Article

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Abstract

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Face and gaze perception in borderline personality disorder: An electrical neuroimaging study

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ABSTRACT
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In this study we wanted to investigate the temporal-spatial dynamics of spontaneous gaze processing in BPD. We used a 2-back-working-memory task, in which neutral faces with direct and averted gaze were presented. Gaze was used as an emotional modulator of event-related-potentials to faces. High density EEG data were acquired in 19 females with BPD and 19 healthy women, and analyzed with a spatio-temporal microstates analysis approach.

Independently of gaze direction, BPD patients showed altered N170 and P200 topographies for neutral faces. Source localization revealed that the anterior cingulate and other prefrontal regions were abnormally activated during the N170 component related to face encoding, while middle temporal deactivations were observed during the P200 component. Post-task affective ratings showed that BPD patients had difficulty to disambiguate neutral gaze.

This study provides first evidence for an early neural bias toward neutral faces in BPD independent of gaze direction and also suggests the importance of considering basic aspects of social cognition in identifying biological risk factors of BPD.

1. Introduction
Borderline personality disorder (BPD) is a mental illness characterized by emotional dysregulation and impaired social relationships. Affective dysregulation might be the consequence of an interaction between early life adversities and an inherited enhanced sensitivity to affective and social cues (Carpenter and Trull, 2013; Crowell et al., 2009; Gunderson and Lyons-Ruth, 2008; Linehan, 1993; Linehan and Wilks, 2015).

Several studies have found that BPD patients show a negative emotional bias in face recognition (Mitchell et al., 2014). Interestingly, the substantial impairment in identifying facial emotions is most pronounced during neutral face processing (Domes et al., 2008; Donegan et al., 2003; Dyck et al., 2009; Meyer et al., 2004; Mitchell et al., 2014; Silbersweig et al., 2007). BPD patients exhibit a negativity bias in the appraisal of faces depicting neutral expressions (Domes et al., 2009): some studies, for example, demonstrated that they are inclined to identify anger (Domes et al., 2008), and fear (Wagner and Linehan, 1999) emotions. Functional magnetic resonance imaging (fMRI) studies indicate abnormal activation to neutral faces in the amygdala, and the anterior cingulate (Donegan et al., 2003; Minzenberg et al., 2007; Soloff et al., 2017).

Gaze direction conveys information about the emotional expression of a face (Itier and Batty, 2009) and humans are sensitive to it from birth (Farroni et al., 2002). Direct gaze prompts social stimulus processing (Mares et al., 2016; Senju and Johnson, 2009) and increases the perception of approach-related affective states such as anger and joy, while averted gaze increases the perception of avoidance-related
affective states such as fear and sadness (Adams and Kleck, 2005, 2003). Some studies indicate that BPD patients judge the affective information conveyed by gaze differently than controls. These studies used the ‘Reading Mind in the Eyes’ test (RMET), in which subjects select the affective state that best describes the picture of the eyes presented (Baron-Cohen et al., 2001). A study by Fertuck et al. (2009) showed that BPD patients, relative to healthy subjects, have an increased ability to discriminate mental states based on the eye regions. This enhanced sensitivity has been proposed to be a precursor of their social impairments. However, Scott et al. (2011) showed that high BPD traits in healthy participants are associated with a negative bias to judge positive and neutral eyes in the RMET test. Evidence of abnormal gaze interactions comes also from behavioral studies that have investigated infants and mothers with BPD interactions (Apter et al., 2016; Crandell et al., 2003). On the other hand, Preißler et al. (2010) did not find any difference in the RMET scores between BPD patients and controls. Thus, while the negative bias in face perception of BPD patients is well established, it remains open whether this bias is related to a misinterpretation of the emotional expression conveyed by the gaze. The affective properties of direct and averted gaze have not been investigated systematically in BPD, and nothing is known about the brain correlates of gaze perception in this population.

Event-related potential (ERP) studies regarding face processing in BPD are sparse. The P100 is an early component mainly generated in visual areas associated with a posterior positive voltage distribution (Di Russo et al., 2002; Pascual-Marqui et al., 1994; Seki et al., 1996). Some studies reported modulation of this component by emotional stimuli (Pizzagalli et al., 1999; Pourtois et al., 2004). The N170 is a face-specific ERP component and is supposed to reflect the structural encoding of faces (Bentin et al., 1996). During facial emotion processing, (Izurieta Hidalgo et al., 2016) found enhanced P100 amplitudes and reduced N170 amplitudes in BPD subjects. In a magnetoencephalography study by Merkl et al. (2010), BPD patients have reduced amplitude of the M170 (i.e., the N170 homologous component).

