OPTIMISING CUEING TO IMPROVE WALKING AND FUNCTIONAL ACTIVITIES IN PEOPLE WITH PARKINSON'S DISEASE WHEN ON AND OFF MEDICATION

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PhD

2008

OPTIMISING CUEING TO IMPROVE WALKING AND FUNCTIONAL ACTIVITIES IN PEOPLE WITH PARKINSON'S DISEASE WHEN ON AND OFF MEDICATION

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A thesis submitted in partial fulfilment
of the requirements of
Northumbria University
for the degree of
Doctor of Philosophy

Research undertaken in the School of Health,
Community & Education Studies

October 2008

Thesis abstract.

Gait problems in Parkinson's disease (PD) are complex and not adequately addressed by current medical and surgical options. The focus of this thesis was a desire to optimise the effectiveness of cues after experience of delivering cueing therapy in the context of a multi-centre RCT. Cues provide information on how to adapt the stepping pattern either through external prompts or internally through focussing attention. Cues are known to improve gait in PD but there is a compromise between strategies which have large effects but limited practical application and those which are easily applied in complex situations but have more modest effects.

A laboratory study explored the feasibility of a cueing strategy combining an external rhythmical cue with a focussed instruction to increase step size, targeting both temporal and spatial parameters. A group of 15 PD and 12 age and sex matched controls were tested and gait was measured with an instrumented walkway which uses pressure activated sensors. The combination cue was compared with two single parameter cueing strategies, a rhythmical auditory cue and an attentional strategy asking subjects to walk with large steps. Gait was assessed under single and dual tasks to establish the attentional demands of the different cues. Walking speed and step amplitude significantly increased with the attentional strategy and combination cue in single and dual tasks in PD and controls (see chapter 3). The combination cue had an additional benefit in significantly reducing stride time and double limb support time variability in PD subjects, whilst variability increased in controls (see chapter 4).

The effects of cues on and off medication was tested in the home in a group of 50 PD subjects using the same dual task paradigm to explore the mechanisms underlying cueing compared to dopamine on gait control. Gait was measured using an in-shoe footswitch system allowing reliable gait data to be collected in the home. Walking speed and stride amplitude significantly improved with all cues in the single and dual tasks on medication and with the attentional strategy and combination cue off medication suggesting that cues have a different mechanism to dopamine. The greatest improvements were seen with the combination of cues and medication. Gait variability responded differently to cues on and off medication. The combination cue reduced variability on and off medication for single and dual tasks, the auditory cue reduced variability in all conditions except for single task on mediation and the attentional strategy increased variability in the single task on mediation and had no effect in other conditions (see chapter 5). Cues which are delivered externally result in different mechanisms of gait control than those generated internally.

Measures of gait variability reflect the attentional cost of movement and underlying neural control but there is limited knowledge on their validity. The final stage of the research examined the clinical characteristics associated with increased gait variability to increase understanding of these variables. Non-cued gait variability was strongly associated with disease severity, but cued gait variability was not adequately explained suggesting involvement of more diverse parameters (see chapter 6).

These findings provide new knowledge on the mechanism underlying cued gait, the involvement of dopaminergic pathways and the attentional cost of different cues. Focussed instruction can alter the response to an external cue in the form of a rhythmical auditory tone, targeting both temporal and spatial gait parameters and reducing the attentional cost of walking.

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Acknowledgements.

Declaration

I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work.

Name: Katherine Baker

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Date: October 5th 2008

Chapter 1

Statement of problem.

Parkinson's disease (PD) is a common progressive neurological condition with an incidence of 100-180 per 100,000 of the population in the UK (Dodel *et al.*, 1998). The direct cost of treatment to the NHS has been estimated at approximately £2,298 per patient per year with the total annual cost of care including NHS, social services and private expenditure per patient has been estimated at approximately £5,993 with costs increasing with age and disease severity (Findley *et al.*, 2003). Medical management with dopaminergic replacement therapy remains the gold standard with increasing use of surgical options such as deep brain stimulation therapy.

The cardinal symptoms of PD include; bradykinesia, resting tremor and rigidity, in addition non-motor symptoms include executive dysfunction, depression and fatigue. Parkinson's disease subjects show abnormalities of the spatiotemporal, kinematic and kinetic gait components compared to age matched healthy subjects (Morris & Iansek, 1996; Morris *et al.*, 1999; Sofuwa *et al.*, 2005) as well as an increased risk of falls (Bloem, Steijns & Smits-Engelsman, 2003). Dopaminergic medication dramatically improves the motor symptoms of PD, however after an initial 'honeymoon' period patients become progressively more disabled despite treatment, as dopa-resistant motor and non-motor symptoms are seen (Rascol *et al.*, 2003). Approximately 5 years after medication commences motor fluctuations will often occur with walking ability varying throughout the day. Gait and balance problems persist in the presence of dopaminergic therapy (Thanvi & Lo, 2004).

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External cues can address temporal or spatial gait parameters and are used to improve

gait in PD. Temporal cues such as rhythmical auditory tones are used to modify pace

and are easily applied in different environments and during functional tasks

(Rochester *et al.*, 2005; Nieuwboer *et al.*, 2007). However, the effect of temporal

cues on gait are relatively modest and vary between studies, possibly because of the

different ways cues are applied (Freeman, Cody & Schady, 1993; Howe *et al.*, 2003;

Cubo, Leurgans & Goetz, 2004; Rochester *et al.*, 2005; Hausdorff *et al.*, 2007; Arias

& Cudeiro, 2008). Spatial cues, such as lines on the floor set at the desired step

length, target stride amplitude and tend to have a greater emphasis on correction to

normal values. Studies of spatial modalities have reported larger effects, however

functional application is limited (Morris *et al.*, 1994; 1996; Lewis, Byblow & Walt,

2000). Attentional strategies are used to focus an individual's attention on a specific

aspect of gait, commonly encouraging people to concentrate on increasing stride

amplitude, and have shown similar large effects as visual spatial cues (Morris *et al.*,

1994; Behrman, Teitelbaum & Cauraugh, 1998; Werner, 2003; Farley & Koshland,

2005; Lehman, 2005). When using attentional strategies people are required to

constantly attend to their own performance which utilises attentional resource,

meaning their application is limited in dual or multi tasks or in complex environments

(Morris *et al.*, 1996). Cue modalities have greatest impact on the parameter at which

they are targeted although improvement can also be seen to a lesser extent in other

parameters.

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Previous work has shown that external rhythmical cues can be integrated into
complex functional tasks, supporting the use of such strategies to improve walking in
a functional context (Rochester *et al.*, 2005). Rochester (Rochester *et al.*, 2007)
proposed the need for further investigation of response to different modalities of cue
and during performance of tasks of different levels of complexity in order to increase
the understanding of the mechanism of cueing and optimise the delivery of cues as
rehabilitation strategy.

It is unknown whether improvements in gait could be optimised if both temporal and
spatial gait parameters were targeted simultaneously (Rochester *et al.*, 2007). No
previous studies have examined the feasibility of combining an external pacing cue
with an attentional strategy to increase step amplitude. The external auditory tone
could be used to not only pace stepping but also to prompt the person to continue to
increase step size. This would be achieved by modifying the instruction given before
using the cue, the person is taught to associate the auditory tone with taking a bigger
step. The proposal is, this will diminish the need for the constant monitoring needed
by attentional/internally generated strategies, thereby reducing attentional cost and
improving applicability.

The work presented in this thesis is aimed at optimising the application of cues to
improve gait and functional activities in people with PD and increase the
understanding of the mechanism of effect of cues. As discussed, the cueing strategies
which have been used to date have various limitations in terms of effect or

application; the current studies aim to explore ways of gaining maximum benefit by adapting the way in which cues are delivered. A strategy is developed which targets both the spatial and temporal dysfunction typically seen in people with Parkinson's disease. By examining different cueing strategies in both single and dual tasks, the attentional cost can be evaluated as well as giving an indication of their practical application. This has important implications when considering the increased reliance on cortically mediated motor control due to disruption of automatic pathways in addition to the impairments in executive function and attention often seen in PD (Dalrymple-Alford *et al.*, 1994). In addition the role of dopaminergic mechanisms in motor control and cue use is tested by applying cues in the presence and absence of dopaminergic medication. This will inform the delivery of cues across the medication cycle and may provide a therapeutic option for maximising the effect of medication.

Chapter 1

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Chapter 2

Background to the research.

This chapter will present several areas of the literature which are relevant to this thesis. The pathophysiology of Parkinson's disease will be briefly discussed, with particular attention to the cause of the gait dysfunction typically seen and the cognitive symptoms of PD. Dual tasking studies are explored in order to gain insight into the attentional cost of walking in PD and what factors influence this. Current evidence for the use of cues is reviewed in order to identify the limitations of previously used strategies to optimise the delivery of cues.

2.1. Origin of movement disorder in PD.

The basal ganglia are an integrative system with a role in planning, sequencing and executing movements, regulating muscle tone and force and have a role in motor learning; dysfunction can lead to hypo or hyper kinetic movement disorders depending on the specific location of damage (Labyt et al., 2003; Lundy-Ekman, 2007). In the case of Parkinson's disease (PD) death of dopamine producing cells in the substantia nigra reduces activity in the motor areas of the cerebral cortex via the thalamo-cortical loop, particularly the supplementary motor area (SMA), which reduces the ability to initiate movements, particularly those that are internally generated or involve sequences (Grafton, 2004; Lundy-Ekman, 2007). This also leads to slowness in switching from one movement to another or from one sub-movement to the next in a sequence (Morris & Iansek, 1996).

The basal ganglia are also implicated in non-motor functions and are connected to frontal areas via several cortico-subcortical loops involving predominantly; the SMA, the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex and the anterior cingulate (AC), all of which are directly and indirectly influenced by dopamine (Brooks, 2001). The basal ganglia's role in cognition is discussed in more detail in section 2.3.

Particularly in relation to gait, studies of parkinsonian and healthy brain function have proposed two main functions of the basal ganglia; planning of the force and amplitude of movement through the maintenance of motor set and the timing and sequencing of movements through the provision of internal motor cues which result in the smooth running of well learned movement sequences (Georgiou et al., 1994; Cunnington et al., 1995; Morris & Iansek, 1996).

This hypoactivation of the SMA and motor cortex has been shown to normalise with levodopa therapy in early, drug naïve PD subjects (Buhman et al., 2003). The improvement in initiation of volitional movement seen with levodopa is associated with increased SMA and DLPFC blood flow, however although this underactivty and the overactivity of the lateral premotor cortex is seen to improve with medication, they are not normalised in later disease stages (Haslinger et al., 2001).

Imaging studies have also been used to explore the differences in motor execution when on and off medication. Cunnington (Cunnington et al., 2001) reported a

reduction in activity of the anterior cingulate and the DLPFC in PD subjects when off medication compared to when on medication, these areas have substantial input to the pre-SMA and also contribute to the cognitive abnormalities seen in PD. When on medication there was also a reduction in activity of the lingual gyrus and precuneus which reflects a more normal pattern of activation (Cunnington et al., 2002). It remains unclear whether these relative changes in different brain structures on and off medication will influence the ability to use cues to improve gait, this is explored in chapter 5. There is a clear need for rehabilitation strategies which complement the effect of levodopa medication which remains the gold standard treatment in PD.

2.2. Gait dysfunction in PD.

The disruption in automatic motor control described in the previous section results in the typical parkinsonian gait pattern. Parkinson's disease subjects show abnormalities of the spatiotemporal, kinematic and kinetic parameters of gait compared to age matched healthy subjects (Morris & Iansek, 1996; O'Sullivan et al., 1998; Morris et al., 1999; Mitoma et al., 2000; Nieuwboer et al., 2001; Sofuwa et al., 2005). People with PD walk with reduced velocity, stride length and stepping frequency and increased time spent in double limb support (Morris & Iansek, 1996; O'Sullivan et al., 1998; Morris et al., 1999; Mitoma et al., 2000; Nieuwboer et al., 2001; Sofuwa et al., 2005). Push off at the ankle joint is significantly reduced and range of motion of the lower limb joints during gait diminishes as the disease progresses (Sofuwa et al., 2005). There is a relationship between disease severity and the degree of gait disturbance (Mitoma et al., 2000; Morris et al., 2005). Episodic gait problems such as

freezing of gait, the unpredictable and sudden inability to start or continue walking and festination are found in around half of patients with advanced disease (Giladi, 2001).

The majority of brain imaging studies in PD use upper limb tasks to identify the neural circuitry involved in different types of activities. These findings are theoretically applied to more gross movements including gait. SPECT (single-photon emission computed tomography) is able to capture neural activity several minutes after the tracer chemical is administered. This allows subjects to perform a gait task and be scanned immediately after, to identify the brain areas involved. Hanakawa (Hanakawa et al., 1999b) used this technique to show the gait disturbance in PD is associated with underactivity in the medial frontal motor areas, such as the pre-SMA and cerebellar hemisphere.

Morris and colleagues (Morris et al., 2005) suggest a mismatch between the cortically selected movement amplitude and the actual size of movements in PD due to defective basal ganglia output to the SMA and pre-motor cortex. The under-scaling of movement in PD is seen across all joints and the same pattern is reciprocated in healthy subjects when walking at stride lengths matched to PD subjects (Morris et al., 2005). In addition, PD subjects show disruption in the temporal aspects of gait, with a mismatch in the step frequency - amplitude relationship (Almeida et al., 2007). Healthy adults increase step amplitude and frequency in a linear fashion (Winter, 1991) up to what Morris terms the 'break point' (Morris et al., 1998), where no

further increase in amplitude is seen. The 'break point' happens much sooner in PD (Morris et al., 1998). It is unclear whether this mismatch in amplitude and frequency is a result of defective motor set and or internal cueing or is a postural control mechanism which prevents the individual walking with a size of step beyond their safe limit. This suggests that any intervention aimed at improving gait in PD should take into account both the spatial and temporal gait parameters in order to restore this relationship and should also ensure that by doing so, safety and stability are not compromised.

Stride length and walking speed have been shown to be dopa– responsive whereas step frequency is not and therefore is assumed to be under the control of non-dopaminergic systems (Pederson, Eriksson & Oberg, 1991; Morris & Iansek, 1996; McIntosh et al., 1997; Morris et al., 1998; Almeida et al., 2007), however the relationship between stride frequency and stride length does change when medication is withdrawn as people increase step frequency to maintain walking speed because they are unable to increase stride length (Pederson, Eriksson & Oberg, 1991). Morris (Morris et al., 1998) found the 'break point' at which subjects are unable to increase stride amplitude in response to an increase in step frequency is delayed with levodopa but not normalised.

Repeated gait measures have been found to be highly stable when on medication but not off medication (Morris & Iansek, 1996). Despite improvements with medication,

gait performance and postural stability remains reduced compared to age matched healthy adults (Horak, Frank & Nutt, 1996; Thanvi & Lo, 2004).

A relatively new domain of gait analysis research is the study of gait variability as a measure of locomotor control or dyscontrol. In healthy adults the variability of gait parameters from one stride to the next is minimal, thought to reflect efficient automatic gait control (Beachet *et al.*, 2005; Hausdorff, 2005; Jordan, Challis & Newell, 2007). Increased variability is therefore thought to reflect poor automatic gait control. Loss of automatic control of gait results in greater reliance on compensatory motor mechanisms which utilise more cognitive and attention resource (Mulder, Zijlstra & Geurts, 2002). Increased gait variability which increases with loss of automaticity could provide a measure of the attentional cost of walking. Gait variability has been shown to correlate more strongly with scores on complex motor tasks and not a simple tapping task supporting the link with cognition (Hausdorff et al., 2005).

Studies of healthy adults have shown a U shaped relationship between speed and variability, with variability being least at preferred walking speed and increasing at speeds above and below (Maruyama & Nagasaki, 1992; Jordan, Challis & Newell, 2007). Danion (Danion et al., 2003) demonstrated that this relationship is more complex, with variability of stride time being determined by the relationship between stride amplitude and frequency. This has implications for populations who because of

constraints e.g. bradykinesia in PD or impaired balance responses in older fallers cannot maintain their 'optimum' gait pattern.

Although older adults tend to walk more slowly and with shorter strides than younger adults, studies have shown that gait variability is unaffected by age (Hausdorff *et al.*, 1997; Grabiner, T & Grabiner, 2001; Hausdorff *et al.*, 2001; Hausdorff, Rios & Edelberg, 2001; Owings & Grabiner, 2004; Yogev *et al.*, 2005) suggesting that not only is the gait patterning mechanism maintained with ageing, but also demonstrates the disassociation of gait variability from mean spatiotemporal gait parameters. Mulitvariate analysis has shown that the changes in gait variability seen in PD are not explained by bradykinesia and walking speed (Baltadjieva et al., 2006).

Increased gait variability is seen in older adults who have a cautious gait, a history of falls or fear of falling (Hausdorff *et al.*, 1997; Hausdorff *et al.*, 2001; Hausdorff, Rios & Edelberg, 2001; Herman *et al.*, 2005) and gait variability has been shown to be predictive of falls (Hausdorff *et al.*, 1997; Maki, 1997; Hausdorff *et al.*, 2001; Schaafsma *et al.*, 2003) demonstrating an association between increased variability and the ability to maintain a safe walking pattern. This highlights the importance of including measures of variability when evaluating changes in gait in response to an intervention. Due to the association of increased variability and falls risk it is important to identify tasks, situations and also interventions which have an impact on gait variability. Chapters 4 and 5 will evaluate the impact of task complexity, medication status and the influence of internal and external cues on gait variability.

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Several studies have shown increased gait variability in PD subjects compared to age

matched controls at both self selected and fast walking speeds (Blin, Ferrandez &

Serratrice, 1990; Hausdorff *et al.*, 1998; Hausdorff *et al.*, 2003; Schaafsma *et al.*,

2003; Yogev *et al.*, 2005; Baltadjieva *et al.*, 2006). Increased variability is seen in

early stage medication naïve subjects (Baltadjieva et al., 2006) and becomes more

pronounced with disease progression (Blin, Ferrandez & Serratrice, 1990; Hausdorff

et al., 1998; Hausdorff, Balash & Giladi, 2003; Hausdorff *et al.*, 2003). Gait

variability correlates with disease severity (Blin, Ferrandez & Serratrice, 1990) but is

also significantly raised in de novo patients very early in the disease (Baltadjieva et

al., 2006). The increased variability seen in PD is thought to reflect reduced

automaticity of gait control and is therefore directly related to basal ganglia

dysfunction (Hausdorff et al., 1998).

As with walking speed and stride length, measures of gait variability deteriorate in

the presence of dual tasks (Hausdorff, Balash & Giladi, 2003; Yogev *et al.*, 2005; Del

Olmo *et al.*, 2006) and this change is associated with the complexity of the task

(Dubost et al., 2006), see section 2.4. It appears that increasing the complexity of the

walking task has a destabilising effect on gait in those people who rely on more

cortical means of motor control.

A strong correlation between poor executive function and increased gait variability

has been demonstrated in elderly fallers (Rapport *et al.*, 1998; Beachet *et al.*, 2005;

Herman *et al.*, 2005; Springer *et al.*, 2006), people with PD (Hausdorff, Balash &

Giladi, 2003; Hausdorff *et al.*, 2005; Yogev *et al.*, 2005), Alzheimer's disease

(Sheridan et al., 2003), and those with affective disorders (Hausdorff et al., 2004).

This is in addition to evidence for the relationship between dual task walking speed

and executive function (Rochester *et al.*, 2004; Coppin *et al.*, 2006; Holtzer *et al.*,

2006; Rochester *et al.*, 2008). There is an increasing appreciation of the role of

cognition in gait (Snijders *et al.*, 2007; Yogev-Seligmann, Hausdorff & Giladi, 2008)

(see section 2.3) and gait variability may provide a sensitive measure of this. Further

work is needed however to determine normal values for variability measures to allow

comparison of changes in different pathologies.

Dopaminergic medication has been shown to influence gait variability. Schaafsama

(Schaafsma *et al.*, 2003) reported a significant increase in stride time variability when

off medication and proposed a role of the dopaminergic pathways in maintaining gait

rhythmicity. Despite a trend towards increased stride time variability when off

medication, Blin et al (Blin et al., 1991) found no significant change with levodopa.

There are several potential reasons for the differences in these findings, including

walkway length and time since intake of medication in the on medication phase.

Stride to stride variability of timing is said to reflect the gait patterning mechanism

and the rhythmicity of locomotor control, whereas variability of the support phases of

gait (swing, stance and double limb support time) are thought to mirror dynamic

equilibrium and postural control mechanisms (Gabell & Nayak, 1984). However the

study of these variables is relatively new and more work is needed to determine

exactly what the different parameters of variability are measuring. Disassociation of variability and mean spatiotemporal gait parameters has been shown in several studies of PD gait (Schaafsma *et al.*, 2003; Baltadjieva *et al.*, 2006; Hausdorff *et al.*, 2007), suggesting that they are measuring distinct mechanisms.

Chapters 4 and 5 will describe the influence of task, medication and cues on gait variability, while chapter 6 will examine which clinical characteristics explain gait variability in cued and non-cued gait in people with PD in order to increase understanding of the mechanism behind the loss of gait stability. Chapter 6 will also assess the validity of these measures by examining factors which contribute to increased variability.

2.3. Cognition in PD.

It is well documented that in the absence of dementia people with PD show deficits in cognitive domains and the profile of these deficits is similar to that seen in patients with lesions of the pre-frontal cortex (Brown & Marsden, 1988). In particular poor scores on tests of executive function are seen early in the disease and become increasing complex with disease progression (Kulisevsky, 2000). Executive function is a term used to describe processes which use and modify information from sensory brain areas to modulate and produce behaviour, this group of skills is necessary for effective goal directed behaviour (Yogev-Seligmann, Hausdorff & Giladi, 2008). Particular aspects of executive function which show poor performance can include loss of flexibility in information processing, difficulty shifting and maintaining set

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(Brown & Marsden, 1990). De novo patients have shown poor performance on the

Stroop test, suggesting difficulty in establishing and maintaining a new response set

which reflects less effective mechanisms for resisting interference (Dujardin et al.,

1999), this has implications for dual task performance which will be discussed in

more detail in section 2.4.

Attention can be defined as the information processing capacity of an individual with

the assumption that this is limited and any task performed utilises a given amount of

that capacity. Attention is driven by the need to prioritise sensory information;

selecting some stimuli and ignoring others which may be unnecessary or irrelevant to

the current task (Woollacott & Shumway-Cook, 2002). Non-demented PD subjects

perform worse on tests of focused and divided attention than age-matched healthy

subjects (Van Zomeren & Brouwer, 1994). Brown and Marsden (Brown & Marsden,

1988) found that PD subjects performed as well as controls on a task requiring

attention shifting when given external cues. Thus the impairment was evident only

when the subjects were forced to rely upon internal control for maintaining attention.

