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Self-referential Processing in Remitted Depression: An Event-Related Potential Study

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ABSTRACT

BACKGROUND: Identifying mechanisms of major depressive disorder that continue into remission is critical, as these mechanisms may contribute to subsequent depressive episodes. Biobehavioral markers related to depressogenic self-referential processing biases have been identified in adults with depression. Thus, we investigated whether these risk factors persisted during remission as well as contributed to the occurrence of stress and depressive symptoms over time.

METHODS: At baseline, adults with remitted depression (n = 33) and healthy control subjects (n = 33) were administered diagnostic and stress interviews as well as self-report symptom measures. In addition, participants completed a self-referential encoding task while electroencephalography data were acquired. Stress interviews and self-report symptom measures were readministered at the 6-month follow-up assessment.

RESULTS: Drift diffusion modeling showed that compared with healthy individuals, adults with remitted depression exhibited a slower drift rate to negative stimuli, indicating a slower tendency to reject negative stimuli as self-relevant. At the 6-month follow-up assessment, a slower drift rate to negative stimuli predicted greater interpersonal stress severity among individuals with remitted depression but not healthy individuals while controlling for both baseline depression symptoms and interpersonal stress severity. Highlighting the specificity of this effect, results were nonsignificant when predicting noninterpersonal stress. For self-relevant positive words endorsed, adults with remitted depression exhibited smaller left- than right-hemisphere late positive potential amplitudes; healthy control subjects did not show hemispheric differences.

CONCLUSIONS: Self-referential processing deficits persist into remission. In line with the stress generation framework, these biases predicted the occurrence of interpersonal stress, which may provide insight about a potential pathway for the re-emergence of depressive symptoms.

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Major depressive disorder (MDD) is a major public health problem associated with significant economic and psychosocial burden (1,2). Although effective treatments for MDD are available (3), approximately 85% of adults who remit from depression experience a recurrence within 15 years (4). Therefore, identifying biobehavioral markers that persist into remission may lead to the development of novel interventions that could prevent future recurrences.

A core feature of MDD is maladaptive self-schemas that often develop from childhood experiences (5,6). Across development, these schemas contribute to depressogenic processing biases whereby information perceived as negative and self-relevant increases depression risk (7,8). Negative self-schemas and depressogenic processing biases emerge in childhood, persist into adulthood, and predict MDD onset and worsening (9–17). These findings suggest that depressogenic self-referential processing biases emerge early in development and are critical for understanding depression.

Studying individuals with remitted depression is important for establishing whether depressogenic self-referential processing biases are state dependent. Although not currently in episode, these individuals remain vulnerable to recurrences (18,19). Notably, studies of remission cannot determine whether a given deficit reflects a precursor or scar of depression, but they reduce the confounding effects of current symptoms while evaluating vulnerability factors. Presently, it is unclear whether depressogenic self-referential processing biases persist into remission, as meta-analyses have yielded mixed results (20–22). Some studies reported that individuals with remitted depression and those who are currently depressed exhibit the same bias (23–26), and yet other studies showed a bias similar to healthy adults (27,28). The predictive validity of self-referential processing biases also is mixed, with some studies showing that negative biases predicted symptom recurrence (29) whereas others did not (30). Given these equivocal findings, research is needed to clarify whether depressogenic self-referential processing biases persist into remission and, accordingly, predict depression recurrence.

Modeling Processing Biases

An informative self-referential processing metric is drift rate (v), which is derived from drift diffusion modeling and integrates

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responses and reaction time (RT) to estimate the information accumulation rate to make a binary decision (31–35). Drift diffusion modeling calculates trial-by-trial variability, reducing the influence of outlier trials and baseline group differences (e.g., psychomotor slowing), thereby providing an enhanced measurement of processing speed than the central tendency of RT (35). Drift rate reflects the average slope of RT to make a decision (35,36), where larger absolute values correspond to faster, more consistent responses and smaller values reflect slower, less consistent responses (37). Drift rates to negative stimuli predict depression severity (13,38) and differentiate depressed from nondepressed individuals (36,39). It remains unknown, however, whether these patterns persist into remission.

Neurophysiological Correlates of Self-referential Processing

Several event-related potentials (ERPs) have been implicated during self-referential processing. The P2 is associated with early semantic and emotional monitoring (40,41) and typically peaks between 100 and 200 ms poststimulus in centroparietal regions (42,43). In addition, the late positive potential (LPP) is associated with elaborative processing and memory encoding (42,44). The LPP can be divided into two components: an early LPP (peaking around 300–600 ms in parieto-occipital regions), corresponding to task engagement and motivation, and a late LPP (peaking after 600 ms in frontocentral regions), reflecting longer-term emotional encoding (45,46).

