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Abstract

Current models explaining motor functional neurological disorders (FND) integrate both the neurobiological mechanisms underlying symptoms production and the role of psychosocial stressors. Imaging studies have suggested abnormal motor control linked to impaired emotional and stress regulation. However, little is known on the biological stress regulation in FND. Our aim was to study the biological and perceived response to stress in patients with motor FND.

Reference


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Biological and perceived stress in motor functional neurological disorders

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Background: Current models explaining motor functional neurological disorders (FND) integrate both the neurobiological mechanisms underlying symptoms production and the role of psychosocial stressors. Imaging studies have suggested abnormal motor control linked to impaired emotional and stress regulation. However, little is known on the biological stress regulation in FND. Our aim was to study the biological and perceived response to stress in patients with motor FND.

Methods: Sixteen patients with motor FND (DSM-5 criteria) and fifteen healthy controls underwent the Trier Social Stress Test. Hypothalamo-pituitary-adrenal axis (HPA) response was evaluated with salivary cortisol and autonomous sympathetic response with salivary alpha-amylase. Area under the curve was computed to reflect background levels (AUCg) and change over time (AUCi).

Results: FND patients had significantly higher background levels (AUCg) of both stress markers (cortisol and amylase) than controls. The biological response (AUCi) to stress did not differ between groups for both markers but the subjective response showed an interaction effect with patients reporting higher levels of stress than controls.

Conclusion: This study confirms a baseline HPA-axis and sympathetic hyperarousal state in motor FND related to life adversities. During a social stress, dissociation between perceived stress and biological markers was observed in patients only, reflecting a dysregulation of interoception capacity, which might represent an endophenotype of this disorder.

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- Conversion disorder
- Cortisol
- Amylase
- Stress
- Trier social stress test

ABSTRACT

1. Introduction

Motor functional neurological disorder (FND) – or conversion disorder (DSM-5, 2013) – is a disabling medical condition affecting a large number of young patients (Carson and Lehn, 2017), often with chronic disability (Gelaff et al., 2014) due to neurological symptoms, such as gait difficulties, tremor or weakness. FND represents the second commonest cause for a neurological consultation after headache (Stone et al., 2010). Over the last century, FND has traditionally been viewed as “psychogenic” with reference to a psychological cause in form of “conversion” of an intra-psycho conflict into physical symptoms (Kanaan, 2017). Although psychiatric stressors have long been considered as causal factors, experts have agreed recently that the onset and maintenance of the physical neurological deficit cannot always be linked to a causal psychological stressor (Stone et al., 2011), as reflected in the new DSM-5 classification (DSM-5, 2013). The dualism that the cause had to be either psychological or physical (a so-called “organic” neurological condition) has been resolved and FND is now considered a neuropsychiatric condition (Carson, 2014): it manifests with neurological symptoms that are linked to (and not caused by) psychological risk and/or maintaining factors (Hinon et al., 2006; Kroenke, 2007; Reuber et al., 2007; Hubschmid et al., 2015). Indeed, there is evidence from increased rates of childhood trauma (Roelofs et al., 2002; Sar et al., 2004) and life adversities (Roelofs et al., 2005) in motor FND, which may play a role as predisposing factors. The mechanism on how these psychological factors may predispose or maintain a neurological motor symptom is still unclear. Evidence from neuroimaging studies suggests that the limbic system dealing with
psychological stimuli (Voon et al., 2010; Aybek et al., 2015) or trauma (Aybek et al., 2014) (amygdala and hippocampus) is aberrantly functionally connected to regions responsible for the neurological symptom (supplementary motor area and right temporoparietal region). The hypothesis is that there is an emotional hyperarousal state in FND with increased amygdalar response to stimuli, even with positive valence (Voon et al., 2010), as well as a lack of habituation to negative stimuli (Aybek et al., 2015). Little is known on this hyperarousal state and in particular few studies looked at biological markers of hyperarousal such as stress biological parameters in motor FND. We thus hypothesized that this hyperarousal state will be reflected in abnormal biological measures of the stress systems.