Due to this improvement with an external prompt several authors have proposed that

the executive dysfunction in PD arises from the inability to use internal cues to direct

behaviour (Brown & Marsden, 1988; 1990; 1991b; Stam et al., 1993; Dalrymple-

Alford et al., 1994) These deficits in the use of internal control may be emphasised

by a generalised reduction in attentional capacity (Woodward, Bub & Hunter, 2002).

The basal ganglia receive input from and project to a vast proportion of the cerebral cortex as well as brain stem motor areas and therefore play a role in affective and cognitive behaviours as well as motor control (Fielding, Georgiou-Karistianis & White, 2006; Sammer et al., 2006). Striato-prefrontal loops are involved in the regulation of some fundamental aspects of cognitive control (Dujardin et al., 1999). The dorsolateral prefrontal circuit, lateral orbitofrontal circuit and the anterior cingulate circuit, are all implicated in executive functioning (Royall et al., 2002). The anterior cingulate (AC) and dorsolateral prefrontal cortex have specific roles in prioritisation, voluntary direction of attention towards a stimulus and performance monitoring and therefore play an important role in dual tasking or divided attention tasks (Wu & Hallett, 2005b; Adrienne Johnson & Zatorre, 2006; Yogev-Seligmann, Hausdorff & Giladi, 2008).

Berding (Berding et al., 2001) studied the brain glucose metabolism of people with advanced PD without dementia and found reduced metabolism, and therefore activity, in the thalamus and prefrontal cortex when on compared to off medication corresponding to poorer performance on tests of executive function on medication. The effect of dopaminergic medication on cognition is complex and not well understood. Studies have reported improvement, impairment and absence of effect of levodopa on cognitive function (see reviews by Cools (Cools, 2006) and Kulisevsky (Kulisevsky, 2000)). These discrepancies can in part be explained by methodological differences, particularly the different cognitive domains that are tested. Two review papers (Kulisevsky, 2000; Cools, 2006) have identified differences in cognitive

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response to levodopa according to disease stage, particularly related to the

progression of dopamine depletion over time from the dorsal to the ventral striatum.

The dorsal and ventral striatum are thought to have functionally distinct roles in

cognition. Depletion of dopamine producing cells in PD begins in the dorsal striatum

and progresses to the ventral striatum. Therefore in order to restore dopamine levels

in the dorsal striatum, the ventral striatum may be relatively over dosed, which may

explain some of the conflicting findings on tests of cognitive function (Kulisevsky,

2000; Cools, 2006).

There is growing evidence to support the role of cognition in gait. Coppin (Coppin et

al., 2006) found the impact of executive function on gait in a large sample of

community dwelling older adults to be task dependent. The author proposed that

executive function plays an important role in ability to adapt to complex

environments and to adequately allocate attentional resource, possibly because of

greater degree of locomotor control and sensory integration needed in more complex

situations or when performing more than one task.

Yogev-Seligmann (Yogev-Seligmann, Hausdorff & Giladi, 2008) provided a

theoretical framework (summarised in figure 2.1) for the influence of particular

aspects of executive function on gait and also stressed the implications for patient

groups who not only have poor executive function but also rely more on cortical

means of motor control due to reduced automatic drive, such as PD.

Figure 2.1. Theoretical impact of specific domains of executive function on gait (adapted from Yogev-Seligmann (Yogev-Seligmann, Hausdorff & Giladi, 2008)).

INTACT	DOMAIN OF EXECUTIVE FUNCTION	DEFICIENT
Formulation of goal or intention	VOLITION	Reduced drive/motivation to move
Understands influence of the task/environment on self and vice versa	SELF AWARENESS	Inaccurate estimation of limitations/ inappropriate evaluation of hazards
Able to identify steps needed to carry out a task	PLANNING	Inability to plan ahead/ does not anticipate problems or need to make changes
Ignores irrelevant and responds to relevant features of task/environment	RESPONSE INHIBITION	Difficult to 'ignore' unnecessary information and focus on walking
Compares action with intended action and makes appropriate adjustments	RESPONSE MONITORING	Inability to modify walking as task/environment demands or walking performance change
Correctly prioritises and allocates attention in order to maximise performance while maintaining safety	ATTENTION/DUAL TASKING	Inappropriately prioritises elements of task, with 'distraction' from gait

2.4. Dual tasking studies.

The role of attention in normal gait is to identify the behaviourally relevant information and discard non-relevant information reaching the senses simultaneously (Adrienne Johnson & Zatorre, 2006). In motor control studies, dual task paradigms are used as a measure of automaticity and the processing resources necessary for any given task (Abernethy, 1988). This type of methodology is based on the premise that concurrent performance of more than one task will lead to deterioration in the execution of one or both tasks. There are varying opinions as to why this

deterioration takes place. One theory states that the attentional or information

processing capacity of an individual is limited and by asking people to perform dual

or multi tasks, that limit will be exceeded (Woollacott & Shumway-Cook, 2002).

Another theory uses structural interference to explain dual task interference,

suggesting when both tasks utilise overlapping neural pathways, interference will

occur (Abernethy, 1988). It seems likely that both of these models of attention in

motor control have relevance depending on the tasks used. Which task will show

interference in a dual task paradigm depends very much on the individual, the tasks

used and the priority placed on those tasks (Galletly & Brauer, 2005).

When designing a dual task paradigm the choice of task is important. As mentioned

above it is important to identify whether the tasks will use shared or distinct

processing resources (Ebersbach, Dimitrijevic & Poewe, 1995). Consideration should

be also be made as to whether the tasks chosen reflect functional activities,

particularly if the research is being used to inform a therapeutic measure or

intervention. There is some controversy as to whether or not performance of the

primary task should remain stable, with changes only being seen in the concurrent or

secondary task (Woollacott & Shumway-Cook, 2002). This allows the attentional

cost of the primary task to be more clearly identified (Abernethy, 1988). However, in

functional situations it is rare that such strict distinction between the tasks could be

made. It is perhaps more relevant to everyday life to observe the interactions between

tasks and explore more generally their impact on each other (Woollacott &

Shumway-Cook, 2002). By observing effects in both the primary and secondary task,

researchers are able to identify the priority placed on each task by the individual, for example do subjects prioritise gait and balance tasks in order to maintain safety (Bloem *et al.*, 2001a). Faulkner studied a large sample of community dwelling older adults and found that an increase in a secondary reaction time task was associated with reduced risk of falls whereas deterioration in gait in the same task was associated with an increased risk of falls (Faulkner et al., 2007).

Another important factor to consider is the instruction given to the subjects; are they told to prioritise one task over another? By asking a person to focus primarily on one task over the other, their response to a dual task can be significantly altered (Canning, 2005; McCulloch, 2007), whereas observing the response to a dual task without being instructed to focus on one specific aspect gives valuable information regarding the individuals prioritisation of the tasks (Beachet *et al.*, 2005; Bloem *et al.*, 2006; Beauchet *et al.*, 2007). Beauchet used a backward counting task while walking to demonstrate that younger subjects prioritise the gait element of the task and show deterioration in the counting task (Beachet et al., 2005), whereas, older adults (aged 75 and over) show deterioration in gait with particular increase in stride time variability (Beauchet et al., 2007). This suggests an age related difference in the allocation of attention. Bloem (Bloem *et al.*, 2001a; Bloem *et al.*, 2001b) also found that young healthy subjects made more errors in a concurrent cognitive task compared to older adults and those with PD, the authors suggested that the younger adults were adopting a 'posture first' strategy in order to preserve stability.

Chapter 2

Task complexity has also been found to influence the level of dual task interference

with many studies showing a clear relationship between increasing task complexity

and therefore demand on attentional resources and postural or gait interference

(Brown & Marsden, 1991a; Morris *et al.*, 1996; Bloem *et al.*, 2001a; Bloem *et al.*,

2001b; O'Shea, Morris & Iansek, 2002; Verghese *et al.*, 2002; Rochester *et al.*, 2004;

Yogev *et al.*, 2005; Springer *et al.*, 2006). Galletly and Brauer (Galletly & Brauer,

2005) measured the difficulty of a language and a mathematical cognitive task in

sitting to establish the relative difficulty of each task and found the language task to

be more complex, but found no difference in dual task interference in gait between

the tasks. Similarly O'Shea (O'Shea, Morris & Iansek, 2002) found no difference in

the level of interference with gait with a digit subtraction (cognitive) and coin

transference (motor) secondary task. This suggests that other factors relating to the

secondary task are important in addition to complexity. Comparison of dual task

effects across studies is often difficult due to the multitude of both cognitive and

motor tasks used and also the context within which they are applied. Another

consideration is whether the tasks involved were novel to the subjects or well

practiced (Bond & Morris, 2000).

The classic 'stops walking while talking test' was found to have good predictive

value for falls in the elderly in a sample including some subjects with dementia or

depression (Lundin-Olsson, Nyberg & Gustafson, 1997). The same test was not found

to be predictive of falls in a sample of PD subjects (Bloem *et al.*, 2001a). A verbal

fluency task while walking however was found to be no more predictive of falls than

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single task walking speed in a similar sample of older adults aged over 85 years (Bootsma-van der Weil et al., 2003). The authors felt that an important distinction here was the type of task, as the SWWT test uses general conversation where the subject would perhaps be more inclined to stop walking in order to turn and face the other person. Other studies have shown a relationship between falls and poor performance on both motor and cognitive dual tasks (Verghese *et al.*, 2002; Faulkner *et al.*, 2007). Fallers who have displayed increased gait variability in response to dual tasks have also shown poorer performance on tests of executive function (Springer et al., 2006).

Increased dual task interference on gait and balance has been observed post stroke suggesting increased attention demands for motor control (Bowen *et al.*, 2001; Brown, Sleik & Winder, 2002; Hyndman *et al.*, 2006). In comparison to PD subjects however, stroke subjects appear to prioritise the gait task, showing greater decrements in the concurrent task, suggesting an appropriate allocation of resources in order to maintain safety (Hyndman et al., 2006). A study of people with Alzheimer's disease showed an increase in stride time variability during a dual task compared to an age matched control sample, the authors concluded that as cognitive function declines so does the ability to maintain stable gait (Sheridan et al., 2003). The study also supported the view that control of gait variability and other parameters such as walking speed are controlled by different mechanisms (Hausdorff, Balash & Giladi, 2003) as neuropsychological tests were able to predict increased stride to stride variability but not changes in gait speed.

Gait variability has been found to be sensitive to the ability to divide attention.

Several studies have shown that younger adults show no effect of dual tasks on gait

variability (Hollman, Salamon & Priest, 2004; Springer *et al.*, 2006), thought to be

due to a very stable gait patterning mechanism, suggesting minimal attentional cost of

gait (Ebersbach, Dimitrijevic & Poewe, 1995). In addition, older adults have been

shown to display increased gait interference of walking speed compared to younger

adults, however changes in gait variability have been comparably small (Hollman,

Salamon & Priest, 2004; Yogev *et al.*, 2005; Springer *et al.*, 2006), suggesting that

alteration of walking speed may be a response to the additional demands of a dual

task but healthy subjects are able to do this without compromising gait stability.

When automatic gait control is disturbed as with Parkinson's disease, compensatory

mechanisms are used which result in increased attentional involvement (O'Shea,

Morris & Iansek, 2002; Wu & Hallett, 2005a). The compensatory motor control used

by people with PD appears to be resource demanding which leaves limited reserve to

cope with the demands of additional tasks (Bond & Morris, 2000). As people with PD

are utilising a more cortical method of motor control, they have less attentional

resource available to cope with the pressures of additional tasks (Rochester *et al.*,

2004; Rochester *et al.*, 2008). In addition executive dysfunction leads to difficulty in

correctly prioritising motor tasks (Bloem *et al.*, 2006), and attentional problems make

processing more than one task simultaneously and sustaining attention to a task very

difficult due to the impairment in the switching mechanism required to process

information in parallel owing to frontal lobe and basal ganglia dysfunction (Hozumi et al., 2000).

PD subjects demonstrate greater dual task interference on walking of both motor and cognitive tasks compared to age matched controls (Ebersbach, Dimitrijevic & Poewe, 1995; Bond & Morris, 2000; O'Shea, Morris & Iansek, 2002; Rochester et al., 2004). Identifying which tasks are more likely to cause interference in PD is difficult due to vast array of secondary tasks used. O Shea (O'Shea, Morris & Iansek, 2002) found no difference between the level of interference with cognitive and motor tasks, suggesting it is complexity rather than type of task is important. Rochester (Rochester et al., 2004) found increased interference with tasks with a cognitive element, however this may have been related to complexity. Gradually increasing the complexity of a secondary task caused a linear increase in the amount of gait interference and freezing of gait observed in another study (Bloem et al., 2001a).

Differential effects of dual tasks have been found for PD subjects with and without freezing of gait. Camicioli (Camicioli et al., 1998) used a verbal fluency concurrent task which was found to increase the number of steps taken in freezers but not non-freezers. Subjects were tested both on and off medication and interestingly when on medication freezers and non-freezers performed similarly in a single task walking test but the between group differences were retained in the dual task. These findings may suggest that people with PD with freezing of gait may have either an additional attentional deficit or they are utilising more attentional resource to maintain gait.

Imaging studies show increased activation of parietal (role in mediating stimulus

response and attending to behaviourally relevant stimuli) and lateral pre-frontal areas,

in particular the DLPFC during dual task performance in healthy adults (Adrienne

Johnson & Zatorre, 2006; Erikson, Colcombe & Wadhua, 2007). Wu and Hallett

(Wu & Hallett, 2005a) examined a motor learning task involving sequential finger

tapping with a dual cognitive task. PD subjects were able to achieve automaticity of

the finger tapping task (measured by the fact that performance on the secondary task

was not affected) but required more practice to do so. In contrast to controls, similar

patterns of brain activity were seen pre and post automaticity being achieved,

suggesting that although the outward performance was similar, PD subjects used less

efficient means of motor control to produce it.

Rarely in everyday functional activities are we able to attend to only one task, but

rather individuals must be able to respond to dual/multi tasks with flexibility, be able

to allocate the appropriate attentional resources, monitor changes in task demands and

make appropriate adjustments (Springer *et al.*, 2006; McCulloch, 2007). To achieve

this requires executive functioning, particularly to recognise any risk inherent in a

task and be able to modify behaviour accordingly (Coppin et al., 2006), see section

2.3 for a more detailed discussion of the influence of cognition on gait. The impact of

task complexity on walking in PD highlights the importance of assessing cognitive as

well as motor influences on gait (Woollacott & Shumway-Cook, 2002; Rochester *et*

al., 2004; Hausdorff *et al.*, 2005; Snijders *et al.*, 2007). This also has implications for

the generalisation of gait measures taken outside of the individual's own environment as they will not necessarily be representative of their true functional ability.

In the past, people with PD have been advised to avoid dual tasks in order to maintain safety (Morris, 2006), this may not be realistic until the very advanced stages of disease when activity is severely limited. An exploratory study has shown that in people with mild to moderate PD, a 3 week training programme where subjects walked with various additional tasks of increasing complexity improved dual task gait performance (Canning, Ada & Woodhouse, 2008). It remains unclear whether this would generalise to everyday activities but further investigation of the ability to train dual tasks is now warranted. Voelcker-Rehage and Alberts (Voelcker-Rehage & Alberts, 2007) found that both young and older adults were able to reduce dual task interference with practice but the relative improvement was less in the older group. In addition cues have been successful in improving dual task walking in a number of studies, see section 2.5.

The studies presented in this thesis use a dual task paradigm to evaluate the attentional demands of three different cueing strategies. Subjects were not told to prioritise either the gait or secondary task, as part of the research was to determine whether the presence of the cue would act to prioritise gait. In addition, subjects were tested in their own home. Studying the primary task of interest (in this instance, gait) in the individuals natural setting improves ecological validity and reflects more realistically the resources available to the person (Abernethy, 1988). The complexity

of the community environment however has to be considered as an additional demand

on attentional resources (Shumway-Cook et al., 2002) and in some groups has been

shown to have more influence on gait than an additional task (Lord et al., 2006).

2.5. Cueing studies.

It is the automatic, predictable movement sequences which are impaired in PD with

the main deficit in motor performance seen when no specific instructions or cues are

given (Cunnington et al., 1995). A dramatic improvement in motor performance of

people with PD is seen when a cue is provided which has led researchers to attempt to

identify the differential neural pathways involved in externally versus internally

guided movements (Jahanshahi, Brown & Marsden, 1992; Catalan *et al.*, 1999;

Cunnington *et al.*, 2001; Debaere *et al.*, 2003).

In healthy subjects the SMA and DLPFC are activated predominantly by tasks which

are internally generated. Externally triggered movements produce significantly less

activation of the frontal cortex than self initiated movements and the SMA is less

active (and is activated later) when movement occurs in response to a trigger as it's

role in preparation of movement is less necessary (Jueptner *et al.*, 1996; Jenkins *et*

al., 2000; Weeks *et al.*, 2001; Cunnington *et al.*, 2002; Debaere *et al.*, 2003).

Therefore there is greater neural activity involved in internally generated movement

whereas externally cued movement are more reactive with motor preparation being

minimised (Weeks et al., 2001), this could be expressed in terms of attentional cost.

When comparing the response of PD subjects during self initiated and externally cued movements to that of controls, important differences have been found. PD subjects show a failure to properly activate the anterior SMA during self initiated movements (Catalan et al., 1999). Several imaging studies have provided evidence that alternative brain areas are activated in PD suggesting compensation for the cortico-subcortical dysfunction (Albani et al., 2001).

Attention to movement and attention to sensory stimulation involves the medial frontal cortex. When instructed to attend to their movement during a simple task healthy subjects show activation of the anterior cingulate and SMA but not the prefrontal cortex which is expected to be involved when deciding which movement to make and when (Johansen-Berg & Matthews, 2002). When PD subjects are asked to attend to their actions there is a failure to show the normal increase in SMA activation and Rowe (Rowe et al., 2002) concludes that the motor abnormalities seen in PD are due (in part) to a functional disconnection of the SMA and premotor cortex from prefrontal influences.

In a comparison of PD subjects and age matched controls during a reaction time task, controls reacted more quickly during self initiated movements whereas PD subjects were quicker when externally triggered, it seems that distinct brain pathways exist for self initiated versus externally cued voluntary motor movements (Jahanshahi, Brown & Marsden, 1992). Praamstra (Praamstra et al., 1998) suggested that knowledge of these compensatory pathways would contribute to our understanding of the motor

impairments in Parkinson's disease. This in turn would allow the refinement of

rehabilitation approaches.

In support of the findings of imaging studies, gait dysfunction in PD improves with

cues (Rubinstein, Giladi & Hausdorff, 2002). As defined by the Rescue trial external

cues provide temporal or spatial stimuli associated with the initiation and ongoing

facilitation of a motor activity (Nieuwboer *et al.*, 2007). Different modalities of the

external cue (auditory, visual, somatosensory), and parameters of the cue (temporal or

spatial) can be manipulated to provide information about the spatiotemporal

characteristics of gait, such as frequency (step frequency) or amplitude (size of step).

In addition to external cues, attentional strategies such as instructions to increase step

length offer an alternative to external cues and rely more on cognitive mechanisms of

motor control and are internally generated (Morris *et al.*, 1996; Behrman, Teitelbaum

& Cauraugh, 1998; Werner, 2003; Farley & Koshland, 2005; Lehman, 2005).

Work by Morris et al., has shown that the primary gait deficit in PD is the ability to

generate sufficient amplitude of movement and thus the size of step (Morris, 1994).

It is therefore argued that increasing step size should be the primary goal of therapy in

order to normalise gait. Whilst visual cues are the most effective in normalising gait

(Morris *et al.*, 1996; Lewis, Byblow & Walt, 2000; Galletly & Brauer, 2005), they are

not practical to use in the community and are also limited in the home, therefore the

practicality of these cues for rehabilitation is limited. Attentional, or internal, cues

(focussing on a specific aspect of gait) are also used to influence stride amplitude and

studies have shown that PD subjects are able to modify gait appropriately when given specific instructions (Morris *et al.*, 1996; Behrman, Teitelbaum & Cauraugh, 1998; Canning, 2005; Farley & Koshland, 2005). Table 2.1. summarises single session testing of spatial cues.

Auditory cues target the temporal parameters of gait by pacing step frequency. They are practical and easy to apply in a variety of settings but have more modest effects (Thaut *et al.*, 1996; McIntosh *et al.*, 1997; Howe *et al.*, 2003; Rochester *et al.*, 2005; Willems *et al.*, 2006; Hausdorff *et al.*, 2007; Nieuwboer *et al.*, 2007; Rochester *et al.*, 2007) (see table 2.2.).

As discussed in section 2.2. both the temporal and spatial parameters of gait are altered in PD whereas cues tend to address only one aspect. While some alteration is seen other parameters, the main effect of cues is seen in the parameter at which it is targeted, spatial cues (visual and attentional) increase walking speed through increased stride amplitude, while rhythmical auditory cues increase walking speed via their effect on step frequency and in some studies a subsequent effect on stride amplitude (see tables 2.1. and 2.2.).

Table 2.1. Studies of the immediate effects of spatial cues (visual and attentional) on spatiotemporal gait parameters of PD subjects. All results shown are single task, on medication unless otherwise stated.

	Walking speed	Stride amplitude	Step frequency
Behrman et al 1998 8 PD (mild-moderate disease severity). Instructions to i) deliberately swing arms ii) walk while counting aloud iii) walk with large steps iv) walk fast	'Large steps' instruction: 50% increase. 'Walk fast' instruction: 65 increase.	'Large steps' instruction: 32% increase. 'Walk fast' instruction: 67% increase.	'Large steps' instruction: 20% reduction. 'Walk fast' instruction: 31% crease.
Canning 2005 12 PD (mild – moderate disease severity). Instructions to attend to; i) maintaining bigger steps Dual task.	4.5% increase.	13% increase.	No effect.
Morris et al 1996 16 PD (mild-moderate disease severity). Attentional cue - shown criterion stride length and asked to reproduce. Visual cues set at controls stride.	Attentional: 37% increase. Visual: 46% increase.	Attentional: 36% increase. Visual: 35% increase.	Attentional: 3% reduction. Visual: 4% reduction.
Suteerwattananon et al 2004 24 PD (mild to moderate disease severity). Visual cues set to controls stride length.	4% increase.	18% increase.	9% reduction.

Table 2.1. ctd.

Morris et al 1994 12 PD (mild disease severity). Visual cues set at controls stride length.	20% increase.	28% increase.	No effect.
Lewis et al 2000 14 PD (mild-moderate disease severity). Visual cues set at controls stride length.	10% increase.	22% increase.	13% reduction.
Galletly and Brauer 2005 16 PD (moderate disease severity). Visual cues set at controls stride length. Single and dual tasks.	No effect.	Single and dual tasks: 18% increase.	4% reduction single task gait. 15% reduction in dual task.