Prior research has shown that while healthy adults exhibit greater P2 amplitudes for positive versus negative self-referential stimuli, currently depressed individuals show the opposite pattern (28,47) or no differentiation (48). Regarding the LPP, adults with depression show greater amplitudes to negative versus positive self-referential stimuli, whereas healthy adults show the opposite pattern or no differences (28,47–49). Therefore, adults with depression exhibit greater arousal to negative stimuli while healthy individuals show enhanced attendance to positive stimuli. Only one study, to our knowledge, has probed these markers in adults with remitted depression (28). Remitted individuals exhibited larger P2 amplitudes for negative than positive stimuli but showed the opposite pattern for the LPP. Thus, early attentional capture for negative self-referential stimuli may persist into remission, whereas elaborative processing and encoding may not. Given limited power in this study, further research is needed to elucidate whether neurophysiological markers of depressogenic self-referential processing persist into remission and prospectively contribute to symptoms.

Furthermore, the majority of electrophysiology research probing self-referential processing has analyzed all words viewed [e.g., (28,48)]. However, self-referential processing may be best measured by focusing on endorsed words (47,50). For example, healthy adults show greater LPP amplitudes to endorsed versus rejected positive words (50). At the same time, individuals with depression do not differ on early and late ERPs following endorsed versus rejected positive stimuli (47). These findings suggest that endorsement of stimuli may affect ERP amplitudes, but more research is needed.

Hemispheric Laterality of Self-referential Processing

Classic models of MDD feature impairments in self-appraisal, approach mechanisms, and emotional arousal, potentially explained by reduced left hemispheric activation (51,52). Lesion studies suggest that self-referential processes are localized to the right hemisphere (53–55), while increasing evidence suggests that activation is diffuse across hemispheres with autobiographical information as well as personal and emotional traits processed in the right and left hemispheres, respectively (54,56–58). Contemporary evidence provides some support for classic models of MDD, suggesting that blunted left hemispheric activation is implicated in depression (59–61). Only one study, to our knowledge, has probed laterality in remitted adults during self-referential processing (28). Remitted adults showed greater right than left LPP amplitudes, suggesting that blunted left hemisphere activity may be trait-like. Although functional magnetic resonance imaging is not directly analogous with electrophysiology research, compared with healthy adults, individuals with depression exhibited greater left than right dorsolateral prefrontal cortex activation during self-referential processing (62). In addition, adults who received MDD treatment exhibited reduced dorsolateral prefrontal cortex asymmetries, which corresponded to decreased depressive symptoms (63). Thus, asymmetrical dorsolateral prefrontal cortex activation may be an important component of depression symptomology. However, research is needed to determine whether these lateralized effects persist into remission.

Stress Generation Framework

Decades of research have demonstrated a reciprocal relationship between stress and depression, which is more commonly referred to as stress generation (64). Namely, it is now known that depressogenic vulnerability factors may shape the type of stress exposure, particularly among individuals with remitted depression, rendering some individuals more susceptible to experience interpersonal stressors, which over time may lead to the re-emergence of depression (65,66). In line with the stress generation framework, depressogenic self-referential processing biases, which are believed to remain stable among individuals with remitted depression, negatively affect individuals' views of themselves, the world, and the future (i.e., cognitive triad) (67) and, accordingly, may profoundly affect day-to-day interpersonal interactions, leading to greater interpersonal stress. Over time, interpersonal stress exposure may then serve as a catalyst for the re-emergence of depression symptoms because these stressors frequently precede depressive episodes (65,66) and often hasten their development (68,69).

Goals of the Present Study

An important next step is to test whether depressogenic bio-behavioral markers (15,70) related to self-referential processing persist into remission. First, we hypothesized that compared with healthy adults, adults with remitted depression would exhibit more negative processing biases and slower negative drift rates to negative words. Second, relative to healthy adults, adults with remitted depression would show larger early (P2) and late (LPP) ERP amplitudes to negative than positive words.

Given prior research (28,59–61), we also expected that remitted, but not healthy, adults would show reduced left compared with right LPP amplitudes to endorsed positive words. Finally, as a preliminary test of the stress generation framework, we examined whether depressogenic biobehavioral markers were longitudinal predictors of interpersonal stress and depression symptoms.

METHODS AND MATERIALS

Participants

Healthy control adults and adults with remitted depression between 20 and 35 years old were recruited from a previously completed parent project that evaluated familial risk for depression and anxiety (71,72). For this study, inclusion criteria included right-handedness and English fluency (see the Supplement for additional criteria). Based on these criteria, 104 of the 745 participants from the parent project were recontacted. Remitted adults reported a past major depressive episode; however, this could not have occurred within the 2 months before the assessment. Healthy control adults reported no lifetime mental disorders. A total of 36 participants were ineligible owing to a current MDD episode (n = 9) or because they declined to participate (n = 27). Two participants completed the study, but their electroencephalography (EEG) data were unusable. The final sample included 33 healthy control adults and 33 adults with remitted depression (mean age = 24.94, SD = 3.28 years). Sample characteristics are summarized in Table 1.

