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Altered N170 and Mood Symptoms in Bipolar Disorder: An Electrophysiological Study of Configural Face Processing

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Abstract

Objectives: Altered social behavior during mood episodes in bipolar disorder often bears detrimental and long-lasting interpersonal consequences. Abnormal face processing may play a role linking brain functions to clinical symptoms and behavior. This study aimed to understand configural face processing in bipolar disorder as a function of basic communicative attributes of the face and mood symptoms using event-related brain potentials (ERP). **Methods:** Forty-two participants with Bipolar I Disorder (BP) and 43 healthy controls (HC) viewed face stimuli varying in emotion (neutral, fearful), head orientation (forward, deviated), and gaze direction (direct, averted) while ERP were recorded. Configural face processing was indexed by the N170 wave. **Results:** BP had comparable overall N170 amplitude and peak latency as HC, though timing was more variable in BP. Abnormal N170 modulations by communicative face attributes were observed in BP: exaggerated sensitivity to emotion (fearful > neutral) in the left hemisphere, and reduced sensitivity to gaze-head incongruency (where N170 is normally larger to faces with incongruent than congruent gaze and head direction) in the right hemisphere. The former was not associated with mood symptoms, suggesting a heightened trait-like sensitivity to negative emotions. The latter was correlated with higher manic symptoms, indicating that an impaired perceptual sensitivity to faces of features signaling incongruent social attention may underlie social deficits observed during mania. **Conclusions.** These findings suggest a pathophysiological role of altered configural face processing in the phenomenology of bipolar disorder, and call for further investigations to evaluate its potential as a biomarker and treatment target.

Keywords: bipolar disorder; event-related potentials (ERP); social cognition; mania; face processing; emotion

INTRODUCTION

Bipolar disorder is a severe mental illness frequently accompanied by functional impairment. Emerging findings suggest that deficits in social cognition—the ability to process social information accurately and efficiently—are a critical determinant of psychosocial dysfunction in the disorder (1). One fundamental social cognitive process is reception of facial communication (2). Disruption in face processing and the misperception of social cues from faces may be one mechanism that links altered brain functions to observed clinical symptoms and social dysfunctions in bipolar disorder. For example, if a person has difficulties perceiving the focus of attention of others, they may misperceive irrelevant social information as self-relevant. This could lead to or reinforce grandiosity (if the misperceived social attention is interpreted as positive) or paranoia (if interpreted as negative) that are prevalent during mania. Conversely, if one fails to perceive self-directed attention from others, they may have difficulties participate productively in social interactions and consequently withdraw, as is often observed during the depressive state of the bipolar illness. Furthermore, if a person fails to detect (or has heightened sensitivity to) threat and negative emotion signaled by others' facial expressions and gaze direction, they may lack appropriate inhibition and have a propensity for engaging in impulsive, risk-taking, and reckless behavior (or be highly sensitive to negative social information and susceptible to mood reactivity). These all have detrimental interpersonal and functional consequences. Emerging data support that face processing is altered in bipolar disorder (reviewed below), but its neural mechanisms and relationship to symptoms and behavior remain to be illustrated. Knowledge of the neural and clinical correlates of face processing in bipolar disorder would enhance our understanding of functional difficulties in the illness and inform interventions. To this end, this study examined the N170 wave, a face-sensitive event-related brain potentials (ERP) component, during processing of faces with different attributes key to facial communication, and investigated how it is associated with mood symptoms in bipolar disorder.

Three Basic Attributes of the Face That Influence Face Processing

Faces are a ubiquitous source of social cues. Humans can infer others' attention, intention, and mental state from three basic attributes of the face: gaze direction, head

orientation, and facial expression. Gaze provides the most direct cue of one's focus of attention and communicative intention. The ability to perceive eye contact and follow others' gaze develops in infancy (3) and serves as a basic building block of subsequent development of higher-order social cognitive functions, including theory of mind and perspective-taking (4). When gaze direction is obscure, head orientation becomes the "default" indicator of attention direction, for its robust signals of the face contour and shape of facial features (e.g., nose) (5). Because both gaze direction and head orientation convey the direction of attention, when they are in incongruent directions, accuracy and speed of judgments of both gaze direction and head orientation are compromised (6,7). Another powerful cue of mental state is facial expression. In addition to affecting face evaluation on its own, it appears to interact with gaze direction. Perception of both gaze direction and emotion is facilitated or enhanced when the underlying approach/avoidant intent of gaze and emotion is matched (e.g., direct gaze in angry face, or averted gaze in fearful face) (8,9). These behavioral findings suggest that gaze direction, head orientation, and facial emotion are key factors modulating face processing.

N170: Index of Configural Face Processing

Research findings concerning the N170 wave have provided neural evidence that these three communicative face attributes influence face perception early on in the visual processing stream. N170 is a negative-going ERP component detected maximally around 170 ms post-stimulus at lateral occipito-temporal sites, and typically shows a right dominance (10). It is dubbed the "face-sensitive" ERP component because it is larger to faces than to objects. N170 is widely thought to index holistic encoding of face structure, with evidence coming from observations of increased amplitude and latency during processing of inverted (vs. upright) faces (11), eye region only (vs. full face) (12), and faces of other race (vs. own race) (13). Since, in these situations, face configuration is disrupted and/or unfamiliar, the increased amplitude and latency are thought to reflect more effortful and slowed processing, presumably because more analytical processing is engaged in place of configural processing. The configural face processing interpretation of N170 is consistent with N170's demonstrated sensitivity (larger amplitude) to other unconventional presentations of faces. These include horizontally rotated (vs. forward) faces (14), faces with incongruent (vs. congruent) gaze-head direction (15), and emotional (vs. neutral) faces (16).

Altered Face Processing in Bipolar Disorder

Although there is a plethora of research on face processing in psychiatric illnesses with prominent social deficits, such as autism and schizophrenia, research in this area is relatively new for bipolar disorder and has largely focused on the aspect of emotion recognition or identification. Behavioral and neuroimaging data so far generally support impairment in facial emotion recognition in individuals with bipolar disorder (17–19) and those at genetic risk (19). Such impairment is often viewed as limbic and prefrontal cortex dysfunctions (20,21), but there is evidence that visuospatial ability is affected in the disorder and first-degree relatives (22), implicating a role of altered early visual processing. In particular, one study showed that, compared with healthy controls, medication-free bipolar patients made more errors on a Gestalt completion test and tended to rely on individual facial features rather than simultaneous integration of multiple face elements for face recognition (23). This suggests that configural face processing may be compromised in bipolar disorder and contribute to deficits in recognizing facial emotion, making N170 a particularly suitable measure to investigate this question.

Thus far, only a few studies have investigated face processing in bipolar disorder using N170 (24–29). Most have found reduced amplitude (24,26–28) and, in some cases, delayed latency (25,29). However, most of the findings are extremely difficult to interpret and generalize due to the heterogeneity in samples and methodologies. These included patient characteristics (e.g., age, sex distribution, diagnosis) and the tasks used (gender discrimination, emotion recognition, oddball paradigm, go/no-go paradigm). N170 acquisition and measurement methods also varied widely, including choice of the reference electrode(s), filter settings, length of baseline, electrode sites where N170 was measured, time window used and how it was derived, use of peak amplitude vs. mean amplitude to measure N170, and correction for multiple comparisons. Merits and problems of some of these ERP-related practices have been discussed in depth elsewhere (30) and will not be detailed here. Nevertheless, it is important to point out that all studies, excepting one (29), included only a small sample of bipolar patients (*n* ranged from 9 to 18). Additionally, since N170 amplitude and latency can be significantly modulated by task demand (31), it is unclear if findings of reduced or slowed N170 truly reflected deficits in configural face encoding in bipolar disorder, or were driven by the cognitive demands of the tasks used (e.g., emotion processing, response inhibition). Wynn et al. (29) conducted the largest study to date (52 bipolar patients, 30 healthy controls) examining N170 in the context of gender and emotion identification. The authors found non-significantly different N170 amplitude, but

delayed latency, in bipolar patients as compared with healthy controls, suggesting preserved (though slowed) configural face processing in the bipolar illness.

