Automatic avoidance tendencies in patients with Psychogenic Non Epileptic Seizures

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ABSTRACT

Introduction: Psychogenic Non Epileptic Seizures (PNES) have been theorized to reflect a learned pattern of avoidant behavior to deal with stressors. Although such observation may be relevant for our understanding of the etiology of PNES, evidence for this theory is largely build on self-report investigations and no studies have systematically tested actual *avoidance behavior* in patients with PNES. In this study, we tested automatic threat avoidance tendencies in relation to stress and cortisol levels in patients with PNES and healthy controls (HCs).
Methods: The approach and avoidance (AA) task was administered to 12 patients with PNES and 20 matched HCs at baseline and following stress-induction using the Cold Pressor Test (CPT). The AA task requires participants to evaluate the emotional valence of pictures of angry and happy faces by making arm movements (arm flexion or extension) that are either affect-congruent (avoid-angry; approach-happy) or affect-incongruent (approach-angry; avoid-happy) with their intuitive action tendencies. Saliva cortisol was measured throughout the experiment.
Results: Patients, but not HCs, showed increased approach-avoidance congruency-effects for angry faces on the AA task at baseline, with relatively slower approach of angry faces, which was overall associated with basal pre-task cortisol. This congruency-effect disappeared after the CPT.
Discussion: The present findings provide an objective confirmation of previous suggestions from self-report studies indicating that PNES patients show relatively increased avoidance tendencies to social threat cues. The registering of threat *avoidance behavior* may prove to be a clinically valuable contribution to evaluate psychological treatment effectiveness and perhaps even PNES prognosis.

1. Introduction

Avoidance behavior is hypothesized to be an important precipitating and perpetuating factor for Psychogenic Non Epileptic Seizures (PNES).[1] It has been suggested that PNES are a learned pattern of avoidant behavior to deal with stressors.[2] The ictal state of altered awareness associated with PNES is also said to act as an avoidance response to protect the individual from experiencing stressful events or from memories of those events.[3] Findings from self-report investigations suggest that patients with PNES experience their lives as more stressful and use more maladaptive, escape and avoidance oriented coping strategies, i.e.

behavioral efforts to avoid conflicts or stress, compared to healthy controls (HCs).[3,4] Increased dissociative tendencies have also been found in patients with PNES[3,5] and this has been considered to protect individuals from unacceptable psychological stress factors and may therefore be considered as an avoidant coping strategy.[6]

Most evidence so far comes from self-report measures, but there are also a few neurobiological and experimental findings supporting the increased stress- and threat sensitivity in patients with PNES. For example, PNES patients show increased basal cortisol levels,[7,8] and high cortisol levels have been widely associated with increased avoidance tendencies.[9–13] A recent experimental study has also shown that PNES patients demonstrate an increased attentional bias for angry faces, but not for happy faces[14] and this was related to basal cortisol levels.[15] These results of increased biological and cognitive stress-sensitivity in patients with PNES may be consistent with the commonly self-reported avoidant strategies to cope with stressors, but actual threat avoidance *behavior*, hypothesized to precipitate and

perpetuate the disorder, has not yet been objectively tested in patients with PNES.

A systematic and objective method to study human avoidance behavior to social threat stimuli is provided by the social approach-avoidance (AA) task.[16] This reaction time task requires participants to evaluate the emotional valence of pictures of angry and happy faces by making arm movements (arm flexion or extension) that are either congruent or incongruent with their intuitive action tendencies (see[16] for a photograph of the task-set up). Affect-congruent movements involve arm-extension (avoidance) in response to a negative stimulus (angry face) and arm-flexion (approach) in response to a positive stimulus (happy face). Affect incongruent movements involve reversed mappings (i.e. avoid positive and approach negative stimuli). With this paradigm a congruency-effect is typically found, indicating faster responses for affect-congruent arm movements than for affect-incongruent arm movements.[10,17,18] This task is sensitive to anxiety[11,19,20] and cortisol[12,13]: anxiety and increased cortisol levels have consistently been found to be associated with increased congruency-effects for angry faces, indicative of social avoidance tendencies.