The stress response is mediated by two main pathways: the rapid autonomous sympathetic response with epinephrine/norepinephrine secretion and the slower hypothalamic-pituitary-adrenal axis (HPA) response with cortisol secretion. Both can be non-invasively investigated by measuring salivary amylase (a protein secreted by the parotid glands during sympathetic stimulation) (Rohleder et al., 2004; Nater et al., 2005) and salivary cortisol (reliably reflecting HPA activation) (Hellhammer et al., 2009). A recent study looked at morning awakening cortisol levels in 33 patients with motor FND, which were found similar to levels in healthy controls (Maurer et al., 2015) but no studies looked at amylase levels in motor FND and no studies specifically tested the biological response to stress. A robust way to probe for stress response is to expose participants to a social stressor, like a job interview setting, and monitor the increase of salivary stress parameters (cortisol and amylase) (Birker, 2011). We chose the Trier Social Stress Test (TSST) as the most reliable and validated protocol to induce such stress, paralleled by a robust cortisol and amylase release (Kirschbaum et al., 1993b).

The aim of our study was to explore 1) the sympathetic and HPA axis biological functions and 2) perceived stress levels in response to a social stress (TSST) and in relation to life stressors (background hyperarousal) in patients with motor FND compared to healthy controls.

2. Methods & materials

2.1. Participants

Sixteen patients with motor FND were recruited from the Neurology Department of Geneva University Hospital. The diagnosis was established according to DSM-5 criteria of Conversion Disorder (Functional Neurological Symptom) code F44.4 and a board-certified neurologist confirmed the presence of positive functional features (DSM criteria B).

Details of the clinical presentation are presented in Table 1.

Fifteen age and gender-matched healthy controls (HC) were recruited through announcements. Exclusion criteria for both groups were: self-report of 1) a neurological condition (past or present), 2) a current psychiatric condition such as psychotic disorder, substance abuse or depression with acute suicidality, 3) insufficient knowledge of French. Patients suffering from comorbidities such as anxiety or depression (without suicidality) were included. All participants provided written informed consent (Swiss Ethics approved protocol CER14-008).

Upon arrival to the laboratory, participants were asked if they had smoked marijuana, coca or other amphetamine substances, chewing gum and any intense physical activity in the hour preceding the session. The participants were immediately centrifuged (10 min at 3000 rpm) and saliva was then subjected to cortisol and amylase release (Kirschbaum et al., 1993b).

The aim of our study was to explore 1) the sympathetic and HPA axis biological functions and 2) perceived stress levels in response to a social stress (TSST) and in relation to life stressors (background hyperarousal) in patients with motor FND compared to healthy controls.

2.2. Stress induction

Participants were instructed to prepare and present a video and audio-recorded job interview speech in front of two unknown examiners for 5 min according the TSST protocol (Kirschbaum et al., 1993a). Then they performed a 5-min calculation task (*count from 2023 to 0 while subtracting 17 each time*). Both examiner 1 leading the interview (VM) and examiner 2 (GP or JW) refrained from providing emotional or supporting feedback (such as smile or nodding). This is important to induce an uncertainty component and reliably increase cortisol (Abelson et al., 2014).

2.3. Saliva samples collection

Nine saliva samples were collected (as shown in Figs. 1–3) by chewing a cotton-swab during 1 min (Sarstedt-Salivette®). Samples were immediately centrifuged (10 min at 3000 rpm) and saliva was frozen (−20 °C). All experimental sessions took place from 1:30 pm to 4:30 pm. Participants were instructed to refrain from heavy meals, coffee, coke or other fizzy soft drinks, chewing gum and any intense physical activity in the hour preceding the session.

2.4. Perceived stress response

In parallel of saliva sampling, participants filled in a self-report evaluation of stress using a visual analogue scale (VAS: 0 = no stress to 10 = very high stress).

