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Stress-evoking emotional stimuli exaggerate deficits in motor function in Parkinson's disease

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ABSTRACT

Recent animal studies have shown that stress can profoundly affect motor behaviour and worsen motor deficits associated with Parkinson's disease (PD) by acting on the dopaminergic system, possibly due to stress-associated emotional changes. However, systematic investigation of the influence of acute emotional stressors on motor function in PD is scarce. Here we examined the effect of repeated exposure to negative emotional stimuli on grip-force control in PD. Eighteen patients with idiopathic PD (tested off-medication) and 18 healthy controls produced an isometric precision grip contraction at 15% of maximum force while viewing a series of unpleasant, pleasant, or neutral emotional images (blocked presentation; without visual feedback of force output). Force output was continuously recorded together with change in forearm muscle activity using electromyography. While viewing unpleasant images, PD participants exhibited increased variability and 4–8 Hz oscillations of force output, and greater flexor muscle activity. With feedback occluded, the decay in force amplitude was pronounced, but not modulated by emotion. In contrast, in controls, the decay in force amplitude was attenuated while viewing unpleasant images compared with pleasant and neutral images. The findings in PD may reflect an increased number of motor units discharging and reduced ability to use sensory feedback to alter the descending drive. Modulation of synaptic input to the motoneuron pool could result from acute stress-induced enhancement of sympathetic activity and/or amplification of dopamine depletion. Corroborating previous findings in animal models of PD, exposure to stress-evoking emotional stimuli can exacerbate impairments in fine motor control in individuals with PD.

1. Introduction

There is a growing body of literature supporting the long-held notion that stress, both acute and chronic, plays a key role in Parkinson's disease (PD) (for reviews, see Metz, 2007; Hemmerle et al., 2012). Such literature is consistent with our clinical and laboratory (hitherto unpublished) observations that motor symptoms of PD can be temporarily exacerbated by stress. For example, we and others have observed a steady limb can become markedly tremulous simply by beginning to discuss a sensitive issue, or by having performance assessed in a laboratory task (Raethjen et al., 2008). A natural question is whether acute stress might further affect skilled, goal-directed movements that are already impaired in PD, such as the ability to control precise grip-forces, as well as exacerbating motor symptoms.

Acute stress, originally viewed as non-specific adaptive physiological responses to demands on the body (Selye, 1936), can profoundly influence motor behaviour by acting on the dopaminergic system, possibly through a mechanism of stress-associated emotional changes (Metz et al., 2005). Evidence from animal research has shown, in rats for instance, that acute exposure to a stressor impairs accuracy of skilled movements (Metz et al., 2005) and enhances locomotor activity in open-field tests (Roth and Katz, 1979), while anxiolytic drugs reverse these effects (Metz et al., 2003). Rodent models of PD have shown that stress can acutely (Snyder et al., 1985; Keefe et al., 1990) and chronically (Snyder et al., 1985; Smith et al., 2008; Hemmerle et al., 2013) worsen PD-like motor deficits, possibly by accelerating dopaminergic cell degeneration. However, the role stress, and in particular acute affective stressors, may play in modulating motor function in individuals

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with PD remains to be elucidated.

Neurodegeneration of dopaminergic pathways in PD not only affects neural circuits involved in motor control giving rise to the cardinal features of PD (tremor, bradykinesia, and rigidity); dysfunction of motor basal ganglia-thalamocortical circuits also impairs control of skilled movements (Alexander et al., 1990; Galvan et al., 2015), particularly those involving manual dexterity. There is extensive evidence showing PD is associated with fundamental abnormalities in precision grip-force control, affecting a constellation of everyday activities. For example, individuals with PD exhibit impaired force maintenance and increased force variability, especially when visual feedback is occluded (Vaillancourt et al., 2001a, 2001b), slower rates of force development (Neely et al., 2013; Pradhan et al., 2015), and longer relaxation times (Robichaud et al., 2005). Research in healthy older adults has also shown that precision grip-force is influenced by acute stress. Physical stressors can significantly exacerbate force variability (Noteboom et al., 2001; Christou et al., 2004), an effect which is again augmented when feedback is absent (Christou, 2005).

Besides impacting motor control, neurodegeneration of dopaminergic pathways in PD also results in dysfunction of mesocorticolimbic pathways integrated with the basal ganglia. These limbic-basal ganglia circuits are implicated in non-motor symptoms of PD that precede motor symptoms (Rane and King, 2011), such as symptoms of depression, anxiety, and apathy (Aarsland et al., 2009). Moreover, individuals with PD show deficits in emotional processing, especially negative emotions, including impaired recognition of emotional prosody and expression (Péron et al., 2012), diminished facial expressivity (Bowers et al., 2006a), and blunted startle reactivity (Miller et al., 2009), where startle modulation correlates with disease severity (Bowers et al., 2006b).

Although intimate associations between emotion and motor control are well-documented (Blakemore and Vuilleumier, 2017), and in particular in PD, research points to a link between stress-induced emotional changes and dysfunctional motor behaviour (Metz, 2007), systematic investigations of the influence of stress on voluntary motor function in PD are scarce. Here we investigated emotion-motor interactions by examining whether acute stress-evoking aversive emotional information modulates the control of force production in individuals with PD.

We used an established emotional-force control paradigm in which participants produce submaximal isometric precision grip-force while viewing high and low arousing affective images. However, unlike our previous studies where the emotional conditions were randomised (Blakemore et al., 2016a, 2016b), each block of trials contained images with the same affective valence (i.e., blocked viewing of positive, negative, or neutral images). Repeated exposure to stimuli of the same affective valence permits examination of a strong, sustained emotional state that sensitises emotional reactivity (Bradley et al., 1996; Smith et al., 2005). Furthermore, blocked viewing of aversive images can induce an acute stress response, elevating physiological arousal, sympathetic nervous system activity, and neuroendocrine responses, for example, of cortisol and norepinephrine (Codispoti et al., 2003; Mendonça-de-Souza et al., 2007; Sánchez-Navarro et al., 2012).

Based on our previous findings (Blakemore et al., 2016a), we hypothesised in healthy volunteers that force output would be maintained closer to the target level while viewing negative emotional images relative to positive and neutral images. This negative-valence modulation of force output could be associated with increased muscle activity in the forearm flexor and extensor muscles, reflecting increased muscle tone associated with defensive behaviour to threatening stimuli (Bradley et al., 2001; Koutsikou et al., 2014; Blakemore et al., 2016a). For PD participants, we hypothesised that repeated exposure to aversive emotional stimuli would further exacerbate existing PD-related impairments in grip-force control, evidenced by difficulties maintaining force at a constant level, increased variability and low-frequency power of force output, and greater muscle activity in the forearm flexor muscle due to its agonist role in precision grip, and the presence of rigidity in PD participants. Such findings would provide quantitative validation of the notion that stressors can amplify motor deficits in PD, and may have clinical relevance for the development of interventions that aim to reduce stressors to optimise motor function in these individuals.

Table 1
Demographics and clinical characteristics of Parkinson's disease (n = 18; 9 female) and healthy control participants (n = 18; 9 female). Data shown as mean ± standard deviation.

