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Eye-gaze processing in the broader bipolar phenotype revealed by electrical neuroimaging

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ABSTRACT

Previous studies have documented atypical brain responses to faces in individuals with bipolar disorder (BD) and in their relatives. In view of previous findings of atypical face processing in youths at risk for BD, the aim of this study was to examine whether BD patients and offspring would show differential activation in networks of the social brain when processing eye-gaze.

Data from 18 euthymic BD patients and 18 offspring, as well as 36 age-matched healthy controls, were collected using a delayed face-matching paradigm, event related potentials and electrical neuroimaging methods.

The P200 component, which is implicated in facial cues decoding, differentiated the BD groups from their age-matched controls. P200 source reconstruction indicates impairments conveyed by eye-contact in a network involved in experiencing others' social intentions in BD patients (supplementary motor cortex, precentral gyrus, inferior parietal lobe), and the engagement of compensatory prefrontal mechanisms for modulating these functions in BD offspring. When viewing faces that had an averted gaze, BD patients and offspring showed a hypo-activation, compared to controls, particularly in regions involved in experiencing others' feelings (post-central gyrus in BD patients / ventral premotor cortex in offspring). Therefore, the neural mechanism for decoding shifts in eye-gaze may be a familial characteristic of BD.

1. Introduction

Bipolar disorder (BD) is a highly heritable affective disorder that likely develops from the interaction between genetic and environmental risk factors (Vieta et al., 2018). The core symptomatology of BD includes depressive and maniac episodes, as well as a failure to regulate emotions (Phillips et al., 2008).

Understanding social signals enables individuals to develop emotional skills (Grossmann, 2010). Due to its crucial importance in human interactions and emotional development, several studies have focused on face processing abilities in BD (Wessa and Linke, 2009). Evidence shows that individuals suffering from BD have impairments in emotional face recognition (Wessa and Linke, 2009), and this deficit in affective face labeling is already apparent in youth at risk of BD (Rosen and Rich, 2010).

Recent studies suggest that individuals with BD are also impaired in more specific face-related landmarks, such as processing another person's gaze (Berchio et al., 2017; Tso et al., 2017; Yao et al., 2018). Shifts in gaze have a communicative value (i.e., sharing a focus of attention with others), social meaning (e.g., intimacy/dominance), as well as emotional significance (i.e., signal of approach/avoidance) (Itier and Batty, 2009; Senju and Johnson, 2009). Mood disorders are associated with altered mother-infant gaze synchrony (Lotzin et al., 2015), and BD patients tend to over-perceive eye contact (Yao et al., 2018). These findings raise the possibility that abnormalities in gaze perception and its communicative meanings may contribute to the affective impairments that characterize BD spectrum.

Neuroimaging studies have indicated that large-scale networks in

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the brain are dedicated to processing social information (Kennedy and Adolphs, 2012), such as eye-gaze shifts (Senju and Johnson, 2009). These networks, which are considered an integral part of the "social brain", are involved in detecting socially salient stimuli and triggering emotional responses [i.e., amygdala networks; see (Adolphs, 2010)], thinking about the internal states of others [i.e., temporal pole and medial prefrontal networks; see Dodell-Feder et al., 2011], empathizing with others [networks centered in the insula/anterior cingulate (De Vignemont and Singer, 2006; Hillis, 2014)], and understanding intention and action [parietal-frontal networks (Rizzolatti et al., 2009)].

Using tasks that assess face perception, many fMRI studies have demonstrated specific functional abnormalities of the "social brain" in BD (Brotman et al., 2014; Pavuluri et al., 2007; Strakowski et al., 2005; Townsend and Altshuler, 2012). The majority of these works have shown abnormal coupling between prefrontal–limbic networks when processing faces, showing persistent hypo-activations of prefrontal regions (Strakowski et al., 2005; Townsend and Altshuler, 2012). More importantly, there is also evidence that, during face processing, offspring of BD parents show prefrontal-limbic network dysfunction (Chang et al., 2017; Manelis et al., 2015), indicating a general dysfunction of brain networks involved in face processing as a potential endophenotype of BD.

Event Related Potentials (ERP) can inform us about brain mechanisms necessary for social perception with a time resolution on the order of milliseconds. ERPs typically evoked from viewing faces include the visual P100 (Herrmann et al., 2005a; Pizzagalli et al., 1999), N170 (Bentin et al., 1996), and middle latency components (i.e., 200–300 ms) (Olofsson et al., 2008). While the P100 is related to face categorical perception (Herrmann et al., 2005b; Liu et al., 2002), the N170 is believed to reflect face encoding (Bentin et al., 1996), and middle latency components are usually associated with stimuli decoding and task-related response processes (es., P200/N250) (Olofsson et al., 2008). While most studies have found altered P100/N170 patterns to emotional facial expressions in BD, suggesting that first order categorical units are compromised (Degabriele and Lagopoulos, 2012; Degabriele et al., 2011; Howells et al., 2014), neural descriptions of eye-gaze processing are often lacking. Notably, to date, no study has investigated the relevance of eye-gaze processing across the bipolar disorder spectrum. To provide evidence of this, we had investigated the effects of direct and averted gaze on face recognition in BD (Berchio et al., 2017). In that study, we found that euthymic BD patients showed reduced P200 amplitudes in response to shifts in eye-gaze, relative to healthy controls. This component is associated with face decoding (Latinus and Taylor, 2006), as well as decisional processes (Polezzi et al., 2008). This result encouraged us to investigate whether this trait marker was also present in high-risk offspring.

The goal of the present study was to examine specific eye-gaze abnormalities across brain networks involved in face processing in BD offspring, as well as to explore similarities of this manifestation in BD patients. In this study, we reapplied our delayed gaze recognition paradigm (Berchio et al., 2016) during a high-density EEG recording. To investigate large-scale brain networks, we used microstate analyses in combination with electrical neuroimaging [see Murray et al., 2008]. We expected atypical differentiation in direct versus averted gaze to be reflected in ERP networks sensitive to face processing in BD offspring, particularly those sensitive to detecting socially salient stimuli and mentalizing the internal states of others [i.e., prefrontal-limbic regions (Kennedy and Adolphs, 2012)]. We expected to find similarities in the ERP features of BD patients and BD offspring. Finally, given our previous findings in BD patients (Berchio et al., 2017), we expected to find an abnormal P200 response to eye-gaze shifts that is even more enhanced by direct gaze.

2. Methods

2.1. Participants

2.1.1. Recruitment

Participants were BD patients, offspring of BD parents and healthy controls recruited through the Mood Disorders Unit of the Mental Health and Psychiatry Department, University Hospital of Geneva. Study recruitment targeted BD patients with a well-established diagnosis [as detailed elsewhere, see Berchio et al., 2017] who were followed up at the Mood Disorders Unit, and BD patients known to have offspring between 15 and 25 years old. Within the BD group, there was no direct genetical link between patients and offspring. Participants were excluded if they did not speak French, **or** had a history of head injury or neurological disease. Healthy controls were further excluded if they had any neurological or psychiatric illness. All research procedures were approved by the local Ethical Committee for Human Research, and informed consent was obtained from each participant and the legal guardian (for minors under 18 years old).

