Doorway-provoked freezing of gait in Parkinson's disease

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Doorway-provoked freezing of gait in Parkinson's disease

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ABSTRACT

Background Freezing of gait in Parkinson's disease can be difficult to study in the laboratory. Here we investigate the use of a variable-width doorway to provoke freeze behaviour together with new objective methods to measure it. With this approach we compare the effects of anti-parkinsonian treatments (medications and deep-brain stimulation of the subthalamic nucleus) on freezing and other gait impairments.

Methods Ten 'freezers' and 10 control participants were studied. Whole-body kinematics were measured while participants walked at preferred speed in each of four doorway conditions (no door present, door width at 100, 125 and 150 % shoulder width) and in four treatment states (offmeds/offstim, offmeds/onstim, onmeds/offstim, onmeds/onstim).

Results With no doorway, the Parkinson's group showed characteristic gait disturbances including slow speed, short steps and variable step timing. Treatments improved these disturbances. The Parkinson's group slowed further at doorways by an amount inversely proportional to door width, suggesting a visuomotor dysfunction. This was not improved by either treatment alone. Finally, Freeze-like events were successfully provoked near the doorway and their prevalence significantly increased in narrower doorways. These were defined clinically and by two objective criteria which correlated well with clinical ratings. The risk of Freeze-like events was reduced by medication but not by deep-brain stimulation.

Conclusions Freeze behaviour can be provoked in a replicable experimental setting using the variable-width doorway paradigm, and measured objectively using two definitions introduced here. The differential effects of medication and deep-brain stimulation on the gait disturbances highlight the complexity of Parkinsonian gait disorders and their management.

INTRODUCTION

Parkinson's disease (PD) can cause 'freezing' episodes where the feet become involuntarily 'stuck to the ground'. This phenomenon has proved difficult to study in the laboratory, meaning that its pathophysiological basis and treatment remain poorly understood. Here we describe a new approach for provoking and measuring freezes in a controlled setting. The work addresses three important challenges in studying freeze behaviour.

First, how can we evoke freezes in laboratory settings? Here we exploit the fact that freezing episodes occur in tight spaces or doorways for around half of PD patients who freeze [1]. Recent studies have built on this observation by showing that in laboratory settings 'freezers' (PD patients susceptible to freezing episodes) slow down excessively as they approach a doorway [2,3]. In the present study our first aim was to evoke freezing using this previously developed variable-width doorway paradigm [2], where the doorway is scaled to each individual's shoulder width. This approach complements work using sudden obstacle appearance [4], surface translation [5], or slowing [6], to provoke freeze behaviour in a simple, naturalistic and replicable manner.

Second, how should we measure freezes? Traditionally, freezing is a clinically-defined phenomenon that reflects the patient's subjective impression that their feet are 'glued to the floor'. Sometimes a freeze event is obvious to an observer, but it becomes increasingly difficult to be certain if episodes are short and the external signs of the patient's internal struggle to move are not apparent. Here we follow a recent trend [4,7] and develop two separate objective measures of freezing to complement clinical definitions and allow better comparison of data collected in different laboratories under diverse conditions.

Third, can we use these approaches to assess current treatments of freezing? To investigate this we measure doorway-provoked freeze behaviour in a group of patients treated with medications and deep-brain stimulation of the subthalamic nucleus (STN-DBS). While STN-DBS improves clinical [8,9] and kinematic [10-13] aspects of gait, there is mixed evidence on whether it reduces the number of freezing episodes [14,15]. Here we establish whether the variable-width doorway paradigm provides a suitable method for assessing the risk of freezing under different treatment states. The resulting data must be considered specific to our particular patient sample and surgical group; nevertheless they further our understanding both of how to study and how to treat freezing of gait in PD.

METHODS

Research was approved by the joint ethics committee of the National Hospital for Neurology and Neurosurgery (NHNN) and UCL Institute of Neurology, London, UK. Written informed consent was obtained before testing.

Participants

Ten patients with idiopathic PD (8 males, mean age 59.8yrs, s.d. 7.3yrs), and ten matched healthy controls, (HC: 8 males, mean age 62.8yrs, s.d. 5.8yrs) took part. Patients were recruited from the NHNN and classified by a movement disorders neurologist as presenting with freezing of gait. They had no serious cognitive impairments, assessed by a neurologist, or uncorrected visual impairments. The mean duration of PD was 14.6 years (sd 4yrs). All had been implanted with bilateral STN electrodes using an MRI-guided technique [16,17]. Stimulators had been fitted on average 4.02 years prior to testing (sd 2.5 yrs) and the response had stabilised. Treatments are shown in Table 1.

PD participants visited the laboratory twice within a month. On each occasion, they were first tested 'off medication' (> 12 hours withholding medication). One hour after taking their normal morning dose, tests were repeated 'on medication'. On the first visit tests were performed with the stimulator turned on, and on the second visit >15 minutes after the stimulator had been turned off. This allowed efficient data collection, especially off medication.

Apparatus

Kinematic data were obtained using a CODA motion-capture system (Charnwood Dynamics, Rothley, UK), with markers placed bilaterally on the lateral malleolus, 2nd metatarsal head, posterior aspect of calcaneus at height of toe marker, anterior superior iliac spine (ASIS) and sacrum. Two vertical planks of wood, each 15cm wide formed a doorway extending from the ground to a pelmet at 210cm. Door width was adjusted using a motor.

Design & Procedure

Walking task: Participants walked a 6.32m straight path. A set of trials started with a walk in one direction followed by one in the opposite direction, repeated to give four trials per set providing the patient was able. Each block started with a set of no-door trials, followed by three sets of door trials, where door width was scaled to 150, 125, or 100% of the participant's shoulder width (left to right acromion). Door width order was randomised between participants. PD participants completed one block in each treatment state. They were instructed to pass through the doorway naturally. *Perceptual task:* Perception, including perception of door width, can be altered in PD [18,19]. To assess this we had participants judge the width of doorway they could just pass through, as described in [2]. *Turn task:* Axial turns can be a potent trigger of freezing [20]. Since participants may turn slightly in the approach to a doorway, we wanted to check if this movement contributed to the freezing we observed in doorways. We therefore had participants

complete a short turning task consisting of two tight 360° turns clockwise and two anticlockwise in each testing block. *Clinical measures:* The cardinal motor features of PD were assessed with the Unified Parkinson's Disease Rating Scale Part III (UPDRS; [21]). Freezing at home was assessed using the FOG Questionnaire (FOG-Q;[22]).

Analysis

Gait variables: Position data were low-pass filtered in both directions at 10 Hz with a 2nd order Butterworth filter. Toe-off and heel-strike were selected by a custom Matlab (MathWorks Inc, Natick, MA, USA) routine and visually confirmed by a single trained observer. Stride time was the time between successive foot-strikes of the same foot. Stride time variability was measured by the coefficient of variation of stride times, considered across both feet. Stride length was the distance travelled by the heel in the transverse plane during a stride. On each trial we calculated the mean value of these freeze-related gait variables [3,23, 24] in a 2.8m region surrounding the door (as in [2]), and averaged across trials of the same type to give mean values for each door and treatment condition.

