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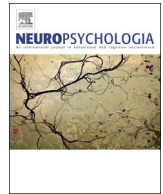
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Aversive stimuli exacerbate defensive motor behaviour in motor conversion disorder



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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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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).

Table 1

Demographics and characteristics of functional neurological symptom disorder patients and healthy control participants.

	FND	HC
Age (years)	40 ± 11	28 ± 3 ^a
(range)	(19–53)	(24–34)
Gender	8F : 2M	6F : 4M
Handedness ^b	8R : 2L	10R : 0L
Most affected side	5R : 5L	N/A
Symptoms ^c		
tremor	1	N/A
dystonia	2	N/A
paresis (flaccid)	7	N/A
Symptom duration (months)	31 ± 32	N/A
Maximum force ^d (N)	50.6 ± 18.9	48.8 ± 11.8
Total HADS score	12 ± 6	9 ± 6
(range anxiety subscale)	(2–15)	(0–10)
(range depression subscale)	(2–10)	(0–10)
SAM valence ratings		
pleasant	6.7 ± .7 ^e	6.8 ± .7 ^e
unpleasant	2.4 ± .7	2.6 ± .9
SAM arousal ratings		
pleasant	6.0 ± .9	5.8 ± 1.2
unpleasant	5.6 ± 2.1	6.3 ± 1.2

^a Age, handedness laterality quotient, maximum force, HADS score, and SAM ratings were compared between groups using a two-samples *t*-test. For all comparisons, $p > .2$, except for age, where $p = .01$.

^b Handedness confirmed by Edinburgh Handedness Inventory (Oldfield, 1971).

^c Sensory symptoms were also present in some patients: hypoesthesia ($n = 8$), paresthesia ($n = 2$).

^d Maximum force values represent the average across hands as there was no difference in force between the left and right hands for either group or between the affected and unaffected hands for patients (see [Supplementary Material](#)).

^e $p < .001$ comparing pleasant with unpleasant within each group. Data shown represent mean ± standard deviation.

A black bar, located at the bottom of the screen, represented the amount of force produced. This bar could move vertically as participants pressed on the force device, providing visual feedback of their force production. Participants were instructed to alter their force output to match the black bar elevation with that of the white target bar.

Following this initial feedback period (variable duration; 5–7 s), participants were presented with one of three conditions for 6 s: Condition 1 (feedback) was a control condition in which the black and white bars remained on the screen for the remainder of the trial, providing continuous visual feedback of force. In Conditions 2 and 3, visual feedback was removed and the screen was entirely replaced with either a pleasant or unpleasant emotional image, respectively. Sixty-four emotional images were selected from the International Affective Picture System (Lang, et al., 2008), based on their normative valence and arousal ratings. In all conditions, participants were instructed to maintain the target force output (10% of maximum) as accurately as possible throughout the entire trial until the next fixation cross (inter-trial interval). Participants completed 96 trials, distributed in 4 blocks (~6 min each) of 24 trials (2 blocks for each hand; 48 trials per hand). Within each block there were 8 trials of each condition, presented in a pseudo-random order. The block order alternated between each hand and was randomised for each participant. A rest period was provided after completion of the first two blocks, enabling acquisition of the anatomical scan.

Following MRI scanning, participants viewed all emotional images for a second time to provide subjective appraisals of their affective content. Ratings of valence and arousal were completed using a computerised version of the 9-point Self-Assessment Manikin (SAM) scale (Bradley and Lang, 1994).

2.3. Behavioural data analysis

The force-time series data were segmented into seven 1 s epochs for each trial, beginning 1 s before the onset of each condition (epoch 0) until the end of image presentation (epochs 1–6). For each epoch, mean force (expressed as a percentage of maximum force) and coefficient of variation (CV) were calculated for each experimental condition and hand, for each participant. Initial analyses to examine between-hand differences in force output revealed no main effect or interactions with group or condition, indicating consistent effects of condition irrespective of the performing hand. Symptom side in patients (i.e., most versus least affected hand) also had no effect (see [Supplementary Material](#)). Behavioural data were therefore pooled across hands.

Performance during each condition was examined by conducting repeated-measures mixed ANOVA including group (between-subjects factor; FND, HC) and condition (within-subjects factor; pleasant, unpleasant, feedback) on mean force and CV for epochs 1–6. To ensure any differences in performance were not attributable to differences in baseline force levels, we also examined force output and CV in the final 1 s when visual feedback was provided for each trial (epoch 0), in a separate group by condition repeated-measures ANOVA. Mean subjective valence and arousal ratings were analysed with separate repeated-measures mixed ANOVA to compare group and emotional condition (pleasant, unpleasant). Finally, to ensure behavioural performance was not affected by age differences between groups (Table 1), all analyses were repeated including age as a covariate to control for potential confounding.

2.4. Imaging data analysis

MRI data were acquired on a 3T scanner and submitted to standard preprocessing procedures (see [Supplementary Material](#)). We used a multiplex sequence with short TR (650 ms) allowing us to probe for brain activity changes with precision during the force production time-window. We first constructed a general linear model (GLM1) comparing the main experimental conditions for each participant. Data were concatenated across runs (2 runs for movements of each hand), and each run contained three conditions. Every trial was modelled using the onset of the bar display (indicating the target force level). The six contrast images (3 conditions x 2 hands versus rest) generated for each participant were used to construct a flexible factorial model for second-level analyses, which modelled group by condition and participant as a main effect. Like the behavioural data, results were pooled over hands for all subsequent fMRI analyses (see [Supplementary material](#)).

A second model (GLM2) was constructed to examine brain regions quantitatively modulated by force output for each group separately. This GLM comprised one categorical regressor containing all trials, modelled with the onset of the bar display, and one parametric modulator containing force output (Blakemore, et al., 2016; Schmidt, et al., 2009). Linear regression coefficients for the force modulator were computed for each participant and analysed at the second-level using one-sample *t*-tests. Both GLMs were convolved with a standard hemodynamic response function.

