Reductions in regional theta power and fronto-parietal theta-gamma phase-amplitude coupling during gaze processing in bipolar disorder

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Abstract

Impaired social cognition is common in bipolar disorder (BD) and predicts poor functional outcomes. A critical determinant of social cognition is the ability to discriminate the eye gaze direction of others, and its alteration may play a role in functional impairment in BD. However, the neural mechanisms underlying gaze processing in BD are unclear. Because neural oscillations and their communications through inter-region synchronization are crucial neurobiological mechanisms supporting cognition, this study aimed to understand their role in gaze processing in BD. Electroencephalography (EEG) was recorded during a gaze discrimination task for 38 participants with BD and 34 healthy controls (HC). Time-frequency decomposition of EEG was used to examine: 1) oscillatory power over bilateral posterior and midline anterior locations associated with early face processing and higher-level cognitive processing, and 2) connectivity between locations via theta-gamma phase-amplitude coupling (PAC). Compared to HC, BD showed reductions in midline anterior and left posterior theta power, as well as diminished bottom-up and top-down theta-gamma PAC between anterior and posterior sites. Reduced theta power and theta-gamma PAC were related to slower response times during gaze discrimination. These findings suggest that altered theta oscillations and anterior-posterior dysconnectivity between areas associated with higher-level cognition and early face processing may underlie impaired gaze processing in BD. While future studies are needed to determine the causal nature of these relationships, this work represents a first step towards translational research by providing neural targets for future neuromodulatory interventions to improve social cognition and functioning in BD.

Keywords: bipolar disorder, EEG, neural oscillations, social cognition, gaze processing

Introduction

Bipolar disorder (BD) is a severe psychiatric condition associated with poor functional outcomes, including impaired familial relations and poorer social adjustment (Sanchez-Moreno et al., 2009; Tatay-Manteiga et al., 2018). Evidence suggests that social cognitive deficits contribute to this dysfunction in BD (Vlad et al., 2018). A critical determinant of social cognition is the ability to accurately discriminate the eye gaze direction of others, and its alteration may play a role in the functional impairment in BD. The present study sought to inform our understanding altered social cognition in BD by investigating the neural correlates of altered gaze perception in BD.

As humans, the ability to accurately discriminate gaze direction allows us to make informed judgements about others' intentions and inner states (Shepherd, 2010). Successful gaze discrimination relies on a range of basic- and higher-level cognitive processes (Itier & Batty, 2009). At the most basic level, we encode sensory information. Then, facial features including gaze direction (Berchio et al., 2017), head orientation (Itier et al., 2007), and facial emotion (Berchio et al., 2017, 2019; Carretié et al., 2001) are integrated to form a holistic representation (Bentin et al., 1996; Itier & Batty, 2009). At higher levels, we inhibit automatic judgements or emotional reactions to make informed judgements about others' mental states (Sabbagh et al., 2004) and intentions (Carrick et al., 2007; Itier & Batty, 2009). Neuroimaging data show that earlier processes depend on temporal brain areas specialized for processing facial features (Allison et al., 2000), while higher-level processes rely on more frontal areas involved in higher level cognitive processes like self-referential processing and cognitive control (Cavanagh & Frank, 2014). Studies have shown that disrupted gaze perception observed at the behavior level is associated with altered regional neural activity and connectivity between these regions (Tso,

Burton, et al., 2021; Tso, Angstadt, et al., 2021). This suggests that effective gaze perception depends on the integrity of both local neural activity and inter-regional communications in the brain.

Behavioral studies show that BD is associated with altered face processing and theory of mind (ToM) (Samamé et al., 2012) and emerging evidence also indicates gaze processing abnormalities in BD. BD may over endorse eye contact relative to HC (Yao et al., 2017) and have difficulties inferring others' intentions and emotional states from the eye region (Marotta et al., 2018). Difficulties with gaze perception may contribute to poorer social functioning (Tso et al., 2020) and may also play a role in the presentation of core symptoms associated with BD. For example, chronic over-perception of self-directed gaze in BD could interact with cognitive and affective states to exacerbate feelings of inflated self-esteem or grandiosity during hypo/mania (e.g., "Everyone is looking at me. I must be famous."). Thus, altered gaze perception in BD has both clinical and broader functional importance. Understanding the neural mechanisms which perpetuate these difficulties is a crucial step towards translational research designing novel, targeted interventions (Chase et al., 2020; Reinhart et al., 2015; Yamada et al., 2021, 2022)).