Procedure

The University of Illinois at Chicago Institutional Review Board approved study procedures. Data were collected from May 2017 through May 2019. Participants provided informed consent. During the first visit, participants were administered clinical interviews and self-report measures to assess demographic data, current depression symptoms, and medication use. Following this assessment, EEG data were acquired while participants completed a self-referential processing task

Table 1. Descriptive Statistics for the Sample Stratified by Group

Variables	HC	remMDD	t/χ^2 (df)	p	$d/\Delta/\phi/V$
Biological Sex[a], n (%)			0.07 (1)	.792	−0.033
Female	23 (69.70%)	22 (66.67%)			
Male	10 (30.30%)	11 (33.33%)			
Age, Years, Mean (SD)	24.61 (3.08)	25.27 (3.49)	0.82 (64)	.413	0.203
Race[a], n (%)			9.50 (5)	.091	0.379
African American/Black	3 (9.09%)	6 (18.18%)			
Asian	8 (24.24%)	3 (9.09%)			
Hispanic	8 (24.24%)	10 (30.30%)			
Middle Eastern	3 (9.09%)	0 (0%)			
Multiple races	0 (0%)	3 (9.09%)			
White	11 (33.33%)	11 (33.33%)			
Marital Status[a], n (%)			0.13 (1)	.720	−0.044
Married or partnered	4 (12.12%)	5 (15.15%)			
Never married	29 (87.88%)	28 (84.85%)			
Highest Education[a], n (%)			1.05 (2)	.592	0.126
Some college, trade school, or current student	5 (15.15%)	6 (18.18%)			
Two- or 4-year degree	14 (42.42%)	17 (51.52%)			
Some graduate/professional school or graduate degree	14 (42.42%)	10 (33.30%)			
Employment[a], n (%)			2.43 (3)	.489	0.192
Full-time	14 (42.42%)	17 (51.52%)			
Part-time	6 (18.18%)	6 (18.18%)			
Student	11 (33.33%)	6 (18.18%)			
Unemployed	2 (6.06%)	4 (12.12%)			
Interpersonal Stress Severity, Mean (SD)					
Baseline[a]	18.94 (18.38)	34.91 (20.97)	3.29 (64)	.002	0.810
6 mo[b]	1.79 (4.81)	9.45 (10.49)	3.05 (24.74)	.005	1.593
IDAS Depression, Mean (SD)					
Baseline[a]	28.06 (4.96)	36.70 (8.73)	4.94 (50.70)	<.001	1.743
6 mo[c]	31.86 (6.42)	41.43 (12.24)	3.39 (31.74)	.002	1.493

$d/\Delta/\phi/V$ = effect sizes for t test or χ^2; Welch's correction was used where appropriate.
HC, healthy control; IDAS, Inventory of Depression and Anxiety Symptoms; remMDD, remitted major depressive disorder.
[a]HC subjects: n = 33; remitted depressed individuals: n = 33.
[b]HC subjects: n = 28; remitted depressed individuals: n = 20.
[c]HC subjects: n = 28; remitted depressed individuals: n = 23.

(see the Supplement for additional EEG task data collected). At the 6-month follow-up, healthy control subjects (n = 29; 87.88%) and remitted adults (n = 25; 75.76%) were readministered a structured stress interview and self-report measures. Baseline depression symptoms and interpersonal stress severity did not differ among completers versus noncompleters ($p > .605$). Participants were remunerated $120 for the baseline assessment and $45 for the follow-up.

Clinical Interviews

Structured Clinical Interview for DSM-5. Lifetime mental disorders were assessed using the semistructured Structured Clinical Interview for DSM-5 (73). Research has demonstrated strong reliability and validity (74), particularly relating to MDD (75).

Stress and Adversity Inventory. The Stress and Adversity Inventory (76) was administered at the baseline and 6-month follow-up visits to assess stress occurring over the lifetime and past 6 months, respectively. Given prior research focusing on stress generation (65,66), analyses focused on interpersonal stress. To test the specificity of our effects, we estimated models with noninterpersonal stress (see the Supplement for details). The Stress and Adversity Inventory has previously shown excellent test-retest reliability [r = 0.90−0.95 (76,77)].

Self-report Questionnaire

Inventory of Depression and Anxiety Symptoms. The Inventory of Depression and Anxiety Symptoms (78) is a 99-item self-report measure assessing depression and anxiety symptoms over a 2-week period. The Inventory of Depression and Anxiety Symptoms has shown strong psychometric properties (79). Analyses focused on the 20-item general depression subscale (78,79), which demonstrated excellent internal consistency at baseline (α = 0.86) and follow-up (α = 0.90).

Experimental Task

Self-referential Encoding Task. A self-referential encoding task (11,67) was administered using Presentation software (v.18.2, NeuroBehavioral Systems). Participants viewed 40 positive and 40 negative words (see the Supplement for word list). On each trial, a word was presented for 200 ms followed by a fixation cross for 1800 ms and then an untimed prompt, "Does this word describe you?" Participants responded "Yes" or "No" on a button box. Intertrial intervals were jittered between 1575 and 1775 ms. After completing 80 trials, participants counted backward from 50, handwrote words viewed from memory, and completed a recognition task including 80 words from the task and 80 foils.

