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Improvements in rate of development and magnitude of force with intense auditory stimuli in patients with Parkinson's disease

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Abstract

Patients with Parkinson's disease can show brief but dramatic normalization of motor activity in highly arousing situations, a phenomenon often termed paradoxical kinesis. We sought to mimic this in a controlled experimental environment. Nine patients with Parkinson's disease and nine age-matched healthy controls were asked to grip a force dynamometer as quickly and strongly as possible in response to a visual cue. A loud (96 dB) auditory stimulus was delivered at the same time as the visual cue in ~50% of randomly selected trials. In patients with Parkinson's disease, the experiment was conducted after overnight withdrawal of antiparkinsonian drugs and again 1 h after patients had taken their usual morning medication. Patients showed improvements in the peak rate of force development and the magnitude of force developed when loud auditory stimuli accompanied visual cues. Equally, they showed improvements in the times taken to reach the peak rate of force development and their maximal force. The paradoxical facilitatory effect of sound was similar whether patients were off or on their usual antiparkinsonian medication, and could be reproduced in age-matched healthy controls. We conclude that motor improvement induced by loud auditory stimuli in Parkinson's disease is related to a physiological phenomenon which survives both with and after withdrawal of antiparkinsonian medication. The potential independence of the mediating pathways from the dopaminergic system provides impetus for further investigation as it may yield a novel nondopaminergic target for therapeutic manipulation in Parkinson's disease.

Introduction

It has long been known that intense stimuli can shorten the reaction time and increase the rate of development and magnitude of response force in healthy subjects (Woodworth, 1938; Angel, 1973). Indeed, this effect can be so marked that it leads to shorter reaction times and faster and stronger responses than can be achieved through maximal effort of will alone (Anzak *et al.*, 2011). Interest in this phenomenon is heightened by the existence of a similar effect, traditionally called paradoxical kinesis (Souques, 1921), in patients with Parkinson's disease (PD). This disease is dominated by dopaminergic denervation of the basal ganglia and, as a consequence, patients make slow and small voluntary movements. Paradoxical kinesis describes the remarkable normalisation of motor activity in PD patients that may follow intense stimuli as diverse as the sound of a car accident (Daroff, 2008), the sensation of an earthquake (Bonanni *et al.*, 2010a) or the sight of a fire or bolting horse (Glickstein & Stein, 1991). The phenomenon suggests the existence of neural systems that can override parkinsonian impairment, systems that, if identified and manipulated, might yield novel and more effective therapies for motor impairment in PD.

So could reports of paradoxical kinesis in fact be florid examples of an essentially physiological process, precipitated by intense stimulation, which remains preserved in PD? There is already evidence to suggest that this is at least partly true in that startling stimuli are able to elicit reactions in PD that have a dramatically shortened reaction time (RT), just as in healthy subjects (Valldeoriola *et al.*, 1998). Here we test whether, under similar conditions, patients with PD also retain the ability to make responses with increased magnitude and rate of development of force, over and above that possible through maximal effort of will alone. Two former studies have demonstrated that PD patients are able to overcome their self-determined maximal speeds under temporally pressing conditions (Majsak *et al.*, 1998; Ballanger *et al.*, 2006), but the results of these are ambiguous as the response benefit might have arisen through anticipatory increases in attention and visuomotor processing speeds. Here we use a simpler paradigm that obviates anticipatory effects (Anzak *et al.*, 2011) and, moreover, we address the novel and important question of the effect of dopaminergic state on any improvements in the magnitude and rate

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of development of force following intense auditory stimuli. Paradoxical kinesia has previously been attributed to behavioural energization through the release of 'dopamine reserves' by intense stimuli (de la Fuente-Fernández & Stoessl, 2002), but any independence of the phenomenon from dopaminergic state would heighten the relevance of the underlying neural systems as a potential novel target for therapeutic manipulation in PD.

Materials and methods

Nine patients with PD (mean disease duration 11 years, mean age 61 years, range 51–75 years; eight males) and nine age-matched healthy controls (mean age 63 years, range 49–73 years; seven males), were recruited to the study. Clinical details of the patients are available in Table 1. The mean percentage improvement in the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) on treatment with levodopa (L-DOPA) was 42.7 ± 2.9% ($P < 0.0001$). Note that whilst the motor UPDRS scores of Patient 8 suggest only a modest amelioration whilst taking (ON) L-DOPA, the patient exhibited significant improvements in peak force, peak rate of development of force and respective times to reach these two parameters ON as opposed to whilst not taking (OFF) drugs (two-tailed Student's *t*-tests between OFF and ON drug recordings in visual (V) and combined audiovisual (AV) cue conditions independently; $P < 0.05$). Accordingly, and so as not to introduce retrospective selection of cases, the patient's results are included in the study. Experiments were conducted with the understanding and written consent of each participant in accordance with the Declaration of Helsinki, and were approved by the local ethics committee. Grip force was measured one hand at a time in each subject using an isometric dynamometer (G100; Biometrics Ltd, Cwmfelinfach, Gwent, UK), with standard Jamar design and its handle in the second position. Subjects were seated with their shoulders adducted (so that elbows rested against the trunk), their elbows flexed at ∼90° and their forearms in neutral, as recommended by the American Association of Hand Therapists (Fess, 1992).