2.5. Mood and Trauma

Mood was assessed with the BDI depression scale (Beck et al., 1961) and STAI anxiety state and trait scales (Laux, 1981). Life events that occurred within the previous five years were recorded with the Amiel-Lebigre questionnaire (Amiel-Lebigre, 1985). The sum of negative (e.g. “Suicide in close family”) and change of life situation events (e.g. “Arrival of a new member of the family in your house”) were computed when conducting correlations with neurological markers. The Amiel-Lebigre questionnaire provides a subjective rating of each life events on a 0–100 scale (0 = no impact on my life, 100 = major impact on my life).

Childhood trauma was assessed across 5 domains (sexual, physical and emotional abuses, physical and emotional neglect) with the Childhood trauma questionnaire (CTQ) (Bernstein and Fink, 1998). As cortisol stress response following a social stressor is known to be dampened in sexually abused subjects (Schalinski et al., 2015), we repeated the analysis for subgroups of sexually abused (n = 8) or non-abused (n = 8) defined by a cut-off > 5 in the sexual abuse subscore.

### Table 1
Demographical and Clinical Data.

<table>
<thead>
<tr>
<th></th>
<th>FND patients (N = 16)</th>
<th>Healthy Controls (N = 15)</th>
<th>P value (T test, Fisher test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46 ± 15</td>
<td>39 ± 13</td>
<td>*ns</td>
</tr>
<tr>
<td>Gender</td>
<td>14F:2M</td>
<td>12F:3M</td>
<td>*ns</td>
</tr>
<tr>
<td>Cycle/Menopause</td>
<td>5:9</td>
<td>6:6</td>
<td>*ns</td>
</tr>
<tr>
<td>Medication</td>
<td>7 none:5BZD, 3AD, 1AE</td>
<td>14none:1AD</td>
<td>*p &lt; 0.01</td>
</tr>
<tr>
<td>BDI</td>
<td>8 ± 5.5</td>
<td>3.5 ± 4.6</td>
<td>*p &lt; 0.05</td>
</tr>
<tr>
<td>STAI Trait</td>
<td>41.1 ± 12.1</td>
<td>37.9 ± 9.0</td>
<td>*ns</td>
</tr>
<tr>
<td>STAI State</td>
<td>36.9 ± 10.1</td>
<td>33.7 ± 8.8</td>
<td>*ns</td>
</tr>
<tr>
<td>CGI</td>
<td>3 none</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Symptoms duration (months)</td>
<td>33.1 ± 4.0</td>
<td>39.7 ± 0.6</td>
<td>*p &lt; 0.01</td>
</tr>
<tr>
<td>Symptoms type</td>
<td>6 weakness</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Cycle/Menopause</td>
<td>53:1</td>
<td>53:1</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>1 none:1BZD, 2AD, 4AE</td>
<td>11none:1BZD</td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>10 ± 4</td>
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<tr>
<td>STAI Trait</td>
<td>41.1 ± 12.1</td>
<td>37.9 ± 9.0</td>
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<td>STAI State</td>
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<td>*p &lt; 0.01</td>
</tr>
<tr>
<td>Symptoms type</td>
<td>6 weakness</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

BZD: benzodiazepines, AD: antidepressant, AE: antiepileptic, NA: not applicable, ns: non-significant, BDI: Beck Depression Inventory, STAI: Anxiety Score, CGI: Clinical Global Impression Score
2.6. Duration and severity of FND and medication

Duration was calculated from onset of main symptom to date of inclusion (months). Severity was assessed with the Clinical Global Impression (CGI) score (0 = no neurological impairment, 1 = minimal, 2 = moderate, 3 = severe, 4 = very severe) and the continuous score of the “Mobility subscale” of the Neuro-Qol (Quality of Life in Neurological Disorders) (Cella et al., 2012), which evaluates the impact of physical impairment of individuals living with neurological conditions, rating mobility difficulties in daily life activities with a maximum score of 40 (full mobility). Use of CNS-acting medication such as benzodiazepine, antidepressant, antiepileptic and neuroleptic was recorded.

