



Biological and perceived stress in motor functional neurological disorders



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ABSTRACT

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 (AUC_G) and change over time (AUC_I). Life adversities and perceived subjective stress on a visual analog scale (VAS) were correlated with biological responses.

Results: FND patients had significantly higher background levels (AUC_G) of both stress markers (cortisol and amylase) than controls. The biological response (AUC_I) 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. After stress, controls showed a strong correlation between subjective and objective sympathetic values (amylase) but not patients. The number and subjective impact of adverse life events correlated with cortisol AUC_G in patients only.

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.

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 (Gelauff 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-psyche 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 (Hinson 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

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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 temporo-parietal 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 hypothalamo-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) (Birkett, 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 to fill in all relevant questionnaires. Following this preparation phase (~1 h), subjects were left to relax for 20 min (relaxation phase). They were then taken to the test room where the investigator instructed them on the TSST procedure in the presence of the examiners. They were then given 10 min to prepare their speech (see below) in the relaxation room.

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 to the TSST protocol (Kirschbaum et al., 1993a). Then they performed a 5-min calculation task (“count from

Table 1
Demographical and Clinical Data.

	FND patients (N = 16)	Healthy Controls (N = 15)	P value (T test*, Fisher test *)
Age (years)	46 ± 15	39 ± 13	*ns
Gender (Female:Male)	14F:2M	12F:3M	*ns
Cycle:Menopause	5:9	6:6	*ns
Medication	7 none:5BZD, 3AD, 1AE	14none:1AD	*p < 0.01
BDI	8 ± 5.5	3.5 ± 4.6	*p < 0.05
STAI Trait	41.1 ± 12.1	37.9 ± 9.0	*ns
State	36.9 ± 10.1	33.7 ± 8.8	*ns
CGI	3 none 2 minimal 3 moderate 8 severe	NA	
Mobility NeuroQoL	33.1 ± 4.0	39.7 ± 0.6	*p < 0.01
Symptoms duration (months)	73 ± 85 (range 4–300)	NA	
Symptoms type	6 weakness 5 tremor 2 gait 3 jerks	NA	

BZD: benzodiazepines, AD: antidepressant, AE: antiepileptic, NA: not applicable, ns: non-significant, BDI: Beck Depression Inventory, STAI: Anxiety Score, CGI: Clinical Global Impression Score

2023 to 0 while subtracting 17 each time”). Both examiner 1 leading the interview (VM) and examiner 2 (GFP 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 1:30pm to 4:30pm. 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 biological 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-

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