Freezes and freeze-like events: We report three separate measures of freeze behaviour. Clinical ratings were made from video by an experienced neurologist (PL), blind to treatment condition. Each of our two objective definitions of 'freeze-like events' (FLEs) is based on the assumption that freezes are rare, episodic events which should be considered relative to each participant's baseline walking performance. In the first definition (Fig 1A), a FLE is an unusually long period of double support for that person. For each participant in each treatment condition we calculated a distribution of double support times, and defined an unusually high double support time as being more than 3.1 standard deviations above the mean for that condition. In the second, separate definition (Fig 1B), a FLE is an extremely slow period of

walking for that person. For each participant in each treatment condition, we calculated baseline velocity across the middle 3.32m of the walkway on no-door trials, and defined a FLE as a period in which velocity dropped below 10% of baseline. These criteria were set to be stringent but also capable of detecting shorter freezes. For further details and validation, see Supplementary materials.

Statistical analysis: Two repeated measures ANOVAs were conducted on each gait parameter. The first assessed the factors of door width, stimulation and medication in PD participants; the second, group differences with factors door width and group (HC *vs* PD participants in off/off state). For freezing, we report the number of trials on which one or more freezes or FLEs occurred and the total time spent in FLE's; and use multiple logistic regression analysis [25] to quantify how the risk of a FLE depended on door width and treatment. This describes the relationship between predictor variables (e.g. medication state) and a dichotomous outcome variable (FLE or non-FLE trial). The first stage of this analysis is to calculate, in each treatment or door width condition, the *odds* : p (FLE trial) / p (non-FLE trial). The *odds ratio* then compares odds in different conditions (e.g. on *vs* off medication). Importantly, odds ratios significantly lower than one indicate that the risk of a FLE is significantly different between conditions. For each FLE definition a single logistic regression analysis was conducted which measured the independent effects of medication, stimulation and door width on FLE risk, with statistics adjusted for the presence of multiple variables. To assess perceptual judgements in PD participants we used an ANOVA with factors medication and stimulation; to compare the HC group with the PD group off/off we used a second ANOVA. Because of unequal variances, non-parametric Mann-Whitney U and Friedman tests were used to compare turn time across groups and treatment states respectively.

RESULTS

Clinical measures

The mean score on the FOG-Q was 10.2 (sd 3.8), indicating moderately severe freezing. Mean UPDRS part III motor scores were: off stim/off meds, 39.4 (sd 9.7); off stim/on meds, 30.6 (sd 12.7); on stim/off meds, 22.2 (sd 10.1), on stim/onmeds, 14.1 (sd 8.2). Scores were lower with stimulation alone than with medication alone, perhaps because medication dosages were not as high as pre-operative levels, or because the effects of medication alone are reduced after chronic stimulation [26].

Gait variables

Walking velocity dropped as the body approached the door (Fig 2), with larger drops for narrower doors. Analyses of gait parameters (Tables 2 & 3) showed that in the PD group, door width significantly affected all variables. Medication improved the mean levels of all variables (i.e. increased velocity and stride length, and decreased stride time variability), but changed the scaling to door width only of stride time variability. Stimulation improved the mean levels only of velocity and stride length, and did not change scaling to door width of any variable. Significant group by door width effects for all variables indicated that PD participants and healthy controls scaled their responses to door width differently. When compared to the HC group, PD participants had amplified responses, such that the same reduction in door width led to greater drops in velocity and stride length, and a greater rise in stride time variability.

Freeze behaviour

On clinical ratings and both separate FLE definitions, freeze or FLE frequency increased as door width narrowed (Fig 3A), and was reduced by medication but not stimulation (Fig 3A,B).

Statistical analyses showed that for both FLE definitions, FLE risk was significantly reduced by medication ($p<0.001$) but not stimulation (Fig 3D). Comparing FLE risk on medium and narrow door conditions with a wide door baseline condition showed that risk significantly increased as doors became narrower (Fig 3C). After controlling for the effects of medication, medium doors doubled or trebled FLE risk, and narrow doors increased the risk approximately tenfold compared with the wide-door trials ($p <0.001$). We could not perform statistical analyses on duration data because of the uneven spread of FLEs across conditions. However, the longest FLEs occurred at the narrowest door width (Supplementary materials) and in the untreated condition; the trend was for both treatments to decrease FLE duration (Supplementary materials).

Perceptual and motor performance

Because of fatigue, one participant did not complete the perceptual task and one did not complete the turning task. Explicit judgements of door width by PD participants (Fig 4A) were not affected by medication ($F(1,8)=.53$, $p=.487$) or stimulation ($F(1,8)=2.920$, $p=.126$), with no interaction ($F(1,8)=1.931$, $p=.202$). These judgements were not different between HC and PD groups ($t(17)=-0.079$, $p=.938$).

The time to turn 360° was significantly different between HCs and untreated PD participants (Mann-Whitney $U = 2.0$, $p<0.001$; Fig 4B), and significantly affected by treatment state ($\chi2(3)=13.41$, $p=.004$). However, turn time in the PD group did not significantly correlate with the extent of slowing experienced in doors (velocity drop from no-door to narrow door condition in off/off state) ($p=.167$, $p=.668$). Thus neither perceptual performance nor turning ability could account for slowing and freezing in doorways.

DISCUSSION

We used a variable-width doorway paradigm and two quantitative freeze-like event (FLE) definitions to provoke and measure freezing in a replicable manner. We then compared the effects of medications and STN-DBS on walking and freezing within the same, naturalistic setting.

Slow walking and its treatment

Patients exhibited characteristic parkinsonian gait disturbances of short steps and low velocity [23]. As in other studies, both medication and STN-DBS improved these symptoms [13,24]. Doorways produced striking additional effects on PD gait. Narrower doors caused shorter strides in healthy controls, but consistent with previous studies [2,3] this effect was greatly amplified in the PD group. We assume that these gait disturbances are specific to PD freezers since a previous study [3] found clear differences in the slowing phenomenon between the FOG and non-FOG groups. Slowing at doorways did not likely result from changes in the background stride lengths of the groups, since medications and STN-DBS significantly increased this but did not improve the slowing effect of doors (there were no door-width by treatment interactions). Rather, the observed slowing may result from a visuomotor process, where visually specified information about door width determines how much one must slow down to pass through the door accurately. The dramatic slowing of PD freezers is consistent with the hypothesis that visuomotor processing is different in these patients, specifically that they produce exaggerated responses to visual information [2]. This perspective may help explain the exaggerated responses of PD patients in other tasks [27-30]. An alternative explanation is that the doorway removes attention from walking, thus interfering with voluntary compensation for an underlying short stride length [31]. Neither medication nor STN-DBS alleviated door width-related slowing. This is of course specific to our patient sample and should be tested across

different patient and surgical groups; however, the failure of medications to change door width-related slowing replicates an earlier study with a different, non-implanted group [2]. Together these studies suggest that brain regions other than the basal ganglia may play a role in door-provoked slowing. Interestingly, lateral premotor areas of cortex in PD patients have been reported to show excessive activation to visual information during walking [32] and may process visual information for walking as they do for reaching [33-35].