2.7. Saliva samples analysis

After thawing, samples were centrifuged again and 100 μl saliva aliquots were collected. Cortisol concentration was measured directly (without extraction) on a cobas c-501 analyzer (Roche) by an electrochemiluminescent immunoassay (ECLIA). The analytical detection limit of the cortisol assay was 0.5 nmol/l and inter-assay imprecision at 8.0 nmol/l was 11.5% (coefficient of variation, CV), while intra-assay CV was < 6.0% at the same concentration.

Amylase activity was determined in diluted saliva samples (1:1000) on a cobas c-501 analyzer, using a synthetic oligosaccharide as substrate and measuring the production of p-nitrophenol with a colorimetric method (increase of absorbance). The analytical lower limit of the assay was 3 U/L and inter-assay imprecision 1.1% (CV) at 168 U/L and 1.7% at 52 U/L, while intra-assay CV were < 1.0% for the same activities. The analytical procedures were accredited according to international ISO-15189 norms.

2.8. Statistics

Analyses were performed with R software. For repeated measures analysis, a linear mixed model (lmer) was used, with fixed effects of factors group and time and random effects of the factor subject in order to account for individual differences. To correct for potential confounding effects of mood and menstrual cycle, these variables (BDI, STAI-T, cycle) were added as covariates of no interest in the model. For

Fig. 1. Objective and Perceived Stress.
Stress induction (TSST) occurs at time 0 and lasts 20 min. AUCg: area under the curve with respect to ground. AUCi: area under the curve with respect to increase. Panel A: HPA axis Stress as measured with salivary cortisol showing a main effect of time and a main effect of group (higher AUCg in patients) but no interaction. Panel B: Autonomous Stress as measured with salivary alpha-amylase showing a main effect of time and a main effect of group (higher AUCg in patients) but no interaction. Panel C: Perceived Stress as measured with the 0–10 Visual Analog Scale showing a significant main effect of time across group and a time*group interaction with increased perceived stress in patients after the TSST as compared to before (higher AUCi in patients).
correlation analyses, a Pearson coefficient was calculated ($r$) and $p$ values were estimated using a regression with a $p$ value threshold significance at $p < 0.05$.

2.9. AUC calculations

In order to account for the two different effects in our repeated measures study, namely the background hormonal levels and the change over time after stress, we used area under the curve (AUC) calculations that have shown to be robust in psychoendocrinology (Pruessner et al., 2003). These two formulae resulted in two variables indicating a) the total amount of hormone released (AUCg) and b) the time-dependent changes of hormonal release during and after the social stress (AUCi).

3. Results

Demographic data of the two populations are presented in Table 1. Patients and controls were comparable in terms of gender, age, time of menstrual cycle, state and trait anxiety. FND patients had higher depression scores than controls ($p < 0.05$).

3.1. Objective biomarkers (cortisol and amylase)

Both objective stress biomarkers – cortisol and amylase- showed a significant main effect of group (cortisol $F(1,29) = 4.9$, $p < 0.05$, amylase $F(1,30) = 8.95$, $p < 0.01$) with higher levels in patients (Fig. 1). The TSST introduced a statistically significant increase in both biomarkers (main effect of time $F(8,232) = 8.01$; amylase: $F(8,240) = 7.55$, $p < 0.001$ for both), albeit groups did not react differentially (interaction group*time $p > 0.05$). The main effect of group was reflected in a significant difference between groups in the AUCg values with strong effect sizes for both biomarkers (Cortisol effect size 0.83: FND $1776 \pm 696$ nmol/l, Controls $1297 \pm 438$ nmol/l, $p < 0.05$, $t = 2.27$, df = 29, Amylase effect size 0.92 U/l: FND $79'822'500 \pm 53'803'345$ U/l, Controls $42'309'33 \pm 20'343'461$ U/l, $p < 0.05$, $t = 2.66$, df = 30).

Reflecting the absent group x time interaction, we found no statistical differences when calculating changes of concentration in respect of time (AUCi) between both groups.

3.2. Life events

Recent (5-years) life events were analyzed by number and subjective impact for events related to change or negative events (Fig. 2). A two—way ANOVA showed no significant differences between groups for either type of events. We thus merged both types of events for further analysis.