Affective impairments in BPD may be the result of an inability to control negative emotions (Perez et al., 2016; Silbersweig et al., 2007; Soloff et al., 2015). Working Memory (WM) load has a regulatory influence on emotional processing (Erk et al., 2007; Van Dillen et al., 2009). Many studies have described lower P300 amplitudes during action monitoring in patients with BPD (de Bruijn et al., 2006; Houston et al., 2005; Patrick, 2008; Ruchsoow et al., 2008), and it has been proposed that this suppression may reflect impulsivity and externalized symptoms in BPD (de Bruijn et al., 2006; Houston et al., 2005; Izurieta Hidalgo et al., 2016; Ruchsoow et al., 2006). However, it remains largely unclear whether social cue processing, such as gaze direction, may affect cognitive control at this latency.

In this study, we aimed to investigate the temporal dynamics of spontaneous gaze processing in BPD patients, and the influence of gaze perception on cognitive control. Gaze direction has emotional significance in faces with a neutral expression (Adams and Kleck, 2005), and BPD patients might be specifically sensitive to neutral faces (see Mitchell et al., 2014). Since emotional arousal has been proposed to impair cognitive control in BPD (Fertuck et al., 2009; Hurlemann et al., 2007; Skodol et al., 2002), we aimed to investigate the influence of gaze perception on WM. For this purpose, we used a 2-back WM paradigm, in which neutral faces with direct and averted gaze were presented (Berchio et al., 2016). High temporal resolution ERP data were acquired during the 2-back WM task, and to investigate the temporal properties of face perception in BD we used a spatio-temporal microstates approach (Michel and Murray, 2012).

2. Methods

2.1. Participants

Thirty-eight female participants took part in the study: 19 patients diagnosed with BPD, according to the DSM-IV-R criteria, and 19 healthy controls. The mean age was 25.0 years (SD = 5.385) in the BPD group and 23.4 years (SD = 6.001) in the healthy control group. WM function was assessed with the digit memory span Wechsler sub-scale (Wechsler, 1997).

Of the original 38 participants, two subjects were excluded (one BPD patient and one control) because of poor quality of the data. The complete sample was used only for the behavioral analyses (performance and affective rating).

All participants provided written informed consent, and the study was approved by the local ethical committee of the Geneva University Hospital.

2.2. Clinical assessment and symptom severity

BPD diagnosis as well as severity was assessed by the French version of the Structured Clinical Interview for DSM-IV Axis II Disorders BPD part (BPD severity index: M = 6.777, SD = 1.506). In addition, participants completed the State-Trait Anxiety Inventory (Spielberger, 1983). Depression was determined using the Hamilton Depression Rating Scale (Montgomery and Asberg, 1979). The two groups were matched in laterality, educational level, age, and WM digit span. Demographic and clinical characteristics are presented in Table 1.

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According to the French version of the Diagnostic Interview for Genetic Studies (DIGS) (Preisig et al., 1999), BPD patients were free of any current axis I diagnoses, and current comorbidities included: eating disorders (n = 7), post-traumatic stress disorder (n = 9), anxiety disorder (n = 3), and attention-deficit-hyperactivity disorder (n = 3).

Healthy control subjects had no history of psychiatric illness as also assessed with the DIGS, and had not taken medications or substances by their own report.

Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control participants (n = 19)</th>
<th>Patients with BPD (n = 19)</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: M, SD</td>
<td>25 (5.38)</td>
<td>23.4 (6.0)</td>
<td>0.881</td>
<td>0.383</td>
</tr>
<tr>
<td>Gender: male, n</td>
<td>19</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handedness: right, n</td>
<td>18</td>
<td>19</td>
<td>(X^2) 0.234</td>
<td></td>
</tr>
<tr>
<td>Education: M, SD</td>
<td>2.4 (0.60)</td>
<td>2.4 (0.59)</td>
<td>(X^2) 0.984</td>
<td></td>
</tr>
<tr>
<td>University studies</td>
<td>9</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>9</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working Memory (digit span):</td>
<td>M, SD</td>
<td>6.2 (0.06)</td>
<td>8.891 (1.53)</td>
<td>−1.297 0.202</td>
</tr>
<tr>
<td>MADRS: M, SD</td>
<td>1.67 (2.38)</td>
<td>9.05 (5.50)</td>
<td>5.381</td>
<td>0.000</td>
</tr>
<tr>
<td>STAI-state: M, SD</td>
<td>26.45(10.89)</td>
<td>54.22 (12.06)</td>
<td>7.544</td>
<td>0.000</td>
</tr>
<tr>
<td>STAI-trait: M, SD</td>
<td>29.66 (11.30)</td>
<td>59.83 (7.33)</td>
<td>9.967</td>
<td>0.000</td>
</tr>
<tr>
<td>CTQ:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score: M, SD</td>
<td>37.47 (19.08)</td>
<td>61.76(17.31)</td>
<td>4.100</td>
<td>0.000</td>
</tr>
<tr>
<td>Emotional Abuse: M, SD</td>
<td>6.65 (5.09)</td>
<td>17.16(5.14)</td>
<td>6.330</td>
<td>0.000</td>
</tr>
<tr>
<td>Physical Abuse: M, SD</td>
<td>5.59 (4.75)</td>
<td>9.05(4.22)</td>
<td>2.378</td>
<td>0.022</td>
</tr>
<tr>
<td>Sexual Abuse: M, SD</td>
<td>5.70 (4.97)</td>
<td>10.41(5.74)</td>
<td>2.699</td>
<td>0.010</td>
</tr>
<tr>
<td>Emotional Neglect: M, SD</td>
<td>12.52 (7.54)</td>
<td>14.225(7.57)</td>
<td>0.777</td>
<td>0.441</td>
</tr>
<tr>
<td>Physical Neglect: M, SD</td>
<td>7.00 (3.43)</td>
<td>9.55(3.73)</td>
<td>2.197</td>
<td>0.034</td>
</tr>
</tbody>
</table>