2.1.2. Demographic variables

Data from 18 euthymic BD patients (M: 34.94, SD: 9.29) and 18 offspring (M: 19.72, SD: 3.375) were included in the present study and respectively matched for age with 36 healthy controls (+/− 3 years old). The age, handedness, gender, and education level of BD patients,

Table 1
Demographic and clinical features of the two study groups and their age-matched controls.

Characteristics	BD p. (n = 18)	Controls (n = 18)	p	BD offspring (n = 18)	Controls (n = 18)	p
Age: mean, *sd*	34.94 (9.29)	35.03 (10.37)	0.65	19.72 (3.37)	19.50 (3.03)	.83
Gender: male, *n*	11	11	0.49(X^2)	6	8	.19(X^2)
Handedness: right, *n*	15	16	0.50(X^2)	18	17	1.0(X^2)
*Education: graduate d., *n*	10	8	0.09(X^2)	3	4	.95(X^2)
IQ: *mean, sd*						
WM	9.66(1.71)	10.01(2.09)	0.47	9.75(1.97)	9.98(2.23)	.66
Arithmetic	18.40 (2.21)	17.61 (2.76)	0.36	16.82(3.68)	16.18(3.43)	.96
YMRS: *mean, sd*	0.72 (1.56)	0.76 (1.27)	0.91	0.27 (1.17)	0.38 (0.61)	.72
MADRS: mean, *sd*	3.29 (3.40)	1.30 (1.56)	*0.03	2.27 (2.34)	1.77 (2.53)	.54
STAI-state: *mean, sd*	37.80 (21.62)	26.25 (3.48)	**0.00	30.18 (7.39)	26.77 (6.29)	.14
STAI-trait: *mean, sd*	42.66 (9.98)	30.91 (5.55)	**0.00	39.26 (6.40)	34.44 (9.30)	.085
CTQ:						
Total score: *mean, sd*	36.85 (10.41)	35.06 (7.81)	0.54	32.40(5.61)	35.44(19.85)	.53
Emotional Abuse: *mean, sd*	8.57 (4.19)	6.73 (1.94)	0.09	7.20(2.03)	7.55(4.65)	.76
Physical Abuse: *mean, sd*	5.71 (1.47)	5.80 (1.42)	0.85	5.60(1.07)	6.11(4.47)	.64
Sexual Abuse: *mean, sd*	7.07 (3.28)	5.00 (0)	*0.01	5.80(2.35)	6.22(4.71)	.73
Emotional Neglect: *mean, sd*	9.35 (2.94)	10.80 (4.42)	0.23	7.60(2.29)	9.38(4.64)	.15
Physical Neglect: *mean, sd*	6.14 (1.69)	6.73 (2.43)	0.38	6.20(1.33)	6.16(3.05)	.96

*Education levels were classified into three groups : 3 = university studies; 2 = high school; 1 = no high school.

offspring, and healthy controls are summarized in Table 1.

2.1.3. Offspring family description

BD offspring were included if one of their parents had a diagnosis of BD type I or II, as documented by medical record. Ten parents were males. Parents' mean age of BD onset was 22 years old (minimum age = 15; maximum age = 38), and their diagnosis was confirmed either before having children (n = 10) or, within the first six years of their offspring's life (n = 4) (For four of them, this information was unknown).

2.1.4. Clinical assessment

For BD patients, unaffected offspring and healthy controls, assessment of psychiatric disorders was conducted using the French version of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994; Preisig et al., 1999), by a trained psychologist (ALK, PC). All participants were healthy when the interview was conducted. Symptoms of mania and depression were evaluated using the French versions of the Young Mania Rating Scale [YMRS (Favre et al., 2003; Young et al., 1978)] and the Montgomery-Asberg Depression Rating Scale [MADRS (Montgomery and Åsberg, 1979; Pellet et al., 1980)], respectively. WM capacities were assessed by two subtests of the WAIS-R (Wechsler, 1981): the arithmetic, as well as the forward and backward digit span. All patients were euthymic and met criteria for BD type I (n = 10) and II (n = 8) [as described in (Berchio et al., 2017), n.b. to reduce the age-gap between the BD patients and offspring groups, the oldest BD patient and the respective control were excluded from analyses in this study]. Nine BD parents met criteria for BD type I, seven for type II (Disorder subtype was lost for three BD parents).

The State-Trait Anxiety Inventory was administered to determine state and trait levels of anxiety [STAI state and trait (Spielberger, 1970)]. Early life traumatic experiences were assessed using the Childhood Trauma Questionnaire [CTQ, French version (Bernstein et al., 2003; Paquette et al., 2004)].

2.2. Paradigm

During a high-density EEG recording, participants performed a delayed face-matching task that assesses implicit eye-gaze processing [paradigm and stimuli described in detail in Berchio et al., 2016]. Stimuli were neutral faces with either direct or averted gaze. Faces were presented for 1 s each and were interleaved by 2-second intervals during which a fixation cross appeared. The experimental timing is shown in Fig. 1. The task required subjects to recognize whether the identity of the face was the same as the one that had been presented two faces ago. Subjects used their right hand to respond to each stimulus by pressing a down arrow for match stimuli and an up arrow for non-match stimuli. A match-trial consisted of a 'target face' (with direct gaze or averted gaze) and a 'matched face': a face identical to the one presented two trials before (same facial identity and gaze direction). We presented a total of 120 match-trials: 60 for faces with averted gaze, and 60 for faces with averted gaze. Experimental conditions consisted of: (1) target faces with direct gaze, (2) target faces with averted gaze, (3) matched faces with direct gaze, (4) matched faces with averted gaze. Match-trials and non-match trials were presented with a ratio of 40 to 60. The entire EEG session was divided into three blocks of 6 min each and lasted approximately 15 min. E-Prime (2.0) was used to present the stimuli and the triggers for the EEG.

2.3. ERP acquisition and pre-processing

EEG was acquired with a 256-channel EGI system (Electrical Geodesic Inc., OR, USA), using the vertex electrode (Cz) as acquisition reference, a sampling rate of 1000 Hz, and electrode impedances kept below 30 k-ohms.

EEG pre-processing and ERP averaging were performed using the software Cartool 3.60 (Brunet et al., 2011) (https://sites.google.com/site/cartoolcommunity/).

The data were band-pass filtered offline at 0.3–40 Hz (2nd order Butterworth, 12 db/octave roll-off) and segmented into epochs that began 100 ms before stimulus onset and ended 600 ms after. Data containing ocular and muscular artifacts were rejected by visual inspection, and the remaining clean epochs were averaged. High-voltage channels were interpolated (3D spline interpolation method). To reduce peripheral artifacts, data were reduced to 204 channels (see Berchio et al., 2016). ERPs were down-sampled to 250 Hz, re-referenced to an average reference, and baseline corrected (100 ms pre-stimulus). In all groups, separate ERPs were obtained for match-back trials: 'target faces' with direct and averted gaze, and 'matched faces' with direct and averted gaze.

