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Disrupted avoidance learning in functional neurological disorder: Implications for harm avoidance theories☆

Laurel S. Morris[a,b], Benjaman To[c], Kwangyeol Baek[c], Yee-Chien Chang-Webb[c], Simon Mitchell[c], Daniela Strelchuk[c], Yevheniia Mikheenko[b], Wendy Phillips[d], Michael Zandi[d], Allison Jenaway[e], Cathy Walsh[c,d], Valerie Voon[a,c,f,*]

[a] Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge CB2 3EB, United Kingdom
[b] Department of Psychology, University of Cambridge, Cambridge CB2 3EB, United Kingdom
[c] Department of Psychiatry, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 0QQ, United Kingdom
[d] Department of Molecular Neuroscience, UCL Institute of Neurology, United Kingdom
[e] Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, United Kingdom
[f] NIHR Cambridge Biomedical Research Centre, Cambridge, United Kingdom

ARTICLE INFO

ABSTRACT

Background: Functional neurological disorder (FND) is an elusive disorder characterized by unexplained neurological symptoms alongside aberrant cognitive processing and negative affect, often associated with amygdala reactivity.

Methods: We examined the effect of negative conditioning on cognitive function and amygdala reactivity in 25 FND patients and 20 healthy volunteers (HV). Participants were first conditioned to stimuli paired with negative affective or neutral (CS + /CS −) information. During functional MRI, subjects then performed an instrumental associative learning task to avoid monetary losses in the context of the previously conditioned stimuli. We expected that FND patients would be better at learning to avoid losses when faced with negatively conditioned stimuli (increased harm avoidance). Multi-echo resting state fMRI was also collected from the same subjects and a robust denoising method was employed, important for removing motion and physiological artifacts.

Results: FND subjects were more sensitive to the negative CS + compared to HV, demonstrated by a reinforcement learning model. Contrary to expectation, FND patients were generally more impaired at learning to avoid losses under both contexts (CS + /CS −), persisting to choose the option that resulted in a negative outcome demonstrated by both behavioural and computational analyses. FND patients showed enhanced amygdala but reduced dorsolateral prefrontal cortex responses when they received negative feedback. Patients also had increased resting state functional connectivity between these two regions.

Conclusions: FND patients had impaired instrumental avoidance learning, findings that parallel previous observations of impaired action-outcome binding. FND patients further show enhanced behavioural and neural sensitivity to negative information. However, this did not translate to improved avoidance learning. Put together, our findings do not support the theory of harm avoidance in FND. We highlight a potential mechanism by which negative contexts interfere with adaptive behaviours in this under-explored disorder.

1. Introduction

Functional neurological disorder (FND), also known as conversion disorder, is characterized by unexplained neurological symptoms, including movement, seizures or sensory symptoms that are unrelated to an underlying neurological or medical disorder. It has been proposed that excessive negative affect and anxiety can exacerbate a deficient top-down regulatory system, leading to psychogenic or 'functional' neurological symptoms (Perez et al., 2012; Voon et al., 2010; Aybek et al., 2014; Voon et al., 2016; Carson et al., 2012). There is a relatively high prevalence of these unexplained neurological symptoms in neurology outpatient clinics (Stone et al., 2009), however we have a limited understanding of the etiology of FND. Therefore the delineation of cognitive and neural disturbances in this group is critical.

In healthy populations, learning to associate and avoid external stimuli with probable negative outcomes is vital for the selection of appropriate behaviour and environmental adaptation. Several lines of evidence suggest that FND patients are more sensitive to negative conditioning, with heightened responses to both negative affective stimuli (Bakvis et al., 2009a; Bakvis et al., 2009b) and arousal (Voon et al., 2010; Seignourel et al., 2007). Negative conditioning involves the progressive association of a neutral stimulus with fearful or negative outcomes, causing transference of negative saliency to the previously neutral stimulus (CS +). Subsequently, a fear response can be elicited from the presentation of the CS + alone, which becomes intrinsically fearful. This conditioning can be vital for rapid, automatized responses to environmental threats or danger, usurping the need for slow and deliberative cognitive processes that could hinder survival. However, FND is often characterized by a high prevalence of affective and anxiety symptoms (Bowman and Markand, 1996; Sar et al., 2004), which could be governed or exacerbated by excessive negative conditioning. Indeed, patients with psychogenic non epileptic seizures, a prevalent manifestation of FND, show increased attentional bias to negative social stimuli (angry faces) associated with higher resting cortisol levels (Bakvis et al., 2009a; Bakvis et al., 2009b; Bakvis et al., 2010). One possible theory by which FND patients express their symptoms is related to unconscious harm avoidance in which symptom expression occurs to avoid a stressful family or work situation.