The total number (mean number ± standard deviation: FND $13.6 \pm 9.2$, Controls $15.1 \pm 10.6$) or the subjective total impact of the events (FND: $713 \pm 602$, Controls: $713 \pm 602$) did not differ between groups either. However, the total number of events significantly correlated with baseline cortisol (AUCg) in patients, but not in controls (FND: $r = 0.67$, $p = 0.01$, Controls: $r = -0.09$, $p > 0.05$) as did the total impact of events (FND: $r = 0.6$, $p < 0.05$, Controls: $r = -0.03$, $p > 0.05$). Amylase values (AUCg) did not correlate
(p > 0.05) with total life events impact (r = 0.33) or number (r = 0.24) in patients nor in controls (impact r = 0.33, number r = 0.27). Note that both types of events, even when analyzed separately, showed the same pattern of correlations.

3.3. Childhood trauma

FND patients reported more childhood sexual abuse (9.4 ± 5.6 vs. Controls: 5.8 ± 2.1, p < 0.05, effect size 0.85, t = 2.33, df = 29) but no other trauma (Fig. 3). Half of FND patients (50%) had a sexual abuse subscore of > 5, indicating some degree of abuse, whereas only 3 healthy controls had a similar score (20%). When we separated FND patients in sexually abused (N = 8) and non-sexually abused subgroups (N = 8), the curves revealed a blunted response for both cortisol and amylase in abused patients as compared to non-sexually abused healthy controls. Pre-stress values were comparable to non-abused FND patients but lower levels were found after stress (T-test statistics are represented on Fig. 3, we did not conduct between groups ANOVAs due to small sample of subgroups − only 3 abuses controls).

3.4. Perceived stress

Reported stress values (VAS) showed a main effect of time (p < 0.001) across groups, reflecting increase subjective stress after the social stress task (Fig. 1, Panel A). No main effect of group was observed but a significant interaction group*time (p < 0.05) showing a higher subjective stress response in patients. Respectively, AUC values of subjective stress were not different between groups using the AUCg measurement, but differed significantly when calculated in respect of time (AUCI: FND 196 ± 180, Controls 83 ± 174, p < 0.05, effect size 0.65). In both groups, no correlations between VAS scores and biological values were found at rest (samples before TSST). After stress, a positive correlation was found in healthy controls, but not in FND patients, between VAS and cortisol values (at 20 min:FND r = −0.13, p > 0.05; Controls r = 0.60, p < 0.05 and 30 min:FND r = −0.17, p > 0.05; Controls r = 0.56, p < 0.05) and VAS and amylase values (at 20 min: FND r = 0.13, p > 0.05; Controls r = 0.66, p < 0.001) (this correlation is illustrated in Fig. 4).

3.5. Duration and severity of motor symptoms and medication

Duration and severity of the disorder (Mobility NeuroQoL) did not correlate (p > 0.05 for all Pearson correlations) with objective biomarkers or subjective stress (AUCg: dur ~ cort, r = 0.45, dur ~ sAA, r = −0.08, dur ~ VAS, r = −0.14; sev ~ cort, r = −0.22, sev ~ sAA, r = −0.45, sev ~ VAS, r = 0.02). No differences were found between patients under medication (9 subjects) and those without medication (7 subjects) for cortisol (AUCg: Med 1963 ± 690, NoMed 1674 ± 784, p = 0.45, AUCI: Med 180 ± 264, NoMed 345 ± 248, p = 0.29), amylase (AUCg: Med 90392.5 ± 61979, NoMed 66232.5 ± 41618, p = 0.39, AUCI: Med −4127.5 ± 58436, NoMed −286 ± 18152, p = 0.87) and VAS scores (AUCg: Med 334 ± 203, NoMed 366 ± 76, p = 0.72, AUCI: Med 217 ± 181, NoMed 167.5 ± 192, p = 0.63).

