



Aversive stimuli exacerbate defensive motor behaviour in motor conversion disorder



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ARTICLE INFO

Keywords:

Emotion
Force control
Freezing
Functional symptoms
Cerebellum vermis

ABSTRACT

Conversion disorder or functional neurological symptom disorder (FND) can affect the voluntary motor system, without an organic cause. Functional symptoms are thought to be generated unconsciously, arising from underlying psychological stressors. However, attempts to demonstrate a direct relationship between the limbic system and disrupted motor function in FND are lacking. We tested whether negative affect would exacerbate alterations of motor control and corresponding brain activations in individuals with FND. Ten patients and ten healthy controls produced an isometric precision-grip contraction at 10% of maximum force while either viewing visual feedback of their force output, or unpleasant or pleasant emotional images (without feedback). Force magnitude was continuously recorded together with change in brain activity using fMRI. For controls, force output decayed from the target level while viewing pleasant and unpleasant images. Patients however, maintained force at the target level without decay while viewing unpleasant images, indicating a pronounced effect of negative affect on force output in FND. This emotional modulation of force control was associated with different brain activation patterns between groups. Contrasting the unpleasant with the pleasant condition, controls showed increased activity in the inferior frontal cortex and pre-supplementary motor area, whereas patients had greater activity in the cerebellum (vermis), posterior cingulate cortex, and hippocampus. Engagement of a cerebellar-limbic network in patients is consistent with heightened processing of emotional salience, and supports the role of the cerebellum in freezing responses in the presence of aversive events. These data highlight a possible neural circuit through which psychological stressors elicit defensive behaviour and modulate motor function in FND.

1. Introduction

Motor functional neurological symptom disorder (FND), also called motor conversion disorder, is characterised by neurological symptoms affecting voluntary motor control, such as paralysis or tremor, that are incompatible with organic damage to the nervous system (American Psychiatric Association, 2013). It is a frequent cause for disability, representing approximately 3–5% of all new neurological outpatients (Stone et al., 2009). Conversion or functional symptoms are thought to be generated unconsciously, often associated with underlying psychological stressors or trauma (Scott and Anson, 2009; Vuilleumier, 2005). Psychiatric comorbidity, particularly anxiety and depressive disorders, is common (Binzer, et al., 1997; Crimlisk, et al., 1998), and negative life events predict symptom severity (Roelofs, et al., 2005); however the

underlying neural mechanisms remain unclear (Vuilleumier, 2014).

An association between physical symptoms and emotions has been underscored since the early 19th century. Freud's psychodynamic theory posited that unconscious conflict and affective motive give rise to bodily symptoms (Babinski, 1909; Breuer and Freud, 1955; Freud and Breuer, 1895). The notion of a defensive mechanism, 'converting' mental conflict into functional symptoms, was highlighted in early disease classifications (American Medical Association, 1952), and continues to influence current conceptual approaches to understanding functional disorders (Vuilleumier, 2014). Yet, recent neuroscientific investigations in FND patients have generally attempted to link motor symptoms to particular neuroanatomical substrates (for a review see Vuilleumier and Cojan, 2011), with little emphasis on linking physiological to causal psychological mechanisms.

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<http://dx.doi.org/10.1016/j.neuropsychologia.2016.11.005>

Received 20 June 2016; Received in revised form 6 October 2016; Accepted 4 November 2016

Available online 11 November 2016

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Evidence from neuroimaging and electrophysiological studies has implicated modulation of several neural structures that lie at the intersection of affective-motor processing; though heterogeneity of clinical deficits and experimental tasks have led to inconsistent results. Increased activity in anterior cingulate and orbitofrontal cortices in functional paralysis has been linked to emotional and motivational processes that might inhibit motor circuits during attempted movement (Devinsky, et al., 1995; Marshall, et al., 1997), and/or to action-monitoring processes abnormally hyperactive during movement initiation (Roelofs, et al., 2006). Enhanced functional connectivity of the motor cortex with posterior cingulate and ventromedial prefrontal cortices in one patient with functional paralysis was imputed to abnormal self-monitoring and emotion regulation (Cojan, et al., 2009). Abnormal engagement of the supplementary motor area (SMA) and amygdala was also found during motor preparation of cued actions in FND (Voon, et al., 2011). In another study using a precued reaction time task, patients with functional paresis demonstrated impaired performance and enhanced EEG activity over centroparietal regions during motor preparation. It was hypothesised patients may have assigned higher emotional relevance to precues signalling movement of the symptomatic limb, enhancing preparatory neural activity in premotor areas (Blakemore, et al., 2013). Furthermore, reduced activity in the basal ganglia and thalamus was associated with functional paralysis (Vuilleumier, et al., 2001), whereas increases in basal ganglia and cerebellum were related to functional dystonia (Schrage, et al., 2013). Dysfunction of striatohalamocortical circuits and their intimate connections with limbic and prefrontal circuits offer numerous pathways through which affective and motivational processes can modulate goal-directed action (Alexander, et al., 1990; Brown and Pluck, 2000; Vuilleumier, 2005).

