Insights into the neural control of locomotion from walking through doorways in Parkinson's disease

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Abstract

Recent evidence suggests that a network of brain areas may be involved in visually guided walking. Here we study patients with Parkinson's disease (PD) who experience 'freezing' behaviour to investigate the visual control of locomotion and the role of the basal ganglia in this system. We use a variable-width doorway to measure the scaling of motor output to visual input specifying door width. By measuring walking behaviour as participants passed through the doorway, we show that both PD and healthy control participants scaled their locomotor outputs to door width. Both groups reacted to narrower doors by walking more slowly with shorter strides. However, the changes were greater in the PD group, where walking speed dramatically decreased while approaching the doorway. Such a pattern could help explain why doorways cause freezing episodes in PD. Neither explicit perceptual judgements of door width, nor performance on motor tasks, predicted the door behaviour. On the basis of these findings, we propose that PD is associated with a visuomotor disturbance, such that responses to action-relevant visual information are exaggerated. In the PD group, dopaminergic medications improved many baseline gait variables but did not affect their sensitivity to door width, suggesting that this visuomotor effect is not mediated by the basal ganglia. This hypothesis provides a novel framework for interpreting a variety of results with PD patients.

Keywords: Parkinson's disease; Visuomotor control; Basal ganglia; Locomotion; Dopaminergic medication; Freezing

Introduction

Though vision is crucial for safe walking through everyday environments, we know relatively little about the neural circuits underlying visually guided walking. Nevertheless, evidence suggests that the visual control of walking involves multiple, interacting brain mechanisms. Basic locomotor patterns may be produced by central pattern generators in the brainstem and spinal cord (Orlovsky, Deliagina & Grillner 1999; Dietz, 2003), as well as by circuits connecting the basal ganglia (BG) with the supplementary motor area (SMA) (Malouin *et al*, 2003; Jahn *et al*, 2004; Wang *et al*, 2008a). There is evidence to suggest that visual information is integrated with these locomotor control processes either by these same BG-SMA loops or by parietal and premotor cortices (PMC). In cats, lesions to posterior parietal cortex (PPC) cause an inability to modify walking patterns on the basis of visual input; and the firing rate of PPC cells increases as the animal prepares to modify its steps on the basis of visual information (Drew *et al*, 2008). Neuroimaging studies of imagined locomotion in humans suggest that both PMC and SMA (Wang *et al*, 2008b; Wang *et al*, 2009; Jahn *et al*, 2004) are involved in the visual control of locomotion. As described above, the SMA is intricately linked to the basal ganglia so the implication of this last result is that circuits involving the basal ganglia may mediate visually controlled walking. The serious technical limitations on measuring brain activity during walking in humans means that evidence from converging methods will be crucial in developing a full model of these neural control networks.

Studying Parkinson's disease (PD), in which the basal ganglia is damaged and a wide variety of walking problems are present, may provide insight into the neural control of walking as well as being an important application area. PD impairs the amplitude (Blin, 1991) and timing (Hausdorff *et al*, 2003) of walking, but also alters responses to visual inputs (Davidsdottir *et al*, 2008). For some patients, visual stimuli such as doorways or roads can trigger 'freezing' episodes during which the person feels as if his feet are glued to the floor

(Rahman *et al*, 2008; Schaafsma *et al*, 2003). In contrast, transverse lines on the ground can increase stride length or release a freeze ('paradoxical kinesia'; Martin, 1967; Dunne, Hankey & Edis, 1987; Azulay *et al*, 1999). A parsimonious explanation for these disparate phenomena is that they result from involuntarily exaggerated responses to action-relevant visual information during walking in PD. As a result, visual information may promote or constrain walking depending on what possibilities it suggests for action: lines on the ground become readily stepped over but road-crossings produce an exaggerated slowing down which may in turn cause freezing episodes (Chee *et al*, 2009).

The strongest test of this hypothesis would be provided by a visuomotor task where the size of a visual feature is varied parametrically and the manner in which PD participants scale their motor responses to the feature is measured. This type of paradigm has been used to show that participants scale many aspects of movement to visual features such as obstacles (Patla & Goodale, 1996) and doorways (Higuchi *et al*, 2006). A recent study employed such a method to study responses to doorways in participants with PD (Almeida & Lebold, 2009). Participants with and without freezing of gait, as well as healthy participants, were instructed to walk through a door which was fixed at one of three widths. In this situation, visual information about the width of the doorway must be used to control the walking pattern if the participant is to avoid colliding with the door frame (Warren & Whang, 1987). Specifically, the participant must walk with an increasing degree of accuracy along a central path as the doorway is narrowed. Even in healthy participants, this constraint might affect behaviour in several ways. For example, it could slow the walking speed (Higuchi *et al*, 2006) similar to the speed-accuracy trade-off captured by Fitts' law (Fitts, 1954). If PD participants have exaggerated responses to action-relevant visual information, then the response to door width should be unnaturally amplified in the PD group, so that a change in door width should have very marked effects on PD participants. Indeed in Almeida & Lebold (2009) PD freezers showed sharper responses to decreasing door width than PD non-

freezers or healthy controls. As the doors narrowed, step length became shorter, and step length and duration became significantly more variable in PD freezers than in other groups.