Subjects were presented with a series of imperative visual cues (V), separated by 11–13 s, and instructed to 'squeeze as fast and hard as you possibly can when the light comes on and maintain this for the duration of the light' (red light-emitting-diode illuminated for 5 s). In half of these trials, randomly selected, a loud auditory stimulus (0.3 s duration, 1 kHz, 96 dB) was delivered binaurally through headphones, with onset simultaneous with that of the V cue, to give the AV cue. Stimulus intensity was measured with a Brüel and Kjaer 2260 Observer (Brüel and Kjaer, Nærum, Denmark). Subjects were, however, asked to just focus on responding to the V cues. In requesting subjects to grip both as strongly and quickly as possible, we aimed to incorporate an RT component to the paradigm. The intention here was to provide confirmation of the loudness of the auditory stimulus, as it is well-documented that such stimuli lead to a significant shortening of RT (Valls-Solé *et al.*, 1999; Carlsen *et al.*, 2004, 2009; Reynolds & Day, 2007; Anzak *et al.*, 2011).

The choice of sound pressure level and duration was influenced by considerations of safety and tolerability for each subject when receiving this stimulus through headphones ∼40 times (when summating recordings across experimental runs in both hands and in the OFF and ON medication states). Note that loudness is a subjective measure and should not be confused with sound pressure level or intensity as the human auditory system integrates the effects of sound pressure level (SPL) over any window shorter than 600–1000 ms. Hence, although our SPL was somewhat less than that used in most startle studies, the duration of our stimulus was longer.

Twenty trials were collected in each experimental run. Trials were approximately equally divided (allowing for the randomisation process in each session) into those with V and AV cues. Both the number of trials executed and the intertrial interval were decided upon given the necessity to collect a sufficient number of trials whilst keeping the experiment tolerable for our patients with PD when OFF medication. Intertrial intervals were similar to those previously used in investigations of the StartReact phenomenon (Valls-Solé *et al.*, 2005; Carlsen *et al.*, 2009). Trials were carried out in a blocked design, and left- and right-hand recordings were counterbalanced across subjects. Patients with PD were always recorded OFF medication first, then again ∼1 h after taking their usual morning dose of antiparkinsonian medication (average L-DOPA equivalent dose administered, 133 mg;

Table 1. Patient details

Patient number	Age (years)	Disease duration (years)	Morning medication	Daily L-DOPA equivalent dose (mg)	UPDRS part III	
					OFF	ON
1	75	12	100 mg L-DOPA	300	30	20
2	60	12	100 mg L-DOPA 1 mg Rasagiline 200 mg Entacopone 8 mg Ropinirole XL	600	23	11
3	67	17	200 mg L-DOPA 0.7 mg Pramipexol 10 mg Selegeline	800	19	11
4	71	7	100 mg L-DOPA	400	21	12
5	57	4	100 mg L-DOPA	300	24	13
6	61	17	100 mg L-DOPA 5 mg Bromocriptine	300	12	6
7	51	10	100 mg L-DOPA 200 mg Entacapone 10 mg Selegeline 100 mg Amantadine	300	15	8
8	70	8	200 mg L-DOPA 0.7 mg Pramipexol	400	24	18
9	52	12	200 mg L-DOPA 100 mg Amantadine	800	15	8

FIG. 1. (A) Grip forces averaged after realignment to response onset in patients with Parkinson's disease off medication. (Ai) Each patient's normalized mean force from visual cue only (V) trials, in left and right hands. (Aii) Each patient's normalized mean force from trials in which a loud auditory stimulus was delivered as the visual cue came on (AV). Each patient is colour-coded with the same colour in Ai and Aii. (Aiii) Group average of V and AV trials across nine patients (n = 18 hands). (B) Yank (rate of force development) averaged after realignment to response onset off medication. (Bi) Each patient's normalized mean yank from V trials, in left and right hands. (Bii) Each patient's normalized mean yank from AV trials. Each patient is colour-coded with the same colour in Bi and Bii. (Biii) Group average of V and AV trials across nine subjects (n = 18 hands). The black and grey bars combined indicate those timings over which the two traces were different at the 5% significance level. The black bar on its own denotes those timings over which the two traces were different at the 1% significance level.

FIG. 2. (A) Grip forces averaged after realignment to response onset in patients with Parkinson's disease on medication. (Ai) Each patient's normalized mean force from visual cue only (V) trials, in left and right hands. (Aii) Each patient's normalized mean force from trials in which a loud auditory stimulus was delivered as the visual cue came on (AV). Each patient is colour-coded with the same colour in Ai and Aii. (Aiii) Group average of V and AV trials across nine patients (n = 18 hands). (B) Yank (rate of force development) averaged after realignment to response onset on medication. (Bi) Each patient's normalized mean yank from V trials, in left and right hands. (Bii) Each patient's normalized mean yank from AV trials. Each patient is colour-coded with the same colour in Bi and Bii. Note the prominent action tremor in one patient. (Biii) Group average of V and AV trials across nine subjects (n = 18 hands). The black and grey bars combined indicate those timings over which the two traces were different at the 5% significance level. The black bar on its own denotes those timings over which the two traces were different at the 1% significance level.

range, 100–200 mg). Improvement with medication was confirmed through assessment of finger tapping, wrist rigidity and tremor (using the corresponding items of the motor UPDRS). Healthy controls were also asked to undertake two experimental runs, with a 45- to 60-min break in between, in order to match any practice, habituation or fatigue effects in the patients.

EMG was recorded from sternocleidomastoid (SCM), and amplified and bandpass-filtered (10–1000 Hz) using a D360 amplifier (Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK). Analogue correlates of the visual and auditory stimuli, EMG and dynamometer output were then digitized through a 1401 A-D converter (Cambridge Electronic Design, Cambridge, UK) and sampled at a rate of 2048 Hz onto a computer using SPIKE2 version 5 software (Cambridge Electronic Design).