Freeze behaviour and its treatment

We used two criteria to define objectively freeze-like events (FLEs). These agreed well with clinical ratings of freeze behaviour and provide objective measures comparable to inter-rater reliability (Supplementary material). Future studies should validate these measures in a larger cohort of patients. However, considering the data in this way removed the subjective element from defining freeze events, and provided measures which allow reliable, replicable identification of freezes, even those of short duration. These measures showed that freeze behaviour tends to occur near a doorway and with greater frequency as door width decreases. This confirms the observation that doorways elicit freeze behaviour in PD [1] and shows that the doorway is a powerful tool for experimentally manipulating freezing in a simple, naturalistic and replicable manner. Doorway-evoked freezing can be used as an important complement to other recently described methods of evoking freezes in laboratory settings [4, 5, 6], and future work may wish to compare these methods experimentally.

A particularly influential theory of freezing is that it is caused by a reduction in baseline stridelength coupled to a sequence effect (progressive shortening of steps during walking) [6]. As discussed above our data are partially consistent with the relation between slowing and freezing – here we found that both were sensitive to door width. Indeed the slowing produced by

visuomotor dysfunction could in turn cause freezing through a sequence effect [6,36,37]. Indeed, closing eyes can help reduce freezing [38]. However, the differential effects of the two treatments suggest that other mechanisms may have contributed to freezing in the current study. That is, both treatments significantly improved baseline walking speed and door-width related slowing, whereas only medication reduced the risk of freezing (STN-DBS did not). The results are consistent with the suggestion that high stride time variability is associated with freezing [39] because, like freezing, it was improved by medication but not by STN-DBS. This discussion of how gait variables relate to freezing is based on the variation we naturally observed across different treatment conditions. In future work it would be ideal to also experimentally manipulate gait variables, for example by asking patients or healthy controls to walk at a different stride length.

The lack of a STN-DBS effect on freezing is especially notable for several reasons. First, STN-DBS increased walking speed and stride length. Second, in the same session, UPDRS scores were improved more by STN-DBS than by medication. Third, the postoperative drug doses were less than would have been given if the disease had progressed without surgery, yet, in contrast to STN-DBS, medication still reduced FLE risk . Consistent with previous work [15], the relative weakness of STN-DBS as a therapeutic tool is therefore quite specific to freezing. Of course, this need not generalise to all PD patients. The effects of STN on post-operative freezing are best predicted by the pre-operative response to levodopa [15] and stimulation parameters must be carefully adjusted [14]. While STN-DBS may effectively reduce freezing in some patients, the present study highlights its potential limitations and the need to continue exploring new treatments for this disabling symptom of PD. However, the assessment of treatments is not straightforward as freezing is a complex phenomenon with idiosyncratic properties [40]. Much

work is therefore needed to develop theories of freezing which can account for the pattern of behaviour in the wide range of situations where it occurs.

Summary

The variable-width doorway paradigm coupled with reproducible measurements of freeze behaviour provides a new experimental approach for investigating freezing. Using this approach, we show that the risk of freezing is highly sensitive to door width. The differential effects of treatments in this setting suggest separable mechanisms for the patients' slow walking, door width-related slowing, and door width-related freezing, and highlight the need to explore alternative treatments for severe freezing of gait.

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Author roles: Cowie was involved in the conception, organization and execution of the project; statistical analysis, and manuscript writing & review. Limousin was involved in the conception, organization, and execution of the project, and manuscript review. Peters was involved in the conception, organization and execution of the project, and manuscript review. Hariz was involved in the organization of the project and manuscript review. Day was involved in the conception & organization of the project, statistical analysis, and manuscript writing & review.

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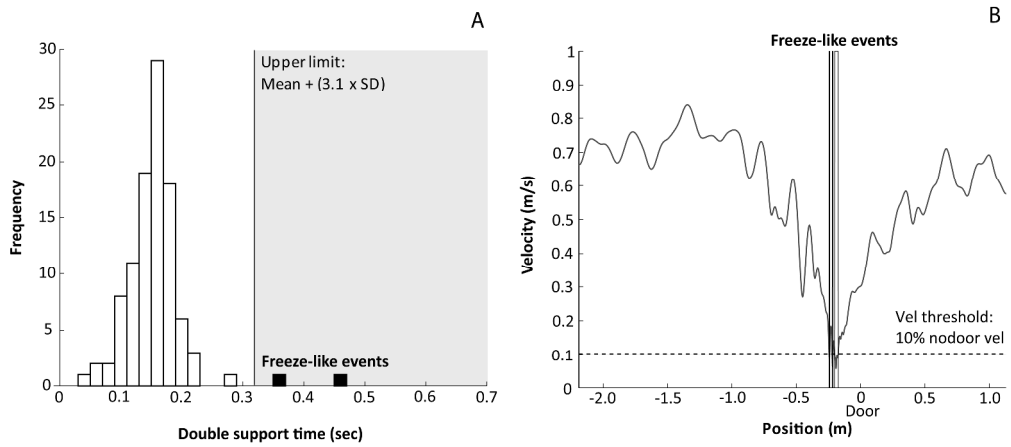
FIGURE LEGENDS

Figure 1 Freeze-like event (FLE) definition shown for one example patient. FLEs defined as (A) outliers in distribution of double support times for each participant within each condition (B) times where velocity falls <10% of mean value on no-door trials.

Figure 2 Walking velocity. Pelvis midpoint velocity in direction of progression, as a function of position in space. Traces for single PD participant in off/off state. Data filtered at 1Hz, plotted for each door condition. Dashed lines show measurement region.

Figure 3 Freezes. Total freeze / FLE trials observed per condition across all PD participants by (A) door (B) treatment condition. Effects of (C) door width (D) treatment condition on odds ratio (FLE risk). Mean and 95% confidence intervals shown.

Figure 4 Perceptual and motor performance. Means and standard errors shown by group and treatment for (A) passability judgements (B) time to turn 360°.



