The effect of stress induction on working memory in patients with psychogenic nonepileptic seizures

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A B S T R A C T

Although psychogenic nonepileptic seizures (PNES) are considered a stress-induced paroxysmal disintegration of cognitive functions, it remains unknown whether stress indeed impairs cognitive integrative functions, such as working memory (WM), in patients with PNES. An N-back task with emotional distracters (angry, happy, and neutral faces) was administered at baseline and after stress induction (Cold Pressor Test) to 19 patients with PNES and 20 matched healthy controls. At baseline, patients displayed increased WM interference for the facial distracters. After stress induction, group differences generalized to the no-distracter condition. Within patients, high cortisol stress responses were associated with larger stress-induced WM impairments in the no-distracter condition. These findings demonstrate that patients’ cognitive integrative functions are impaired by social distracters and stress induction. Moreover, the stress- and cortisol-related generalization of the relative WM impairments offers a promising experimental model for the characteristic paroxysmal disintegration of attentional and mnemonic functions in patients with PNES associated with stress.

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1. Introduction

Psychogenic nonepileptic seizures (PNES) are paroxysmal, involuntary behavioral patterns that mimic epileptic events but lack ictal epileptiform activity in the brain and for which no organic cause can be identified. PNES are characterized by a sudden and time-limited alteration of consciousness and are associated with a disturbance in controlling cognitive, emotional, and/or behavioral functions [e.g., 1]. This paroxysmal disintegration of attentional and mnemonic functions is thought to be associated with stress factors [2,3; for reviews see 4,5]. Results of a few recent studies suggest that PNES are associated with increased stress sensitivity, as evidenced by increased cognitive threat vigilance [6] and increased activity of biological stress systems [6–9]. The ways in which threat and stress induction interfere with working memory (WM), a profound cognitive integrative function that may be relevant to this disorder, remain unclear. This study was therefore designed to test the effects of threat and stress induction on WM functions in patients with PNES.

We recently investigated attentional processing of masked threat stimuli in patients with PNES [6]. People with PNES have high interpersonal psychotrauma rates [for reviews see, e.g., 4,10,11], and so pictures of angry facial expressions are considered relevant threat stimuli for them. We administered an emotional Stroop task in which angry, happy, and neutral facial expressions were presented subliminally and backwardly masked. Compared with healthy control participants, patients with PNES displayed heightened interference for the masked angry faces specifically, indicating attentional hypervigilance for social threat cues at a preconscious level. Other studies showed increased activity of biological stress systems such as the hypothalamus–pituitary–adrenal (HPA) axis with cortisol as its end product. Increased cortisol levels in patients with PNES were reported not only following a seizure [8] but also temporally independent of seizure occurrence [9]. Patients with PNES also showed elevated cortisol levels associated with a delayed recovery of the HPA axis after dexamethasone administration in one study [7] but not in another [9]. Finally, we found indications of decreased heart rate variability in patients with PNES [6], also taken as an indication of hyperarousal and hypervigilance [12]. Together these findings are suggestive of increased cognitive and biological stress sensitivity in patients with PNES. These results may support the notion that, in circumstances of stress, patients with PNES show impairments in cognitive integrative functions [2,13], but such a relationship has not yet been tested directly.

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One of the most crucial integrative cognitive functions needed for almost every voluntary action is WM. WM is a limited-capacity system serving to maintain relevant information in short-term memory and to suppress irrelevant information [14]. On the basis of our previous research we hypothesized that social threat cues, such as angry facial expressions, as well as stress induction, may significantly interfere with WM performance in patients with PNES. Threat interference with WM performance can be reliably tested using an N-back task with emotional distractors [15]. This task requires participants to monitor sequences of letters in various cognitive loads and to ignore the distracter pictures. We used several social (emotional) distracter pictures (pictures of angry, happy, and neutral facial expressions) to test whether WM performance in patients with PNES would be more negatively affected by social threat distracter pictures compared with healthy controls (HCs). Second, because PNES are considered a paroxysmal disintegration of attentional and mnemonic functions associated with stress, we tested whether stress induction would result in a generalization of WM impairment to all distracter pictures in patients with PNES. The emotional WM task was therefore administered before and directly after stress induction. WM performance is particularly sensitive to cortisol [16–18], so we tested whether stress-induced cortisol was associated with the hypothesized generalization of WM impairment in patients with PNES. Stress was induced using the Cold Pressor Test (CPT). This physiological stress procedure consists of immersion of the nondominant hand in ice water and is known for its activating effect on both the sympathetic nervous system (SNS) and the HPA axis [19–22].