Analysis was performed in MATLAB. Peak yank (where yank is defined as the rate of change of force, calculated by differentiation of the force signal) and peak force were the primary variables of interest, and had the advantage that they could be measured trial by trial without realignment to compensate for differences in premotor reaction times. Two further variables derived were time to reach peak force and time to reach peak yank, which necessarily required realignment of trials to response onset in order to maintain an independence of these parameters from variability in premotor reaction time. Response onset was defined as the point at which force exceeded 3 SD of the baseline over the 0.5 s prior to presentation of the visual cue. Premotor reaction time was further operationally defined as the time interval between cue onset and this point. Premotor reaction time is more usually considered to be the interval between cue presentation and EMG onset (Botwinick & Thompson, 1966). However, we found the use of EMG to be suboptimal in the context of maximal grips because of movement artefact and sampling error, given that many muscles are activated in this task. Grand averages of peak force, peak yank, premotor reaction time, time to reach peak force and time to reach peak yank in V and AV trials were calculated after deriving each of these variables from the individual grips made by a subject, and calculating averages for that subject, before averaging across subjects. Group mean percentage changes in variables were calculated as the average of the mean percentage changes in each subject.

The method described above provided unbiased calculations of the average peak yank and peak force, independent of the average time to reach peak yank and average time to reach peak force, respectively. However, in order to graphically display the average grip trace for both force and yank, we averaged across individual grips at each millisecond time point (Figs 1 and 2). Note that force and yank traces for each individual's hand were first normalised to the average of each subject's peak force and peak yank, respectively, in each hand in the V condition. In this way, any potential skew which may have been introduced by particularly strong individuals or by dominance of hands, when averaging across all subjects, was limited.

Evidence of an overt startle response characterised by short latency SCM activity (Brown *et al.*, 1991) was also sought. Here, we had to avoid contamination of our results with SCM responses related to coactivation once the maximal grip had been initiated. We avoided this confound by comparing maximal rectified SCM activity occurring within the first 150 ms after onset of the AV cues across trials, with the maximal SCM activity occurring within the first 150 ms after V cues across trials. A startle response was considered present if the former index exceeded the latter by > 3 SD in a given subject. Coactivation related to the grip would have been expected to be similar between trial types. Moreover, we aimed to ensure our latency of interest for SCM responses was shorter than the mean latency to co-activation (average AV premotor reaction time in patients with PD ON medication, 156 ms; healthy controls in first experimental run, 152 ms).

Statistical analyses were performed in MICROSOFT OFFICE EXCEL 2003, MATLAB and SPSS Statistics 17 (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov tests confirmed that data were normally distributed. Variability in kinematic profiles between individuals was offset by always performing paired comparisons of trial types within subjects. When comparing the effect of stimulus and drug state or experimental run within the patient group, a repeated-measures ANOVA was applied. However, when comparing across PD and Control groups, we used a mixed-design repeated-measures ANOVA in which PD and Control were defined as separate groups. Those statistical tests that reached significance ($P < 0.05$) and, where appropriate, survived correction for multiple comparisons using the Bonferroni correction (Curran-Everett, 2000), are indicated with an asterisk (*) in the text. Means ± SEM are specified.

Results

Force parameters in patients with PD

Mean peak yanks across subjects increased from 106.5 ± 15.7 kg/s in V trials to 121.7 ± 17.4 kg/s in AV trials, in the OFF drug state. Similarly, increases from 105.4 ± 11.5 kg/s in V trials to 123.1 ± 13.9 kg/s in AV trials were observed in the ON drug state. Subsequent application of a repeated-measures ANOVA with factors Drug state (OFF and ON L-DOPA) and Stimulus (V and AV) to mean peak yanks generated on each side by each of our patients with PD (18 hands) identified a main effect of Stimulus ($F_{1.00,17.00} = 9.16$,

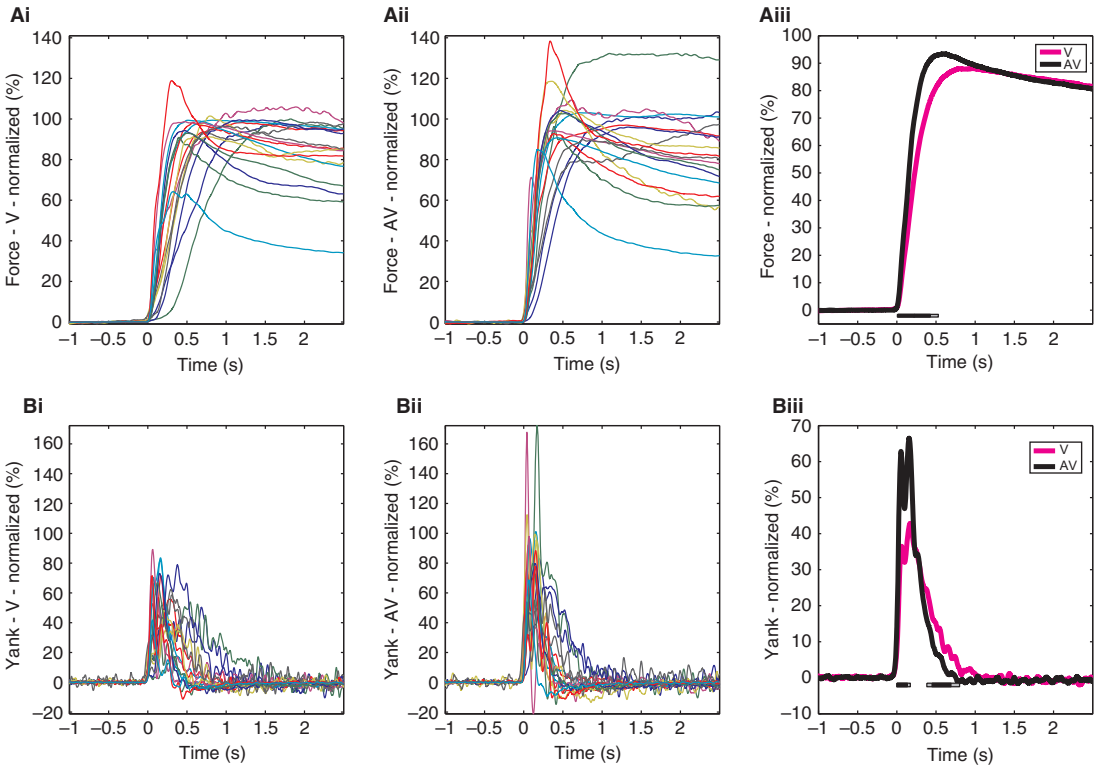

FIG. 1.