2.3.1. Behavioral analysis

Differences in clinical and demographic characteristics between groups were evaluated using unpaired two-tailed t-tests and Chi-Square statistics when appropriate.

A repeated measures ANOVA was used to examine differences in accuracy and median reaction times (RTs). Only the RTs of correct responses were analyzed.

Before performing ANOVAs, regression analyses were implemented to evaluate the extent to which behavioral performance (accuracy and RTs) was predicted by age. Effects were considered statistically significant at $p < .05$.

On the ANOVA models, Gaze ('direct' vs 'averted') and Identity recognition ('target' vs 'matched faces') were entered as within-subject factors, and group as a between-subject factor. Alpha levels were set to $p < .05$ on all ANOVAs, and Bonferroni corrections were applied for all comparisons.

2.3.2. ERP analyses

2.3.2.1. Effects of age. Assessment of age was performed as a preliminary step to microstates analyses (see Section 2.4.2.2), since ERP age-related changes in response to faces are well documented (Daniel & Bentin, 2012). Effects of age were quantified by the means of topographic analysis [i.e., Topographic ANOVA, 'TANOVA' see Koenig et al., 2011], to test for the involvement of differential brain networks in different age ranges indexed by different scalp topographies (Murray et al., 2008). Permutation tests were performed within a time window ranging from 0 to 400 ms post-stimulus onset, collapsing experimental conditions, and using age as a covariate. As a normative sample, only healthy participants (n = 36) were entered into this analysis. Alpha was set to $p < .05$, and permutation tests were computed with 5000 randomization runs. The TANOVA analysis was computed using RAGU software (http://www.thomaskoenig.ch/index.php/work/ragu/1-ragu).

2.3.2.2. Microstates analyses. Differences in large scale brain network activations evoked by the stimuli were estimated using a modified k-means cluster analysis [technical details can be found in Michel and Koenig, 2018; Murray et al., 2008]. This method, also called microstates analysis, aims to identify periods of temporal map stability (microstates) and test whether these periods are different or equal between conditions and groups.

ERP grand means were submitted to the clustering procedures. The resulting microstate maps were then back-fitted to the individual ERPs by assigning each time point to the maximally correlated cluster map (Note that in contrast to microstate analysis of spontaneous EEG, map polarity is not ignored in ERPs). We first determined whether specific classes of microstates were present or absent (frequency 'f' number of participants) in both groups. For those maps that had the same frequency of occurrence in both groups we examined whether they differ in the amount of global explained variance 'GEV'. We also examined differences in latencies based on the time frame of the maximum GFP of

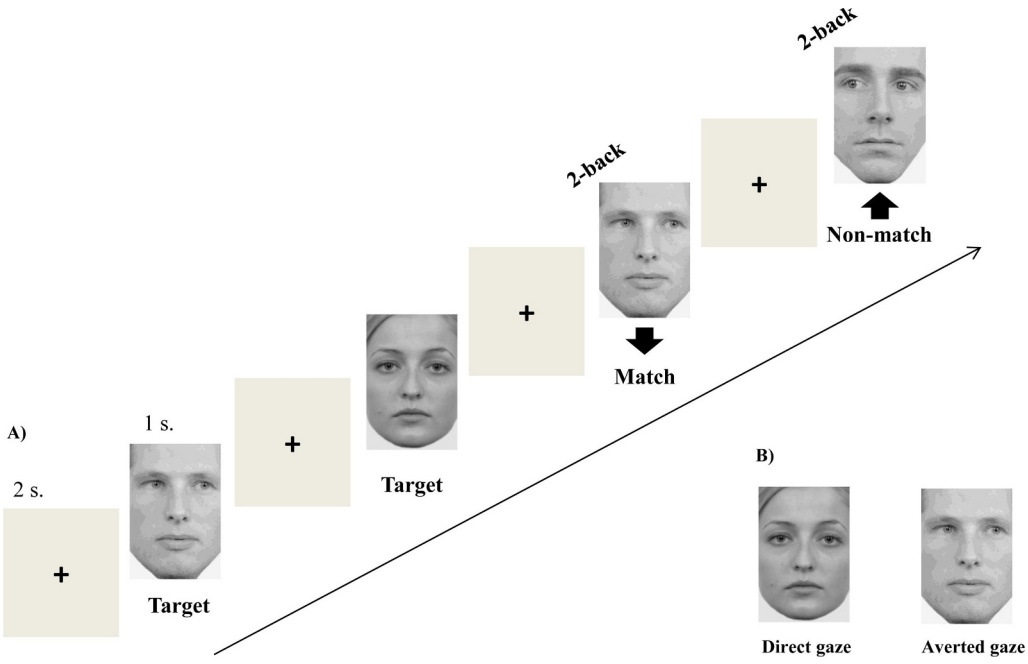

Fig. 1. Experimental paradigm. Each stimulus was presented for 1 s. and the inter-trial interval was 2 s. (a) The task requires participants to judge whether each face has the same identity as the one that occurred two trials ago. Illustrative 'matched face' trials are displayed for direct gaze condition and averted gaze condition. (b) Experimental conditions were faces with direct gaze and averted gaze.

each map. For each experimental condition (i.e., target faces with direct/averted gaze, matched faces with direct/averted gaze), BP and offspring were compared with their age-matched controls. Based on visual inspection of the plots, variables of interest did not match the criteria for a normal distribution. Therefore, to determine whether statistically significant differences between groups existed, each variable was statistically tested using Kruskal–Wallis one-way ANOVA and post hoc Mann–Whitney *U*-tests.

The association between GEV and symptomatology was assessed using Pearson correlation coefficients.

2.3.2.3. Electrical neuro-imaging. To explore differences between groups' brain responses to gaze, we used a linear distributed inverse solution model (LAURA, (de Peralta et al., 2001)). Time windows of interest were selected by statistically significant results at the scalp level. Source localization was performed on an anatomically constrained head model [L-SMAC model (Brunet et al., 2011)] using an averaged brain template (Montreal Neurological Institute, http://www.bic.mni.mcgill.ca/brainweb) on 5018 voxels distributed homogeneously in the grey matter. After the computation of the LAURA inverse solution, data from each solution point were normalized using a modified z-score transformation implemented in Cartool (3.70). This normalization approach uses the background activity of the norm of the inverse solution over time to estimate a baseline and a scaling factor for each solution point (Bréchet et al., 2019; Michel and Brunet, 2019)). The normalization factor is determined on the basis of all ERPs for each subject.

To reduce risk of type I error, we performed a contrast analysis using a randomization test [($p < .05$, for the duration of the whole time interval)], and source analyses were performed on AAL brain regions of interest (Tzourio-Mazoyer et al., 2002). Based on the significant differences of the randomization test, post hoc ROI comparisons were performed using unpaired t-tests ($p < .05$).