Thus far, only a few studies have examined the neural mechanisms of altered gaze processing in BD. One functional magnetic resonance imaging (fMRI) study found that, during gaze discrimination, individuals with BD exhibit reduced activation of medial prefrontal areas (implicated in higher level cognitive processing) and tempo-parietal areas (specialized for face processing) (Tso, Burton, et al., 2021). Along similar lines, one electroencephalography (EEG) study found general reductions in event-related potential (ERP) amplitudes over fronto-parietal areas during gaze perception in BD (Berchio et al., 2017). Together this suggests abnormal local recruitment of fronto-parietal regions involved in gaze processing. Recent perspectives on the

neurobiology of BD emphasize the role of dysfunctional brain connectivity in the phenomenology of BD (Chase & Phillips, 2016; Dima et al., 2013; Perry et al., 2019; Yoon et al., 2020), leading some to frame BD as a disorder of functional dysconnectivity between cognitive/affective networks (Strakowski et al., 2012). Therefore, to fully understand the neural bases of aberrant gaze perception in BD, we must consider the role of *impaired neural communications*, in addition to local dysfunctions.

EEG is a promising means of investigating questions of this kind. EEG can detect *neural oscillations*, electrical signals emanating from coordinated neuronal populations (Buzsáki & Draguhn, 2004). Neural oscillations are thought to reflect event-related functional de/synchronization (i.e., de/coupling) in the brain and, therefore, offer insight into functional network dynamics underlying cognitive processes (Bastiaansen et al., 2011) like gaze perception. Oscillations occur in different frequency bands simultaneously (including theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), gamma (>30 Hz)) and activity at different frequencies are thought to reflect different physiological mechanisms underlying cognitive processing. For example, midline anterior theta is associated with higher-level cognitive processes like ToM (Seymour et al., 2018) and cognitive control (Cavanagh & Frank, 2014), while gamma over sensory cortices is linked to perceptual processing (Herrmann et al., 2010). Increasing evidence suggests that the synchrony or ‘coupling’ of oscillations from distal neural populations may underlie neural communications by way of cross-frequency phase-amplitude coupling (PAC), whereby the amplitude of high-frequency activity in one region is modulated by the phase of low-frequency activity at another (Canolty & Knight, 2010). Theta-gamma PAC is one of the most common forms of coupling in the human cortex and can shed light on inter-region communications supporting cognition. Studying neural oscillations using EEG, therefore, has the potential to

provide insight into both regional activity and network dynamics (Bastiaansen et al., 2011) supporting gaze processing.

To date, no electrophysiology studies have examined neural oscillatory abnormalities associated with gaze processing in BD. However, studies examining the neural oscillatory correlates of *face processing* in BD offer some preliminary insights. Studies of affective and configural face processing using magnetoencephalography (MEG; measures magnetic fields produced by neural activity) show decreased midline anterior gamma in BD compared to healthy controls (HC) (Lee et al., 2010; Liu et al., 2012). In addition, there is evidence of alterations in the face-sensitive N170 ERP component over parietal regions during face processing in BD (Degabriele et al., 2011; Ibáñez et al., 2012; Sokhadze et al., 2011) (but between-study results are mixed (Feuerriegel et al., 2015)). Because N170 occurs primarily in the theta range (Tang et al., 2008), altered N170 in BD could signal underlying theta-band abnormalities. Together, these findings indicate that examining parietal and midfrontal oscillatory activity, particularly in theta and gamma bands, could provide insight into the neurobiology of abnormal gaze processing in BD.

The present study

The present study sought to address the existing knowledge gaps of neural oscillatory correlates of altered gaze perception in BD. To achieve this, we used time-frequency analysis of EEG data collected from BD and HC during a gaze discrimination task. We analyzed activity over midfrontal and parietal scalp areas that have previously been associated with higher-level cognitive processing and early face processing, respectively. Analyses captured both local oscillatory activity and inter-regional communications between these key locations during gaze

processing. To characterize local oscillatory activity in BD and HC, we examined oscillatory power over separate midfrontal and parietal scalp locations in theta and gamma frequency bands. To characterize information flow between these areas in BD and HC, we examined top-down and bottom-up theta-gamma PAC between midfrontal and parietal locations.