Our analyses focussed on the following main contrasts: (1) Given our previous work showing different force production to unpleasant stimuli in healthy volunteers (Blakemore, et al., 2016), we first compared the different emotion conditions in each group. From GLM1, we identified regions showing greater activity in the unpleasant compared to pleasant condition ($U > P$) and vice versa ($P > U$), separately for patients and controls. Significant clusters of brain activity from these contrasts may, however, simply reflect emotional processing rather than force production during emotional processing. Thus to identify areas related to concurrent force control, we repeated these analyses ($U > P$, $P > U$ contrasts), masking inclusively ($p < .001$) by brain areas that significantly correlated with force output (identified

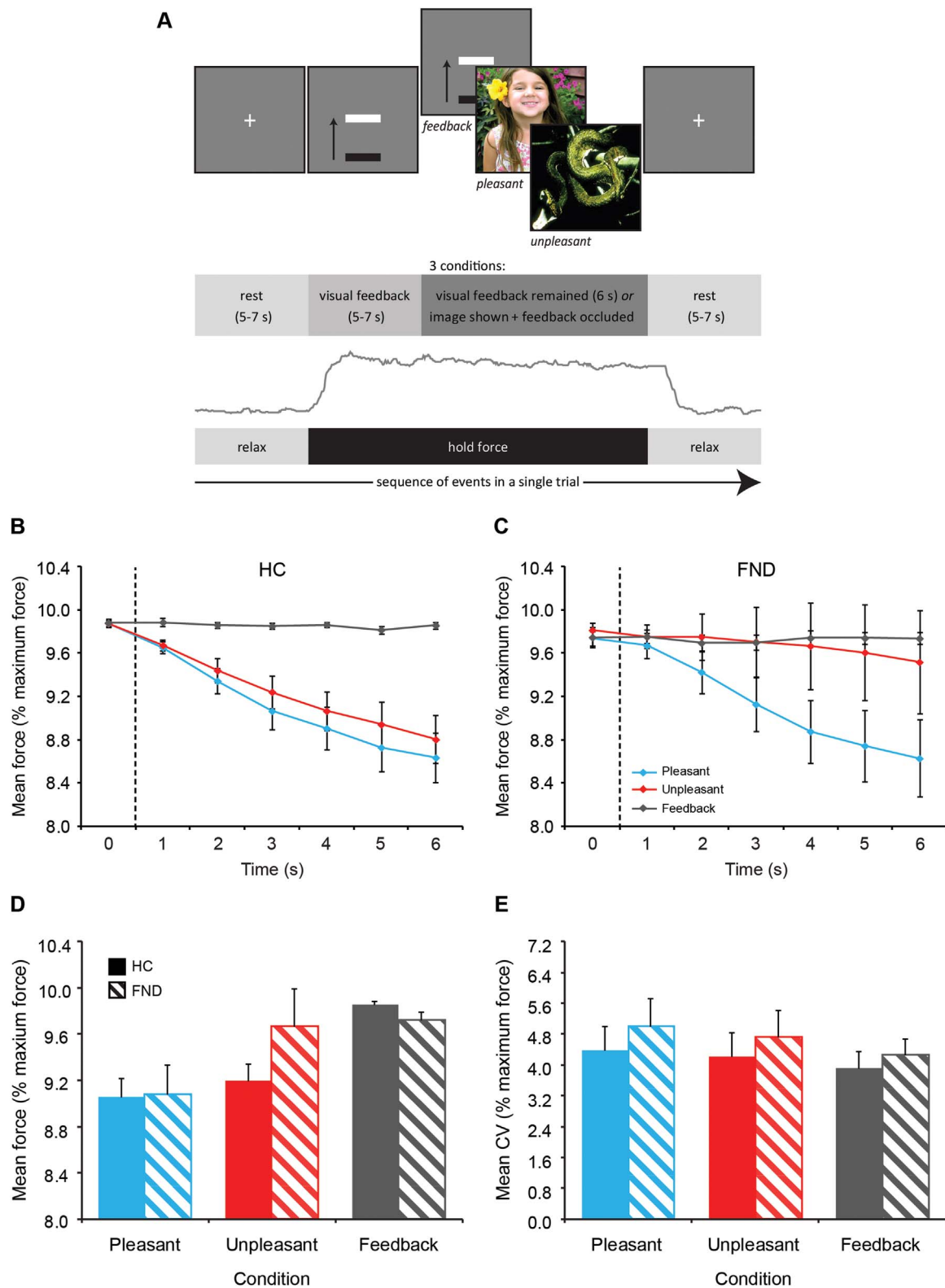


Fig. 1. Behavioural data. **A**, Sequence of screens displayed for each trial in the emotional-force control task. **B–C**, Mean force (expressed as % maximum force) in each 1 s epoch for each condition, beginning 1 s before the onset of each condition (time=0) for **B**, patients, and **C**, controls. **D**, Mean force (% maximum force), and **E**, mean coefficient of variation (% maximum force), both calculated over the 6 s of image presentation. Error bars in each graph represent standard error. .

from GLM2) for each group. (2) We then performed a conjunction analysis (GLM1) to find activations in the U > P contrast that were common to both groups. (3) Next, for direct comparison of task-related differences between patients and controls, we identified brain regions showing a greater differential response between unpleasant and

pleasant stimuli (GLM1) for one group, but no such response in the other group (U > P contrast for patients versus controls, and for controls versus patients) using an exclusive masking procedure with a threshold of $p = .05$ (the contrast to be masked was thresholded at $p < .001$). This exclusive mask therefore removed all voxels reaching

significance in the $U > P$ contrast for one group that overlapped with significant voxels in the $U > P$ contrast for the other group; the more liberal the exclusive mask threshold, the more conservative the masking procedure. Similar analyses using exclusive masking procedures have been used in other clinical studies (e.g., Desseilles, et al., 2009; Piguet, et al., 2016; Schwartz, et al., 2008; van der Stouwe et al., 2015) and provide a rigorous way to delineate group differences characterised by unique activation patterns between patient and control cohorts. Group differences were also assessed by formal interaction contrasts at the whole-brain level, using small volume correction (SVC) based on regions of interest (ROI) activated in the main effect of unpleasant versus pleasant stimuli for patients and controls. Each ROI (8 mm sphere centred on activation peaks) was defined from clusters activated in this contrast, separately for controls and patients, and then used for SVC when testing for the interactions: (i) controls $[U > P] > \text{patients } [U > P]$, and (ii) vice versa). (4) Finally, analyses comparing the emotional conditions to the feedback condition ($U > F$, $P > F$) for one group compared with the other were also performed (see [Supplementary material](#)). Significant activations surviving a threshold of $p < .001$ (uncorrected) were retained, with significant clusters corrected at the cluster level ($p < .05$; FWE), unless stated otherwise (for the rationale of similar thresholds used in affective paradigms, see [Lieberman and Cunningham, 2009](#)).

To ensure our results were not affected by differences in age between group, we repeated the analyses using a two-sample t -test ($U > P$ contrast for each group), including age as a covariate. Significant clusters were not different to those obtained with the flexible factorial model without the covariate. Additionally, the age regressor was not associated with any significant activations, even at liberal threshold ($p < .05$, uncorrected).

3. Results

3.1. Behavioural performance

As illustrated in [Fig. 1B,C](#), there was a striking difference in mean force output over time unique to patients with FND, and specific to the unpleasant condition. Statistical analyses confirmed a significant group by condition interaction $F_{(2,440)}=11.6$, $p=.001$, [Fig. 1D](#)). Follow-up analyses revealed, as expected for controls considered alone, a significant main effect of condition ($F_{(1,140)}=99.7$, $p=.001$). Force was maintained close to the target level throughout the trial when visual feedback was presented, but significantly decayed over time when feedback was replaced with pleasant or unpleasant affective images ($p < .001$). However, consistent with our earlier findings ([Blakemore, et al., 2016](#)), force output was closer to the target level for unpleasant compared with pleasant images ($p < .001$), an effect presumably reflecting the motivationally-salient nature of aversive stimuli driving stronger engagement of the defensive system ([Blakemore, et al., 2016; Bradley, et al., 2001](#)).