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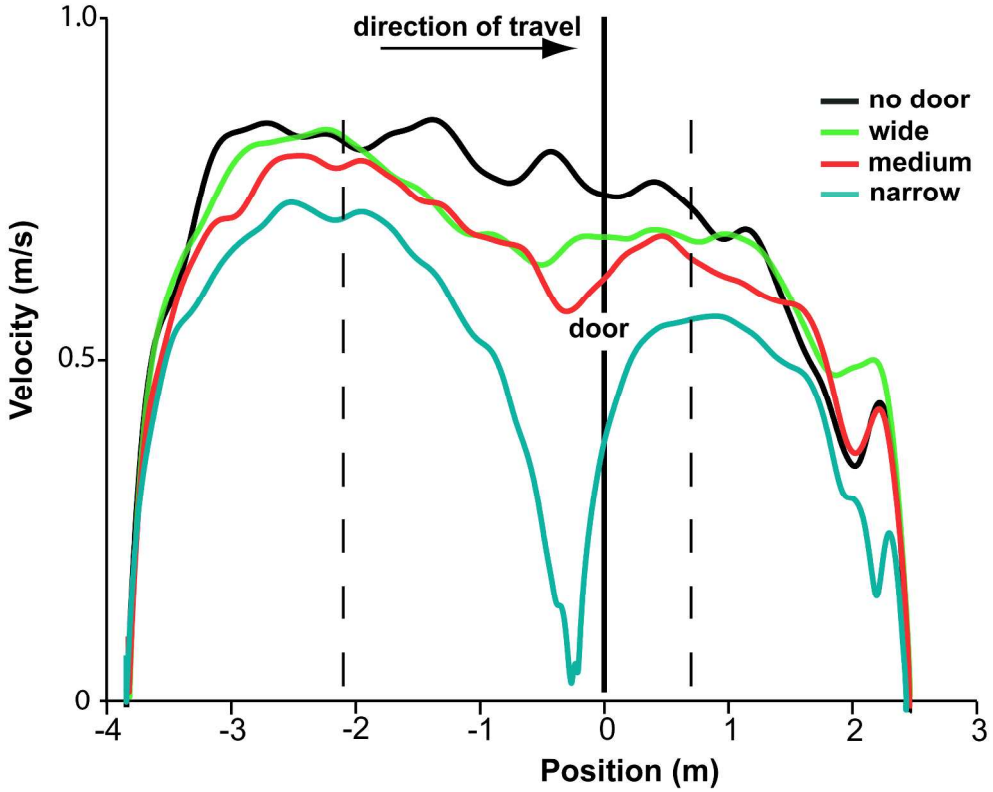

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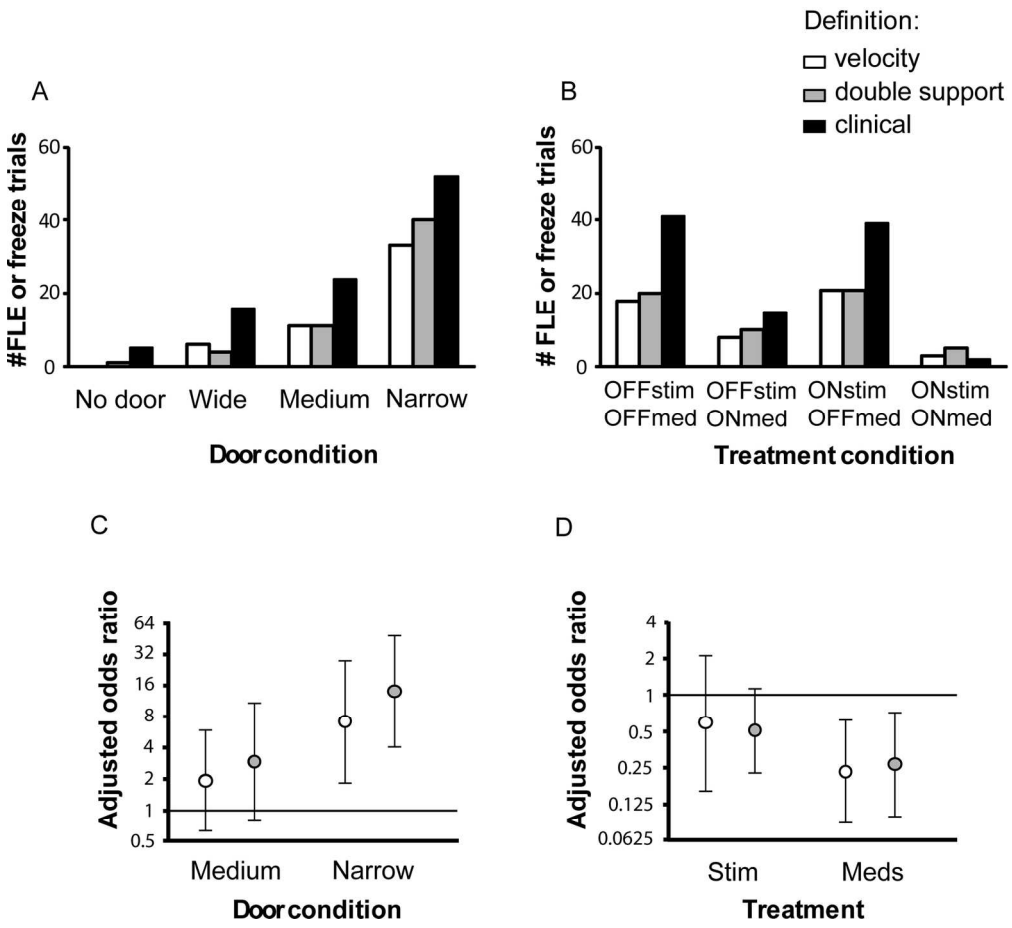

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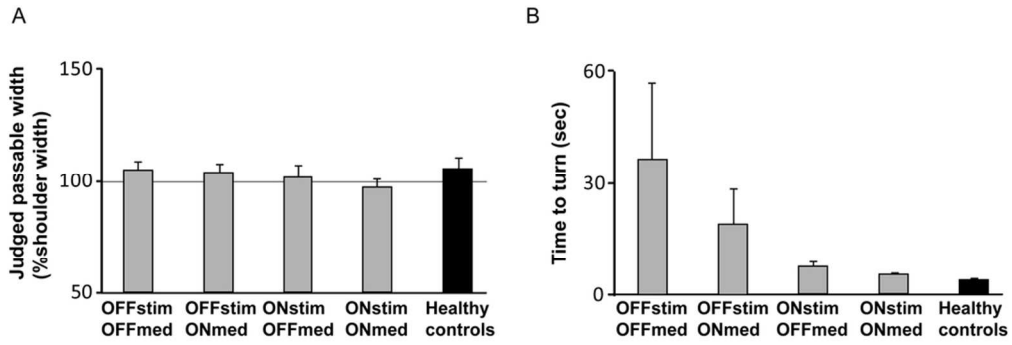

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Table 1. Treatments.

Participant	Stimulation parameters						Medications	
	Amplitude (V)		Frequency (Hz)		Pulse width (µs)		Type	Daily dose (mg)
	L	R	L	R	L	R		
1	4.1	2.85	145	145	60	60	Ropinirole Amantadine	24 300
2	3	3.1	150	150	60	60	Sinemet Cabergoline	1000 2
3	3.6	2.8	145	130	60	60	Sinemet Amantadine Entacapone Rasagiline	600 100 200 1
4	4	3	180	180	60	60	Sinemet Ropinirole Amantadine	900 15 300
5	3.6	3.6	145	145	90	60	Madopar Sinemet Ropinirole	500 200 20
6	2	3.4	130	130	60	60	Madopar Pramipexole	300 1.608
7	3.5	4.3	185	185	60	90	Madopar Ropinirole Amantadine Selegiline	500 15 200 5
8	3.8	3.2	130	130	60	90	Sinemet Ropinirole Amantadine	150 12 200
9	3.8	3.5	130	130	60	60	Madopar Entacapone	500 600
10	3.7	3.8	130	130	60	60	Madopar Ropinirole Amantadine	500 6 200

Sinemet and Madopar expressed as mg levodopa.