Table 2.2. Studies of the immediate effects of temporal cues (rhythmical auditory, somatosensory and visual cues) on spatiotemporal gait parameters of PD subjects.
All results shown are single task, on medication unless otherwise stated.

	Walking speed	Stride amplitude	Step frequency
Almeida et al 2007 19 PD OFF, 24 PD ON. Auditory cue at 60, 80 and 100 beats per minute. ON and OFF medication.	No effect.	No effect.	More difficult to synchronise with cue on than off medication.
Arias & Cudeiro 2008. 25 PD (mild to severe disease severity). Rhythmical auditory and visual and a combination of cues at preferred stepping frequency and 70 to 110% of fastest stepping frequency.	At preferred stepping frequency: no effect. Increased at 80 – 110% cue frequency.	At preferred stepping frequency: increased with auditory and auditory+visual Increased at 80 – 110% cue frequency.	Able to synchronise with range of cueing frequencies.
Ebersbach et al 1999 22 early PD (11 early untreated, 11medicated with mild to mod disease severity). Auditory cue at 20% below preferred stepping frequency.		Reduced by 13% in the treated PD subjects and by 6% in the early untreated subjects.	
Hausdorff et al 2007 29 PD (mild – moderate). Auditory cue at preferred stepping frequency and 110%	At preferred stepping frequency: 4% increase At 110%: 9% increase	At preferred stepping frequency: 4% increase	Synchronised with cue at both frequencies.

Table 2.2 ctd.

of preferred pace.		At 110%: 4% increase	
Howe et al 2003 11 PD (mild disease severity). Auditory cue at 85, 92.5, 107.5 and 115% of preferred stepping frequency.	Increased with frequencies above and reduced with frequencies below preferred stepping frequency. Increased by 17% at 115% cueing frequency.	No effect at any frequency.	Able to synchronise at a range of frequencies.
McIntosh et al 1997 21 PD (moderate disease severity), 20 controls. RAS (auditory cue embedded in music) at baseline and 110%. ON and OFF medication.	PD on medication increased speed by 36%. PD OFF medication increased speed by 26%.	PD on medication increased stride length by 19%. PD OFF medication increased stride length by 19%.	Able to synchronise with cue both ON and OFF medication
Morris et al 1994 12 PD (mild disease severity). Auditory cue set at controls preferred and fast stepping frequency.	At preferred pace of controls subjects – no effect on walking speed At fast pace of controls – increase	At preferred pace of controls subjects - no effect on stride amplitude. At fast pace of controls - increase	Able to entrain cadence to that of controls at preferred but not fast pace.
Rochester et al 2005 20 PD (mild to moderate disease severity). Auditory cue at preferred stepping frequency. Single and dual tasks.	Single task – no effect. Dual task – 13% increase.	Single task – no effect. Dual task – 8% increase.	Able to synchronise with cue in single and dual tasks.

Table 2.2 ctd.

Study			
Rochester et al 2007 153 PD (mild/mod/severe severity). Rhythmical auditory, visual and somatosensory cues at preferred stepping frequency. Single and dual tasks.	Single task – reduced will all cues. Dual task – increased with auditory (4%) and somatosensory (2%) cues. 16% increase seen with auditory and combination	Single task – reduced with all cues. Dual task – increased by 4% with visual, 6% with auditory and somatosensory cues. 5% increase with auditory and combination	Single task – reduced with all cues. Dual task – reduced with all cues. Increase with auditory and combination
Suteerwattananon et al 2004 24 PD (mild to moderate disease severity) i) Auditory cue at 125% preferred stepping frequency ii) Combination of auditory cue and visual cue set to match stride length of controls			
Willems et al 2006 20 PD. Auditory cues at 80%, 90%, 100%, 110% and 120% preferred stepping frequency	Speed increased by 11% at 110% cue freq and 13% at 120% cue freq.	5% increase in stride length at 90% cueing frequency and a reduction of 4% at 120% cue freq.	Able to synchronise at a range of frequencies.

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Arias (Arias & Cudeiro, 2008) examined influence of auditory and visual rhythmic

cues, separately and combined. The auditory cue increased stride amplitude and

reduced gait variability, whereas the rhythmic visual cue had no effect. The

combination of the auditory and visual cues was equally but no more effective than

the auditory cue alone. The combination of two rhythmical cues provided no added

information and only addressed the temporal gait parameters. In contrast

Suteerwattananon (Suteerawattananon et al., 2004) examined the combination of a

rhythmical auditory cue and a visual spatial cue. The auditory cue increased speed

and the visual cue increased stride length when applied individually. When combined,

the same effects as with the auditory cue were seen. The subjects appeared to attend

to the auditory cue but were unable to modify their step size in response to the visual

cue at the same time, possibly because the two sources of external information were

too attentionally demanding.

Training with rhythmical auditory cues has been shown to significantly improve

temporal gait stability of gait (Fernandez del Olmo & Cudeiro, 2005; Yogev *et al.*,

2005; Hausdorff *et al.*, 2007) and is correlated with increased activity in the

cerebellum, dentate nucleus and the temporoparietal junction which are all areas

involved in the time keeping mechanism of motor control (Del Olmo et al., 2006).

When an external auditory cue was used to artificially restrain gait at stepping

frequencies 20% below preferred cadence, variability of step length was seen to

increase in PD subjects. Using a range of cueing frequencies (from 60 to 150 beats

per minute) a U shaped response was seen with variability deteriorating at the 2

extremes and improving at frequencies closer to subjects preferred stepping

frequency (Del Olmo et al., 2006). This suggests some promise in the use of external

cueing to improve variability of gait in PD but also emphasises the importance of

optimising cue delivery in terms of modality and parameter. While temporal

variability is improved with rhythmical cues, variability of stride length has been

shown to improve with visual spatial cues (Lewis, Byblow & Walt, 2000) suggesting

a specificity of effect.

Studies of treadmill walking in PD are also relevant to the area of externally cued

movement as the treadmill imposes an external pace (Frankel-Toledo et al., 2005).

When measuring gait while walking on the treadmill, improvements are seen in

walking speed, stride length and gait variability which supports the view that the

treadmill acts as an external pacemaker (Frankel-Toledo et al., 2005).

Hanakawa and colleagues (Hanakawa et al., 1999a) examined PD and healthy control

subjects walking on a treadmill and used SPECT imaging to identify which brain

areas were activated when transverse and parallel lines were placed on the treadmill.

Walking over transverse lines reduced step frequency; this was associated with

increased activity in the posterior parietal cortex (PPC) and the cerebellum which was

greater than that seen in control subjects. The PPC provides input to the pre-motor

cortex (PMC). The authors concluded that the cerebellar/PPC inputs which were over

activated in PD were able to compensate for the deficient basal ganglia when

provided with task relevant sensory information. The study also reported increased

activation in the anterior cingulated (AC) when walking with visual cues, an area associated with increased attention to action. This raises the question of whether it is the specific information contained within a cue which results in gait modification or simply that the cue acts to increase attention to the task of walking.

Pohl and colleagues (Pohl et al., 2003) examined the effects of treadmill training without body weight support in people with mild to moderate disease severity, at the fastest tolerated speed and found significantly greater improvements in walking speed and stride length compared to conventional therapy as well as a reduction in time spent in double limb support. An RCT compared the effects of conventional physiotherapy and a 4 week course of treadmill training with body weight support in people with moderate disease severity (Miyai *et al.*, 2000; Miyai *et al.*, 2002). Walking speed, stride length and severity of motor symptoms measured with the UPDRS were significantly improved with the treadmill training only (Miyai et al., 2000) and importantly these effects were maintained 4 months after the intervention (Miyai et al., 2002). The body weight support allowed the subjects to train at higher speeds. The gait measurements were taken during over ground walking suggesting some transfer of effect of training on a treadmill; however subjects were instructed to walk as fast as possible which is in effect an attentional cue. This generalization effect of treadmill walking was also seen after a single 20 minute treadmill walking session (Bello, Sanchez & Fernandez-del-Olmo, 2008) with increased speed and step amplitude.

Chapter 2

A systematic review by Lim suggested that despite strong evidence that rhythmical

cues enhance walking in PD, little is known about the generalisation of effects to

functional situations and tasks, and the optimum delivery of cues remains unclear.

Galletly and Brauer (Galletly & Brauer, 2005) raised question of whether cues are an

added task; when applying cues in a functional setting, it is important to establish

their demand on attentional resource in order to ensure safety will not be

compromised.

Attentional cues have been shown to be effective during dual tasks when subjects are

instructed to focus attention on the gait component of the task, addressing the need to

rely on executive function to prioritise the task (Canning, 2005). Covert observation

has shown however, that despite successful training with an attentional strategy to

improve gait, PD subjects do not continue to use the strategy when there is no

external prompt (instruction/expectation) to do so (Morris et al., 1996), which

questions their functional application, particularly in those with executive

dysfunction.

External cues have been shown to reduce dual task interference in PD which suggests

that walking with cues requires less attention than non-cued walking.(Rochester *et

al.*, 2005; Rochester *et al.*, 2007). It seems that external cues may reduce the need for

planning and preparation of movement which is important in PD when we consider

PD subjects are unable to appropriately divide attention and have an impaired ability

to internally regulate movement (Almeida, Wishart & Lee, 2002).

This thesis aims to refine the delivery of cues by addressing two main issues. Firstly the need to address both spatial and temporal gait parameters will be explored through a novel cueing strategy which targets both step size and frequency. Secondly the attentional cost of internal and external cueing strategies is evaluated using a dual task paradigm. Finally the influence of dopaminergic medication on cueing effect will be assessed which will provide information on which neural pathways are used during cued gait.

2.6. Gait analysis.

Gait analysis is carried out to identify gait abnormalities, make diagnosis, determine appropriate therapy and monitor progress. There is a wide choice of methodologies and equipment which can now be used. When analysing gait there is a trade off between accuracy and ease of application (Webster, Wittwer & Feller, 2005). This is particularly pertinent when studying people with Parkinson's disease as context and environment can influence the gait pattern. For the studies presented in this thesis it was particularly important to find reliable methods of gait analysis which were not cumbersome or intrusive, that could be used during a functional activity and in part could be used in the home setting.

The GAITRite gait analysis system is an instrumented walkway which detects the timing and relative distance between pressure activated sensors to calculate gait parameters. The reliability of the GAITRite has been established in various patient groups including rheumatoid arthritis (Rome & Hanchard, 2005), Huntingdon's

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disease (Rao, Quinn & Marder, 2005), cerebral palsy (Sorsdahl, Moe-Nilssen &

Strand, 2008) as well as being sensitive in distinguishing control subjects and those

with gait pathology (Rao, Quinn & Marder, 2005). GAITRite has also been shown to

be valid and reliable in determining the footfall patterns of people with early and mid

stage PD, is able to discriminate between subjects with PD and healthy controls

(Nelson et al., 2002) and is sensitive to changes on and off medication (Chien et al.,

2006).

The concurrent reliability of the GAITRite system has been established against

various gait analysis systems. McDonough (McDonough et al., 2001) studied 27

young women and compared data from the GAITRite with chalked foot prints and a

stopwatch, finding excellent correlation for the spatial parameters but only poor to

moderate correlation for the temporal parameters which was thought to reflect the

subjectivity involved when identifying gait events with the stopwatch. In contrast,

Selby Silverstein (Selby-Silverstein & Besser, 1999) found high correlation between

the GAITRite and chalked footprints for both the spatial and temporal parameters but

also identified a systematic error. Webster (Webster, Wittwer & Feller, 2005)

compared GAITRite with a multiple camera 3-dimensional motion analysis gait

measurements of people post knee replacement and found excellent agreement at self-

selected and fast speeds for both averaged and individual step parameters. Cutlip

(Cutlip et al., 2000) found the agreement between GAITRite and a single camera

motion analysis system reduced with increasing speed. Test retest reliability of the

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GAITRite has been shown to be excellent in both young and older adults

(McDonough *et al.*, 2001; Menz *et al.*, 2004).

Examining gait in the laboratory setting provides a safe, controlled environment, however testing subjects in their own home reflects more realistically how a subject would respond to a given situation (Abernethy, 1988). The initial feasibility studies of the work presented here were carried out in the laboratory and these findings were then extended to the home environment to maximise the ecological validity. The complexity of the environment outside of the laboratory is assumed to place additional demand on attentional resources and may have more influence on gait than a secondary motor or cognitive task (Shumway-Cook *et al.*, 2002; Lord *et al.*, 2006). In addition subjects were tested when off medication and it would not be feasible to travel into the laboratory. It was therefore necessary to find a reliable means of gait analysis which could be applied in the home to provide detailed gait measurements and was unobtrusive and easy to wear.

The Stride Analyzer records foot floor contacts over a specified distance and times each foot contact in order to calculate gait parameters. Footswitches are placed inside shoes and attached to a portable data logger worn at the subject's waist. The system is highly portable and can be used easily in the home setting.

Bilney (Bilney, Morris & Webster, 2003) tested the concurrent validity of the GAITRite and Stride Analyzer systems using a group of 25 healthy subjects walking

at slow, normal and fast speeds and found excellent agreement for speed, stride length

and cadence at all speeds. In a study screening 53 elderly people living in residential

care, gait speed data collected with the Stride Analyzer was found to be a sensitive

tool in identifying those in need of physiotherapy assessment and treatment as a result

of various pathologies (Harada et al., 1995).

Reliability of the Stride Analyzer has been confirmed in subjects with neurological

impairment, including stroke (Hill *et al.*, 1994; Evans, Goldie & Hill, 1997) and PD

(Morris *et al.*, 1996; Bilney, Morris & Webster, 2003). Hill et al (Hill et al., 1994)

recommended repetition of more than 2 trials when collecting data from people with

variable gait patterns which would include PD subjects, this was incorporated into the

experimental protocol.

2.7. Scope of thesis.

This thesis aims to consider the complex factors contributing to gait difficulty in PD

in order to better understand the mechanism by which they can be improved. The

influences on gait are summarised in figure 2.2. This oversimplifies the multifaceted

nature of parkinsonian gait dysfunction but tries to bring together the areas of the

literature which have been discussed in this chapter and which will be explored

further in this thesis.

Figure 2.2. Factors which can be manipulated to improve gait performance in people with PD.

```
                          ┌─────────────────────┐
                          │        CUES         │
                          │   People are able to │
                          │  modify gait when given │
                          │    the appropriate   │
                          │     information      │
                          └─────────────────────┘
                                    │
                                    ▼
┌──────────────────┐      ┌─────────────────────┐      ┌──────────────────┐
│      TASK        │      │    Optimising gait   │      │    MEDICATION    │
│  Gait deficit least │ ──▶ │    in PD depends     │ ◀── │   Improves but    │
│   prominent in    │      │   on a number of     │      │     does not      │
│    absence of     │      │     conditions       │      │   normalise gait  │
│  distraction and in │     └─────────────────────┘      └──────────────────┘
│  non-challenging   │                 ▲
│   environments    │                 │
└──────────────────┘      ┌─────────────────────┐
                          │        OTHER        │
                          │  Cognitive and affective │
                          │  symptoms have a role in │
                          │   motor performance  │
                          └─────────────────────┘
```
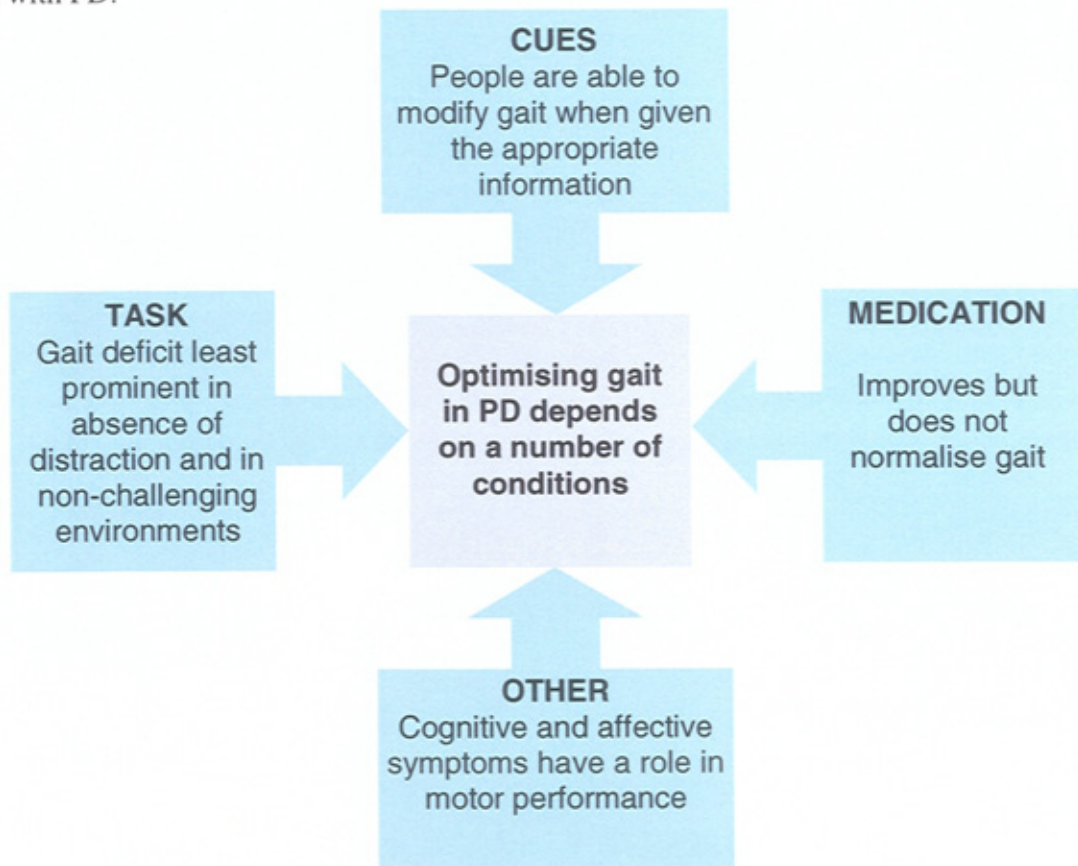
Imaging studies have used relatively simple upper limb tasks to explore the

differences in neural processing when movement is internally or externally driven.

Studies of cued gait have provided behavioural evidence that movement is enhanced

in PD when specific instruction or cues are given, thought to be due to the different

neural pathways utilised. As cognition and particularly competition for attentional

resources has been shown to have an influence on gait quality and safety it is

important to establish the cost in terms of attention or cognitive load when using

cues, which may reflect the compensatory motor control being used. This is

especially important for those people who have reduced automatic gait control and

therefore greater reliance on cortical means of gait control and also where executive

function and attentional performance is below normal, as in PD.

There is a lack of comparison between the different types of cueing strategies used to

improve walking in PD, both in terms of their effects on gait and also their attentional

cost. The optimal delivery of cues also remains unclear. The studies presented in this

thesis use different types of cues in a dual task paradigm in order to address this

issue. In addition, a novel cueing strategy is tested which aims to address some of the

weaknesses seen with previously tested cueing strategies, see figure 2.3.

Another contribution of the current work is to explore the impact of dopaminergic

medication on cueing. This provides information on the mechanism of effect of cues

as well as important clinical information about the utility of such strategies across the

medication cycle.

Figure 2.3. The combination cue strategy, addressing the spatial and temporal gait abnormalities in PD.
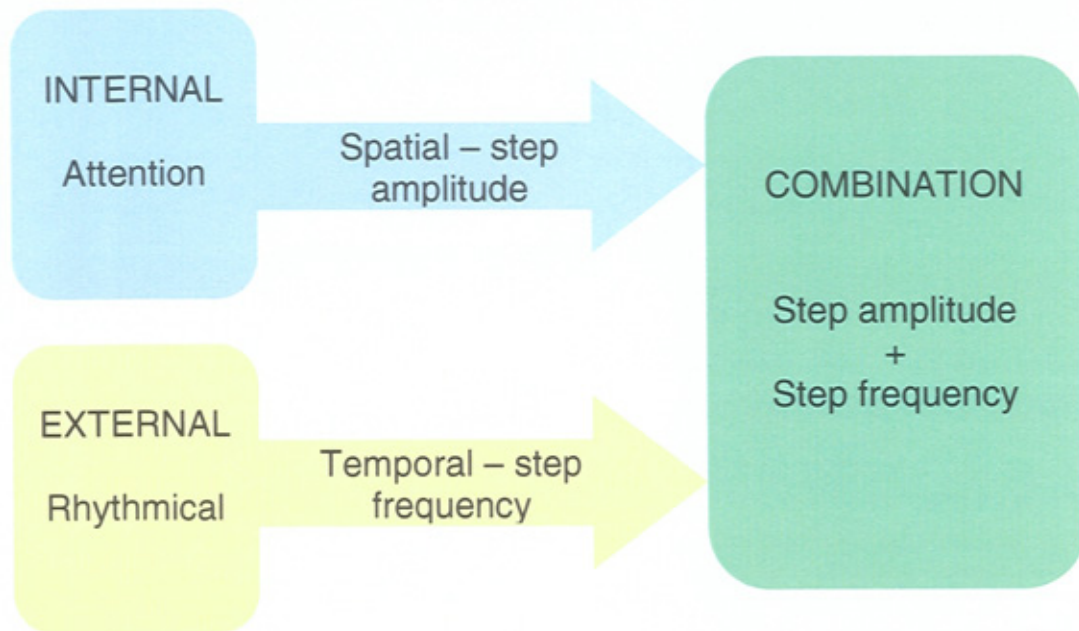
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Chapter 3

3.1. Abstract

The aim of this study was to compare the effect of a rhythmical auditory cue, an attentional strategy asking the individual to focus on increasing step amplitude, and a combination of both cues on gait in people with Parkinson's disease (PD) during single and dual tasks. A repeated measures study design was used, in which subjects performed single and dual motor tasks under different cueing conditions. 15 subjects with idiopathic PD and a comparison group of 12 healthy subjects were tested in the Human Movement Analysis Laboratory, Northumbria University, UK. PD subjects were tested on medication. Three cueing strategies were compared: a rhythmical auditory cue (walking in time to a metronome beat delivered at 10% below preferred stepping frequency), an attentional strategy (concentrate on taking big steps) and a combination cue (asked to take big steps in time to a metronome beat). The primary outcome measures were; walking speed, step amplitude and step frequency. Compared to walking without cues, walking speed and stride amplitude of PD subjects were significantly improved with both the attentional and combination cue strategies in both single and dual tasks. Smaller, non-significant effects were seen with the auditory cue alone. Step frequency was significantly reduced with all cues. Comparing PD subjects walking with cues to control subjects non-cued walking revealed that step amplitude was normalised with the attentional and combination cues in both the single and dual tasks and with the auditory cue in the dual task. Walking speed was normalised in the dual task only with the attentional and combination cues. The attentional strategy and the combination of a rhythmical

auditory cue with an attentional strategy were equally effective and significantly

improved walking speed and step amplitude during both single and dual tasks.