To get a fuller understanding of configure face processing in bipolar disorder, it is necessary to examine how the three face attributes that are key to facial communication (i.e., emotion, gaze direction, and head orientation) interact and impact face processing. To the best of our knowledge, no studies have addressed this in bipolar disorder. Furthermore, it is unclear from the literature whether altered face processing is related to mood symptoms, as some have reported impaired emotion recognition as a stable deficit in bipolar disorder (17) while others found it to be dependent on mood state (32).

The Present Study

This study represents the first attempt in the literature to examine the effects of three face attributes key to facial communication (emotion, head orientation, gaze direction) on configural face processing in bipolar disorder. We used face stimuli varying in emotion (neutral, fearful), head orientation (forward, deviated), and gaze direction (direct, averted) to examine how these factors interact and impact N170 in a relatively large sample of bipolar patients and healthy controls. To minimize issues due to cognitive demand and unequal performance, a simple two-forced choice gaze discrimination task (putatively easier than tasks depending on emotion identification and other cognitive processes that are likely to be impaired in bipolar disorder) was used, and only correct trials were included to derive N170 for group comparisons. We explored whether bipolar patients would show abnormal N170 modulations by gaze direction, head orientation, and/or emotion as compared with healthy controls. Given previous reports of anomalous functional brain lateralization in bipolar patients that may be state dependent (33), we also explored hemispheric differences in N170 abnormalities in bipolar disorder and examined their associations with mood symptoms.

MATERIALS AND METHODS

Participants

Participants aged 18-60 were recruited from a university outpatient specialty clinic and inpatient psychiatric unit, and through community advertisements. Diagnoses were established using the Diagnostic Interview for Genetic Studies (34) or Structured Diagnostic Interview for DSM-IV (35). Exclusion criteria for all participants included: 1) a history of closed head injury,

neurological disorders, or serious medical illnesses that could result in significant changes of brain functions; 2) alcohol or substance abuse/dependence in past 6 months; and 3) mental retardation. For healthy controls, additional exclusion criteria included personal history of DSM-IV Axis-I disorders and history of bipolar or psychotic disorders in first-degree relatives. Written informed consent was obtained from each participant after study procedures were fully explained by trained research personnel. The study was conducted in accordance to a protocol approved by the University of Michigan Medical School Institutional Review Board and consistent with the Helsinki Declaration of 1975.

Forty-four individuals with Bipolar I Disorder and 44 healthy controls completed the study. One bipolar subject was excluded from the analyses due to excessive artifacts. One other bipolar patient and one healthy control were excluded for their N170 amplitudes exceeding 3 standard deviations above their respective group mean. Data of the remaining 42 bipolar patients and 43 healthy controls were included in the analyses of this report. The two groups did not significantly differ in age, sex, and education. At the time of testing, 35 bipolar patients were taking psychiatric medications (including mood stabilizers, SSRIs, antipsychotics, and anxiolytic medication), while 3 were medication-free; medication information of 4 bipolar patients was unavailable. Detailed demographic and clinical data of the participants are presented in Table 1.

Data from 32 of the healthy controls were included in a previous study (36).

Clinical Assessments

Current mood was assessed using the Beck Depression Inventory (BDI) (37) and Altman Self-Rating Mania Scale (ASRM) (38). ASRM scores for three and BDI scores for two bipolar patients were erroneously not collected.

Experimental Task

Participants viewed black-and-white face images that varied in emotion (neutral, fearful), head orientation (forward, 30° deviated), and gaze direction (direct, averted) (39,40). Participants performed a simple gaze discrimination task: to decide whether the face was looking at them or not (yes/no). A total of 512 face images (64 trials × 8 conditions) were presented in a pseudo-random order, divided into 4 blocks with a self-paced break between blocks, using E-Prime 1.0. In each trial, a fixation cross was first presented (500 milliseconds; ms), followed by a face (100 ms), then a fixation cross (up to 2,000 ms) during which participants were to give a response. Immediately after a button press or 2,000 ms has lapsed, whichever occurred first, a

blank screen (1,000 ms) was shown before the next trial started. See Fig. 1 for sample stimuli and illustration of the task procedure. The task typically lasted 20 to 25 minutes.

ERP Data acquisition and Processing

EEG was recorded using a 32-channel lycra cap with Ag/AgCl electrodes using the standard International 10-20 montage (Brain Products, GmbH, Munich, Germany) during the task. Data was sampled at 2,000 Hz and referenced to FCz during recording. Electrooculography was collected using one electrode positioned below the right eye, which was referenced to the Fp2 electrode. Electrode impedance was kept at or below 5 kΩ.

Data were processed offline using Brain Products Vision Analyzer 2.0 software. EEG data were resampled at 250 Hz. Data were then re-referenced to average mastoids ([TP9 - TP10]/2) and segmented into 1.2-s epochs (200 ms baseline, 1000 ms post-stimulus). This was followed by a 0.01-Hz high-pass filter and a 30-Hz low-pass filter (zero-phase shift and 24 dB/octave roll-off), correction for ocular movements using a regression algorithm (41), and baseline correction. Data exceeding ±80 μV were automatically rejected, and remaining artifacts were manually removed. Correct trials were averaged to produce an ERP waveform for each of the eight experimental conditions. Since N170 is maximal at the bilateral occipito-temporal sites, the P7 and P8 channels were the closest electrode sites in our montage and thus were selected to measure N170. Due to the proximity of these two sites to the mastoids, data were re-referenced to the averaged signal across the scalp (42).

Visual inspection of the waveforms revealed a great inter-subject variability in N170 latency, particularly in the bipolar group. Thus, to accurately measure N170 amplitude, personalized time windows were used to obtain N170 mean amplitude. This was accomplished using customized codes implemented in Matlab R2015b. Firstly, for each participant, N170 peak was identified by locating the minimum point of their averaged ERP wave (across all correct trials) between 130 and 200 ms, a typical time window suggested by the literature (43). Then, N170 amplitude was defined as the mean amplitude within a ±40 ms window around this peak. Visual inspection of the ERP waves indicated that while every participant showed detectable N170 on the right hemisphere (P8 site), some participants showed negligible N170 on the left (thus the "peak" simply reflected noise). Given this observation and the consideration that N170 is typically right-lateralized (10), only data from the P8 site was used to detect peak and identify the personalized N170 window. The mean number of correct trials averaged together for N170

peak detection was 401 (SD = 46.1) for healthy controls and 365 (SD = 65.0) for bipolar patients, $t(83) = 2.97$, $p = .004$.

Note that the statistical analyses concerning N170 in this study focused on amplitude (see below), and peak latency was not obtained for individual experimental conditions. This was because peak latency is extremely susceptible to noise and is a non-linear measure (30). Its measurement becomes especially problematic when the target ERP component is small (as is the case with N170) and the number of trials that goes into the averaged wave varies between conditions (as was the case in this study because the number of correct trials varied across conditions and between subjects). Therefore, N170 peak latency was obtained, from the average waves using all correct trials, only for the purposes of identifying personalized time windows to measure N170 mean amplitude, and for group comparison of overall N170 latency (i.e., across all conditions).

Statistical Analyses

Behavioral performance (accuracy, reaction time) and N170 amplitude data were analyzed using linear mixed models (LMM). LMM has multiple advantages over traditional repeated- or mixed-measures ANOVA for ERP research. It is more robust against unbalanced cells and has the capability of including subjects with missing data in one or more conditions (e.g., due to artifacts or few correct trials), offering increased statistical power (44). Additionally, LMM aims to select the simplest model that provides the best fit to the data (44), instead of evaluating every possible main effect and interaction as in ANOVA, which leads to inflated Type I errors as researchers very rarely correct for multiple comparisons (30).

LMMs were estimated using restricted maximum likelihood (REML). For N170 data, due to the complexity of the study design/data structure that involved 4 within-subject variables (Emotion, Head, Gaze, Laterality) and one between-subjects variable (Group), LMM analyses were done in two phases to enhance the interpretability of the results. In Phase I, a separate model was built for each hemisphere to characterize group differences without considering the complexity of laterality. In this phase, models were built using a step-up strategy. Individual intercept was specified as a random effect, and Emotion, Head, and Gaze specified as repeated-measures with covariance modeled using the diagonal structure. Initial models included Emotion, Head, Gaze, and Group as fixed effects. Then, 2-way interactions between these variables were added as fixed effects in the model; significant interactions were retained and

non-significant ones were removed from the model. This step was repeated with each level of higher-order interaction terms until the final model was reached for each hemisphere. Significant group interactions in the final LMMs were followed up with contrast analyses to identify differential within-subject effect(s) between the two groups that drove the interactions.