2. Methods

2.1. Participants

Patients with PNES who had been admitted to a tertiary epilepsy center were recruited by the attending neurologists. 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 ictal diminished or loss of adequate responsiveness, or postictal memory impairments of the ictal event), (3) the occurrence of at least two seizures in the year prior to the experiment, (4) no history of concomitant epileptic seizures, (5) no comorbid neurological disease diagnosis, (6) no diagnosis of endocrine disorder(s), and (7) 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. Emotional N-back task

Working memory performance was investigated at baseline and following the physiological stress induction by the counterbalanced administration of two different versions of the emotional N-back task (e-N-back task). The e-N-back task is a modified version (based on, e.g., [15]) of the N-back WM task described by Cohen et al. [23]. The original N-back task consisted of visually presenting a pseudorandom sequence of letters and asking participants to respond to a prespecified letter. It included memory conditions whereby the load on WM varies as a function of the number of letters skipped for a target match. The N-back adapted for the present study included three workload conditions: 0-back, 2-back, and 3-back. In the 0-back condition, participants monitored a sequence of letters for any occurrence of a single prespecified letter. In the 2-back and 3-back conditions, participants observed a sequence of letters and responded by pressing the “target” button when the current letter was identical to the letter presented 2 and 3 trials back, respectively. Participants were instructed to respond by pressing the nontarget button if the presented letter did not meet the “target” criterion. The target/nontarget buttons were counterbalanced for left/right between participants.

The e-N-back task consisted of superimposing the original N-back task onto one of four distractors (i.e., no picture and pictures of neutral, happy, and angry faces). Models were selected from the Karolinska Directed Emotional Faces stimulus set [24,25].

In this way, the task consisted of three workload conditions (0-, 2- and 3-back) and 4 distractor conditions (no distracter and neutral, happy, and angry faces), leading to a total of 12 randomly assigned conditions. Each condition contained one block of 16 trials. Each trial consisted of three subsequent components: first, the intertrial interval consisting of a black screen (500 ms); second, the presentation of the letter (e.g., ‘P’) superimposed on the distracter (500 ms); and third, an asterisk (*) superimposed on the distracter (2500 ms). Each block of 16 trials was preceded by 6 practice trials. Within each facial background block 16 different models displaying the same emotion were presented once and the same models were used for every facial background block. The male/female ratio was counterbalanced within each block.

Working memory performance was operationalized using error rates (errors of omission and errors of commission) and reaction times (RTs). It is inherent to the 3-back condition that the first 3 trials are nontarget trials. To keep the different workload conditions as comparable as possible, the first 3 trials for all 12 blocks contained nontarget trials that were excluded from analyses, leaving 6 nontarget and 7 target trials within each block and a total of 156 (72 nontarget and 84 target) trials in the e-N-back task.

2.2.2. Effort and compliance

WM performance is directly influenced by the amount of effort employed by the participants, so we determined participants’ efforts by administrating the Amsterdam Short-Term Memory test (Amsterdamse Korte Termijn Geheugen Taak, AKTG [26]). This relatively simple task requires participants to read five neutral words aloud and then perform a single distracting arithmetic task. Subsequently, five more words are given, three of which were previously presented. The participants are instructed to name the three words that were previously presented. The score is determined by the number of words named correctly. No points are awarded for the arithmetic tasks, as these serve as distracter items. When employing large amounts of effort, all participants without evident cognitive disorders should be able to complete this relatively simple task, with few errors, in approximately 10 minutes. An error rate of ≥5 indicates task underachievement [26]. As a result, participants with an AKTG score of ≥5 were excluded from subsequent analyses.