4. Discussion

4.1. Background biological markers of stress

This study showed that patients suffering from motor FND have significantly higher levels of salivary cortisol (marker of the HPA axis stress system) and amylase (marker of sympathetic autonomous stress system) than matched healthy controls. These results seem to differ
from recent findings (Maurer et al., 2015) of equivalent diurnal cortisol levels in 33 patients with motor FND and 33 healthy controls. In the latter study cortisol levels were examined at bedtime and the following morning upon spontaneous awakening, 30 min later, at noon and at 3 pm during a two-day hospitalization stay. In our study, subjects were tested in the afternoon during a single visit in the laboratory between 1.30 pm and 4.30 pm. The only comparable time point is the 3 pm measure from Maurer et al., which shows higher values in FND patients as represented graphically with log values. As raw data are not provided no direct statistical can however be done between our studies. These two studies seem to suggest that awakening cortisol might be similar to controls in FND but is heightened in the afternoon. In line with our findings, heightened cortisol only in the afternoon have been reported in patients suffering from non-epileptic seizure (NES) (Tunca et al., 2000; Bakvis et al., 2010a) another form of conversion disorder.

A study in 12 NES patients (Bakvis et al., 2011) and 20 healthy controls, with a design comparable to ours, collected salivary cortisol between 1.15 pm and 4 pm — before and after physical stress induction (Cold pressure test) — and found significantly higher background levels in patients. Taking the circadian cortisol rhythm into account, it is thus possible that cortisol levels in FND remain high during afternoon hours and do not follow the same diurnal variation as in healthy subjects. In order to confirm this hypothesis further research examining the diurnal cortisol slope specifically in patients with motor FND is needed.

To our knowledge, data on amylase have never been collected in motor FND. Our results of increased autonomous sympathetic nervous system activity in motor FND is in line with increased mean heart rate (reflecting sympathetic arousal) found in children and adolescent suffering from FND (motor and NES) (Kozlowska et al., 2015). Furthermore, a recent study found decreased vagal tone in motor FND by measuring indexes of heart rate variability (RMSSD: Root mean squared successive differences of interbeat intervals) reflecting parasympathetic tone (Maurer et al., 2016). Altogether, this suggest imbalance between sympathetic and parasympathetic tone in motor FND.

In the NES literature, only one study looked at amylase and found comparable levels between patients and healthy controls (Bakvis et al., 2010a). On the other hand, heart rate variability indexes (CSI: cardio-sympathetic index) values reflecting increased sympathetic tone have been found in NES patients (Ponnusamy et al., 2011) compared to healthy controls (but no difference with epileptic patients). Just like in motor FND (Maurer et al., 2016), lower vagal tone (RMSSD) was found in NES patients compared to controls (Bakvis et al., 2009a; Ponnusamy et al., 2011) suggesting decreased emotion regulation (Beauchaine, 2015) and increased emotional reactivity, factors that may affect the stress response. Indeed, as demonstrated in children with FND (motor and NES), low baseline vagal tone was related to impaired autonomous regulation (lower heart rate increase than healthy controls) following stressful cognitive tasks, reflecting stress vulnerability (Kozlowska et al., 2015).

Our data, together with findings from studies in NES patients, suggest that HPA and sympathetic stress parameters are increased in both forms of FND (motor and NES).

4.2. Biological response to a social stress versus perceived response to a social stress

Regarding the biological response to stress, patients showed similar responses to healthy controls (for both cortisol and amylase) suggesting a normal physiological adaptation to social stress. To our knowledge, no study has reported biological data in response to a social stress in motor FND and only one study used the same stressor as ours (TSST) in a cohort of 19 NES patients to look at the effect of stress induction on preconsciowus threat processing but, like in our study, no differences between NES and controls were found in cortisol levels responses (Bakvis et al., 2009a). Another study in 19 NES investigated working memory with another stress induction paradigm (Cold Pressure test) and here again, patients did not differ from controls in their cortisol levels responses (Bakvis et al., 2010b).