For patients, there was also an effect of condition ($F_{(2,219)}=19.5$, $p=.001$), where force output was successfully maintained close to the target in the feedback condition, indicating patients were able to perform normally on this motor task. Force output decayed from the target level in the pleasant condition that was not different from controls. Importantly, when viewing unpleasant images, patients maintained force output close to the target level, with no decay in mean force relative to the feedback condition. This modulation of force output in the unpleasant condition significantly differed from the controls ($p=.003$), and indicates a pronounced effect of negative affect on force output in patients that persisted throughout image presentation.

Regarding variability of force output ([Fig. 1E](#)), a main effect of condition on CV was found ($F_{(2,476)}=12.1$, $p=.001$). CV was smaller when feedback was present compared with when it was occluded ($p < .01$). Performance variability did not differ between group or emotion

conditions, and the group by condition interaction was non-significant.

Results from additional analyses confirmed the effect of aversive stimuli on force control was independent of participant age, baseline force levels, and individual differences in subjective appraisal of the image's affective content. First, we obtained the same pattern of results when including age as a covariate, indicating our results were unrelated to the difference in age between groups. Second, we found no difference in force output or CV during the final second of the target display (epoch 0) between groups or conditions, indicating the above results cannot be ascribed to differences in baseline motor performance. Finally, analyses of subjective valence and arousal ratings indicated the ratings in both groups were similar to the normative ratings ([Lang, et al., 2008](#)). Reliable differences between our conditions were confirmed by a significant effect of condition on valence ($F_{(1,18)}=119.7$, $p=.001$), with unpleasant images rated as more negative than pleasant images, but no difference in arousal between unpleasant and pleasant images ([Table 1](#)). No group or group by condition interaction were found for either rating, indicating the images elicited similar responses in patients and controls.

3.2. Neuroimaging results

We first examined brain activation during the unpleasant condition, where force production was enhanced within each group, relative to the pleasant condition ($U > P$ contrast; GLM1). These contrasts highlighted a number of regions showing differential increases that were common to patients and controls, encompassing the posterior cerebellum and amygdala, but also visual areas in fusiform, occipital, and temporal cortices ([Table 2](#)). However, the $U > P$ contrasts also revealed additional cortical activations unique to each group: Controls engaged several prefrontal cortical areas, most notably the medial and inferior frontal gyrus, and the insula. In contrast, significant prefrontal activity (especially IFG) for unpleasant images was absent in patients, even at lower threshold ($p < .01$, uncorrected). Instead, patients showed greater activity in the hippocampus and cerebellar vermis, not seen in controls. No significant clusters were found for the reverse contrast ($P > U$) for either group.

Because the former contrasts reflect brain activity associated with both emotion processing and motor control during the force maintenance period, we further examined the impact of emotion on motor processes by testing for enhanced activation in the $U > P$ contrast using only those voxels that were significantly correlated with force output, for each group separately (inclusive masking procedure based on parametric force effects; [Table S2](#)). Results from this analysis revealed differential increases in a specific subset of the regions above ([Table S3](#)); notably the IFG and posterior cerebellum for the controls, and the hippocampus, amygdala, visual areas, putamen, and cerebellum (both posterior lobe and vermis) for the patients. No significant modulation of IFG was observed in patients. Parametric activations correlating with force output irrespective of emotion context ($p < .001$) primarily highlighted the cerebellum in both groups, plus left IFG in controls and left cingulate, right insula, hippocampus, and visual areas in patients (GLM2, [Table S2](#)). Taken together, these findings highlight brain areas critically involved in the modulation of force maintenance as a function of emotional context.

Next, to identify the distinctive emotional effects for each group, we tested for activations in the $U > P$ contrast from one group that survived an exclusive mask generated from the same contrast in the other group (at $p < .05$; GLM1, [Table 3](#)). The masking procedure ensured identification of activations that were significant and unique in one group only, with no similar trend in the other group. The effect of unpleasant images specific to controls (not seen in patients) was underpinned primarily by activity in the bilateral IFG (extending to the anterior insula) and pre-SMA ([Fig. 2](#)). As expected for controls ([Blakemore, et al., 2016](#)), rIFG activity was greater for unpleasant than pleasant images; but patients showed no differentiation between

Table 2

Whole brain voxel-wise activations within-group. Significant clusters obtained from GLM1 and their MNI coordinates (centre of mass), voxels, and Z-score during force production in the presence of unpleasant compared to pleasant images, separately for patients and controls.^a

		MNI coordinates (mm)			Voxels	Z-score
		x	y	z		
HC: U > P						
L	Inferior Frontal Gyrus [BA 47] ^b	−33	17	−17	41	5.53
R	Insula	30	23	−17	214	6.61
R	Medial Frontal Gyrus [BA 8]	3	38	46	72	5.62
R	Superior Frontal Gyrus [BA 10]	12	65	19	6	4.98
R	Superior Frontal Gyrus	6	26	64	6	4.85
L	Amygdala	−18	−4	−17	14	5.53
R	Fusiform Gyrus	48	−49	−17	21	5.64
L	Posterior Middle Temporal Gyrus [BA 39]	−60	−64	7	25	5.98
R	Anterior Middle Temporal Gyrus [BA 21]	48	8	−35	20	5.27
R	Superior Temporal Gyrus	60	−58	16	54	5.34
R	Superior Temporal Gyrus	45	17	−26	9	5.04
L	Middle Occipital Gyrus [BA 19]	−42	−88	13	5	4.85
L	Cerebellum Posterior Lobe (VIIb) ^b	−15	−76	−41	34	5.55
FND: U > P						
L	Amygdala ^b	−18	−4	−23	8	5.04
L	Hippocampus ^b	−30	−13	−17	5	4.74
R	Fusiform Gyrus ^b	45	−49	−17	457	7.43
R	Anterior Middle Temporal Gyrus ^b	48	11	−38	14	4.97
L	Inferior Occipital Gyrus ^b	−45	−79	−5	229	5.79
L	Middle Occipital Gyrus [BA 19]	−39	−91	13	7	4.74
R	Cerebellum Anterior Lobe Vermis ^b	0	−55	−38	50	6.09
R	Cerebellum Posterior Lobe (VIIb) ^b	6	−76	−41	5	4.96

^a Clusters listed were corrected for multiple comparisons ($p < .05$; FWE, minimum 5 voxels).