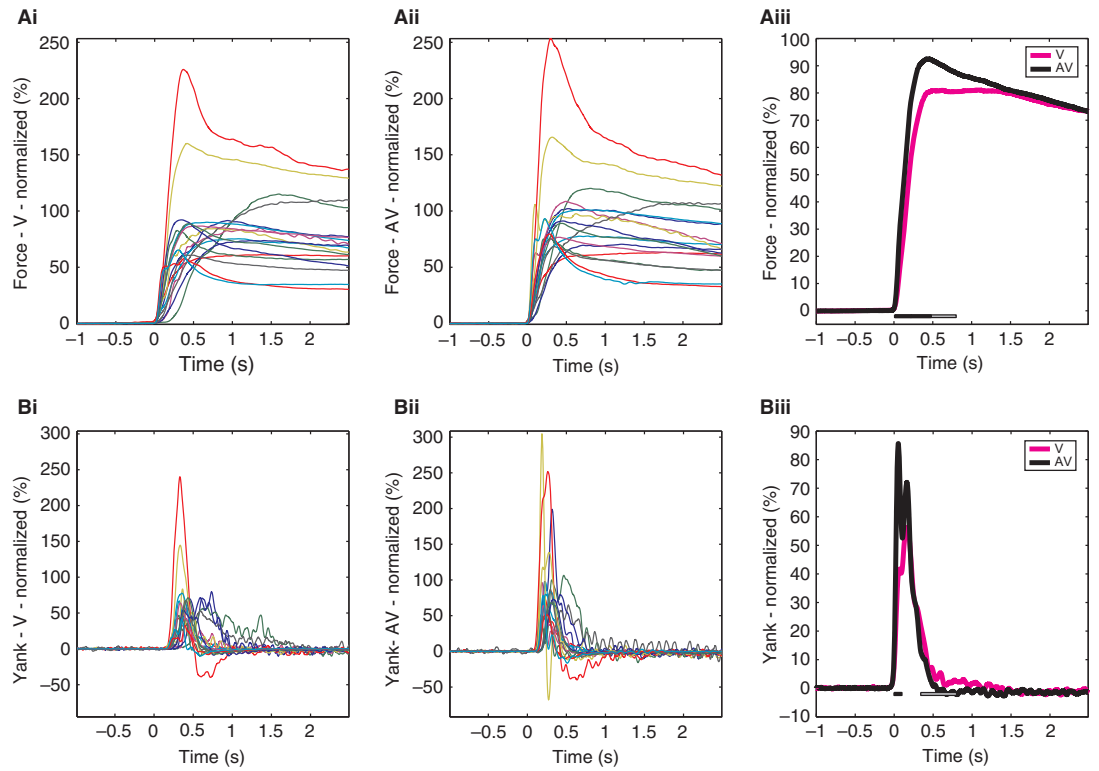

FIG. 2.

P = 0.008) which was independent of the dopaminergic state (Drug state × Stimulus interaction, $F_{1.00,17.00}$ = 0.230, P = 0.638). There was no overall effect of Drug state ($F_{1.00,17.00}$ = 0.00, P = 0.985). Thus, averaging across drug states for each stimulus type, a mean increase in peak yank of 20.0 ± 7.1% (P = 0.008, two-tailed paired t-test between V and AV stimuli) with AV cueing was observed (Fig. 3).

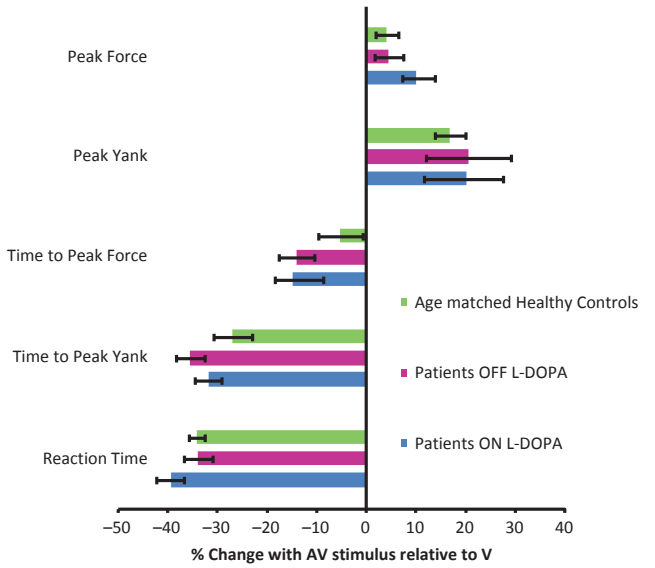

FIG. 3. Average percentage changes with AV relative to V stimuli, in patients with Parkinson's disease off and on their usual antiparkinsonian medication and in age-matched healthy controls averaged across experimental runs 1 and 2. A percentage increase means that the measure is greater in AV trials than in V trials.