Table 2. Mean gait variables.

		HC				PD															
		Off stim Off med				Off stim On med				On stim Off med				On stim On med							
		no	w	m	n	no	w	m	n	no	w	m	n	no	w	m	n	no	w	m	n
Velocity (m/s)	*mean*	1.09	1.15	1.14	1.08	.77	.71	.66	.53	.96	.84	.82	.72	.95	.94	.84	.75	1.10	1.09	1.04	0.98
	se	.03	.04	.04	.04	.12	.11	.09	.10	.09	.11	.09	.09	.07	.08	.08	.09	.08	.07	.08	.09
Stride Length (m)	*mean*	1.23	1.24	1.23	1.18	.86	.76	.73	.54	1.07	.95	.90	.80	1.02	.97	.87	.79	1.19	1.12	1.06	1.00
	se	.02	.03	.03	.03	.11	.11	.09	.09	.10	.12	.09	.09	.07	.07	.08	.08	.08	.08	.08	.10
Stride time cv (%)	*mean*	2.03	2.28	2.42	3.36	5.04	11.09	12.10	45.43	4.41	5.96	6.33	17.30	3.89	5.32	8.68	14.67	3.39	3.88	5.06	8.54
	Se	.19	.18	.22	.50	1.64	3.82	3.83	20.24	1.12	1.53	1.77	7.42	0.51	1.17	2.46	3.41	0.46	0.54	0.99	1.92

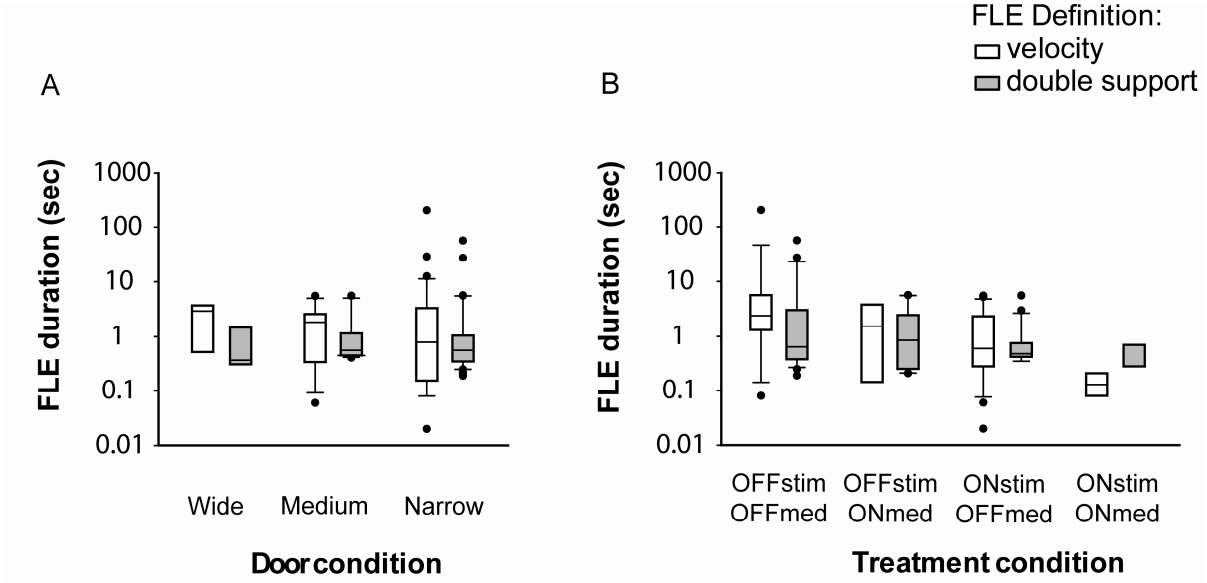
Group means and standard errors for PD participants and healthy controls, at four door widths (no: no door; w: wide door; m: medium door; n: narrow door). Shown in four treatment states.

Table 3. Gait variable ANOVAs.

		Velocity		Stride length		Stride time variability	
	d.f.	***F***	***p***	***F***	***p***	***F***	***p***
PD Group ANOVAs							
stim xmed x dr	3,27	0.33	.807	0.23	.877	2.18	.114[G]
stim x meds	1,9	0.07	.796	0.33	.580	1.98	.193
meds x door	3,27	1.90	.153	1.66	.199	5.87	**.003**[G]
stim x door	3,27	1.57	.219	1.85	.163	1.88	.157[G]
stimulation	1,9	23.53	**.001**	15.47	**.003**	2.05	.186
medication	1,9	15.43	**.003**	11.67	**.008**	7.91	**.020**
door	3,27	36.85	**.000**	42.45	**.000**	6.93	**.001**[G]
PD offoff *vs.* HC ANOVAs							
door x group	3,54	9.39	**.000**	9.66	**.000**	3.83	**.015**
door	3,54	13.81	**.000**	20.44	**.000**	4.34	**.050**[G]
group	1,18	18.22	**.000**	25.00	**.000**	5.14	**.036**

Two ANOVAs for each of three variables. (i) PD: effects of door width, stimulation and medication (ii) PD off /off *vs* healthy participants: effects of door width and group. p values (< .05) shown in bold. G: Greenhouse-Geisser corrected values.

Supplementary material: Freeze Duration



Supplementary Fig 1 Freeze duration. Total duration of FLEs in FLE trials by (A) Door condition (B) Treatment condition. Boxes show group median and IQ range. Circles denote outliers.

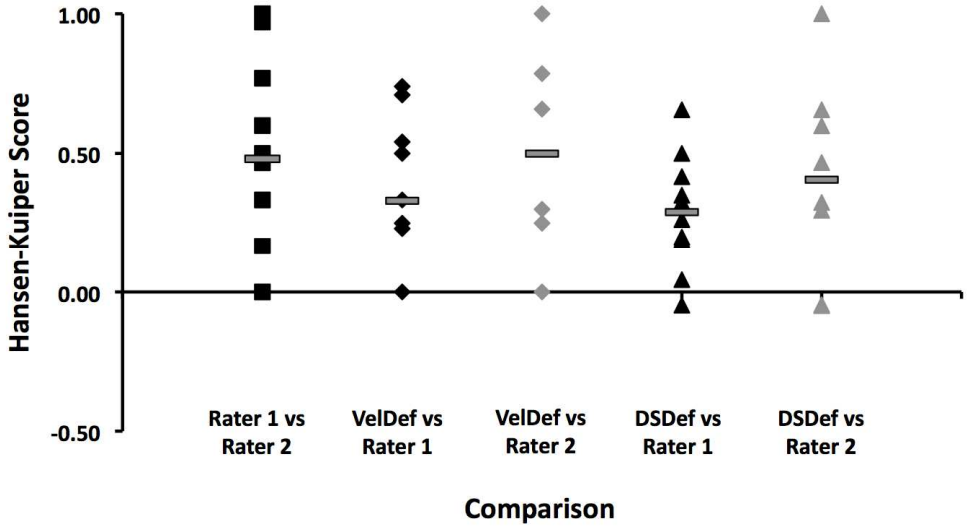
Supplementary material: Freeze-like-event Definitions

In order to validate our two objective measures of FOG, we compared each measure with clinical ratings using the Hansen-Kuiper or True Skill Score. This is a means of assessing how well one categorical predictor agrees with another, and takes into account both the hit rate and the false alarm rate of the predictor. In this case the dependent variable to be predicted is "FOG or non-FOG trial". The score is given by

POD – POFD
Where POD = H/(H+M) and POFD = F/(Z+F)
And H= hits; M = misses; F = false alarms; Z=correct rejections.