Phase II of the LMM analyses was to test if the significant Group interaction observed in each hemisphere in Phase I (Emotion × Group for left hemisphere, Gaze × Head × Group for right hemisphere) was specific to that particular hemisphere or applicable to both hemispheres. Models were built using data from both hemispheres. Individual intercept and laterality were specified as random effects, and Emotion, Head, Gaze, and Laterality specified as repeated-measures with covariance modeled using the diagonal structure. The initial model included Emotion, Head, Gaze, Laterality, Group, along with Emotion × Group and Gaze × Head × Group as fixed effects. Three alternative models were built by replacing either or both of the two group interaction terms with their higher-order interactions with laterality (i.e., Laterality × Emotion × Group, Laterality × Gaze × Head × Group). The model with the best fit, quantified by having the lowest information criteria, was chosen to be the winning model. The presence of a significant Laterality × Emotion × Group and/or Laterality × Gaze × Head × Group interactions in the winning model would suggest that the group interaction(s) observed in Phase I were hemisphere-specific.

Finally, each N170 abnormality observed in the bipolar group from the LMM analyses were correlated with two mood symptom scores (ASRM, BDI) using parametric (Pearson) and non-parametric (Spearman) correlations.

All statistical analyses were performed with IBM Statistical Package for the Social Sciences (SPSS) version 24.

RESULTS

Behavioral Data

Descriptive statistics of accuracy and reaction time for the eight experimental conditions broken down by group are summarized in Supplemental Table 1. Results of the final LMMs are summarized in Table 2, and significant effects are illustrated in Fig. 2. A Head × Gaze interaction was evident for both accuracy and reaction time. Participants were generally highly accurate except for the deviated faces with direct gaze, similar to the finding of a previous study

(36). Participants took longer to respond to direct gaze presented in deviated than in forward head orientation, while the reaction time for averted gaze was constant across head orientations. Bipolar patients were less accurate and slower than healthy controls. There was a significant Gaze × Group interaction in both accuracy and reaction time. Specifically, the gaze effect in healthy controls (higher accuracy and shorter reaction time with averted than direct gaze) was significantly reduced among bipolar patients.

N170 Data

The grand average N170 waves for the two groups are displayed in Fig. 3. The overall N170 peak latency did not differ between healthy controls (166 ± 9 ms) and bipolar patients (170 ± 15 ms), $t(64.4) = -1.37$, $p = .18$, but the bipolar group showed significantly more inter-subjects variability than healthy controls, $F = 13.83$, $p < .001$.

Descriptive statistics of N170 amplitude for the eight experimental conditions broken down by group are summarized in Supplemental Table 2. Results of the final LMM obtained for each of the hemispheres are summarized in Table 3. In both hemispheres, significant emotion and head effects were observed across all participants. Specifically, fearful faces elicited larger N170 than did neutral faces, and deviated head elicited larger N170 than did forward head. Gaze direction did not modulate N170 by itself in both hemispheres. All of these findings are consistent with the literature (14–16,36).

In both hemispheres, group effect was not significant, indicating that bipolar patients did not differ from healthy controls in terms of overall N170 amplitude in each hemisphere. However, two significant group interactions were detected. In the left hemisphere, there was a significant Emotion × Group interaction, driven by an exaggerated emotion effect (i.e., larger N170 to fearful than neutral faces) in the bipolar group as compared with healthy controls (Fig. 4A). In the right hemisphere, a significant Head × Gaze interaction was observed, such that faces with incongruent head-gaze direction elicited larger N170 than did faces with congruent head-gaze direction. This head-gaze incongruency effect differed between groups as indicated by the significant Head × Gaze × Group interaction. Post hoc contrast analyses showed that this head-gaze incongruency effect was virtually absent in bipolar patients as a group (Fig. 4B).

Results of the LMM analyses considering data of both hemispheres are summarized in Supplementary Table 3. The best model (Alternative Model 3) included Laterality × Emotion × Group and Laterality × Gaze × Head × Group as fixed effects, confirming that the exaggerated

emotion effect and reduced head-gaze incongruency effect in the bipolar participants were hemisphere-specific.

Clinical Correlates of N170 Abnormalities

The exaggerated emotion effect found in the left hemisphere of bipolar patients did not show any significant correlations with either mood symptom scores. However, reduced head-gaze incongruency effect found in the right hemisphere in the bipolar group was significantly correlated with higher manic symptoms as measured with ASRM (r = 0.36, p = .031; ρ= 0.39, p = .016) (Fig. 5).

DISCUSSION

This study used a simple gaze discrimination task to probe configural face processing in bipolar disorder. In a relatively large sample of participants with Bipolar I Disorder and healthy controls, we found that patients showed comparable overall N170 amplitude as healthy controls. This is consistent with Wynn *et al.* (2013), the largest N170 study in bipolar disorder thus far, that N170 amplitude was not reduced in the patient group. We also found that patients' overall peak latency was comparable with healthy controls, but with a wider inter-subject variability, causing a "short and stout" appearance of their grand average waves compared with healthy controls'. The lack of statistical group differences in overall N170 latency in this study was contrary to Wynn et al.'s report of delayed latency in bipolar patients. This discrepancy may be due to the methodological differences between these two studies. Wynn et al. used the method of difference wave (subtracting the ERP of object processing from the ERP of face processing) to isolate N170 (to ensure it contains face-specific activity only), and the data were processed with a severe high-pass filter (1 Hz), which may have shifted forward the timing of the ERP waves (30). It is unclear whether these caused systematic biases to one group or the other. Taken together, we replicated Wynn et al.'s finding of overall intact holistic encoding of face structure as indexed by N170 amplitude in bipolar disorder, although it remains to be investigated whether this operation is slowed.

Despite overall intact N170, however, bipolar patients showed abnormal modulations by face attributes that are influential to facial communication. While healthy controls showed a previously documented (15) sensitivity to faces with incongruent head and gaze directions in the right hemisphere, this effect was virtually absent in the bipolar group. Faces with incongruent

head-gaze direction (including forward faces with averted gaze and deviated faces with direct gaze), configurally, represent unconventional structural presentations of the face. Semantically, they convey conflicting focuses of attention as suggested by the different head orientation and gaze direction. The normal N170 accentuation to these faces suggests increased effort in encoding and integrating face elements, which may serve as a mechanism to facilitate detection of conflicting social signals embedded in a face. The ability to detect incongruent social signals is instrumental in accurately assessing others' mental state, evaluating ongoing interpersonal dynamics, and guiding appropriate social responses. The reduction in this head-gaze incongruency effect on N170 observed in bipolar patients indicates an impaired perceptual sensitivity to facial features signaling incongruent social attention. It is worth noting that bipolar patients did show normal N170 sensitivity to deviated head orientation (14,15,36), as suggested by a significant Head effect in all participants but a non-significant Head × Group interaction on N170 amplitude. This suggests that altered configural face perception in bipolar disorder is nuanced and is not readily captured by decreased sensitivity to head orientation as demonstrated in schizophrenia (36), confirming the importance of examining multiple core face attributes to fully understand how face processing is altered in bipolar disorder. The reduced head-gaze incongruency effect on N170 was significantly associated with more severe manic symptoms. This provides support that altered behaviors during the manic state, which are often characterized by interpersonal difficulties, may be related to altered face perception. The association between manic symptoms and right-hemisphere N170 abnormality is in line with the view that "right hemisphere deficits" previously reported in bipolar disorder and mania likely reflect transient lateralized abnormalities (e.g., due to neurotransmitter imbalance) that fluctuate with mood state rather than permanent brain lesions or structural abnormalities (33). The emerging field of computational psychiatry would be instrumental in enhancing our understanding of how specific changes in the synaptic and circuitry levels give rise to collective electrophysiological signals and cognitive functions in bipolar disorder. Incorporating comprehensive measures of social cognition, particularly those that assess the ability to identify others' mental state in dynamic and ecologically valid scenarios, in future studies will help further elucidate the role of configural face processing in social functioning and investigate its promises as a treatment target in bipolar disorder.