	HC	PD	p-value[a]
Age (years)	67 ± 7	65 ± 7	ns
Education (years)	13 ± 3	12 ± 2	ns
Handedness[b] (%)	86 ± 21	91 ± 14	ns
Duration of disease (years)	–	9 ± 5	
MDS-UPDRS motor[c,d]	–	31.9 ± 11.9	
Rigidity		2.1 ± .8	
Postural tremor		.4 ± .7	
Kinetic tremor		.6 ± .6	
Rest tremor		.8 ± 1.2	
Hoehn-Yahr[c,d]	–	2.3 ± .8	
Maximum force (N)	63.5 ± 29.5	52.4 ± 17.8	ns
HADS anxiety subscale[d] *(range)*	3.2 ± 2.9 *(0–6)*	5.2 ± 3.0 *(0–10)*	ns
HADS depression subscale[d] *(range)*	1.6 ± 1.7 *(0–7)*	4.1 ± 2.7 *(0–9)*	.002
MoCA score[d]	27.9 ± 2.0	27.1 ± 2.2	ns
SAM valence ratings			
Pleasant	6.3 ± .6	6.8 ± .7	
Unpleasant	2.4 ± .8	2.2 ± .6	
Neutral	5.3 ± .2	5.4 ± .4	
SAM arousal ratings			
Pleasant	5.4 ± 1.4	6.1 ± 1.0	
Unpleasant	5.9 ± 2.0	6.5 ± 1.2	
Neutral	3.7 ± 1.2	4.4 ± 1.0	

[a] Obtained from independent samples t-test analysis; ns $p > .05$.
[b] Handedness laterality quotient calculated using the Edinburgh Handedness Inventory (Oldfield, 1971).
[c] Scores obtained from PD patients *off*-medication (average time since last dosage of dopaminergic medication, 14.0 ± 2.3 h). Rigidity and tremor scores are for the right upper limb extremity.
[d] Scores obtained during the experimental session.

2. Material and methods

2.1. Participants

Eighteen participants meeting the United Kingdom Parkinson's Disease Society's criteria for idiopathic PD (Hughes et al., 1992) were recruited from the Movement Disorders Clinic at the New Zealand Brain Research Institute. PD participants were tested in a morning session 'off' antiparkinsonian medication. This was defined as not having taken any medication since the last scheduled dose of the day before. Five PD participants were taking psychotropic medications (see supplementary materials for medication details). The severity of parkinsonism *off*-medication varied from mild to severe (as determined on the day of experimental testing; Table 1): MDS-UPDRS Part III motor score range 12–54 (Movement Disorder Society-Unified Parkinson's Disease Rating Scale; Goetz et al., 2007); stage I-IV on the Hoehn and Yahr Scale (Hoehn and Yahr, 1967). PD participants were included if they had been previously classified as being in the cognitively normal range following comprehensive neuropsychological testing (Dalrymple-Alford et al., 2010, 2011). This testing was completed on average 7 ± 5 months prior to the experimental session. Given the variable delay between comprehensive neuropsychological testing and our experimental session, PD participants were screened again during the experimental session to reassess neurocognitive status using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) (Table 1). PD participants were also re-screened during the experimental session for the presence of mood disorders using the Hospital Anxiety and

Depression Scale (HADS; Zigmond and Snaith, 1983). Exclusion criteria included atypical parkinsonian disorder, history of dyskinesia, and history of other neurologic conditions. Eighteen healthy control (HC) participants were recruited and carefully matched to the patients according to age, sex, handedness, and years of education. Control participants also completed the MoCA (Nasreddine et al., 2005) and HADS (Zigmond and Snaith, 1983) during the experimental session.

All participants were right-handed (Oldfield, 1971) and completed the task with their right hand. All PD participants had right-side dominant motor symptoms, as determined by patient subjective reports, corroborated by the side-specific MDS-UPDRS motor items (right-side items: 14.6 ± 5.5, range = 6–25; left-side items: 7.8 ± 4.5, range = 0–18; scores out of 44). Testing only right-handed participants with right-side dominant motor symptoms avoided any confounding of hand or side-affected on our task. Participants were excluded if they had upper limb pain or injuries, a major psychiatric disorder in the previous 12 months (as assessed by medical history), non-age-normal hearing, or best corrected or uncorrected binocular Snellen visual acuity worse than 6/12. All participants provided written informed consent to all procedures and received monetary compensation of travel costs. The study was approved by the Southern Health and Disability Ethics Committee of the New Zealand Ministry of Health, in accordance with the Declaration of Helsinki.

2.2. Experimental design and procedure

Participants completed one experimental session consisting of an emotional-force control task, a task to give subjective affective ratings of stimuli, and a clinical assessment (HADS, MoCA, MDS-UPDRS Part III). The emotional-force control task and apparatus have been described in detail previously (Blakemore et al., 2016a, 2016b). Here we provide an overview and present details specific to the current experiment (see also supplementary material).

Participants produced a sustained isometric precision grip contraction by pinching a force-measuring device between their thumb and index finger at 15% of their maximum force. A measurement of maximum force output was determined at the beginning of the session (see supplementary material). PD participants completed the task with their most affected limb (all right side), determined by patient subjective reports and corroborated with the MDS-UPDRS motor score. Each of the experimental trials commenced with the presentation of a fixation cross on the display. Subsequently, two bars were presented, signalling the initiation of force production. A stationary white horizontal bar located in the centre of the screen represented the target force to be maintained (15% of the participant's maximum force). A black bar, initially located at the bottom of the screen, represented the instantaneous amount of force being produced. It moved vertically as participants pressed on the force device, providing continuous visual feedback of their force output. Using this visual feedback, participants were instructed to make the black bar reach the height of the white target bar and maintain that for 6 s. The visual feedback was then removed and the screen was entirely filled with an emotional image for 6 s, during which participants were instructed to maintain the target level of force output as accurately as possible until presentation of the next trial (signalled by the fixation cross reappearing).

Seventy-two emotional images were selected (see supplementary material) from the International Affective Picture System (IAPS; Lang et al., 2008), comprising three conditions (24 pleasant, 24 unpleasant, 24 neutral) based on their normative valence and arousal ratings (Supplementary Table S1). The conditions differentiated in the normative values for emotional valence ($p < .001$), while the normative values for arousal were matched between the unpleasant and pleasant conditions, but significantly differed ($p < .001$) from the neutral condition.

Participants completed three blocks of 24 (emotional) trials, where the images within each block were of the same affective valence (i.e., all trials within one block contained either pleasant, unpleasant, or neutral images). The order of blocks was counterbalanced across participants, using all six possible orders. Each block of trials began with an additional 4 trials in which no emotional image was presented, and the black and white bars remained on the screen for the entire duration of the trial providing continuous visual feedback of force output (feedback condition). Participants therefore completed a total of 84 trials (i.e. 72 trials with IAPS images and 12 with continuous visual feedback).

Following the emotional-force control task, participants viewed all emotional images a second time to provide subjective appraisals of their affective content. Ratings of valence and arousal were completed using a self-paced computerised version of the 9-point Self-Assessment Manikin (SAM) scale (Bradley and Lang, 1994), where 1 = unpleasant/low arousal, and 9 = pleasant/high arousal.

2.3. Behavioural measures and analyses

2.3.1. Mean and variability of force output

The force time series data were digitally filtered off-line using a second-order Butterworth filter (20 Hz low-pass cut-off), and then segmented into seven 1 s non-overlapping epochs to characterise each trial. The first epoch (epoch 0) was the final second of the initial feedback phase, by which time it was expected that force output would have stabilised. Epochs 1–6 covered the duration of the emotional image presentation (or the ongoing force feedback period in the 12 trials with continuing feedback). Mean force (expressed as a percentage of maximum force) and coefficient of variation (CV; standard deviation/mean force) were calculated for each epoch in each condition. Performance during each condition (for epochs 1–6) was examined by conducting separate two-factor repeated-measures mixed analysis of variance (ANOVA) including group (PD, HC) and condition (pleasant, unpleasant, neutral, feedback) on mean force and CV. To ensure any differences in performance were not attributable to differences in baseline force levels, we also examined force output and CV in epoch 0 (the final second of the initial feedback phase) in a separate group by condition repeated-measures ANOVA.