In the present study we tested whether PNES patients showed increased threat avoidance tendencies by administrating the AA task to patients with PNES and healthy control participants. Since PNES patients typically report to display increased avoidant behavior in stressful circumstances, the AA task was administered before and after stress-induction, allowing us to evaluate whether social threat avoidance behavior in patients was even more pronounced following stress-induction. Stress was induced using the Cold Pressor Test (CPT). This physiological stress procedure consists of immersing the non-dominant hand in ice water, which is known for its activating effect on both the Sympathetic Nervous System (SNS) and the Hypothalamus-pituitary-adrenal (HPA)-axis, resulting in increased cortisol levels.[21–24] We investigated whether increased cortisol was associated with the hypothesized increased social threat avoidance behavior in patients with PNES.[8,14,15]

2. Methods

2.1. Participants

Patients with PNES, who had been admitted to a tertiary epilepsy centre, were consecutively recruited by attending neurologists between March 2008 and August 2009. Inclusion criteria were: (1) diagnosis of PNES based on an ictal video-EEG recording of a typical seizure, (2) PNES characterized by complete or partial loss of consciousness (specified as an ictal diminished or loss of adequate responsiveness or post-ictal memory impairments of the ictal event), (3) the occurrence of at least two seizures in the year prior to the study, (4) no history of concomitant epileptic seizures, (5) no comorbid neurological disease diagnosis, (6) no diagnosis of endocrine disorder(s), (7) age between 18 and 65 years, and (8) signed informed consent.

The healthy control group was recruited through advertisements in local newspapers. Inclusion criteria were: (1) no psychiatric diagnosis, (2) no medical disease diagnosis, (3) no use of medication, and (4) signed informed consent.

2.2. Measures

2.2.1. Approach-avoidance (AA) task

In this affect-evaluation task[16] participants responded to visually presented pictures of emotional facial expressions by making arm movements toward (arm flexion or approach) or away from (arm extension or avoid) their own body. Eighty grayscale photographs displaying angry or happy facial expressions served as stimuli.[25–27] Both the happy and angry expres-

sions were taken from the same models (total of 40 models; 50% female). The stimuli were subdivided into four fixed series (A1-A2-B1-B2) each with 10 happy and 10 angry expressions from different models. The approach and avoidance responses were given by means of three one-button boxes that were fixed to a vertical stand. Participants were seated to the left of the stand, allowing them to respond with their right hand. For the resting position of the right hand participants were instructed to push the home-button in the middle loosely with the back of the right hand as long as no response was given. The response buttons were positioned above the home-button for the flexion arm movement and below the home-button for the extension arm movement. This allowed participants simply to flex or extend their right arm in responding without the need for precise aiming at the response buttons. Participants were verbally instructed to evaluate the facial expressions (happy or angry) and to respond as fast and accurately as possible to the stimuli by releasing the home button and pressing one of the response buttons. After this, they returned their hand to the home button. All participants received an affect-congruent and an affect-incongruent instruction block of trials, both before (A1-A2) and after (B1-B2) stress-induction. In affect-congruent instruction blocks, participants were instructed to press the upper-button (approach movement) in response to a happy face and to press the lower-button in response to an angry face (avoidance movement). Affect-incongruent instructions blocks involved the opposite stimulus response mappings (approach-angry, avoid-happy). No reference was made in the instructions to congruence and incongruence, approach and avoidance or arm flexion and extension. The order of instruction before and after stress-induction was counterbalanced across participants. Each instruction block was followed by 12 practice trials containing pictures not included in the actual AA task. The start of an individual trial was indicated by the appearance of a central fixation point (100 ms). After an interval of 300 ms the stimulus was presented for 100 ms followed by an inter-trial-interval of 1500 ms. This task provides two behavioral measures, i.e. median reaction times (RT: time between stimulus onset and the release of the home-button) and error rates (percentage incorrect responses).