The present study uses a similar parametric paradigm to that employed by Almeida & Lebold (2009), using kinematics to measure how visually-specified door width affects the magnitude of locomotor responses in PD freezers. We studied this subgroup since they were most prone to exaggerated responses in the Almeida & Lebold study. Our study considers the results in the light of the hypothesis that PD causes exaggerated responses to action-relevant visual information during walking, and examines two key issues: whether gait disturbances at doorways have a perceptual source, and whether they have a dopaminergic basis.

Damage to fronto-parietal circuits (Cronin-Golomb & Braun, 1997) may in some cases of PD cause compression of perceptual space (Lee *et al*, 2001) or neglect-like symptoms . This could mean doorways are perceived to be narrower than they actually are which could cause the walking problems found at doorways (Almeida & Lebold, 2009). To test whether participants with PD misperceive door widths, we asked participants to make an explicit judgement of the minimum door width through which they could fit, and measured veering behaviour as they passed through the doorway. To test whether disturbances around doorways in PD have a dopaminergic basis, we studied PD participants both on and off their dopaminergic medications. As discussed above, the dopaminergic BG control uninterrupted walking, and accordingly levodopa improves basic gait parameters in PD (Blin *et al*, 1991). Evidence for their role in integrating visual inputs into the motor plan is equivocal. Thus, levodopa can improve the freezing behaviour so commonly found in situations where visual input must be integrated into the locomotor plan (Giladi, 2008), but does not do so consistently (Bloem *et al*, 2004). If the visual control of walking through doors involves the BG, we would expect dopaminergic medications to modify not just the levels of basic gait parameters, but the magnitude of visually-driven gait adjustments in PD

participants. Here we use the pattern of response to door width in medicated and non-medicated PD patients to test that hypothesis.

Methods

Participants

Ten patients with idiopathic Parkinson's disease (PD: ten males, mean age 68.3yrs, s.d. 7.3yrs, range 58 – 78 yrs), and ten healthy controls (HC: ten males, mean age 68.4yrs, s.d. 6.2yrs, range 65 – 76 yrs) took part. Patients were recruited from the National Hospital for Neurology and Neurosurgery (NHNN) and classified by a neurologist as presenting with walking difficulties and freezing of gait. Healthy age-matched controls had no history of falls or balance problems. All participants had normal or corrected-to-normal vision and no serious cognitive impairments as assessed in their regular neurology follow-up. Participants with PD were first tested in the 'off' state, after at least 12 hours withholding their anti-parkinsonian medication. One hour after taking their normal dose of medication, tests were repeated in the 'on' state. One patient did not complete tests in the 'off' state. Research was approved by the joint ethics committee of the NHNN and UCL Institute of Neurology, London, UK. Written informed consent was obtained before testing.

Apparatus

A doorway was formed by two planks of wood, each 15cm wide, running from ceiling to ground, and a connecting pelmet 73.5cm wide positioned 210cm above the ground, which corresponded to ~125% average height. The distance between the sides of the doorway could be adjusted using a motor. Kinematics were measured using a CODA motion-capture system (Charnwood Dynamics, Rothley, UK) comprising six CX1 units. This recorded the positions of markers placed on the doors and on participants' bodies. Two markers were placed on each door. On each leg a marker was placed on the ankle (lateral malleolus), 2nd

toe (2nd metatarsal head), heel (posterior aspect of calcaneus at height of toe marker), thigh (greater trochanter), knee (lateral femoral condyle), and pelvis (anterior superior iliac spine (ASIS)). On each arm a marker was placed on the shoulder (acromion), elbow (lateral epicondyle of humerus), and wrist (radial styloid process). Additionally markers were placed on the lower back (sacrum), upper back (C7) and head (4 markers on a small plate attached to a lightweight headband). Force data was collected from two Kistler forceplates (9281 and 9287; Winterthur, Germany) and sychronised to the kinematic data.

Design & Procedure

Walking task: Participants walked along a 6.32m walkway, passing through the doorway when it was present. Door width was scaled to each participant's shoulder width (sw), measured from left to right acromion before the experiment started. The first trial in a set was a walk in one direction ('outwards'); the second trial was in the opposite direction ('back'). A set contained four trials (two outwards, two back), or occasionally two if the patient was not able. Each block started with a set of no-door trials. These were followed by three sets of door trials (150% sw, 125% sw, and 100% sw), for which the order of door-width size was randomised across participants. For a given participant, this order was maintained across different blocks. Participants completed one block off their usual medications and one block on medications.

If necessary, an experimenter demonstrated the procedure for the trial before its start. Instructions were: "Start with your toes on the start line. On the auditory beep, walk through the doorway (when present) to the line at the other end of the room and stop with toes on the line, facing forwards until given instructions to turn around. Walk through the doorway as if it were in your house or in a public place; if necessary you may contact its sides or turn your body. Walk at your normal pace and move your eyes and head as you wish".

Perceptual task: After the walking task, participants completed a judgement task to assess their perception of the gap through which they could fit. With participants seated at 5m from the closed doors, in line with their middle, the experimenter pressed a button to start the doors opening. On these 'opening' trials participants were asked to say 'stop' when the doors reached a width they could just pass through without turning their shoulders. That width was recorded. On 'closing' trials the doors moved inwards and participants said 'stop' when the doors reached a width they could just no longer pass through without turning their shoulders. In each medication state, each participant with PD performed three opening and three closing trials in alternating order. Each HC performed, in alternating order, six opening and six closing trials.