^b These regions also showed significant differential activation in the U > P contrast when inclusively masked ($p < .001$) by regions significantly correlated with force output for each group (see Table S2, S3). BA, Brodmann area; P, pleasant; U, unpleasant; L, left; R, right.

conditions in this region. Similar patterns of results were observed for left IFG and pre-SMA, where activity was greater for unpleasant compared to pleasant images in controls, but not in patients. On the other hand, in patients (unlike controls), viewing unpleasant images while maintaining force output (relative to pleasant images) was associated with increased activity in the cerebellum vermis, extending bilaterally into lobule IX (Fig. 3A), but also in the left hippocampus (Fig. 3B), left posterior cingulate cortex (ventral division according to Vogt et al. (2006), vPCC; Fig. 3C), as well as bilateral areas in lateral occipital gyrus. A significant effect of emotional condition in these regions was absent in controls. The formal group by condition interaction test further confirmed these effects, revealing similar significant activations with SVC in all of the above regions (Table S4).

We also formally determined the overlap of activations across both groups, by performing a conjunction analysis that tested for increased activity in the unpleasant relative to the pleasant condition shared between patients and controls (GLM1). In line with the group results above, such common effects were found in the left amygdala, but also PAG, thalamus, visual areas in fusiform and occipital cortex, as well as the anterior temporal pole (Table 3, Fig. 4). Thus, these areas were consistently modulated by negative affect in both patients and controls.

Finally, in light of our previous work showing a specific association between emotional arousal and activation in amygdala and PAG during

Table 3

Whole brain voxel-wise activations between-groups. Significant clusters obtained from GLM1 and their MNI coordinates (centre of mass), voxels, and Z-score during force production in the presence of unpleasant compared to pleasant images, for controls relative to patients, patients relative to controls, and for the conjunction between patients and controls.^a

		MNI coordinates (mm)			Voxels	Z-score
		x	y	z		
HC [U > P] versus FND [U > P]						
R	Inferior Frontal Gyrus [BA 47]	42	35	−17	570	6.49
L	Inferior Frontal Gyrus [BA 47]	−45	38	−11	104	4.95
L	Anterior Insula	−33	17	−17	129	5.53
R	Medial Frontal Gyrus [BA 8]	3	38	46	461	5.62
R	Superior Temporal Gyrus	57	−58	16	433	5.31
FND [U > P] versus HC [U > P]						
R	Cerebellum Anterior Lobe Vermis	3	−55	−32	164	5.60
L	Hippocampus	−30	−16	−17	53	4.52
L	Posterior Cingulate Cortex	−9	−55	25	34	3.79
L	Middle Occipital Gyrus [BA 19]	−51	−76	−2	101	5.27
R	Inferior Occipital Gyrus [BA 19]	45	−82	−8	202	5.91
Conjunction FND [U > P] & HC [U > P]						
L	Amygdala	−18	−4	−20	55	5.00
R	Periaqueductal Gray	6	−28	−11	21	3.99
L	Thalamus	−3	−13	4	27	3.83
R	Fusiform Gyrus	48	−49	−17	197	5.51
L	Posterior Middle Temporal Gyrus	−57	−64	4	288	5.23
R	Anterior Middle Temporal Pole	48	11	−38	201	4.97
L	Middle Occipital Gyrus [BA 19]	−42	−88	13	144	4.53

^a Clusters listed had a minimum of 20 voxels. BA, Brodmann area; P, pleasant; U, unpleasant; L, left; R, right.

motor force control in healthy individuals (Blakemore, et al., 2016), we further examined these two areas using anatomically defined ROIs. Mean beta estimates for each region, group, and emotional condition were extracted from the first-level and averaged, and analysed using mixed model analyses (lme4 package; R software). Significant main effects of emotion were found for the left amygdala ($t=5.9$, $p=.001$) and right PAG ($t=9.6$, $p=.001$). The main effect of group and the group-by-emotion interaction were non-significant. Thus although amygdala and PAG were, as expected, sensitive to negatively valenced images during force maintenance, contrary to the hypothesis derived from other studies (see introduction), these regions were similarly engaged in patients and controls.

4. Discussion

Functional symptoms have long been proposed to be associated with emotional causes (Babinski, 1909; Freud and Breuer, 1895; Janet, 1893), yet empirical evidence supporting these theories is scarce. Using an emotional-force task that exploits the intimate association between emotion and action tendencies (Coombes, et al., 2008; Frijda, 2009), we sought to bridge abnormal motor function with alterations in affective processing in motor FND. We have previously demonstrated modulation of motor control by negative emotional information in healthy volunteers, consistent with an engagement of defensive beha-

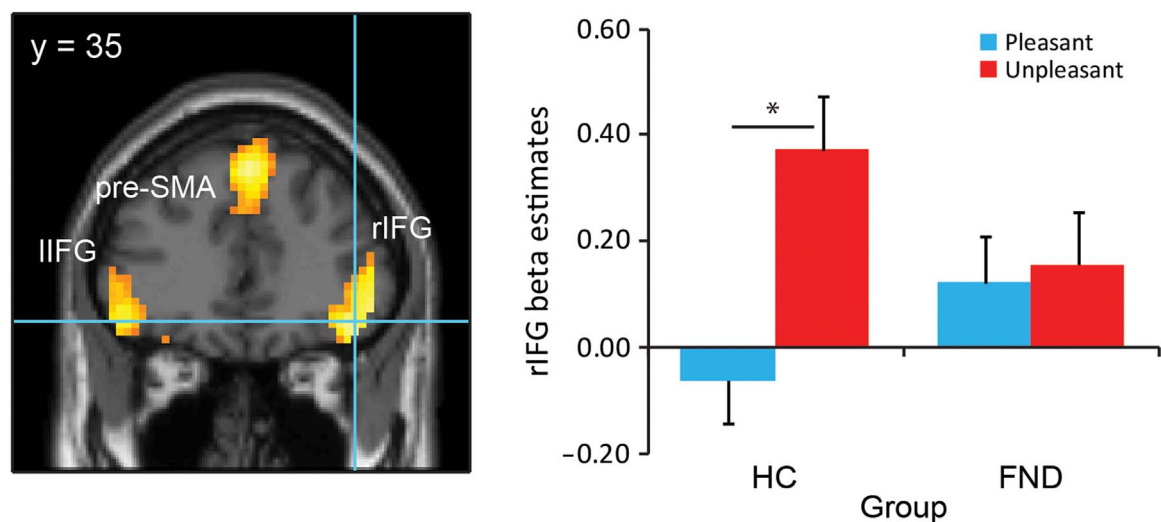


Fig. 2. Differential effects in controls relative to patients. The SPM illustrates the group by emotion interaction, comparing the unpleasant versus pleasant (U > P) contrast in HC relative to FND, using an exclusive masking procedure. Activations in bilateral IFG and pre-SMA survived a threshold of $p < .001$ uncorrected, with a minimum of 20 voxels. Coordinates correspond to the MNI template (x,y,z; mm). Mean beta estimates for right IFG are also shown (extracted from the cluster using an 8 mm diameter sphere centred on the second-level activation peak) and illustrate the differential effects of emotion between groups. A similar pattern of results was found for left IFG and pre-SMA. Error bars represent standard error.

viour in response to motivationally-salient, aversive stimuli (Blakemore, et al., 2016). While these effects were replicated here, we found that patients with FND exhibited a more pronounced influence of negative emotional signals on voluntary force control. Patients showed no significant decay in force production while viewing unpleasant images; they maintained force output at the target level throughout the trial, similar to the condition in which visual feedback was provided, but unlike during viewing of pleasant images. Remarkably, this negative valence-driven effect on force output was almost 2.5 times greater than that observed in controls. Such alteration of motor control in patients provides the first direct support for an abnormal relationship between the emotion and motor systems in FND.