MADRS = Montgomery-Asberg Depression Rating Scale.
CTQ = Childhood Trauma Questionnaire.
* Education levels were classified into three groups: 3 = university studies; 2 = high school; 1 = no high school.
2.3. Behavioral task

The paradigm consisted of a previously validated 2-back gaze-WM task (Berchio et al., 2016), which has been deemed suitable to detect spontaneous gaze recognition during neutral face processing (Fig. 1). In this task, half of the stimuli were presented with direct gaze and half with averted gaze (left and right) (The stimuli were taken from the Radboud Faces Database, (Langner et al., 2010); and the Amsterdam Dynamic Facial Expression Set (van der Schalk et al., 2011)). The stimuli were presented for 1 s, preceded by a fixation cross (2 s). Participants responded by pressing a down arrow key if the face was exactly the same as the face presented two times before, or an up arrow key if the face was different. Each target trial consisted of a non-repeated face (with direct or averted gaze) and a repeated face (with direct or averted gaze) that had been repeated two presentations before.

Before the start of the task, participants completed 10 practice trials. The faces presented during the training session were not presented during the experimental session.

In order to examine cognitive response biases to gaze perception, post-task affective ratings were also obtained. At the end of the experimental paradigm, participants performed an affective rating task. Ten faces were randomly selected from the 2-back WM paradigm. Subjects evaluated “How hostile is this face?” and “How afraid is this face?” on a seven-point Likert scale (from 1 = ‘not at all’ to 7 = ‘extremely’). Each face was displayed for 3 s, preceded by a fixation cross (500 ms).

The 2-back WM task was presented in three experimental blocks of five minutes each. Overall, participation time, including training session, high-density EEG application, and short breaks between blocks totaled in 90 min. Participants performed the 2-back WM task in a Faraday cage, with their head held stationary by a chin-rest 1 m from the computer screen.

2.4. EEG data acquisition and pre-processing

EEG data were acquired with a 256-channel Electrical Geodesic Inc. system (Eugene, OR), with a sampling rate of 1000 Hz, and Cz as acquisition reference. Electrode impedances were kept below 30 kOhm.

Offline analyses were performed using Cartool 3.60 Software (http://www.fhmlab.com/cartool-software/). EEG epochs were segmented 100 ms before and 600 ms after stimulus onsets and were digitally filtered offline at 0.3–40 Hz (causal filter, 24db/octave roll-off). Trials were visually inspected for artifacts, and epochs contaminated by eye blinks, eye movements, and movement artifacts were rejected.

Due to muscle artifact contaminations, peripheral electrodes located on the neck and face were removed, and the original electrodes montage was reduced from 256 to 204 electrodes (see Berchio et al., 2014). Subsequently, bad channels were interpolated using a 3D spline method, and ERP epochs were then re-referenced to the average reference. Lastly, ERP data were down-sampled to 250 Hz.

Separate averages, on correct trials only, were computed for faces with direct gaze (‘non-repeated’ and ‘repeated’) and averted gaze (‘non-repeated’ and ‘repeated’).

No significant differences among groups emerged in the number of trials accepted (two tailed t-test, p < 0.05; non-repeated faces with direct gaze, p = 0.425; repeated faces with direct gaze, p = 0.959; non-repeated faces with averted gaze, p = 0.287; repeated faces with averted gaze, p = 0.842; total number of trials accepted: non-repeated faces with direct gaze, BPD patients: M = 37, SD = 7.06, control participants: M = 39, SD = 9.56; non-repeated faces with averted gaze, BPD patients: M = 39, SD = 8.21, control participants: M = 41, SD = 9.18; repeated faces with direct gaze: BPD patients: M = 37, SD = 7.39, control participants: M = 37, SD = 9.41; repeated faces with averted gaze: BPD patients: M = 39, SD = 7.49, control participants: M = 39, SD = 10.5).