Turn task: The ability to make a tight turn might be relevant to navigating through a doorway. To assess this ability, participants completed a turning task. Standing in the centre of the room on the forceplate, participants made one clockwise and one anticlockwise axial 360° turn per block. Instructions were to start turning on an auditory beep and make a full turn in the direction instructed, keeping within the area indicated (forceplate extent).

Analysis

Preliminary analysis

Position and velocity data were exported from the Codamotion Analysis Software and low-pass filtered in both directions with a 2nd order Butterworth filter operating at 10 Hz. When available, force data was used to define toe-off as the time at which vertical ground reaction force fell below a threshold of 5N, and heel-strike when it rose above 10N (O'Connor *et al*, 2007). Otherwise a custom Matlab (Ver. 6.5, Mathworks, Inc.; Natick, MA, USA) routine selected toe-off when vertical toe velocity reached 50mm/sec and heel-strike when vertical heel velocity reached -50mm/sec (Ghoussayni *et al*, 2004). These threshold values account for the fact that the heel marker continues to travel downwards after landing as the

underside of the heel compresses. A single trained observer then visually inspected data in the sagittal plane to confirm that toe-off was defined as the first frame after which the toe marker moved continuously in the vertical and progression directions, and heel-strike as the frame at which similar movement of the heel marker ended. Atypical (e.g. shuffling) steps from the patient group were visually inspected in the same manner to define foot-off or foot-strike as appropriate.

Space-velocity profile

We first conducted a spatial velocity profile analysis to determine how forward velocity changed across the walked path in different door conditions. Because the door was positioned slightly asymmetrically in the progression axis of the room, to maximise accuracy we considered only trials in the 'outwards' direction. Body position was taken as the pelvic midpoint (average of sacrum and ASIS positions). We analysed trials in the single-task condition (in the 'off' state for PD participants). Data from each trial were sampled every 5cm along the path. These data were averaged across trials in each door width condition to obtain, for each participant, mean curves of pelvic midpoint velocity as a function of location. The mean velocity for each door condition was divided by the mean velocity for the no-door condition. This yielded a normalised velocity profile for each participant in each door condition, showing how velocity changed over the walking path during door trials compared to a no-door baseline. These curves were averaged across participants to obtain grand mean spatial velocity profiles per group per door width.

Gait variables

Based on the spatial velocity profile, gait variables were measured from 2.1m before the door until 0.7m after it. For all variables except PCI (see below) we calculated the mean value across this section, averaging across left and right feet for stride length, toe lift and cadence. For all variables we then averaged across trials of the same type to give a mean

value. Variables were calculated as follows. ***Velocity:*** speed of pelvic midpoint in the direction of travel. ***Stride length:*** distance in transverse plane between heel marker positions one frame after foot-strike, on successive foot strikes with the same foot. ***Toe lift:*** maximum vertical displacement of toe marker during a step. This was the maximum height of the toe marker above the ground between foot-off and foot-strike, minus the toe's height on the ground before the step. For the left foot this 'ground height' was the average left toe height during the previous right step, and vice versa for the right foot. ***Cadence:*** steps per second. Each step was defined from the foot-strike of one foot to the subsequent foot-strike of the other foot. For the next two measures we defined the reference foot for each participant as that with the longest average swing time across trials. ***Normalised double support time (nDS):*** total proportion of the reference foot stride time spent in double support. Stride time was the time between subsequent foot-strikes of the same foot. Within this epoch, two periods of double support were defined as the time from foot-strike of one foot to subsequent foot-off of the other. *nDS* was the sum of these periods divided by the stride time. ***Phase coordination index (PCI)*****:** a measure of temporal symmetry in the stepping pattern, calculated as in Plotnik, Giladi and Hausdorff (2007). For each stride, phase is the proportion of reference foot stride time taken by the opposite foot's step time. An exactly symmetrical stride has a phase of 180°; an asymmetrical stride (where e.g. the left step is quick compared to the right) has phase < 180°. PCI is a composite measure of the average phase deviation from the symmetrical 180°, and the variation of phase within a walking period.

Statistical analysis

For each gait variable we conducted two repeated measures ANOVAs. The first measured the effects of door width (no-door, 150% sw, 125% sw, 100% sw) in the HC group. The second measured the effects of door width and medication (off, on) in the nine PD participants who completed the walking task off and on medications (the 'PD_A' group). For

each parameter we also conducted a mixed-measures ANOVA comparing the HC group with the 'PD_A' group in the off state, with factors door width and group; and a similar ANOVA comparing the HC group with the 'PD_A' group in the on state.

The perceptual judgement task was completed by seven participants in both medication states, one participant only in the 'off' state and two only in the 'on' state. After scaling each participant's response to their shoulder width we used a paired samples t-test to compare the responses of seven PD participants in the off and on states. We next compared the first six trials completed by HC participants with the eight PD participants who completed tests in the 'off' state and nine PD participants who completed tests in the 'on' state. Finally we made these statistical comparisons on the standard deviation of each participant's set of responses. To further test for neglect-like symptoms we measured veering as the deviation from the doorway midline at the point where the pelvic midpoint crossed the doorway. Deviations to the left of the midline were scored as positive and deviations to the right as negative. We then compared HC and PD off performance at each of the three door widths.