2.2.2. Anxiety and depression

The Symptom Check List Revised (SCL-90-R), a self-report questionnaire, was used to assess levels of anxiety and depression.[28,29] The Anxiety subscale consists of 10 items, the Depression subscale of 16 items. Each item inquires about recent physical and psychological complaints that can be scored on a 5-point scale ranging form 'not at all' to 'very much'.

2.2.3. Cold Pressor Test (CPT)

Participants were instructed to immerse their non-dominant hand up to the wrist in an ice-cold water bath (0–4 °C) for as long as possible (maximum of 3 min). This procedure was repeated 3 times at standardized but unpredictable intervals (1–4 min). The CPT or plunge test is known to elicit a robust stress response and simultaneously to activate the SNS and HPA-axis.[21–24]

2.2.4. Cortisol

In order to test the effectiveness of the stress induction, saliva samples for cortisol assessments were registered at 9 assessment points over approximately a 145-min period, divided in a rest, stress and a recovery phase, at respectively: rest: −75, −60, −40, −25, 0; stress: +15, +35; and recovery: +50 and +70 minutes with reference to the start of the stressor. All assessments were performed between 1.15 pm and 4.00 pm.

Saliva samples were obtained using Salivette collection devices with a cotton roll (Sarstedt, Rommelsdorf, Germany).

Saliva sampling (in contrast to blood sampling) is a stress-free non-invasive way to measure cortisol.[30,31] Saliva samples were stored at −20 °C until assayed at a suitable laboratory (http://biopsychologie.tu-dresden.de). Cortisol concentrations in saliva were measured using a commercially available chemiluminescence-immuno-assay kit with high sensitivity (IBL, Hamburg, Germany). Inter- and intra-assay coefficients of variation were below 10%.

2.3. Procedure

Candidate participants were invited for an initial informative session in which they were informed about the specifics of the experiment. With regard to the stress-induction procedure, they were told that stress would be induced by means of a physiological stress procedure, without providing further details in order to prevent possible anticipation effects. On the test day, participants arrived 2 h prior to the first cortisol assessment took place and over 2 h before the cognitive tasks were administered. All participants were previously instructed to minimize physical exercise during the hour preceding the experiment and to avoid large meals, coffee, drinks with low pH or cigarettes, because these variables can affect cortisol levels. After participants provided informed consent, all participants were administered a semi-structured diagnostic interview, to screen for DSM-IV axis I disorders ([32]assessed using the MINI: Mini-International Neuropsychiatric Interview.[33,34] No later then 30 min after arrival, participants had a light lunch (sandwiches and soft drinks). Half an hour later the DSM-IV screening was continued (if necessary), subsequently the SCL-90-R was administered. At 1.15 pm the first cortisol assessment took place (−75 min with reference to the onset of the stressor see Fig. 1), followed by a 15 min relaxation period prior to the second cortisol assessment (−60 min). Directly following the second assessment, a cognitive task was administered of which the details will be published elsewhere,[35] followed by the third cortisol assessment (−40 min). The AA task was administered following the third and prior to the fourth assessment – see also Fig. 1. After the fifth cortisol assessment (0 min), the CPT was introduced and administered. The second administration of the AA task followed the seventh cortisol assessment (+35 min). The protocol was conducted in accordance with the declaration of Helsinki and was approved by the Medical Ethical Committee of the Leiden University Medical Centre (LUMC). All participants received financial compensation for participating in the experiment.