2.3.2. Subjective emotional ratings

Mean subjective valence and arousal ratings were analysed with separate repeated-measures ANOVA to compare group and emotional condition (pleasant, unpleasant, neutral).

2.3.3. Structure of force variability: frequency analyses

Evaluation of the power spectrum of force output during isometric contraction permits examination of the force structure (Baweja et al., 2009). The Fourier analysis method was applied to the force signal to examine the distribution of power in the 0–12 Hz band of the force spectrum (Vaillancourt et al., 2001b; Christou et al., 2004) for each 6 s period following image onset. Autospectral analysis was obtained using Welch's method using a non-overlapping Hanning window size of 1 s (1024 points) resulting in a bin resolution of .977 Hz. The absolute power in each bin and the relative power (the power in each bin expressed as a proportion of the peak power in the spectrum) were calculated to examine whether the experimental conditions influenced the magnitude of power and/or the distribution of power in the 0–12 Hz band of the force spectrum. The absolute and relative power were analysed as both variables have been shown to be modulated by stress (Christou et al., 2004; Christou, 2005) and the amount of visual information in healthy controls and PD (Vaillancourt et al., 2001b; Christou, 2005). For statistical analyses, power was then averaged across three frequency bands: 0–4 Hz, 4–8 Hz, 8–12 Hz (Vaillancourt et al., 2001b). Separate three-factor repeated-measures ANOVA were performed on the absolute and relative power to compare the two groups across the four conditions and three frequency bands. Significant three-way interactions were further examined with post-hoc analyses to determine differences among conditions and frequency

bands, between groups and within each group separately. Because all results for relative power were similar to those of absolute power, we do not report these data in detail. Multiple linear regression was also performed for each group to examine whether the structure of force (power) was related to force variability (CV). Power and CV were log transformed prior to linear regression to decrease the heteroskedasticity of the residuals. The correlation coefficients were assessed to determine the contribution of each frequency band to force variability.

Analyses were conducted using SPSS 22 (IBM SPSS Inc.), and the alpha set at .05. For all ANOVAs (including analyses of muscle activity), the Bonferroni degrees of freedom correction was applied to all multiple pairwise comparisons when a significant F statistic was obtained. Data in text represent mean ± standard deviation.

2.4. Electromyographical data processing and analysis

Surface electromyography (EMG) was recorded continuously and synchronously with the force signal from the right flexor digitorum superficialis (FDS) and right extensor digitorum communis (EDC) (see supplementary materials) as involvement of these extrinsic agonist and antagonist muscles in precision grip is clearly demonstrated (Maier and Hepp-Reymond, 1995b, 1995a). Similar to the force amplitude data, two analyses on the mean rectified EMG data were performed. To examine the change in muscle activity during concurrent motor performance and viewing of affective images, two-factor (group × condition) repeated-measures ANOVAs were used to separately analyse FDS and EDC amplitude for epochs 1–6. Next, to ensure any modulation of EMG activity by condition was not a function of differences in baseline muscle activity, we analysed the FDS and EDC amplitude in epoch 0 using an additional two-factor (group × condition) repeated-measures ANOVA.

3. Results

3.1. Mean and variability of force output

A significant group × condition interaction ($F_{(3,642)} = 36.8$, $p = .001$; $\eta^2 = .06$) was found for mean force output (over epochs 1–6). For controls (Fig. 1A), mean force was higher during viewing of unpleasant images (14.4 ± .8%) compared to during pleasant (14.2 ± 1.0%; $p = .035$; $\eta^2 = .07$) and neutral images (14.1 ± 1.0%; $p = .001$; $\eta^2 = .17$), which did not differ significantly, consistent with our earlier findings in healthy young volunteers (Blakemore et al., 2016a, 2016b). When feedback was occluded, there was little force decay below the target level; that is, force output in the condition where feedback was continuous (14.3 ± .4%) was not different to output in the emotional conditions ($p > .05$; $\eta^2 < .04$).

For PD participants (Fig. 1B), when visual feedback remained present throughout the trial, force output was consistently maintained close to the target level (14.0 ± .4%), indicating no evidence of fatigue or deficits in force control for this visually-guided task (Vaillancourt et al., 2001a). When visual feedback was removed, as expected, PD participants showed a marked decay in force output compared to the feedback condition ($p < .001$; $\eta^2 > .39$). Unlike controls however, the decay in force over time was not modulated by the emotional content of the images (pleasant, 13.0 ± .9%; unpleasant, 13.0 ± 1.3%; neutral, 12.8 ± 1.0%).

Regarding the variability of force output (CV), there was a marked difference between PD participants and controls, specifically for the negative emotional condition (Fig. 1C,D). While overall, CV in PD was higher than in controls, there was a significant group × condition interaction ($F_{(3,642)} = 20.0$, $p = .001$; $\eta^2 = .02$). For PD participants, relative to pleasant (.032 ± .024%) and neutral images (.031 ± .020%), viewing unpleasant images significantly increased force variability (.041 ± .041%; $p < .01$; $\eta^2 > .10$). Conversely for controls, force variability was reduced in the unpleasant (.020 ± .010%) compared to both the pleasant (.023 ± .011%) and neutral conditions (.022 ± .010%; $p < .001$; $\eta^2 > .15$). There was no difference in CV among the pleasant, neutral and feedback conditions for either group.

Analyses of mean force output and CV for the final second of the target display (epoch 0) revealed that initial motor output was similar across all conditions and between PD and controls. Thus any differences in performance were not due to differences in baseline force production. In addition, to determine whether the observed changes in force amplitude could have been due to fatigue or practice effects over the course of the experiment, we compared force output in the emotional conditions among the first, second, and third block presented to each participant. Results from a one-factor repeated-measures ANOVA showed no significant effect of block order for the PD ($F_{(2,214)} = 1.6$, $p = .212$) or control ($F_{(2,214)} = 2.2$, $p = .109$) participants. Thus in PD, force output in block 1 (13.1 ± 1.2%) was similar to force output in block 2 (12.9 ± 1.0%) and block 3 (12.9 ± 1.1%).

3.2. Emotional reactivity

Results for mean force output and CV were also independent of differences in emotional appraisal, as analyses of subjective valence and arousal ratings indicated the IAPS images elicited similar emotional judgments in PD and controls (Table 1). A significant effect of condition was found for valence ($F_{(2,68)} = 383.3$, $p = .001$; $\eta^2 = .97$), and arousal ($F_{(2,68)} = 26.5$, $p = .001$; $\eta^2 = .54$); the effect of group and the group × condition interaction were non-significant for both ratings. For valence, PD participants and controls rated unpleasant images as more negative than neutral and pleasant images, and pleasant images as more positive than neutral images ($p < .001$; $\eta^2 > .80$). For arousal, the neutral images were rated as less arousing ($p < .001$; $\eta^2 > .51$) than unpleasant and pleasant images, which did not differ significantly.