Another N170 abnormality noted in bipolar patients in this study was an exaggerated emotion effect (larger N170 response to fearful than neutral faces) in the left hemisphere. Since emotion processing was implicit in this study, this finding could not be attributed to poor behavioral performance in emotion identification. It has been shown that N170 increases as attention (45), intensity of emotion (46), or perceived personal importance of the stimuli (47) increases. Therefore, exaggerated N170 response to fearful faces in the bipolar group may reflect increased perceived salience of threat-related emotions. This interpretation is consistent with the results of an eye-tracking study, in which bipolar patients were found to attend more to threatening images than did healthy controls, and such a bias was not associated with mood state (48). Similarly, we did not find any associations between mood symptoms and enhanced emotion effect on N170 in our patient group. Such a trait-bias toward threat emerging in an early visual processing stage may constitute a cognitive vulnerability to stressful experience and consequently susceptibility to emotional reactivity in bipolar disorder (48). Previous research suggests that the ability to correctly identify fear is reduced in bipolar disorder, particularly during mania (49). Therefore, the exaggerated N170 response to fearful faces among bipolar patients may also be interpreted as having more difficulty or inputting more effort in encoding fearful expression. We did not include assessments of emotion identification in this study. Future studies examining if the enhanced emotion effect in bipolar disorder indeed corresponds to poorer behavioral performance in fear identification would provide a more definitive interpretation of this N170 abnormality. It would also be valuable to obtain longitudinal data to confirm that this exaggerated N170 response to negative emotions is independent of mood state, and evaluate its potential in serving as a biomarker of bipolar disorder.

Caution is needed when interpreting the results of this study due to several sample-related and methodological limitations. Our bipolar sample contained mostly chronic and medicated patients. Since most patients with bipolar disorder are treated with medications in North America, the results of this study inform face processing in patients we often encounter in the medical settings. However, it is unclear to what extent the observed effects were due to medication or the illness itself; this needs to be clarified in future studies recruiting patients in the early phase of the illness and preferably those who are medication-free or with limited medication exposure. In terms of methods, the routine timing of stimulus onset due to a lack of a temporal jitter between trials in the ERP task might have introduced anticipation brain activity,

confounding the early visual N170 wave. However, the effect on the results was likely minimal, because the intertrial interval was relatively short (1 second) and the task was not a reaction-time task. We used only two electrodes (P7, P8) to measure N170, as other electrode sites reasonably near where N170 is most prominent (e.g., PO7, PO8) were unavailable in the EEG cap used in this study. Although this is not an uncommon practice among N170 studies (16), deriving N170 from multiple electrodes at the low occipito-temporal sites in future studies would improve the reliability and reproducibility of the findings. This is especially important given that the correlation between mania and the reduced head-gaze incongruency effect detected in bipolar disorder would not survive a stringent study-wise Bonferroni correction (alpha adjusted to 0.0125 for four total correlations run). Additionally, we used a 2 (emotion) × 2 (head orientation) × 2 (gaze direction) × 2 (group) mixed design to study how the three basic face attributes differentially interact and affect configural face processing in bipolar disorder relative to healthy people. Such a complex design precludes the inclusion of more than 2 levels of each of the three within-subject variables (e.g., including more categories or intensity levels of emotions, ambiguous gaze directions, or intermediate head deviations), for the task to remain tolerable. There is evidence that the interaction between gaze direction and emotion may depend on the intensity of the facial expression (50) and ambiguity of gaze direction (40). Future studies examining how signal intensity of these face attributes influence configural face processing in bipolar disorder would provide a more ecologically valid understanding of social cognition in the illness. Finally, we did not measure and make group comparisons of N170 latency for individual experimental conditions due to measurement challenges associated with peak latency (30). Whether the N170 amplitude abnormalities observed in patients were also accompanied with slowed processing needs to be clarified in future studies.

To conclude, overall configural face processing as indexed by N170 amplitude appeared to be intact, but with more heterogeneous timing, in bipolar disorder relative to healthy individuals. However, nuanced abnormalities were observed when three face attributes key to facial communication were manipulated in the stimuli: an exaggerated emotion effect in the left hemisphere and a reduced gaze-head incongruency effect in the right hemisphere. The exaggerated emotion effect was not associated with mood state, suggesting a heightened trait-like sensitivity to negative emotions that may contribute to vulnerability to stress and mood instability. The reduced gaze-head incongruency effect was significantly correlated with more

severe manic symptoms, suggesting that an impaired perceptual sensitivity to faces of features signaling incongruent social attention may underlie social deficits observed during mania. These findings together suggest that disruption of configural face processing may play a critical role in the clinical manifestations of bipolar disorder and warrants further investigations to evaluate its potential as a biomarker and treatment target. For example, excessive N170 responses to negative emotions may be used as an index of susceptibility to developing bipolar disorder or mood dysregulations among genetically at-risk individuals and help inform early intervention strategies. Cognitive training and brain stimulation techniques may be used to normalize N170 response to incongruent social attention signals, so to improve clinical and functional outcomes.

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Table 1. *Demographic and clinical characteristics of bipolar patients (BP) and healthy controls (HC).*

Variable	BP (n = 42) Mean ± SD	HC (n = 43) Mean ± SD	t/ X^2	p
Age (years)	41.6 ± 11.0	41.2 ± 12.9	0.12	.90
Sex(male/female)	22 m / 20 f	29 m / 14 f	2.01	.16
Education (years)	15.4 ± 2.8	15.8 ± 2.6	0.55	.59
Duration of illness (years)	24.4 ± 12.0	-	-	-
Altman	3.54 ± 3.72	-	-	-
BDI	11.12 ± 9.27	1.05 ± 1.67	6.85	< .001
Medicated (n, %)[a]	35 (92.1%)	-	-	-
Lithium (n, %)[a]	15 (39.5%)	-	-	-
Antiepileptic (n, %)[a]	3 (7.9%)	-	-	-
Antidepressant (n, %)[a]	20 (52.6%)	-	-	-
Antipsychotic (n, %)[a]	14 (36.8%)	-	-	-
Benzodiazepine (n, %)[a]	10 (26.3%)	-	-	-
Hypnotic (n, %)[a]	3 (7.9%)	-	-	-

a. Medication data of 4 BP were unavailable. Percentage was calculated based on a denominator of 38 instead of 42.

Table 2. *Summary of Final Linear Mixed Models for Accuracy and Reaction Time.*

	Accuracy	Reaction time
Tests for Fixed Effects		
Intercept	$F(1, 84.6) = 3650.0$***	$F(1, 83.3) = 2971.9$***
Emotion	$F(1, 206.3) = 0.3$	$F(1, 329.8) = 0.1$
Head	$F(1,301.9) = 189.2$***	$F(1,427.6) = 169.7$***
Gaze	$F(1,200.3) = 160.4$***	$F(1,429.4) = 4.17$*
Group	$F(1,79.9) = 5.75$*	$F(1,79.9) = 5.75$*
Head × Gaze	$F(1, 297.4) = 210.7$***	$F(1, 428.3) = 207.4$***
Gaze × Group	$F(1, 314.3) = 12.0$***	$F(1, 410.8) = 10.3$**
Estimates of Fixed Effects[a]	*β (s.e.)*	*β (s.e.)*
Intercept	0.82 (0.02)***	742.6 (19.1)***
Neutral emotion	-0.00 (0.01)	1.1 (4.2)
Forward head	-0.01 (0.01)	6.7 (5.1)
Direct gaze	-0.28 (0.02)***	63.7 (8.1)***
HC	0.10 (0.03)***	-72.6 (26.3)**
Direct gaze, Forward head	0.34 (0.02)***	-138.1 (9.6)***
Direct gaze, HC	-0.07 (0.02)***	30.4 (9.5) **
Model Information Criteria		
-2 REML log-likelihood	-674.97	7463.10
AIC	-656.97	7481.10
BIC	-616.30	7521.41
Selective Contrast Estimates	Estimate (s.e.)	Estimate (s.e.)
Gaze × Group[b]	-0.06 (0.02)**	30.4 (9.5)***

a. Redundant parameters omitted.

b. Contrast of (direct – averted) in healthy controls vs. (direct – averted) in bipolar patients. For accuracy, negative value indicates reduced gaze effect (higher accuracy for averted than direct gaze) in bipolar patients compared with healthy controls. For reaction time, positive value indicates reduced gaze effect (longer RT for direct than averted gaze) in bipolar patients relative to healthy controls.