2.4. Statistical analyses

Reaction time (RT) outliers were filtered with a <150 and >1000-ms cut-off. For each participant, the median of the remaining RTs (99%) for the correct responses was calculated per cell (defined by Condition [baseline, post-CPT], Valence [angry, happy], and Movement [approach, avoidance]). Group differences in approach-avoidance tendencies to angry faces on the AA task were analyzed[11] using repeated measures analyses of variance (ANOVA-rm) with Arm movement (approach, avoidance) and Phase (baseline, post-CPT) as within-subjects factors and Group (PNES, HCs) as between-subject factor. Subsequent planned comparisons (post hoc Least Significant Difference, LSD contrasts) were calculated to detail differences further. Effect sizes of significant results are reported with the Partial Eta Squared (η^2). In case of significant group effects in social threat avoidance behavior, we tested whether the effects were due to medication by reanalyzing data excluding patients who were on psychotropic medication. To investigate specificity of possible group findings, we statistically controlled for anxiety and depressive symptoms by subsequently adding SCL-90-R anxiety and depression subscale scores as covariates in the analysis. To assess correlations between approach-avoidance tendencies for angry faces and cortisol, we performed Pearson correlation coefficient between individual AA congruency-effects for angry faces (RT incongruent angry face trials – RT congruent angry face trials) and pre-AA task cortisol levels. All analyses were tested two-tailed (α = .05).

3. Results

3.1. Participants

Participants were 12 patients (mean age 36.8 (SD 12.9) years; 8 female) and 20 HCs (mean age 31.9 (SD 12.7) years; 15 female).[e] Demographic data, menstrual cycle, use of contraceptives, use of psychotropic medication, smoking status, and seizure characteristics are provided in Table 1. Eleven patients had been or were being treated according to the psychological treatment program described in.[40] The last patient received psychiatric treatment in his home region. Patients and HCs did not differ significantly with respect to age, gender, education, use of contraceptives, menstrual cycle and smoking status (see Table 1). As expected, more patients used psychotropic medication and had higher scores than HCs on both the anxiety and depression subscales of SCL-90-R (see Table 1 for further details).

3.2. Manipulation check: cortisol response

A two-way ANOVA-rm for the salivary cortisol levels with Time (9 assessment points) as within-subjects factor and Group (patients, HCs) as between-subjects factor showed main effects for Time ($F(8,22)$ = 7.94, $p < .001$, η^2 = .743) and Group ($F(1,29)$ = 16.02, $p < .001$, η^2 = .356). There was no significant Time × Group interaction ($F(8,22)$ = .75, p = .649). As shown in Fig. 1, the patient group had elevated cortisol levels compared with HCs throughout the experiment. In addition, for both groups, the pre-task cortisol levels were significantly lower in the baseline condition (assessment 3) than after stress-induction (assessment 7 ($F(1,29)$ = 6.50, $p < .016$, η^2 = .183)), indicating that stress-induction using the CPT was successful for both groups. Thus, although patients with PNES showed increased cortisol levels at
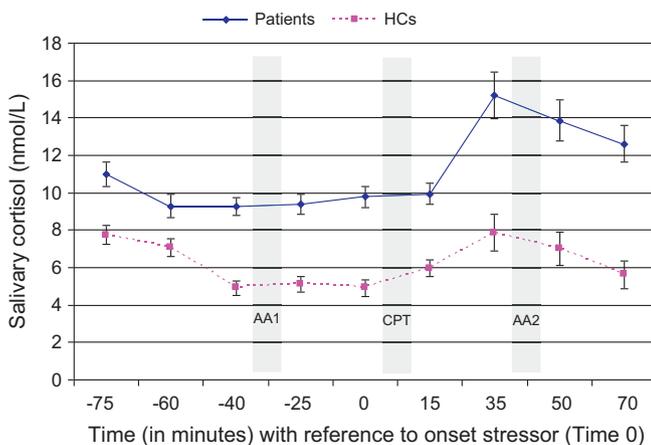
Fig. 1. Cortisol levels (±SE) for 12 patients and 20 HCs for the 9 physiological assessment points. *Notes*: AA1 = first administration AA task; AA2 = second administration AA task; CPT = Cold Pressor Test.