3.3. Force power spectrum

Fig. 2 illustrates the power of motor output from 0 to 12 Hz for PD and controls. For both groups, most of the power (over 90%) was below 4 Hz, with peak power at 1–2 Hz for all conditions. To examine changes in power across the 0–12 Hz force spectrum as a function of emotional condition, we averaged power in three frequency bands; 0–4 Hz, 4–8 Hz, 8–12 Hz (Table 2). The three-way group × condition × frequency band interaction was significant ($F_{(6,852)} = 5.9$, $p = .006$; $\eta^2 = .01$). Post-hoc analyses of this interaction revealed the following key findings: (1) Power was smaller overall for PD participants compared to controls, but only for the 0–4 Hz band. (2) For controls considered alone, there was a main effect of frequency band ($F_{(2,142)} = 35.3$, $p = .001$; $\eta^2 > .03$; Fig. 2A), where 0–4 Hz power was greater than 4–8 Hz and 8–12 Hz power. Additionally for controls, power was not modulated by condition, and the condition × frequency band interaction was not significant. (3) In contrast, in the PD group there was a significant condition × frequency band interaction ($F_{(6,426)} = 25.4$, $p = .001$; $\eta^2 = .01$), where 0–4 Hz power was greatest when visual feedback was provided compared to the emotion conditions where feedback was occluded ($p < .001$; $\eta^2 > .03$; Fig. 2B). (4) Importantly, PD participants showed a significant enhancement of power in the 4–8 Hz band, but this was only found in the unpleasant emotional condition ($\eta^2 > .03$). Thus, unique to participants with Parkinson's disease, viewing of unpleasant images increased power across the middle band of the force frequency spectra (Fig. 2B inset), indicating an amplification of force oscillations in the 4–8 Hz range in PD. All other main effects and interactions were not significant.

Multiple regression analysis indicated a significant relationship between ln(power) and ln(CV) of force output in PD ($R^2 = .72$, $p < .001$; Fig. 3A) that was due to modulation of power in the 4–8 Hz frequency band only. In contrast, the relationship between power and CV in controls was weak ($R^2 = .16$, $p = .001$; Fig. 3B). The result in the PD group indicates that increased force oscillations at 4–8 Hz were directly

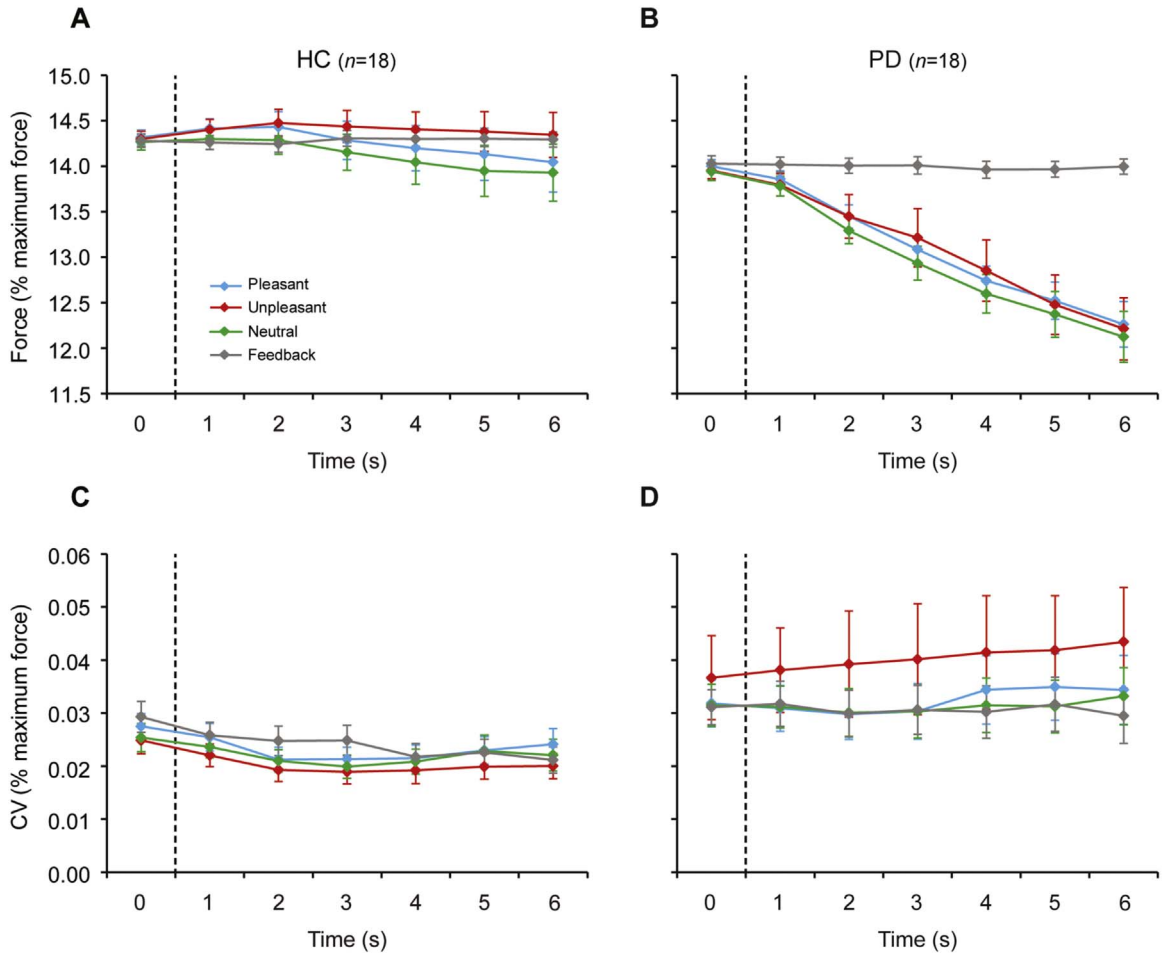

Fig. 1. Behavioural data. *A-B,* Mean force (% maximum force) and *C-D,* mean CV (% maximum force) in each 1 s epoch for each condition, beginning 1 s before the onset of each condition (time = 0) for healthy control (left panels) and Parkinson's disease (right panels) participants. Error bars represent standard error.

related to the fluctuations in force control. As depicted in the representative individual trial data from one HC participant and one PD participant (Fig. 3C,D), force oscillations and 4–8 Hz power of force output were generally greater during concurrent viewing of negatively-valenced images for the PD but not HC participant.

3.4. Neuromuscular activity

Fig. 4 shows the change in EMG amplitude over time in PD and controls. Analyses on the mean rectified muscle activity in epoch 0 revealed that although initial FDS amplitude was greater in PD participants compared to controls (main effect of group; $F_{(1,33)} = 5.7$, $p = .023$; $\eta^2 = .15$), activity in the agonist muscle was not modulated by