For each participant we computed 'door difficulty' as the difference in mean velocity between no-door and narrow door conditions in the single-task condition, over the measurement region previously specified. To assess whether the effect of doors depended on motor abilities, we correlated door difficulty with the time to turn 360° averaged across turn directions; and with motor ability indexed by the Unified Parkinson's Disease Rating Scale part III motor score (UPDRS, Fahn *et al*, 1987). This scale assesses the cardinal motor features of PD with a maximum score of 108 indicating the most severe PD.

Results

Clinical measures

The mean duration of Parkinson's disease was 14.5 years (sd 5yrs, range 8 – 25 yrs). In the 'off' state, the mean UPDRS part III motor score was 26.3 (sd 8.7); in the 'on' state it was 14.8 (sd 3.4). Participants with PD completed the FOG Questionnaire (Giladi *et al*, 2000), which assesses the extent of freezing difficulties in everyday life using six questions with a five-point rating scale (so that a score of 30 indicates the most severe freezing possible). Our group had a mean score on of 13.6 (sd 3.1), indicating moderately severe freezing of gait.

[Fig 1 here]

Space-velocity profile

Fig 1 shows the mean space-velocity profiles on door trials with respect to the baseline no-door condition. For the PD group, decreasing door width caused progression velocity to drop dramatically in the region preceding the doorway and immediately after it. As door width decreased these effects became more pronounced, with velocity dropping to lower values. Velocity reached a trough 0.9 - 0.5m before the doorway and then started to recover. The HC group showed a similar but much smaller effect for the narrow doors only. For both groups, progression velocity at the start of the walk was higher in the door conditions than in the no-door condition. This may have been because the no-door condition was always presented first within a block, when the task was less familiar.

Gait variables

We assessed the mean values of six different gait variables (Fig 2; Table 1) obtained during the segment of the walk between the dashed lines in Fig 1 (2.1m before to 0.7m after the door).

[Fig 2 and Table 1 here]

HC participants: *Door width* significantly affected all variables (Table 1, ANOVA 1), though the size of these effects was quite small.

PD participants: We assessed the effect of *medication* (off, on) and *door width* for group PD_A (Table 1, ANOVA 2). *Medication* had significant effects on all variables except cadence. It improved gait by increasing velocity, stride length and toe lift, and by decreasing nDS and PCI. *Door width* significantly affected all variables except cadence and nDS. In contrast with the HC group, the magnitude of door width effects was large in the PD group. As door width was progressively narrowed, velocity, stride length and toe lift decreased, and PCI increased. However, there was no interaction between *medication* and *door width* for any gait variable. When trial number was added as a factor, there was no effect of trial number and the effects of door width were unchanged. This indicates that any proprioceptive information about door width gathered over multiple consecutive trials did not affect the visually-driven response to door width.

Between-group comparisons: The HC group was compared with the PD_A group in the off state (ANOVA 3). There was a significant main effect of *group* for all variables except cadence, and a significant main effect of *door width* for all variables except cadence and nDS. However, the effect of door width was not the same in the two groups. There were significant interactions between *door width* and *group* for velocity, stride length, nDS and PCI. These interactions arise partly because the directions of the door-width effects were not always the same for the two groups between *no door* and *wide door* conditions. However, they also reflect the fact that in general the effects of door width were greatly amplified in the PD group. ANOVA 4 compared the HC group with the PD_A group in the on state. Again there were significant main effects of group and door width for most variables and interactions for cadence and nds.

Perceptual and motor performance

[Figs 3 & 4 here]

Mean judgements of just-passable door width (Fig 3A) did not differ between PD off and either healthy controls (t(16)=-.752, p=.463) or PD on (t(6)=.033, p=.975). Additionally, judgements did not differ between the PD on and HC groups (t(17)=-.434, p=.670). Judged passable width was around 100% shoulder width, though actual passable width was around 125% shoulder width. Within-participant variability (Fig 3B) was not significantly different between the PD off group and HC (t(16)=.461, p=.651) or PD on (t(6)=-.669,p=.528); or between the PD on and HC groups (t(17)=1.22, p=.239). Outcomes remained non-significant when data were analysed separately for doors opening or doors closing conditions. The extent of veering as participants crossed the door midline (Fig 3C) was not significantly different between the PD off group and control participants on wide(t(17)=1.03, p=.315), medium (t(17)=1.04, p=.313) or narrow (t(17)=-.857, p=.404)doors.

Linear regression showed that neither total UPDRS score (R^2=.426, p=.057) nor average turn time (R^2=.271, p = .186) predicted door difficulty (Fig 4).

Discussion

We identified a variety of abnormal walking responses to doorways in PD patients who regularly experience freezing of gait. Walking through doors was associated with a constellation of gait changes consisting of reduced walking speed, shortened stride length, reduced toe lift, and increased PCI. All these disturbances became more pronounced as the doorway was narrowed. While improving baseline gait parameters, dopaminergic medications did not remove the effects of door width on walking, which suggests the visually-driven door effects are not mediated by the BG.

Motor and perception considerations

Neither UPDRS score nor turning ability significantly predicted the impact of doorways on walking velocity, suggesting the effects were not primarily due to traditionally measured motor problems. Because we constructed the doorway from thin strips of wood, there was minimal blocking of the peripheral visual field. Likewise different doorwidth conditions contained the same visual features, though in a different configuration. It is therefore unlikely that low-level differences in the visual environment cause disturbances at doorways as has previously been suggested (Azulay, 2006).