Furthermore, to ensure that potential group differences in WM performance were not due to poor effort or lack of compliance, response patterns during the WM task were analyzed to check for irregularities. Response patterns consisting of pressing both the target and nontarget buttons within one trial or pressing either the target or the nontarget button consistently within one block were considered signs of noncompliance.

2.2.3. Anxiety and depression

The Symptom Check List Revised (SCL-90-R) is a self-report questionnaire that evaluates a broad range of psychological problems and symptoms of psychopathology [27,28]. SCL-90-R consists of 90 items and each item inquires about recent physical and psychological complaints that can be scored on a 5-point scale ranging from 0 = not at all to 4 = very much. We administered the Anxiety and Depression subscales in the present study. The Anxiety subscale consists of 10 items and subsymes a set of symptoms usually associated clinically with high manifest anxiety (i.e., restlessness, nervousness, tension). The Depression subscale consists of 16 items and reflects a broad range of signs and symptoms of the clinical depressive syndromes (i.e., dysphoric affect, withdrawal of interest in life activities, loss of vital energy).

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2.2.4. Cold Pressor Test
After the baseline administration of the e-N-back task, participants were requested to immerse their nondominant hand up to the wrist in an ice-cold water bath (0–4 °C) for as long as possible up to a maximum of 3 minutes. This procedure was repeated three times at standardized but unpredictable intervals (1–4 minutes). The Cold Pressor Test (CPT) or plunge test is known to elicit a robust stress response and to activate the SNS and HPA axis simultaneously [19–22].

2.2.5. Physiological and subjective measures
To test the effectiveness of the stress induction, several physiological and subjective stress measures were registered. All physiological and subjective stress measures were obtained at nine assessment points over approximately a 145-minute period with five baseline assessment points prior to the stressor and four assessment points after the stressor. Because of the natural fluctuations of cortisol during the day, all assessments were performed at the same time of day between 1:15 and 4:00 PM.

2.2.5.1. Hypothalamus–pituitary–adrenal axis. Saliva samples for cortisol assessments were obtained using Salivette collection devices with a cotton roll (Sarstedt, Rommelsdorf, Germany). Saliva sampling (in contrast to blood sampling) is a stress-free noninvasive way to measure cortisol [29,30]. 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 immunoassay kit with high sensitivity (JBL, Hamburg, Germany). Inter- and intraassay coefficients of variation were below 10%.

2.2.5.2. Sympathetic nervous system. Systolic (SBP) and diastolic (DBP) blood pressures were measured in the nondominant arm using an automatic electronic digital blood pressure monitor, the Omron R5-I, initiated manually. This device met the validation criteria of international guidelines for both systolic and diastolic blood pressure (for more information, see [31]).

2.2.5.3. Subjective anxiety and pain. During saliva sampling, participants were asked to register their subjective experience of anxiety and pain on a visual analog scale (VAS, 0–100).

2.3. Procedure
All physiological and subjective stress measures were obtained at nine assessment points over approximately a 145-minute period, at respectively −75, −60, −40, −25, 0 (rest), +15, +35 (stress), +50, and +70 (recovery) minutes with reference to the start of the stressor. All assessments were performed between 1:15 and 4:00 PM. See also Fig. 1.

Candidate participants were invited for an initial session in which they were informed about the specifics of the experiment. With respect to the stress induction procedure, it was explained that stress would be induced by means of a physiological stress procedure, but no further details were provided, to prevent possible anticipation effects. On the test day, participants arrived 2 hours prior to the first physiological assessment and over 2 hours 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, low-pH drinks, and cigarettes, because these variables can affect cortisol levels. After participants had provided informed consent, they were each screened for DSM-IV axis I disorders [3] using a semistructured diagnostic interview (assessed using the MINI: Mini-International Neuropsychiatric Interview [32,33]). No later than 30 minutes after arrival, participants had a light lunch (sandwiches and soft drinks). Half an hour later, the DSM-IV screening was continued (if necessary), and then the SCL-90-R was administered. At 1:15 PM the first physiological assessment took place (−75 minutes with reference to the start of the stressor; see also Fig. 1), followed by a 15-minute relaxation period prior to the second physiological assessment (−60 minutes). Directly after the second physiological assessment, the e-N-back task was administered for the first time, followed by the third physiological assessment (−40 minutes). Two other cognitive tasks were administered, the details of which will be published elsewhere [34]. After the fifth physiological assessment (0 minutes), the CPT was administered. The sixth physiological assessment (+15 minutes) took place immediately following the CPT, and preceded the second administration of the e-N-back task, followed by the seventh physiological assessment (+35 minutes). The AKTG was administered at the end of the experiment when cortisol returned to baseline levels. For a schematic overview of the entire experiment, see Fig. 1.