Considering that midfrontal theta is associated with higher-level cognition (Cavanagh & Frank, 2014; Seymour et al., 2018), and that higher-level cognition is impaired in BD (Latalova et al., 2011; Marotta et al., 2018; Samamé et al., 2012), we hypothesized that BD would show local reductions in theta power over midfrontal locations. Considering that there is at least some evidence of altered N170 over parietal locations in BD during face processing (Degabriele et al., 2011; Ibáñez et al., 2012; Sokhadze et al., 2011), and that theta activity appears to underlie N170 (Tang et al., 2008), we hypothesized that BD would show local reductions in theta power over bilateral parietal locations. Considering evidence of reduced functional connectivity between higher-level cognitive regions and other brain areas in BD (Strakowski et al., 2012), altered prefrontal cortical functions in BD (Yoon et al., 2020), and difficulties with higher-level cognitive processing—but not low-level perceptual processing—in BD (Yao et al., 2017), we hypothesized that BD would have reduced top-down theta-gamma PAC between fronto-parietal areas during gaze processing. Additionally, little is known about the potential role of intermediate frequency bands in gaze processing in BD, so we also explored whether alpha and beta power differed between BD and HC.

Methods

Participants

The study was completed by 46 participants with BD and 45 HC recruited from local clinics and the community. BD met criteria for bipolar I, while HC had no psychiatric history, according to DSM-IV-TR. Participants had no history of medical conditions with neurological sequelae, $\geq 20/30$ visual acuity on a Snellen chart, and no recent substance use disorder (BD had no substance abuse/dependence in last year, HC in past five years). Additionally, HC had no history of bipolar or psychotic disorders among first-degree relatives. Portions of this data have been published in separate ERP (all HC and BD (Tso et al., 2017)) and time-frequency analyses (HC only (Grove et al., 2020)).

Procedure

The study was approved by the University of Michigan Medical School Institutional Review Board. Participants gave informed consent and were compensated for their time. Study procedures were completed in one visit, during which diagnoses were confirmed using the Structured Clinical Interview for DSM-IV-TR (First et al., 2002) or Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994), EEG was collected during a behavioral task, self-reports were completed, and (subset of participants) neuropsychological tests were administered.

Measures

Gaze discrimination task

A gaze discrimination task was performed during EEG recording (see Tso et al. (2015) for task development (Tso et al., 2015)). Black and white images (Gur et al., 2002) of faces depicting different gaze directions (direct, indirect), emotions (neutral, fearful), and head orientations (forward, deviated 30°) were presented in pseudorandom order (64 trials per condition x 8 conditions = 512 trials) across four blocks. Participants indicated whether faces were looking at them or not via button press (Yes/No). Each trial consisted of a 500ms fixation,

150ms stimulus, up to 2000ms response period (terminated following a response), and 1000ms inter-trial interval (Figure 1). The task was programmed in E-prime 1.0 Professional (Psychology Software Tools, Inc.) and took ~20-25 minutes. Performance was indexed by accuracy and reaction time (RT), excluding non-response trials.

Additional assessments

Patients self-reported mania and depressive symptoms (Altman Self-Rated Mania Rating Scale [ASRM; (Altman et al., 1997)]; Beck Depression Inventory [BDI; (Beck, 1961)]).

Eighteen HC and 14 BD completed additional neuropsychological testing and self-reports which are detailed in the supplement.

EEG acquisition

EEG was recorded online using a BrainAmp MR amplifier (Brain Products GmbH) and a 32-channel cap with Ag/AgCl electrodes (modified international 10-20 system). Data was sampled at 5,000 Hz (referenced to FCz) and filtered online (250 Hz low-pass, 0.016 Hz high-pass). Impedance was kept $\leq 5 \text{ k}\Omega$. Vertical electrooculogram was measured using an electrode under the right eye.

EEG preprocessing

Offline data preprocessing was performed in EEGLAB 14.1.2 (Delorme & Makeig, 2004) in MATLAB R2019a (MathWorks, Inc.). Data were downsampled to 500 Hz and filtered (60 Hz line noise using CleanLine (Mullen, 2012), 0.1 Hz high-pass and 100 Hz low-pass with finite impulse response filter) before manually removing/imputing problem electrodes and removing data segments containing non-stereotypical artifacts (e.g., large muscle movements). Stereotypical artifacts (e.g., eye blinks, heartbeat) were removed using EEGLAB's built-in