Results may range between -1 for total disagreement and 1 for total agreement between rating systems. Using this score, we compared each measure not only with the clinical rater whose data are presented in the paper, but also with a second clinical rater (TF). TF was an experienced neurologist and was blind to the ratings made both by the objective definitions and the by first clinical rater. We compared each objective definition (DS, VelDef) to each clinical rater (PL, TF), giving four comparisons. As a standard of reliability we also compared the two clinical raters against each other. We therefore made a total of 5 comparisons.

The results of these are shown below. Each of the 5 comparison types is shown in a separate column of points. Each point represents a comparison made for one participant. The grey horizontal bars indicate the mean score across all participants.



Considering first the inter-rater reliability between the two clinical raters, it is apparent that agreement is around 0.5, but that there is a large spread of values around this point (*ie* agreement is higher for some subjects). Next considering the four columns to the right, we see that our two objective definitions agree with the clinical raters almost as well as the raters agree with each other. Comparing the definitions with the clinical inter-rater reliability in this way enables quantitative comparison of their validity and indicates that either of these definitions can be used as an objective means of identifying freezes that produces results comparable with inter-rater reliability.

Doorway-provoked freezing of gait in Parkinson's disease

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ABSTRACT

Background Freezing of gait in Parkinson's disease can be difficult to study in the laboratory. Here we investigate the use of a variable-width doorway to provoke freeze behaviour together with new objective methods to measure it. With this approach we compare the effects of anti-parkinsonian treatments (medications and deep-brain stimulation of the subthalamic nucleus) on freezing and other gait impairments.

Methods Ten 'freezers' and 10 control participants were studied. Whole-body kinematics were measured while participants walked at preferred speed in each of four doorway conditions (no door present, door width at 100, 125 and 150 % shoulder width) and in four treatment states (offmeds/offstim, offmeds/onstim, onmeds/offstim, onmeds/onstim).

Results With no doorway, the Parkinson's group showed characteristic gait disturbances including slow speed, short steps and variable step timing. Treatments improved these disturbances. The Parkinson's group slowed further at doorways by an amount inversely proportional to door width, suggesting a visuomotor dysfunction. This was not improved by either treatment alone. Finally, Freeze-like events were successfully provoked near the doorway and their prevalence significantly increased in narrower doorways. These were defined clinically and by two objective criteria which correlated well with clinical ratings. The risk of Freeze-like events was reduced by medication but not by deep-brain stimulation.

Conclusions Freeze behaviour can be provoked in a replicable experimental setting using the variable-width doorway paradigm, and measured objectively using two definitions introduced here. The differential effects of medication and deep-brain stimulation on the gait disturbances highlight the complexity of Parkinsonian gait disorders and their management.

INTRODUCTION

Parkinson's disease (PD) can cause 'freezing' episodes where the feet become involuntarily 'stuck to the ground'. This phenomenon has proved difficult to study in the laboratory, meaning that its pathophysiological basis and treatment remain poorly understood. Here we describe a new approach for provoking and measuring freezes in a controlled setting. The work addresses three important challenges in studying freeze behaviour.

First, how can we evoke freezes in laboratory settings? Here we exploit the fact that freezing episodes occur in tight spaces or doorways for around half of PD patients who freeze [1]. Recent studies have built on this observation by showing that in laboratory settings 'freezers' (PD patients susceptible to freezing episodes) slow down excessively as they approach a doorway [2,3]. In the present study our first aim was to evoke freezing using this previously developed variable-width doorway paradigm [2], where the doorway is scaled to each individual's shoulder width. This approach complements work using sudden obstacle appearance [4], surface translation [5], or slowing [6], to provoke freeze behaviour in a simple, naturalistic and replicable manner.

Second, how should we measure freezes? Traditionally, freezing is a clinically-defined phenomenon that reflects the patient's subjective impression that their feet are 'glued to the floor'. Sometimes a freeze event is obvious to an observer, but it becomes increasingly difficult to be certain if episodes are short and the external signs of the patient's internal struggle to move are not apparent. Here we follow a recent trend [4,7] and develop two separate objective measures of freezing to complement clinical definitions and allow better comparison of data collected in different laboratories under diverse conditions.

Third, can we use these approaches to assess current treatments of freezing? To investigate this we measure doorway-provoked freeze behaviour in a group of patients treated with medications and deep-brain stimulation of the subthalamic nucleus (STN-DBS). While STN-DBS improves clinical [8,9] and kinematic [10-13] aspects of gait, there is mixed evidence on whether it reduces the number of freezing episodes [14,15]. Here we establish whether the variable-width doorway paradigm provides a suitable method for assessing the risk of freezing under different treatment states. The resulting data must be considered specific to our particular patient sample and surgical group; nevertheless they further our understanding both of how to study and how to treat freezing of gait in PD.

METHODS

Research was approved by the joint ethics committee of the National Hospital for Neurology and Neurosurgery (NHNN) and UCL Institute of Neurology, London, UK. Written informed consent was obtained before testing.

Participants

Ten patients with idiopathic PD (8 males, mean age 59.8yrs, s.d. 7.3yrs), and ten matched healthy controls, (HC: 8 males, mean age 62.8yrs, s.d. 5.8yrs) took part. Patients were recruited from the NHNN and classified by a movement disorders neurologist as presenting with freezing of gait. They had no serious cognitive impairments, assessed by a neurologist, or uncorrected visual impairments. The mean duration of PD was 14.6 years (sd 4yrs). All had been implanted with bilateral STN electrodes using an MRI-guided technique [16,17]. Stimulators had been fitted on average 4.02 years prior to testing (sd 2.5 yrs) and the response had stabilised. Treatments are shown in Table 1.

PD participants visited the laboratory twice within a month. On each occasion, they were first tested 'off medication' (> 12 hours withholding medication). One hour after taking their normal morning dose, tests were repeated 'on medication'. On the first visit tests were performed with the stimulator turned on, and on the second visit >15 minutes after the stimulator had been turned off. This allowed efficient data collection, especially off medication.

Apparatus

Kinematic data were obtained using a CODA motion-capture system (Charnwood Dynamics, Rothley, UK), with markers placed bilaterally on the lateral malleolus, 2nd metatarsal head, posterior aspect of calcaneus at height of toe marker, anterior superior iliac spine (ASIS) and sacrum. Two vertical planks of wood, each 15cm wide formed a doorway extending from the ground to a pelmet at 210cm. Door width was adjusted using a motor.