Table 1
Demographic variables and group characteristics for patients with PNES and HCs.

Variable	Patients (N = 12)	Controls[a] (N = 20)	Statistics
Mean age (SD) [years]	36.8 (12.9)	31.9 (12.7)	$F(1,30) = 1.12$, $p = .299$
Gender (*n*: male/female)	4M/8F	5M/15F	$\chi^2(1) = .26$, $p = .612$
Women (*n*: yes/no)			
Using contraceptives	5Y/3N	6Y/9N	$\chi^2(2) = .54$, $p = .762$
Follicular phase[b]	3Y/5N	6Y/9N	$\chi^2(2) = .23$, $p = .988$
Smokers (*n*: yes/no)	8Y/4N	7Y/13N	$\chi^2(1) = 3.02$, $p = .082$
Mean score (SD) SCL-90 depression	37.4 (19.1)	19.4 (4.08)	$F(1,30) = 16.93$, $p < .001$[**]
Mean score (SD) SCL-90 anxiety	23.3 (11.9)	11.9 (2.03)	$F(1,30) = 17.93$, $p < .001$[**]
Seizure characteristics			
Mean age (SD) at onset [years]	33.1 (13.0)	–	
Mean disease duration (SD) [years]	3.8 (3.0)	–	
Mean frequency per 4 weeks (SD)	10 (19.1)	–	
Medication (*n*)[c]			
Current psychotropic medication	4	–	
SSRI	4		
Benzodiazepine	2		
Current AEDs	0	–	
Previous AEDs	5	–	
Levetiracetam	2		
Carbamazepine	4		
Valproate	2		
Current DSM IV-axis I disorders (*n*)[d]	10	–	
Mood disorder	3		
Anxiety disorder			
Agoraphobia	5		
Panic disorder	2		
General anxiety disorder	2		
Post traumatic stress disorder	4		
Obsessive compulsive disorder	1		
Somatoform disorder			
Chronic pain	1		

[a] The majority of saliva samples for 1 HC did not contain sufficient saliva for cortisol analysis.
[b] Menstruation cycle was indeterminable in 1 patient and 2 control participants.
[c] Because some patients used more than 1 AED or psychotropic medication, the sum of *n* exceeds the total *n*.
[d] Because patients often met more than 1 DSM IV axis I criteria, the sum of *n* exceeds the total *n*.
[**] $p < .001$.

baseline, stress-induction led to comparable increases in cortisol levels in each group

3.3. Approach-avoidance (AA) task

3.3.1. RTs angry faces

An ANOVA-rm for the RTs for angry faces with Phase (baseline, post-CPT) and Arm movement (approach, avoidance) as within-subject factor and Group (PNES, HCs) as between-subject factor showed no main effects for Group ($F(1,30) = 1.32$, $p = .260$), Arm movement ($F(1,30) = .01$, $p = .915$) and Phase ($F(1,30) = .02$, $p = .881$). There was a non-significant trend towards a Group × Arm movement interaction ($F(1,30) = 3.97$, $p = .056$). Most importantly, there was a Phase × Group × Arm movement interaction ($F(1,30) = 6.84$, $p = .014$, $\eta^2 = .186$). Post hoc *F*-tests for each Phase separately indicated that the Group × Arm movement interaction was significant at baseline ($F(1,30) = 8.13$, $p = .008$, $\eta^2 = .213$) but not following stress ($F(1,30) = .00$, $p = .984$). This significant effect at baseline remained significant when both SCL-90-R anxiety and depressive symptoms subscale scores were entered as covariates into the analysis Group × Arm movement ($F(1,28) = 6.73$, $p = .015$, $\eta^2 = .194$), suggesting that this effect was not related to group differences in anxiety and depressive symptoms. This Group × Arm movement interaction also remained significant at baseline ($F(1,26) = 13.40$, $p = .001$, $\eta^2 = .340$) when four patients who used psychotropic medication were excluded from this analysis, demonstrating that this effect could not be explained by medication use. Interestingly, as can be seen in Fig. 2, only the patients displayed a significant effect for Arm movement at baseline ($F(1,11) = 5.10$, $p = .045$, $\eta^2 = .317$).