Independent Component Analysis (ICA) algorithm (on -250–750ms epochs¹). Aided by SASICA (Chaumon et al., 2015) and ICLABEL (Pion-Tonachini et al., 2019), components that clearly indicated non-neural activity were identified and removed from the continuous data, which were then segmented into longer epochs (-1,500–2,300ms) to avoid edge artifacts in later time-frequency decomposition (Cohen & Grafman, 2014). The data were then re-referenced to the common average, baseline adjusted (-200–0ms baseline), and subject to automatic rejection of epochs containing data $> \pm 100 \mu\text{V}$. Non-response trials were removed because we could not confirm participants were attending to the task and, therefore, we could not assume a similar mental state as other trials. Trained research staff performed a final visual inspection of the resulting stimulus-locked epochs, manually rejecting epochs that still contained obvious non-neural artifacts missed by earlier processing steps. Only participants with $> 70\%$ of trials after preprocessing were included for analysis. This resulted in exclusion of 8 BD and 9 HC (most excluded HC were due to a defective cap that was replaced mid-study), yielding a final analysis sample of 34 HC and 38 BD. In the final sample, BD averaged 452 ± 39 trials remaining after preprocessing and HC averaged 445 ± 43 trials.

Time-frequency analysis

We performed time-frequency decomposition on cleaned stimulus-locked epochs. We used data from P7, P8, and Fz. The bilateral posterior sites—P7 and P8—were chosen because EEG activity associated with early face processing is maximal at these scalp sites (Nguyen & Cunnington, 2014; Tso et al., 2017). The midline anterior site—Fz—was chosen because EEG

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¹ ICA was applied to this time window because this window was most likely to contain largely stereotypical artifacts (e.g., eye blinks after stimulus offset, stereotypical muscular activity from routinely tensing jaw just before stimulus onset), as opposed to broader windows containing inter-trial time periods where non-stereotypical artifacts (e.g., large, non-routine muscle movements) were more predominant.

work has highlighted aberrations associated with higher-level cognitive processes over frontocentral regions during face/gaze processing in BD (Berchio et al., 2017). Time-frequency decomposition was performed on 3–50 Hz activity covering theta through gamma activity. Morlet wavelet convolution was used with 3 cycles at the lowest frequency (3 Hz) to 15 cycles at the highest (50 Hz). We performed the decomposition on longer (-1,500–2,300ms) epochs to avoid edge artifacts (Cohen & Grafman, 2014) within the -200–750ms window of interest from which we sought to extract spectral features.

Power

Spectral power was calculated using event-related spectral perturbation (ERSP) (Makeig, 1993) which indexes stimulus-evoked changes in oscillatory power. ERSP was standardized in Decibels and normalized to the mean of a pre-stimulus baseline (-200 to -50ms). ERSP was calculated for all sites (P7, P8, Fz) from 3 to 50Hz for all post-stimulus time-points (0–750ms). For each frequency band, we identified a time-frequency window of interest from which to extract spectral features using procedures outlined by Cohen and Grafman (2014). We collapsed spectral plots across groups, electrodes, and conditions to generate a grand mean spectral plot of post-stimulus power change from baseline (Figure 2A). This plot was used to identify time-frequency windows from which mean power was extracted for analyses on theta (4–8 Hz, 68–324ms), alpha (8–12 Hz, 244–742ms), beta (12–30 Hz, 244–554ms), and gamma (30–50 Hz, 122–742ms) power.

Connectivity

The Kullback-Leibler Modulation Index (KLMI) (Tort et al., 2010) was used to measure cross-frequency PAC between theta phase and gamma amplitude. It measures a statistical relationship between two frequency bands (covariance of phase and amplitude for each latency

across trials). Biological support for inferring directed connectivity using measures like KLMI is provided by intracranial studies showing modulation of high-frequency amplitude by phase of low-frequency activity occurs in numerous species and brain regions (Cohen & Grafman, 2014). Using PACTools (Martínez-Cancino et al., 2019), KLMI was calculated as an index of theta-gamma PAC for 4 site pairings (bottom-up: P7→Fz, P8→Fz; top-down: Fz→P7; Fz→P8) at all post-stimulus time points (0–750ms). Values were multiplied by 10,000 for ease of interpretation. We used the same time-frequency window selected for theta power analyses (68–324ms) for theta-gamma PAC analyses. We confirmed this window coincided with meaningful theta-gamma PAC changes relative to baseline by superimposing it over a grand mean KLMI plot averaged over site pairings and participants (Figure 2B). Mean KLMI was extracted for each site pairing within this 68–324ms window for analyses.