It can be concluded that the cortisol response to a social stressor (TSST) is normal in both motor FND and NES and that the cortisol response to a physical stressor (Cold Pressure test) is normal in NES while it has not been tested yet in motor FND. However, It should, be underscored that cortisol and amylase stress response are known to be blunted in sexually abused patients (Elzinga et al., 2008; Gordis et al., 2008; Schalinski et al., 2015). When we separated our patients in two sub-groups we found such dampened response in abused patients. As only few controls reported sexual abuse (N = 3), we were not able to fully control for this factor. To obtain a definite answer on this topic, future study designs should test larger groups of non-abused FND patients as well as abused healthy controls, as abuse may act as a confounding variable when stating that stress response is normal in conversion disorder.
Regarding perceived stress, our FND cohort reported a significantly higher subjective response (VAS AUCi values) than controls, when their biological responses (cortisol and amylase AUCi) were comparable to controls. Such dissociation between subjective perception and objective measurement in FND has also been observed in motor perception; patients with functional tremor subjectively reported 65% more tremor time than objectively measured by actigraphy (Parees et al., 2012b). Perception arises from integrating sensory information from the environment with internal predictions about the expected data (priors) (Edwards et al., 2012) and it has been hypothesized that in FND more weight is put on prior expectation (Parees et al., 2012a), thus biasing perception towards what is expected (forward prediction) with less weight on the actual feedback information. One could hypothesize that in our stress experiment, FND patients expected more stress, which resulted in higher subjective VAS scores.

When looking at correlation between VAS scores and objective biological values at each time point, a positive correlation was observed in controls just after the stress test for amylase and cortisol, reflecting one’s capacity to accurately detect shifts in arousal states. In patients, such correlation was absent despite the fact that stress response (AUC of cortisol and amylase) was similar to that of controls. This might occur due to an already aroused system at baseline, making it difficult to detect any further change in level (ceiling effect). Or this might reflect an impaired detection of biological cues, which accords with findings of poorer interoceptive awareness found in subjects with FND (Ricciardi et al., 2016). Under stress, healthy individuals are known to display better interoceptive awareness (Schulz et al., 2013), which may account for the better correlation between biological stress cues and perceived stress we found in the control group. To confirm this hypothesis, further research is needed and in particular a test addressing specifically interoceptive awareness before and after stress induction in FND.

4.3. Influence of life events

We found a strong positive correlation in patients between background cortisol levels (AUCg) and number of events ($r = 0.67$, $p < 0.01$) as well as subjective impact of events ($r = 0.6$, $p < 0.05$), confirming a link between life adversities and biological regulation of the HPA axis system. There are two ways to interpret this correlation: life events may cause the stress hyperarousal by over stimulating the stress system — “the more adverse events — the more cortisol secretion”. If this were a physiological response, however, the correlation should also be seen in healthy controls who had similar number of life events. An alternate interpretation is that high background cortisol levels are not a consequence of adverse events but constitute a predisposition in certain individuals to develop FND. A longitudinal study looking at links between HPA axis arousal and life events followed a cohort of children from age 9–14yo until they reach 18yo and collected prospectively the occurrence of negative life events (LeMoult et al., 2015) as well as onset of a psychiatric disorder (depression). Life events predicted the onset of psychiatric illness only in subjects with baseline elevated AUCg cortisol. The authors argued that elevated total cortisol production potentiate susceptibility to environmental adversity. In FND, such mechanism can be postulated arguing that the hyperarousal of the HPA axis might predispose individuals to develop FND rather than being a mere consequence of adverse life events. Adverse events may then act as non-specific triggers. Other factors reflecting very early autonomic hyper-reactivity, such as altered feeding, sleeping or tactile reactivity in infants, have been shown to predict the subsequent development of functional symptoms (Rask et al., 2013). In line with this concept, triggers of a physical nature (Stone et al., 2009; Parees et al., 2014) and not only psychological stressors like adverse life events have been linked to FND onset. In one NES study, baseline cortisol levels were found to positively correlate with attentional bias (longer reaction times) to angry masked stimuli (Balvis et al., 2009b). One can hypothesized that elevated cortisol in patients with motor FND renders them more susceptible to external stimuli.