2.5. Analysis of the behavioral data

Behavioral data (accuracy and median reaction times (RT)) were subjected to a repeated measures ANOVA using Group (BDP patients, controls) as a between-subjects factor and Load (‘non-repeated faces’, ‘repeated faces’) and Gaze (direct gaze, averted gaze) as within-subjects factors. ANOVAs alpha levels were set to p < 0.05, followed by Bonferroni-corrected post hoc comparisons.

For the affective rating, planned two-way contrasts tested the hypothesis that BPD patients would exhibit relatively higher negative bias compared to their control counterparts when processing neutral faces (for a review see Mitchell et al., 2014). Planned two-way contrasts were used to investigate between-group differences on the affective ratings (p values set to p < 0.05, Bonferroni adjustment for multiple comparisons).

2.6. ERP topographic analysis

The high-density ERPs were analyzed with electrical neuroimaging methods that focus on differences of the scalp potential fields evoked by stimuli in the two groups (Michel et al., 2001; Michel and Murray, 2012; Murray et al., 2009). This reference-free method is based on a pattern analysis approach that identifies ERP components in terms of subsequent periods of stable potential fields, represented by maps, and tests whether these potential maps are different between conditions and groups. It is a physical law that whenever the map topography has changed, the distribution and/or orientation of the active dipoles in the brain have changed (Lehmann, 1987; Vaughan, 1982).

The spatio-temporal analysis included four steps (Brunet et al., 2011):

1. The eight grand mean ERPs (4 conditions, 2 groups) were jointly subjected to a modified k-means cluster analysis (Pascual-Marqui...
et al., 1995). The k-means cluster analysis is a classical iterative pattern recognition method which starts with an initial guess of maps and terminates when successive iterations differ negligibly. The result is a certain number of prototype maps (also called cluster maps) that best represent the whole data set. The optimal number of clusters is determined by cross-validation which is derived by dividing the global explained variance by the degrees of freedom, the latter depending on the number of electrodes (Pascual-Marqui et al., 1995). More details on the cluster analysis can be found elsewhere (Murray et al., 2009). The cluster analysis is completely data-driven, i.e. blind to the temporal succession of the maps, the conditions and the groups the maps belong to. In our case, a total of 1000 maps (eight ERPs of 500 ms duration at 250 Hz) entered the cluster analysis.

2. The resulting cluster maps were back-fitted to the grand-mean data by assigning each individual map to the cluster map it best correlated with. Only the spatial correlation is considered by first normalizing each map to the unitary global field power. This back-fitting results in labeling the ERPs at each time point with a given cluster map.

3. Based on the back-fitting of the cluster maps to the grand mean ERPs, time windows of interest were determined within which different maps were attributed to the different conditions or groups. These cluster maps were then back-fitted to the individual ERPs of each subject and the number of time frames that a given cluster map was present during this interval was determined. This parameter was then statistically tested using repeated measures ANOVA with Gaze (‘direct’, ‘averted’), Load (‘non-repeated’, ‘repeated’) and Map (‘Map x’, ‘Map y’) as within-subjects factors, and Group (‘BPD patients’, ‘controls’) as a between-subjects factor. Since this work aims to investigate differences between groups, post hoc analyses were performed only on significant group main effects and interactions. Planned comparisons were used in post-hoc analyses.

Topographic map differences between groups were also examined by a non-parametric randomization test called ‘topographic ANOVA’, or TANOVA (for technical detail see Lehmann and Skrandies, 1980; Murray et al., 2008) for each time point. The purpose of this analysis was to check whether there were stable topographic differences between conditions and/or groups that escaped the global microstate analysis approach and to avoid false negative results. The TANOVA included Gaze (‘direct’, ‘averted’) and Load (‘non-repeated’, ‘repeated’) as within-subjects factors, and Group (‘BPD patients’, ‘controls’) as a between-subjects factor. The randomization test was performed with 5000 randomization runs, and alpha was set to $p < 0.05$. The TANOVA analysis was computed using RAGU software (http://www.thomaskoenig.ch/index.php/work/ragu/1-ragu).

2.7. Effect on field strength

ERP differences between groups were also investigated with a global test on the field strength (Michel and Murray, 2012). Global field power (GFP) is the sum of the squared potential differences for all of the electrodes recorded (for more details, see Lehmann and Skrandies, 1980), and it can be considered as a global index of synchronization of the neuronal activity (Skrandies, 1990).

