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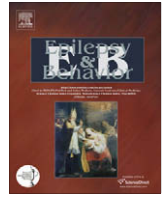Brief Communication

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

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ABSTRACT

Previous studies have provided evidence for a vigilant attentional bias toward threat stimuli and increased basal diurnal cortisol levels in patients with psychogenic nonepileptic seizures (PNES). Because cortisol levels may be predictive of threat vigilance, we reanalyzed previous data on threat vigilance in 19 unmedicated patients with PNES and found a positive correlation between baseline cortisol levels and attentional bias scores for threat stimuli ($r = 0.49$, $P = 0.035$). There was no such relationship in healthy matched controls ($n = 20$) or in patients with epileptic seizures ($n = 17$). These findings provide the first evidence linking an endocrine stress marker to increased threat sensitivity in PNES and support new integrated psychoneurobiological models of PNES.

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1. Introduction

Although psychogenic nonepileptic seizures (PNES) are related by definition to psychological stress factors [1], little is known about the cognitive and biological stress sensitivity of patients presenting with PNES. Several studies have indicated that patients with PNES report higher rates of psychological trauma, such as sexual abuse, compared with healthy controls or controls with epilepsy [see 2 for a review]. In addition, patients with PNES report more avoidant coping behavior [3–5] and increased fear sensitivity [6]. However, all these findings rely on self-reports, and to our knowledge, only one study has investigated whether PNES are associated with increased threat sensitivity using an objective threat processing (reaction time) task. Bakvis et al. [7] found increased threat vigilance, as indicated by an attentional bias for displays of angry faces in an emotional Stroop task, in individuals with PNES as compared with matched healthy controls (HC). In addition, two studies have reported increased basal cortisol levels in patients with PNES [8,9], one of which indicated that the basal hypercortisolism was independent of current seizures [9]. Cortisol

may enhance processing of angry faces [10,11] and, although these findings are suggestive of a relationship between basal cortisol levels and threat vigilance in patients with PNES, no studies have directly tested this premise. We reanalyzed previous data on threat vigilance in 19 unmedicated patients with PNES and related the previously reported attentional bias (AB) scores for angry faces [7] to newly analyzed baseline (pretask) cortisol levels. In addition, we tested the specificity of eventual effects by investigating the same relationship in the HC reported in Bakvis et al. [7] and in a new control group of 17 patients with epileptic seizures (ES). We predicted that the cortisol levels would be positively correlated to the enhanced AB scores for angry faces of patients with PNES.

2. Methods

2.1. Participants

Nineteen patients with PNES and 20 HC from the Bakvis et al. study were included in the study [7]. Patients with PNES who were being treated at SEIN, Epilepsy Institute in The Netherlands, were recruited by the attending neurologists. The main inclusion criteria were (1) diagnosis of PNES based on an ictal video/EEG recording of a typical seizure and (2) no current use of medication (see Table 1 for demographics, seizure characteristics, and menstrual cycle

Table 1
Group characteristics.

Variable	Healthy controls group (N = 20)	Patients with PNES (N = 19)	Patients with epileptic seizures (N = 17)	Statistics
Age	22.1 (4.2)	27.6 (7.3)	42.4 (12.9)	$F(2,56) = 26.6$, $P < 0.001$
Number of women	18	15	11	$\chi^2(2) = 3.5$, $P = 0.17$
Number of women using contraceptives[a]	10	6	1	$\chi^2(2) = 6.1$, $P < 0.05$
Number of women in luteal phase[b]	8	7	4	$\chi^2(2) = 0.48$, $P = 0.79$
Age at onset, years		21.1 (7.9)	20.7 (15.1)	$F(1,34) = 0.01$, $P = 0.93$
Disease duration, years		6.5 (7.4)	21.7 (15.7)	$F(1,34) = 14.23$, $P < 0.01$

[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.