Perceiving the door width as narrower than veridical could cause the slowing we observed. For example, if a door of 125% shoulder width were perceived as 100% shoulder width one might slow down to speeds appropriate for that width. This might occur in several ways. Doors could be perceived as narrower than veridical because of a perceptual distortion of space. To test this we had participants judge the width of the door that they could just pass through. Our participants' judgements were closer to shoulder width than judgements measured using different methods in previous research (Lee *et al*, 2001; Warren & Whang, 1987). However, the PD group made explicit judgements of door width as accurately as healthy controls, and judgements were unaffected by medication. Increased lateral sway in the PD group could effectively make body width greater in comparison with door width, but one would expect this to be reflected in the explicit judgements, which are unlikely to change as participants approach the door (Lee *et al*, 2001; Berti, Rabuffetti, Ferrarin *et al*, 2002). We also measured the extent to which participants veered as they passed through the door. On crossing the doorway, PD participants were on average within 1cm of the door centre. This is in contrast to the large veering amplitudes measured in neglect patients passing through a doorway (Robertson, Hogg, & McMillan, 1998; Berti, Rabuffetti, Ferrarin *et al*, 2002) and was not significantly different to control performance. We conclude that misperception of door width was not responsible for group differences on the walking task. This contrasts with Lee *et al* (2001), who found neglect-like perceptual

problems in left-sided PD patients. Our group in fact included a majority of these patients yet we found no such problem. More work on a larger sample of PD patients would be useful in resolving this conflict.

Attention considerations

It is possible that doorways divert attention from walking, and this diversion causes PD participants' slowing responses. On one hand, simply as a visual stimulus the door may incur an attentional cost, which might cause disproportionate effects in PD. However as mentioned above, there were few purely featural visual differences between door width conditions, so this effect is unlikely to explain the observed dramatic effects of door width. On the other hand, as an accuracy constraint the door may focus attention on walking, which can greatly benefit PD participants (Azulay *et al*, 2006). It is therefore unlikely that the former outweighs the latter enough to produce the slowing effects of doors which we observed.

Visual control of walking in PD

As we suggested in the introduction, visual information about door width was used to control the walking pattern even in a healthy population. Changes to gait variables in the HC group may have arisen partly from an order effect in that the no-door condition was always presented first. However, just considering those trials in which the doors were present and door width was randomised, velocity and stride length were related to the width of the doorway: the narrower the doorway, the more cautious was the gait.

This visual control seen in the HC group sheds light on the problems apparent in the PD group. While gait variables were affected by the doorway in both HC and PD groups, the groups' behaviour differed in two major ways. First, the baseline level of most variables was weaker in the PD group (hypokinetic, rigid gait produced by decreased stride length and toe

lift; higher PCI, reflecting asymmetric walking). Second, narrowing the doorway caused more consistent and proportionally much larger changes to walking in the PD group than in the HC group. For example, the drop in velocity from wide to narrow doors was ~6% for healthy controls but ~18% for the PD Off group. This different magnitude of motor response to visual input suggests a visuomotor processing difference between PD and HC groups. For narrow doors accurate passage could only be achieved if walking was slowed prior to the doorway. Our data show that the response to this constraint was amplified in PD patients, whose slowing and stride shortening before the doorway was exaggerated in comparison with the HC group. The data therefore support our hypothesis that PD causes exaggerated responses to the visual information relevant to locomotor control – in this case, information about door width.

Our results are in agreement with those of Almeida & Lebold (2009). Both studies found a similar pattern of response for stride length. We found additional effects for velocity, perhaps because our range of door widths was narrower and scaled to each participant's shoulder width. Both studies found that average cadence was not different between groups. Finally both studies found that timing variability was more affected by doors in PD - though Almeida & Lebold measured step time variability while we measured PCI.

The strong responses to action-relevant visual information in our task are strikingly similar to those found in other walking (Schubert *et al*, 2005), balance (Bronstein, 1990) and manual (Praamstra *et al*, 1998) tasks. The amplified motor responses to visual inputs in most of these studies parallel those in our task. It has been suggested that over-weighting of visual information might be a learned response to poor kinaesthetic feedback (Azulay, 2006, Demirci *et al*, 1997). Poliakoff *et al* (2007) found a speeding effect for action-relevant visual information in HC but not PD participants. Though this is apparently discrepant with our

results, it also highlights the fact that strong responses to visual information may only affect a subgroup of PD participants, for example those who are prone to freezing.

Freeze behaviour in doorways

Previous work on freezing of gait has suggested that specific walking patterns are associated with freezing episodes. For example, freezing behaviour is associated with a progressive reduction in step size (the sequence effect) set on top of a low baseline step length (hypokinesia) (Nieuwboer *et al*, 2001; Iansek *et al*, 2006; Chee *et al*, 2009). We have shown that doorways provoke decreases in velocity and stride length. This in turn may cause doorway freezing commonly reported in PD patients. Freezing has also been linked to irregular stride timing or arhythmicity (Hausdorff *et al*, 2003; Plotnik *et al*, 2007; Nieuwboer *et al*, 2007). Walking through a narrow door is an inherently asymmetric task and we found most timing asymmetry in the narrow door condition. Our results are therefore also consistent with the hypothesis that timing irregularities may contribute to freezing in everyday situations such as passing through a door. Freezing is extremely difficult to elicit in laboratory situations (Giladi & Nieuwboer, 2008) and future work should directly examine the relation of freezing to gait difficulties with doorways.