GFP data differences were evaluated with randomization tests (Koenig et al., 2011), using Gaze (‘direct’, ‘averted’) and Load (‘non-repeated’, ‘repeated’) as within-subjects factors, and Group (‘BPD patients’, ‘controls’) as a between-subjects factor. This analysis was performed from 0 to 500 ms post-stimulus onsets. Alpha was set to $p < 0.05$, and the analysis was computed with 5000 randomization runs. Effects were considered statistically significant and physiologically plausible for consecutive time frames of at least 10 ms.

Furthermore, to adjust for increased type-I error due to multiple comparisons, and to verify that the GFP results were stable over time, post-hoc analyses were performed (for the technical details, see Koenig et al., 2011). Since this work aims to investigate differences among groups, post hoc analyses were performed only on significant group main effects and interactions. The GFP analysis was computed using the RAGU software (Koenig et al., 2011).

2.8. Source analysis

We used the Local Auto Regressive Average (LAURA), a linear distributed inverse solution based on biophysical constraints (Menendez et al., 2001; Michel et al., 2001) to estimate the intracerebral current density underlying each microstate. To compute the lead field, we used an anatomically constrained head model that employs a local spherical model of three shells for each electrode (Birot et al., 2014; Brunet et al., 2011; Spinelli et al., 2000). Current density distribution was calculated for 5018 solution points located in the grey matter, on the on the Montreal Neurological Institute (MNI) brain template head (http://www.bic.mni.mcgill.ca/brainweb). The 204 electrodes were co-registered on the MNI template head surface.

To compare the brain electrical sources between groups, a randomization statistic was applied involving 5000 permutation runs and $p$-values less than 0.01. Permutation statistics were used to adjust for multiple comparisons (Maris and Oostenveld, 2007).

3. Results

3.1. Behavioral analysis

3.1.1. Accuracy

Across groups, participants were generally better at recognizing faces with averted gaze (main effect of gaze $F(1,36) = 74.455, p = 0.000$, post hoc test, $p = 0.000$) and target faces that were repeated (main effect of Load $F(1,36) = 6.901, p = 0.012$; post hoc test, $p = 0.012$).

The ANOVA also revealed a significant Load $x$ Gaze interaction ($F(1,36) = 9.151, p = 0.004$); participants were better at identifying non-repeated faces with averted gaze than other conditions (all $p < 0.001$); moreover, repeated faces with averted gaze were more often correctly recognized than repeated faces with direct gaze ($p = 0.003$). There was no group difference in accuracy.

3.1.2. RT

The ANOVA revealed significant main effects of Load ($F(1,36) = 5.011, p = 0.031$) and Gaze ($F(1,36) = 6.197, p = 0.017$). Overall, participants showed faster RT to non-repeated faces ($p = 0.031$) and responded slower to faces with averted gaze ($p = 0.05$). There was also a significant Group $\times$ Gaze interaction ($F(1,36) = 4.111; p = 0.05$): post hoc comparisons showed that BPD patients tend to recognize faces with averted gaze faster than faces with direct gaze ($p = 0.05$), which was not the case for controls.

3.1.3. Affective rating

For the affective rating, we only found marginally significant effects. Compared to healthy controls, BPD patients are slightly inclined to perceive neutral faces with direct gaze ($p = 0.058, t = 1.954$) and with averted gaze ($p = 0.066, t = 1.895$) as more hostile.

3.2. ERP analysis

Fig. 2 illustrates the result of the cluster analysis of the grand mean ERPs. It displays the GFP of the ERP for each condition and the cluster map that each time point was assigned to, under the GFP curve.
Fig. 3 (A) shows butterfly plots of the ERPs for the different conditions for the two groups. It shows that four main components were elicited during the 500 ms post-stimulus, replicating previous ERP studies on face processing, and known as P100, N170, P200, and a late positive potential. The ERPs were very similar among the different stimulus conditions, but differences in amplitude between the two groups are seen.

The cross validation revealed that nine maps best explained the whole 1000 maps that entered the cluster analysis (see Fig. 2). Each of them was present during a certain time period that covered the different components seen in Fig. 2. The first component around 100 ms is represented by cluster map A, which has the typical topography of the visual P100 component (occipital positivity). All four conditions were labeled with the same map during this period in both groups. This was not the case for the second component, where all conditions of the control group were labeled by cluster map C, while all conditions of the BPD group were labeled with cluster map B. Though the maps look visually similar and resemble the well-known N170 topography, the fitting procedure very systematically distinguished these two maps between patients and controls. The same was true for the next component that was labeled with cluster map E in all conditions of the control group and with cluster map D in all conditions of the BPD group. The map topographies were again very similar and resemble the known P200 component, but still clearly statistically distinguished the two groups. Finally, the last period was labeled with the same cluster map F in all conditions and in both groups.