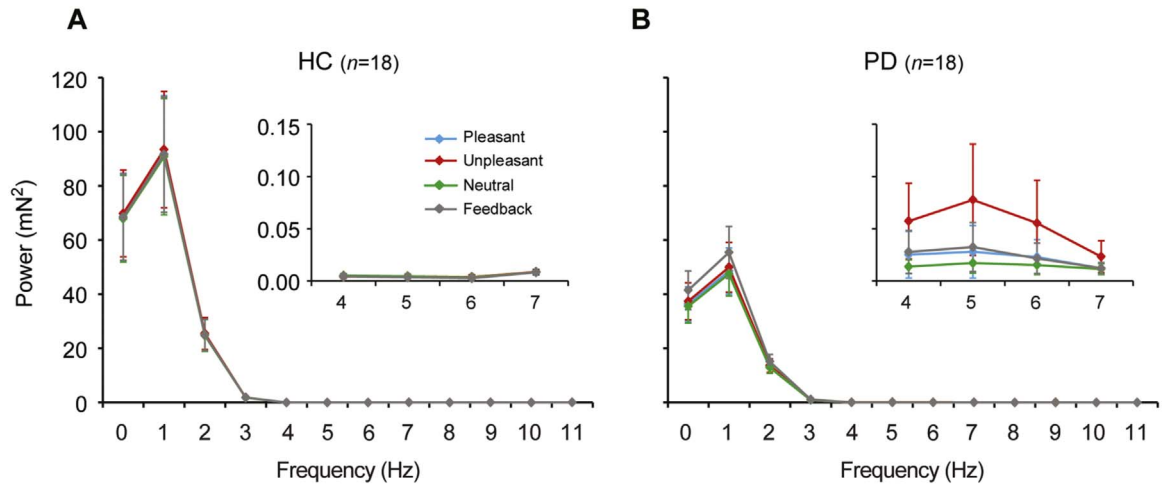

Fig. 2. Power spectrum of force output. Mean power (mN^2) in each condition for *A,* healthy control and *B,* Parkinson's disease participants. Data were analysed in three frequency bands: 0–4 Hz, 4–8 Hz, 8–12 Hz. Inset graphs highlight data in the 4–8 Hz band. Error bars represent standard error.

Table 2
Power spectral estimates of force output across 0–12 Hz in each emotional condition for Parkinson's disease and healthy control participants.

	Absolute power (mN^2)					
Frequency bins	0–4 Hz		4–8 Hz		9–12 Hz	
Condition	PD	HC	PD	HC	PD	HC
Pleasant	24.767	46.790	.022	.005	.006	.005
Unpleasant	25.492	47.626	.053	.005	.006	.005
Neutral	24.225	46.289	.014	.005	.003	.005
Feedback	28.288	46.686	.023	.005	.004	.005

condition. Greater overall flexor muscle activity in PD is consistent with the presence of mild rigidity (Vaillancourt and Newell, 2000; see Table 1). While EDC amplitude was also greater in PD compared to controls, this was not significant ($p = .153$; $\eta^2 = .06$). Like FDS, EDC amplitude was not modulated by emotional condition.

During concurrent viewing of the emotional images and force output (epochs 1–6), there was an additional increase of forearm flexor muscle activity in individuals with Parkinson's disease that was unique to the unpleasant condition. FDS amplitude was greater overall for PD (11.6 ± 9.0%) compared to controls (6.2 ± 3.1%; $\eta^2 = .15$; main effect of group; $F_{(1,208)} = 34.5$, $p = .001$; $\eta^2 = .14$). Post-hoc analyses of the group × condition interaction for FDS amplitude ($F_{(3,624)} = 2.8$, $p = .037$; $\eta^2 = .01$) indicated that for PD participants (Fig. 4B), FDS amplitude was significantly greater in the unpleasant condition (12.6 ± 10.8%) compared to the neutral (11.2 ± 9.5%) and visual feedback conditions (11.5 ± 8.4%; $p < .05$; $\eta^2 > .06$). For controls (Fig. 4A), FDS amplitude was smaller while viewing neutral images (5.8 ± 3.1%) compared to pleasant (6.2 ± 3.6%) and unpleasant images (6.2 ± 2.8%), and the feedback condition (6.4 ± 3.1%; $p < .03$; $\eta^2 > .06$). For the extensor muscle, there were significant main effects of group ($F_{(1,208)} = 11.7$, $p = .001$; $\eta^2 = .05$) and condition ($F_{(3,624)} = 9.0$, $p = .001$; $\eta^2 = .01$) on EDC amplitude but no interaction. EDC amplitude was greater for PD participants (4.5 ± 2.0%) than controls (3.8 ± 1.5%; $p = .001$; $\eta^2 = .05$), and significantly smaller in the neutral condition compared to all other conditions in both PD and controls ($p < .005$; $\eta^2 > .06$).

3.5. Effect of depression, disease severity, and disease duration on force control

Although the HADS depression score was greater for the PD group than for controls ($t_{(34)} = 3.3$, $p = .002$; $\eta^2 = .24$; Table 1), none of the