Implications for models of visually controlled walking

In conjunction with current literature, the present results suggest there are at least two neural circuits involved in everyday locomotion with obstacles (in this case, a doorway). First, the BG or their circuits with SMA regulate a basic locomotor pattern. Second, a separate non-dopaminergic system mediates visual inputs to walking. These modify locomotor plans according to visually specified constraints.

A primary cause of PD is a lack of striatal dopamine, which directly impairs BG function. The clear improvement of walking parameters with dopaminergic medications confirms BG involvement in basic walking patterns. The BG seem to play a role in controlling

both step amplitude and rhythm since both were improved by medications in the present study. This is in agreement with previous studies which suggest that the BG both maintain cortically-selected step sizes and send appropriately timed internal cues for each step to cortex (Iansek, 2006). Nevertheless, since patients were able to maintain a compensatory high average cadence irrespective of medications, the results are consistent with the additional involvement of other structures such as the cerebellum (Wang *et al*, 2008a) in the timing of locomotor sequences.

Visual inputs may be used to adjust the basic locomotor pattern considered above. Our results suggest that when this occurs, a second neural system becomes involved. Since the effects of door width are not responsive to dopaminergic medications (there are no door width by medication interactions), our results suggest that this system is located outside the dopaminergic BG. In the PD freezing group studied, there is damage to both the BG and this second visuomotor system. Studying PD participants who freeze therefore provides insight into the nature of locomotor control areas outside the basal ganglia.

The most likely candidates for involvement in such a visuomotor control system are PPC and PMC. The introduction to this paper reviews some of the evidence for their roles in the visually guided walking of healthy participants. For several reasons, the role of PMC may be particularly helpful in explaining the present results. First, lateral PMC is highly activated when PD patients control actions using external rather than internal cues (e.g. visual inputs; see Berardelli *et al*, 2001). Second, it is a key part of the human affordance processing system (Chao & Martin, 2000; Creem-Regehr & Lee, 2005). The affordance of an object is its visually-specified relevance for action (Gibson, 1979). For instance, visual information tells us that a chair affords sitting or a step affords climbing. This information is automatically obtained on viewing an object (Tucker & Ellis, 1998), and may be thought of as a key output of the visual system to the motor system. The affordance of the door specifies that it can only be safely passed through at a certain speed which depends on door width. It is the

response to this information which seems to be exaggerated in PD participants. A PET study confirms that PMC mediates locmotor affordance processing, since PMC was more active when participants stepped over transverse lines than lines parallel with the direction of walking (Hanakawa *et al*, 1999). Importantly, this difference was more pronounced in PD participants than in control participants performing the same step. This overactivity may therefore reflect exaggerated responses to visual information for walking in PD. These may be helpful when stepping over transverse lines but unhelpful when walking through a doorway.

Acknowledgements: Thanks to all participants, and to Mr Daniel Voyce for engineering support. **Funding:** This work was supported by Medical Research Council [grant number G0502136] and the Wellcome Trust.

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Figure legends

Fig 1: Mean velocity of pelvic midpoint in direction of progression, plotted against body position in space. Doors at zero. Shown separately for PD and HC groups and three door widths. At each spatial point values for each participant have been normalised to the value in the *no door* condition. Thick lines show group mean; shaded areas show group standard error. Dashed lines show measurement region (see text).

Fig 2: Parameter means and standard errors for datasets PD_A (participants who completed walking task in both medication states) and healthy controls (HC). Conditions as appropriate for each group: Off or On (off meds, on meds). In each condition four points from left to right represent *no door*, *wide door*, *medium door*, *narrow door* conditions respectively. nDS: normalised double support time. PCI: Phase Coordination Index. Full parameter definitions in text.

Fig 3: A Participants' judgments of the door width that they could just pass through. Values for HC participants are based on their first six trials, and for all PD participants who completed the task in that state. Mean and standard errors of judgments, expressed as a proportion of (i) shoulder width and (ii) measured passable width. **B** Group mean and standard errors of each participant's variability of response. **C** Lateral deviation from the door midline as pelvic midpoint crosses doorway. Leftward deviations are positive; rightward deviations are negative. Group mean and standard errors shown.

Fig 4: Door difficulty predicted by **A** UPDRS total score **B** time to turn 360°. On all scales higher scores indicate worse performance. All values are from the 'off' state.

Table 1. Repeated measures ANOVAs for each of six variables.

ANOVA 1: Healthy participants: effects of door width. ANOVA 2: PD participants: effects of door width and medication. ANOVA 3: PD participants off meds *vs* healthy participants. ANOVA 4: PD participants on meds *vs* healthy participants. Each line shows relevant degrees of freedom (df), F and p values. P values less than .05 are shown in bold.