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3.2. Introduction.

As discussed in chapter 2 (section 2.5) cueing strategies have been shown to improve

gait in people with PD by addressing either the timing or scaling of movement

(Morris *et al.*, 1994; 1996; McIntosh *et al.*, 1997; Behrman, Teitelbaum & Cauraugh,

1998; Lewis, Byblow & Walt, 2000; Howe *et al.*, 2003; Suteerawattananon *et al.*,

2004; Canning, 2005; Rochester *et al.*, 2005; Willems *et al.*, 2006; Hausdorff *et al.*,

2007; Rochester *et al.*, 2007; Arias & Cudeiro, 2008). However the cueing strategies

previously studied have limitations in either effect or practical application.

With the different modalities of cue, there is greatest impact on the gait parameter at

which it is targeted but changes in other parameters often occur as a secondary

response for example modification of step frequency can result in a change in step

amplitude and vice versa. Walking speed is influenced by changes in step amplitude,

step frequency or both.

The importance of the instruction when delivering a cue has been emphasised

(Behrman, Teitelbaum & Cauraugh, 1998; Canning, 2005; Rochester *et al.*, 2005).

Behrman (Behrman, Teitelbaum & Cauraugh, 1998) compared the effect of different

instructional sets on gait in PD subjects, finding that subjects were able to modify

their walking pattern in accordance with the instructions given. Interestingly speed

and stride amplitude were improved with instructions not only to adapt these specific

parameters but also as a consequence of modifying other parameters such as

increasing arm swing. This may have been a general effect of increasing attention to

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gait with the subjects being more focussed on the task of walking. A dual task

paradigm was used in a previous study to demonstrate that attentional focus could

both enhance and diminish gait performance. When subjects were instructed to attend

to their walking during a dual motor task their speed and step amplitude improved,

whereas when they were instructed to attend to the task of carrying a loaded tray,

walking performance deteriorated (Canning, 2005).

Previous studies have attempted to optimise the effect of cues by combining

modalities. Suteerawattananon et al (Suteerawattananon et al., 2004) examined PD

subjects walking with visual and auditory cues, both in isolation and together and

found no added benefit in combining the cues. This may be because both of the cue

types presented external information, and in view of the difficulties people with PD

have attending to multiple sources of information, the subjects were only able to

process one. Or perhaps there was a limit to the scope for improvement and the single

cues had already saturated this and there was therefore no further benefit to be had by

combining cues, however when the relatively small effect sizes with auditory cues

reported in other studies are considered this seems unlikely.

Another study compared rhythmical cues delivered via an auditory tone, a flash of

light and also the effect of delivering both together (Arias & Cudeiro, 2008). The

auditory cue alone and the combination of the auditory and visual cues were both

more effective than the visual cue with no difference in effect between them. In

agreement with Suteerawattananon, there was no added benefit of combining cues,

possibly in this case because both modalities of cue were delivering the same temporal information at the same frequency.

Despite the benefits of cues on gait, generalisation of cue use to facilitate the performance of functional activities and in complex environments has received less attention. People with PD have difficulty performing dual tasks (Bond & Morris, 2000; Bloem *et al.*, 2001; O'Shea, Morris & Iansek, 2002; Rochester *et al.*, 2004; Yogev *et al.*, 2005), argued to result from attentional overload and inability to use automatic movement control leading to increased reliance in cortically mediated means of motor control, this is discussed in detail in chapter 2, section 2.4. Deficits in executive function reported in PD (Brown & Marsden, 1990; Dalrymple-Alford *et al.*, 1994; Dujardin *et al.*, 1999) may exacerbate dual task difficulties as this will impact on the ability to appropriately allocate attention to gait during dual and multi tasks (Bloem *et al.*, 2001; Rochester *et al.*, 2004; Yogev-Seligmann, Hausdorff & Giladi, 2008). It is therefore important to find therapeutic strategies which can be integrated into functional activities, in addition examining the effect of cues in a dual task paradigm allows the attentional cost of such strategies to be evaluated (Rochester *et al.*, 2005; Rochester *et al.*, 2007).

Spatial visual cues have also been found to be effective during a dual cognitive task (Galletly & Brauer, 2005), however there would be practical restraints on using such a strategy during a motor task. In contrast Rochester et al (Rochester *et al.*, 2005; Rochester *et al.*, 2007) found that PD subjects could use rhythmic cues to improve

gait in a functional task in the home setting, proposing that cues reduce the attentional demand of walking in a dual task. However, further work is needed to fully understand the attentional demands and mechanism of effect of cues in order to optimise their delivery (Rochester et al., 2007).

To date no functional cueing strategies which address both the spatial and temporal parameters of gait have been described. Combining a rhythmical auditory cue to prompt step frequency with a spatial cue to normalise step amplitude in order to address both the temporal and spatial components of gait in people with PD may provide an alternative to address issues of generalisation and maximise the influence of rhythmical cues. The presence of the external cue may reduce the need for constant monitoring by prompting the individual to focus on step amplitude thus overcoming limitations of executive function and increased attentional requirements.

This exploratory pilot study aimed to address the feasibility of such a combination cue in a small scale pilot study carried out in the laboratory setting. The following questions were addressed: (1) are individuals with PD able to effectively combine a rhythmical auditory cue with an attentional strategy, (2) does the combination cue provide greater benefits than the attentional strategy or auditory cue alone and (3) can these cues be used to improve gait during a dual task.

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3.3. Methods.

Subjects.

This exploratory study used a convenience sample of 15 people with idiopathic PD,

and a comparison group of 12 healthy control subjects matched for age. Ethical

consent for the study was granted by Sunderland Local Research Ethics Committee,

UK. All subjects gave informed written consent (see appendices (i) and (ii) for study

information sheet and consent form). The following criteria were used to recruit PD

subjects: diagnosis of idiopathic PD (by a consultant neurologist with a specialist

interest in movement disorders), absence of any other neurological problem, absence

of dementia (score above 24 on Mini Mental State Examination (Folstein & Folstein,

1975)), absence of any severe co-morbidity likely to affect gait, adequate sight and

hearing with glasses or hearing aid if required (this was determined informally by

ensuring the subject was able to read the study information sheet and hear the cueing

device), independently mobile indoors without a walking aid, no severe dyskinesia

(above 2 on Modified Dyskinesia Scale (Goetz, Stebbins & HM, 1994)) or prolonged

off periods and age 80 years or less. Subjects who scored ≥ 1 on item 3 of the

Freezing of Gait Questionnaire (Giladi et al., 2000) were classified as freezers. The

control group subjects were fit and well with no severe co-morbidity; MMSE score of

≥ 24; adequate vision and hearing and aged 80 years or less.

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Experimental Design.

The study used a repeated measures experimental design which compared three different cue types under single and dual task conditions. Order and practice effects were controlled for by counterbalancing the walking alone and dual task conditions and randomising the order of cue presentation (figure 3.1). All testing took place in the Human Movement Analysis Laboratory at Northumbria University. Testing took approximately 45 minutes during which time the PD group were in the ON phase of the medication cycle (1 hour after medication intake) confirmed using a visual analogue scale with which the subjects rated their current status on a scale from 'ON' to severely 'OFF'.

Figure 3.1. Experimental design. PD (n=15) and control (n=12) subjects walked with and without cues under single and dual task conditions. Cueing trials were randomised, single and dual tasks were counterbalanced.
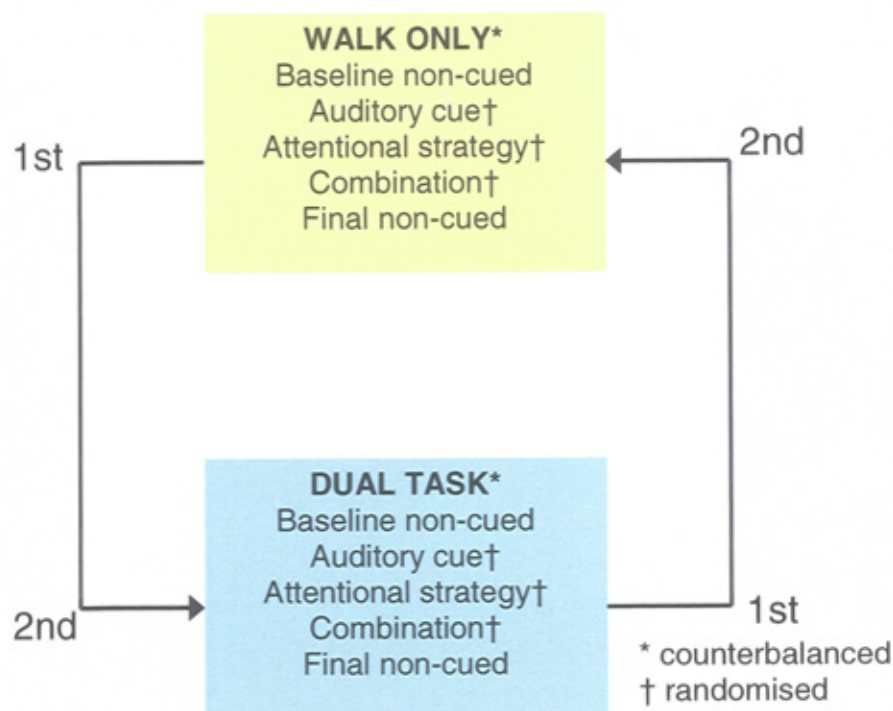
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Experimental protocol.

Subjects performed 10 trials in both the single and dual task conditions (Table 3.1),

the order of single and dual task was counterbalanced. Three non-cued baseline trials

preceded the cueing trials (Table 3.1.) with a final non-cued baseline trial after the

cueing trials in order to examine short term carry over effects of cue use. Subjects

performed two trials with each cue type in a randomised order. Trials were performed

one after the other with a maximum of 1 minute between trials while equipment was

reset.

Table 3.1; Protocol for cued and non-cued trials. 10 trials as described below were
completed in the single and dual tasks. Non-cued trials were performed before and
after the cued trials. The cued trials* were randomised.

Cue Type	Description and instructions
BASELINE – NON-CUED	Baseline. Non-cued walking *Instructions: 'walk at your own comfortable pace'* Performed 3 times
AUDITORY*	External rhythmical auditory cue set at 10% below preferred stepping frequency *Instructions: 'as you walk try to step your feet in time to the beat'* Performed twice
ATTENTION*	Instruction to focus on 'walking with big steps' given before each trial *Instructions: 'as you walk try to take big steps'* Performed twice
COMBINATION*	External rhythmical auditory cue set at 10% below preferred stepping frequency, associated with 'taking a big step' *Instructions: 'take a big step in time to the beat'* Performed twice
FINAL NON-CUED	Final trial. Non-cued walking completed immediately after cued trials *Instructions: 'walk at your own comfortable pace'* Performed once

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For each trial subjects walked a distance of 8m over a GAITRite mat[a] with and
without cues under two different conditions; (1) single task (walking alone); (2) dual
task (walking and carrying a tray with 2 cups of water placed on it). This task was
chosen to reflect a functional, ecologically valid activity and has been used in
previous studies (Bond & Morris, 2000; Rochester *et al.*, 2004).

1. Single task - Walk only: The subjects were seated in a chair, then stood up
and walked along an 8m walkway stopping when they touched a designated
point on a table (figure 3.2).

2. Dual task: The subjects were seated in a chair, stood, collected a tray with
2 cups of water placed on it from a table beside the chair, walked along the 8m
walkway carrying the tray and stopped when they placed the tray on a
designated point on a table (figure3.2). The level of water in the cups and
position of the cups on the tray was standardised. Subjects were instructed not
to prioritise either the tray carrying or the walking task but rather to
concentrate on the task as a whole, therefore dividing attention.

Figure 3.2. Experimental protocol. Subjects started in a seated position, stood when given the instruction to 'go when you are ready', then walked along an 8m walkway over a GAITRite mat, stopping when they touched the target on the bench. In the dual task condition, the same procedure was followed but subjects collected a tray with two cups of water after standing from the chair and carried this along the walkway and placed it on the bench.

Table with target for tray

GAITRite mat (4.57m in length with active area of 3.66m)

Walkway 8m in total

Table with tray and cups

Chair
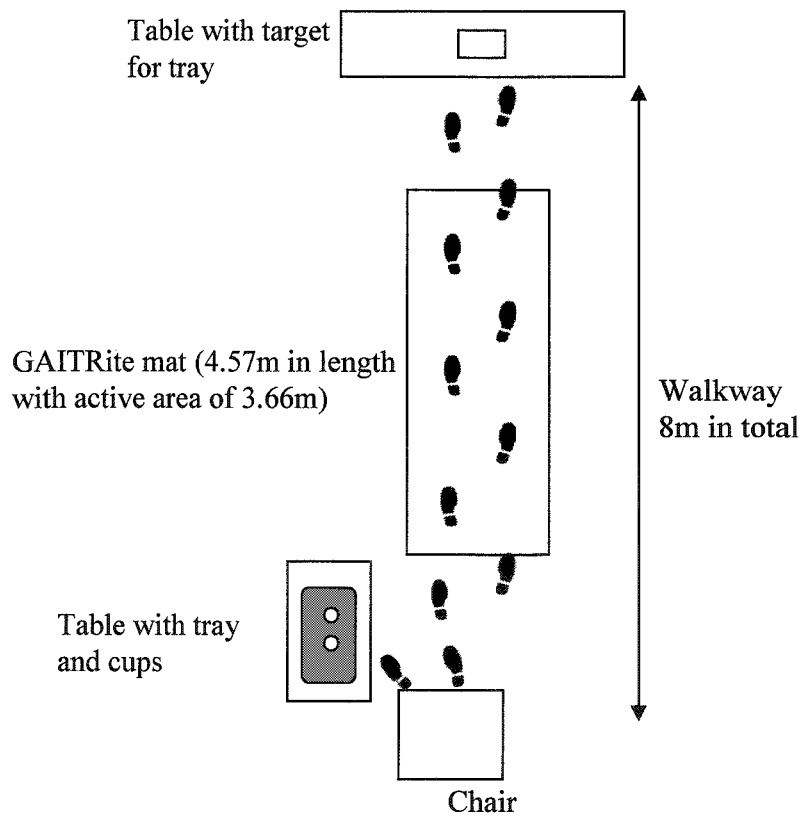
Primary Outcome Measures.

Walking speed (m/min), step amplitude (m) and step frequency (steps/min) collected using the GAITRite mat[a].

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Baseline Measures.

Demographic data were collected for subjects including; gender, age (years) and

height (m). For the PD group disease duration and severity were recorded; scored with

the Hoehn and Yahr scale (Hoehn & Yahr, 1967) which rates disease progression on a

scale of 1 to 5, Unified Parkinson's Disease Rating Scale, Section III (motor subscale)

(Fahn & Elton, 1987) which scores the motor signs of PD including speech, facial

expression, tremor, rigidity, bradykinesia, balance and gait, Freezing Of Gait

Questionnaire (Giladi et al., 2000) which rates the symptom of freezing according to

frequency, situations which cause freezing and severity of freeze, Modified

Dyskinesia Scale (Goetz, Stebbins & HM, 1994) which scores the symptom of

dyskinesia on a scale of 0 to 4 according to interference with motor tasks.

Equipment.

Rhythmical auditory cues were given using a prototype cueing device[b] (figure 3.3),

which delivered a rhythmical sound set at 10% below preferred stepping frequency.

Preferred stepping frequency of each participant was calculated using the mean of

three repetitions of a 10m walk test. The choice of cueing frequency was made to

enable the subjects to synchronise with the cue during both the single and dual task

and also to allow time for a larger step.

Figure 3.3. Prototype cueing device. The device delivers a rhythmical beat via an auditory, somatosensory or visual cue at a chosen frequency between 40 and 140 beats per minute. In the present study, the device was used to deliver an auditory tone.
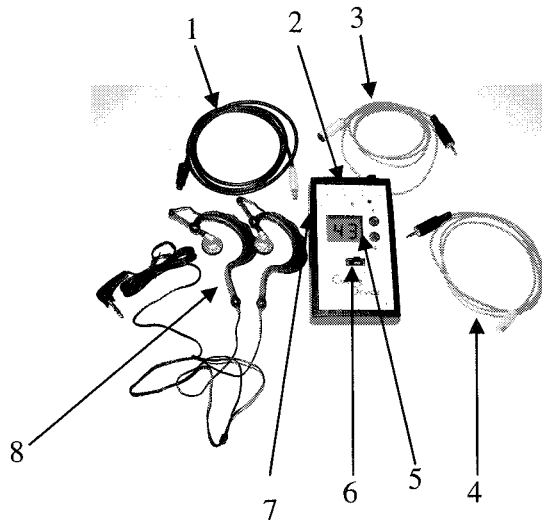
1. Lead to allow connection of cueing device to analysis equipment
2. Connection ports for auditory, visual and somatosensory cues
3. Somatosensory cue – vibrating cylinder worn on the wrist
4. Visual cue – rhythmical flash of light worn on rim of spectacles
5. Frequency display showing beats per minute
6. Selection of cue modality
7. On/off switch
8. Earphones for use with auditory cue

The GAITRite mat[a] (figure 3.4) recorded gait parameters: walking speed (cm/s), step frequency (steps/min) and step amplitude (cm) which measures the distance from the centre of the heel on one foot to the centre of the heel of the opposite foot. These units were converted to m/min for walking speed and m for step amplitude to facilitate comparison with subsequent chapters. The mat was positioned in the middle section of the walkway in order to record the most stable phase of each walk, reducing the effects of acceleration and deceleration. The GAITRite system[a] is a flexible electronic walkway providing an automated means of measuring the spatial and temporal parameters of gait using a carpet embedded with sensors which detect footfalls. It has been shown to give valid and reliable data. The carpet is 457cm long with an active area of 366cm, the sampling rate is 32.2 – 38.4 Hz.

Figure 3.4. The GAITRite system; a pressure sensitive walkway which automates the collection of temporal and spatial gait data.
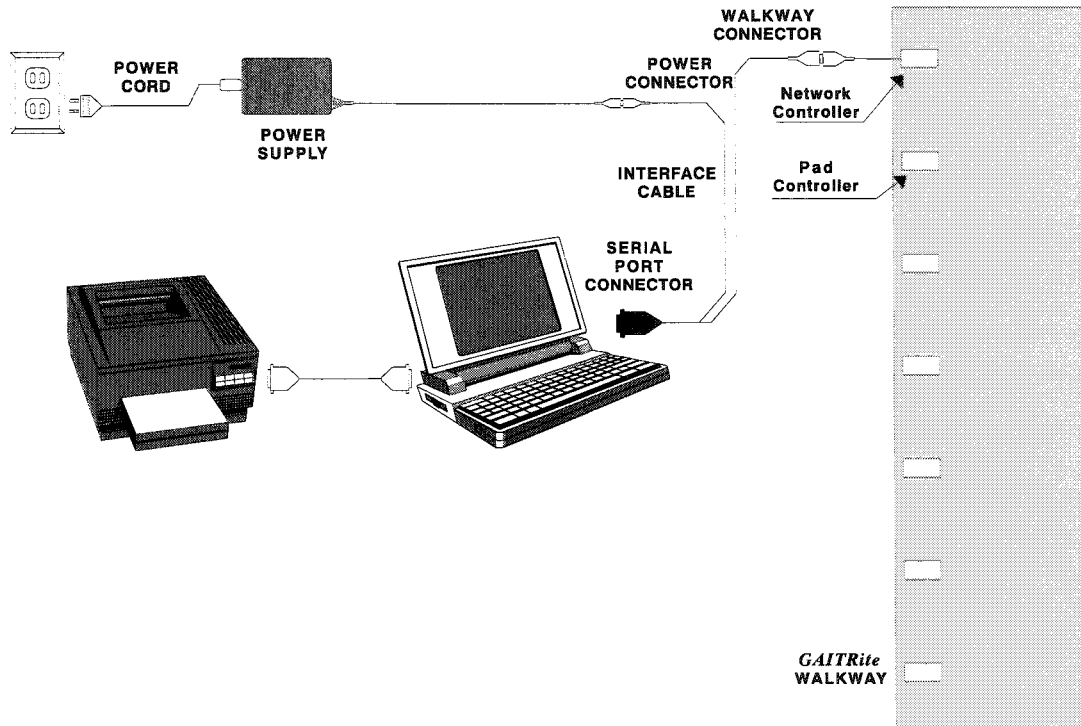
Data Analysis. Data were analysed using SPSS for Windows (Version 12)[c]. Data

were inspected for distribution using Shapiro-Wilks statistic. All data were normally

distributed therefore parametric statistics were used for analysis. A mixed design

repeated measures analysis of variance was used to compare walking speed, step

amplitude and step frequency for the effect of participant type (PD and control), cue

type (auditory; attention; combination) and task type (single and dual task).

Pair-wise comparisons with Bonferroni adjustments were used to identify significant

differences between trials. Two-tailed tests with a *P* value of 0.05 or less were

considered statistically significant.

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3.4. Results.

The primary aim of this study was to explore the feasibility of combining cue

strategies in order to modify both spatial and temporal gait parameters in people with

PD. The auditory and attentional cues alone were compared to the combination cue

in order to determine whether there was added benefit. Single and dual tasks were

used to not only examine the effect of cues on functional gait performance but also to

allow the attentional demands of each of the strategies to be compared. 27

experiments were performed in 15 PD and 12 control subjects. Each subject

completed 10 single task walking trials and 10 dual task walking trials under cued

and non-cued conditions.

Subject Characteristics.

15 people with a diagnosis of idiopathic PD, 6 men, 9 women, mean age 68.83 (3.30)

and 12 healthy older adults, 5 men, 7 women mean age 71.50 (2.58) took part in the

study (Table 3.2). PD and control subjects were matched for height ($P = 0.67$) and

sex, however a small but significant difference existed between the ages of the groups

($P = 0.045$) with the control subjects mean age being 2.67 years older. There was no

significant difference in scores on the MMSE ($P = 0.37$) with all subjects scoring

above the cut off of 24, indicating an absence of dementia. The PD group had mean

disease duration of 6.15 (3.16) years and Hoehn and Yahr ratings ranged from 2 to 3

(Table 3.2) indicating mild to moderate disease severity (Table 3.2). Ten of the PD

subjects were classified as freezers using the Freezing of Gait Questionnaire.

Table 3.2. Subject characteristics for PD (n=15) and Control (n=12) subjects. Values shown are mean and standard deviation. A *P* value of ≤ .05 was considered significant and significant differences are indicated by an *.