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
Working memory performance was operationalized as the percentage errors of total given answers and reaction times (RTs). To normalize distributions, RTs were subjected to natural log transformation before analyses. Possible group differences in WM performance, physiological, and subjective stress measures were analyzed using repeated-measures analyses of variance (rm-ANOVAs), and subsequent planned comparisons (post hoc least significant difference [LSD] contrasts) were calculated to further detail differences. In case of significant group effects in WM, reanalysis without patients who were on psychotropic medication was performed. To investigate the specificity of possible group findings and to statistically control for the amount of variance explained by anxiety and depression, we subsequently added SCL-90-R Anxiety and Depression subscale scores as covariates in the WM analysis. Correlations between cortisol and WM scores were calculated using Spearman ρ correlations. All analyses were tested two-tailed (α = 0.05).

3. Results
3.1. Participants
3.1.1. Effort and compliance
Of the 25 patients with PNES and the 23 HCs who participated in the current study, 6 patients and 3 HCs were post hoc excluded from analyses. The first patient “failed” the effort test with an error rate exceeding 5, a score indicative of task underachievement. Five patients and two HCs were excluded from analysis based on the response pattern analysis of the e-N-back task: One patient and one HC pushed both the target and nontarget response buttons for the greater part of the trials, four patients and one HC pushed only one button (either target or nontarget) in two or

<table>
<thead>
<tr>
<th>Assessment</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td></td>
<td></td>
<td>N-back 1</td>
<td>Other1</td>
<td>Other2</td>
<td>CPT</td>
<td>N-back 2</td>
<td>Other1</td>
<td>Relax</td>
</tr>
<tr>
<td>Time in min</td>
<td>−75</td>
<td>−60</td>
<td>−40</td>
<td>−25</td>
<td>0</td>
<td>+15</td>
<td>+35</td>
<td>+50</td>
<td>+70</td>
</tr>
</tbody>
</table>

Fig. 1. Schematic overview of the experiment. Physiological and subjective stress measures were obtained at nine assessment points: −75, −60, −40, −25, 0 (rest), +15, +35 (stress), +50, and +70 minutes, respectively, with reference to the start of the stressor. CPT, Cold Pressor Test; AKTG, Amsterdamse Korte Termijn Geheugen Taak. 1Approach and Avoidance Task. 2Sternberg Task.
more conditions. One HC was excluded because the majority of the saliva samples did not contain sufficient saliva for cortisol analyses.

3.1.2. Demographics

The remaining 19 patients (15 females) had a mean age of 35.3 (SD = 11.4) years. Demographic data, menstrual cycle, use of contraceptives, use of psychotropic medication, smoking status, and seizure characteristics are provided in Table 1. The remaining 20 HCs (15 females) had a mean age of 31.2 (SD = 12.7) years. 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. Patients 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 checks: Stress induction

3.2.1. Cold Pressor Test duration

There were no group differences in the total mean time (in minutes) that participants kept their hand in the ice water [PNES 3.6 (SD = 3.2), HC 5.5 (SD = 3.5), F(1,37) = 2.70, P = 0.104].

3.2.2. Cortisol levels

A two-way rm-ANOVA for salivary cortisol levels with time (nine assessment points) as within-subject factor and group (patients, HCs) as between-subject factor showed a main effect for time [F(8,30) = 9.35, P < 0.001] and a nonsignificant trend for group [F(1,37) = 3.01, P = 0.091]. There was no significant time × group interaction [F(8,30) = 1.42, P = 0.230]. For both groups, cortisol levels were increased following the CPT (average cortisol level for assessments 6 and 7) compared with baseline (average cortisol level for assessments 1–5) [F(1,37) = 4.15, P < 0.049] (see Fig. 2).