Behavioral analyses focused on processing bias and drift rate. Processing bias scores were computed by dividing the number of positive or negative words that were endorsed and later recalled by the total number of words endorsed. Hierarchical Drift Diffusion Model for Python [v.0.6.0 (80)] was used to compute drift rate. More positive drift values for positive words ($v > 0$) reflect more rapid evidence accumulation leading to an endorsement as self-referential. Conversely, more negative values for negative words ($v < 0$) reflect more rapid evidence accumulation leading to a rejection as self-referential (see the Supplement for details).

EEG Recording, Data Reduction, and Analysis

Continuous EEG data were recorded using a 64-channel elastic cap and the ActiveTwo BioSemi system (BioSemi). Data were sampled at 1024 Hz, using a low-pass fifth-order sync filter with −3-dB cutoff at 208 Hz. The BioSemi ActiveTwo replaces a conventional ground electrode with two electrodes that form a feedback loop, a common mode sense active electrode located between PO3 and POz and a driven right leg electrode located between POz and PO4. Vertical and horizontal eye movement were monitored using electrodes above and below the left eye and near the outer canthi of both eyes, respectively.

BrainVision Analyzer 2.1 (Brain Products GmbH) was used to process EEG data offline. Data were re-referenced to the average reference, and offline filters (0.1–30 Hz) were applied. Ocular artifacts were corrected by subtracting the ocular channels' voltages (81). EEG data were segmented 200 ms before stimulus onset and extended to 1200 ms. Intervals for individual channels were rejected using an automated procedure applying the following criteria: 1) a voltage step >50 μV between sample rates; 2) a voltage difference >100 μV every 200 ms within a trial; 3) a minimum and maximum allowed amplitude of −100 μV and 100 μV, respectively; and 4) a maximum voltage difference of <0.50 μV within a 100-ms interval.

ERPs were time locked to positive and negative words (see Tables S1 and S2 for average number of segments per condition; see the Supplement for Spearman-Brown split-half reliability). Based on maximal amplitudes within topographical maps (Figures S1 and S2), the P2 was scored as the average amplitude over POz during 200 to 280 ms, and the early LPP was scored as the average amplitude over Pz during 300 to 500 ms after stimulus. The late LPP was scored as the average amplitude over FPz and AFz between 500 and 1200 ms after stimulus. These electrodes were selected based on visual inspection of topographical maps and our prior research (11,67). These studies, however, used a different EEG system (HydroCel GSN) with a denser array of electrodes (128 channels) and a higher impedance threshold (below 75 kΩ). Thus, to minimize the potential effect of noise, these prior studies averaged across electrodes.

Additional analyses focused on trials of endorsed positive words. Mean amplitudes from right (FP2/AF4) and left (FP1/AF3) prefrontal electrodes were used to assess laterality of the late LPP for endorsed positive words. Residualized scores were calculated using right electrodes as the predictor variable and left electrodes as the outcome variable in a linear regression to compute standardized residuals. Thus, more positive residuals indicate greater left than right amplitudes, and more negative scores indicate greater right than left amplitudes. Residualized difference scores are preferred because they isolate variance unique to a specific condition (82). Previous work suggests that the LPP is reliable with at least eight trials (83), and thus, 1 healthy control subject was removed from analyses of positive endorsed trials at midline electrodes, and 2 participants (healthy control: n = 1; remitted depressed: n = 1) were removed from laterality analyses. Most participants

(n = 47; 71%) endorsed fewer than eight negative words (healthy control: n = 27; remitted depressed: n = 20), preventing the analysis of endorsed negative words.

Data Analysis

Analyses were conducted in SPSS v.27 and R v.3.6.1 (see Table S3 for sample sizes of each group analysis). Pearson correlations were calculated among behavioral, ERP, and symptom severity variables. Bayesian inference (as part of the Hierarchical Drift Diffusion Model package) was used to compare the posterior distribution for drift rate between groups for negative and positive words, with significance defined as <5% overlap (Bayesian q value < .05).

Repeated-measures analyses of covariance tested the group (healthy control, remitted depressed) × valence (positive, negative) interaction for processing bias, P2, early LPP, and late LPP while controlling for current depression symptoms (see the Supplement for endorsement, recall, and recognition). The group × laterality analysis also controlled for baseline depression symptoms.

To determine whether significant biobehavioral indices predicted interpersonal stress and depression symptom severity at the 6-month follow-up, we conducted separate linear regressions controlling for baseline stress and depression severity as well as baseline depression. A square root transformation for 6-month stress severity was used to reduce positive skew, and predictors in these models were mean centered. Reported slopes and standard errors from stress models were squared. To reduce the impact of outliers, 6-month depression scores were winsorized.