In addition to these novel behavioural findings, our fMRI results identified a network of cerebellar-limbic and frontal regions that were differentially modulated during force control in the unpleasant (relative to pleasant) condition for patients and controls, respectively. In particular, the vermis, vPCC, and hippocampus were highlighted as key neural sites showing greater activation to negative affect in patients. These regions may thus play a role in aberrant integration of affective and motor information in FND, for example by promoting excessive defensive motor actions in high arousing aversive contexts. Conversely, both medial prefrontal cortex (mPFC) and more lateral regions in IFG, two areas known to be associated with motor control and response selection (Mostofsky and Simmonds, 2008), showed greater increases in controls during the negative emotion condition, whereas the amygdala and PAG exhibited no difference between groups.

An effect of negative affect on force output accords with and extends our earlier findings in healthy participants (Blakemore, et al., 2016). Using a similar paradigm, we reported that unpleasant stimuli with high levels of motivational significance attenuated force decay due to stronger engagement of the aversive motivational system and greater motor mobilization (Bradley, et al., 2001), which may reflect a defensive immobility reaction accompanied by heightened attention and sensory processing (Bradley, et al., 2011). Here we found that this behavioural effect was exaggerated in motor FND. According to the defense cascade model (Bradley, et al., 2001; Lang, et al., 1997), this indicates that the defensive system engagement was greater in patients than in controls, in line with the notion that FND may result from abnormal affective responding (Babinski, 1909; Freud and Breuer, 1895; Vuilleumier, 2014). The maintenance of higher force in the

unpleasant condition by patients is akin to freezing behaviour (reduced body motion and increased muscle tone), observed in various animal species in the presence of threat or stress (Blanchard, et al., 2001; Blanchard and Blanchard, 1986; Mobbs, et al., 2007). Comparisons of defensive actions in animals (such as freezing, motor arrest, protective immobility, or playing dead) with functional symptoms have already been drawn by others (Kretschmer, 1948; Nijenhuis, et al., 1998; Whitlock, 1967). It is thought that the triggering and maintenance of functional symptoms by psychological stressors may be underpinned by these primitive, stereotyped behaviours, as a non-conscious avoidance or coping mechanism (Vuilleumier, 2005). Interestingly, high levels of cortisol and pre-exposure to psychosocial stressors lead to greater fear responses and longer freezing duration in monkeys (Kalin, et al., 1998).

Activation of the defensive system by emotional cues has already been investigated in patients with functional symptoms. Seignourel et al. (2007) found normal potentiation of the startle eyeblink response (a protective reflex following abrupt stimuli) following unpleasant stimuli in FND, but potentiated responses following pleasant stimuli, rather than startle inhibition as seen in controls, indicating aversive physiological reactivity to both negative and positive emotions in these patients. Other studies point to a general arousing effect, where patients have shown increased amygdala activity to fearful and happy faces compared to neutral faces (Voon et al., 2010a), a failure to habituate skin conductance to acoustic stimuli and higher baseline arousal levels (Lader and Sartorius, 1968), and increased levels of baseline cortisol (Bakvis, et al., 2010).

Our behavioural findings, however, were not due to the arousing nature of emotional images per se, because force decayed as expected when viewing positive images. Furthermore, force output in the pleasant condition did not differ between patients and controls. A selective effect of negative emotions in our study is therefore inconsistent with a general effect of arousal in FND. However, none of the previous studies (e.g., Seignourel, et al., 2007; Voon et al., 2010a) investigated the effect of arousal on voluntary motor output, but instead focussed on passive exposure conditions. It is possible that differences in emotional valence emerge only when concurrent affective processing and volitional motor control are required. Additionally, our between-group differences in force decay in the unpleasant condition cannot simply be due to stronger emotional appraisal of negative images by patients or differences in baseline force output. Patients and controls evaluated the valence and arousal of images at a similar