* $p < .05$ ** $p < .01$ *** $p < .001$

Table 3. *Summary of Final Linear Mixed Models for N170 Amplitude.*

	Left hemisphere (P7)	Right hemisphere (P8)
Tests for Fixed Effects		
Intercept	$F(1, 82.9) = 78.1$***	$F(1, 83.0) = 137.0$***
Emotion	$F(1, 547.3) = 18.8$***	$F(1, 540.6) = 46.8$***
Head	$F(1, 537.4) = 25.8$***	$F(1, 539.2) = 75.1$***
Gaze	$F(1, 542.8) = 0.3$	$F(1, 532.4) = 0.0$
Group	$F(1, 82.9) = 1.0$	$F(1, 83.0) = 0.0$
Emotion × Group	$F(1, 547.5) = 7.1$**	--
Head × Gaze × Group	--	$F(4, 346.3) = 4.34$**
Estimates of Fixed Effects[a]	*β (s.e.)*	*β (s.e.)*
Intercept	-2.53 (0.40)***	-4.12 (0.47)***
Neutral emotion	0.37 (0.08)***	0.40 (0.06)***
Forward head	0.27 (0.05)***	0.46 (0.11)***
Direct gaze	0.03 (0.05)	-0.11 (0.12)
HC	-0.43 (0.56)	-0.08 (0.65)
Neutral, HC	-0.28 (0.11)**	--
Direct gaze, Forward head, HC	--	0.33 (0.23)
Direct gaze, Deviated head, HC	--	-0.07 (0.17)
Averted gaze, Forward head, HC	--	-0.18 (0.16)

Model Information Criteria		
-2 REML log-likelihood	1777.02	1920.81
AIC	1795.02	1920.81
BIC	1835.31	1961.09
Selective Contrast Estimates	Estimate (s.e.)	Estimate (s.e.)
Emotion × Group[b]	-0.285 (0.107)**	--
Head × Gaze × Group[c]	--	0.287 (0.117)*

a. Redundant parameters are omitted.

b. Contrast of (neutral – fearful) in healthy controls vs. (neutral – fearful) in bipolar patients. Negative value indicates increased emotion effect (larger N170 for fearful) in bipolar patients relative to healthy controls.

c. Contrast of (faces with congruent head-gaze direction – faces with incongruent head-gaze direction) in healthy controls vs. (faces with congruent head-gaze direction – faces with incongruent head-gaze direction) in bipolar patients. Positive value indicates reduced head-gaze incongruency effect (i.e., normally larger N170 to faces with incongruent than congruent head-gaze direction) in bipolar patients compared with healthy controls.

* $p < .05$ ** $p < .01$ *** $p < .001$

FIGURE LEGENDS

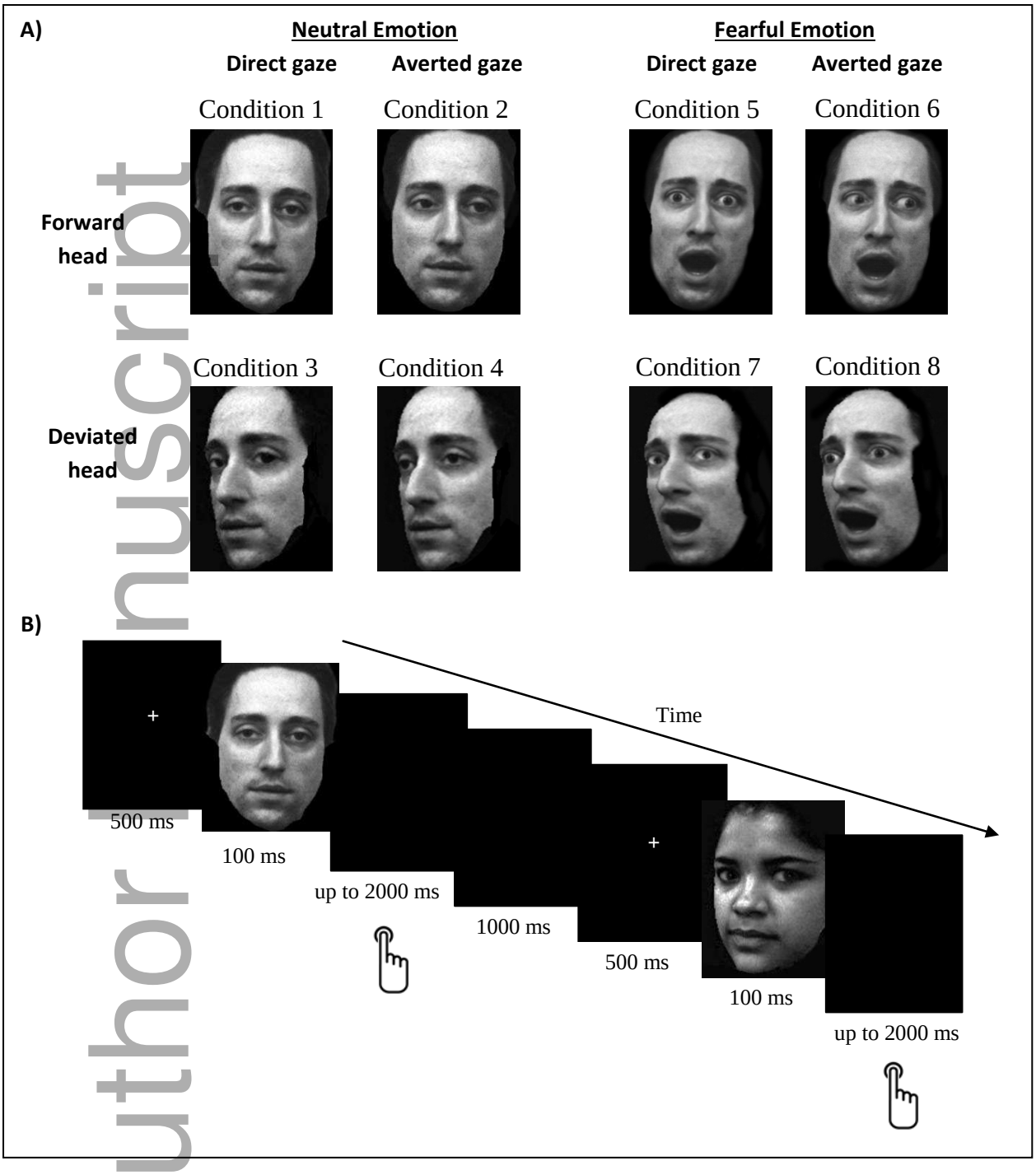
Fig. 1. **Gaze discrimination task.** A) Sample face stimuli of the eight experimental conditions of the gaze discrimination task. B) Procedure of the gaze discrimination task.

Fig. 2. **Behavioral performance differences between the bipolar disorder (BP) and healthy control (HC) groups on the gaze discrimination task.** Upper panel: The BP group was less accurate than HC overall, and this was driven by reduced accuracy for faces with averted gaze in BP compared with HC (i.e., BP participants showed same hit rate but more false alarm of eye contact). Lower panel: The BP group had overall longer reaction time than HC, and lacked the gaze effect observed in HC where averted gaze took less time to respond than direct gaze.

Fig. 3. **Grand average waves at bilateral occipito-temporal sites (P7 and P8) for the healthy controls (HC: *n* = 43) and bipolar disorder group (BP: *n* = 42).** Negative is plotted upward. Gray vertical lines indicate 170 ms post-stimulus.

Fig. 4. **N170 differences between healthy controls (HC) and patients with bipolar disorder (BP).** A**)** Exaggerated emotion effect on N170 in the left hemisphere in BP compared with HC). **B)** Absence of head-gaze incongruency effect" (i.e., normally larger N170 to faces with incongruent than congruent head-gaze direction) in the right hemisphere in BP. Negative is plotted upward. Gray solid vertical lines indicate the mean N170 peak latency of the corresponding group (HC: 166 ms; BP: 170 ms), and gray dashed lines indicate ± 40 ms from the peak. Black vertical lines in bar graphs indicate standard errors.