RESULTS

Descriptive Analyses

Compared with the healthy adults, adults with remitted depression reported more severe depression symptoms. Drift rate to negative stimuli positively correlated with depression symptoms, suggesting that requiring more time to reject negative words as self-relevant was related to greater symptom severity (Table 2).

Behavioral Phenotypes

Means, standard deviations, and ranges for endorsement, processing bias, and drift rate are summarized in Table S4.

Processing Bias. The main effect of group was nonsignificant ($F_{1,59}$ = 0.19, p = .668, η_p^2 = 0.003). There was a significant main effect of valence ($F_{1,59}$ = 12.69, p = .001, η_p^2 = 0.177). Participants exhibited greater positive than negative processing biases. The group × valence interaction was nonsignificant ($F_{1,59}$ = 0.43, p = .515, η_p^2 = 0.007).

Drift Rate. When examining the posterior probability distributions of drift rate (Figure 1), healthy control subjects exhibited significantly greater negative drift rates (mean = −2.34, SD = 0.24, 95% CI = −2.79 to −1.89) than remitted individuals (mean = −1.73, SD = 0.23, 95% CI = −2.19 to −1.29), which corresponded to a between-group overlap of 2.6% (q = .026). Thus, remitted individuals exhibited slower evidence accumulation needed to reject negative words compared with healthy control subjects. Comparatively, healthy control subjects showed a similar positive drift rate (mean = 1.10, SD = 0.22, 95% CI = 0.68 to 1.51) compared with remitted individuals (mean = 1.17, SD = 0.22, 95% CI = 0.75 to 1.57) that did not differ between groups (q = .41), suggesting that similar evidence accumulation rates were needed to endorse positive words.

Early and Late ERPs

All Words Viewed: P2. When analyzing all positive and negative words, the main effects of group ($F_{1,62}$ = 0.29, p = .592, η_p^2 = 0.005), valence ($F_{1,62}$ = 0.86, p = .358, η_p^2 = 0.014),

Table 2. Correlations Among Symptoms, Behaviors, and Neurophysiological Components

	Variables	1	2	3	4	5	6	7	8
1	Baseline depression symptoms[a]	–	–	–	–	–	–	–	–
2	6-month depression symptoms[b]	0.556[c]	–	–	–	–	–	–	–
3	Baseline interpersonal stress severity[a]	0.292[d]	0.251	–	–	–	–	–	–
4	6-month interpersonal stress severity[e]	0.462[c]	0.485[c]	0.462[c]	–	–	–	–	–
5	Negative drift rate[a]	0.511[c]	0.374[f]	0.153	0.426[f]	–	–	–	–
6	Positive drift rate[a]	−0.231	−0.409[f]	−0.004	−0.082	−0.467[c]	–	–	–
7	FP1/AF3 (Positive endorse)[g]	−0.126	−0.173	−0.364[f]	−0.242	−0.016	−0.046	–	–
8	FP2/AF4 (Positive endorse)[g]	−0.027	0.041	−0.218	−0.090	−0.119	−0.127	0.744[c]	–
9	Residualized LPP (Positive endorse)[g]	−0.159	−0.324[d]	−0.301[d]	−0.271	0.110	0.074	0.669[c]	0.000[h]

Depression measured by the IDAS General Depression subscale. Residualized difference wave between FP1/AF3 and FP2/AF4 for endorsed positive stimuli.

IDAS, Inventory of Depression and Anxiety Symptoms; LPP, late positive potential.

[a]Healthy control subjects: n = 33; remitted depressed individuals: n = 33.

[b]Healthy control subjects: n = 28; remitted depressed individuals: n = 23.

[c]p < .001.

[d]p < .05.

[e]Healthy control subjects: n = 28; remitted depressed individuals: n = 20.

[f]p < .01.

[g]Healthy control subjects: n = 31; remitted depressed individuals: n = 32.

[h]In linear regression, the correlation between predictors and the residual is always zero.