3. Results

3.1. Demographic and clinical variables

No significant differences were found in gender, laterality (Edinburgh inventory, (Oldfield, 1971)), or education level between groups (BD patients vs age matched-controls, BD offspring vs age-matched controls; see Table 1).

As shown in Table 1, BD patients showed statistically more depressive symptoms than controls and had higher scores on Trait/State-anxiety. BD patients also showed higher CTQ scores than controls (emotional/ sexual abuse subscales).

BD offspring showed slightly higher scores than controls in Trait-anxiety. However, there were no differences in State-anxiety, depressive, manic and CTQ scores, or rates of WM performance between BD patients and offspring and their age-matched controls.

3.2. Behavioral performance

Regression analyses evaluated the extent to which behavioral scores ('Target', 'Matched faces') were predicted by age. Regression equations were not significant for accuracy [age: $F(4, 67) = 0.76$, $p_s > .25$], or RTs [age: $F(4, 67) = 0.94$, $p_s > .33$]. Therefore, age was not a significant predictor of behavior.

Behavioral scores were subsequently entered into repeated measures ANOVA models, with Group as a three-level between-subject factor. Accuracy was significantly modulated by Gaze [$F(1, 69) = 163.456$, $p < .001$] and Identity recognition [$F(1, 69) = 12.319$, $p < .001$]. A significant interaction between Identity recognition x Gaze was also found [$F(2, 69) = 12.177$, $p < .001$]. Post hoc ANOVA comparisons indicate that faces with averted gaze were recognized more accurately than faces with direct gaze ($p < .001$), and that participants were more accurate in detecting target faces than matched faces ($p < .001$). There were no main effects or interactions of Group.

A repeated measures ANOVA comparing RTs between the three groups yielded a significant main effect of Identity recognition [$F(1, 69) = 277.29$, $p < .01$], and a significant interaction of Identity recognition x Gaze [$F(2, 69) = 5.218$, $p < .05$]. Post hoc ANOVA comparisons indicated that, overall, participants were faster in detecting matched faces than target faces ($p < .01$), especially for averted gaze (all $p_s < .001$). No significant Group effects occurred. Altogether, these results showed that behavioral performance was modulated by gaze shifts and face recognition, and these effects did not depend on group membership.

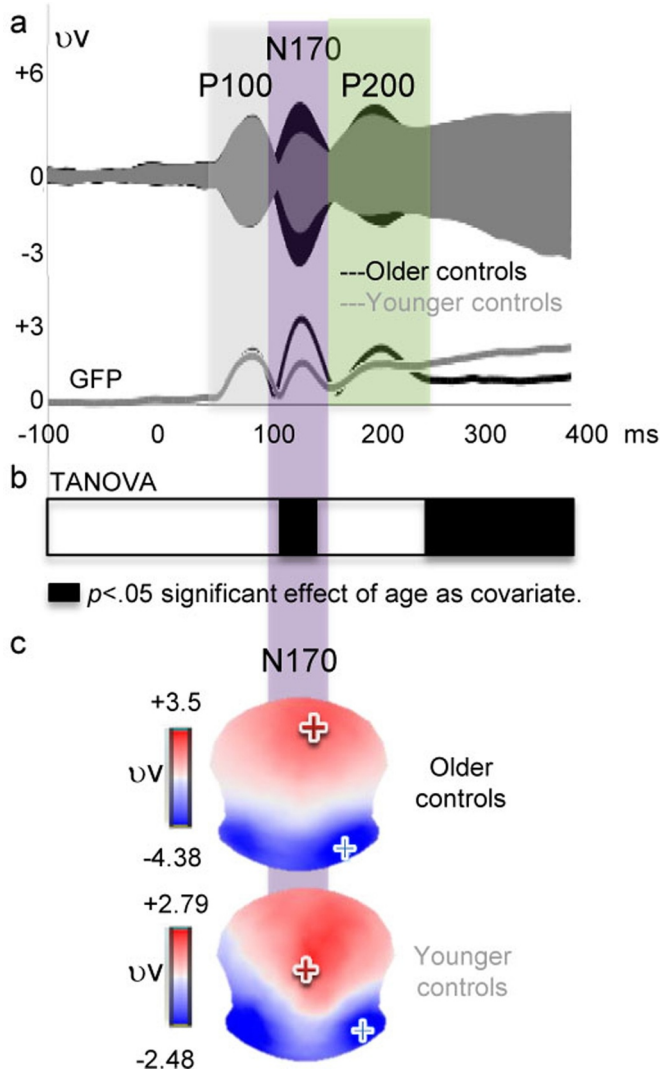

Fig. 2. Event related potentials (ERP) to faces in younger controls (15–25 years old; light gray) and older controls (25–54 years old; black). (a) Time course of the face-components (P100, N170, and P200) and their global field power traces are plotted; the corresponding time periods are indicated by solid shaded areas. (b) Topography analyses, with age as covariate, showed significant effects of age at the N170, and at the late latencies. (c) N170 topographies of younger controls and older controls are displayed. Maximum and minimum voltage topographies are indicated by red and blue crosses, respectively.

3.3. ERP analysis

3.3.1. Age-related changes

As expected, faces evoked three dominant ERP components: the P100, the N170, and the P200. Visual inspection of the waveform indicated that the older sample (25–54 years old) showed considerable augmented N170 amplitudes and reduced deflections at late latencies than younger controls (15–25 years old).

The TANOVA results revealed significant effects of Age at the N170 (time window: 120–160 ms, $p < .001$) and at late latencies (time window: 264–400 ms, $p < .004$).

3.3.2. Microstates analysis

To account for age-related changes in ERP, two separate cluster analyses were performed: one for BD patients and their age-matched controls, and another for BD offspring and their age-matched controls.

3.3.2.1. BD patients vs age-matched controls. Four classes of microstates were identified for the three main ERP components (see Fig. 3 left). Two different maps were identified during the P200 between BD patients (Map 3) and their age-matched controls (Map 4). To verify this cluster classification, maps 3 and 4 were fitted back to the individual data in the P200 time window (180–256 ms).

The Kruskal-Wallis ANOVA on the presence/absence of Map 3 revealed significant group effects for target faces with direct gaze [$H = 8.693$, $df = 2$, $p = .013$], and for matched faces both with direct [$H = 6.085$, $df = 2$, $p = .048$] and averted gaze [$H = 7.928$, $df = 2$, $p = .019$]. For map 4, the Kruskal-Wallis ANOVA indicates group differences for target faces with direct [$H = 11.053$, $df = 2$, $p = .004$] and averted gaze [$H = 7.231$, $df = 2$, $p = .027$]. Post hoc tests confirmed increased presence of Map 3 in BP compared to controls for target faces with direct gaze (BP $f = 15$, controls $f = 5$; z adjusted $= 2.769$, $p = .005$), and matched faces both with direct (BP $f = 14$, controls $f = 7$; z adjusted $= 2.314$, $p = .020$) and averted gaze (BP $f = 15$, controls $f = 7$; z adjusted $= 2.678$, $p = .007$). Post hoc comparisons also indicated lower occurrence of microstate class 4 in BP than in controls for target faces both with direct (BP $f = 5$, controls $f = 15$; z adjusted $= 2.769$, $p = .005$) and averted gaze (BP $f = 13$, controls $f = 5$; z adjusted $= -3.288$, $p = .001$). Experimental conditions that were not found to differ in their occurrences between groups were further submitted to post hoc comparisons of their GEV. This analysis revealed a reduced GEV of Map 4 in BP compared to age-matched controls for target faces with averted gaze (BP $M = 0.04$, $SD = 0.04$, controls $M = 0.087$, $SD = 0.07$; z adjusted$= 2.343$, $p = .019$); and a reduced GEV of Map 4 in BP compared to age-matched controls for matched faces with direct gaze (BP $M = 0.038$, $SD = 0.07$, controls $M = 0.064$, $SD = 0.05$; z adjusted$= -2.01$, $p = .043$). For the frequency/GEV of each class of microstate see Fig. 4.