Patients were slower in affect-incongruent (angry-approach) trials than in affect-congruent (angry-avoid) trials. HCs did not show such an effect for Arm movement ($F(1,19) = .72$, $p = .408$). Additionally, at baseline, patients responded significantly slower than HCs to the affect-incongruent (angry-approach) trials
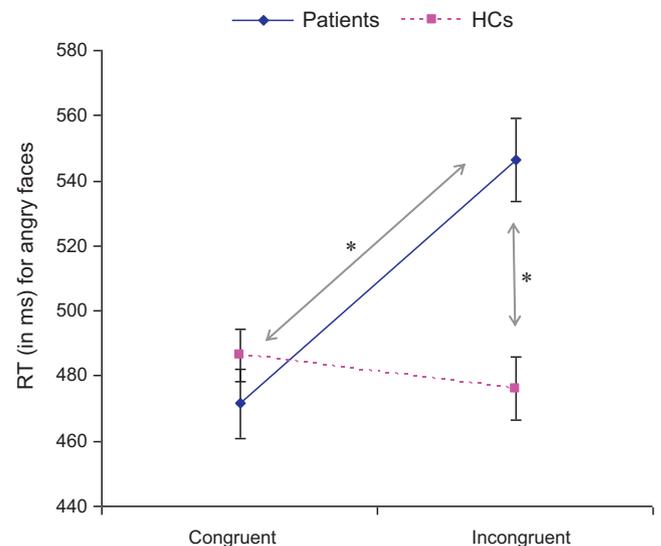
Fig. 2. RTs (±SE) for congruent and incongruent angry face trials for 12 patients and 20 HCs on the Approach-Avoidance (AA) task. Patients show increased AA congruency-effects for angry face responses with a relative slowing to approach compared to avoid angry face stimuli. *Note*: *$p < .05$.

Table 2
Overview of RTs (±SE) and % error rates separately for group, phase, arm movement and emotion.

Group	Phase	Arm movement	Emotion	RT	% Error
Patients (n = 12)	Baseline	Congruent	Happy	457.54 (21.59)	13.3
			Angry	471.46 (20.94)	15.0
		Incongruent	Happy	518.58 (27.04)	12.5
			Angry	546.54 (25.59)	8.3
	CPT	Congruent	Happy	500.29 (25.19)	5.0
			Angry	525.46 (26.09)	5.8
		Incongruent	Happy	512.63 (26.36)	10.8
			Angry	495.08 (27.96)	4.2
HCs (n = 20)	Baseline	Congruent	Happy	458.20 (16.73)	5.0
			Angry	486.40 (16.22)	11.5
		Incongruent	Happy	475.63 (20.94)	9.5
			Angry	476.18 (19.82)	7.5
	CPT	Congruent	Happy	465.65 (19.51)	9.5
			Angry	491.58 (20.21)	12.0
		Incongruent	Happy	477.20 (20.42)	7.5
			Angry	461.68 (21.66)	9.5

($F(1,30) = 4.73$, $p = .038$, $\eta^2 = .136$) and this was not the case for the affect-congruent (angry-avoid) trials ($F(1,30) = .32$, $p = .577$).

3.3.2. RT happy faces and error rates

The same ANOVA-rm for happy faces resulted in no significant effects involving Group (all $p > .273$ – for a complete overview of RTs see Table 2). Similar analyses for the error rates resulted in no significant effects.

Thus, PNES patients showed increased approach-avoidance congruency-effects for angry faces on the AA task at baseline, with relatively slower approach of angry faces. This effect was no longer present after the CPT.