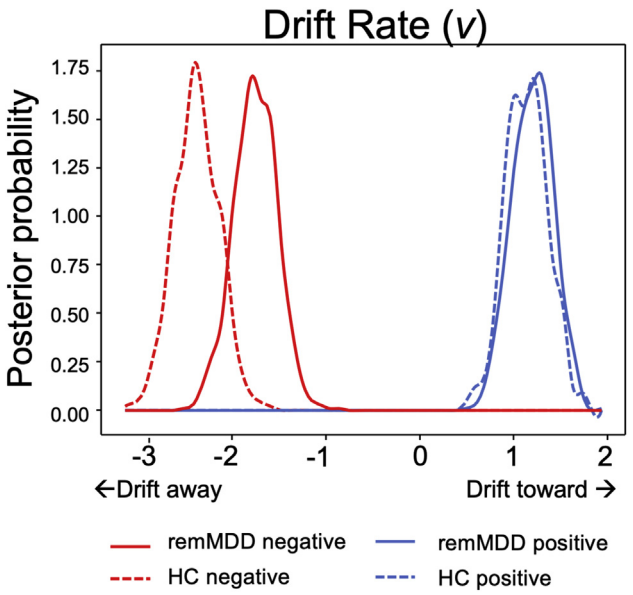

Figure 1. Distribution of drift rate (*v*) for healthy control (HC) subjects (dashed lines) (n = 33) and individuals with remitted major depressive disorder (remMDD) (solid lines) (n = 33) for positive (blue lines) and negative (red lines) stimuli. These results show that individuals with remMDD exhibited slower drift rate to negative stimuli than did the HC subjects. However, the two groups did not differ in their drift rate to positive stimuli.

and group × valence interaction were nonsignificant ($F_{1,62}$ = 1.12, p = .295, η_p^2 = 0.018) (Figure S1).

All Words Viewed: Early and Late LPP. For the early LPP, the main effects of group ($F_{1,63}$ = 0.13, p = .718, η_p^2 = 0.002), valence ($F_{1,63}$ = 0.39, p = .535, η_p^2 = 0.006), and group × valence interaction were nonsignificant ($F_{1,63}$ = 0.10, p = .752, η_p^2 = 0.002) (Figure S2). When probing the late LPP, the main effects of group ($F_{1,63}$ = 0.10, p = .756, η_p^2 = 0.002), valence ($F_{1,63}$ = 0.66, p = .419, η_p^2 = 0.010), and group × valence interaction were nonsignificant ($F_{1,63}$ = 0.27, p = .604, η_p^2 = 0.004) (Figure S3).

Endorsed Positive Words Only: P2. When focusing only on endorsed positive words, the groups did not differ on P2 amplitudes (t_{62} = 0.60, p = .548, d = 0.151).

Endorsed Positive Words Only: Early and Late LPP. When examining the early LPP following endorsed positive words, the groups did not significantly differ (t_{63} = 0.75, p = .456, d = 0.186). For late LPP at the midline, no between-group differences emerged (t_{63} = −0.55, p = .582, d = −0.137). However, given prior research showing asymmetrical frontal activity during self-referential processing (28) and the pronounced laterality effects in the topographical map (Figure 2), we tested for asymmetrical differences in frontal electrodes. After controlling for current depressive symptoms,