The Kruskal-Wallis ANOVA on map latencies revealed significant differences between groups for matched faces with averted gaze of Map 3 [$H = 9.126$, $df = 2$, $p = .010$] and Map 4 [$H = 6.327$, $df = 2$, $p = .042$]. However, group differences on Map 3 (BP $M = 40.83$, $SD = 42.09$, controls $M = 57.27$, $SD = 36.83$) and 4 (BP $M = 52$, $SD = 38.30$, controls $M = 29$, $SD = 38.31$;) were not confirmed by post hoc Mann–Whitney U tests ($p > .10$). No other significant differences were found [all $H < 6.327$, $df = 2$, all other $p_s > .141$].

3.3.2.2. BD offspring vs age-matched controls

K-means cluster analysis revealed six different classes of microstates for the P100, N170 and P200 (see Fig. 3 right). Differences between groups were found at the N170 (Map 3: offspring, Map 4: age-matched controls) and at the P200 (Map 5: offspring, Map 6: age-matched controls). To test whether group differences were statistically meaningful, N170 and P200 maps were fitted back to the individual ERP at the corresponding time windows (124–172 ms for N170, and 160–228 ms for P200).

For the presence/absence of the N170 maps, the Kruskal-Wallis ANOVA showed no group differences for map 3 [all $H < 5.533$, $df = 2$, all $p_s > .063$] and map 4 [all $H > 2.901$ $df = 2$, all $p_s > .23$]. Post hoc Mann–Whitney U tests confirmed the absence of GEV differences between groups for all conditions (all $p_s > .09$). Therefore, topographic differences between groups were not confirmed by the fitting procedure. The results of the Kruskal-Wallis ANOVA had significant effects for matched faces with averted gaze for map 3 ($p = .030$) on map peak latencies. A post hoc contrast indicated that map 3 had a shorter latency in controls than in offspring (offspring $M = 40.5$, $SD = 31.29$, controls $M = 17$, $SD = 28.36$; z adjusted $= -2.951$, $p = .003$).

For the P200, the Kruskal-Wallis ANOVA indicated that groups were different in the occurrence of map 5 for matched faces with averted gaze [$H = 7.206$, $df = 2$, $p = .027$]. No other group differences were found [all $H < 4.947$ $df = 2$, all other $p_s > .084$]. For matched faces with averted gaze, a post hoc test confirmed augmented occurrence of map 5 in offspring ($f = 14$) compared to controls ($f = 6$) (z adjusted=

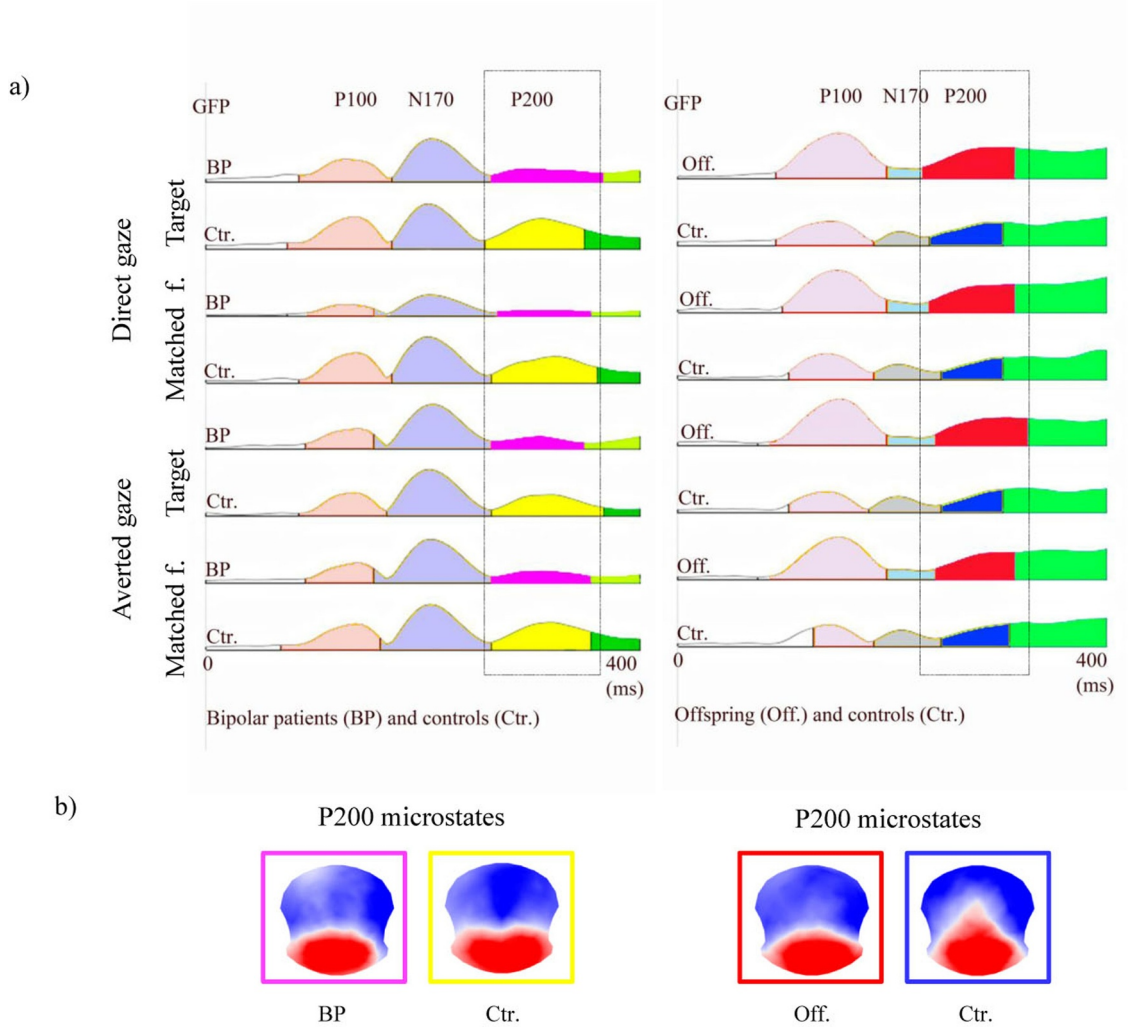

Fig. 3. Grand-averages and determination of number of clusters (k-means cluster procedure). (a) For each group and condition, responses evoked by faces are summarized by global field power traces. Suggested numbers of clusters are shown by different colors. Left: clusters classification identified for bipolar patients and age-matched controls. Right: for bipolar offspring and age-matched controls. (b) Significant differences between groups were found at the P200 component.