Fig. 5. **Clinical correlate of N170 abnormality in bipolar disorder.** Reduced head-gaze incongruency effect on N170 was associated with higher mania symptoms as measured with Altman Self-Rating Mania Scale (ASRM) in bipolar patients.



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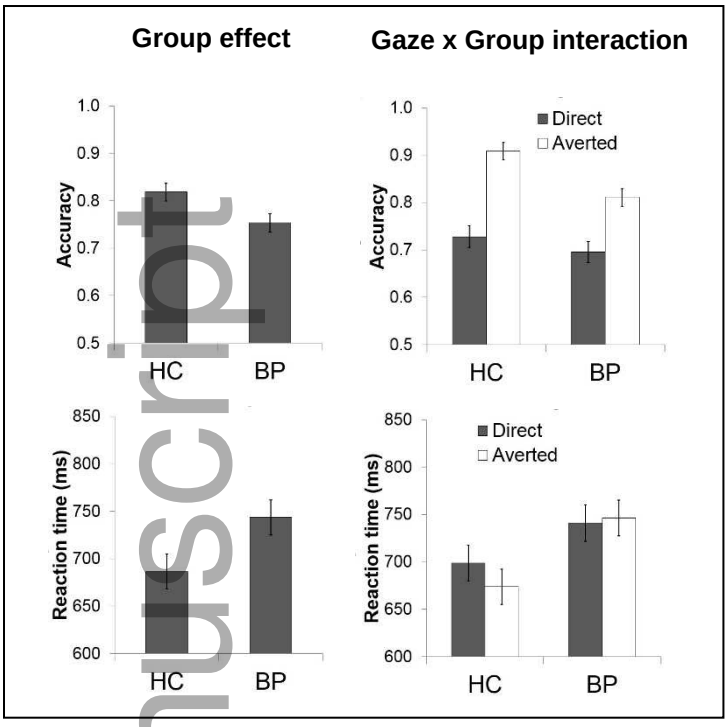
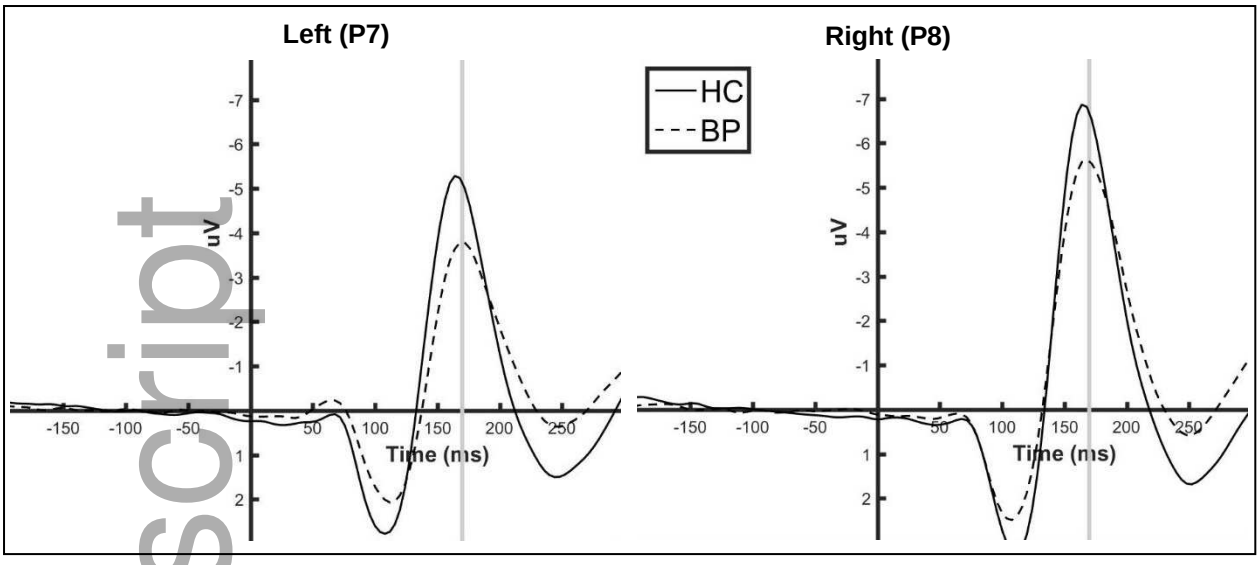


Fig. 2. **Behavioral performance differences between the bipolar disorder (BP) and healthy control (HC) groups on the gaze discrimination task.** Upper panel: The BP group was less accurate than HC overall, and this was driven by reduced accuracy for faces with averted gaze in BP compared with HC (i.e., BP patients showed same hit rate but more false alarm of eye contact). Lower panel: The BP group had overall longer reaction time than HC, and lacked the gaze effect observed in HC where averted gaze took less time to respond than direct gaze.



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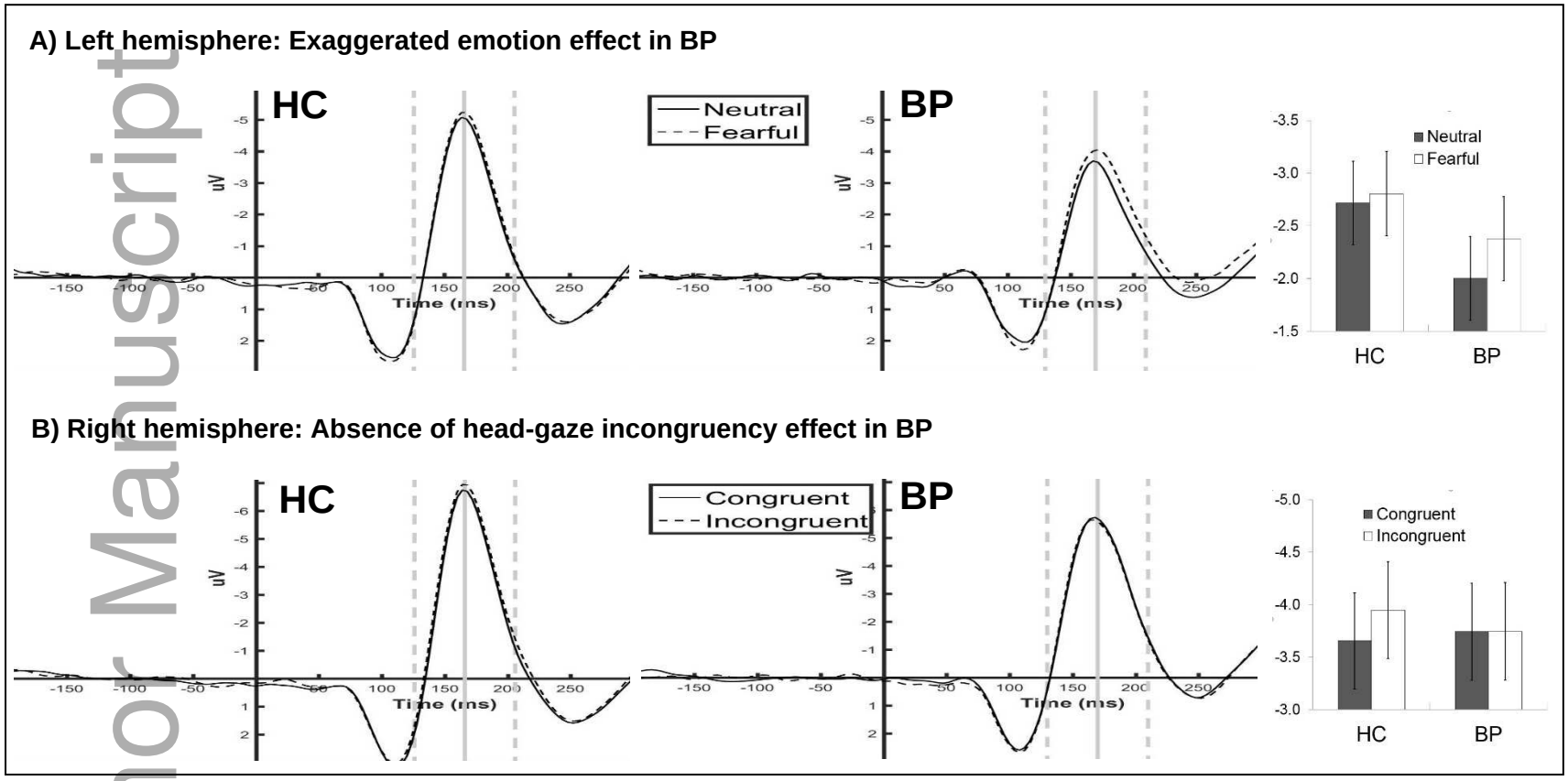


Fig. 4. **N170 differences between healthy controls (HC) and patients with bipolar disorder (BP).** A**)** Exaggerated emotion effect on N170 in the left hemisphere in BP compared with HC). **B)** Absence of head-gaze incongruency effect" (i.e., normally larger N170 to faces with incongruent than congruent head-gaze direction) in the right hemisphere in BP. Negative is plotted upward. Gray solid vertical lines indicate the mean N170 peak latency of the corresponding group (HC: 166 ms; BP: 170 ms), and gray dashed lines indicate ± 40 ms from the peak. Black vertical lines in bar graphs indicate standard errors.