A few other studies have focused on upstream influences of emotional processes on the pathophysiology of FND by using affective tasks without any motor component. Aybek and colleagues (2015) reported enhanced amygdala responses to threat signals (fearful faces) in FND patients, suggesting impaired emotional regulation, while Voon et al. (2010a) demonstrated increased functional connectivity between the amygdala and SMA when viewing fearful and happy faces in patients with “productive” functional motor symptoms (e.g., tremor, dystonia). Enhanced amygdala-SMA connectivity, together with increased dorsolateral prefrontal cortex and decreased hippocampus activity, was also reported during recall of autobiographical traumatic events in functional paresis (Aybek, et al., 2014). These results may be due to higher states of emotional arousal associated with FND (Horvath, et al., 1980; Lader and Sartorius, 1968). Exaggerated startle reflex responses to arousing images in conversion patients (Seignourel, et al., 2007) is consistent with this notion. In line with this, Bakvis and colleagues (2010) demonstrated patients with psychogenic non-epileptic seizures have higher levels of baseline cortisol, indicative of higher stress state. These patients also showed increased avoidance behaviour, compared to controls, in a task requiring directional movements towards or away from their body in response to angry (but not happy) faces, consistent with a defensive strategy to cope with impending threat (Bakvis et al., 2009a, 2009b, 2011). Additionally, increased activity in the periaqueductal gray (PAG) and SMA was found in FND patients during processing of negative (sad and fearful) faces, indicating modulation of defense-like behaviour to aversive stimuli (Aybek, et al., 2015).

Together, these findings provide indirect evidence of abnormal limbic-motor interactions, and point to a potential link between emotional arousal and modulation of brain regions involved in motor control, which may at least partly contribute to aberrant motor behaviour in FND. However, despite this apparent close coupling of emotion and motor processing in FND, evidence for a direct relationship between altered limbic processing and altered motor control is lacking.

Here we specifically probed for emotion-motor interactions in

motor FND patients, using a motor force paradigm previously used in healthy volunteers (Blakemore, et al., 2016). This task requires precise control of submaximal isometric force output while viewing high arousing (pleasant, unpleasant) and low arousing (neutral) emotional images, permitting direct and quantitative examination of emotion-modulated motor behaviour (Coombes, et al., 2008). Our previous results in healthy volunteers showed that force was maintained closer to the target level while viewing negative emotional images relative to positive or neutral images (Blakemore, et al., 2016). Further, augmented force control by negative information was mediated by a cortico-subcortical network involving the amygdala, PAG, and right inferior frontal gyrus (IFG). These findings were imputed to stronger engagement of motor pathways associated with the aversive motivational system due to the threat-relevant content of unpleasant stimuli, which may trigger a passive defensive coping mechanism, increasing attentional focus and motor immobility (Bradley, et al., 2001; Frijda, 2009). We proposed that such adaptive defensive behaviour was analogous to freezing responses observed in animals (Blakemore, et al., 2016), whereby body movements are reduced and muscle tone is increased when a distant threat is perceived (Blanchard, et al., 2001; Blanchard and Blanchard, 1986; Marks, 1987). Freezing is thought to help animals avoid detection and prepare for active defensive behaviour (e.g., fight or flight).

Given the role of affective stressors in the aetiology of functional symptoms, we adapted this paradigm to test the hypothesis that negative affect may exacerbate alterations of motor control in individuals with FND. We predicted that motor FND would be associated with a relative amplification of force output changes in response to unpleasant stimuli, compared to healthy control participants, accompanied with differential modulation of brain areas mediating interactions between limbic and motor processes (including amygdala, PAG, IFG), and presumably playing a key role in automatic/unconscious defensive actions.

2. Material and methods

2.1. Participants

We tested ten FND patients (with motor symptoms) diagnosed according to the DSM-5 criteria (American Psychiatric Association, 2013), recruited from the neurology clinic at the University Hospital of Geneva, and ten healthy control volunteers (HC) recruited from the general population (Table 1). No patients had any history of neuropathology, and all underwent a full clinical examination by a neurologist and appropriate paraclinical tests to rule out any organic disease (see Table S1 for medication details). Healthy volunteers reported no mental disorder in the past 12 months, and no history of neurological disorder. Participants were included if they had normal hearing and speech, normal or corrected-to-normal vision and no contraindications to MRI scanning. Participants completed the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983). All participants provided written informed consent and received monetary compensation. The study was approved by the Geneva University and Hospital ethics committee.

2.2. Emotional-force control task

Participants produced a sustained isometric precision-grip contraction at 10% of their maximum force by pinching a force-measuring device between their thumb and index finger. Maximum force for each hand was determined before entering the scanner (see Supplementary material). Each trial began with a fixation cross presented in the centre of the screen for a variable period (5–7 s), followed by the presentation of two bars, which indicated the initiation of force production (Fig. 1A). A white stationary horizontal bar located in the centre of the screen represented the target force (10% of the participants' maximum force).

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