3.4. Threat avoidance and baseline cortisol

To test whether approach-avoidance tendencies for angry faces at baseline were overall correlated with the pre-task cortisol levels, we calculated a Pearson correlation coefficient between the individual RT congruency-effects for angry faces (RT incongruent angry faces – RT congruent angry faces) and pre-task cortisol levels (both at baseline) and found a positive correlation ($r = .38$, $p = .034$[f]). As expected, participants with high basal pre-task cortisol showed increased delays for the incongruent angry face trials relative to the congruent trials.

When each group was tested separately, the correlations did not reach significance [patients ($r = .23$, $p = .482$); HCs ($r = .00$, $p = .100$[g])].

4. Discussion

The aim of this study was to investigate avoidance behavior in patients with PNES. Specifically, we aimed to test suggestions from previous self-report studies suggesting that PNES is associated with increased threat avoidance tendencies. Secondly, we tested whether social avoidance behavior was increased after stress-induction and whether it was related to cortisol levels. Three relevant findings emerged from this study. First, patients with PNES showed increased avoidance tendencies to social threat cues on the AA task at baseline. Secondly, for both groups together, the angry face congruency-effect was related to baseline cortisol levels. Thirdly, stress-induction did not further increase but rather decreased the angry face congruency-effect in patients with PNES. Below we will detail these findings and discuss their implications.

The finding of a relative preference to avoid rather than approach angry faces in patients with PNES may be interpreted as being in line with previous findings from self-report studies of increased avoidant coping in patients with PNES.[3–5] The AA congruency-effect in patients with PNES was specific for angry faces, and did not occur for happy faces. Previous studies using approach-avoidance tasks showed increased avoidance tendencies to angry faces in anxious populations.[11,19,20] When we statistically controlled for anxiety the congruency-effect for angry face responses in patients with PNES remained significant, indicating that these findings cannot be fully attributed to the patients' self-reported anxiety levels. The angry face congruency-effect in patients with PNES could also not be explained by other patient characteristics such as increased depressive symptoms, and use of psychotropic medication. As a result it seems justified to conclude that the finding of a relative delay in threat approach behavior may be a specific marker associated with PNES. The relative preference to avoid rather than to approach angry face cues observed in patients in this experimental set-up was mainly attributed to a relative slowing when patients had to make an approaching arm-movement to angry faces compared both to HCs and to their own angry-avoid trials. These results indicate that the behavior of patients with PNES is not affected by angry faces when their behavior is in accordance with their instinctive avoidant action tendency. But when patients have to behave in a manner incongruent to their instinctive avoidant action tendency in response to social threat stimuli, i.e. approach, behavioral interference occurs. Such reaction time cost is generally observed when an automatic motor response (avoidance of angry face) needs to be inhibited in favor of the selection of a rule driven motor response conflicting with this automatic action tendency (approach angry faces[11]). Recent fMRI studies using this task have shown that the left ventrolateral prefrontal cortex (vlPFC) plays a crucial role and is significantly recruited during these affect-incongruent response conditions.[37,38] The fact that patients demonstrated altered approach-avoidance behavior in response to angry faces extends previous findings of an increased attentional bias for angry faces in patients with PNES,[14] now showing that angry faces not only draw more attention but also elicit relative inhibition of approach-related motor responses.

Previous investigations using self-report measures indicated that PNES patients report reliance on avoidance behavior particularly in stressful situations.[3–5] Based on these results, we expected patients to display even more pronounced threat avoidance behavior following stress-induction. Contrary to our expectations, however, no behavioral group differences were present following the CPT. These results are in line with previous experimental findings in patients with PNES in which the attentional vigilance for angry faces at baseline was no longer present after stress-induction.[14] A possible explanation for this normalization following stress-induction may be associated with the after-math effect of the stress-induction procedure. The CPT stress paradigm includes a social evaluative component and the investigator who is present during the CPT, is also present during the second administration of the AA task. This may have resulted in a decreased significance of the emotional value of the angry faces during the second administration of the AA task.