Statistical analyses

We performed analyses in RStudio 1.4.1717 using an alpha level for significance of $p < .05$. Participants did not provide permissions for open-access data sharing so the raw data is not publicly available. However, to promote transparency and replicability, statistical analysis codes are available at https://osf.io/gqwm9/?view_only=9feb489868ec471999e7cf866f5abdfa.

To confirm HC and BD were well-matched demographically, we performed Welch's t -tests on age/education and a chi-squared test on sex, with Cohen's d and ϕ (ϕ) effect sizes. Welch's test is more robust than student's t -test for issues common in human research (e.g., unequal samples/variances) (Delacre et al., 2017).

Power and connectivity

We tested group differences in spectral power at midline anterior (Fz) and bilateral posterior sites (P7, P8) using Welch's t -tests (i.e., 4 frequencies x 3 sites = 12 tests) with Cohen's

d effect sizes. Welch's t -tests were also used to assess group differences in theta-gamma PAC (i.e., $[P7 \rightarrow Fz, P8 \rightarrow Fz, Fz \rightarrow P7, Fz \rightarrow P8] = 4$ tests). We controlled the expected proportion of false positives for these 16 tests with a False discovery rate (FDR) correction for multiple comparisons using the 'p.adjust' R function. We report uncorrected p-values as ' p ' and FDR-corrected p-values as ' p^{FDR} '.

Correlations with task performance and social/executive functioning measures

Gaze discrimination

Spearman's correlations (uncorrected) were used to evaluate relationships between power/theta-gamma PAC and gaze discrimination accuracy and RT. In the full sample, we found strong correlations between the bottom-up and top-down theta-gamma PAC pairings (see supplement). Thus, to reduce the number of correlations, principal component analysis (PCA) was used to extract one bottom-up theta-gamma PAC component (from $P7 \rightarrow Fz, P8 \rightarrow Fz$ PAC) and one top-down theta-gamma PAC component (from $Fz \rightarrow P7, Fz \rightarrow P8$ PAC) that were used in correlational analyses.

Social and executive functioning (exploratory)

We explored whether power and theta-gamma PAC during gaze discrimination related to measures of social functioning (SAS-SR) and executive functioning (ToL) using uncorrected Spearman's correlations. This was done using a portion of our sample (14 BD, 18 HC) that completed these additional assessments.

Sensitivity analyses

Post-hoc sensitivity analyses evaluated whether results were robust to changes in medication intake, response accuracy, and task condition. Complete details are provided in the supplement.

Results

As shown in Table 1, groups did not vary by age, ($t[66.4] = 0.10, p = .919, d = 0.02$), sex ($X^2[1] = 0.10, p = .750, \phi = -0.07$), or education ($t[64.7] = 1.96, p = .055, d = 0.48$).

Power

BD had reduced midline anterior (Fz; $t[53.8] = 3.5, p = .001 [p^{FDR} = .007], d = 0.85$) and left posterior (P7; $t[54.3] = 3.1, p = .003 [p^{FDR} = .007], d = 0.76$) theta power relative to HC (Figure 3). Differences in right posterior theta power were not significant (P8; $t[64.5] = 2.0, p = .051 [p^{FDR} = .113], d = 0.48$). Gamma—as well as alpha and beta—power did not differ between groups at any site (p 's $> .05$; full results in supplement).

Connectivity

As shown in Figure 4, BD had reduced bottom-up (P7→Fz: $t[40.8] = 4.0, p < .001 [p^{FDR} = .004], d = 0.99$; P8→Fz: $t[52.0] = 3.3, p = .002 [p^{FDR} = .007], d = 0.8$) and top-down theta-gamma PAC (Fz→P7: $t[40.8] = 3.3, p = .002 [p^{FDR} = .007], d = 0.81$; Fz→P8: $t[44.3] = 3.3, p = .002 [p^{FDR} = .007], d = 0.80$).

Correlations with task performance and social/executive functioning measures

Gaze discrimination

Compared to HC, BD were slower ($t[66.5] = -2.3, p = .024, d = -0.54$) and less accurate on the gaze discrimination task ($t[69.8] = 3.1, p = .003, d = 0.72$). Across participants, slower RT's were associated with reduced midline anterior theta power ($\rho = -0.37, p = .001$), bilateral posterior theta power (P7: $\rho = -0.23, p = .047$; P8: $\rho = -0.34, p = .004$), right posterior alpha power (P8: $\rho = -0.23, p = .049$), and bottom-up ($\rho = -0.30, p = .010$) and top-down theta-

gamma PAC ($\rho = -0.34, p = .004$). Associations between RT and other power metrics were not significant. Accuracy did not correlate with power/theta-gamma PAC measures.