Neurally, negative emotional stimuli (Aybek et al., 2014) and affective stimuli irrespective of valence (Voon et al., 2010) engender greater amygdala responses in FND patients. The amygdala largely orchestrates associative learning by linking previously neutral stimuli with representations of affective value, ascribing salience to environmental cues (Everitt et al., 2003). The basolateral amygdala mediates the initial acquisition of fear via CS-US associations (Fanselow and LeDoux, 1999; Jovanovic and Ressler, 2010) and the centromedial amygdala regulates the fear response (Jovanovic and Ressler, 2010; LeDoux, 1998) particularly in terms of physiological responses, like startle and freezing (Davis et al., 1982; LeDoux, 1992). The amygdala also plays a crucial role in the processing of emotional control and management (Cardinal et al., 2002) and via projections to the prefrontal cortex (PFC) and nucleus accumbens, the amygdala mediates motivational salience to direct goal-directed behaviour (Cardinal et al., 2002). The PFC plays an important role in mediating executive function, including goal selection, planning, anticipation and implementation (Alvarez and Emory, 2006). Specifically, the dorsolateral PFC sustains and coordinates attentional resources for goal-directed behaviour and flexibly shifts attention and valuations during learning (Rudorf and Hare, 2014; Dias et al., 1996; Arnsten and Rubia, 2012; Arnsten, 2009; Rogers et al., 2000; Hornak et al., 2004; Remijnse et al., 2005). It also importantly provides top-down regulation of attentional, inhibitory and emotional processes. In patients with FND, connectivity of the dorsolateral PFC with other motor cortical regions seems to be blunted, potentially reflecting an impairment in higher order action intention and selection (Voon et al., 2016).

Connectivity between the dorsolateral PFC and amygdala is associated with the capacity to modulate negative emotional responses with cognitive strategies (Banks et al., 2007) thereby being an expected important link in FND. However, while previous studies have demonstrated reduced connectivity between these regions in patients who have difficulty controlling affective responses (generalized social anxiety disorder (29) depression (Dannlowski et al., 2009), compulsive sexual behaviour (Schmidt et al., 2017)), there have been no studies specifically assessing the relationship between amygdala and dorsolateral PFC in FND patients during affective learning.

It is unclear how the enhancement in negative conditioning observed in FND impacts cognitive ability, and how this is expressed neurally. There is some evidence that FND patients are more likely to engage dissociative or avoidance-related strategies for coping with difficult life events, rather than planning and problem solving, or using

the cognitive skills necessary to adapt to a dynamic world (Goldstein et al., 2000). Therefore, in this study, we examined the effects of negative conditioning on goal-directed avoidance learning in patients with FND. Subjects were conditioned to aversive (CS +) and neutral (CS −) stimuli. Then, during fMRI, subjects performed a goal-directed learning task to avoid losses, while being presented with the previously conditioned stimuli. We expected that FND subjects would be generally better at avoiding monetary loss (e.g. greater harm avoidance) and that the presence of the negative CS + would further enhance such avoidance learning. We also expected that FND patients would show elevated amygdala reactivity to the negative CS + and loss outcomes and that simultaneous dorsolateral PFC activity would be blunted.

2. Methods

2.1. Participants

Data were collected from 25 FND patients and 20 healthy volunteers (HV). The FND subjects were recruited both from neurologists and psychiatrists at Addenbrookes Hospital and via the FND Hope website (http://fndhope.org/). Diagnoses were made or confirmed by a neurologist from the FND clinic in Addenbrooke's Hospital, using the DSM-4 TR diagnostic criteria. All participants were screened by a psychiatrist for comorbidities and to record symptom severity. The FND patients were screened both clinically and using the Mini International Neuropsychiatric Inventory (MINI). Healthy controls were screened using the MINI. Symptom severity was rated for duration and severity (1 = Mild, limited impact on daily functioning; 2 = Moderate, noticeable impact on daily functioning with restriction of some activities; 3 = Severe, marked impact on daily functioning with restriction of activity in multiple domains. 4 = Very severe, impairment in all or virtually all domains of activity). Exclusion criteria included subjects below the age of 18, any other major neurological, current major depression greater than moderate severity, psychotic or bipolar disorder and substance use disorder. Current mild major depression and elevated depression scores with no current major depression diagnosis were allowed in the FND group. Symptoms of pain, motor (paralysis or weakness, non-epileptic seizures, tremor, chorea, tics, gait abnormalities, dystonia, myoclonus) and sensory (somatosensory, vision, hearing) functions were assessed in clinical interview that included duration and severity. All subjects were able to remain still in the scanner. HV were recruited via community-based advertisements. All participants provided written informed consent and were reimbursed for their time. The study was approved by the University of Cambridge Research Ethics Committee.

2.2. Task

See Fig. 1 for a task schematic. Outside of the scanner participants first performed a conditioning task. Subjects were seated in front of a laptop with headphones. One of four abstract shapes (cues) were paired with either a negative outcome (aversive sound and image) or a neutral outcome (neutral tone and image) for 30 trials per cue (total of 120 trials). Trials started with a 2000–4000 ms varying fixation cross, followed by the cue (1500 ms) and immediately followed by the aversive or neutral outcome (2000 ms). Participants were instructed to watch the screen and count how many times a blue frame appeared. The aversive images were rated as unpleasant images from the International Affective Pictures System (Lang et al., 2008) and paired with unpleasant sounds including high pitched screaming and nails scratching a blackboard. The neutral images were rated as neutral images from IAPS and paired with a neutral sound from a musical instrument. Separately, two new abstract images were presented both 30 times each in the absence of any outcomes, to control for effects of familiarity of stimuli and to distinguish it from any aversive or neutral information. Thus subjects were exposed to two CS +, two CS − and two familiar