-2.600, $p = .009$). All the remaining experimental conditions were submitted to post hoc comparisons of their GEV. Post hoc Mann–Whitney U tests indicate reduced GEV of map 5 in controls compared to offspring for matched faces with direct gaze (offspring $M = 0.064$, $SD = 0.07$, controls $M = 0.019$, $SD = 0.050$; z adjusted = -1.989, $p = .046$). For map 6, age-matched controls showed greater GEV than offspring for matched faces with averted gaze (offspring $M = 0.017$, $SD = 0.04$, controls $M = 0.043$, $SD = 0.047$; z adjusted = 2.236, $p = .018$), and a slightly higher explained variance for matched faces with direct gaze (offspring $M = 0.025$, $SD = 0.05$, controls $M = 0.045$, $SD = 0.054$; z adjusted = 1.854.236, $p = .063$). No other statistical group effects were found (all $p_s > .13$). For the frequency/ GEV of each class of microstate see Fig. 4.

The Kruskal-Wallis ANOVA on map latencies showed significant group effects for matched faces with averted gaze for both maps 5 [$H = 9.126$, $df = 2$, $p = .010$], and map 6 [$H = 6.327$, $df = 2$, $p = .042$]. No other significant differences were found [all $H < 3.921$, $df = 2$, all $p_s > .141$]. Post hoc tests confirmed shorter latencies in offspring than controls for map 5 (offspring $M = 31.94$, $SD = 36.97$, controls $M = 58.77$, $SD = 32.74$; z adjusted = -2.951, $p = .003$), and longer latencies in offspring than controls for map 6 (offspring $M = 58.66$, $SD = 32.66$, controls $M = 23.88$, $SD = 34.86$; z adjusted = 2.401, $p = .016$).

3.3.3. Post hoc correlation analysis

Post hoc correlation analyses with clinical scores were performed within the BD groups. Given that BD patients had significantly higher levels of anxiety and depression, as well as higher CTQ scores (emotional/ sexual abuse subscales) than controls (see Table 1), post hoc correlation analyses were conducted to assess relationships between clinical symptoms and the GEV of the predominant P200 map (i.e., Map 3). Higher ratings of State-anxiety [$r(17) = .481$, $p < .05$], and CTQ emotional abuse [$r(17) = .528$, $p < .05$] subscale scores were positively correlated with higher GEV values. No other significant correlations were found (all $p_s > .05$).

BD offspring demonstrated a tendency for higher Trait-anxiety levels than controls; nevertheless, this difference is unlikely to have influenced the GEV of the predominant P200 map (i.e., Map 5), as no significant Pearson's correlations were found between the GEV and Trait-anxiety scores ($p_s > .05$).

3.4. Electrical neuro-imaging: post hoc exploration of differences in brain activation

To further investigate the neural correlates of eye-gaze processing in BD, contrast analyses for the groups (BD patients/offspring vs age-matched controls) in the source space were performed separately for faces with direct gaze and averted gaze.

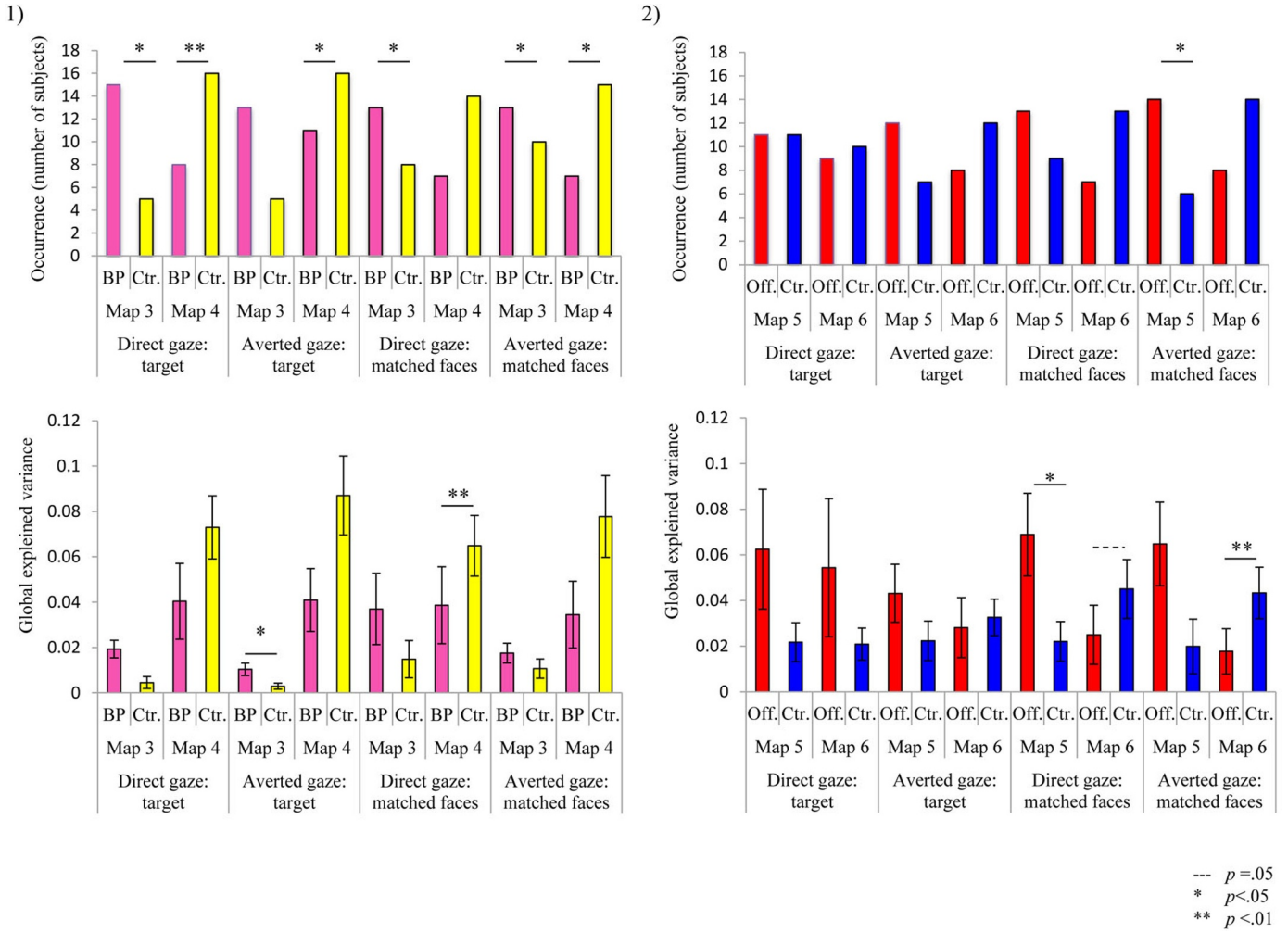

Fig. 4. P200 maps and back fitting procedure to individual data. (a) Bipolar patients vs age-matched controls. b) Bipolar offspring vs age-matched controls. For each cluster map and experimental condition, the upper part of the figure shows the frequency of occurrence (i.e., number of participants), the lower part shows the Global Explained Variance. Asterisks/dashed lines indicate significant differences between groups (**$p < .01$; *$p < .05$;— $p = .05$).