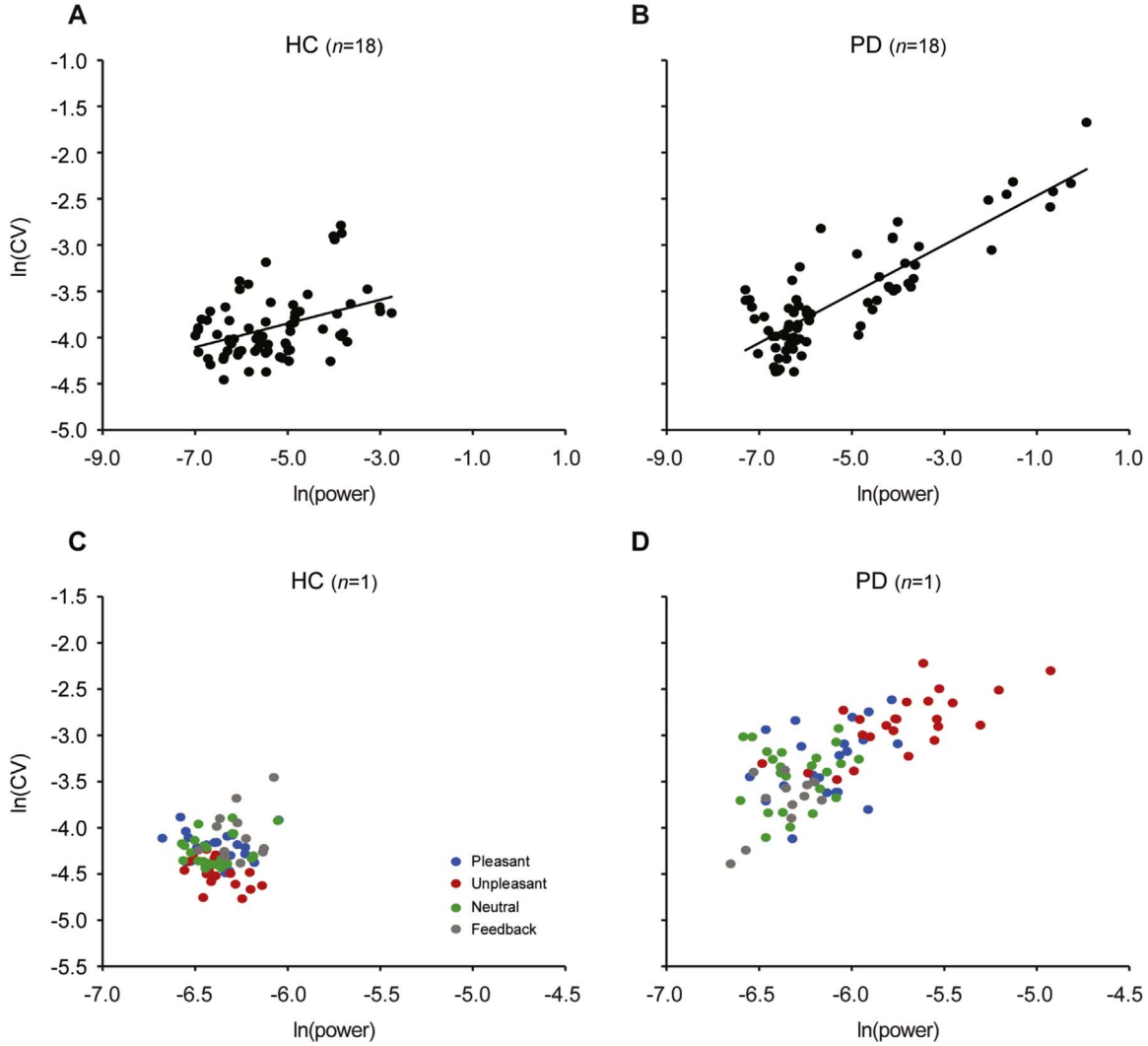

Fig. 3. Relation between power from 4 to 8 Hz in the force spectra and force variability. Data were log transformed prior to linear regression analysis. *A-B,* Group data for healthy control (left panels) and Parkinson's disease (right panel) participants. Each data point represents the average value from one of the four conditions for each participant. *C-D,* Exemplar graphs illustrating individual trial data separately highlighting the four conditions for one HC participant (left panel, $R^2 = .01$) one PD participant (right panel, $R^2 = .49$). Similar to the group data in *A-B,* a linear relationship between ln(power) and ln(CV) can be observed for the PD participant, with greater power and variability present in the unpleasant condition.

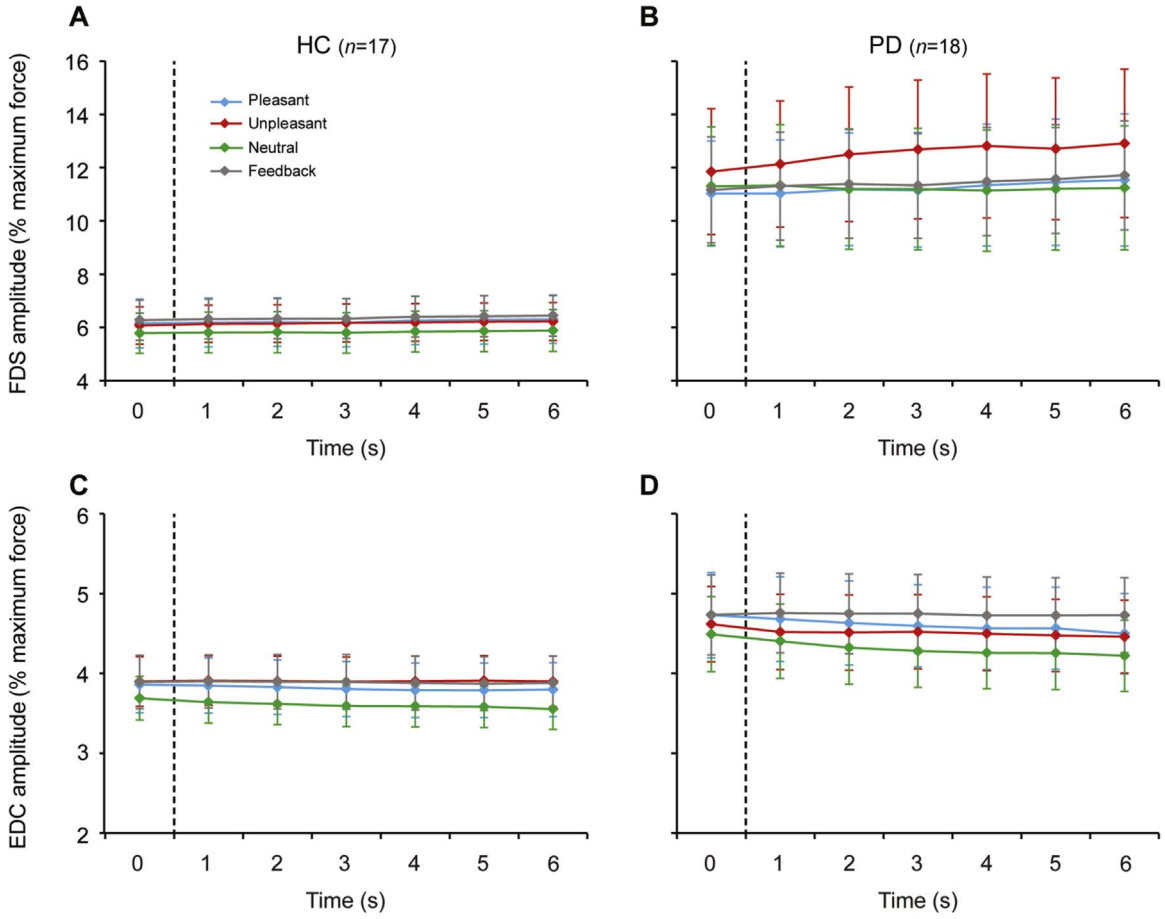

Fig. 4. Muscle activity data. *A-B,* Mean FDS amplitude (% maximum force), and *C-D,* mean EDC amplitude ((% maximum force) in each 1 s epoch for each condition for healthy control (left panels) and Parkinson's disease (right panels) participants. The values plotted represent the raw EMG amplitude values normalised to the muscle's corresponding maximum amplitude obtained in the maximum exertion tasks. Error bars represent standard error.

participants showed levels of depression (or anxiety) considered to be clinically significant (where cut-off scores of 8 and 11 for each subscale are considered normal in the general population and in PD, respectively; Zigmond and Snaith, 1983; Rodriguez-Blazquez et al., 2009). Nevertheless, to ensure performance was not affected by differences in depression between groups we repeated the above analyses including the HADS depression score as a covariate to control for potential confounding. The pattern of results for mean force, CV, force power, and EMG amplitude when HADS depression score was included in the model as a covariate was not different to those obtained without the covariate included. Moreover, we performed Pearson correlations to examine whether depression score was correlated with emotional reactivity in the PD participants for mean force, CV, force power, and EMG amplitude. Here emotional reactivity was defined as the difference score for each measure between the unpleasant and neutral emotional conditions (Bowers et al., 2006b). All correlations were non-significant (all $r < .38$, all $p > .12$). Together, these results indicate that the differential effects of negative emotion on force control in PD and HC participants were not driven by differences in depression score.

Given the findings of Bowers et al. (2006b) that startle eyeblink responses to aversive stimuli was influenced by disease severity, we also examined whether emotional reactivity on our force control task was influenced by disease severity and duration. In contrast to Bowers et al. (2006b), we found no relationship between emotional reactivity for mean force, CV, force power, or EMG amplitude and the MDS-UPDRS motor score off-medication (all $r < .15$, all $p > .54$), the Hoehn-Yahr score (all $r < .06$, all $p > .81$), and disease duration (all $r < .15$, all $p > .55$). However, duration of disease was correlated with Hoehn-Yahr ($r = .58$, $p = .005$).

4. Discussion

This study examined whether negative emotional signals impair precision grip-force control in Parkinson's disease. During concurrent viewing of emotional images and isometric force output, our PD group tested *off*-medication demonstrated greater variability of force maintenance (coefficient of variation), increased power at 4–8 Hz in the force spectrum, and greater forearm flexor EMG amplitude that was specifically associated with repeated exposure to unpleasant images. Consistent with our hypotheses and previous findings in animal models of PD (e.g., Metz et al., 2005; Smith et al., 2008; Hemmerle et al., 2013), these data provide novel evidence that aversive stimuli can further exaggerate deficits in fine motor control in individuals with PD.