	PD	CONTROL	*P* VALUE
Number of subjects	15	12	
Mean Age (Mean ± SD)	68.8 (3.3)	71.5 (2.6)	0.045*
Height (cm) (Mean ± SD)	165.9 (10.9)	165.4 (8.3)	0.67
MMSE Score (Mean ± SD)	27.9 (2.17)	28.6 (1.8)	0.037
Sex (men/women)	6/9	5/7	
Disease duration (Mean ± SD)	6.5 (3.2)		
UPDRS Motor Score (Mean ± SD)	23.4 (9.2)		
Hoehn & Yahr Stage	2 – 3 subjects 2.5 – 4 subjects 3 – 8 subjects		
Freezers/non freezers	10 / 5		

Baseline (non-cued) gait performance.

During the non-cued baseline trials PD subjects walked more slowly than controls, with shorter steps and reduced step frequency in both the single (walking speed: T=4.241, $P<0.001$; step amplitude: T=3.318, $P=0.003$; step frequency: T=3.089, $P=0.005$) (Table 3.4) and dual tasks (walking speed: T=3.374, $P=0.002$; step amplitude: T=2.613, $P=0.015$; step frequency: T=2.519, $P=0.021$) (Table 3.5).

With the addition of the dual task, PD subject's non-cued step amplitude significantly reduced (T=2.224, $P=0.034$), walking speed and step frequency did not significantly change. Control subjects walked more slowly (T=3.810, $P=0.001$), with smaller steps (T=3.695, $P=0.001$) but no significant change in step frequency.

Main and interaction effects.

Table 3.3 shows main and interaction effects of cues, subjects type and task. There

was a significant main effect of subject type for walking speed (F=25.65, $P<0.001$),

step amplitude (F=29.13, $P<0.001$) and step frequency (F=4.18, $P=0.046$) with the

PD group walking consistently slower, with smaller steps and a reduced step

frequency across all conditions. A significant main effect of task type was seen for

walking speed (F=5.47, $P=0.023$) and step amplitude (F=11.49, $P=0.001$) with

subjects walking more slowly and with shorter steps in the dual task in both cued and

non-cued trials. No effect of task was observed for step frequency. There was a

significant main effect of cues for all parameters (walking speed: F=48.70, $P<0.001$;

step amplitude: F=232.60, $P<0.001$; step frequency: F=44.21, $P<0.001$), changes

with cues are described in detail in the next section. No interaction of cues*type or

cues*task existed for any of the gait variables, with PD and control subjects

responding to cues in a similar pattern in both single and dual task.

Table 3.3. Main and interaction effects of cues, subject type and task on walking
speed, step amplitude and step frequency. Shaded cell represent significant effects.

		Walking Speed	Step Amplitude	Step Frequency
Main effects	Cues	F=48.697 P<0.001	F=232.597 P<0.001	F=44.209 P<0.001
	Type	F=25.649 P<0.001	F=29.133 P<0.001	F=4.176 P=0.046
	Task	F=5.474 P=0.023	F=11.487 P=0.001	F=0.004 P=0.950
Interaction	Cues*Type	F=0.322 P=0.26	F=0.142 P=0.112	F-0.571 P=0.313
	Cues*Task	F=0.571 P=0.631	F=0.383 P=0.78	F=0.565 P=0.633

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Single task.

Table 3.4 shows the cued and non-cued mean spatiotemporal gait parameters of PD

and control subjects in the single task. Figure 3.5 shows the change with cues

compared to baseline non-cued trials.

Table 3.4. PD and control subjects mean (SD) spatiotemporal gait parameters in the
single task: cued and non-cued trials. Shaded boxes indicate significant changes
compared to the baseline non-cued trials.

	Walking speed (m/min)		Step amplitude (m)		Step frequency (steps/min)	
	PD	Control	PD	Control	PD	Control
Baseline no cue	60.66 (10.98)	76.38 (7.44)	0.58 (0.07)	0.66 (0.06)	104.6 (11.9)	115.4 (5.8)
Auditory	59.04 (10.86)	70.32 (10.68)	0.59 (0.06)	0.67 (0.07)	99.5 (12.4)	104.9 (8.8)
Attention	67.08 (12.54)	83.46 (8.46)	0.68 (0.09)	0.82 (0.08)	98.4 (13.1)	102.6 (7.2)
Combination	66.54 (13.08)	83.1 (13.14)	0.68 (0.08)	0.81 (0.08)	98.6 (14.7)	102.3 (9.4)
Final no cue	61.68 (8.46)	75.78 (7.2)	0.6 (0.07)	0.69 (0.07)	103.1 (10)	110.4 (8.2)

Walking Speed.

Both the attentional (PD: $P<0.003$; control: $P=0.034$) and the combination cue (PD:

$P=0.013$; control: $P=0.024$) resulted in a significantly increased walking speed

compared to non-cued baseline by 10-11% in PD subjects (figure 3.5.a) and 9% in

control subjects (Table 3.4). In contrast the auditory cue reduced speed by 2.4% in

PD and 8.5% in control subjects which was not significant. The difference in PD

subject's performance with each cue type can be seen in figure 3.5.a. For PD and

control subjects, there was no difference between the attention and combination cues,

however both resulted in significantly greater walking speed than the auditory cue

which caused a small decrease (PD: attention: $P<0.001$, combination: $P=0.006$;

control: attention: $P=0.001$, combination: $P<0.001$). Walking speed in the final non-

cued trial was not significantly different to that in the baseline non-cued trial,

suggesting no short term carry over effect of cues on walking speed.

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Step amplitude.

Step amplitude was also significantly increased with the attentional (PD: $P<0.001$; control: $P<0.001$) and combination cues (PD: $P<0.001$; control: $P<0.001$) (Table 3.4). PD subjects increased step amplitude by 18 and 17% respectively with the attention and combination cues (figure 3.5.b), whereas control subjects increased by 24 and 22% respectively. The auditory cue caused a small increase in step amplitude of 2.6% in PD subjects and 1.5% in control subjects; this was not significant. When comparing cueing conditions, no difference was seen between the attentional and combination cues, with both resulting in significantly greater step amplitude than the auditory cue (PD: attention: $P<0.001$, combination: $P<0.001$; control: attention: $P<0.001$, combination: $P<0.001$) (figure 3.5.b). The improvements in step amplitude were not retained in the final non-cued trial.

Step frequency.

Step frequency was significantly reduced in PD subjects by approximately 5% and in control subjects by approximately 10% with all cues in the single task (PD: auditory: $P=0.013$, attention: $P=0.042$, combination: $P=0.041$; control: auditory: $P=0.005$, attention: $P<0.001$, combination: $P=0.004$) (Table 3.4). There were no significant differences in step frequency between cue types in either PD or control subjects (figure 3.5.c). Step frequency in the final non-cued trial was not significantly different to that in the baseline non-cued trial.

Figure 3.5. Change scores in mean spatiotemporal gait parameters of PD subjects in the single task. The values represent percentage change with each cue type and in the final non-cued trial compared to baseline non-cued walking. Error bars represent standard deviation. * indicates significant changes in absolute values compared to non-cued baseline. ◘ indicates significant differences between cues.

a) Walking speed.
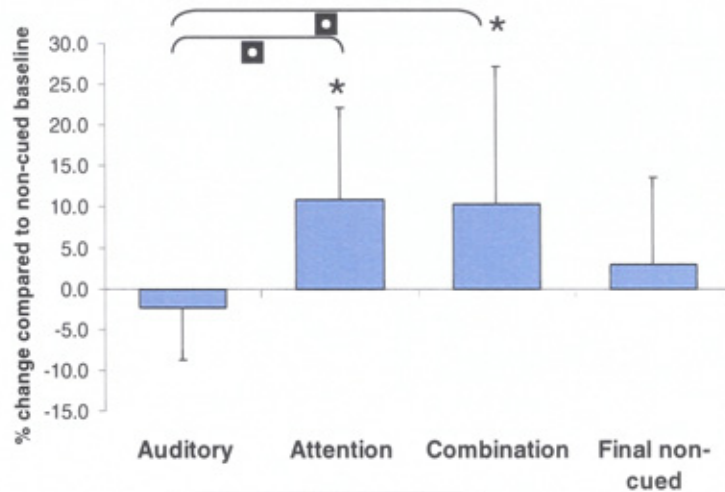
b) Step amplitude.
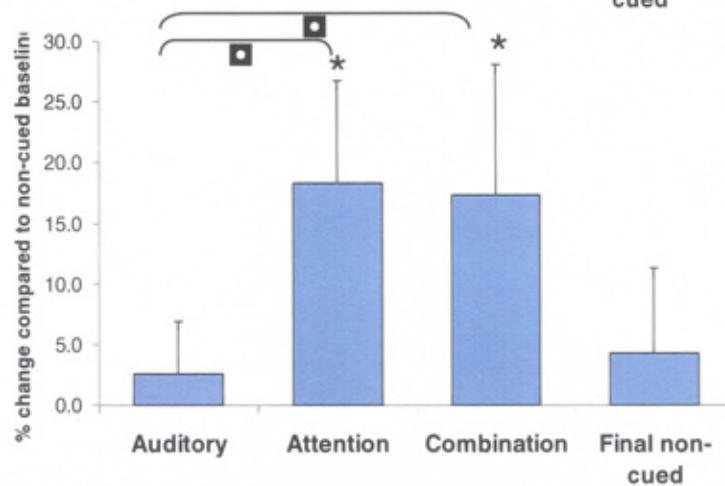
c) Step frequency.
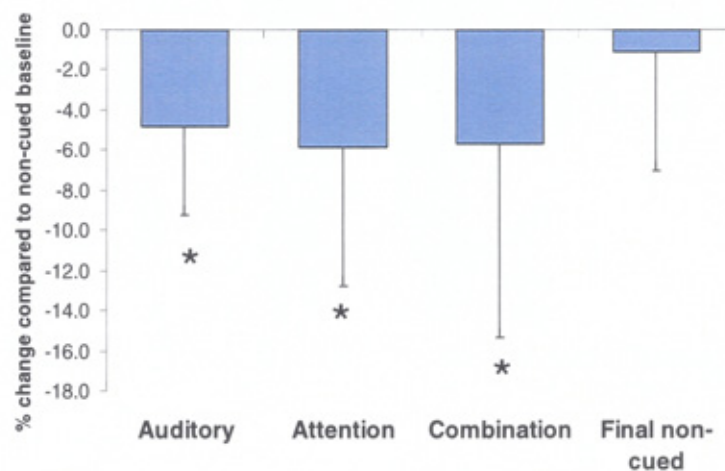
Dual task.

Table 3.5 shows the cued and non-cued mean spatiotemporal gait parameters of PD

and control subjects in the dual task. Figure 3.6. shows the change with cues

compared to baseline non-cued trials in the dual task. Similar patterns of change with

cues were observed in both PD and control subjects in the dual task compared to the

single task.

Table 3.5. PD and control subjects mean (SD) spatiotemporal gait parameters in the dual task: cued and non-cued trials. Shaded boxes indicate significant changes compared to the baseline non-cued trials.

	Walking speed (m/min)		Step amplitude (m)		Step frequency (steps/min)	
	PD	Control	PD	Control	PD	Control
Baseline no cue	55.68 (10.08)	66.48 (5.04)	0.52 (0.06)	0.58 (0.05)	106.2 (11.9)	114.6 (4.6)
Auditory	54.66 (11.7)	63.78 (7.8)	0.54 (0.06)	0.60 (0.06)	101.4 (14.1)	105.4 (7)
Attention	60.78 (12.72)	76.26 (11.4)	0.63 (0.08)	0.75 (0.09)	96.6 (14.3)	101.6 (8.9)
Combination	61.56 (12.54)	75.3 (12.72)	0.62 (0.08)	0.75 (0.08)	100.4 (14.5)	100.2 (10.3)
Final no cue	57.78 (10.02)	69.42 (5.7)	0.56 (0.07)	0.62 (0.06)	103.6 (12.4)	111.6 (7.5)

Walking speed.

In the dual task condition significant increases in walking speed of 9.1% in PD

subjects and 14.7% in control subjects were observed with the attentional cue (PD:

P=0.037; control: P=0.018) and an increase of 10.7% in PD subjects and 13.3% in

controls with the combination cue (PD: P=0.028; control P=0.035) (Table 3.5). The

auditory cue caused a small reduction in walking speed of 1.8% in PD and 4.1% in

control subjects, this was not significant. Comparing the effect on walking speed of

the three cue types, no difference was seen between the attention and combination

cues in either PD or control subjects (figure 3.6.a). Walking speed with the auditory

cue was significantly reduced compared with the attention (PD: P=0.002; control:

P=0.001) and combination cues (PD: P<0.001; control: P=0.001). No carry over of

improvement in walking speed was observed in the final non-cued trial.

Step amplitude.

Step amplitude in the dual task condition was significantly increased with the
attention cue by 20.3% in PD subjects ($P<0.001$) and 29.3% in control subjects
(P<0.001). With the combination cue, PD subjects increased step amplitude by 17.5%
($P<0.001$) and controls by 29.3% (P<0.001) (table 3.5). The auditory cue caused a
small increase in step amplitude of 2.8% in PD subjects and 3.4% in control subjects
which was not significant. Comparing cue types showed no significant difference
between the attention and combination cues, however they both resulted in step
amplitude significantly greater than with the auditory cue (PD: $P<0.001$; control:
P<0.001) and combination cues (PD: $P<0.001$; control: P<0.001) (figure 3.6.b). Step
amplitude in the final non-cued trial remained significantly increased ($P=0.038$),
suggesting some short term carry over of cueing effect.

Step frequency.

Step frequency was significantly reduced with all cues in PD subjects by around 5%
with the auditory ($P=0.018$) and combination ($P=0.009$) cues, and by 9.3% with the
attentional cue ($P<0.001$) (figure 3.6.c). Control subjects reduced step frequency by
8% with the auditory cue ($P=0.002$), 11.3% with the attentional cue ($P=0.003$) and
12.6% with the combination cue ($P=0.003$) (Table 3.5). There was a significant
difference in step frequency with the auditory and attention cues in PD ($P=0.042$) and
control subjects (P=0.007). No difference was found between the baseline and final
non-cued trials.

Figure 3.6. Change scores in mean spatiotemporal gait parameters of PD subjects in the dual task. The values represent percentage change with each cue type and in the final non-cued trial compared to baseline non-cued walking. Error bars represent standard deviation. * indicates significant changes in absolute values compared to non-cued baseline. ▫ indicates significant differences between cue types.

a) Walking speed.
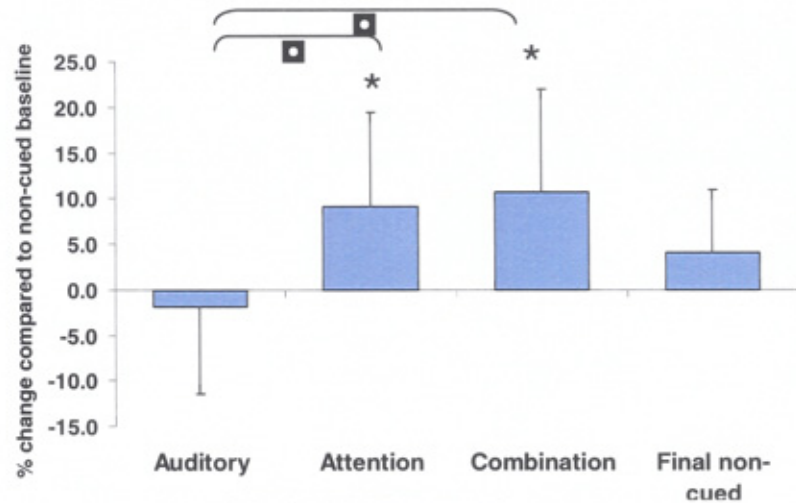
b) Step amplitude.
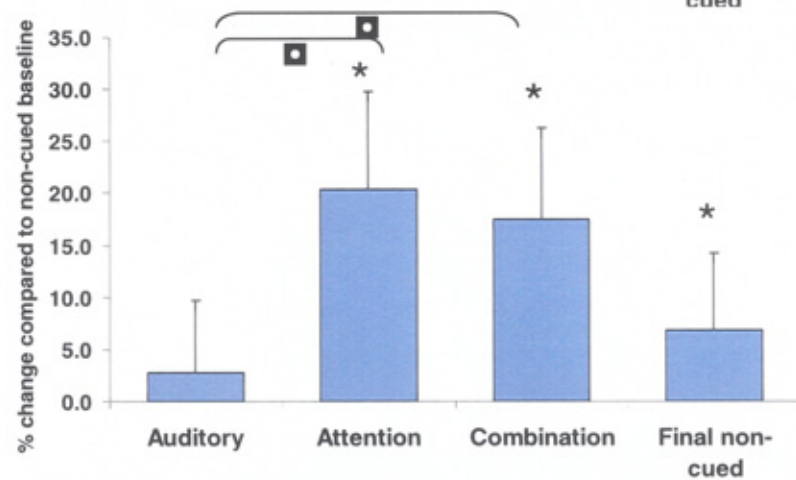
c) Step frequency.
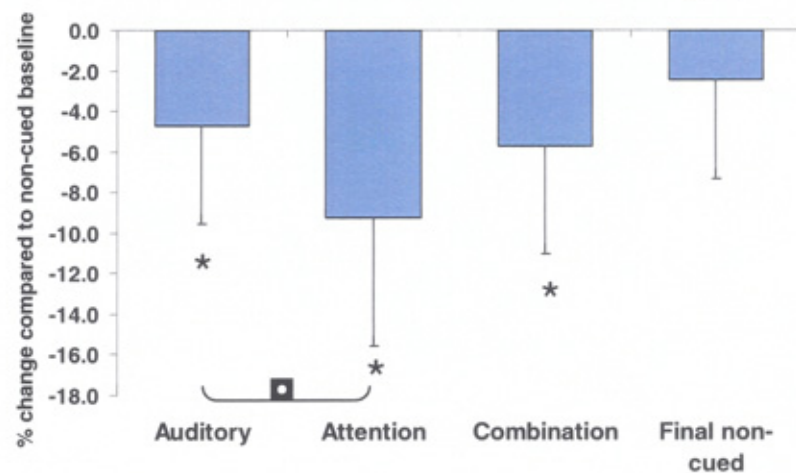
Chapter 3

Do cues normalise gait to control levels?

Post hoc tests were carried out to compare cued gait in PD subjects with non cued

gait in control subjects to explore whether cues were able to reduce the impact of PD

and return gait to control values. PD and control subjects showed significant

differences in all gait parameters during the non-cued baseline trial.

Single task.

Walking speed in PD subjects remained significantly reduced compared to control's

non-cued baseline with all cues (auditory: $P<0.001$; attention: $P=0.025$; combination:

$P=0.028$) (figure 3.7a). However PD step amplitude with the attention and

combination cues was no longer significantly different compared to control non-cued

baseline and was therefore normalised (attention: $P=0.566$; combination: $P=0.707$)

(figure 3.7.b) but remained significantly reduced with the auditory cue ($P=0.005$).

Step frequency remained significantly reduced in the PD group with all cue types

(auditory: $P<0.001$; attention: $P<0.001$; combination: $P=0.001$) (figure 3.7.c).

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Figure 3.7. Comparison of cued gait in PD subjects with non-cued gait in control subjects in the single task. The horizontal black line represents control subjects mean non-cued gait performance. The blue bars represent PD subjects mean gait performance in the non-cued baseline and with each cue type, expressed as a percentage of control subject's non-cued baseline.

a) Walking speed

b) Step amplitude

c) Step frequency
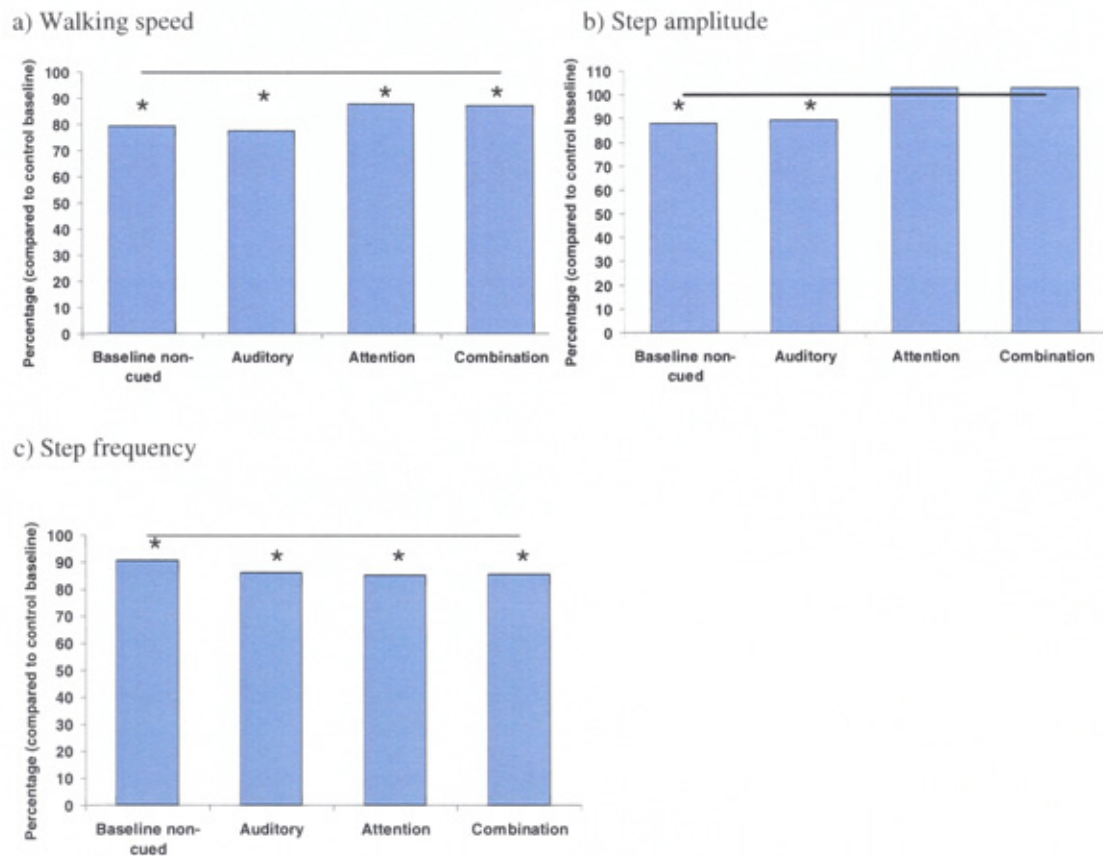
Dual task

PD subjects walking speed with the attention (*P*=0.13) and combination (*P*=0.183) cues was no longer significantly different to control non-cued gait in the dual task condition, but remained significantly reduced with the auditory cue (P=0.002) (figure 3.8.a). Step amplitude was normalised with all cue types (auditory: P=0.062; attention: *P*=0.063; combination: *P*=0.175) (figure 3.8.b). Step frequency remained

significantly reduced in the PD group with all cue types (auditory: P=0.003; attention:

$P<0.001$; combination: $P=0.002$) (figure 3.8.c).