Previous investigations have shown that behavioral responses to (social) threat are related to cortisol levels.[10–13] In this study we confirmed these findings showing a positive association between pre-task baseline cortisol and the relative slowing in angry face approach behavior at baseline for both groups together. When testing this association within both groups separately, a comparable positive, but non-significant, relation was found in the patient

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[f] Repeating this analysis with the 3 basal pre-task cortisol measurements calculated with Area under the curve with respect to ground (AUCg; for more details,[36] formula 2), resulted in a comparable outcome ($r = .37$, $p = .040$).

[g] Repeating this analysis with the 3 basal pre-task cortisol measurements calculated with AUCg resulted in comparable outcomes [patients ($r = .29$, $p = .359$); HCs ($r = .12$, $p = .637$)].

group, which may become significant when tested in larger groups. We found no association between baseline cortisol and the angry face congruency-effect in the HCs.

Before discussing the implications of the current findings, some strengths and limitations of the present study should be considered. An important strength of this study is that all patients were diagnosed using the gold standard (see e.g.[39] for a review): an ictal video-EEG registration of a typical seizure in order to confirm the absence of epileptiform activity, making PNES diagnosis maximally reliable. Another strength of the present study, besides statistically controlling for patient characteristics such as depressive symptoms, anxiety and medication use, is that participating HCs were comparable to patients based on several relevant factors such as age, gender, menstrual cycle, use of contraceptives, smoking and educational level, minimizing the effect of random factors on the present results. The most obvious limitation of the present study is the relative small patient group size, and its associated limited statistical power. We therefore emphasize that the present results need to be interpreted with caution and surely need replication. Future studies could investigate the social threat approach-avoidance tendencies in patients with PNES using larger groups of patients to unravel further the specific effects of cortisol on their threat approach and avoidance tendencies. Furthermore, based on findings of Selkirk et al.[40] differentiating PNES patients reporting sexual abuse from PNES patients not reporting a sexual abuse history, it would be interesting for future studies to investigate the effect of sexual abuse on threat avoidance tendencies in patients with PNES. This is especially relevant since previous studies demonstrated that patients with PNES who report a sexual trauma, displayed increased attentional interference by angry faces and demonstrated elevated cortisol levels compared to PNES patients without a sexual trauma report.[8,14] The additional use of brain imaging techniques would provide an opportunity to investigate whether altered vlPFC activity is associated with increased difficulty to inhibit automatic threat avoidance tendencies in patients with PNES, or whether group differences in social threat avoidance behavior are rather associated with increased limbic activity associated with social threat processing, or both. Also, because patients with PNES report using increased avoidant coping strategies in stressful situations, it would be interesting to study threat avoidance behavior in patients with PNES using cortisol administration.[12] Cortisol administrations prevent possible attentional confounds induced by a real life stress induction, which may have been associated with a stress-induction protocol used in the present and an earlier study.[14] Finally, because avoidance behavior is considered as an important precipitating and perpetuating factor for PNES[1–3] adequate use of coping strategies and fear avoidance are focuses in most therapies used for PNES.[41,42] It may be worth investigating whether changes in patients' self-report coping strategies and avoidance behavior are confirmed by changes in automatic threat avoidance tendencies after successful treatment. In addition, it would be clinically highly relevant to investigate whether (changes in) threat approach and avoidance behavior could serve as a predictor for PNES prognosis.

5. Conclusion

The present results suggest increased social threat *avoidance behavior* in patients with PNES at baseline, which was overall associated with basal pre-task cortisol. Positive emotional stimuli did not affect behavioral approach-avoidance responses in patients with PNES and their behavioral threat avoidance responses normalized after stress-induction. Because PNES are considered as avoidant behavior to cope with threatening and stressful situations,[2,3] the objective registering of social threat avoidance behavior may prove to be a clinical valuable contribution to evaluate psychological treatment effectiveness and perhaps even the prognosis of PNES.

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