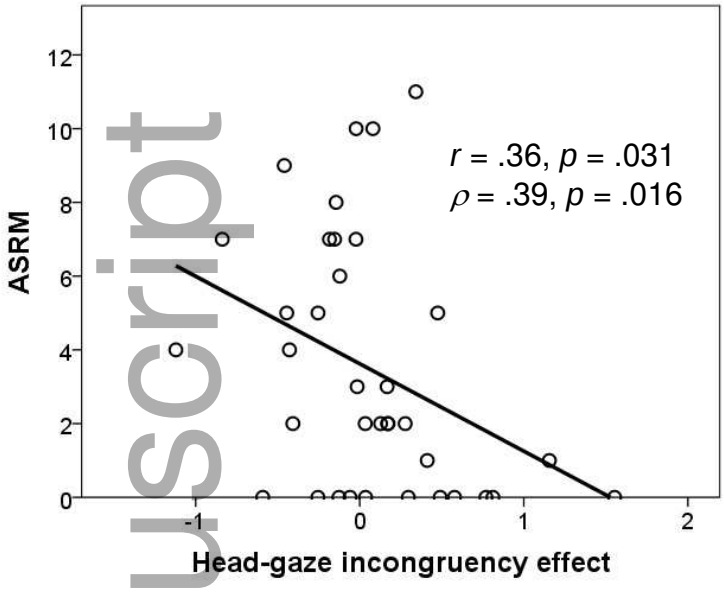
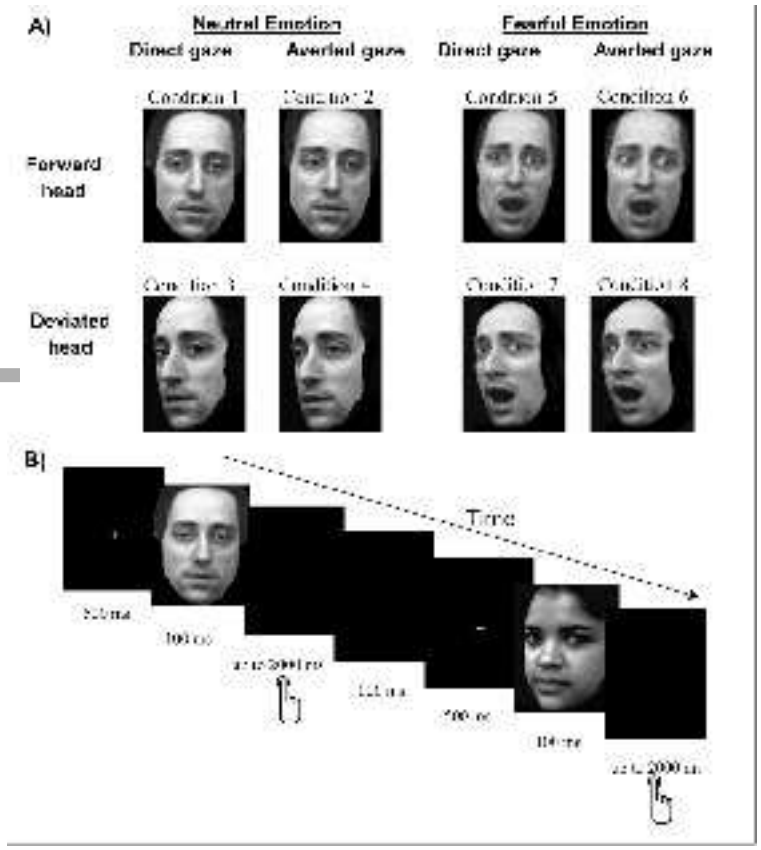


Fig. 5. **Clinical correlate of N170 abnormality in bipolar disorder.** Reduced head-gaze incongruency effect on N170 was associated with higher mania symptoms as measured with Altman Self-Rating Mania Scale (ASRM) in bipolar patients, as indicated by parametric (Pearson r) and non-parametric (Spearman ρ) tests.



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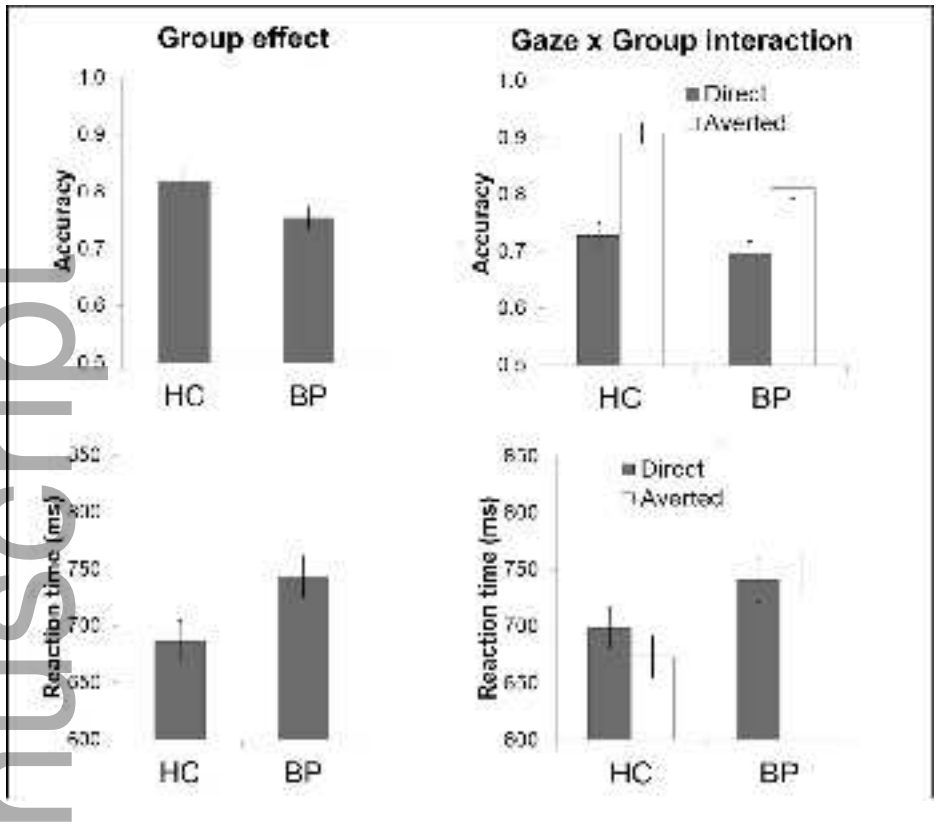