Figure 3.8. Comparison of cued gait in PD subjects with non-cued gait in control subjects in the dual task. The horizontal black line represents control subjects mean non-cued gait performance (expressed as 100%). The blue bars represent PD subjects mean gait performance in the non-cued baseline and with each cue type, expressed as a percentage of control subject's non-cued baseline.

a) Walking speed

b) Step amplitude
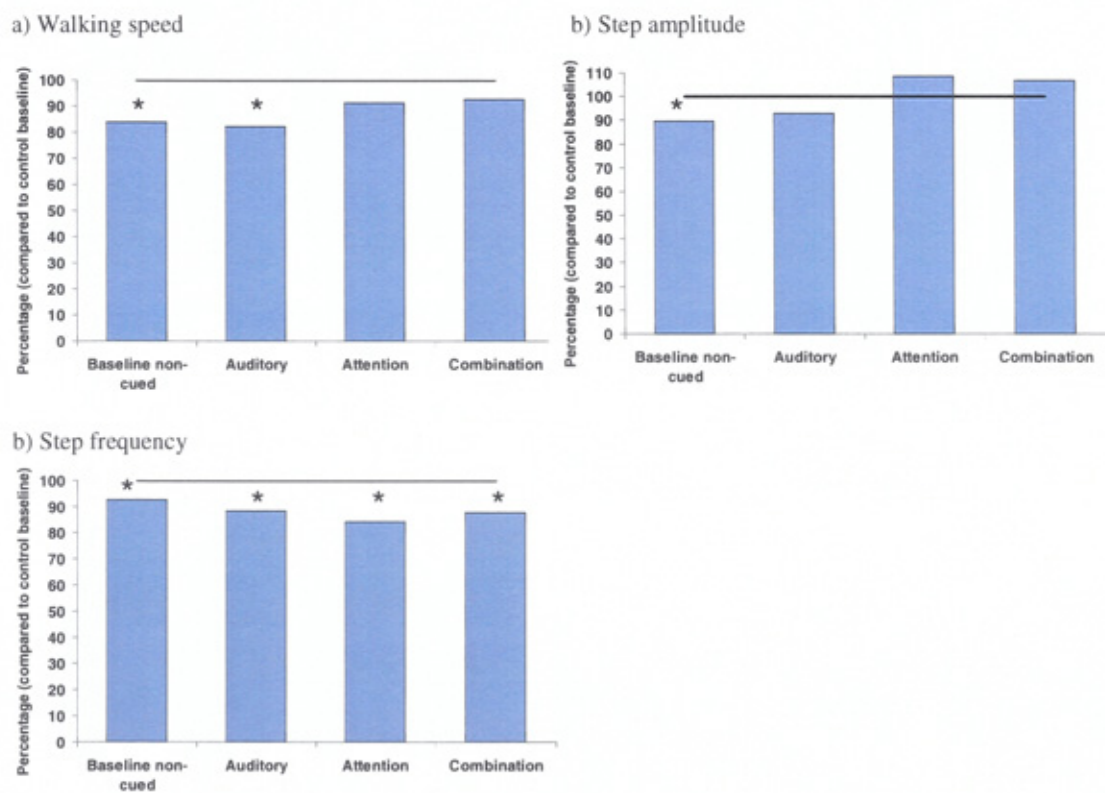
b) Step frequency

Chapter 3

Summary of findings

- During the non-cued baseline trials, PD subjects walked with reduced speed, step amplitude and step frequency in both the single and dual tasks compared to controls.

- PD and control subjects walked with reduced speed and step amplitude, but not step frequency during a dual task in both cued and non-cued trials.

- Walking speed and step amplitude increased while step frequency decreased with the attentional and combination cues for single and dual task conditions. No difference in performance was observed with these cues in PD or control subjects.

- The auditory cue alone significantly reduced step frequency but did not affect walking speed or step amplitude in PD and control subjects in the single or dual task.

- The response to cues was the same in both single and dual tasks.

- PD and control subjects responded in a similar pattern to cues.

- In the single task, PD step amplitude was normalised to that of controls with the attentional and combination cues.

- In the dual task, both walking speed and step amplitude of PD subjects were normalised with the attention and combination cues, step amplitude was normalised with the auditory cue.

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3.5. Discussion.

During non-cued walking, PD subjects walked with reduced speed, step amplitude and step frequency in both the single and dual tasks compared to controls, in agreement with others (O'Sullivan *et al.*, 1998; Mitoma *et al.*, 2000; Nieuwboer *et al.*, 2001).

The primary aim of this study was to extend the findings of previous work to determine whether people with PD were able to effectively combine a rhythmical auditory cue with an attentional strategy in order to improve gait. Our results show that subjects successfully combined the cue types, modifying step amplitude and frequency, and this was equally effective in normalising walking speed and step amplitude but was not superior to the attentional strategy alone. Studies combining cue types are rare, one study investigated the effect of combining a rhythmical auditory cue at 25% above preferred stepping frequency with a visual spatial cue (stripes on the floor) and compared this to each of the cue types in isolation (Suteerawattananon et al., 2004). The visual cue alone increased step amplitude but had no effect on speed as step frequency was reduced, in contrast the auditory cue increased speed by increasing step frequency but had no impact on step length. The combination of the visual and auditory cues resulted in a similar increase in speed to the auditory cue alone via its effect on step frequency, but despite the spatial component of the cue, no increase was seen in step amplitude, and there was no additional benefit over the auditory cue alone of combining cue types. Subjects were unable to utilise the spatial information provided by the visual cue at the same time as

responding to the temporal information of the auditory cue. This may have been due to the attentional demand of using two different external cue types together resulting in gait interference, subjects were unable to attend to two sources of external information and make the appropriate adjustments to respond to both, it seems that in the absence of any information to prioritise one over the other they chose to attend to the auditory tone. Another study (Arias & Cudeiro, 2008) examined the effect of combining two rhythmical cues, providing the same temporal information simultaneously, one via an auditory tone and the other via a visual flash of light. No benefit was seen in the combination of cues with the effects of the auditory alone and the combination of the auditory and visual cues being equally effective.

In the present study the combination of an external and attentional strategy did not provide additional benefit over the cues used in isolation. In contrast to the combination of an auditory and visuo-spatial cue (Suteerawattananon et al., 2004) subjects were able to maintain the increase in step amplitude seen with the attentional strategy while responding to the auditory cue. This suggests benefit when having to attend to only one source of external information.

As expected, the attentional strategy caused significant improvements in walking speed and step amplitude. This supports previous findings which have shown that people with Parkinson's disease are able to effectively modify their gait pattern during a single task when given appropriate instruction to do so (Morris *et al.*, 1994; 1996; Behrman, Teitelbaum & Cauraugh, 1998; Canning, 2005). Interestingly,

although the attentional strategy provided no information about timing of steps,

subjects reduced step frequency when using this strategy, this may have been

necessary to allow the larger step and may explain why amplitude but not speed was

normalised to that of controls in the single task. This does not support the findings of

Morris (Morris et al., 1996) who proposed that by directing attention to and

improving the spatial deficit in PD gait, all gait parameters were normalised.

In healthy adults, there is a linear relationship in the increase in step amplitude and

step frequency in order to achieve an increase in speed (Winter, 1991). This

relationship was explored in Parkinsonian gait by Morris (Morris et al., 1998) who

found that the normal linear relationship is still present but on a reduced scale and is

lost at a lower step frequency and step amplitude. The authors concluded that

disturbance in movement timing is not the cause of the gait deficit seen in PD,

however in order to explore the relationship between stride length and cadence,

subjects were paced with a metronome and therefore the generalisation to non-cued

walking is limited.

In the present study the rhythmical auditory cue alone caused a small increase in step

amplitude and a reduction in step frequency with an overall reduction in walking

speed, which did not reach significance. Previous studies have shown increases in

step amplitude of PD subjects in single task walking with rhythmical auditory cues at

frequencies ranging from 10% below to 10% above preferred stepping frequency

(McIntosh et al., 1997; Willems et al., 2006; Hausdorff et al., 2007). In contrast,

others have shown no effect (Morris *et al.*, 1994; Howe *et al.*, 2003; Rochester *et al.*, 2005; Rochester *et al.*, 2007). Similarly, varying effects of rhythmical cues on walking speed are reported with some studies finding a positive effect (McIntosh *et al.*, 1997; Howe *et al.*, 2003; Suteerawattananon *et al.*, 2004; Willems *et al.*, 2006; Hausdorff *et al.*, 2007) while others found no effect (Morris *et al.*, 1994; Rochester *et al.*, 2005; Rochester *et al.*, 2007). It is difficult to account for the difference in response between studies but factors such as the instructions given with the cue and the disease stage of the sample may offer some explanation.

As the current study was establishing the feasibility of combining cues a conservative cueing frequency of 10% below preferred stepping frequency was chosen. This choice was made to ensure subjects were able to safely synchronise with the cue while performing a dual task and also while increasing step amplitude in the combination cue.

The second question of this study was to evaluate whether the combination cue was more effective than the auditory or attentional cues alone. The combination of cues did not provide additional benefit over the use of the attentional strategy alone. Although the effect of the combination cue was not greater than the attentional strategy, the current study did not address the impact of cue frequency on the combination cue. The auditory and combination cues resulted in a similar reduction in step frequency as seen with the attentional cue; however this was in response to the information provided by the rhythmical cue. If subjects were able to maintain the

increased step amplitude at a higher step frequency, the overall effect would be a greater increase in walking speed. Previous cueing studies which have specifically examined the impact of cue frequency have shown greater changes in walking speed at cueing frequencies above preferred stepping frequency. Further work is needed to establish whether subjects are able to maintain increased step amplitude at increased step frequency when given instruction to do so, this will be addressed in chapter 5.

The final question of the study was to determine whether the cues were effective during a dual task, and if the response to the different cue strategies was able to offer any information as to their attentional cost. A range of secondary tasks have been used in dual task studies which include secondary cognitive and motor tasks (Camicioli *et al.*, 1998; Bond & Morris, 2000; Bloem *et al.*, 2001; O'Shea, Morris & Iansek, 2002; Rochester *et al.*, 2004; Galletly & Brauer, 2005; Yogev *et al.*, 2005), resulting in gait interference of both PD and healthy older subjects. The task in this study was chosen to be functional and familiar to the subjects and therefore have greater ecological validity. O'Shea (O'Shea, Morris & Iansek, 2002) suggested there is a critical level of task complexity which must be met for interference to occur. The relatively simple dual motor task used in our study resulted in a significant deterioration in walking speed and step amplitude of both PD and control subjects during the non-cued baseline trials and can therefore be argued to have reached a critical level of difficulty. This also agrees with previous studies reporting an interference effect on gait of a secondary motor task (Bond & Morris, 2000; Bloem *et al.*, 2001; O'Shea, Morris & Iansek, 2002; Rochester *et al.*, 2004).

Cues improved gait of PD subjects in the dual task, with walking speed and step amplitude being normalised with the attention and combination cues, while the auditory cue normalised step amplitude only. The lack of an interaction effect of cues by task demonstrates a similar pattern of response in the single and dual tasks. In addition although performance of the secondary task was not formally measured, none of the subjects in the study dropped the tray or spilt water in the dual task. This suggests that subjects were able to integrate the cues into a functional task and the cues did not cause increased gait interference. It was important, particularly for the combination cue, to ensure that the strategies did not act as an additional task rather than facilitating gait which would be the case if they required large amount of attentional resource.

Dual task interference has been shown to improve with rhythmical auditory cues (delivered at preferred stepping frequency) in a previous study, suggesting potential for cues to reduce the attentional cost of walking (Rochester *et al.*, 2005; Rochester *et al.*, 2007). Galletly and Brauer (Galletly & Brauer, 2005) also emphasised the importance of establishing the attentional cost of cueing strategies, particularly when applying cues as a therapeutic intervention in a functional situation. They found that PD subjects were able to use visual spatial cues to improve gait in a dual task, and proposed that because of this cues were not acting to focus attention as previously suggested as the authors felt any impact on attention would increase dual task interference. In contrast, Rochester (Rochester *et al.*, 2005; Rochester *et al.*, 2007)

argues that cues act to reduce dual task interference by removing the need to prioritise and monitor movement.

The improvement in single and dual task gait performance with cues provides behavioural evidence which supports findings from brain imaging studies using upper limb tasks. Externally triggered movements produce significantly less activation of the frontal cortex than self initiated movements which indicated a reduced role of attention and executive functions (Jenkins *et al.*, 2000; Weeks *et al.*, 2001; Debaere *et al.*, 2003). In addition, the SMA is less active when movement is externally cued as it's role in preparation of movement is less necessary (Jenkins *et al.*, 2000; Weeks *et al.*, 2001; Debaere *et al.*, 2003). Therefore there is greater neural activity involved in internally generated movement whereas externally cued movement are more reactive with motor preparation being minimised,(Weeks et al., 2001) and may therefore result in reduced attentional cost.

Interestingly the attentional strategy significantly improved walking speed and step amplitude, normalising gait in the PD group in the dual task. Previous studies have reported reduced effectiveness of attentional strategies during dual tasks due to requirements for constant vigilance (Morris et al., 1996). Canning (Canning, 2005) found that when subjects were asked to direct attention to a specific aspect of gait, attentional strategies were effective during a similar tray carrying task to the present study. However, importantly the measurement of gait by Morris and colleagues was covert and the subjects perceived no need to remain vigilant to the attentional strategy

which perhaps is more reflective of a functional situation. In the present study
subjects were aware that their gait was being measured which may have made them
more vigilant in using the strategy, making it more likely that they continued to use
the attentional strategy during the dual task.

The rhythmical auditory cue improved step amplitude during the dual task, but this
was not significant. This is in contrast to previous studies where significant increases
in step amplitude were observed with rhythmical auditory cues delivered at preferred
stepping frequency during dual and multi-task performance in the home (Canning,
2005; Rochester *et al.*, 2005; Nieuwboer *et al.*, 2007; Rochester *et al.*, 2007).
However as previously discussed the cueing frequency in the present study was 10%
below preferred stepping frequency, therefore despite a small increase in step
amplitude, the overall effect was a small reduction in speed.

Interestingly PD subjects were less accurate than control subjects in synchronising
with the cue. In both single and dual tasks, mean step frequency of PD subjects was
reduced by around 5% compared to non-cued walking with the auditory and
combination cues, while control subjects reduced step frequency by around 10%,
reflecting the cue frequency. Synchronisation was not made worse when asked to take
a large step in time to the beat (combination cue) compared to the auditory cue alone,
again suggesting that subjects did not find the combination cue too demanding. In
contrast, when using the attentional cue subjects also significantly reduced step
frequency. This was a spontaneous response to increasing step amplitude as no

instruction was given to alter the step frequency. Unlike the auditory and combination

cues which showed a stable effect on step frequency in single and dual tasks, the

reduction in step frequency with the attentional cue was greater in the dual task in

PD, but not controls subjects. This may be because subjects found it more difficult to

maintain large steps in the dual task without the prompt from the auditory cue, and

the reduction in step frequency is a compensation for this.

It is possible that executive dysfunction may effect cue use during dual tasks. Tthe

combination cue may provide a prompt which the person simply responds to by

directing attention to gait without the need for constant vigilance. This method may

be a practical alternative for those patients who find attentional strategies difficult to

use in a functional setting because of distractions in the environment or problems

with executive function.

Limitations of the study

This exploratory study involved a small sample of PD and control subjects which

limits the ability to generalise to the wider population. There was a significant

difference in the ages of the PD and control groups with the controls being around 2

years older which may reduce the differences between the groups as walking speed

and step amplitude are known to reduce with normal ageing as does dual task ability

(Woollacott & Shumway-Cook, 2002). The small number of people with PD also

prevented further sub-group analysis, for example to discriminate freezers from non-

freezers although no subjects experienced freezing during the phase of the walk which was analysed this may still be a factor which alters response to cues. The testing environment of the laboratory also reduces transfer of these findings; chapter 5 will describe a larger study which addressed this by testing subjects in their own home. A more complex dual task would have allowed us to more fully evaluate the attentional cost of the cueing strategies as the task used does not necessarily transfer to more complex tasks such as crossing a busy street. All subjects were tested in the 'on' phase of the medication and little is known about the effects of cues on gait in the 'off' medication phase, this will be addressed in chapter 5 where subjects are tested both 'on' and 'off' medication in order to explore the impact of dopaminergic medication on cueing effect.

Clinical Application and Conclusions.

This study has extended the findings of previous work in demonstrating that an attentional strategy and a combination cue strategy were equally effective in improving walking speed and step amplitude during both single and dual tasks. The combination cue strategy appears to offer an effective and practical alternative for gait deficits in Parkinson's disease in addition to rhythmical auditory cues or attentional strategies alone, and perhaps has potential for situations of increased attentional demand or where problems of executive dysfunction exist. This chapter has dealt only with mean spatiotemporal gait parameters; the next chapter will examine the effect on gait variability of the same cueing strategies. Variability is

thought to reflect automatic gait control and will be used as a more sensitive measure

of the attentional cost of the cueing strategies.

Chapter 3

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Suppliers.

a. CIR Systems Inc, 60 Garlor Dr, Havertown, PA 10983, USA.
b. TEMEC Instruments Inc, Spekhofstraat 2, 6466 LZ Kerkrade, The Netherlands.
c. Version 12; SPSS Inc, 233 S Wacker Dr, 11th Fl, Chigago, IL 60606, USA.

Chapter 4

The effect of cues on gait variability – reducing the attentional cost of walking in people with Parkinson's disease.

4.1. Abstract.

PD subjects have increased gait variability, reflecting disrupted automatic gait control and greater attentional demand during walking. Cues have been shown to improve the spatiotemporal gait parameters, but the effect on gait variability remains unclear. This study aimed to investigate the attentional cost of three cueing strategies by examining their effect on gait variability in single and dual task walking. 14 people with Parkinson's disease and 12 age matched control subjects were studied under single and dual walking tasks in the Human Movement Analysis Laboratory, Northumbria University, UK. PD subjects were tested on medication. Three cueing strategies were compared: a rhythmical auditory cue (walking in time to a metronome beat delivered at 10% below preferred stepping frequency), an attentional strategy (concentrate on taking big steps) and a combination cue (asked to take big steps in time to a metronome beat). The primary outcome measures were; coefficient of variation of step time and double limb support time. Step time variability of PD subjects reduced with all cues in the single and dual task and this was significant with the combination cue. DLS time variability was reduced in PD subjects with the attention and combination cues in the single task only. In contrast gait variability was not significantly altered in control subjects with cues. The reduction in PD subjects gait variability with cues suggests they may reduce the attentional cost of walking. The

results also highlight the disassociation of mean spatiotemporal gait parameters and

measures of gait variability.

Chapter 4

4.2 Introduction.

As discussed in chapter 2 (section 2.2) people with PD have increased variability of

both spatial and temporal gait parameters compared to age matched controls, thought

to be as a result of reduced automaticity which results in increased cognitive control

and therefore greater attentional cost of gait control (Blin, Ferrandez & Serratrice,

1990; Hausdorff *et al.*, 1998; Hausdorff *et al.*, 2003; Schaafsma *et al.*, 2003; Frankel-

Toledo *et al.*, 2005; Yogev *et al.*, 2005), see chapter 2 for a more detailed discussion.

Variability of step or stride time is said to reflect a disturbance of the gait patterning

mechanism whereas variability in the support phases of the gait cycle (e.g. stance

time and double limb support time) has been attributed to dynamic balance

mechanisms (Gabell & Nayak, 1984).

Dual tasks are difficult for people with PD and increase gait variability (Hausdorff *et

al.*, 2003; Yogev *et al.*, 2005). In addition, people with executive dysfunction, of

which attention is a component, are shown to have increased gait variability

(Sheridan *et al.*, 2003; Hausdorff *et al.*, 2005; Springer *et al.*, 2006; Beauchet *et al.*,

2007). It appears that the added demands of dual or multi tasks have a destabilising

effect on gait in those people who rely on more cortical means of motor control, and

these same populations are more likely to score poorly on tests of executive function

(Sheridan *et al.*, 2003; Hausdorff *et al.*, 2005; Springer *et al.*, 2006; Beauchet *et al.*,

2007).

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As discussed in previous chapters, cues improve spatiotemporal gait parameters in

people with PD. It may be assumed that this improvement would translate into

reduced gait variability; however there is a lack of studies examining the impact of

cues on gait variability. In addition variability measures often respond differently to

mean parameters such as walking speed and step length, for example in response to

dual tasks or dopaminergic medication (Blin, Ferrandez & Serratrice, 1990;

Hausdorff *et al.*, 1998; Schaafsma *et al.*, 2003; Frankel-Toledo *et al.*, 2005). Studies

of healthy adults have shown a U shaped relationship between speed and variability,

with variability being least at preferred walking speed and increasing at speeds above

and below. Danion (Danion et al., 2003) showed however that the relationship was

more complex with specific contributions of both step length and step frequency.

A recent study examined the influence of an external rhythmical cue on gait

variability of PD subjects during single task walking (Hausdorff et al., 2007). Results

showed that at preferred stepping frequency, the cue had no effect on variability, but

when increased to 10% above preferred frequency, variability of stride and swing

time variability were improved (Hausdorff et al., 2007). A previous study showed

that walking in time to a rhythmical auditory cue set at 20% below preferred stepping

frequency increased stride time variability of PD subjects (Ebersbach et al., 1999).

Clearly the frequency of the cue is important in determining effect on gait variability,

and it may be that other aspects of cue delivery could be optimised in order to

improve not only mean spatiotemporal gait parameters but also gait variability.

Visual cues in the form of stripes on the floor reduce stride length variability

suggesting some specificity of effect to the parameter at which the cue is targeted (Lewis, Byblow & Walt, 2000).

As explored in the previous chapter, different modalities of cue are used to target different parameters of gait. All cues can be argued to utilise attention in some way as they are associated with a specific instruction, however depending on the type of cue the response to the instruction is internally generated (as with the attentional cue) or externally driven (as with rhythmical auditory cues). The attentional cost of internally generated cues which rely on the person to prioritise responding to the cue and maintain this while walking may be greater than that of external cues where the presence of the cue itself removes the need to allocate attention. Due to the different information provided by these different cueing strategies and their potentially different attentional costs it is important to evaluate their impact on gait variability, particularly when considering the link between increased variability and falls risk (Maki, 1997; Hausdorff *et al.*, 2001; Hausdorff, Rios & Edelberg, 2001; Schaafsma *et al.*, 2003; Hausdorff *et al.*, 2004).

Previous work suggested that external cues may be less attentionally demanding than internally generated strategies and are effective during dual tasks (Rochester *et al.*, 2005; Rochester *et al.*, 2007). Attentional strategies have also been shown to be difficult to use during dual tasks (Morris et al., 1996). This study aimed to investigate the difference between internally generated cues and externally delivered cues on gait variability. An external rhythmical cue, an attentional strategy and a

combination of the two were compared and cues were tested under single and dual task conditions in order to test the effects of increased attentional demands on cue use. The previous chapter examined the spatiotemporal gait responses to the three cue types and found that both the attentional and combination cues were effective in improving walking speed and step amplitude, this study sought to investigate whether this was at the cost of gait stability.