3.3. Statistical analysis of the ERP topographies

In order to test whether the topographic differences between the two groups for the N170 and P200 components hold statistically on the individual level, the cluster maps were fitted to the individual ERP of each subject and the number of time frames that the different cluster maps were attributed to were determined. In the first window (110–165 ms, N170 time window) the cluster maps B and C were fitted to the individual data, while maps D and E were fitted to the second window (170–300 ms, P200 time window). Separate 2 × 2 × 2 ANOVAs were then performed for the two time windows of interest with Gaze (‘direct’, ‘averted’), Load (‘non-repeated’, ‘repeated’) and Map (‘Map B’ vs ‘Map C’ or ‘Map D’ vs. ‘Map E’, respectively) as within-subjects factors, and Group (‘BPD patients’, ‘controls’) as a between-subjects factor.

In the N170 time window a significant Maps x Group interaction (F(34,1) = 8.337, p = 0.006) was found. No significant main effects of the factors ‘Load’ or ‘Gaze’ and no interactions with these factors were found. Post-hoc tests comparing the two maps between the groups independent of the stimulation condition showed that map C was significantly more present in the control group (F(34,1) = 8.336, p = 0.006) while map B was significantly more present in the BPD group (F(34,1) = 8.337, p = 0.006) (see Fig. 4).
In the P200 time window the $2 \times 2 \times 2$ ANOVA on the number of time frames again showed a significant Map $\times$ Group interaction ($F(34,1) = 8.908, p = 0.005$). Post-hoc tests comparing the two maps between the groups independent of the stimulation condition showed that map E was significantly more present in the control group ($F(34,1) = 9.249, p = 0.004$) while map D was significantly more present in the BPD group ($F(34,1) = 7.971, p = 0.005$) (see Fig. 4).

To further test for topographic differences in time windows that did not reveal different clusters between groups in the Grand Mean analysis we computed a topographical ANOVA (see Methods) for each time point. This analysis revealed significant main effects of group in the time windows of the N170 ($p < 0.05$; time window: 130–140 ms) and the P200 ($p < 0.05$; time window: 230–500 ms), but failed to show differences during the P100 component. However, it also indicated sustained difference during the late positive component where the microstate analysis failed to differentiate two different microstates. Post hoc analysis of the main effect of Group were performed in the time windows of significant differences, whereby the second window was split in a window corresponding to the P200 (230–250 ms) and the late positive component (250–500 ms). To verify whether these effects were robust over time, the TANOVA was re-calculated for each average time interval (see Koenig et al., 2011). Post hoc analyses confirmed significant topography differences at the N170 ($p = 0.043$), P200 ($p = 0.004$) and at the last positive component ($p = 0.007$).
3.4. Effect on field strength

The GFP analysis revealed significant main effects of Gaze (from 70 to 90 ms (p = 0.040)), Load (335–500 ms (p = 0.020)) and Group (from 90 to 110 ms (p = 0.018)) (Fig. 5). The group effect was found in the time window of microstate A. Post hoc comparisons revealed higher GFP values for the controls as compared to the BPD patients (p = 0.020).

3.5. Sources analysis

We restricted the source analysis on the two time windows where the microstate analysis revealed differences between the two groups: the N170 and P200 microstates. Since no differences between conditions were found, we first averaged the evoked potentials of all conditions for each subject and transformed these average evoked potentials in the inverse space using the source localization procedure described in the method section. We then averaged the estimated current density at each solution point within the time windows of the N170 and P200, respectively. Since the Grand Mean analysis showed that the beginning and end of each microstate differed slightly between conditions (see Fig. 2), we narrowed the time windows to minimize the effect of the preceding or following microstate on the results. For the N170 microstate the selected time window was from 120 to 165 ms, and for the P200 microstate between 170 and 255 ms. The mean current density values of each solution point were then compared between the two groups using a randomization test, separately for the two time windows.

At the interval of the N170 microstate, BPD patients showed greater activation in a network of frontal brain regions: the right inferior frontal gyrus, the right orbitofrontal cortex, the left superior frontal gyrus, and the bilateral anterior cingulate.

Finally, source localization in the time window of the P200 showed that BPD patients had less activation of the right middle temporal gyrus, and increased activation in the right middle frontal gyrus (see Table 2, and Fig. 3, B).

3.6. Post hoc analyses on clinical severity and ERP effects

3.6.1. Comorbid psychiatric disorders

Anxiety, mood disorders, and post-traumatic stress disorder (PTSD) may impact face and gaze processing. Therefore, to control for these potential confounding variables, we compared BPD patients with co-morbid emotional psychiatric disorders (anxiety, mood disorder, PTSD, n = 9) and without (n = 9). Based on the results of the microstates analysis, we compared the number of time frames of maps B and C (N170 time window) and of maps D and E (P200 time window).