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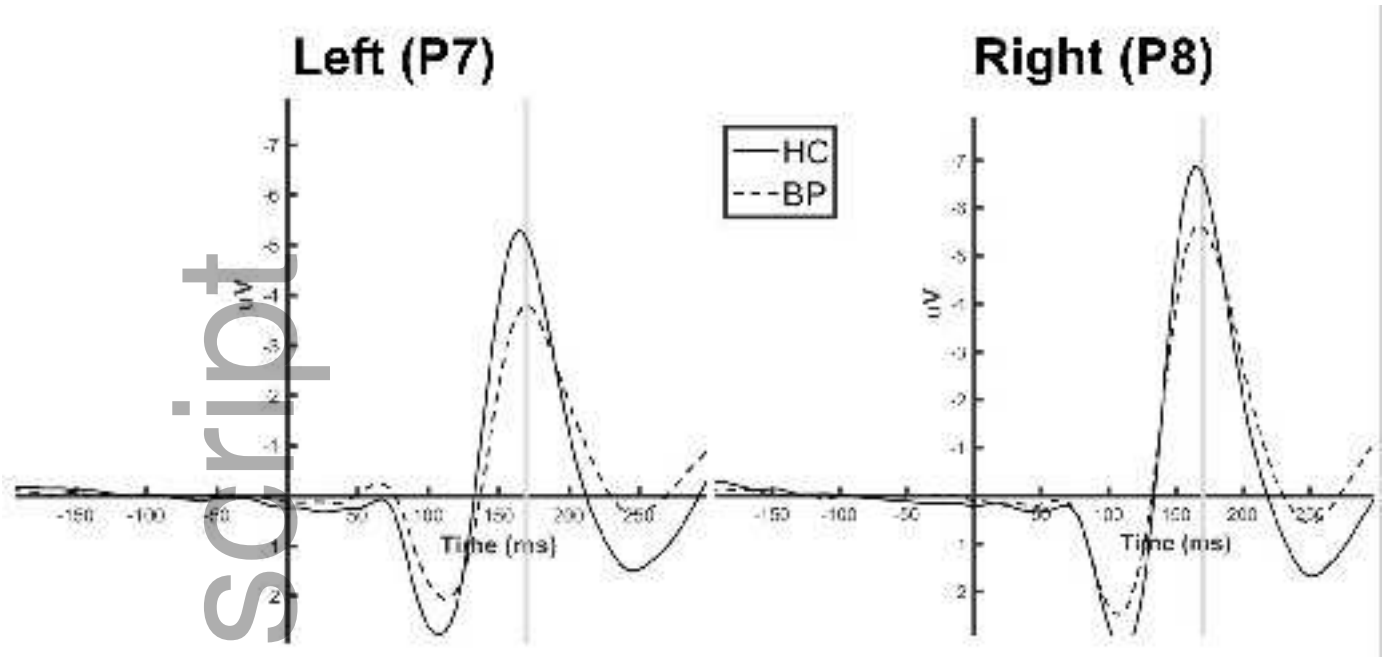

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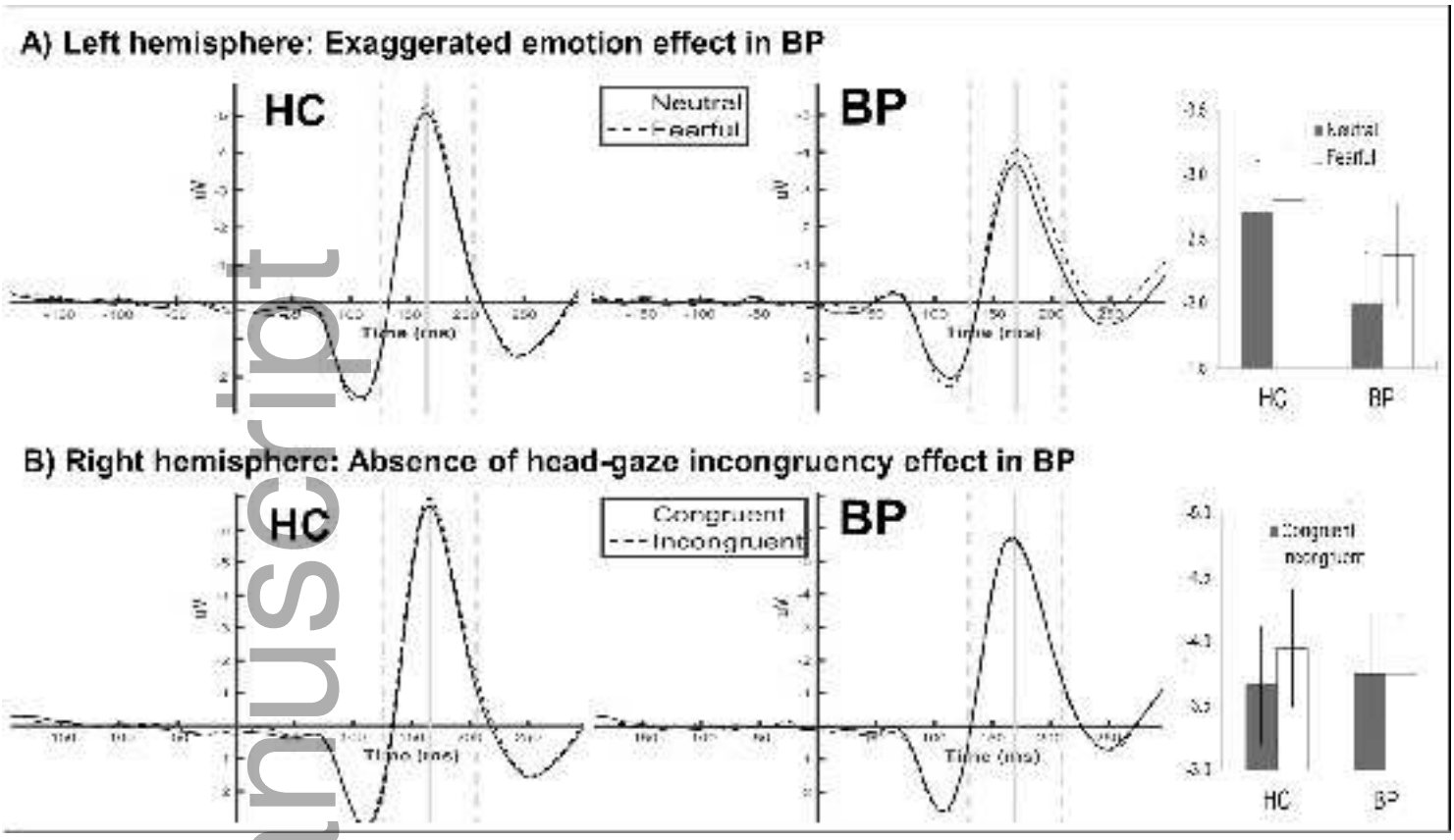

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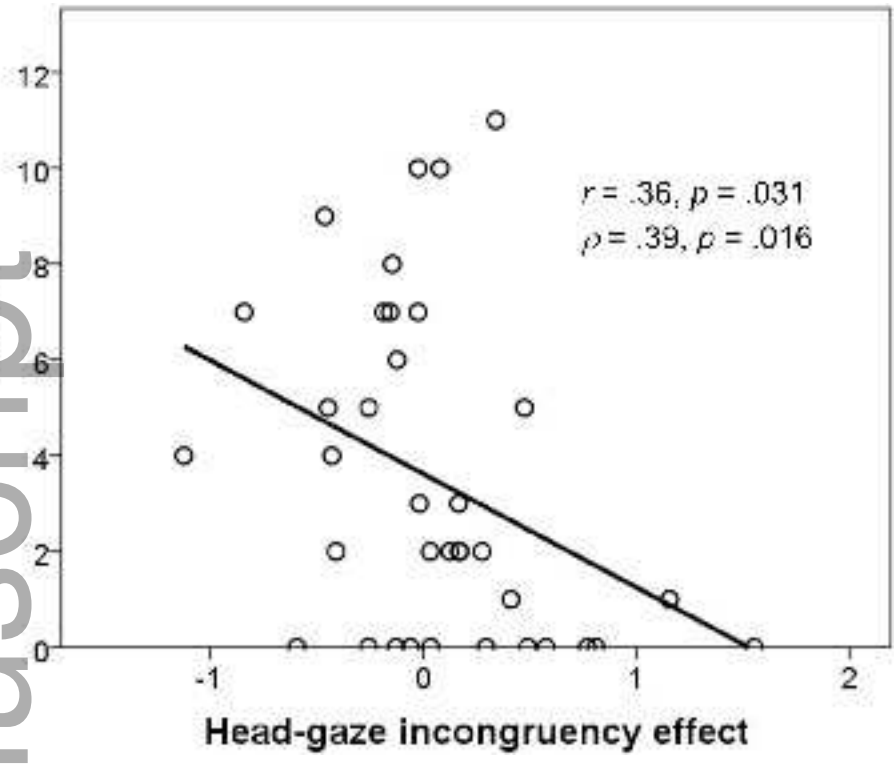

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