Brief Communication

Basal cortisol is positively correlated to threat vigilance in patients with psychogenic nonepileptic seizures

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information, and see [7] for detailed inclusion criteria). In addition, 17 patients with ES without suspicion of (a history of) comorbid PNES based on EEG recording (with or without additional neuroimaging data), medical history, seizure semiology, and antiepileptic drug treatment (AED) experience, who were being treated at SEIN, were recruited by their neurologist. Sixteen patients with ES had drug treatment (AED) experience, who were being treated at SEIN, aging data), medical history, seizure semiology, and antiepileptic

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy controls group (N = 20)</th>
<th>Patients with PNES (N = 19)</th>
<th>Patients with epileptic seizures (N = 17)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>22.1 (4.2)</td>
<td>27.6 (7.3)</td>
<td>42.4 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Number of women</td>
<td>18</td>
<td>15</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Number of women using contraceptives[^a]</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Number of women in luteal phase[^b]</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Age at onset, years</td>
<td>21.1 (7.9)</td>
<td>20.7 (15.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>6.5 (7.4)</td>
<td>21.7 (15.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^a] Use of contraceptive was unknown in one patient with PNES.

[^b] Menstruation cycle was indeterminable in two patients with PNES and one healthy control.

2.2. The emotional Stroop task

The preconscious attentional processing of happy and angry faces was assessed using a masked pictorial emotional Stroop task [12]. Facial stimuli of 10 different individuals (5 males, 5 females) were taken from Ekman and Friesen’s Pictures of Facial Affect [13], each displaying a neutral, a happy, and an angry expression. The facial stimuli were presented for 14 ms. Immediately after stimulus presentation the pictures were replaced by a masking stimulus. The masking stimuli consisted of randomly cut, reassembled, and rephotographed pictures of faces. At each trial, the stimulus and mask were presented in the same color (red, green, or blue), and participants were instructed to vocalize this color as fast and accurately as possible. On vocal response initiation (timing of which was registered by means of voice-key registration: reaction time [RT] in milliseconds), the presentation of the masking stimulus was terminated. After a random intertrial interval (2–4 seconds), new trials started with a 750-ms lasting fixation point. A total of 30 happy, 30 angry, and 30 neutral faces were presented in random order with the restriction that the same color was never repeated more than twice consecutively. The AB score for angry faces was based on correct responses only, and calculated by subtracting the mean individual RTs for neutral face trials from the individual mean RTs for angry face trials.

2.3. Cortisol

Baseline cortisol was analyzed from saliva sampled approximately 40 minutes before task administration using Salivette collection devices (Sarstedt, Rommersdorf, Germany). Saliva samples were stored at −20 °C before assaying. Biochemical analysis of free cortisol in saliva was performed using a competitive electrochemiluminescence immunoassay (ECLI, Elecsys 2010, Roche Diagnostics), as described elsewhere [14].

2.4. Statistical testing

Group differences in AB scores were analyzed using statistical analyses of variance (ANOVA), and subsequent least-significant-difference (LSD) planned comparisons were calculated to further detail group differences. Correlations between baseline cortisol and AB scores were calculated using Pearson’s correlations. Given the strong directedness of the hypotheses for the AB scores, group differences in AB scores were tested one-tailed; the other analyses were two-tailed (p < 0.05). Effect sizes of significant results are reported using partial eta squared (η^2). Because groups differed with respect to age (see Table 1), we controlled for age by subsequently adding it as a covariate into the group ANOVA for the AB scores. Because groups differed with respect to use of contraceptives by women (see Table 1), we controlled for this variable in case of significant effects involving cortisol (using partial correlations).

3. Results

One-way ANOVA for the AB scores for angry faces, with group (HC, PNES, ES) as between-subject factor, indicated significant group differences: F(2,56) = 2.85, P = 0.033, one-tailed; η^2 = 0.097 (Fig. 1). This effect remained when controlling for age (age added as a covariate to the analysis): F(3,56) = 2.80, P = 0.035, η^2 = 0.097. LSD planned comparisons indicated significant differences for patients with PNES versus those with ES (P = 0.032) and versus HC (P = 0.016), but not for patients with ES versus HC (P = 0.42). Groups did not differ with respect to their baseline cortisol levels (HC: M = 6.7, SD = 2.80; PNES: M = 6.9, SD = 2.96; ES: M = 5.7, SD = 3.10; F(2,55) = 0.95, P = 0.39), but, as expected, within the PNES group we found a significant positive correlation between the AB score for angry faces and baseline cortisol levels (r = 0.49, P = 0.035) (see Fig. 2). This effect remained when controlling for menstrual cycle (r = 0.49, P = 0.039) and use of contraceptives.
relationships for happy faces in all groups (all $P = 0.84$) control group for angry faces, and there were no such differences between the PNES and control groups. We used Fisher’s $t$-test to test whether the reported correlations between baseline cortisol levels and AB scores for angry faces differed significantly between the PNES and control groups. We used Fisher’s $r$-to-$Z$ transformation to normalize the distribution of correlation coefficients, which allows the use of a $Z$ test to compare the correlations. Comparison of the correlations for patients with PNES with those for ES controls revealed a significant difference, as indicated by a $Z$ score of 1.64 ($P = 0.05$) and the PNES–HC comparison showed a trend toward significance, with $Z = 1.52$ ($P = 0.064$).

4. Discussion

This study showed that baseline (pretask) cortisol levels were positively correlated to threat vigilance in 19 unmedicated patients with PNES. These effects remained when controlling for use of contraceptives and menstrual cycle. The effects were specific for PNES and were absent for control groups consisting of healthy individuals and patients with ES, respectively. The relationship between baseline cortisol and threat vigilance in patients with PNES in our study is relevant in the light of recent observations of increased basal cortisol levels in patients with PNES [8,9] and may contribute to our insight into possible stress factors implicated in the increased threat vigilance in PNES. According to cognitive theories of medically unexplained symptoms (MUS) [16] and more recent integrated psychoneurobiological theories of MUS [2], increased activity in neurobiological stress systems and increased attention to threat make part of a state of hypervigilance that, in turn, may play a crucial role in the presence of MUS as well as dissociative symptoms [7,9]. In addition, increased threat vigilance on a masked emotional Stroop task [17], as well as hypercortisolism [18], has been reported for patients with a primary diagnosis of dissociative disorder as well. Taken together, these and previous findings in PNES show great overlap with previous findings in patients with a dissociative disorder. Although the findings need to be replicated, preferably in larger patient samples, the present results provide the first evidence of a direct relationship between the biological stress marker cortisol and cognitive threat sensitivity in PNES and provide a starting point, as well as preliminary support, for integrated psychoneurobiological theories for this complex disorder [2]. If replicated, these findings, together with evidence for increased basal cortisol levels in PNES [9], may help to fine-tune psychological as well as pharmacological interventions for PNES [19].

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References