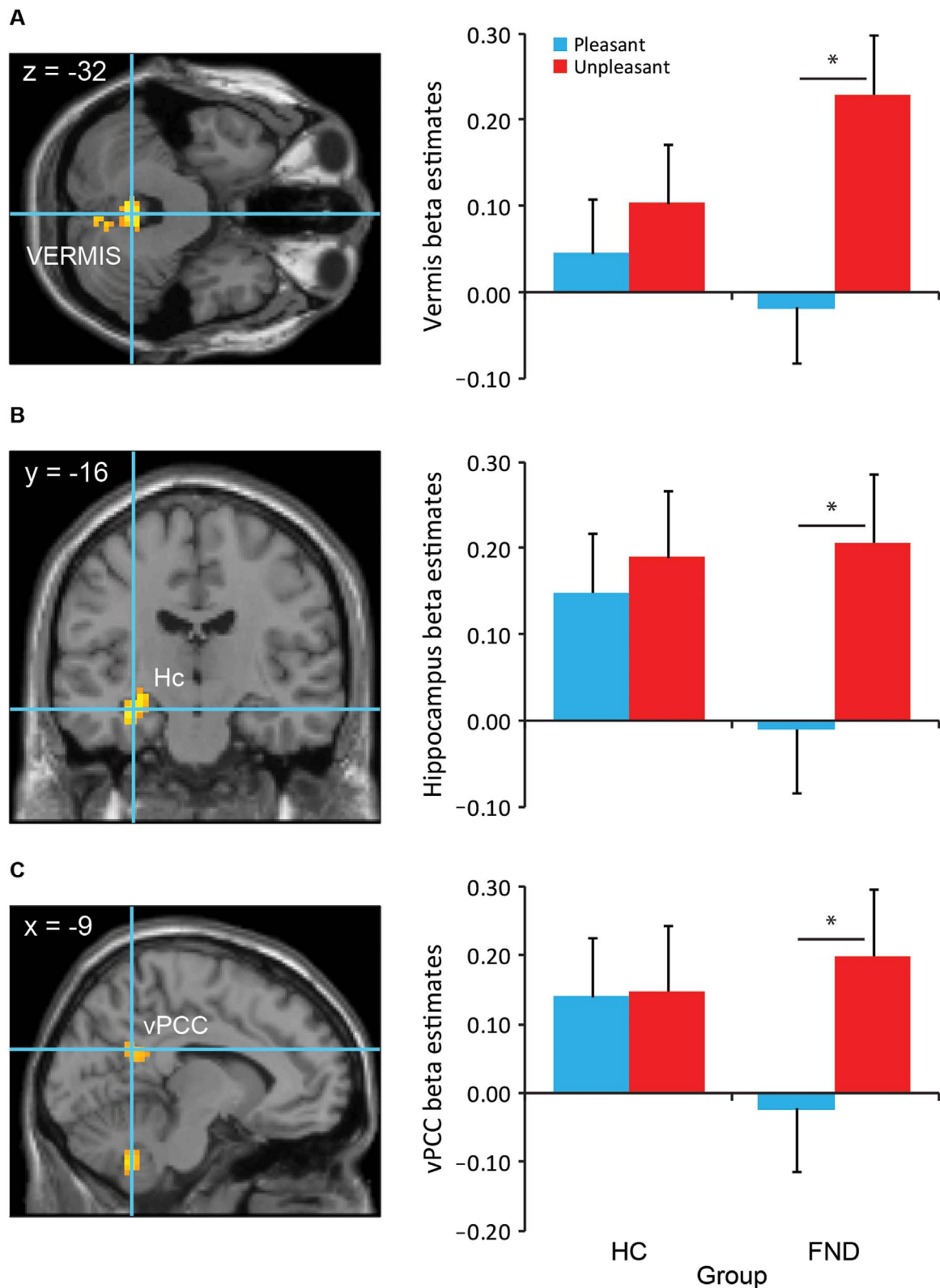


Fig. 3. Differential effects in patients relative to controls. SPMs illustrate the group by emotion interaction in the **A**, cerebellum vermis, **B**, hippocampus (Hc), and **C**, vPCC, when comparing the unpleasant versus pleasant (U > P) contrast in FND relative HC, using an exclusive masking procedure. Activations survived a threshold of $p < .001$ uncorrected, with a minimum of 20 voxels. Coordinates correspond to the MNI template (x,y,z; mm). Mean beta estimates for each region are also shown (extracted from the cluster of interest using an 8 mm diameter sphere centred on the second-level activation peak) and illustrate the differential effects of emotion between groups. Error bars represent standard error.

intensity. Moreover, maximum force and force immediately prior to image onset was not different between groups. In agreement with previous reports (Kanaan, et al., 2007; Seignourel, et al., 2007), a decoupling between affective experience and behavioural reactivity

may reflect the non-volitional nature of FND, where modulation of emotion and motor processing occur outside conscious awareness (Blakemore, et al., 2013, 2015).

A dissociation between affective experience and emotion-motor

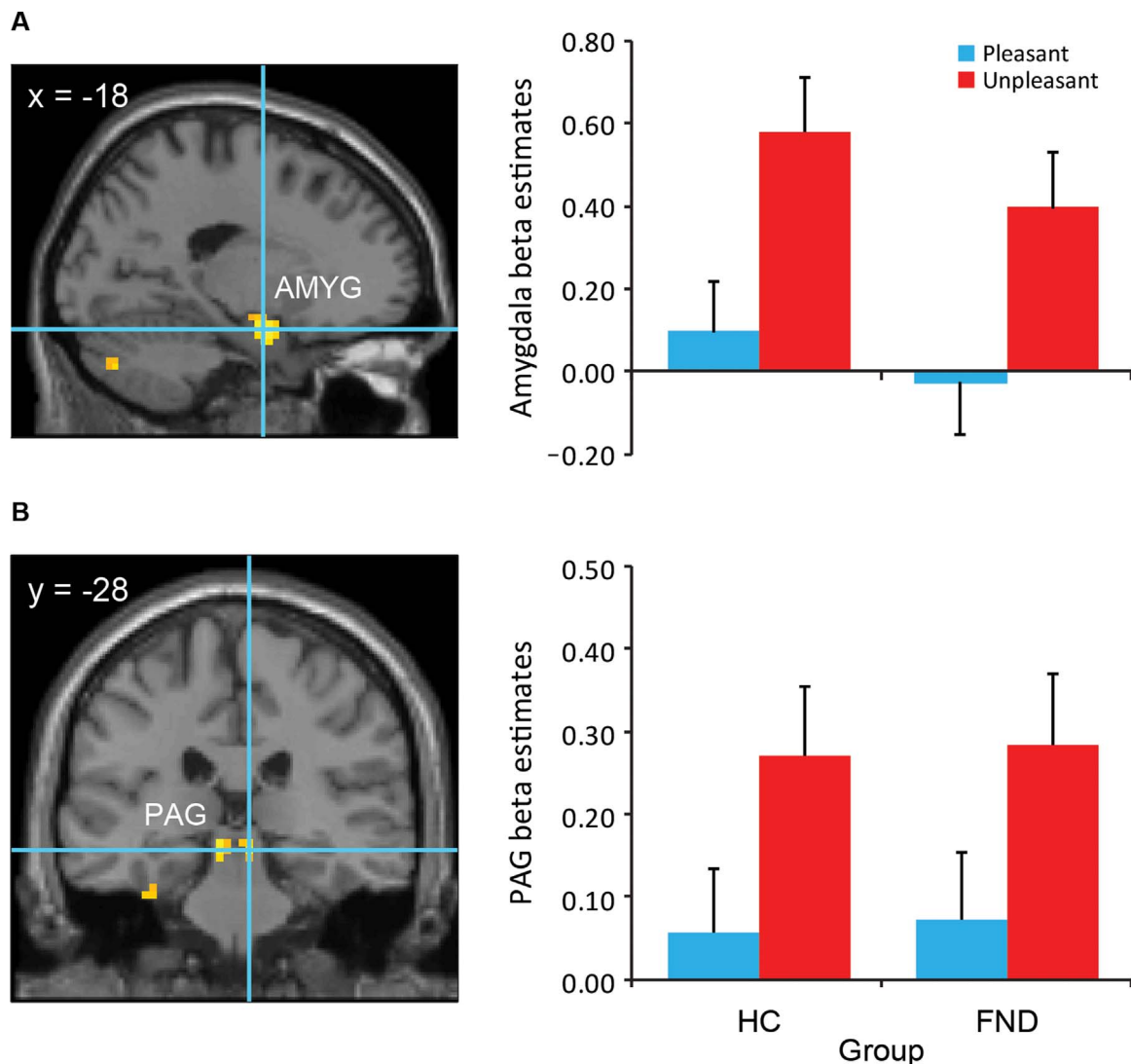


Fig. 4. Conjunction effects between patients and controls. SPMs illustrate the significant conjunction results for **A**, left amygdala (AMYG) and **B**, PAG, when comparing shared activations from the unpleasant versus pleasant (U > P) contrast in both FND and HC. Activations survived a threshold of $p < .001$ uncorrected, with a minimum of 20 voxels. Coordinates correspond to the MNI template (x,y,z; mm). Mean beta estimates for the amygdala and PAG are also shown (extracted for each group and emotional condition from first-level analyses, based on anatomically defined regions of interest) and illustrate the significant main effect of emotion. Error bars represent standard error.

interactions was also evident at the neural level. Despite similar emotional responses in amygdala and visual areas between groups, the exacerbated defensive behaviour in patients was accompanied by differential activity in brain regions involved in motor preparation and behavioural control. Controls relative to patients activated the bilateral IFG and pre-SMA in response to negative images (U > P contrast), consistent with our previous findings (Blakemore, et al., 2016), whereas patients relative to controls (U > P contrast) had greater activity in the cerebellum vermis, in addition to vPCC and hippocampus, with no significant effect in prefrontal cortex.