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 localization-related epilepsy (11 temporal lobe epilepsy [TLE], three frontal lobe epilepsy, two uncertain) and one had primary generalized epilepsy. AED treatment included monotherapy ($n = 15$) with carbamazepine ($n = 9$) or valproic acid ($n = 6$) and polytherapy ($n = 1$) with carbamazepine and clobazam. One patient was not on AED treatment.

All participants were instructed to minimize physical exercise during the hour preceding the experiment and to avoid large meals, coffee, drinks with low pH, and cigarettes, because these variables can affect cortisol levels. All participants had normal or corrected-to-normal vision. The study was approved by the local ethics committee, and all participants provided written informed consent and received financial compensation for participation.

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, Rommelsdorf, Germany). Saliva samples were stored at −20 °C before assaying. Biochemical analysis of free cortisol in saliva was performed using a competitive electrochemiluminescence immunoassay (ECLIA, 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 ($\alpha = 0.05$). 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; $\eta^2 = 0.097$ (Fig. 1). This effect remained when controlling for age (age added as a covariate to the analysis): $F(3,56) = 2.80$, $P = 0.035$, $\eta^2 = 0.097$. 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
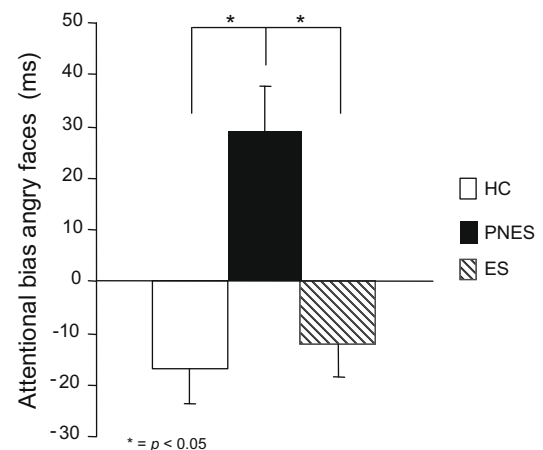

Fig. 1. Attentional bias (AB) scores for angry faces (reaction time [RT] in angry face trials – RT in neutral face trials) for healthy controls (HC), patients with psychogenic nonepileptic seizures (PNES), and patients with epileptic seizures (ES).
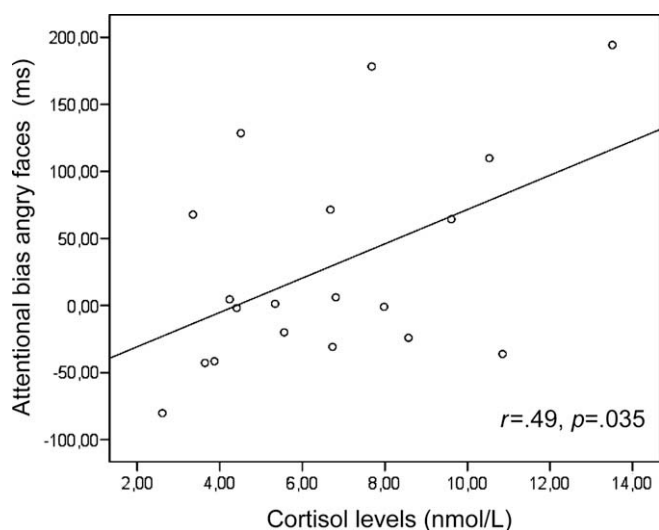
Fig. 2. Correlation between pretask cortisol levels and attentional bias (AB) scores for angry faces in patients with psychogenic nonepileptic seizures (PNES).

($r = 0.49$, $P = 0.037$) by means of partial correlations. There was no such relationship for the HC ($r = -0.001$, $p = 0.99$) or ES ($r = -0.07$, $P = 0.84$) control group for angry faces, and there were no such relationships for happy faces in all groups (all $P > 0.64$). Finally, we tested 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-r' 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 (for independent groups, see [15]) 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 re-

sults 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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