Design & Procedure

Walking task: Participants walked a 6.32m straight path. A set of trials started with a walk in one direction followed by one in the opposite direction, repeated to give four trials per set providing the patient was able. Each block started with a set of no-door trials, followed by three sets of door trials, where door width was scaled to 150, 125, or 100% of the participant's shoulder width (left to right acromion). Door width order was randomised between participants. PD participants completed one block in each treatment state. They were instructed to pass through the doorway naturally. *Perceptual task:* Perception, including perception of door width, can be altered in PD [18,19]. To assess this we had participants judge the width of doorway they could just pass through, as described in [2]. *Turn task:* Axial turns can be a potent trigger of freezing [20]. Since participants may turn slightly in the approach to a doorway, we wanted to check if this movement contributed to the freezing we observed in doorways. We therefore had participants

complete a short turning task consisting of two tight 360° turns clockwise and two anticlockwise in each testing block. *Clinical measures:* The cardinal motor features of PD were assessed with the Unified Parkinson's Disease Rating Scale Part III (UPDRS; [21]). Freezing at home was assessed using the FOG Questionnaire (FOG-Q;[22]).

Analysis

Gait variables: Position data were low-pass filtered in both directions at 10 Hz with a 2nd order Butterworth filter. Toe-off and heel-strike were selected by a custom Matlab (MathWorks Inc, Natick, MA, USA) routine and visually confirmed by a single trained observer. Stride time was the time between successive foot-strikes of the same foot. Stride time variability was measured by the coefficient of variation of stride times, considered across both feet. Stride length was the distance travelled by the heel in the transverse plane during a stride. On each trial we calculated the mean value of these freeze-related gait variables [3,23, 24] in a 2.8m region surrounding the door (as in [2]), and averaged across trials of the same type to give mean values for each door and treatment condition.

Freezes and freeze-like events: We report three separate measures of freeze behaviour. Clinical ratings were made from video by an experienced neurologist (PL), blind to treatment condition. Each of our two objective definitions of 'freeze-like events' (FLEs) is based on the assumption that freezes are rare, episodic events which should be considered relative to each participant's baseline walking performance. In the first definition (Fig 1A), a FLE is an unusually long period of double support for that person. For each participant in each treatment condition we calculated a distribution of double support times, and defined an unusually high double support time as being more than 3.1 standard deviations above the mean for that condition. In the second, separate definition (Fig 1B), a FLE is an extremely slow period of

walking for that person. For each participant in each treatment condition, we calculated baseline velocity across the middle 3.32m of the walkway on no-door trials, and defined a FLE as a period in which velocity dropped below 10% of baseline. These criteria were set to be stringent but also capable of detecting shorter freezes. For further details and validation, see Supplementary materials.

Statistical analysis: Two repeated measures ANOVAs were conducted on each gait parameter. The first assessed the factors of door width, stimulation and medication in PD participants; the second, group differences with factors door width and group (HC *vs* PD participants in off/off state). For freezing, we report the number of trials on which one or more freezes or FLEs occurred and the total time spent in FLE's; and use multiple logistic regression analysis [25] to quantify how the risk of a FLE depended on door width and treatment. This describes the relationship between predictor variables (e.g. medication state) and a dichotomous outcome variable (FLE or non-FLE trial). The first stage of this analysis is to calculate, in each treatment or door width condition, the *odds* : p (FLE trial) / p (non-FLE trial). The *odds ratio* then compares odds in different conditions (e.g. on *vs* off medication). Importantly, odds ratios significantly lower than one indicate that the risk of a FLE is significantly different between conditions. For each FLE definition a single logistic regression analysis was conducted which measured the independent effects of medication, stimulation and door width on FLE risk, with statistics adjusted for the presence of multiple variables. To assess perceptual judgements in PD participants we used an ANOVA with factors medication and stimulation; to compare the HC group with the PD group off/off we used a second ANOVA. Because of unequal variances, non-parametric Mann-Whitney U and Friedman tests were used to compare turn time across groups and treatment states respectively.

RESULTS

Clinical measures

The mean score on the FOG-Q was 10.2 (sd 3.8), indicating moderately severe freezing. Mean UPDRS part III motor scores were: off stim/off meds, 39.4 (sd 9.7); off stim/on meds, 30.6 (sd 12.7); on stim/off meds, 22.2 (sd 10.1), on stim/onmeds, 14.1 (sd 8.2). Scores were lower with stimulation alone than with medication alone, perhaps because medication dosages were not as high as pre-operative levels, or because the effects of medication alone are reduced after chronic stimulation [26].

Gait variables

Walking velocity dropped as the body approached the door (Fig 2), with larger drops for narrower doors. Analyses of gait parameters (Tables 2 & 3) showed that in the PD group, door width significantly affected all variables. Medication improved the mean levels of all variables (i.e. increased velocity and stride length, and decreased stride time variability), but changed the scaling to door width only of stride time variability. Stimulation improved the mean levels only of velocity and stride length, and did not change scaling to door width of any variable. Significant group by door width effects for all variables indicated that PD participants and healthy controls scaled their responses to door width differently. When compared to the HC group, PD participants had amplified responses, such that the same reduction in door width led to greater drops in velocity and stride length, and a greater rise in stride time variability.

Freeze behaviour

On clinical ratings and both separate FLE definitions, freeze or FLE frequency increased as door width narrowed (Fig 3A), and was reduced by medication but not stimulation (Fig 3A,B).

Statistical analyses showed that for both FLE definitions, FLE risk was significantly reduced by medication ($p<0.001$) but not stimulation (Fig 3D). Comparing FLE risk on medium and narrow door conditions with a wide door baseline condition showed that risk significantly increased as doors became narrower (Fig 3C). After controlling for the effects of medication, medium doors doubled or trebled FLE risk, and narrow doors increased the risk approximately tenfold compared with the wide-door trials ($p <0.001$). We could not perform statistical analyses on duration data because of the uneven spread of FLEs across conditions. However, the longest FLEs occurred at the narrowest door width (Supplementary materials) and in the untreated condition; the trend was for both treatments to decrease FLE duration (Supplementary materials).

Perceptual and motor performance

Because of fatigue, one participant did not complete the perceptual task and one did not complete the turning task. Explicit judgements of door width by PD participants (Fig 4A) were not affected by medication ($F(1,8)=.53$, $p=.487$) or stimulation ($F(1,8)=2.920$, $p=.126$), with no interaction ($F(1,8)=1.931$, $p=.202$). These judgements were not different between HC and PD groups ($t(17)=-0.079$, $p=.938$).

The time to turn 360° was significantly different between HCs and untreated PD participants (Mann-Whitney $U = 2.0$, $p<0.001$; Fig 4B), and significantly affected by treatment state ($\chi2(3)=13.41$, $p=.004$). However, turn time in the PD group did not significantly correlate with the extent of slowing experienced in doors (velocity drop from no-door to narrow door condition in off/off state) ($p=.167$, $p=.668$). Thus neither perceptual performance nor turning ability could account for slowing and freezing in doorways.

DISCUSSION

We used a variable-width doorway paradigm and two quantitative freeze-like event (FLE) definitions to provoke and measure freezing in a replicable manner. We then compared the effects of medications and STN-DBS on walking and freezing within the same, naturalistic setting.