The cerebellum plays a critical role in controlling motor function, but also in non-motor domains such as emotional processing (Snow, et al., 2014), through its extensive corticocerebellar connections with limbic regions (Stoodley and Schmahmann, 2009). We found increased activation in the posterior lobule VIIb for unpleasant images in both groups, in accordance with others showing this region is implicated in encoding multimodal aversive processing (Moulton, et al., 2011; Schraa-Tam, et al., 2012). Cerebellar activation unique to patients however, was observed more ventrally, in the vermis. Lesion studies in humans point to an integral role of the vermis in affective regulation (Schmahmann and Sherman, 1998), associative learning (Turner et al., 2007), and fear conditioning (Maschke, et al., 2002). Moreover,

emotional processing alone may not be sufficient to activate the vermis, but this structure may selectively be involved in regulating motor processes in emotional (particularly fear-related) contexts (Snow, et al., 2014). Coombes et al. (2012) reported increased vermal activity when force was produced concurrently with emotional image viewing, but not during passive image viewing. Similarly, in patients we found increased vermal activity for the U > P and unpleasant > feedback contrasts, but no significant activations for the reverse contrasts, or for the feedback condition alone. Moreover, in non-human animals, the vermis plays an important role in defensive freezing behaviour (Snow, et al., 2014). Vermal-lesioned rats and mice with cerebellar mutations demonstrate reduced freezing and impaired conditioned fear responses, notably diminished bradycardia, a typical physiological index of freezing (Sacchetti et al., 2004; Supple and Leaton, 1990; Supple et al., 1987). Conversely, electrical stimulation of the vermis elicits freezing (Berntson and Torello, 1982). Adding to this literature, our results show that threat-evoked effects on motor control also engages the human cerebellum. More specifically, higher activity of the vermis when force is maintained at the target level in response to aversive stimuli supports the notion that FND is associated with exaggerated defensive behaviour.

Interestingly, the vermis is also implicated in emotional memory

(Damasio, et al., 2000; Sacchetti, et al., 2002), through direct and indirect anatomical connections with the hippocampus, amygdala, and PAG (Heath and Harper, 1974; Snider and Maiti, 1976). An intimate functional relationship between the vermis and hippocampus has been documented (Newman and Reza, 1979), including in fear-related memories (Maren and Holt, 2004). In agreement, together with increased activity of the vermis, we found differential activation of the hippocampus in the unpleasant condition (versus pleasant) specific to patients. Modulation of a cerebellar-hippocampal circuit subserving defensive behaviour may reflect a disturbance in emotional learning in FND, leading to exacerbated behavioural reactivity in particular contexts. The presentation of unpleasant images could possibly engage associations stored in long-term memory (Henke, 2010), tagging stimuli with threat-related information or personal relevance. This could result from past history of psychosocial stressors, which are thought to promote functional symptoms (Roelofs, et al., 2005), as also proposed for pathological anxiety (Rosen and Schulkin, 1998). Kanaan et al. (2007) also reported increased activity in hippocampus in a single patient with functional paralysis when exposed to trauma-related narratives.

The vPCC is another brain region critically implicated in the integration of emotion and memory (Eryilmaz et al., 2014; Maddock et al., 2003; Vogt et al., 2003), but also self-reflection (Johnson, et al., 2002; Kircher, et al., 2001) and retrieval of autobiographical information (Addis, et al., 2007). The vPCC has dense connections with the hippocampus and parahippocampal cortex (Kobayashi and Amaral, 2007; Vogt et al., 2006), and may serve to detect and assess the affective self-relevance of current or past events via direct downstream projections to the anterior cingulate cortex (Vogt et al., 2006). Increased vPCC activity for unpleasant (versus pleasant) stimuli in patients is therefore compatible with heightened evaluation of visual stimuli for emotional relevance and salience. Viewing unpleasant images might lead to an overestimation of threat and self-relevance, possibly through retrieved episodic memories linked to negative life events (Brown, 2004). Increased PCC activity was also observed in patients with functional tremor by Voon et al. (2011), who concluded that patients may aberrantly assign “stimuli, states or memories as self-relevant or salient”. Similarly, Cojan et al. (2009) found greater PCC activity during motor preparation in a patient with functional paralysis, thought to reflect abnormal self-referential processes that may alter subjective motor agency. Taken together, these findings indicate that vPCC and hippocampus outflow could mediate abnormal access to self-relevant information in memory, which in turn could modulate motor control circuits and action readiness (Frijda, 2009), facilitating excessive defensive responses or other stereotyped behaviours (Vuilleumier, 2014). Such connections between limbic structures involved in memory and emotion with motor pathways in cerebellum, but also basal ganglia (Vuilleumier, et al., 2001), SMA (Voon et al., 2010a, 2011), and prefrontal regions (Cojan, et al., 2009) might constitute dedicated networks for the selection and regulation of defensive motor behaviour in aversive emotional contexts (Newman and Reza, 1979). Reciprocal connections between limbic structures and the cerebellum mean the vermis is well placed to integrate and regulate information about sensory stimuli, motor output, and emotional state.

We note however that the pattern of relative increases to negative stimuli observed in patients differed between the cerebellum (with selective activation to negative stimuli when compared to controls) and limbic memory circuits (with apparent decrease to positive stimuli when compared to controls). Although direct comparisons between groups might be partly confounded by differences in baseline fMRI signal, this pattern indicates that only cerebellum activity directly paralleled force output, consistent with a direct role of this region in motor control. A possible alternative interpretation for the differential effects of emotion in hippocampus and vPCC could be that patients tend to disengage these regions during the viewing of pleasant images, due to reduced access to positive memory associations, unlike controls.

Thus FND might be associated with blunted reactivity to positive emotions at the neural level, but decoupled from direct consequence on affective experience and overt motor behaviour. In any case, this would indeed suggest that force output itself is not proportional to activity level in these regions; indeed the limbic memory circuits might act by regulating other regions more directly responsible for exerting or controlling force output, including cerebellum.