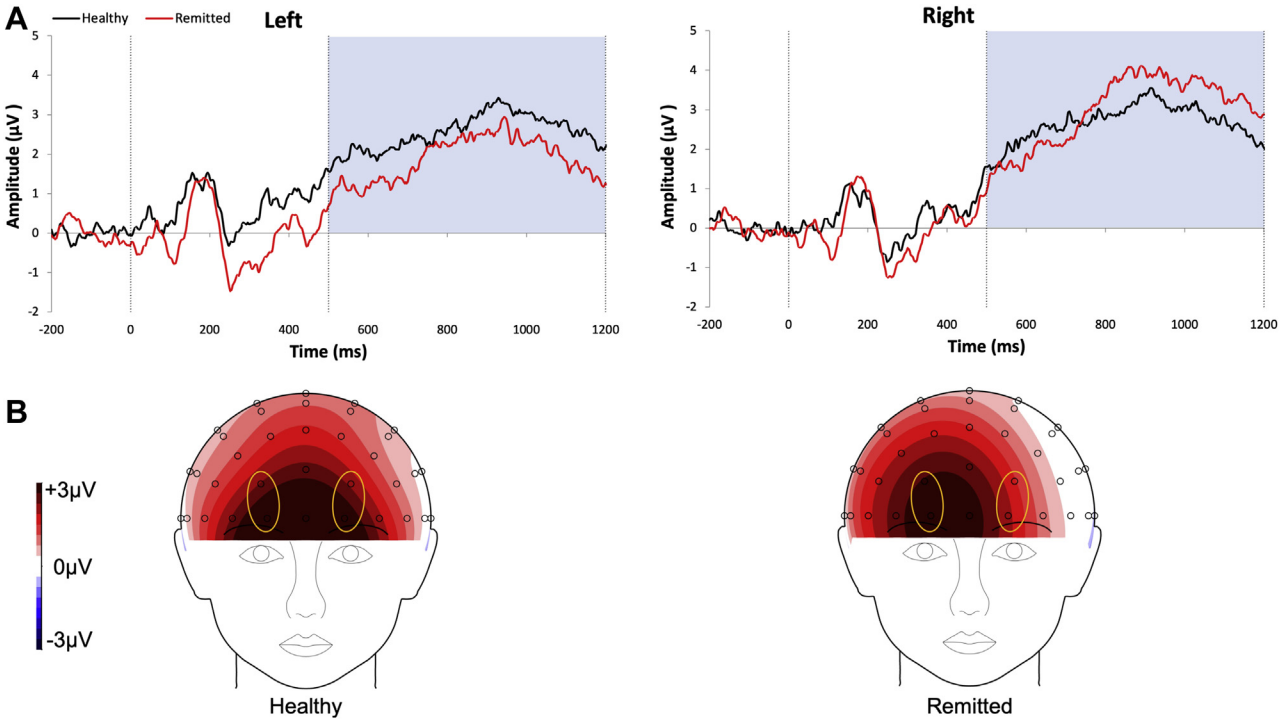

Figure 2. **(A)** Waveforms depicting the amplitudes of positive endorsed stimuli in the left (FP1, AF3) and right (FP2, AF4) electrodes with healthy control subjects (black line) (n = 31) and individuals with remitted depression (red line) (n = 32); shaded area is window for the late late positive potential. **(B)** Topographical maps showing prefrontal electrodes for healthy control subjects (left) and individuals with remitted depression (right). Highlighted in yellow circles are the electrodes of interest: FP1/AF3 and FP2/AF4.

the group × laterality interaction was significant ($F_{1,60}$ = 4.01, p = .0496 η_p^2 = 0.063). Follow-up comparisons indicated that remitted individuals exhibited a significantly greater right than left LPP (p = .002, η_p^2 = 0.154), whereas healthy adults did not (p = .841, η_p^2 = 0.001). Similar effects also were found without covarying for depression symptoms (Supplement).

Predicting Stress and Depression Symptom Severity Over Time

Stress Severity. After controlling for baseline depression symptoms and interpersonal stress severity, the group × negative drift interaction predicted interpersonal stress severity at the 6-month follow-up (B = 0.75, SE = 0.12, p = .017, partial R^2_{adj} = 0.108). Post hoc analyses revealed a positive association between negative drift and interpersonal stress severity for remitted adults (B = 0.99, SE = 0.09, p = .002) but not healthy adults (p = .495) (Figure 3). Highlighting specificity of this effect, neither the group × negative drift interaction nor main effect for negative drift predicted noninterpersonal stress (ps > .637).

A subsequent model testing the group × lateralized late LPP interaction did not reveal a significant effect (B = 0.36, SE = 0.22, p = .210, partial R^2_{adj} = 0.015). The lateralized late LPP did not predict interpersonal stress (B = −0.08, SE = 0.06, p = .245, partial R^2_{adj} = 0.009).

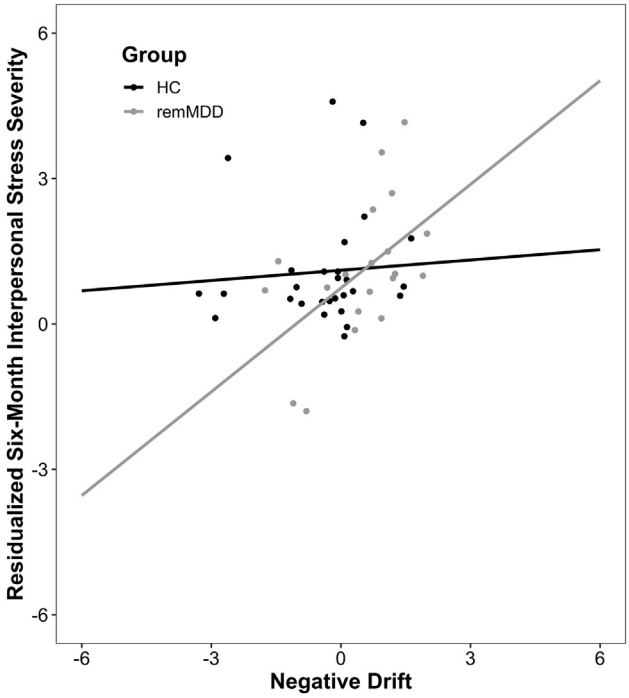

Figure 3. Plot of the interaction between group (healthy control [HC] subjects, black; individuals with remitted major depressive disorder [remMDD], gray) and negative drift scores predicting squared root residualized interpersonal stress severity at the 6-month follow-up, controlling for baseline depression symptoms and interpersonal stress severity. HC: n = 28; remMDD: n = 20.

Depression Symptoms. In separate models controlling for baseline depression symptoms, neither the group × negative drift (β = 0.18, SE = 0.27, p = .520, partial R^2_{adj} = −0.012) nor group × lateralized late LPP interaction (β = −0.26, SE = 0.27, p = .342, partial R^2_{adj} = −0.002) predicted depression symptoms at the follow-up. Although negative drift was not a main effect predictor of follow-up depression symptoms (β = 0.14, SE = 0.13, p = .294, partial R^2_{adj} = 0.003), lateralized late LPP (i.e., reduced LPP in the left vs. right hemisphere) showed a nonsignificant trend for predicting follow-up depression symptom severity (β = −0.24, SE = 0.13, p = .063, partial R^2_{adj} = 0.054).