		Velocity		**Stride length**		**Cadence**		**Toe lift**		**nds**		**PCI**	
	d.f.	***F***	***p***	***F***	***p***	***F***	***p***	***F***	***p***	***F***	***p***	***F***	***p***
ANOVA 1: HC													
door width	3,27	3.995	**.018**	7.273	**.001**	11.607	**.000**	3.231	**.038**	5.511	**.004**	3.364	**.033**
ANOVA 2: PD													
door width x medication	3,24	0.894	.458	1.616	.212	1.618	.211	1.525	.234	1.13	.357	2.325	.100
door width	3,24	11.10	**.003**	12.23	**.000**	1.176	.318	8.244	**.001**	2.509	.141	7.612	**.016**
medication	1,8	35.93	**.000**	21.26	**.002**	0.258	.625	15.77	**.004**	13.44	**.006**	11.737	**.009**
ANOVA 3: PD off *vs.* HC													
door width x group	3,51	6.787	**.000**	6.127	**.001**	1.273	.293	2.284	.090	5.572	**.002**	6.056	**.001**
door width	3,51	11.02	**.000**	19.90	**.000**	1.803	.193	12.71	**.000**	1.481	.244	14.215	**.000**
group	1,17	25.58	**.000**	34.70	**.000**	.096	.761	24.10	**.000**	6.99	**.017**	12.759	**.002**
ANOVA 4: PD on *vs.* HC													
door width x group	3,51	2.619	.061	1.256	.299	8.076	**.005**	1.210	.316	3.321	**.027**	1.718	.175
door width	3,51	6.742	**.001**	10.421	**.000**	2.591	.063	5.492	**.002**	.278	.841	6.320	**.001**
group	1,17	7.104	**.016**	11.295	**.004**	.276	.606	5.894	**.027**	1.141	.300	3.981	.062