ERP were averaged and collapsed across experimental conditions (target vs matched faces), and a distributed linear inverse solution was applied to the individual data of each subject. Source analyses were performed on the average time window of the P200 microstate identified in the cluster analysis (from 180 to 240 ms).

3.4.1. Faces with direct gaze: P200 microstate

BD patients demonstrated significantly lower activation to direct gaze in the left dorsal prefrontal cortex ($t = +2.23$; $p = .032$, dipole max $_{\text{current density}}$ = superior frontal gyrus/ Brodmann area (BA) 9), left dorsal premotor cortex ($t = +2.86$; $p < .001$; dipole max $_{\text{current density}}$ = supplementary motor area/BA 6), right inferior frontal lobe ($t = +2.24$; $p = .035$, dipole max $_{\text{current density}}$ = precentral gyrus/rolandic operculum), right parietal lobe ($t = +2.18$; $p = .035$; dipole max $_{\text{current density}}$ = inferior parietal lobule/BA 40), and right dorsal temporal lobe ($t = +2.21$; $p = .033$; dipole max $_{\text{current density}}$ = superior temporal gyrus/ BA area 42) compared to age-matched controls.

On the other hand, BD offspring had greater activity than age-matched controls in several frontal regions: the right dorsal prefrontal cortex ($t = -2.20$; $p = .025$; dipole max $_{\text{current density}}$ = superior frontal gyrus/ BA 9), right medial frontal cortex ($t = -2.10$; $p = .043$; dipole max $_{\text{current density}}$ = orbital frontal gyrus/BA 10), and left medial frontal cortex ($t = -3.09$; $p = .004$; dipole max $_{\text{current density}}$ = middle frontal gyrus/BA 11). The right post central lobe ($t = +2.16$; $p = 0.038$; dipole max $_{\text{current density}}$ = paracentral lobule/BA 6) also showed greater activation in BD offspring.

Illustrative comparisons are shown in Fig. 5.

3.4.2. Faces with averted gaze: P200 microstate

In the averted gaze condition, BD patients showed reduced activation in the left caudate nucleus ($t = +2.79$; $p = .008$; dipole max $_{\text{current density}}$ = caudate body), bilateral medial cingulate cortex (left: $t = +2.38$; $p = .022$; right: $t = +2.35$; $p = .024$; dipole max $_{\text{current density}}$ = cingulate gyrus/ BA 24), left lingual gyrus ($t = +2.11$; $p = .042$; max $_{\text{current density}}$ = BA 18), and left somato-sensory cortex ($t = +2.28$; $p = .028$; dipole max $_{\text{current density}}$ = postcentral gyrus/BA 3), and augmented activation in the right superior temporal lobe ($t = -2.28$; $p = .039$; dipole max $_{\text{current density}}$ = superior temporal gyrus/ BA 42).

Compared to age-matched controls, BD offspring had significantly reduced activation in left lateralized regions for averted gaze in the insula ($t = +2.73$; $p = .009$), ventral frontal lobe ($t = +2.18$; $p = .035$; dipole max $_{\text{current density}}$ = precentral gyrus/BA 44), and putamen ($t = +2.31$; $p = .026$), and in the right temporal lobe ($t = +2.44$; $p = .019$; dipole max $_{\text{current density}}$ = superior e temporal gyrus/ BA 21).

Illustrative comparisons are shown in Fig. 5.

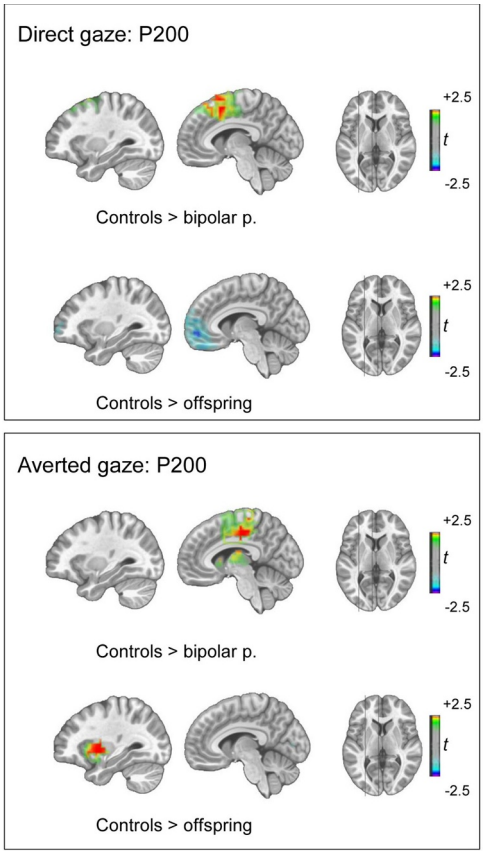

Fig. 5. Main effect of direct gaze, P200. Healthy controls showed greater activation to direct gaze than bipolar patients in the left superior frontal gyrus and supplementary motor area. Bipolar offspring showed greater activation than controls in the left orbital frontal cortex. Main effect of averted gaze, P200. Contrast analysis indicated greater activation to averted gaze in controls compared to bipolar patients in the in the left pre-central lobe, medial cingulate cortex, and caudate nucleus. Bipolar offspring showed lower activation than controls in the ventral premotor cortex.
Striking differences between groups are displayed using t values ($p < .05$). Areas in red-green depict regions where age-matched controls showed significantly more activation than BD patients/offspring, and those in blue-purple indicate where BD groups showed more activation than age-matched controls.

4. Discussion

Developmental studies have focused on understanding the precursors of the affective difficulties in BD, including face perception. Although several studies propose neuro-biological explanations for the origins of these impairments, differences in attention to socially relevant information have been poorly investigated. This study's findings indicate atypical eye-gaze processing in BD and offer some insights into how the social brain's development is altered in offspring of parents with BD relative to individuals who have no family history of BD (independent of the clinical phenotype).

In this study, BD patients and offspring were practically indistinguishable from control groups in their responses to faces in early ERP components. During averted gaze recognition, only a minimal effect was observed in offspring for the latency of their representative map. On one hand, the prolonged latency may point to a compensatory mechanism of gaze encoding in offspring, but at the same time, these results suggest that early visual processing of eye-gaze is overall preserved in BD patients and offspring. In contrast, the P200 differentiated BD patients and offspring from their age-matched controls. The P200 is sensitive to decoding ambiguous facial signals (Calvo et al., 2013), and emotional features (Kanunikov and Pavlova, 2017; Paulmann and Pell, 2009; Shannon et al., 2013).