No added benefit was seen in the previous chapter of combining the attentional strategy of focussing on increasing step size with a rhythmical auditory cue. Gait variability has been shown to be a more sensitive gait parameter and may reveal differences in these cueing strategies not seen when examining mean spatiotemporal parameters alone. By controlling both temporal and spatial gait parameters, the available motor responses to the task of walking may be reduced and therefore variability may improve. In addition the presence of the external cue may reduce attentional cost which is associated with measures of variability.

The following research questions were addressed; firstly, is there a difference between cue types in their effect on different aspects of gait variability and is this response different in PD and healthy subjects? Secondly do cues reduce gait variability under dual task conditions? Finally, is there any short term carry over of the effect of cues when they are removed?

Chapter 4

4.2. Methods.

Subjects.

Data presented in the current chapter was collected at the same time as the mean

spatiotemporal data presented in chapter 3 using the same sample and methods. Due

to recording problem, individual footfall data of one PD subject was not available and

therefore this subject could not be included in the gait variability analysis. Refer to

chapter 3 for inclusion criteria. A detailed description of the experimental protocol is

presented in chapter 3.

Primary outcome measures.

Step time variability and double limb support (DLS) time variability were recorded

using the GAITRite mat[a]. The co-efficient of variation was calculated from the

individual footfall data. For each trial subjects walked a distance of 8m over a

GAITRite mat[a] which recorded step time (s) and double limb support time (s) in

addition to the mean spatiotemporal parameters presented in the previous chapter.

Data Analysis.

Data were analysed using SPSS for Windows (Version 12)[b]. Data were inspected for

distribution using Shapiro-Wilks statistic and all were normally distributed.

For each subject, repetitions of trials using the same cue type were pooled in order to

increase the number of steps used to calculate variability. The number of steps used to

calculate the coefficient of variability (CV) for step time and double limb support

time ranged from 5 to 20;

120

$$CV = 100*standard\ deviation/mean$$

A mixed design repeated measures analysis of variance was used to compare the

effect of subject type (PD and control), task type (single and dual) and cue type

(auditory; attention; combination). Two-tailed tests with a P value of 0.05 or less

were considered statistically significant for main effects and Bonferroni adjustments

were used to correct for multiple comparisons in post hoc between trials pair-wise

comparisons.

Chapter 4

4.3. Results.

The primary aim of this study was to explore the impact of different cueing strategies on gait variability in people with PD and healthy controls. Single and dual tasks were used to not only examine the effect of cues on gait performance but also to allow the attentional demands of externally and internally generated cueing strategies to be compared. 26 experiments were performed in 14 PD and 12 control subjects. Each subject completed 10 single task walking trials and 10 dual task walking trials under cued and non-cued conditions.

Subject Characteristics.

14 people with idiopathic PD, 5 men, 9 women, mean age 69.3 (3.4) years and a comparison group of 12 age matched healthy subjects mean age 71.5 (2.6) years were studied (Table 4.1). No differences were found in age and height between PD and control subjects with a P value of $\leq .05$ being considered significant. MMSE scores did not differ between groups and all subjects scored above 24 indicating the absence of dementia. PD subjects had a mean disease duration of 6.6 (3.3) years and a median Hoehn and Yahr rating of 3 indicating mild to moderate disease.

Table 4.1. Subject characteristics for PD (n=14) and Control (n=12) groups. Values shown are mean and standard deviation unless otherwise stated. Hoehn & Yahr and UPDRS scores were measured when subjects were ON medication.

	PD	Control	P value
Number of subjects	14	12	
Age (years)	69.29 (3.36)	71.50 (2.58)	0.075
Sex (men/women)	5 men/9 women	5 men/7women	
Height (cm)	165.57 (11.27)	165.42 (8.33)	0.969
MMSE Score	27.71 (2.16)	28.58 (1.83)	0.285
Hoehn and Yahr (median)	2x2, 4x2.5, 8x3 (3)		
Disease duration	6.64 (3.25)		
UPDRS Motor Score	22.86 (9.26)		
Freezers/non freezers	9 / 5		

Baseline (non-cued) gait performance.

Single Task: Step time variability (T=3.275, P=0.003) and DLS time variability (T=2.331, P=0.028) were significantly higher in PD subjects compared to control subjects in the non-cued single task trials (Table 4.2).

Dual Task: Step time variability (T=2.872, P= 0.008) was significantly higher in the PD group in the non-cued dual task trials but there was no longer a significant difference in DLS time variability between PD and control subjects (Table 4.2).

Step time variability increased significantly during non-cued walking in PD (T=2.42, P=0.023) and control subjects (T=2.485, P=0.021) in the dual task compared to the single task. In contrast there was no significant difference in either group for DLS time variability between the single and dual tasks during non-cued walking at baseline.

Table 4.2. Comparison of PD and control subjects at baseline (non-cued walking) Shaded boxed indicate significant differences between groups.

		PD Mean (SD)	Control Mean (SD)	PD vs Control P value
Single Task	Step time CV (%)	5.86 (1.7)	3.97 (1.17)	0.003
	DLS time CV (%)	11.46 (1.61)	9.96 (1.68)	0.028
Dual Task	Step time CV (%)	6.34 (1.25)	5.07 (1)	0.008
	DLS time CV (%)	11.75 (2.24)	10.74 (1.89)	0.231

Main and interaction effects.

A significant main effect of cues was seen for both step time variability (F=4.299, P=0.005) and DLS time variability (F=6.53, P<0.001) with interactions of cues*subject type for both variables (step time variability: F=3.638, P=0.011; DLS time variability: F=3.513, P=0.016) (Table 4.3). PD subjects tended to show a reduction in variability with cues whereas controls subjects showed little effect but tended to increase step time variability. There was no interaction of cues*task type with subjects responding similarly to cues in both the single and dual tasks. DLS time variability showed significant main effects of subject type (F=6.019, P=0.018) and task type (F=5.007, P=0.03) with variability being greater in PD subjects compared to controls in both cued and non-cued trials and in dual compared to single task trials.

Table 4.3. Main and interaction effects of cues, subject type and task on gait variability. Shaded cell represent significant effects

		Step time CV	DLS time CV
Main effects	Cues	F=4.299 P=0.005	F=6.53 P<0.001
	Type	F=1.705 P=0.198	F=6.019 P=0.018
	Task	F=1.589 P=0.213	F=5.007 P=0.03
Interactions	Cues*Type	F=3.638 P=0.011	F=3.513 P=0.016
	Cues*Task	F=1.395 P=0.244	F=1.163 P=0.327
	Cues*Type*Task	F=0.825 P=0.492	F=0.688 P=0.565
	Type*Task	F=1.044 P=0.312	F=0.139 P=0.711

Effect of cues during the single task.

Table 4.4 describes step time and DLS time variability of PD and control subjects in

cued and non-cued trials in the single task.

Table 4.4. Gait variability of PD (n=14) and control (n=12) subjects in the single task: cued and non-cued trials. Shaded boxes indicate significant changes compared to non-cued baseline with the direction of change shown with arrows.

	PD		Control	
	Step time CV (%) Mean (SD)	DLS time CV (%) Mean (SD)	Step time CV (%) Mean (SD)	DLS time CV (%) Mean (SD)
Baseline non-cued	5.86 (1.7)	11.46 (1.61)	3.97 (1.17)	9.96 (1.68)
Auditory	5.08 (1.6)↓	9.06 (2.38) ↓	6.15 (1.59)↑	9.59 (2.01) ↓
Attention	5.43 (1.66) ↓	8.38 (1.59) ↓	5.78 (2.02) ↑	10.81 (2.75) ↑
Combination	4.01 (1.06) ↓	7.43 (1.73) ↓	4.79 (1.76) ↑	8.93 (2.43) ↓
Final non-cued	4.89 (2.26) ↓	6.82 (4.42) ↓	4.27 (1.84) ↑	8.38 (3.7) ↓

Step time variability.

A significant interaction between cue type*subject type (F=3.087, P=0.019) was found for step time variability in the single task, where cues reduced variability in PD subjects whilst increasing in control subjects (Table 4.4). Further post hoc analysis comparing cued trials with the baseline non-cued trials, showed the reduction in step time variability in PD subjects was significant with the combination cue (P=0.02) (Figure 4.1.a). Cues increased step time variability in controls, however this was not significant. (Figure 4.1.a). There was no short term carry over effect observed in the final non-cued trial in PD or control subjects (Figure 4.1.a).

DLS time variability.

A significant main effect of cue type (F=5.57, P=0.003) and subject type (F=4.526, P=0.04) was seen for DLS time variability with no interaction (Table 4.4). Post hoc analysis showed that DLS time variability reduced with all cues in PD subjects and this was significant with the attention (P=0.001) and combination (P<0.001) cues, but not the auditory cue (Figure 4.1.b). There were no significant changes in DLS time variability in the control group with cues (Figure 4.1.b). There was a short term carry over effect of cues on DLS time variability observed in PD subjects (P=0.023) but not control subjects in the final non-cued trial (Figure 4.1.b).

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Figure 4.1. Gait variability of PD and control subjects in cued and non-cued trials in the single task. Coloured bars represent mean variability, blue for PD subjects, purple for controls. Error bars indicate the standard deviation. * indicates significant change compared to non-cued baseline.

a) Step time variability

b) DLS time variability
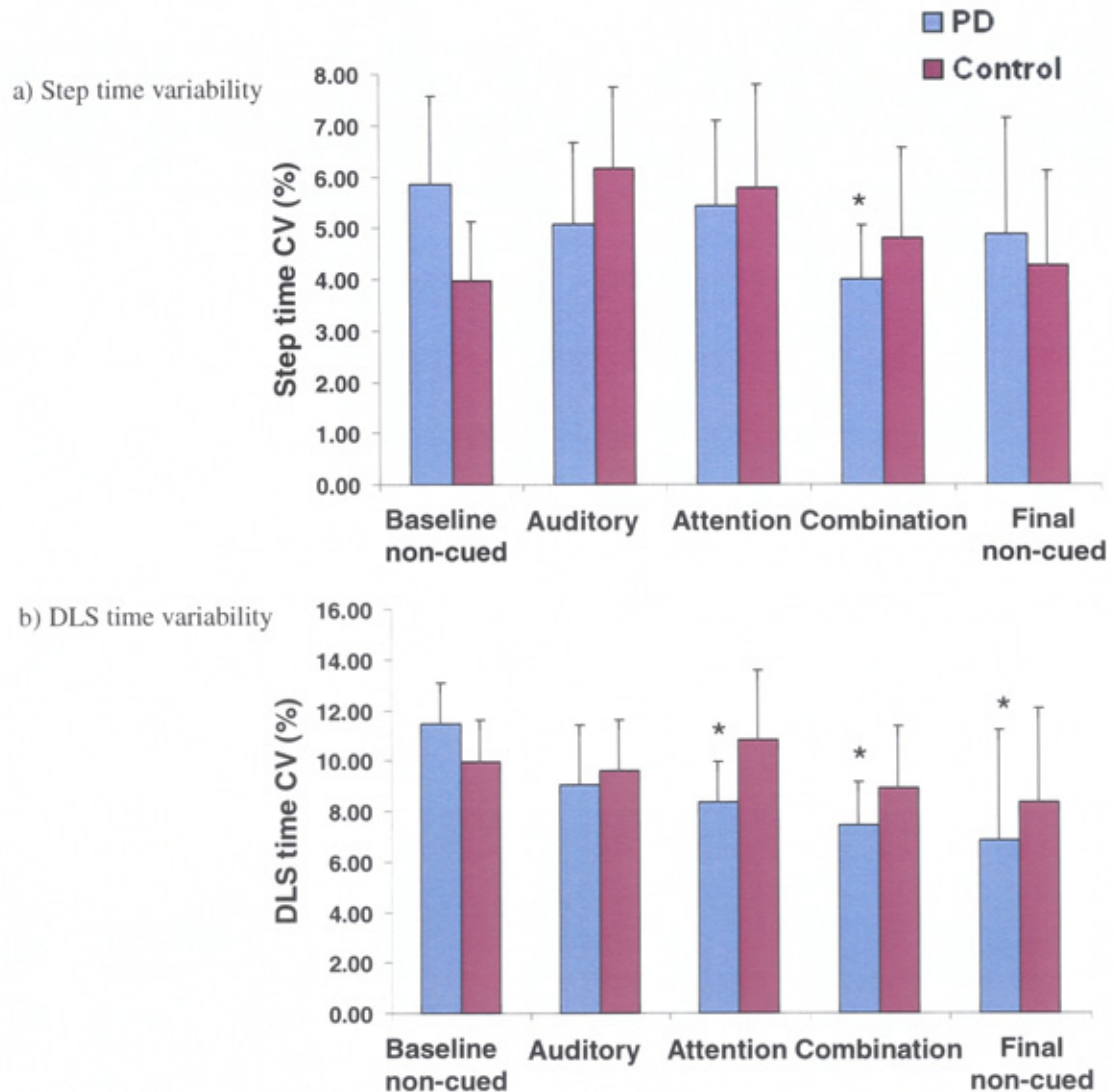
Effect of cues during the dual task.

Similar patterns of change were observed with cues during the dual task. Table 4.5

describes step time and DLS time variability of PD and control subjects in cued and

non-cued trials in the dual task.

Table 4.5. Gait variability of PD (n=14) and control (n=12) subjects in the dual task: cued and non-cued trials. Shaded boxes indicate significant changes compared to non-cued baseline with the direction of change shown with arrows.

	PD Step time CV (%)	DLS time CV (%)	Control Step time CV (%)	DLS time CV (%)
Baseline non-cued	6.34 (1.25)	11.75 (2.24)	5.07 (1)	10.74 (1.89)
Auditory	5.33 (1.49) ↓	9.24 (3.45) ↓	5.1 (1.05)↑	9.78 (2.83) ↓
Attention	5.88 (1.43) ↓	9.64 (2.9) ↓	5.48 (1.93) ↑	10.77 (3.91) ↑
Combination	4.65 (1.29) ↓	9.21 (3.03) ↓	4.49 (0.43) ↓	11.42 (3.32) ↑
Final non-cued	5.6 (1.67) ↓	6.83 (4.12) ↓	5.08 (2.35) ↑	10.63 (4.68) ↓

Step time variability.

A significant main effect of cue type was found for step time variability in the dual task condition (F2.639, P=0.048) but no significant effect of subject type or interaction effects (Table 4.5). Post hoc analysis showed all cues reduced variability compared to baseline in the PD group and this was significant with the combination cue (P=0.025) (Figure 4.2.a). No significant changes were seen in the control group with cues. There was no carry over effect of cues observed in the final non-cued trial in PD or control subjects (Figure 4.2.a).

DLS time variability.

DLS time variability showed a significant effect of cue type (F=2.831, P=0.029) but no significant effect of subject type or interaction effects (Table 4.5). DLS time variability reduced with all cues in PD subjects, however post hoc analysis showed no significant changes. No significant changes were seen in the control group (Figure 4.2.b). There was a short term carry over effect of cues on DLS time variability

observed in PD subjects (P=0.003) but not control subjects in the final non-cued trial

(Figure 4.2.b).

Figure 4.2. Gait variability of PD and control subjects in cued and non-cued trials in the dual task. Coloured bars represent mean variability, blue for PD subjects, purple for controls. Error bars indicate the standard deviation. * indicates significant change compared to non-cued baseline.

a) Step time variability

b) DLS time variability
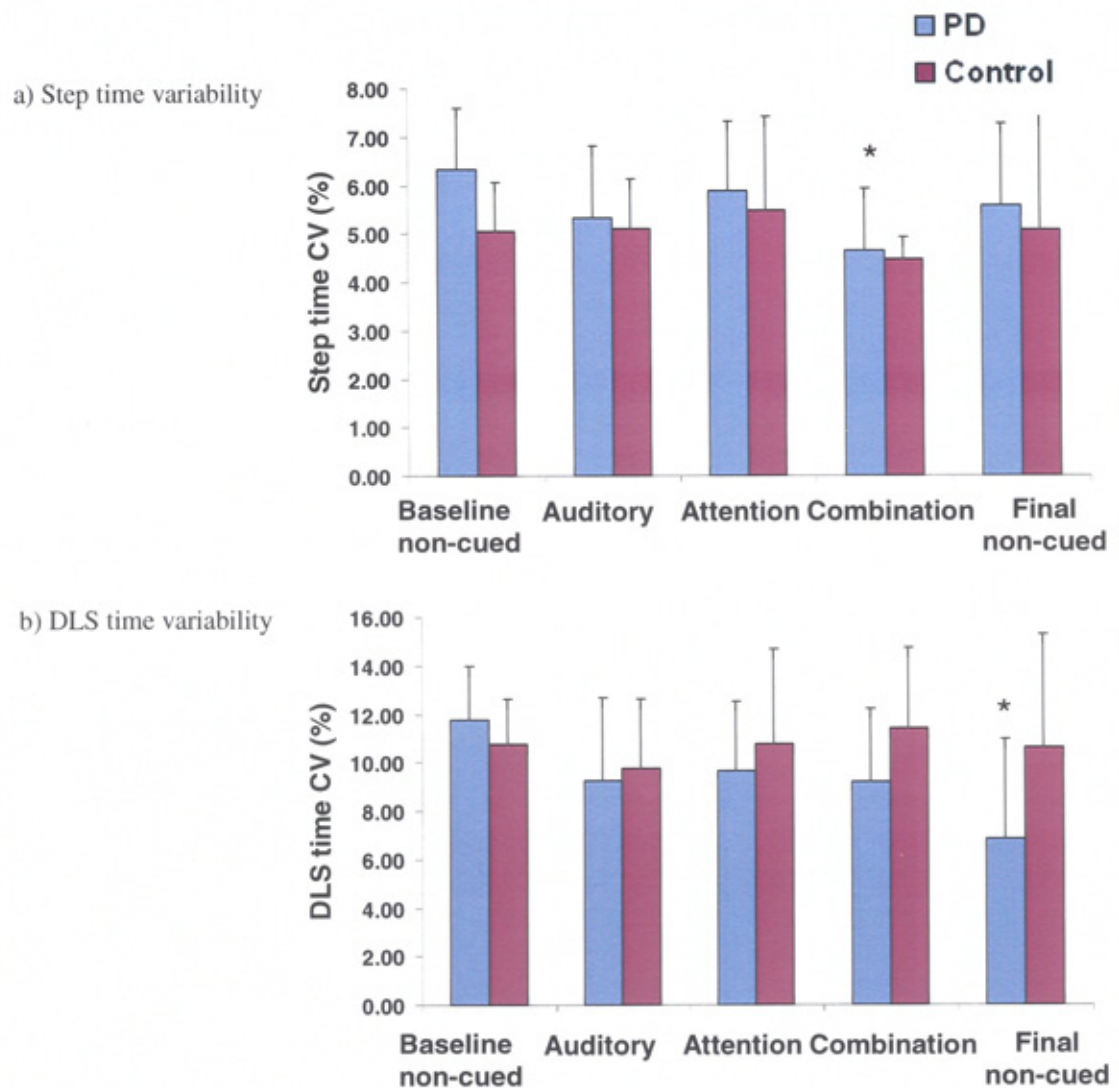
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Do cues normalise gait variability in PD subjects?

Post hoc tests were carried out to compare PD subjects gait variability in cued trials

with non cued gait variability in control subjects to explore whether cues were able to

reduce the impact of PD and return variability to control values.

Single task.

Step time variability.

In the single task non-cued baseline, PD subjects had significantly greater step time

variability than controls (T=3.275, P=0.003). With the auditory and combination

cues, PD subjects step time variability was not significantly different to controls

single task baseline (auditory: T=2.014, P=0.06; combination: T=0.095, P=0.925),

suggesting variability was normalised (Figure 4.3.a). Step time variability with the

attention cue was significantly increased compared to controls at baseline (T=2.588,

P=0.016) (Figure 4.3.a).

DLS time variability.

In the single task non-cued baseline trials, PD subjects DLS time variability was

significantly higher than that of control subjects (T=2.331, P=0.028). With the

auditory cue DLS time variability of PD subjects was not significantly different to

controls baseline (T=1.094, P=0.285) (Figure 4.3.b). DLS time variability with the

attention (T=2.466, P=0.021) and combination cues (T=3.768, P=0.001) was

significantly reduced compared to controls at baseline (figure 4.3.b).

Figure 4.3. Comparison of cued gait variability in PD subjects with non-cued gait variability in control subjects in the single task. The horizontal black line represents control subjects non-cued gait variability. The blue bars represent PD subjects gait variability in the non-cued baseline and with each cue type, expressed as a percentage of control subject's non-cued baseline. * indicates significant difference between control baseline and PD cued variability.

a) Step time variability

a) DLS time variability
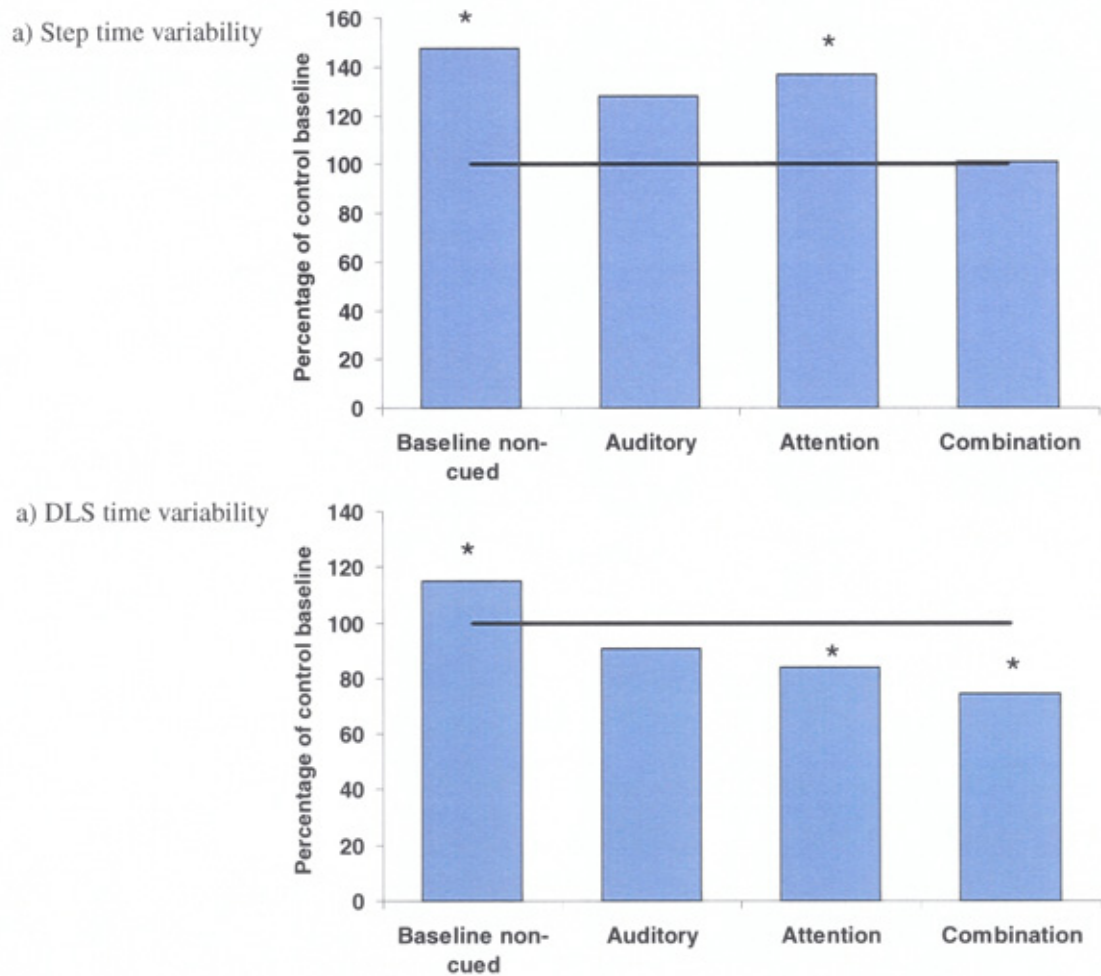
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Dual task.