Mean peak force increased from 17.0 ± 1.5 kg in V trials to 17.7 ± 1.5 kg in AV trials in the OFF drug state. Increases from 15.1 ± 1.0 kg in V trials to 16.1 ± 1.0 kg in AV trials were observed in the ON drug state. Application of a further repeated-measures ANOVA to mean peak forces similarly identified a main effect of Stimulus ($F_{1.00,17.00}$ = 7.23, *P = 0.016) but no Drug state × Stimulus interaction ($F_{1.00,17.00}$ = 0.695, P = 0.447) or effect of Drug state ($F_{1.00,17.00}$ = 2.52, P = 0.131). The mean increase in peak force with AV cueing across drug states was 6.1 ± 2.1% (*P = 0.016, paired t-test).

In order to further investigate the manner in which V and AV trials differed for the above-mentioned variables, the distributions of normalised (see Materials and methods) peak yanks and peak forces elicited in each patient across drug states were plotted (Fig. 4). This figure suggests that, although the range of movement capabilities was similar in the two conditions, AV trials were associated with an increased proportion of stronger grips selected from within this range, as also occurs in healthy subjects (Anzak *et al.*, 2011). Application of two-sample Kolmogorov–Smirnov tests identified significant differences between the V and AV distributions for peak yank (*P < 0.0001) and peak force (*P = 0.0026), which was manifest as a skew of the AV relative to V distributions towards higher forces and yanks. The peak yank distribution skew increased from 2.239 for V trials to 2.369 for AV trials and the peak force distribution skew increased from 2.414 for V trials to 2.454 for AV trials.

Temporal parameters in patients with PD

In line with the improvements in peak yank with AV cueing, time to reach peak force from movement onset also decreased, from 873 ± 115 ms in V trials to 786 ± 105 ms in AV trials in the OFF drug state. Decreases from 738 ± 107 ms in V trials to 638 ± 93 ms in AV trials were observed in the ON drug state. Application of repeated-measures ANOVA to mean time to reach peak force further identified a trend towards an effect of Stimulus ($F_{1.00,17.00}$ = 4.29, P = 0.054) independent of dopaminergic state (Drug state × Stimulus interaction, $F_{1.00,17.00}$ = 0.075, P = 0.788). The mean reduction in time to peak force, averaged across drug states, was 7.6 ± 6.2% with AV compared to V cueing (P = 0.054, paired t-test). There was an additional main effect of Drug state ($F_{1.00,17.00}$ = 6.50, *P = 0.021), which was consistent with the expected amelioration of bradykinesia with L-DOPA. The reduction in time to peak force, averaged across V and AV trials, was 14.2 ± 5.2% (*P = 0.021, paired t-test) on compared to off medication.

Time to reach peak yank also decreased from 238 ± 35 ms in V trials to 143 ± 19 ms in AV trials in the OFF drug state. Decreases from 196 ± 27 ms in V trials to 135 ± 16 ms in AV trials were observed in the ON drug state. Application of a repeated-measures ANOVA to the mean time to reach peak yank also showed a main effect of Stimulus ($F_{1.00,17.00}$ = 15.36, *P = 0.001), a trend towards an effect of Drug state × Stimulus interaction ($F_{1.00,17.00}$ = 4.28, P = 0.054) and an effect of Drug state ($F_{1.00,17.00}$ = 5.51, *P = 0.034). The reduction in time to peak yank with AV cueing averaged across drug states was 31.7 ± 4.3% (*P = 0.001, paired t-test). The reduction in time to peak yank, averaged across V and AV trials, was 7.6 ± 6.3% (*P = 0.034, paired t-test) on compared to off medication.

RTs also decreased from 252 ± 14 ms in V trials to 163 ± 8 ms in AV trials in the OFF drug state. Similarly decreases from 236 ± 11 ms in V trials to 156 ± 6 ms in AV trials were observed in the ON drug state. An ANOVA of mean premotor reaction times showed a main effect of Stimulus ($F_{1.00,17.00}$ = 127.3, *P < 0.001) independent of dopaminergic state (Drug state × Stimulus interaction, $F_{1.00,17.00}$ = 0.317, P = 0.581), and no effect of Drug state ($F_{1.00,17.00}$ = 2.59, P = 0.126). The mean reduction in premotor RT was 33.7 ± 1.9% (*P < 0.001 paired t-test).

Comparisons with age-matched healthy controls

We applied a mixed design repeated-measures ANOVA with factors Stimulus (V and AV), Group (patients with PD and age-matched healthy controls) and Drug state/Experimental run (OFF L-DOPA in patients with PD/ first experimental run in controls and ON L-DOPA in patients with PD/ second experimental run in controls). This confirmed a significantly improved response to the AV stimulus in all parameters of movement measured in both patients with PD and age-matched healthy controls (i.e. main effect of Stimulus but no Stimulus × Group interactions). The differential behaviour in V and AV trials was retained across the two groups despite differences in absolute values due to better baseline performance in healthy controls, as demonstrated by the main effects for Group in peak yank (114.2 ± 7.3 kg/s in patients with PD and 162.6 ± 9.7 kg/s in healthy controls; $F_{1.00,34.00}$ = 5.972, *P = 0.049) and time to peak yank (178 ± 13 ms in patients with PD and 117 ± 6 ms in controls; $F_{1.00,34.00}$ = 6.76, *P = 0.014) and a trend towards an effect for Group in peak force (16.5 ± 0.6 kg in patients with PD and 20.7 ± 1.0 kg in healthy controls; $F_{1.00,34.00}$ = 3.127, P = 0.086). There was an absence of significant group interactions for the remaining temporal and force parameters. The Drug state/Experimental run factor was significant, with net increases in peak force for the first set of stimulus presentations (eg OFF state in patients and first run in healthy subjects), and decreases in time to peak force and time to peak yank across groups in the second set of stimulus presentations. Note that the factor Drug state/Experimental run includes drug and fatigue effects, which cannot be disambiguated given that the OFF drug state in patients was always tested first. However, the fact that there was a main effect of Drug state/Experimental run, whereby peak force was higher in the first run regardless of group, suggests that fatigue effects may have dominated over any drug effects. Conversely, the lower peak force in