Potential within-group differences were evaluated using an unpaired Student’s t-test. On the number of time frames of maps B, C, D, and E these analyses revealed no significant differences between groups (all p₁ > 0.5).

3.6.2. Correlations

We additionally performed Pearson correlations to explore the relationship between the CTQ clinical scores (physical abuse, physical neglect, emotional abuse, sexual abuse) and the number of time frames of microstates B, C and D, E.

In the BPD group, we observed no correlations between CTQ scores and the number of time frames of all the microstates (all p-values > 0.05).

4. Discussion

In this study, we used high-density EEG to explore the spatio-temporal dynamics of gaze perception in women with BPD. A key finding of our work is that BPD patients showed significantly lower P100 amplitude for neutral faces and microstate abnormalities at the N170 and P200. EEG source imaging revealed that while the anterior cingulate and other prefrontal regions were more activated during face encoding, right medial temporal deactivation was observed at later stages. On the behavioral side, BPD patients recognized faces with an averted gaze more quickly, and they tended to perceive direct and averted gaze as more hostile, in comparison to the control group.

4.1. Behavioral data

Neither group differed in general task performance. However, patients with BPD tend to recognize faces with averted gaze more quickly than faces with direct gaze. Averted gaze is considered an emotional and social signal of avoidance (Adams and Kleck, 2005). One of the main clinical features of BPD is the fear of being abandoned (Gunderson and Lyons-Ruth, 2008). Due to these clinical features, it could be argued that BPD patients showed an increased sensitivity to neutral faces with averted gaze. Nevertheless, our results did not support this, since no difference between gaze conditions was found at the brain level.

Analysis of the affective rating showed that BPD patients had a slightly higher tendency than healthy controls to perceive neutral faces with direct or averted gaze as being more hostile. BPD patients’ enhanced negative emotion perception to neutral faces is consistent with previous findings (Crowell et al., 2009; Kakar et al., 2017). Thus, our findings seem to indicate a stronger negative bias for neutral faces, regardless of gaze direction possibly because neutral faces are more ambiguous in their social meaning in terms of signaling potential social rejection.

4.2. ERP results

At the P100 latency, irrespective of gaze direction, BPD patients showed decreased global field power during face processing. Early stages of visual processing are already implicated in face recognition (e.g. Herrmann et al., 2005), so the abnormal P100 amplitudes may reflect an early general deficit in neutral face perception.

Consistent with a previous study (Izurieta Hidalgo et al., 2016), we found that faces strongly modulated the N170 component in BPD patients. Independently of gaze direction and WM load, microstate analysis showed different map dominance between the two groups. Significant topography differences between groups were confirmed by the TANOVA analysis. Consequently, our data suggest that face encoding was globally altered in our BPD sample. In contrast, our results may indicate that gaze direction does not affect the N170 component in BPD.

Table 2

Microstates source localization.

<table>
<thead>
<tr>
<th>Microstate</th>
<th>L/R</th>
<th>p</th>
<th>Source current density (μV × cm²)</th>
<th>BPD group</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N170</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>L</td>
<td>0.006</td>
<td>3.3 × 10⁻⁴</td>
<td>2.1 × 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>Inferior frontal gyrus, opercular part</td>
<td>R</td>
<td>0.004</td>
<td>1.2 × 10⁻⁴</td>
<td>7.6 × 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>Inferior frontal gyrus, orbitofrontal part</td>
<td>R</td>
<td>0.004</td>
<td>1.2 × 10⁻⁴</td>
<td>7.7 × 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>Anterior cingulum</td>
<td>L</td>
<td>0.006</td>
<td>8.2 × 10⁻⁴</td>
<td>5.6 × 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>P200</td>
<td>L/R</td>
<td>p</td>
<td>Source current density (μV × cm²)</td>
<td>BPD group</td>
<td>Controls</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>R</td>
<td>0.010</td>
<td>1.2 × 10⁻³</td>
<td>7.7 × 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>R</td>
<td>0.009</td>
<td>1.2 × 10⁻⁴</td>
<td>2.6 × 10⁻⁴</td>
<td></td>
</tr>
</tbody>
</table>
While the N170 component peaked relatively early (in the average at around 140 ms) compared to some other studies (e.g., Eimer and Holmes, 2007, 2002; Hinojosa et al., 2015; Rossion, 2014), the topographic configuration clearly corresponded to the N170 typically described.

