Again, slower response (i.e., RT) when processing happy facial expressions supports the idea that the ability to detect happy facial expressions could be diminished in depression, or it may require increased cognitive effort on their part.

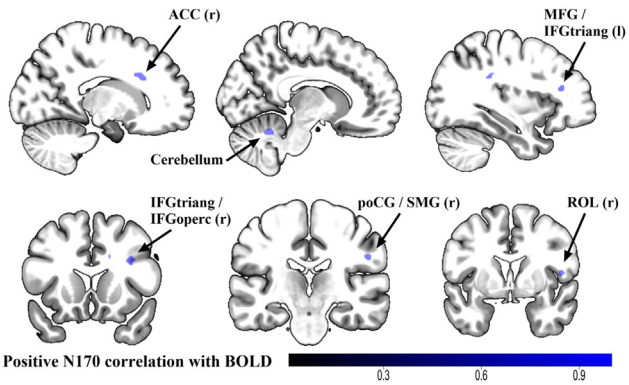

Figure 3. Statistical parametric map showing association between the blood oxygen level–dependent (BOLD) signal during the task correlating positively with N170 values ($p < .05$, familywise error cluster corrected). The anterior cingulage cortex (ACC) included the subgenual and middle cingulate and paracingulate gyri. IFGoperc, inferior frontal gyrus opercular part; IFGtriang, inferior frontal gyrus triangular part; l, left hemisphere; MFG, middle frontal gyrus; poCG, postcentral gyrus; r, right hemisphere; ROL, Rolandic operculum; SMG, supramarginal gyrus.

The Effect of Emotion

Across all participants, happy trials elicited higher N170 amplitudes than neutral, indicating an emotion-dependent effect where emotionally salient information (happy faces) elicits a stronger N170 component than less salient cues (neutral faces) irrespective of group or presentation time. Across groups, emotion-specific effects are observed including faster RT during happy target and slower RT during sad target trials. This indicates that happy faces may be detected more rapidly or with greater ease (64–66).

This advantage of processing happy facial expressions over sad or neutral might be impaired in depression. Earlier studies found that MDD shows greater robust effect (5,6). In this study, findings suggest that MDD differs from HC not only in the occurrence of depressive symptoms (BDI-II) but also in their adoption of emotion regulation strategies. Individuals with MDD exhibit deficits in emotion regulation strategies (assessed by the Difficulties in Emotion Regulation Scale and CERQ). Notably, higher scores were observed on CERQ subscales related to negative symptoms associated with the MDD group, such as rumination and self-blame, while the HC group scored higher on positive-associated CERQ subscales. Consistent with earlier studies (23), these results show an impaired emotion regulation and processing in MDD, indicating a biased pattern in their emotional responses.

The Effect of Unconsciousness

Slower RT in unconscious trials suggests a higher cognitive effort, potentially leading to compromised performance and a reduction in N170 amplitudes and BOLD responses. This supports the use of N170 as an indicator of varying levels of consciousness within facial emotion processing as it was found in previous studies (39). Although conscious trials led to a higher N170 amplitude in both groups (than unconscious trials), the MDD group showed similar N170 values in conscious trials compared with unconscious trials in the HC group, indicating a reduced face recognition ability in MDD. In addition, during conscious compared with unconscious stimulus processing, BOLD responses increased not only in

Table 6. Brain Regions With Significant Negative Correlation of Brain Activity and N170 Amplitudes

Label	Cluster Number	Maximum	% Cluster	*k*	MNI x	MNI y	MNI z
Fusiform Gyrus (R)	1	1	23.36%	137	48	−40	−8
Middle Temporal Gyrus (R)		2	13.87%				
Inferior Temporal Gyrus (R)		3	13.14%				
Supplementary Motor Area (L)	2	1	95.83%	48	−8	12	56
Middle Frontal Gyrus (L)	3	1	100%	28	−34	22	42
Superior Frontal Gyrus, Medial (R)	4	1	100%	20	10	60	18
Amygdala (R)	5	1	27.78%	18	30	4	−16
Middle Frontal Gyrus (R)	6	1	66.67%	15	32	24	32
Middle Cingulate and Paracingulate Gyri (R)	7	1	7.14%	14	4	−6	28
Superior Frontal Gyrus (L)	8	1	100%	13	−12	32	52
Middle Temporal Gyrus (L)	9	1	100%	11	−50	−54	12
Crus I of Cerebellar Hemisphere (L)	10	1	100%	10	−34	−78	−24

Familywise error–corrected cluster-level $p < .05$. *k* refers to the number of voxels. Clusters were labeled with AAL3 toolbox in SPM12. Clusters labeled with "outside" or smaller than $k < 10$ are not reported.