Social and executive functioning (exploratory)

BD had poorer executive functioning ($t[27.7] = 2.6, p = .013, d = 0.95$) and self-reported social functioning than HC ($t[21.5] = 2.2, p = .035, d = 0.84$). Across participants, reduced top-down theta-gamma PAC correlated with poorer self-reported social functioning ($\rho = 0.52, p = .002$), but not executive functioning ($\rho = 0.35, p = .052$). Neither executive functioning nor social functioning were associated with top-down theta-gamma PAC or theta power (full results in supplement).

Sensitivity analyses

Full results of sensitivity analyses are in the supplement. To summarize, power/theta-gamma PAC did not vary in BD based on lithium intake and power differences were unchanged when only correct trials were analyzed. No significant interactions between group and stimulus features (emotion, gaze, head orientation, head-gaze congruency, head-emotion congruency, gaze-emotion congruency) were found.

Discussion

This study found reduced midline anterior and left posterior theta power, and diminished inter-regional theta-gamma PAC during gaze processing in BD. Alterations were associated with slower responses, which were also found in BD.

Reduced theta power in BD

In line with hypotheses, theta power was reduced in BD relative to HC over left posterior and midline anterior locations that have been associated with early face processing and higher-

level cognitive processes. These results were robust to medication differences (similar for lithium-users and non-users), response accuracy (similar for all trials [correct and incorrect] and correct-only trials), and task condition (similar when gaze direction, head orientation, emotion, and facial cue congruency of task stimuli varied). This suggests that theta power reductions in BD were not due simply to less accurate responding in BD or oscillatory changes associated with lithium intake (Atagün, 2016; Atagün et al., 2015). Because findings were similar across task manipulations, theta reductions may reflect a more general alteration in perceptual decision-making in BD. In line with this, others have reported reduced anterior theta in BD during general (non-social) cognitive tasks (Atagün et al., 2013). Additionally, one ERP study found altered attentional and higher-level decision processes during gaze processing in BD (i.e., reduced P200 and P300), but intact configural face processing (indexed by N170) (Berchio et al., 2017). Berchio's (2017) findings also align with our observation of comparable gamma power between BD and HC (thought to reflect sensory processing). It is therefore possible that theta alterations observed here during gaze processing reflect more general alterations in cognition and/or decision-making. Future work should disentangle which aspects reflect general cognitive deficits and which are unique to the context of social/gaze processing.

Finding more prominent theta power disruptions in BD over left, versus right, locations is inconsistent with our hypotheses. However, this may occur because the right hemisphere is generally responsible for holistic face processing, while the left processes discrete facial features (de Moraes et al., 2014). Given that our task required participants to rely on information primarily from the eye region, this suggests that theta power is altered in BD in hemispheres responsible for facial feature processing (eyes). This notion is consistent with behavioral data showing BD experience difficulties inferring others' intentions and emotional states from the eye

region alone (Marotta et al., 2018). Additionally, this overall pattern of results is consistent with fMRI data showing reduced medial-frontal and left—but not right—tempo-parietal activations during gaze processing in BD (Tso, Burton, et al., 2021).

Two additional findings merit further discussion. First, we did not find modulations of theta power by emotion in the full sample or differential modulation of theta power by emotion in BD and HC, but prior work has shown differential modulation of N170 amplitude by emotion of task stimuli in different psychiatric disorders (Feuerriegel et al., 2015). Although the N170 largely consists of low-frequency theta-band activity (Tang et al., 2008), it is not a direct 1-to-1 mapping. In fact, disparate N170 and theta-band results have been reported even within the same research sample (Blume et al., 2015). This may account for the disparity between our results and previous ones. It also shows that spectral information is not redundant to ERP, highlighting the added value that time-frequency analysis provides. Second, we did not observe differences in gamma power between BD and HC, but two prior face processing MEG studies in BD reported gamma power differences relative to HC (Lee et al., 2010; Liu et al., 2012). This may be attributable to measurement differences. Because MEG measures the magnetic fields produced by neuronal activity—while EEG measures their electrical activity directly—the MEG signal is less susceptible to distortions that can affect measurement of high-frequency activity via EEG (e.g., scalp distortions, muscle activity) (Cheyne, 2013). Such distortions may have limited our ability to detect subtle local differences in high-frequency gamma activity.