Slow walking and its treatment

Patients exhibited characteristic parkinsonian gait disturbances of short steps and low velocity [23]. As in other studies, both medication and STN-DBS improved these symptoms [13,24]. Doorways produced striking additional effects on PD gait. Narrower doors caused shorter strides in healthy controls, but consistent with previous studies [2,3] this effect was greatly amplified in the PD group. We assume that these gait disturbances are specific to PD freezers since a previous study [3] found clear differences in the slowing phenomenon between the FOG and non-FOG groups. Slowing at doorways did not likely result from changes in the background stride lengths of the groups, since medications and STN-DBS significantly increased this but did not improve the slowing effect of doors (there were no door-width by treatment interactions). Rather, the observed slowing may result from a visuomotor process, where visually specified information about door width determines how much one must slow down to pass through the door accurately. The dramatic slowing of PD freezers is consistent with the hypothesis that visuomotor processing is different in these patients, specifically that they produce exaggerated responses to visual information [2]. This perspective may help explain the exaggerated responses of PD patients in other tasks [27-30]. An alternative explanation is that the doorway removes attention from walking, thus interfering with voluntary compensation for an underlying short stride length [31]. Neither medication nor STN-DBS alleviated door width-related slowing. This is of course specific to our patient sample and should be tested across

different patient and surgical groups; however, the failure of medications to change door width-related slowing replicates an earlier study with a different, non-implanted group [2]. Together these studies suggest that brain regions other than the basal ganglia may play a role in door-provoked slowing. Interestingly, lateral premotor areas of cortex in PD patients have been reported to show excessive activation to visual information during walking [32] and may process visual information for walking as they do for reaching [33-35].

Freeze behaviour and its treatment

We used two criteria to define objectively freeze-like events (FLEs). These agreed well with clinical ratings of freeze behaviour and provide objective measures comparable to inter-rater reliability (Supplementary material). Future studies should validate these measures in a larger cohort of patients. However, considering the data in this way removed the subjective element from defining freeze events, and provided measures which allow reliable, replicable identification of freezes, even those of short duration. These measures showed that freeze behaviour tends to occur near a doorway and with greater frequency as door width decreases. This confirms the observation that doorways elicit freeze behaviour in PD [1] and shows that the doorway is~~y are~~ a powerful tool for experimentally manipulating freezing in a simple, naturalistic and replicable manner.

Doorway-evoked freezing~~This information~~ can be used as an important complement to other recently described methods of evoking freezes in laboratory settings [4, 5, 6], and f~~. F~~uture work may wish to compare these methods experimentally.

A particularly influential theory of freezing is that it is caused by a reduction in baseline stridelength coupled to a sequence effect (progressive shortening of steps during walking) [6]. As discussed above our data are ~~highly~~ partially consistent with the relation between~~of~~ slowing and

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freezing – here we found that both were sensitive to door width. Indeed ~~and~~ the slowing produced by visuomotor dysfunction could in turn cause freezing through a sequence effect [6,36,37]. Indeed, closing eyes can help reduce freezing [38]. However, the differential effects of the two treatments suggest that other mechanisms may have contributed to freezing in the current study. That is, both treatments significantly improved baseline walking speed and door-width related slowing, whereas only medication reduced the risk of freezing (STN-DBS did not). ~~while door-width related slowing was not significantly improved by either treatment, FLE risk was decreased by medication. This suggests that other mechanisms may have contributed to freezing in the current study. Furthermore baseline slowing was not a likely determinant of freezing, since it was significantly improved by both treatments whereas freezing was only reduced by medication.~~ The results are consistent with the suggestion that high stride time variability is associated with freezing [39] because, like freezing, it was improved by medication but not by STN-DBS. This discussion of how gait variables relate to freezing is based on the variation we naturally observed across different treatment conditions. In future work it would be ideal to also experimentally manipulate gait variables, for example by asking patients or healthy controls to walk at a different stride length.

~~More work is therefore needed to develop theories of freezing which can account for the pattern of behaviour in the wide range of situations where it occurs.~~

The lack of a STN-DBS effect on freezing is especially notable for several reasons. First, STN-DBS increased walking speed and stride length. Second, in the same session ~~and trials~~, UPDRS scores were improved more by STN-DBS than by medication. ~~STN-DBS also increased walking speed and stride length. Second, these other effects were significant even though the stimulator was only off for a relatively short period before testing.~~ Third, the postoperative drug

doses were less than would have been given if the disease had progressed without surgery, yet, in contrast to STN-DBS, medication still reduced FLE risk ~~though STN-DBS did not~~. Consistent with previous work [15], the relative weakness ~~effect~~ of ~~stimulation~~ STN-DBS as a therapeutic tool is therefore quite specific to freezing. Of course, this need not generalise to all PD patients. ~~is only true for our particular group of patients, and treatment must be tailored to individuals.~~ The effects of STN on post-operative freezing are best predicted by the pre-operative response to levodopa [15] and stimulation parameters must be carefully adjusted [14]. W~~However, w~~hile STN-DBS may effectively reduce freezing in some patients, the present study highlights its potential limitations and the need to continue exploring new treatments for this disabling symptom of PD. However, the assessment of treatments is not straightforward as ~~Recent advances show that~~ freezing is a ~~highly sensitive and~~ complex phenomenon with idiosyncratic properties [40]. Much ~~and more~~ work is therefore needed to develop theories of freezing which can account for the pattern of behaviour in the wide range of situations where it occurs ~~understand its neural bases~~.

Summary

The variable-width doorway paradigm coupled with reproducible measurements of freeze behaviour provides a new experimental approach for investigating freezing. Using this approach, we show that the risk of freezing is highly sensitive to door width. The differential effects of treatments in this setting suggest separable mechanisms for the patients' ~~basic~~ slow walking ~~speed~~, door width-related slowing, and door width-related freezing, and highlight the need to explore alternative treatments for severe freezing of gait.

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Author roles: Cowie was involved in the conception, organization and execution of the project; statistical analysis, and manuscript writing & review. Limousin was involved in the conception, organization, and execution of the project, and manuscript review. Peters was involved in the conception, organization and execution of the project, and manuscript review. Hariz was involved in the organization of the project and manuscript review. Day was involved in the conception & organization of the project, statistical analysis, and manuscript writing & review.

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FIGURE LEGENDS

Figure 1 Freeze-like event (FLE) definition shown for one example patient. FLEs defined as (A) outliers in distribution of double support times for each participant within each condition (B) times where velocity falls <10% of mean value on no-door trials.

Figure 2 Walking velocity. Pelvis midpoint velocity in direction of progression, as a function of position in space. Traces for single PD participant in off/off state. Data filtered at 1Hz, plotted for each door condition. Dashed lines show measurement region.

Figure 3 Freezes. Total freeze / FLE trials observed per condition across all PD participants by (A) door (B) treatment condition. Effects of (C) door width (D) treatment condition on odds ratio (FLE risk). Mean and 95% confidence intervals shown.

Figure 4 Perceptual and motor performance. Means and standard errors shown by group and treatment for (A) passability judgements (B) time to turn 360°.