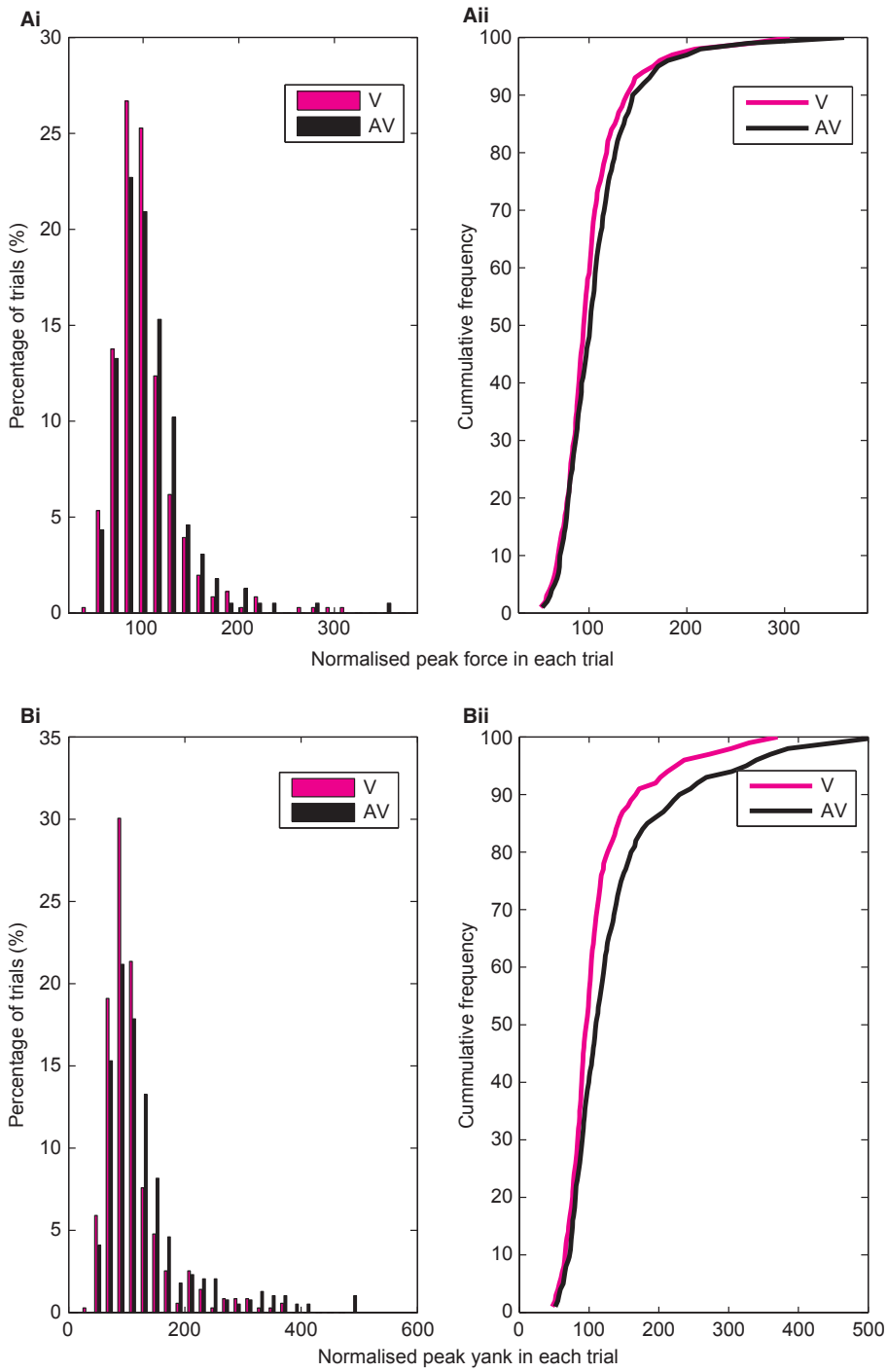

FIG. 4. Peak force and yank distributions. (A) (i) Histogram and (ii) cumulative frequency plot, to show distributions of peak forces generated in each V and AV trial across nine patients with Parkinson's disease (PD) in the OFF and ON L-DOPA states combined, represented as a percentage of each hand's average in the V condition. (B) (i) Histogram and (ii) cumulative frequency plot to show distributions of peak yanks generated in each V and AV trial across nine patients with PD (18 hands) in the OFF and ON L-DOPA states combined, represented as a percentage of each hand's average in the V condition. AV trials have similar ranges of peak force and peak yank as V trials but their distributions in the histograms are more skewed to the right, suggesting that loud auditory stimuli facilitated more of the trials with greater peak force and peak yank to be achieved.

the second run may have contributed to the decreased time to reach (lower) peak force and yanks (see Table 2).

Habituation to the performance-boosting effects of AV trials

We next assessed whether the performance-enhancing effect of the loud sound declined with trial presentation. Application of an ANOVA to peak yanks generated by each of our subjects, with factors Group (PD patients and healthy controls) and Trial position (average percentage change between first two V and AV trials and average percentage change between last two V and AV trials) identified no significant effect of Trial position ($F_{1.00,34.00} = 3.141$, $P = 0.085$) nor a Trial position × Group interaction ($F_{1.00,34.00} = 0.574$, $P = 0.454$). There was also no effect of Group ($F_{1.00,34.00} = 0.398$, $P = 0.532$).