3.2.3. Blood pressure

Separate two-way rm-ANOVAs for SBP and DBP with time as within-subject factor and group as between-subject factor showed main effects for time [SBP F(8,30) = 2.76, P = 0.020; DBP F(8,30) = 8.27, P < 0.001], but no significant effects involving group (all Ps ≥ 0.311). In both groups, blood pressure increased following the CPT (average BP level for assessments 6 and 7) compared with baseline (average BP level for assessments 1–5) [SBP F(1,37) = 6.11, P = 0.018; DBP F(1,37) = 5.48, P = 0.025].

3.2.4. Subjective anxiety and pain

Separate two-way rm-ANOVAs for subjective anxiety and pain with time as within-subject factor and group as between-subject factor showed main effects for time [anxiety F(8,30) = 2.89, P = 0.017; pain F(8,30) = 5.21, P < 0.001]. Again there were no significant effects involving group (all Ps ≥ 0.172). Both groups experienced more pain following the CPT (average pain level for assessments 6 and 7) compared with baseline (average pain level for assessments 1–5) [F(1,37) = 32.85, P < 0.001]. Neither group reported increased anxiety following the CPT compared with baseline [F(1,37) = 2.56, P = 0.118]. Together these findings indicate that physiological stress induction by the CPT was successful. A statistical trend towards a group difference was found only for cortisol; patients showed slightly higher cortisol levels throughout the experiment.

3.3. Emotional working memory performance

3.3.1. Error rates

To test possible group differences in error rates, we conducted a four-way rm-ANOVA with phase (baseline, stress), distracter (no distracter, neutral, happy, and angry faces), and workload (0-, 2-, and 3-back) as within-subject factors and group (patients, HCs) as between-subject factor. A significant main effect for group [F(1,37) = 6.96, P = 0.012] indicated that patients made overall more errors than HCs (see Fig. 3). Most crucially, there was a significant interaction for phase × distracter × group [F(3,35) = 3.58, P = 0.023]. Adding both SCL-90-R Anxiety and Depressive symptoms subscales as covariates into these analyses did not alter these effects [group F(1,35) = 6.96, P = 0.004; phase × distracter × group F(3,33) = 3.69, P = 0.021], suggesting that these effects were not related to group differences in anxiety and depressive symptoms. Fig. 3 illustrates group differences at baseline for the social distracter conditions and generalization of the group differences to the no-distracter condition following stress. This observation was supported by subsequent analyses. Post hoc F tests for each Distracter condition separately

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Table 1

Demographic and clinical characteristics for 19 patients with PNES and 20 healthy controls (HCs).  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (N=19)</th>
<th>HCs (N=20)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, years</td>
<td>35.3 (11.4)</td>
<td>31.2 (12.7)</td>
<td>F(1,37) = 1.14, ns</td>
</tr>
<tr>
<td>Number of women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>15</td>
<td>χ²(1) = .09, ns</td>
</tr>
<tr>
<td>Using contraceptives</td>
<td>8</td>
<td>5</td>
<td>χ²(2) = 1.29, ns</td>
</tr>
<tr>
<td>In follicular phase</td>
<td>3</td>
<td>6</td>
<td>χ²(2) = 1.22, ns</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td>χ²(1) = 3.31, ns</td>
</tr>
<tr>
<td>Primary/secondary</td>
<td>14</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Higher</td>
<td>5</td>
<td>11</td>
<td>χ²(1) = 0.62, ns</td>
</tr>
<tr>
<td>Smokers</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Taking psychotropic medication</td>
<td>5</td>
<td>0</td>
<td>χ²(1) = 6.04, *</td>
</tr>
<tr>
<td>Mean (SD) SCL-90-R score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>31.2 (13.80)</td>
<td>18.75 (3.73)</td>
<td>F(1,37) = 15.04, b</td>
</tr>
<tr>
<td>Anxiety</td>
<td>19.1 (8.10)</td>
<td>11.55 (1.79)</td>
<td>F(1,37) = 16.34, c</td>
</tr>
<tr>
<td>Mean (SD) seizure frequency</td>
<td>10.5 (22.46)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05.  
*a P < 0.001.  
*b One patient did not report seizure frequency.
patients displayed more WM interference than HCs for the facial distracter conditions but not for the no-distracter condition. Following stress induction, group differences in WM impairment generalized to all conditions including the no-distracter condition.