These data therefore also suggest that a low salience or self-relevance of positive emotional signals may cause FND patients to have difficulties efficiently forming memories (Fernández, et al., 1999) with positive emotional or motivation-related content, in keeping with higher incidence rates of depressive symptoms in this population (Binzer et al., 1997; Stone et al., 2010). Activation of the left hippocampus in particular, plays an important role in the retrieval of autobiographical memories, and scales with the degree of emotionality and personal significance (Addis, et al., 2004). Poor encoding or consolidation of pleasant events in memory could hinder recollection of positive memories during viewing of pleasant images, requiring less involvement of the hippocampus and vPCC (Eldridge, et al., 2000), but conversely exacerbate negative biases related to stressful or trauma events. A diminished arousal response to pleasant stimuli was also proposed to explain modulation of force control to pleasant and unpleasant images in subclinical depression (Naugle, et al., 2010). Such an interpretation is consistent with previous work (Sterpenich, et al., 2014) showing decreased hippocampal activity to positive stimuli in individuals who have difficulty maintaining internal arousal and motivation. Interestingly, these same individuals also showed enhanced emotional reactivity to negative emotional information. Thus, an explanation of a (unconscious) dampened arousal response to positive stimuli in FND is not necessarily incompatible with an explanation of an emotional bias to negative stimuli. However, future studies will be needed to disentangle the role of enhanced reactivity to negative emotion and reduced responses to positive emotions in FND, and how this may be mapped onto brain circuits mediating emotion regulation, memory, and motor control.

Contrary to previous reports (Kanaan et al., 2007; Voon et al., 2010a), we found no differential emotional effects in the amygdala. Both patients and controls demonstrated increased amygdala activity for unpleasant versus pleasant images. Likewise, no difference between groups was observed in the PAG, a midbrain region crucial for the generation of defensive freezing (Bandler and Shipley, 1994; Brandão, et al., 2008; Hermans, et al., 2013; Satpute, et al., 2013) and implicated in emotion-modulated force control (Blakemore, et al., 2016). These results do not support the hypothesis that these areas would be abnormally modulated in FND. The discrepancy might be due to the use of more general aversive images, whereas previous studies used social threat stimuli (faces and trauma-recall). Furthermore, the lack of significant IFG activation in patients in the U > P contrast does not imply an absence of response to unpleasant stimuli. Rather, patients showed a loss of valence-specific effects in IFG and mPFC, as these areas responded to general arousal, with similarly enhanced activation to pleasant and unpleasant stimuli. Although this remains speculative without direct comparisons against a neutral emotion condition, this notion would accord with general arousing effects (Seignourel et al., 2007; Voon et al., 2010a).

Some strengths and limitations of our study need to be considered. The strength lies in using concomitant measures of brain activity and motor output during volitional motor control to directly probe for disrupted emotion-motor interactions in FND. Previous studies have simply inferred alterations in motor system processes by upstream emotional influences (Marshall et al., 1997; Voon et al., 2010b; Vuilleumier et al., 2001) without using emotional stimuli, or assessed emotion processing without any measure of voluntary movement (Voon et al., 2010a). Here we directly tested historical views (Babinski, 1909; Breuer and Freud, 1955; Freud and Breuer, 1895; Janet, 1893) that abnormal physical symptoms in FND are causally

linked to emotion triggers. For this reason, we also included patients with a range of functional motor symptoms, similar to other recent studies (e.g., Voon et al., 2010a). Whilst we found significant group effects in affective-motor processing at the neural and behavioural level, our results need to be interpreted cautiously due to our relatively small sample size. However, to date there are few neuroimaging studies in FND (with motor symptoms) with sample sizes greater than ten, given difficulties in recruitment and cooperation of patients (e.g., Aybek, et al., 2014, n=12; Voon et al., 2010a, n=16). Moreover, as noted by Friston (2012), a small sample size need not preclude the validity of the positive results. Exploratory analyses on subsamples of patients with a history of negative (e.g., paralysis) or positive (e.g., tremor) symptoms, or predominantly motor or sensory deficits (not described in detail here) revealed a qualitatively similar pattern of results for force output and brain activity (see [Supplementary material](#)). Additional research comparing subtypes with a larger sample size would permit a formal quantitative assessment and definitive conclusion regarding various subtypes. Additionally, although patients were on average older than the controls, we included age as a covariate in all analyses to control for any age-effects. Age did not correlate with force magnitude or brain activity in any region of interest. Effects of medication and/or psychiatric comorbidity could have also influenced our results. While these possibilities cannot be ruled out, we found no difference in HADS score between groups. Passive defensive behaviour is not uniquely associated with FND. Freezing has also been linked to other threat-related psychopathology, for instance, immobility during trauma is thought to play a role in the aetiology of post-traumatic stress disorder (PTSD; Hagenaars et al., 2014). While it is possible individuals with PTSD might also show a pronounced effect of unpleasant stimuli on force control in our task, given that the key diagnostic criterion in FND is altered functioning of the voluntary motor system, it is reasonable to speculate that the neural networks involved in aberrant emotion-motor processing in FND would differ to PTSD. Whether distinct or similar neurobiological pathways underpin freezing behaviour in different threat-related psychiatric disorders remains a fruitful area for future research. Memory-related signals from limbic areas, including hippocampus, vPCC, or ventromedial prefrontal cortex (Cojan, et al., 2009; Vuilleumier, 2014) might act to bias different motor selection patterns based on psychopathological mechanisms and personal history of the patients.

It is unlikely anti-depressant or anti-anxiety medication facilitated force maintenance in patients as these medications generally dampen rather than augment emotional reactivity (Outhred, et al., 2013; Patin and Hurlmann, 2011). Moreover, force output in the unpleasant condition was qualitatively similar for those patients 'on' compared to 'off' medication. Finally, demonstrating that negative emotions modulate voluntary movement indicates a prominent role of emotion in FND, but does not demonstrate causality. It remains to be determined whether negative emotions initially trigger motor anomalies, or whether exaggerated defensive reactions are a consequence of FND.

In conclusion, our study reveals for the first time a direct influence of affective information on motor output in conversion disorder, consistent with exacerbated defensive responses to aversive stimuli. Patients engaged a distinct neural network during force production in the presence of negative stimuli, with hyperactivation in the cerebellar vermis, hippocampus, and vPCC, unlike controls who showed enhanced activity in IFG and mPFC. These data indicate heightened tagging of emotional relevance in memory systems, resulting in abnormal translation of negative affective signals into dysfunctional motor commands and excessive freezing-like behaviour. Corroborating early suggestions that emotions and conversion symptoms are inextricably linked (Breuer and Freud, 1955; Freud and Breuer, 1895), this study highlights a possible neurobiological pathway through which psychological stressors promote defensive behaviour and modulate volitional movement outside of conscious awareness. Intervention studies that manipulate affective responses might be usefully consid-

ered in order to facilitate normal motor function in these patients. For example, behavioural interventions in which patients train movement control in the presence of stressors may aid in downregulating hippocampal and vermal activity, similar to therapeutic strategies targeting desensitisation of past trauma in PTSD (Harvey, et al., 2003). Alternatively, because attentional focus is a component of freezing behaviour, interventions may function to reduce stressors by expanding attention to positive low arousing emotional signals during concurrent movement performance. Such training techniques of modifying attention are thought to help manage freezing states and dampen activation of the defense cascade in clinical practice, possibly through top-down modulation of neural networks implicated in the freeze response (Kozłowska, et al., 2015).

Conflicts of interest and sources of funding

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuropsychologia.2016.11.005.

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