TABLE 2 Patients with PD compared with age-matched healthy controls in mixed-design repeated-measures ANOVAs

	Within-subject effects	$F_{1,34}$	P	Between-subject effects	$F_{1,34}$	P
Peak force	Stimulus	9.0	*0.005	Group	3.127	0.086
	Stimulus × Group	0.120	0.731	L-DOPA, Experimental run	12.4	*0.001
				L-DOPA, Experimental run × Group	0.247	0.622
				L-DOPA, Experimental run × Stimulus	0.881	0.355
				L-DOPA, Experimental run × Stimulus × Group	0.043	0.838
Peak yank	Stimulus	38.0	*< 0.001	Group	5.972	*0.049
	Stimulus × Group	1.64	0.209	L-DOPA, Experimental run	2.28	0.140
				L-DOPA, Experimental run × Group	2.38	0.132
				L-DOPA, Experimental run × Stimulus	0.211	0.649
				L-DOPA, Experimental run × Stimulus × Group	0.056	0.815
Time to peak force	Stimulus	6.94	*0.013	Group	0.276	0.603
	Stimulus × Group	0.553	0.462	L-DOPA, Experimental run	7.33	*0.011
				L-DOPA, Experimental run × Group	1.19	0.283
				L-DOPA, Experimental run × Stimulus	1.29	0.264
				L-DOPA, Experimental run × Stimulus × Group	2.16	0.151
Time to peak yank	Stimulus	31.44	*< 0.001	Group	6.76	*0.014
	Stimulus × Group	3.538	0.069	L-DOPA, Experimental run	12.4	*0.015
				L-DOPA, Experimental run × Group	1.57	0.218
				L-DOPA, Experimental run × Stimulus	2.38	0.132
				L-DOPA, Experimental run × Stimulus × Group	2.67	0.112
Premotor reaction time	Stimulus	335.0	*< 0.001	Group	0.048	0.827
	Stimulus × Group	0.020	0.888	L-DOPA, Experimental run	0.073	0.788
				L-DOPA, Experimental run × Group	4.12	0.050
				L-DOPA, Experimental run × Stimulus	0.174	0.680
				L-DOPA, Experimental run × Stimulus × Group	0.183	0.672

* indicates significant results.

However, application of a similar ANOVA to peak forces generated by each of our subjects did identify a significant effect of Trial position ($F_{1.00,34.00} = 7.74$, $*P = 0.009$) but no Trial position × Group interaction ($F_{1.00,34.00} = 0.158$, $P = 0.693$). There was again no effect of Group ($F_{1.00,34.00} = 1.766$, $P = 0.193$). Thus there was no habituation to the performance-boosting effects of loud sounds on peak yank, although there was such an effect on peak force. The latter effect was similar in PD patients and healthy controls.

Startle

Startle responses (defined in Materials and methods) were rare in subjects with PD, occurring in only 10 of 197 AV trials in the off medication state and four out of 198 trials in the on medication state across patients. In healthy controls the startle response was observed slightly more frequently (21 out of 184 AV trials in the first experimental run and 21 out of 195 AV trials in the second experimental run).

Discussion

The findings from our study are three-fold. We observed a significant facilitation of the onset, peak and rate of hand grip force production in our patients with PD in response to loud auditory stimulation, over and above that achieved with maximum effort of will. The effect was observed whether or not patients were treated with dopaminergic medication. Moreover, the phenomenon was reproduced in age-matched healthy controls, corroborating the view that paradoxical kinesia, in so far as it is captured by the present paradigm, may not be a unique hallmark of PD but rather an essentially physiological property of the motor system (Ballanger *et al.*, 2006).

The finding that the facilitatory effect of loud auditory stimuli was present in patients regardless of whether they were on or off medication is a key one. Importantly, our patients were all DOPA-responsive and demonstrated improvements in the time taken to reach peak force and peak yank during the grip task following medication. Despite this, there was no change in the facilitatory effect of loud auditory stimuli between the off and on medication states. Could we have missed a dopaminergic role in the shortening of reaction time and the increasing of the rate of development and magnitude of response force elicited by loud auditory stimuli? In particular, it could be argued that treatment with L-DOPA would be unlikely to promote any phasic release of dopamine with loud auditory stimuli. This, however, seems unlikely. First, if the facilitatory effect really were dopamine dependent, we should have found an attenuation of the phenomenon in PD patients withdrawn from their antiparkinsonian medication compared to age-matched controls. This was not the case. Second, L-DOPA has been shown to increase stimulation-induced phasic dopamine release in the striatum of intact and parkinsonian rats, suggesting that L-DOPA might be successfully converted to dopamine in remaining nigral neurons (Keller *et al.*, 1988; Wightman *et al.*, 1988). In line with this, L-DOPA decreases [^{11}C]raclopride binding in the striatum of parkinsonian patients, which is indicative of increased levels of synaptic dopamine, and this effect increases with progression of the disease (de la Fuente-Fernández *et al.*, 2004). Third, evidence from animal models of paradoxical kinesia also seems to favour a nondopaminergic mechanism. Rats rendered akinetic with intraventricular injections of 6-hydroxydopamine and subsequently treated with a combination of D1 and D2 receptor antagonists are still able to escape from an ice bath and run away when confronted with a room full of cats (Marshall *et al.*, 1976; Keefe *et al.*, 1989).

Several nondopaminergic systems could potentially underlie the facilitatory effect of loud auditory stimuli demonstrated here. Noradrenergic activation as part of the fight-or-flight response to

aversive stimuli remains a candidate mechanism and is supported by studies showing that animals treated with haloperidol are able to overcome their motor difficulties during a stressful situation, during which they also develop high plasma levels of noradrenaline (Yntema & Korf, 1987). In addition, glutamatergic mechanisms in the inferior colliculus, a structure which has been demonstrated to process auditory information and send output to motor centres which induce defensive behaviors such as arousal and escape responses (Melo *et al.*, 2010), may play a role. Important among these centres may be the brain stem reticular formation, which also has multiple cholinergic projections and has long been known to contribute to rapid behavioural responses to abrupt startling or arousing stimuli (Grillon & Baas, 2003).