Diminished theta-gamma PAC in BD

Within BD, we observed reduced theta-gamma PAC between posterior and anterior sites. This apparent impairment in communications between areas associated with early face-processing and higher-level cognitive processes in BD aligns with neuroimaging data showing

reduced anterior-posterior functional connectivity in BD during face processing (Dima et al., 2013). Although we found reductions in both theta-gamma PAC and theta power in BD, we do not assume they are causally connected. Rather, they may be independent processes that frequently co-occur. Consistent with this, we observed significantly reduced theta-gamma P8→Fz PAC in BD despite non-significant reductions in theta power at P8. Others have shown a similar independence of these processes, reporting changes in hippocampal theta-gamma PAC absent observed changes in theta power (Tort et al., 2009).

Exploratory analyses also showed preliminary evidence that top-down theta-gamma PAC during gaze processing may relate to broader (self-reported) social functioning. However, we interpret these results cautiously because they come from uncorrected, exploratory correlations based on a modest sub-sample. To draw more definitive conclusions about the broader relevance of top-down theta-gamma PAC, replications are needed in larger samples.

Potential mechanisms of reduced theta power/theta-gamma PAC

Moving from the neural to the behavioral level, we found that BD were less accurate and slower when making decisions on the gaze discrimination task (i.e., ruling out a possible speed-accuracy tradeoff in BD). We also found that faster—but not more accurate—responses were associated with increased theta power and theta-gamma PAC. These findings align with results from simulations and non-clinical samples showing relations between theta oscillations and processing speed/efficiency (Mueller et al., 2017; Smerieri et al., 2010; van Vugt et al., 2012). In those studies, decreased theta was associated with slower/less efficient processing. Using simulated neural networks, Smerieri and colleagues (2010) showed that theta oscillations affect neuronal firing rates, which influence the network's response time, leading authors to hypothesize that the relation between theta oscillations and response time occurs by way of firing

rates or excitability (Smerieri et al., 2010). These results are relevant to BD for at least two reasons. First, theta oscillations depend on a balance between glutamatergic excitatory neurons and GABAergic inhibitory neurons: the alternating excitation and inhibition between these cells is needed to generate and maintain low-frequency theta rhythms (Nigbur et al., 2011; Smerieri et al., 2010). Second, this excitatory/inhibitory balance may be disrupted in BD as a result of high glutamate concentrations (Ehrlich et al., 2015; Gigante et al., 2012; Kim et al., 2017; Shen & Tomar, 2021) and potentially low GABA concentrations in BD (Bhagwagar et al., 2007) (though GABA findings in BD are mixed (Chiapponi et al., 2016)). Because glutamatergic hyperactivity and GABAergic hypoactivity can disrupt rhythmic balances needed to maintain theta oscillations, they have the potential to diminish theta power and cross-frequency modulation of neural networks (as observed here). While this discussion is speculative, these findings in the literature point to an area of promising potential inquiry. Future work should use magnetic resonance spectroscopy (MRS), pharmacologic challenges, alongside EEG/MEG, to further investigate the relationships between electrophysiological responses and glutamate/GABA concentrations and how they contribute to social perception and functioning in BD.

In summary, our overall pattern of theta-gamma PAC results indicates that inter-regional communications between midline anterior areas associated with more general higher level-cognition and bilateral posterior areas associated with early face processing are disrupted during gaze processing in BD. Future studies should replicate these results in larger samples, and investigate the beneficial effects of normalizing aberrant oscillatory activity on social cognition in BD. Non-invasive brain stimulation techniques, such as transcranial electric current stimulation and transcranial magnetic stimulation have shown some promises in augmenting frequency-specific network dynamics to produce lasting cognitive/perceptual changes (Fröhlich

et al., 2015; Huang et al., 2005; Yamada et al., 2021, 2022)). These may be used in future clinical trials to improve gaze processing and, ultimately, social cognition in BD.