Familial risk for BD has been linked to abnormalities in identifying emotional expressions (Brotman et al., 2008), and corresponding fronto-limbic dysfunctions in processing faces (Ladouceur et al., 2013; Manelis et al., 2015; Olsavsky et al., 2012). In this study, we found dysfunctional P200 topographies particularly pronounced during face recognition, especially for averted gaze. Our findings extend these results by suggesting neural dysfunctions in face decoding during eye-gaze processing.

In BD patients, altered P200 topographies have been found both during target and repetition priming processing. Although our results may indicate modest impairments in BD patients relative to their offspring, these findings also suggest that the P200 atypicality in face decoding may be part of the expression of the underlying vulnerability to BD.

Our findings also indicate varying degrees of impairments in the P200 map within the BD sample. In our previous study, we showed that BD is associated with reduced P200 amplitudes and that this bias is more pronounced for faces with direct gaze than averted gaze (Berchio et al., 2017). This finding was discussed in terms of the interference of affective social cues (i.e., avoidance/approach signals) on face processing. It is therefore possible that eye-gaze shifts, which are central to the processing of others' emotions (Senju and Johnson, 2009), are less efficiently processed in BD patients than in healthy controls.

Since early life experiences influence human social affective development (Morris, Silk, Steinberg, Myers, & Robinson, 2007), and anxiety affects face processing (Moser, Huppert, Duval, & Simons, 2008), we performed analyses of correlations with CTQ scores / levels of anxiety and the explained variance of the P200 microstate. A greater variance was associated with higher State-anxiety and CTQ emotional abuse scores in BD patients, suggesting that P200 topography abnormalities may be reinforced by states of anxiety. However, because no significant correlations were found in BD offspring, this finding also suggests that this effect is specific to BD and is not a marker of risk.

Surface analyses provided a first insight into potentially dysfunctional P200 networks. At the level of the brain's source space, differences between the BD groups and their control counterparts were found in a number of networks known to be involved in social cognition (see Falk and Bassett, 2017; Kennedy and Adolphs, 2012; Schmalzle et al., 2017). For direct gaze, we observed that BD patients and offspring resulted in deviant activation patterns in a network of areas associated with intentions/emotion simulations (see Fabbri-Destro and Rizzolatti, 2008; Gallese et al., 2013), and mentalizing (see Clark and Dumas, 2016; Yang et al., 2015), including key nodes for processing faces (Muller et al., 2018). More specifically, controls had greater activation than BD patients in the left supplementary motor cortex, as well as in the precentral gyrus, inferior parietal lobe, and superior temporal lobe. Augmented activations were observed in BD offspring compared to controls in the right superior frontal gyrus, orbitofrontal cortex, and postcentral lobe, and also in the left orbitofrontal cortex. While hypo-activations in key regions of the mirror system (Cattaneoand Rizzolatti, 2009; Rizzolatti and Craighero, 2004), such as the supplementary motor cortex, precentral gyrus and inferior parietal lobe, are suggestive of impairments conveyed by eye-contact in a network involved in experiencing others' social intentions (Fabbri-Destro and Rizzolatti, 2008) in BD, augmented superior frontal gyrus / orbital-frontal activations may imply the engagement of compensatory higher cognitive mechanisms for building these functions in BD offspring (see Boisgueheneuc et al., 2006; Kennedy and Adolphs, 2012; Moessnang et al., 2017).

In this study, we also found group differences in response to averted gaze. BD patients showed hypo-activations in the post-central gyrus, caudate, lingual gyrus and bilateral medial cingulate cortex compared to age-matched controls. At the same time, developmental risk for BD appeared in the insula, putamen, precentral gyrus and superior

temporal lobe. Some of these regions are recruited when individuals empathize with others (es., insula, somato-sensory cortex, medial cingulate) (Blakemore, 2010; De Vignemont and Singer, 2006; Kennedy and Adolphs, 2012), mirror other's intentions (Rizzolatti et al., 2009), or experience social reward [i.e., striatum (caudate nucleus and putamen) (Wake and Izuma, 2017)]. The superior temporal lobe is additionally employed during eye gaze discrimination (Akiyama et al., 2006; Senju and Johnson, 2009). All of this evidence suggests that in both BD patients and offspring, key nodes of social affective information processing work less efficiently compared with those of controls. It also seems reasonable to assume that differential brain dysfunctions may be due to a social brain that is still developing during adolescence / young adulthood in offspring (Blakemore, 2010).

To note, BD patients and offspring were indistinguishable from the controls in their behavioral responses. All groups had similar performance accuracy and reaction times and, therefore, were capable of recognizing face identity and processing eye-gaze shifts. Our results are consistent with findings in other studies that have investigated implicit face processing in youths at risk of BD (Ladouceur et al., 2013; Manelis et al., 2015). Indeed, our behavioral data complement ERP evidence, indicating that despite the essentially identical performances, the three groups differ in their neural strategies. In BD patients and offspring, atypical brain activity in regions generally linked to the 'social brain' (see Kennedy and Adolphs, 2012) may therefore produce compensatory behavioral abilities. To estimate causative effects, future research should explore compensation through neural homologues, for instance, using paradigms centered on mentalizing/empathizing abilities during eye-gaze processing.

A remarkable strength of this study lies in its focus on the neural correlates of eye-gaze processing in both BD patients and healthy offspring, as well as the comparison with a uniquely age-matched control group. However, divergent brain activation findings within the BD sample may also be related to the fact that brain activations to faces are affected by normal aging (Gunning-Dixon et al., 2003) and maturational changes in social cognition during adolescence (Blakemore, 2010; Blakemore and Choudhury, 2006). Therefore, developmental transversal conclusions about network dysfunctions should be drawn with caution. To gain a better understanding of the nature of these processes, it would be vital to have studies with larger samples targeting younger and older offspring. It is also important to consider that BD offspring in this study were generally asymptomatic, and that, in principle, the atypical patterns of brain activation could instead reflect the presence of a bio-signature of resilience. Additional investigation is needed to assess this possibility using, for example, a longitudinal cohort.

To conclude, adolescence and young adulthood represent a period of vulnerability for BD (Leboyer et al., 2005). Notably, this study sheds new light into this transitional phase, with respect to the neurobiology of social cognition in the BD phenotype. To our knowledge, this is the first study to investigate brain networks in response to eye-gaze in youth who have a familial risk of BD. Our data seem to exclude specific early impairments in face processing in BD offspring, but they suggest that the mechanism by which eye-gaze shifts are decoded in the brain is a familial characteristic of BD. Future studies must provide additional evidence on eye-gaze processing in affective disorders in order to support the notion of such an endo-phenotype associated with BD (Fig. 2).

Acknowledgments

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