It is, however, worth considering precisely how closely our results might relate to paradoxical kinesis as reported in patients with PD. Obvious ethical constraints in inducing frightening or life-threatening situations mean that the direct and systematic study of this phenomenon is practically impossible. The intense stimulus used in the current study was markedly more brief than those described in anecdotal reports of paradoxical kinesis (Schwab & Zieper, 1965; Marshall *et al.*, 1976; Schlesinger *et al.*, 2007; Bonanni *et al.*, 2010a,b). Nevertheless, the stimulus used still had a remarkable effect on all the examined force and temporal parameters related to a maximal hand grip. An important question is whether these improvements in performance would also occur in a more complex series of movements, such as those more commonly described in case reports of paradoxical kinesis. Future experiments investigating the effect of stimulus intensity and duration on a more complex motor paradigm would certainly be of interest.

Another issue is the precise stimulus features which might have precipitated the facilitatory effect observed in our study, and that in anecdotal reports of paradoxical kinesia. Several features could be invoked, including intersensory facilitation (Woodworth, 1938; Dufft & Ulrich, 1999; Miller *et al.*, 1999) and stimulus intensity effects (Angel, 1973; Jaśkowski *et al.*, 1995). The StartReact phenomenon may also have played a role (Valls-Solé *et al.*, 1999; Carlsen *et al.*, 2004, 2009; Reynolds & Day, 2007; Anzak *et al.*, 2011). This is the dramatic shortening of reaction times in trials accompanied by a startling stimulus. However, against a role of this phenomenon is the scarcity of a short-latency response in SCM in our subjects, which is considered to be the most sensitive hallmark of the generalised startle response (Brown *et al.*, 1991). Indeed, the startle response has previously been described as reduced in PD (Miller *et al.*, 2009), and substantial improvements in RT and force parameters may be elicited by loud auditory stimuli without elicitation of an overt startle response (Anzak *et al.*, 2011).

A number of studies have now shown that emotional stimuli can shorten reaction time and increase response force (Baumgartner *et al.*, 2007; Coombes *et al.*, 2007; Schmidt *et al.*, 2009). This raises the possibility that it is phasic arousal or alertness which may play a key role in motor improvement, given that the latter is precipitated by both emotional and loud auditory stimuli. Phasic arousal or alertness should be distinguished from tonic arousal or alertness. The former is the ability to increase response readiness for a short period of time subsequent to external stimuli (Sturm & Willmes, 2001). Phasic arousal or alertness also forms a plausible mechanism for both intersensory facilitation and intensity effects, and has been proposed as the underlying mechanism for force increases in other 'redundant-signal' tasks by which auditory and visual cues are presented independently or alone (Dufft & Ulrich, 1999; Giray & Ulrich, 1993; Mordkoff *et al.*, 1996). Specifically, it has been posited that a cue not only instigates specific processing related to analysis of the stimulus and execution of the response, but also 'immediate arousal' (Sanders, 1983) or 'automatic alertness' (Posner *et al.* 1976; Posner, 2008). Phasic arousal or alertness could in turn exert its influence by improving activation of motor areas (Baumgartner *et al.*, 2007; Jepma *et al.*, 2009) and amplifying the effects of the specific processing stream (Miller *et al.*, 1999; Stahl & Rammsayer, 2005). In this way a more consistent optimum performance could be achieved.

Analysis of the distributions of the peak forces and peak yanks generated in V and AV trials in patients with PD supported just such an effect, evident as an increase in the proportion of stronger grips selected from a similar range of movement capabilities present in both conditions. A similar effect has previously been described in healthy subjects (Anzak *et al.*, 2011). It has been hypothesised that movement parameters are 'selected' from an underlying range of capabilities so as to optimise the use of neuromuscular energy; this concept, describing the likelihood of selecting a certain speed of movement, has been termed 'motor vigor' by Mazzoni *et al.* (2007). It has further been suggested that in an arousing or temporally pressing situation the system is forced to adopt a more 'expensive' trade-off (Ballanger *et al.*, 2006). Thus in our paradigm the arousing or alerting nature of the loud auditory stimulus might improve motor vigor, over and above any considerations of force or speed–energetic cost tradeoffs, thus bringing about a more consistent 'best' performance. Accordingly, we have shown that whilst PD patients cannot produce as large forces and rates of development of force as control subjects, an intense and presumably arousing stimulus may still produce improved task performance. Nevertheless, the role of phasic arousal or alertness remains speculative and further studies are necessary to confirm that our loud auditory stimuli were actually accompanied by phasic activation.

To summarise, loud auditory stimulation in patients with PD resulted in a significant facilitatory effect on peak force, peak yank, time to reach peak force, time to reach peak yank, and RT, over and above that achieved with maximum effort of will. Similar improvements in age-matched healthy controls suggest that paradoxical kinesia, as captured in the current paradigm, may be a physiological property of the motor system. Moreover, the potential independence of the mediating pathways from the dopaminergic system provides impetus for further investigation as it may yield a novel nondopaminergic target for therapeutic manipulation in PD.

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Abbreviations

AV, combined audiovisual; L-DOPA, levodopa; OFF, whilst not taking (drugs); ON, whilst taking (drugs); PD, Parkinson's disease; RT, reaction time; SCM, sternocleidomastoid; UPDRS, Unified Parkinson's Disease Rating Scale; V, visual.

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