In accordance with earlier studies demonstrating people with PD are more reliant on visual information to control isometric grip-force production (Vaillancourt et al., 2001b, 2001a), we found striking decay in force amplitude from the target level when visual feedback was removed and greater overall variability of force output in PD compared to controls. These impairments were unlikely to be a consequence of muscle strength or fatigue, as there was no significant difference between groups in maximal exertion force or EMG amplitude, in isometric force output when feedback was present. Moreover, there was no effect of block order on force amplitude in the emotional conditions; that is, the decay in force amplitude when feedback was occluded was similar from the beginning to the end of the experiment. The decay in force amplitude in PD instead might reflect sensory-motor memory-related deficits in higher order processing (Vaillancourt et al., 2001a). Importantly, we extend the findings of Vaillancourt et al. (2001b), (2001a) by showing that, unlike controls, force variability was further

exacerbated in the unpleasant condition, while force decay was not modulated by the affective content of the images in PD.

Previous studies have demonstrated the potent effect of stressors (noxious electrical stimuli) on the ability to control force output, especially in older adults (Noteboom et al., 2001; Christou et al., 2004; Christou, 2005). Here we show that blocked viewing of unpleasant emotional images (a potential affective stressor) also profoundly influences force variability: markedly increasing it in PD, and, to a lesser extent, decreasing it in controls. Fluctuations in isometric force output are primarily related to oscillations in force between 0 and 12 Hz (Vaillancourt et al., 2001b). As reported by others (Vaillancourt et al., 2001b; Vaillancourt and Newell, 2003; Christou et al., 2004), power was greatest for both groups in the 0–4 Hz band of the force spectrum, with peak power between 1 and 2 Hz, consistent with low-frequency modulation of motor unit discharge strength (Christou et al., 2004). The new finding, however, was an additional prominent increase in power in the 4–8 Hz band in the unpleasant condition, which significantly correlated with force variability, but only for individuals with PD.

It is possible that enhanced 4–8 Hz power in the PD group could be the result of an isometric tremor (Forssberg et al., 2000; Bain, 2007; see also Table 1), reported to be in a similar frequency range (5–7 Hz; Nowak et al., 2013) and thought to be due to an increase in the number of motor units firing (Brown et al., 1997). However if so, isometric tremor only emerged while viewing aversive images, even though the motor task (producing 15% maximum force) was the same in each condition, indicating a specific interaction between negative emotional signals and motor output in PD.

Augmentation of force oscillations between 4 and 8 Hz is similar to enhanced 5–9 Hz force power during stress reported by Christou et al. (2004), also imputed to an increase in the number of motor units discharging at the same rate. Given that stress can increase activity of the sympathetic nervous system and affect motor output, Christou et al. (2004), (2005) proposed that stress-induced increases in force variability may be associated with impaired sensory feedback resulting from elevated sympathetic activity. Sensory feedback from muscle spindles is suppressed with sympathetic stimulation (Roatta et al., 2002) and declines with age (Miwa et al., 1995). In contrast to Christou et al. (2004) however, we found no such low-frequency modulation in the older age-matched controls, indicating that increased force oscillations to aversive stimuli are not simply age-associated. The modality of aversive stimuli (physical versus emotional) may account for this discrepancy. Moreover, although we did not include additional physiological measures of stress, such as hormone or autonomic assessment, previous studies have shown that blocked viewing of aversive images elevates physiological arousal and hormonal responses (for example cortisol, norepinephrine) associated with acute stress responses (Codispoti et al., 2003; Mendonça-de-Souza et al., 2007; Sánchez-Navarro et al., 2012), as well as sympathetic activity (Bradley et al., 1996, 2001). Repeated exposure to stimuli of the same affective valence produces a sustained emotional state, leading to emotional responses that sensitize, rather than habituate (Bradley et al., 1996; Smith et al., 2005). It is therefore plausible that in the present task, the unpleasant condition induced an acute stress response elevating sympathetic activity and physiological arousal. Together with increased reliance on visual feedback in PD, repeated exposure to the aversive images may have therefore reduced the ability to use sensory feedback to modulate the descending drive, leading to increased synaptic input to the motor neuron pool, enhancing force fluctuations in PD.

Consistent with the notion that exposure to a stressor alters motor output through an increased number of active motor units, we found greater EMG amplitude in the forearm flexor muscle in PD in the unpleasant condition. As with force variability and similar to other studies (Noteboom et al., 2001; Christou et al., 2004), this effect was not observed in controls. Thus we found a selective effect of repeated exposure to aversive images on the descending input to the agonist muscle in PD, despite the obligatory synergistic involvement of the forearm extensor (antagonist) muscle in precision grip (Maier and Hepp-Reymond, 1995b, 1995a). Increased flexor muscle activity from stress-induced enhancement of sympathetic outflow and arousal (Roatta et al., 2002; Marmon and Enoka, 2010), likely led to inappropriate co-ordination between the extrinsic agonist and antagonist muscles necessary for precise force control and wrist stabilisation.

In addition to effects on sympathetic activity, stress also modulates dopaminergic activity in mesocorticolimbic systems as well as the nigrostriatal pathway (Finlay and Zigmond, 1997; Hemmerle et al., 2012). Acute stress results in acute dopamine deficiency (as stress augments dopamine release without adequate synthesis), which might cause deficits in skilled movement (for review, see Metz, 2007), particularly in PD where functioning of the dopamine system is already compromised. Although the cortical mechanisms underlying grip-force are not completely understood, there is strong evidence supporting the involvement of posteriorly located basal ganglia nuclei (subthalamic nuclei, globus pallidus internal) in the control of precision grip-force (Prodoehl et al., 2009). We have also shown that emotion-modulated grip-force by negative affect involves the ventrolateral prefrontal cortex (PFC) and amygdala (Blakemore et al., 2016a, 2016b). Together with the basal ganglia, these brain regions are well placed to integrate emotion and motor signals and modulate motor cortex output (Blakemore and Vuilleumier, 2017). Additionally, activity of these regions can be modulated by dopamine (Tessitore et al., 2002; Badgaiyan et al., 2009); the effects of acute stress on dopamine neurons are greatest in the PFC (Finlay and Zigmond, 1997). Based on the extant literature, one could hypothesise that the unpleasant condition temporarily amplified dopamine depletion in PD (Snyder et al., 1985) disrupting dopaminergic control of movement, and possibly down-regulated activity in PFC and amygdala (Tessitore et al., 2002). Modulation of both sympathetic and dopaminergic activity may therefore have contributed to increased grip-force variability, as well as the absence of emotional effect on force amplitude in PD.