Figures

Fig 1

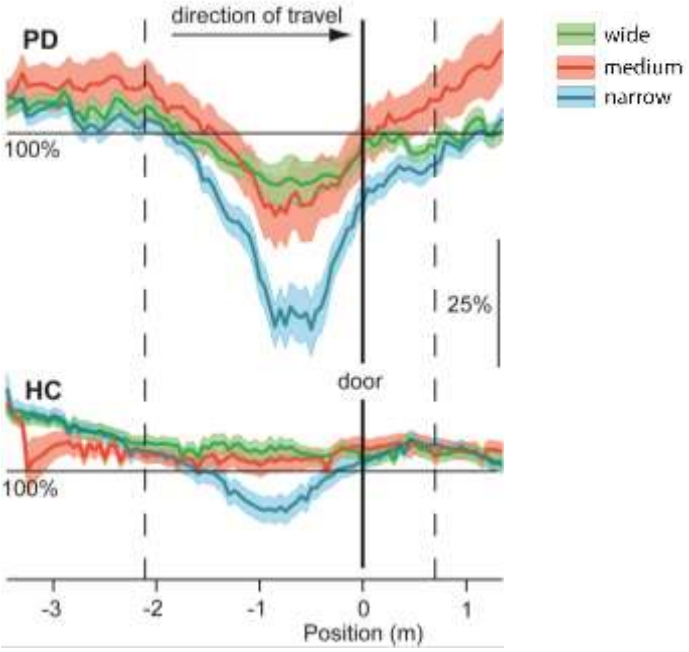

Fig 2

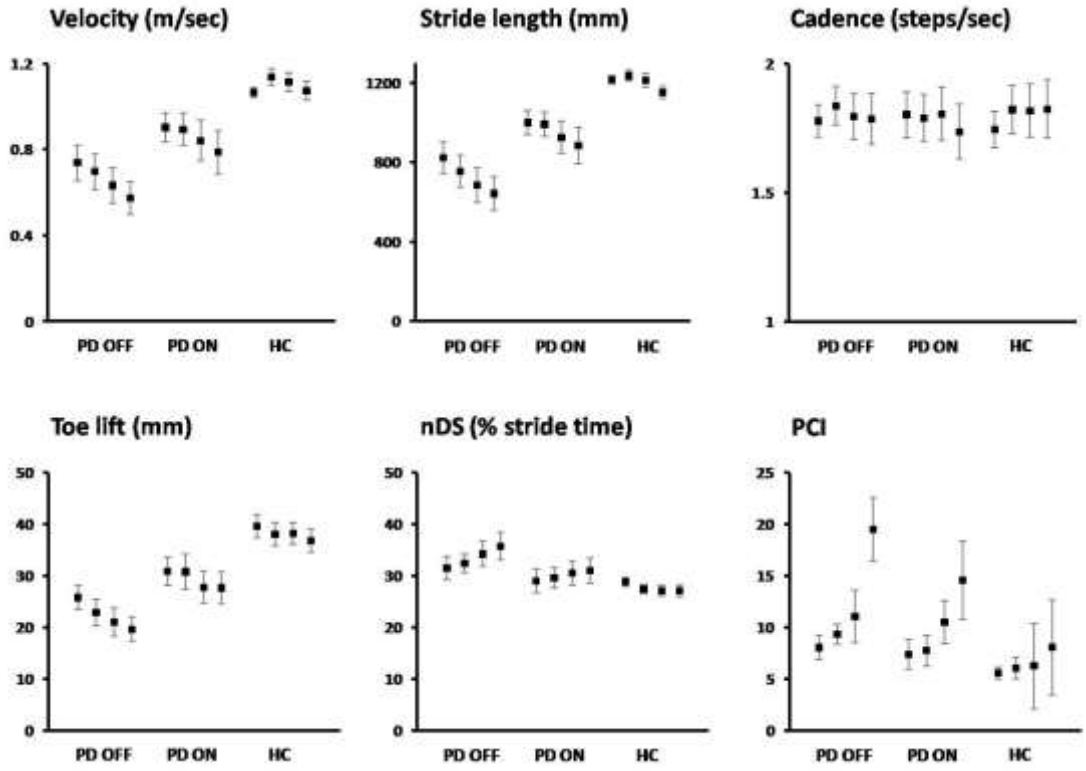

Fig 3

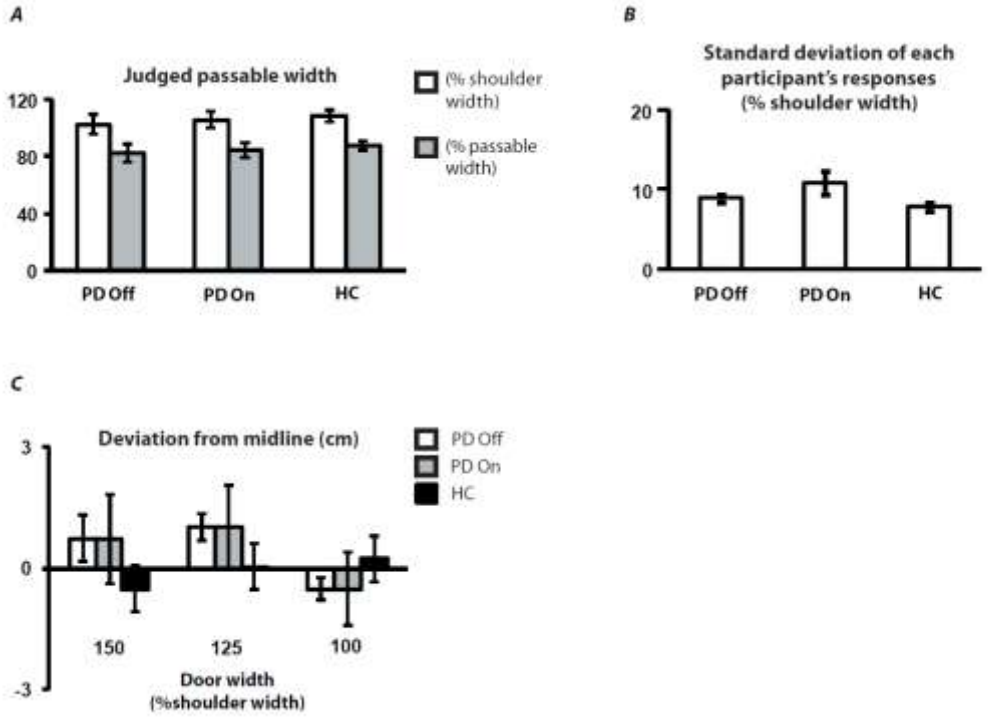
A
Judged passable width
120
80
40
0
PD Off
PD On
HC
(% shoulder width)
(% passable width)
B
Standard deviation of each participant's responses (% shoulder width)
20
10
0
PD Off
PD On
HC
C
Deviation from midline (cm)
3
0
-3
150
125
100
Door width (%shoulder width)
PD Off
PD On
HC

Fig 4

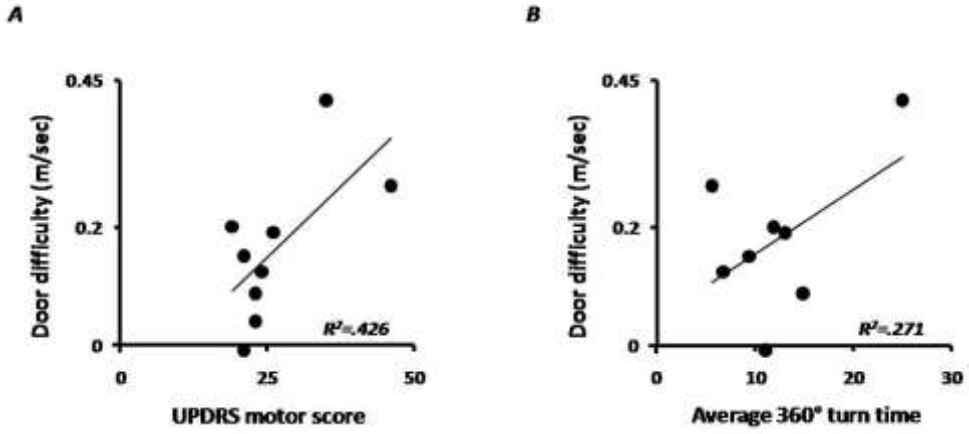
A
Door difficulty (m/sec)
0.45
0.2
0
0
25
50
UPDRS motor score
R²=.426
B
Door difficulty (m/sec)
0.45
0.2
0
0
10
20
30
Average 360° turn time
R²=.271

Figure legends

Fig 1: Mean velocity of pelvic midpoint in direction of progression, plotted against body position in space. Doors at zero. Shown separately for PD and HC groups and three door widths. At each spatial point values for each participant have been normalised to the value in the *no door* condition. Thick lines show group mean; shaded areas show group standard error. Dashed lines show measurement region (see text).

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