L, left; MNI, Montreal Neurological Institute; R, right.

cortical areas (e.g., temporal, frontal, precentral, fusiform, middle cingulate gyri) but also in the insula. This indicates a greater and more successful recruitment of cortical brain areas during the processing of conscious emotional stimuli, which is further underpinned by a fast response during congruent and conscious trials in both groups indicating a facilitated processing in those conditions. Furthermore, fast RT is associated with cortical and subcortical activity increase, whereas slow RT led to mainly cortical activity increase indicating that a fast processing involves both cortical and subcortical areas that are part of the default mode network (67).

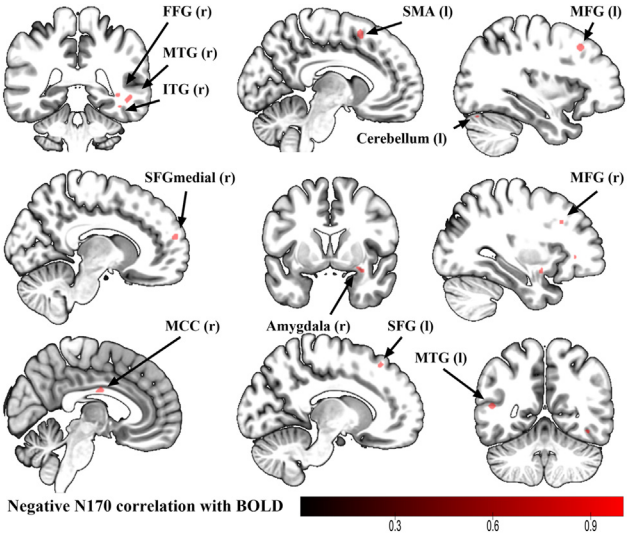

Figure 4. Statistical parametric map showing association between the blood oxygen level–dependent (BOLD) signal during the task correlating negatively with N170 values ($p < .05$, familywise error cluster corrected). FFG, fusiform gyrus; ITG, inferior temporal gyrus; l, left hemisphere; MCC, middle cingulate and paracingulate gyri; MFG, middle frontal gyrus; MTG, middle temporal gyrus; r, right hemisphere; SFG, superior frontal gyrus; SFGmedial, SFG medial; SMA, supplementary motor area.

Our initial hypothesis posited heightened cortical activity (top-down), specifically in the DLPFC and ACC, during conscious stimulus presentation and lower brain activity in these cortical regions in unconscious trials. Through EEG-informed fMRI analysis, higher brain activity is captured in correlation with higher N170 amplitudes in the superior frontal gyrus and middle frontal gyrus as part of the DLPFC (29,30,42,59,68–70). As part of the multiple demand network, the DLPFC along the inferior frontal gyrus, supplementary motor area, and ACC are recruited for a wide range of cognitive functions, e.g., response inhibition and decision making (68). These areas function in identifying significant stimuli within the environment (71). This underscores the involvement of the multiple demand network in detecting socially relevant cues, e.g., facial expressions.

The N170 amplitude is negatively correlated with activity (higher BOLD with higher N170 amplitude) in other cortical areas, e.g., the FFG, which is a core region active in face recognition (72). Moreover, we found negative correlations between N170 and activity in the right amygdala—a key region for emotion processing and detection (29,30,59,70). Previous research found that the effective connectivity between the amygdala and FFG is modulated by the processing of facial expressions suggesting that the amygdala activity strongly influences FFG activity during face recognition (73). The enhancement of FFG activity through the amygdala (bottom-up) seems to be influenced by the stimulus salience given that stimuli of high social or emotional relevance induced a higher connectivity in previous studies (42,73,74). FFG activation was stronger for positively rated faces than negative or neutral ones approximately 170 ms after stimulus onset (70) showing an emotion-dependent activation. Here, no emotion-dependent effects on brain activity changes in correlation with N170 values were found. However, the positive correlation between N170 and BOLD responses was stronger in conscious versus unconscious primer presentation. This indicates that both high EEG and high fMRI signals are linked to conscious stimulus processing in cortical (top-down) and subcortical (bottom-up) brain regions.