The lack of modulation of force amplitude by emotion in PD is in contrast to the finding that negative emotional stimuli attenuated force decay in the age-matched controls in this study, and young healthy volunteers in prior studies (Blakemore et al., 2016a, 2016b). We previously suggested that emotion-modulated force control by negative emotional stimuli reflects engagement of motor pathways associated with the aversive motivational system, due to the motivationally-salient content of the unpleasant images (Bradley et al., 2001), that elicits passive defensive freezing-like behaviour. Here we mean to refer to an adaptive coping behaviour in animals whereby body motion is reduced, attention is heightened, and muscle tone is increased in the presence of threat or stress (Blanchard and Blanchard, 1986; Blanchard et al., 2001; Koutsikou et al., 2014; Blakemore et al., 2016a), rather than the parkinsonian akinetic motor symptom. In the current study, contrary to our hypothesis as well as studies of postural sway in humans that suggest defensive freezing-like behaviour (indexed by reduced sway and increased mean power frequency) during viewing of aversive stimuli involves muscle stiffness or co-contraction of agonist-antagonist muscle pairs (Azevedo et al., 2005; Stins and Beek, 2007; Roelofs et al., 2010), we did not find greater muscle activity in FDS or EDC in controls in the negative emotional condition. However, in addition to attenuated force decay, we did observed for the first time in control participants, a decrease in force variability while viewing unpleasant images, consistent with freezing immobility, when employing a blocked stimuli presentation. It is possible the use of a blocked design may have also elicited an overall cumulative emotional effect on the magnitude of force output in controls, and explain the overall reduction in force decay in the emotional conditions in controls in contrast to other studies using similar moderate target levels of force output (e.g., Coombes et al., 2008; Naugle et al., 2010; Blakemore et al., 2016a; Blakemore et al., 2016b). Alternatively, while sensory feedback during exposure to aversive stimuli may have been impaired in PD, controls may have experienced an amplification of sensory feedback (for example from

increased muscle spindle sensitivity; Horslen et al., 2013), leading participants to overestimate the magnitude of their force output in this task. Indeed, increased anxiety and arousal during postural threat resulted in healthy participants overestimating the amount of perceived sway due to increased sensory gain despite reductions in sway amplitude (Cleworth and Carpenter, 2016).

Unlike controls, however, patients showed no such freezing-like behaviour in the unpleasant condition, perhaps due to a lack of valence-specific activity in ventral prefrontal regions and amygdala. Vaillancourt and colleagues proposed that short-term memory of force output decays faster in PD (Vaillancourt et al., 2001a). Moreover, motor memory processes have been isolated to regions in the PFC including ventral PFC (Vaillancourt et al., 2003). Such an interpretation is in line with the suggestion that increased inhibitory globus pallidus output in PD leads to dysfunction in PFC, which in turn disrupts motor memory and control of internally guided movements (Vaillancourt et al., 2003), particularly when the task involves attentional focus on emotionally-salient information and concurrent force maintenance.

Taken together, we report novel evidence that negative emotional signals exacerbate impairments in force control in Parkinson's disease. The motor deficits observed in PD are unlikely to be due to differences in the participants' affective experience, as the PD group and the controls appraised the affective content of the images at a similar intensity, in line with other studies (Miller et al., 2009; Naugle et al., 2012; Schienle et al., 2015). Our results were also unlikely to be related to differences in depression scores, as when we included the depression score as a covariate, we found no significant depression-related effects. One limitation of our study is the lack of concomitant autonomic or endocrine measures. Inclusion of skin conductance as an index of sympathetic arousal or salivary cortisol as a biomarker of stress, for example, would provide further support to the usefulness of this paradigm as an acute affective stress induction method. Nonetheless, our findings accord with human studies using physical stressors (Christou et al., 2004; Christou, 2005) and with the findings in animal Parkinson's models showing stress-induced motor function impairments (Metz et al., 2005; Smith et al., 2008; Hemmerle et al., 2013), that have been linked with enhanced emotionality (Metz et al., 2005). Although some of our effect sizes are small, the consequences of repeated exposure to a stressor may have cumulative and clinically important outcomes given that chronic stress can have widespread effects on molecular and cellular pathways (for review see Hemmerle et al., 2012), accelerating dopaminergic cell degeneration and complicating disease progression and severity of PD. Moreover, chronic stress is an important risk factor for depression (McGonagle and Kessler, 1990), one of the most common comorbidities in PD (Aarsland et al., 2009) that often goes undiagnosed because of the overlap in clinical presentation as both pathologies involve psychomotor slowing and impairments in emotional processing (Péron et al., 2012).

To more fully understand the role of dopamine in modulating motor function and emotional reactivity under stressful conditions, future research could compare emotion-motor interactions in PD 'on' and 'off' dopaminergic medication. Naugle et al. (2012) reported alterations in gait in PD participants 'on' medication that were similar to controls following the presentation of aversive images, highlighting restoration of function with medication in dopaminergic pathways involved in integrating emotion and motor control processes. Another limitation is that it is possible psychotropic medication had a residual effect on emotion-motor processing; however this is unlikely as anti-depressant or anxiolytic medications generally dampen rather than augment emotional reactivity (Outhred et al., 2013). It is also possible our findings of emotion-modulated grip-force control may be limited to this motor task. Indeed, amplified reactivity to aversive stimuli with intact emotional appraisal is at odds with studies showing blunted startle eyeblink responses and hypoarousal to aversive stimuli in PD, similarly posited to be related to amygdala dysfunction (e.g., Bowers et al., 2006b; Miller et al., 2009). These latter studies randomised presentation of the emotional stimuli to explicitly avoid any emotional induction effects. Additional studies using functional neuroimaging would help elucidate the extent to which amygdala and basal ganglia dysfunction in PD play a role in amplifying or muting emotional reactivity and altering motor function depending on the temporal context of aversive stimuli exposure.

A strength of our study is the inclusion of only right-hand dominant PD participants with predominantly right-sided symptoms (RPD), permitting a relatively homogenous group without any confounding of handedness or side predominantly affected. However, this may also limit generalisation of our results to individuals with PD presenting with predominantly left-sided symptoms (LPD). RPD patients have left-hemispheric (primarily nigro-striatal) neurodegeneration; in our PD cohort, 17 of 18 PD participants also experienced left-sided motor symptoms (off-medication), reflecting bilateral, albeit asymmetric neurodegeneration. Nonetheless, it is possible that hemispheric asymmetry of neurodegeneration impacted our findings. For example, the right hemisphere is thought to play a greater role than the left in processing emotional information, especially for negative emotions (Adolphs et al., 2001). Accordingly, studies have shown dysfunction in emotional processing to be greater in LPD than RPD patients (Ventura et al., 2012; Garrido-Vásquez et al., 2013). However, the evidence is mixed as others have found no differences in affective functioning between RPD and LPD (Blonder et al., 1989; St. Clair et al., 1998). Asymmetric cognitive differences have also been reported: Performance on visual spatial memory tasks is worse for LPD than RPD, while no difference in executive functioning (e.g., inhibition) or attention has been found between groups with lateralized PD (for a review see Verreyt et al., 2011). Interestingly, in healthy volunteers tested on a similar force control task to ours, Vaillancourt et al. (2003) demonstrated that motor memory processes were confined to left prefrontal regions (contralateral to the hand producing force output). Yet with the addition of concurrent viewing of negative emotional stimuli, we showed involvement of right prefrontal cortex, right amygdala and right cerebellum, irrespective of the hand performing the task (Blakemore et al., 2016a). To disentangle any hemispheric- or side-specific differences on this emotional-force control task in PD, future research could directly compare LPD with RPD patients, or alternatively compare force output between the most versus least affected hand. We would expect a similar pattern of results regarding the influence of acute emotional stress on motor function when patients performed this task using their least affected hand, but the magnitude of the effect may be diminished.

In conclusion, there is a growing literature showing that stress impairs a variety of motor functions in animal models of PD (Metz, 2007). We have shown an experimental technique that seems to robustly yield objective evidence corroborating emotional stress-induced changes in motor function in PD, which might be well suited for use in future investigations in human PD. Our findings may inform development of novel therapeutic avenues that focus on reducing acute stressors or altering affective state, as viable non-invasive strategies to improve motor control in PD, complementary to existing rehabilitation and pharmacological interventions.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2018.03.006.

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