4.4. Biological stress and FND symptom

Imaging studies in FND have suggested that an abnormal hyperarousal state could influence sensorimotor processing underlying the physical functional symptom. One highlighted increased amygdala activity — reflecting the hyperarousal — not only to threat stimuli (fear faces) but also positive stimuli (happy faces) (Voon et al., 2010) and another showed lack of physiological habituation over time in FND patients to negative stimuli (sad and fear faces) (Aybek et al., 2015). In both these studies, aberrant functional connectivity was found between amygdala and supplementary motor areas, suggesting a link between amygdalar hyperarousal and motor control in patients with motor FND. No studies to date have directly tested a link between baseline increased cortisol levels and amygdalar hyperactivity in FND but an experimental study was done in healthy controls (van Marle et al., 2009). Stress (confirmed by increased cortisol, increased heart rate and decreased heart rate variability) induced a shift in amygdala activity towards enhance stimuli detection of fear and anger (better sensitivity) but at a cost, as even happy stimuli triggered such response (lower specificity). This shift occurs only in a stress condition and has a role in promoting survival, hence a preference for higher sensitivity, at a cost of lower specificity. Evidence of such loss of specificity — even at baseline without stress induction — has been observed in patients with motor FND (Voon et al., 2010) who displayed similar levels of amygdalar activity when viewing fearful and happy faces whereas healthy individuals controls showed a clear differential amygdalar activity (higher for fearful and lower for happy faces). Future studies should verify whether this shift is correlated with background cortisol values in FND patients.

4.5. Limitations

One major limitation of our study is the homogenous sample of motor FND, which limits the generalizability of our findings to the understanding of FND in a broader way. Moreover, the small sample size did not allow correcting for a potential major confounder, sexual abuse, or differentiating patients according to the duration of the disease. Another potential confound is the use of CNS acting drug in a large proportion of our patients but no differences were detected between the subgroups of patients with and without drugs. Also, the effect of such drugs on HPA axis is rather inhibitory according to the literature: benzodiazepines (Korbonits et al., 1995; Locatelli et al., 2010), antidepressants (Mason and Pariante, 2006) and antiepileptic drugs (Rabinovitz et al., 2004) have been shown to lower cortisol secretion. So even if such effect was possible in our sample, the significant difference we found with higher values in patients should not be explained by a medication effect. The choice of a self-report questionnaire to assess life events was mainly driven by feasibility reasons but has the major drawback of being subject to recall bias and lacks objectivity in the judgment of impact of the life events. Also, it does not take into account the nature of the events, like a potential secondary gain, which may be important in FND (Nicholson et al., 2016).

5. Conclusions

First, our study confirms a hyperarousal stress state in motor FND by showing increased biomarkers of HPA axis and autonomous system when the circadian cycle is at its trough (in the afternoon). Future studies should aim at confirming the hypothesis that this hyperarousal is linked to the physical symptom of FND, possibly through the following mechanisms: by favoring automatic habitual motor response mediated by basal ganglia at the expense of controlled response mediated by prefrontal control.

K. Apazoglou et al.
Second, our study confirms abnormal interceptive abilities in patients with motor FND under stress with a dissociation between perceived and objective stress.

Third, our study confirms that adverse life events play a role in FND as, they are linked to a hyperarousal state, which is specific to motor FND. It does, however, not imply adverse events have a causal link and future studies should aim to refine the role of life events as potential triggers or mediators of the disorder.

Finally our study opens the door to future research aiming to understand why such stress hyperarousal occurs in FND. There is to date little evidence of a genetic background for FND but familial cases have been reported (Stamelou et al., 2013). Gene-environment interaction should also be studied and the recent development of epigenetics offers this possibility (Frodl, 2017).

Conflict of interest

Authors, KA, VM, JW, GFP, SA, declare no conflict of interest related to their work presented in the manuscript entitled “Biological and Perceived Stress in motor Functional Neurological Disorders”.

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