At the latency of the P200 component, microstate analysis also showed significantly different map configurations between the controls and the BPD patients. P200 topography differences were also confirmed by the TANOVA analysis. Taken together, our results suggest that individuals with BPD have altered P200 topographies to neutral faces. A component that has been described at the offset of the N170, and has been associated with increased allocation of attention to emotional stimuli is the early posterior negativity (EPN) (Bayer and Schacht, 2014; Bublatzky and Schupp, 2012; Rellecke et al., 2012; Schupp et al., 2006; Weinberg and Hajcak, 2010). The EPN is calculated using a subtraction between emotional and neutral stimuli, and the topography of the difference map is characterized by a posterior negativity and anterior positivity (Schupp et al., 2006). Interestingly, at this latency, map subtraction between the BPD patients and controls reveals a similar topography with increased negative values at posterior sites for the BPD patients (see Figure Appendix 1). This might indeed suggest that BPD patients may show increased attentional allocation to neutral faces because they consider faces as more emotional than the controls in general.

Importantly, our correlation analysis was not able to show that these ERP abnormalities during gaze processing are correlated with traumatic childhood experiences in BPD.

For the late positive component, the microstate analysis and the analysis of global strength differences did not reveal differences between groups. Interestingly, the TANOVA analysis revealed sustained topographic differences for the late positive component. This finding is partially consistent with previous works in which reduced P300 amplitudes have been consistently described in BPD (for a review see Patrick, 2008), albeit that our results rather point to topographic than amplitude (strength) differences. Nevertheless, it is important to notice that P300 amplitude reduction has been constantly described in BPD, but also that different brain generators might potentially be involved.

4.3. EEG source imaging

Source localization of the N170 revealed that BPD patients during neutral face perception had significantly increased activity in the right inferior frontal gyrus, orbitofrontal cortex, left superior frontal gyrus, and anterior cingulate, all of which are brain regions implicated in emotional/memory-related processes (Geday et al., 2003; Leung et al., 2002; Rossion et al., 2003) and attention regulation (Bush et al., 2000). This is not surprising since affective instability in BPD patients is attributed to frontal-limbic dysregulation (Donegan et al., 2003; Minzenberg et al., 2007; Schmah et al., 2003; Soloff et al., 2017), and anterior cingulate abnormalities have been reported in many studies (Goodman et al., 2011; Hazlett et al., 2005; Krause-Utz et al., 2014; Mitchell et al., 2014; Schutter et al., 2004; Whittle et al., 2009). Therefore, our findings may indicate an affective bias during neutral face encoding.

Source analysis also indicated that - at the P200 - BPD individuals have decreased medial temporal gyrus activations and increased activations of the superior frontal gyrus. The medial temporal gyrus is involved in face expression retrieval (Bonora et al., 2011; Dolcos et al., 2004; Geday et al., 2003; Holt et al., 2006), and abnormal activations in BPD patients have been previously reported during emotion discrimination tasks (Guitart-Masip et al., 2009). Interestingly, these abnormal activations were lateralized to the right hemisphere. Several studies have also documented that the right hemisphere has a special role in emotion processing (Borod et al., 1998; Gainotti, 2012; Nijboer and Jellema, 2012). Together with the key role of the superior frontal gyrus in high-level cognitive functions (Boisgueneuc et al., 2006; Cutini et al., 2008; Li et al., 2013), our results seem to support the hypothesis for an affective and attentional bias during neutral face processing.

5. Conclusion

BPD patients are emotionally sensitive to environmental signals (Carpenter and Trull, 2013; Gunderson and Lyons-Ruth, 2008; Linehan, 1993). It has been proposed that this sensitivity predisposes them to feel negative emotions across social situations, which likely contributes to their tendency to adopt inappropriate behaviours (Carpenter and Trull, 2013). The pattern of the N170 abnormalities, preceded by the reduced field strength of the P100, is consistent with the hypothesis for an abnormal emotional sensitivity to biological stimuli in BPD (Carpenter and Trull, 2013).

It is also important to take into account the evidence that negative environmental experiences are at the root of emotional problems in BPD (see Bandelow et al., 2005; McLean and Gallop, 2005; Weaver and Clum, 1993). In this sense, identifying or excluding potential environmental risk factors leading to poor emotional processing in BPD may also help to prevent negative developmental outcomes for these individuals.

Future research on this topic, using innovative spatial-temporal approaches (see and Murray, 2012), may enrich our understanding of the brain's functional dynamics in BPD and help to develop new therapeutic approaches.

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Fig. A.1. Topographic maps and Evoked Responses for neutral faces showing group differences in the time window of the Early Posterior Negativity (EPN, 170–250 ms). Amplitude analyses were performed, over all traces (unpaired t-test, \( p < 0.05 \)) in the time window of the EPN. (a) In line with previous studies (Schupp et al., 2004; Weinberg and Hajcak, 2010; Dunning et al., 2011), Evoked Responses were re-referenced to the left and right mastoid reference. This analysis revealed significant differences in occipital, posterior and frontal regions. Single waveforms are shown in occipital electrodes. (b) The same analysis was performed on the Evoked Responses referenced to the average reference and revealed group differences in frontal regions only. However, an analogous topographic pattern was observed in the t values map.

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