DISCUSSION

Identifying biobehavioral markers among individuals with remitted depression is essential to clarify risk factors for MDD. Several important findings emerged. First, drift diffusion modeling showed that remitted adults exhibited slower drift rates to negative stimuli (i.e., slower to reject negative words) than healthy adults. Second, slower negative drift rates were cross-sectionally associated with greater depressive symptom severity (Table 2). Third, contrary to our hypotheses, there were no group differences when comparing early or late ERPs for all seen words. However, analyses focusing on LPP amplitudes for endorsed positive words indicated that relative to healthy adults, remitted individuals exhibited reduced LPP amplitudes in the left versus right hemisphere. Last, in line with the stress generation framework, drift rate to negative stimuli predicted interpersonal, but not noninterpersonal, stress severity among remitted individuals over time.

Self-referential Decision Making

Compared with healthy adults, adults with remitted depression exhibited slower negative drift rates, suggesting that they required more evidence to reject negative stimuli as self-relevant. Relative to a central tendency RT approach, drift rate may more precisely probe self-referential decision making, as it is less susceptible to outlier trials and sensitive to biases that persist in remission (33–35,84,85). Drift rate reflects the rate at which an individual accumulates information to derive meaning of a stimulus and respond consistently (31,32,35). Therefore, rejecting negative stimuli may be more challenging for remitted than healthy individuals (86). As prior research found that slower negative drift rates distinguished adults with depression symptoms from healthy individuals (36,38,39,87), these results extend findings and suggest that this impairment persists during remission.

Neurophysiological Markers of Depressogenic Self-referential Processing

Prior self-referential processing research has consistently demonstrated blunted ERP amplitudes to positive versus negative stimuli (28,47–49). This research, however, has not explored whether this effect is being driven by blunted ERP amplitudes for endorsed positive words, which may better capture self-reference attributes. Relative to healthy adults, remitted individuals showed reduced late LPP amplitudes in the left versus right hemisphere to positive endorsed words. Prior results suggest that positive self-referential processing is

reflected in left frontal LPPs (47,48,88,89) and potentially mediated by emotional arousal (57,90–92). Indeed, eliciting emotional arousal is associated with left prefrontal hemispheric activation (93–96), and depressed individuals show impaired emotional arousal and reduced left prefrontal activity (51,52,60,94,97). Moreover, following neurostimulation to left prefrontal regions, individuals with current MDD symptoms show increased emotional arousal and positive self-referential processing compared with baseline (98,99). Therefore, attenuated left late LPP amplitudes in remitted individuals may reflect blunted emotional arousal while processing positive self-referential stimuli. Notably, reduced emotional arousal during positive self-referential processing may impede reinforcement of positive self-schemas, which may increase vulnerability for relapse (100,101). An important next step is to establish whether left frontal LPP amplitudes longitudinally predict MDD recurrence.

Interpersonal Stressful Exposure

Negative drift rate at baseline predicted worsening interpersonal, but not noninterpersonal, stress severity over time for remitted adults. Several studies have shown that negative cognitive biases can promote stress generation, particularly for interpersonal stress (65,102,103). Our findings extend this work by showing that a slower tendency to reject negative words as self-relevant may increase interpersonal stress susceptibility among remitted individuals. Interestingly, as these effects were not found for depression symptoms, cognitive mechanisms for future depressive symptoms may be distinguishable from those involved in experiencing stressors (29). Insomuch as interpersonal stressors may precede relapse (65,66,104), future studies using longer follow-up periods are needed to further test the predictive validity of self-referential processing biases.

Limitations

There are several noteworthy limitations. First, given the study design, it is unclear if biobehavioral markers in remitted individuals are a cause or consequence of depression. Second, we did not analyze the count, duration, severity, or recency of previous depressive episodes, which may influence these findings. For example, in remitted adults, more severe episodes and shorter remission periods predict greater depressogenic self-referential processing biases (30,105). Third, participants endorsed an insufficient number of negative word trials to analyze ERPs in this condition. We observed blunted LPP amplitudes to endorsed positive words, but we could not test ERP-related effects for endorsed negative words. Fourth, although the Stress and Adversity Inventory has many strengths, it cannot tease apart whether stressors were dependent or independent. Last, our sample size was modest, and thus, replicating effects in a larger sample is essential.

Conclusions

Biobehavioral markers of depressogenic self-referential processing persist into symptom remission. Compared with healthy adults, adults with remitted depression showed LPP alterations and greater difficulty rejecting negative stimuli, the latter of which predicted worsening interpersonal stress. It is, therefore, critical for future research to determine whether residual depressogenic self-referential processing biases longitudinally predict MDD recurrence.

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RPA and SAS developed the study concept. GOA, RAK, RPA, SAS, DP, and GMS drafted the paper. VC, RAK, and KLA assisted with data processing and data collection. DP and GOA performed data analysis and interpretation under the supervision of RPA and SAS. All authors approved the final version of the paper submission.

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