In summary, EEG-informed fMRI analyses show that emotion processing involves the integral participation of both

Table 7. Effects on All Extracted BOLD Clusters From Negative Correlation of N170 Values and BOLD Response: Type III Analysis of Variance Table With Kenward-Roger's Method (GLMM With Cluster Values [Model 3])

Factor	Sum of Squares	Mean of Squares	*F*	*p*
Primer Emotion	0.79	0.39	$F_{2,5940} = 0.22$	.802
Consciousness	22.20	22.20	$F_{1,5940} = 12.38$	<.001[a]
Group	0.01	0.01	$F_{1,98} = 0.01$	.936
Gender	2.75	2.75	$F_{1,98} = 1.53$	.219
Cluster Number	3336.51	370.72	$F_{9,5940} = 206.78$	<.001[a]
Consciousness × Primer Emotion	0.81	0.41	$F_{2,5940} = 0.23$	.797
Consciousness × Group	0.27	0.27	$F_{1,5940} = 0.15$	.699
Primer Emotion × Group	1.77	0.89	$F_{2,5940} = 0.49$	.610
Consciousness × Primer Emotion × Group	0.33	0.16	$F_{2,5940} = 0.09$	.913

BOLD, blood oxygen level–dependent; GLMM, general linear mixed model.
[a]$p < .001$.

cortical and subcortical regions. This underscores the concept that cortical activity not only serves exclusively as a subsequent and slower stage in the processing of gaze information (12) but also is involved in fast emotion processing and might be recruited by subcortical brain regions such as the amygdala. As one of the core regions of the salience network (75), the ACC is known to play a crucial role in emotion processing, forming reciprocal connections with components of the emotional perception network (e.g., amygdala) (76). EEG and fMRI signals decreased in unconscious and increased in conscious stimulus processing. Increased EEG/BOLD signal may reflect an increase in cognitive effort during conscious task trials, while fast processing (fast RT) increased brain activity in subcortical regions and the default mode network areas. Although the neurophysiological findings do not provide support for the hypothesis that MDD may exhibit automatic (and unconscious) attentional biases specifically toward negative information, behavioral data show a reduced advantage of classifying happy facial expressions in MDD and therefore reflecting biases in emotion processing.

Limitations

The sample primarily consisted of young individuals. Simultaneous EEG and fMRI recordings may influence data quality due to fMRI-induced artifacts in the EEG signal, potentially limiting the generalizability of the findings. The use of multiband echo-planar image sequences, GRAPPA (generalized autocalibrating partially parallel acquisitions) with a higher acceleration factor or a $2 \times 2 \times 2$ mm^3 image resolution could improve further research. The observed null effects could be driven by very small effects overshadowed by high within-group variability or technical limitations due to simultaneous EEG-fMRI recording. Further studies are needed to ascertain the stability of this effect by incorporating a more diverse sample and using technical methodologies to ensure high-quality data collection.

Conclusions, Implications, and Outlook

The MDD group showed a lower effect size in emotion and consciousness conditions, indicating a diminished capacity for emotion processing than the HC group. Individuals with MDD may exhibit an unconscious emotional bias and altered emotion processing as indicated by slowed RTs toward positive emotions. Our study highlighted the potential role of cortical regions in modulating processing of unconscious emotional stimuli. Both EEG and fMRI signals reflected conscious versus unconscious stimulus processing, while the N170 amplitude was a suitable metric. Additional ERP components (P1 and P3) could be examined in future research to assess their potential in capturing unconscious stimulus perception. Our findings shed light on the relationship between unconscious emotion processing and regulation.

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