A four-way rm-ANOVA for RTs with phase (baseline, stress), distracter (no, neutral, happy, and angry faces), and workload (0-, 2-, 3-back) as within-subject factors and group (patients, HCs) as a between-subject factor was conducted. Main effects for group were present for both angry and neutral faces [F(1,37) = 8.05, P = 0.007, and F(1,37) = 8.04, P = 0.007, respectively] and a statistical trend in the same direction for happy faces [F(1,37) = 3.78, P = 0.060]. The phase×group interactions were not significant for any of the facial distracter conditions (all P ≥ 0.189). In line with these results, additional post hoc F tests indicated that the distracter×group interaction was significant only at baseline [F(3,35) = 3.02, P = 0.043], not following the CPT [F(3,35) = 1.69, P = 0.188]. At baseline, HCs did not display a main effect for distracter [F(3,17) = 0.60, P = 0.626], but patients did [F(3,16) = 6.72, P = 0.004]. Post hoc LSD analyses indicated that within the patient group at baseline, the no-distracter condition differed significantly from all facial distracter conditions (all Ps ≤ 0.003), whereas the facial distracter conditions did not differ mutually (all P ≥ 0.398). There were no other significant interactions for group present (all P > 0.323).

To summarize: at baseline, patients displayed more WM interference than HCs for the facial distracter conditions but not for the no-distracter condition. Following stress induction, group differences in WM impairment generalized to all conditions including the no-distracter condition.

3.3.2. Reaction times

A four-way rm-ANOVA for RTs with phase (baseline, stress), distracter (no, neutral, happy, and angry faces), and workload (0-, 2-, and 3-back) as within-subject factors and group (patients, HCs) as between-subject factor showed no significant (interaction) effects involving group (all P ≥ 0.100).

3.4. Error rates and cortisol levels

To investigate whether the stress-induced effect for the no-distracter condition was associated with stress-induced cortisol responses, we conducted a correlational analysis for the difference scores in WM (error rates following CPT – error rates baseline) and percentage cortisol stress response: [(cortisol + 20 minutes – cortisol 0 minutes)/cortisol 0 minutes] × 100. Results showed a significant positive effect for the patient group (Spearman’s ρ = 0.46, P = 0.046), but not for the HCs (ρ = 0.05, P = 0.818). This finding indicates that patients with high cortisol stress responses also had the most pronounced stress-induced WM declines for the no-distracter condition.

4. Discussion

The aim of this study was to test the effects of social threat and physiological stress induction on WM performance in patients with PNES. Three major findings emerged: First, the presence of social distracters resulted in an impairment of patients’ WM performance, both at baseline and after stress induction. Second, although patients’ general (no-distracter) WM performance was unimpaired at baseline, a significant group difference in this no-distracter condition emerged after stress induction. Whereas HCs improved after stress induction, the patients did not show such an improvement. Third, patients with high cortisol stress responses had larger stress-induced WM impairments in the no-distracter condition. Below we will detail these findings and discuss their implications.