Limitations

These findings should be interpreted considering several limitations. First, we are unable to rule out spurious theta-gamma PAC, or non-sinusoidal activity causing theta-gamma PAC in the absence of true physiological interactions between neural sources (Lozano-Soldevilla et al., 2016), but we took special care and used established techniques (a robust PAC measure in KLMI and removal of non-neural artifacts) to decrease the possibility of spurious PAC. Second, we were not able to localize the observed theta abnormalities to specific brain regions due to the low spatial resolution of EEG. Replication using MEG, with its high spatial resolution, can help address this. Third, our data were cross-sectional, so it is unclear how these findings would change over time alongside variations in manic/depressive symptoms. Longitudinal studies examining within-participant changes in theta-band activity across mood states would offer crucial insights in this area. Fourth, participants completed only a gaze discrimination task, meaning we cannot determine whether our results are specific to gaze discrimination, facial processing, or decision-making more broadly. To facilitate this comparison, future studies should have participants complete a range of behavioral tasks that require attending to eye gaze, face attributes, and non-social stimuli (i.e., general cognitive tasks). Fifth, slower responses in BD may have inadvertently led to more non-response trials on the current task (which were excluded from analyses). Studies using longer response periods may help determine how, if at all, this impacted performance measures in BD.

Conclusions

Aberrant gaze processing in BD was associated with reductions in local theta power (at midline anterior and left posterior scalp locations) and diminished theta-gamma PAC. These findings suggest that altered gaze processing in BD is associated with both altered local cortical activity and disrupted communications between areas associated with early face-processing and higher-level cognitive processing.

Figure 1. Gaze discrimination task. Participants pressed a button to indicate whether the face was looking at them (yes, no). Faces varied in emotion (neutral, fearful), head orientation (forward, deviated), and gaze (direct, indirect). ITI = inter-trial interval; ms = milliseconds.

Table 1: Sample characteristics (N = 72)

	HC (n=34) M (SD)	BD (n=38) M (SD)	<i>t/X²</i>	<i>p</i>	ϕ/d
<u>Demographics</u>					
Age	41.6 (12.9)	41.3 (11.4)	0.10	.919	0.02
Sex (female)	13 (38%)	17 (45%)	0.10	.750	-0.07
Education (years)	16.5 (2.3)	15.4 (2.4)	1.96	.055	0.48
<u>Medications</u>					
Antipsychotics	--	16 (43%)	--	--	--
Anxiolytics	--	8 (22%)	--	--	--
Antidepressants	--	20 (56%)	--	--	--
Mood stabilizers	--	29 (81%)	--	--	--
<u>Clinical</u>					
Mania (ASRM)	--	3.4 (3.4)	--	--	--
Depression (BDI)	--	11.8 (10.2)	--	--	--
<u>Gaze discrimination</u>					
Accuracy (%)	83.0 (7.2)	77.3 (8.5)	3.08	.003	0.71
RT (ms)	681 (102)	749 (145)	-2.32	.024	-0.54

Note. Medication and clinical data were missing for 2 BD. Education data were missing for 3 BD

and 2 HC. Of BD taking mood stabilizers, 13 were taking lithium. M = mean; SD = standard

deviation; ASRM = Altman Self-Rated Mania Scale; BDI = Beck Depression Inventory;

accuracy (%) and RT (ms) = % correct responses and response time (in milliseconds) on gaze

discrimination task, excluding non-response trials; n = number of participants; t = t-statistic; X^2 =

chi squared statistic; *p* = uncorrected *p*-value; ϕ = phi; *d* = Cohen's *d*.

Figure 2. Window selection for power and theta-gamma PAC analyses. A) Grand mean power plot averaged across all electrodes/participants used to identify time windows of meaningful power changes in each frequency-band relative to baseline. Mean power values were extracted from the selected time windows (outlined by white boxes) for analyses. B) Grand mean Kullback-Leibler Modulation Index (KLMI) values averaged across all site pairings/participants used to verify that the selected PAC time window (marked by vertical blue lines) coincided with meaningful theta-gamma PAC changes. Shaded regions show standard error. ms = milliseconds.

*Same time window used to analyze theta power and theta-gamma PAC.

Figure 3. Bilateral posterior and midline anterior spectral power during gaze

discrimination. A) Power at P7, P8, and Fz by group. Rectangles inside plots show windows analyzed for each frequency. B) Group differences in mean power. C) Topographies of mean theta power from 68-324ms. ** $p^{FDR} < .01$.

Figure 4. Theta-gamma PAC between bilateral posterior and midline anterior sites. Plots of Kullback-Leibler Modulation Index (KLMI) values, indexing theta-gamma PAC. Shaded areas show standard error. Horizontal black lines show the time window over which KLMI was averaged for group comparisons (results shown in violin plots). ** $p^{FDR} < .01$.

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