As expected, the current results showed more WM interference by social (facial) threat stimuli in patients with PNES than in HCs. Interestingly and contrary to our expectations, this was not only the case for angry face distracters, but also for happy and neutral face distracters. Compared with HCs, patients made more errors on the e-N-back task when the “to be remembered” letters were positioned on distracting social background stimuli. RT analysis showed no significant group effects, making it unlikely that patients’ increased error rates are due to shorter response latencies. The results were also unrelated to group differences in anxiety and depressive symptoms. The present finding of increased interference of social distracters, irrespective of working load condition, may indicate that the social distracters are potent stimuli that affect cognitive performance in patients with PNES regardless of cognitive load. The current findings are in line with a recent fMRI study in patients with positive motor conversion symptoms, showing increased amygdala activity compared with HCs in response to viewing both positive and negative facial expressions using an incidental affective task [35]. They furthermore extend previous findings of increased cognitive interference by social threat stimuli in patients with PNES [6], although the
previous study indicated increased attentional interference specific for angry faces in patients with PNES. The latter discrepancy might be explained by several methodological differences; for example, in the Stroop study faces were presented subliminally and backwardly masked, whereas in the present study the faces were presented for 3 seconds. Also, the tasks differed in complexity. The Stroop task requires simple color naming of the masks that follow the subliminally presented faces, whereas the e-N-back task is a complex task consuming the limited resources of the WM system.

For patients with PNES, WM performance without distracters was unimpaired at baseline, suggesting that there is no general WM deficit on the N-back task in patients with PNES. The presence of any social distractor, however, caused sufficient interference to lead to significantly impaired WM function in the patient group. Interestingly, after stress induction the general WM functions of HCs improved, but such improvement did not occur in patients with PNES, resulting in a generalization of group differences in WM impairment; that is, patients made more errors on the whole compared with HCs, irrespective of whether a background distractor was presented or not. The improvement of general WM functions in HCs following (mild) stress induction is in line with previous studies reporting improved WM performance in HCs in a mild naturalistic stress context [36]. Also, Lupien et al. [16] demonstrated that mild doses of exogenous cortisol administration had beneficial effects on WM performance, similar to the improvement in WM performance in HCs following stress. However, with varying the levels of administered cortisol, Lupien et al. were able to demonstrate an inverted U-shaped curve for the effect of cortisol on WM performance, where relatively low as well as relatively high levels of exogenous cortisol appeared to have negative effects on WM performance [16]. On the basis of these results, it is not unlikely that our patients with PNES, with their slightly increased cortisol levels already at baseline, have not benefited from an additional cortisol boost due to stress induction, because they (unlike HCs) may have found themselves already on the downward slope of the inverted U-shaped curve.

Another interesting finding was that patients had slightly elevated cortisol levels throughout the experiment (P = 0.9) and that, in patients with PNES, higher cortisol stress responses were associated with larger stress-induced WM impairments in the no-distractor condition. These results resemble earlier findings of a positive association between pretask cortisol levels and impaired cognitive performance in patients with PNES [37], indicating that patients' cognitive impairments may, at least partly, be associated with increased activity neurobiological stress systems. The current finding of a statistical trend toward increased cortisol throughout the experiment in patients with PNES is in accordance with previous studies showing increased basal cortisol levels in PNES at [89].

4.1. Strengths and limitations

Before discussing the implications of the current findings, some strengths and limitations of the present study should be considered. All patients were diagnosed using the gold standard, ictal video/EEG registration of a typical seizure to confirm the absence of epileptiform activity, making PNES diagnosis maximally reliable [38]. Based on a recent discussion suggesting that poor neurological functioning in patients with PNES might be associated with poor effort during task performance [39–42], we thoroughly investigated indications of poor effort and compliance by administering a malingering task and WM task response pattern analyses. As a result we excluded six patients who did not pass our malingering test or who showed signs of poor compliance based on the response pattern analyses. We also excluded two HCs based on these criteria, illustrating the importance of studying effort and compliance in cognitive experiments in general. Another strength of the present study is that participating HCs were unimpaired at baseline, suggesting that there is no general WM deficit of the WM system.

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To summarize, this is the first study to demonstrate that, compared with that of HCs, WM performance in patients with PNES is impaired by social distracting stimuli. Not only threatening distracters, but also neutral and positive social distracters interfered with patients' WM performance. Stress induction resulted in a generalization of these group differences to the no-distractor condition. Interestingly, those patients who had the largest stress-induced cortisol responses also showed the largest stress-induced impairments in general (no-distractor) WM performance. Together, these findings indicate that patients with PNES have problems inhibiting irrelevant social-emotional stimuli. In addition, generalization of WM deficits following stress may mimic the paroxysmal disinhibition of attentional and mnemonic functions in patients with PNES associated with stress.

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