Step time variability.

In the dual task non-cued baseline trials PD subjects showed greater step time

variability than control subjects (T=2.872, P=0.008). There was no significant

difference between control non-cued baseline step time variability and PD subjects

with any cue type (auditory: T=0.515, P=0.611; attention: T=1.664, P=0.109;

combination: T=0.916, P=0.368), all cues normalised step time variability of PD

subjects in the dual task (Figure 4.4.a).

DLS time variability.

There was no significant difference between PD and control subject's DLS time

variability in the non-cued baseline dual task. This did not change with any cue type

(auditory: T=1.34, P=0.193; attention: T=1.125, P=0.272; combination: T=1.518,

P=0.142) (Figure 4.4.b).

Figure 4.4. Comparison of cued gait variability in PD subjects with non-cued gait variability in control subjects in the dual task. The horizontal black line represents control subjects non-cued gait variability. The blue bars represent PD subjects gait variability in the non-cued baseline and with each cue type, expressed as a percentage of control subject's non-cued baseline.

a) Step time variability

a) DLS time variability
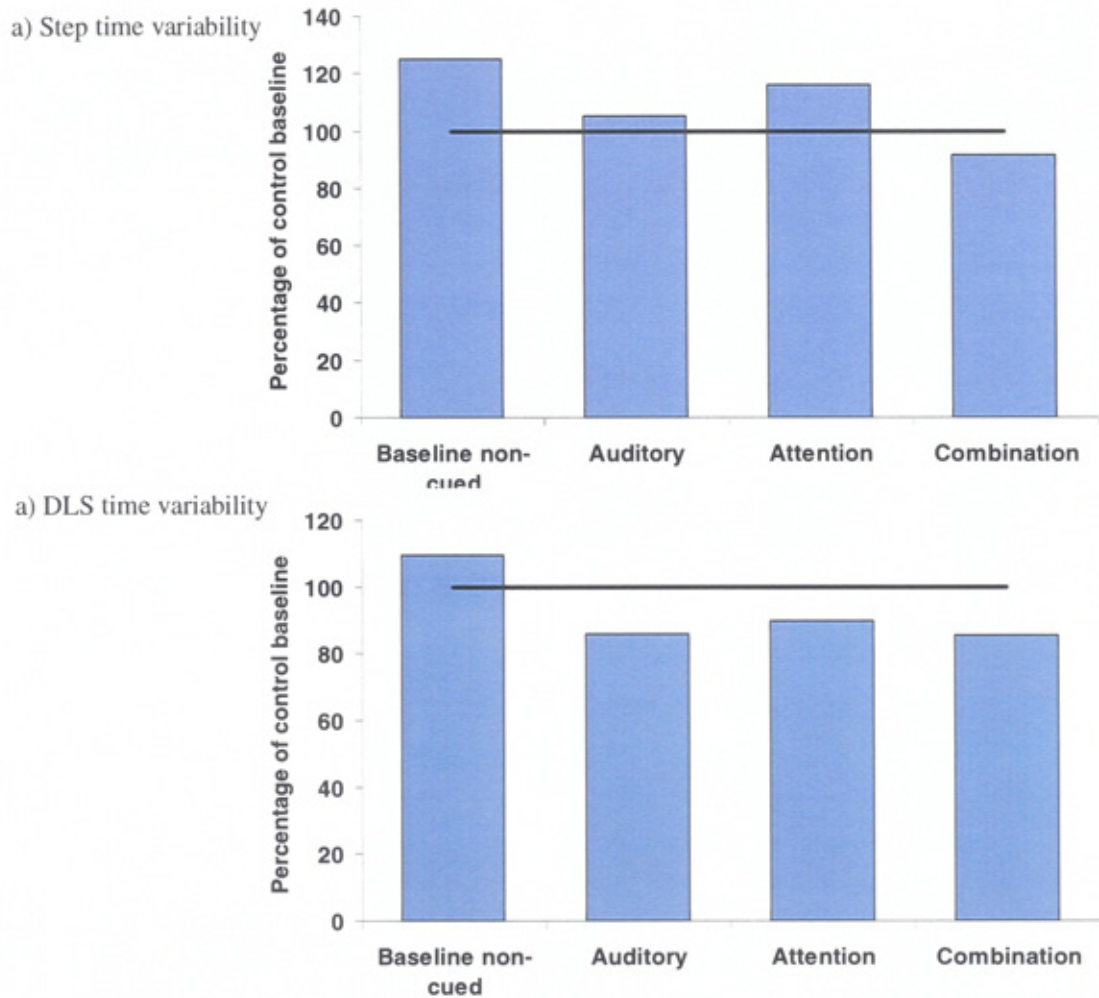
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Summary of results.

- During non-cued baseline trials, PD subjects had increased step time and DLS time variability compared to control subjects in the single task, and increased step time variability in the dual task.

- The dual task increased non-cued step time variability but not DLS time variability of both PD and control subjects.

- An interaction of cues*subject type was seen for step time and DLS time variability. PD subjects became less variable with cues whereas controls subjects either did not change or became more variable.

- Step time variability was significantly reduced in PD subjects with the combination cue in both the single and dual tasks. DLS time variability was significantly reduced with the attention and combination cues in the single task but not the dual task.

- No significant changes were observed in control subjects.

- In the single task, step time variability was normalised to that of control subjects with the auditory and combination cues. DLS time variability was normalised with the auditory cue and was significantly reduced compared to control's baseline with the attention and combination cues.

- In the dual task, PD subjects step time variability was normalised with all cues. DLS time variability did not significantly differ between PD and control subjects at baseline and this did not change with cues.

4.5. Discussion.

In agreement with other studies, PD subjects had increased step time and DLS time

variability compared to control subjects (Blin, Ferrandez & Serratrice, 1990;

Hausdorff *et al.*, 1998; Hausdorff *et al.*, 2003; Schaafsma *et al.*, 2003; Frankel-

Toledo *et al.*, 2005; Yogev *et al.*, 2005; Baltadjieva *et al.*, 2006). This robust finding

is reassuring in terms of the validity of these relatively newly researched variables.

The first question addressed in the present study was whether gait variability

responds differently to internal and external cue types and if this response differs in

PD and control subjects. PD subjects responded in a significantly different way to

cues than controls as seen by the interaction of cues by subject type for step time and

DLS time variability. PD subjects became less variable with cues whereas variability

was not significantly influenced by cues in controls subjects. In the single task, PD

subject's step time variability was normalised to that of control subjects with the

auditory and combination cues. In contrast, DLS time variability was normalised with

the auditory cue and was significantly reduced compared to control's baseline with

the attention and combination cues.

All cue types reduced step time variability in PD subjects compared to baseline

values, in contrast control subjects variability increased with all cue types. There is

evidence that when subjects are required to walk with non-preferred patterns of gait,

reproducibility and stability of the stepping action is compromised (Jordan, Challis &

Newell, 2007). It seems that in healthy adults, cues disrupt the normal gait pattern,

possibly through increased attentional demand or motor adjustments having to be made to follow the cue and walk with a non-preferred gait pattern. In contrast, PD subjects rely more on external input to guide movement (Hanakawa *et al.*, 1999; Shibasaki, Fukuyama & Hanakawa, 2004) and seemed to gain benefit from the presence of cues. Dysfunction in the basal ganglia results in the use of compensatory motor loops being over used in PD which may lead to PD subjects being more receptive to external cueing and more efficient at using them as they do not have intact automatic motor control systems which would perhaps compete with response to the cue.

While PD subjects step time variability reduced with all cues this was significant only with the combination cue, while the attentional strategy had the smallest effect. This raises two issues, firstly the ability of cues to reduce step time variability and secondly the difference between cues in achieving this. Addressing the first issue, step time variability may simply have been reduced through an increase in walking speed or step amplitude as suggested by others. Chapter 3 showed walking speed and step amplitude increased significantly with both the attentional and combination cue types (see chapter 3, figure 3.5), however only the combination cue resulted in a significant reduction in step time variability. This argues against the reduction in step time variability resulting from an increase in walking speed (Maruyama & Nagasaki, 1992). Danion (Danion et al., 2003) proposed that is was the more complex inter-relationship between step length and step frequency which contributed to gait variability. The combination cue which was the only cue to reduce step time

variability targeted both step amplitude and step frequency which may explain its benefit over the single modality cues. However this interpretation is limited as both the combination and attentional cues resulted in very similar changes in walking speed, step amplitude and step frequency in the single task (see chapter 3, figure 3.5). It may therefore be actual presence of the pacing cue in association with increased step amplitude which is successful in improving step time variability.

With regard to the second issue, it has been proposed that the relative attentional demands of cues that are generated internally may be greater as they impose executive demands to plan and prepare the movement (Rochester et al., 2005). An external cue may reduce this demand, acting as a constant prompt and pace maker, reducing attentional cost by removing the need to monitor the actual and desired movements (Rochester *et al.*, 2005; Rochester *et al.*, 2007). As described previously, imaging studies have shown an overall reduction in the amount of neural activity when movement is externally cued with significantly less activation of the frontal cortex than in self initiated movements (Jenkins *et al.*, 2000; Weeks *et al.*, 2001; Debaere *et al.*, 2003). This supports the argument that externally cued movements utilise less cognitive resource and are therefore potentially less demanding of attention.

The rhythmical auditory cue alone, although more effective than the attentional strategy, had less effect on step time variability than the combination cue. This may be partly explained by the cueing frequency (10% below baseline). Hausdorff and

colleagues (Hausdorff et al., 2007) found that a rhythmic auditory cue only had a beneficial effect on gait variability when delivered at a frequency above preferred stepping frequency Another study using a cue delivered at 20% below preferred stepping frequency found increased variability of both step length and step time (Ebersbach et al., 1999). Manipulation of gait speed led to a reduction in variability in one study with the use of a treadmill, the authors arguing the treadmill acts as an external pacemaker in the manner of a cue, interestingly as with the present study, effects on variability of gait timing were observed in PD subjects but not controls. This highlights that more work is indicated in order to determine the optimal frequency of delivery of external rhythmical cues. The choice of frequency in the present study was cautious as it was not known how feasible the combination strategy would be, and to allow subjects to safely synchronise with the cue in both a single and dual task. The next chapter will develop the strategy further using a more appropriate cueing frequency. It is interesting however that the frequency used in the present study was effective in the combination cue, suggesting specific benefit of addressing both the spatial and temporal components of gait.

DLS time variability was reduced significantly with the attentional and combination cues for PD subjects. This parameter of variability may be influenced more by step length, which was targeted by the attentional and combination cues and not the auditory cue, which had the least effect on DLS time variability compared to the other cue types. As variability of the support phases of gait is said to reflect balance mechanisms (Gabell & Nayak, 1984) this is a positive finding. Further study needs to

clarify if cues improve stability and potentially safety in PD subjects and what the implications are of reducing one measure of variability and increasing another as seen with the attentional cue.

This study also aimed to explore the impact of cues on gait variability under dual task conditions in order to increase understanding of the implications of different types of cue on attentional resources. PD subjects have impaired executive functions and also show increased gait variability during dual tasks thought to be due to an inability to appropriately allocate attention (Ebersbach, Dimitrijevic & Poewe, 1995; Hausdorff, Balash & Giladi, 2003; Yogev *et al.*, 2005; Springer *et al.*, 2006). Previous studies have shown that external rhythmical cues can be effective at improving walking in PD subjects during dual tasks, (Canning, 2005; Rochester *et al.*, 2005) possibly by freeing up cognitive resources and reducing attentional cost. PD subjects significantly reduced step time variability with the combination cue possibly due to reduced attentional cost supporting these findings. In contrast to the single task, DLS time variability was not influenced by any cue in the dual task. The effect on balance control may have been limited by the tray carrying task.

In agreement with Hausdorff (Hausdorff et al., 2007) we found a significant short-term improvement in DLS time variability when cues were removed in both single and dual tasks. Conclusions that can be drawn from this are limited due to the very short time between trials. However it does suggest that the benefits of cues are in part retained and this warrants further investigation. Previous investigation involving

training with cues found a reduction in variability of stride time associated with increased activity in the dentate nucleus of the cerebellum and the parietal and temporal lobes, which are associated with time keeping of rhythmical movements (Del Olmo & Cudeiro, 2005).

This exploratory study used a small convenience sample. The experimental protocol and method of data collection allowed a limited number of steps to be recorded (on average around 12) and the sampling rate of the GAITRite mat[a] may have reduced sensitivity. Although Hausdorff (Hausdorff, 2005) comments on the absence of standards and reference values for the study of gait variability it is generally accepted that larger numbers of steps are desirable . Previous studies have reported coefficient of variation values of around 5-6% in PD populations when calculated over hundreds of steps and the present study found comparable levels of variability. Another limitation of the present study is that due to the small sample it was not possible to separate freezers and non-freezers and this may have important implications on the response to cues, also the number of freezers in the sample of mild to moderate Parkinson's disease (64%) may have been disproportionate to the incidence of freezing in the PD population. The MMSE was used as a simple screening test for dementia in the present study, the next chapter develops this work further and includes a more detailed neuropsychological assessment in order to identify specific executive function and attentional deficits which may affect dual task ability and the response to cues.

Overall cues appear to reduce variability in PD and the combination cue strategy was most consistent in this small sample. The effect of cues on gait variability differs between PD and control subjects and appears to highlight the benefits obtained in PD subjects through the use of cues also sustained during a dual task. All cues showed a tendency to reduce variability in PD; however the combination cue was the most effective for both parameters of variability. These results are interesting considering that a combination of cues which give two discreet types of information (temporal and spatial) may have been thought to require more attention than a simple of cue. These preliminary results however suggest this is not the case. This highlights interesting questions regarding the mechanism of action of cues that are generated externally or internally, the application of different cueing strategies and their generalisation to more complex activities of daily living.

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Suppliers.

a. CIR Systems Inc, 60 Garlor Dr, Havertown, PA 10983, USA.
b. Version 12; SPSS Inc, 233 S Wacker Dr, 11th Fl, Chigago, IL 60606, USA.

Chapter 5

The impact of dopaminergic medication and cues on single and dual task walking in people with PD.

5.1. Abstract

Gait performance is known to fluctuate across the medication cycle, with reduced walking speed, stride amplitude and increased gait variability when medication is not working well. Cues are known to improve gait in PD but their effect off medication remains unclear. The aim of this study was to explore the impact of internal and external cueing strategies on gait both on and off medication. A repeated measures study design was used, in which subjects performed single and dual motor tasks under different cueing conditions on two occasions, once on and once off medication. 50 subjects with idiopathic PD were studied in their own home. Three cueing strategies were compared: a rhythmical auditory cue (walking in time to a metronome beat delivered at referred stepping frequency), an attentional strategy (concentrate on taking big steps) and a combination cue (asked to take big steps in time to a metronome beat). The primary outcome measures were; walking speed, stride amplitude, step frequency and variability of stride and double limb support time. No interactions of cues and medication were seen for mean spatiotemporal gait parameters, with improvements seen both on and off medication. On medication, the attention and combination cues were equally effective in increasing speed and stride amplitude and had greater impact than the auditory cue alone in both single and dual tasks. Off medication, the combination cue increased walking speed more than the attentional cue. There was an interaction of cues and medication for stride time variability, the combination cue reduced variability in all conditions, the auditory cue

had no effect in the on medication single task, and significantly reduced stride time variability in all other conditions. The attentional cue increased stride time variability in the on medication single task and had no effect in other conditions. DLS time variability was reduced with the combination cue only, in single and dual tasks and when on and off medication. Two possible reasons for the effectiveness of the combination cue are proposed; firstly by addressing both the temporal and spatial parameters of gait, the mismatch in stride amplitude and frequency is reduced, and secondly the presence of the auditory tone reduces the attentional cost of walking reducing the need for the individual to internally generate the instruction to increase stride amplitude.

Chapter 5

5.2. Introduction.

Levodopa remains the gold standard pharmacological therapy for Parkinson's disease

and aims to restore projections from the striatum in the deficient basal ganglia,

therefore increasing activity in the under activated basal ganglia – SMA loop

(Brooks, 2001). Imaging studies of PD subjects after withdrawal of medication show

a greater reduction in SMA and prefrontal activity compared to on medication with

greater compensatory use of cerebellar and lateral parietal pre-motor connections

(Brooks, 2001). As discussed in earlier chapters, there is evidence to suggest that

movement which occurs in response to an external cue is mediated through different

neural pathways than those which are generated internally, with externally cued

movement being less reliant on basal ganglia – SMA loops (Jenkins *et al.*, 2000;

Weeks *et al.*, 2001; Debaere *et al.*, 2003). It remains unclear whether therapeutic

cueing strategies are influenced by dopaminergic mechanisms via influence on the

underlying neural pathways.

Dopaminergic medication is reported to improve upper limb movements (Kelly et al.,

2002), postural responses (Burleigh-Jacobs et al., 1997) and selected features of

parkinsonian gait (Blin *et al.*, 1991; Pederson, Eriksson & Oberg, 1991; O'Sullivan *et

al.*, 1998; Schaafsma *et al.*, 2003; Bohnen & Cham, 2006). However, with disease

progression there is a ceiling effect of levodopa on gait and balance dysfunction

which becomes increasingly difficult to control (Blin *et al.*, 1991; Bohnen & Cham,

2006). Levodopa appears to preferentially influence the spatial parameters of gait,

addressing the symptom of bradykinesia with improvement in stride amplitude and

walking speed with medication but little or no effect on the temporal parameters of

gait such as step frequency (Blin *et al.*, 1991; Pederson, Eriksson & Oberg, 1991; O'Sullivan *et al.*, 1998). It is suggested that although movement timing relies in part on the function of the basal ganglia, other structures such as the spinal cord and cerebellum also have a role (Thaut et al., 1999) which may explain why timing parameters are more resistant to dopaminergic medication (Almeida et al., 2007).

There is limited evidence of the effect of dopaminergic medication on gait variability with some conflicting reports. Despite a trend towards increased stride time variability when off medication, Blin et al (Blin et al., 1991) found no significant change with levodopa. In contrast Schaafsama and colleagues (Schaafsma et al., 2003) reported a significant increase in stride time variability when off medication. There are several potential reasons for the differences in these findings, including walkway length and therefore the number of strides used to calculate variability, and time since intake of medication in the on medication phase as there is variation in performance throughout the medication cycle.

Few studies have examined the effects of cues on movement when off medication. Morris and colleagues (Morris et al., 2005) compared the response to visual cues when on and off medication. The greatest improvement was seen with the combination of cues and medication. The authors suggest that it is the role of the basal ganglia in motor set which results in a mismatch between the cortically selected movement amplitude and the actual movement produced. Levodopa improves the output of the basal ganglia, which influences movement amplitude but does not fully

restore this function. Visual cues are proposed to then act to increase stride amplitude further though compensatory movement pathways.

Burleigh Jacobs (Burleigh-Jacobs et al., 1997) supported the view that cues and levodopa influence gait via different mechanisms. They compared the influence of external cues and levodopa on anticipatory postural adjustments and found significant improvements with both. There was no cumulative effect of cues and medication, with levodopa having greatest impact on self generated, non-cued movements, thought to be due to the influence on basal ganglia – SMA pathways responsible primarily for internally generated movements. Kelly et al (Kelly et al., 2002) examined the effect of cues and medication during a reaching task and found an interaction of cues and medication, the greatest increase in reaching speed with cues being seen off medication, in agreement with Morris's findings in gait. However, in agreement with Burleigh Jocobs there was no cumulative effect of cues and medication. The authors proposed two possible reasons for this; firstly that there is a ceiling effect to the possible increase in speed in PD and levodopa saturated this leaving no scope for further improvement with cues when on. A second possible explanation supported the view that levodopa preferentially acts on mechanisms underlying internally cued movement. There is therefore some discrepancy in the literature as to whether cues and medication have a cumulative effect, these differences could be attributed to the different tasks studied.

Almeida et al (Almeida et al., 2007) examined the effects of external rhythmical cues on gait variability on and off medication. They found that variability was increased

with cues when on but not off medication, with the off medication group acting more similarly to controls. Due to this finding and the link between increased gait variability and falls, the authors advised caution when using external cues as a strategy to improve gait in people with PD. The cueing frequencies used in the study however were well below preferred stepping frequency (60 to 100 steps per minute) and therefore outside of the range that would be considered therapeutic. There is evidence that constraining gait with very low stepping frequencies increases variability in people with PD (Ebersbach et al., 1999). The authors proposed that cues did not increase variability off medication because subjects were more reliant on compensatory motor pathways and therefore could more easily use the information provided by the cue. In contrast, when on medication, the cue increased variability, as has been shown in healthy subjects (Baker, Rochester & Nieuwboer, 2007a), possibly due to conflicting information when trying to process the cue in the presence of relatively intact basal ganglia – SMA function. These arguments require more exploration as they do not explain why people with PD show improvements in both mean spatiotemporal and variability gait measures when on mediation with more appropriate cueing frequencies (Baker, Rochester & Nieuwboer, 2007a; b; Hausdorff *et al.*, 2007).

The influence of levodopa is not constrained to physical symptoms but also effects cognitive domains, although the effect of dopaminergic medication on cognition is complex and less well understood (Kulisevsky, 2000). As gait is not an entirely automated function but relies on cognitive control (Verghese *et al.*, 2002; Holtzer *et al.*, 2006; Yogev-Seligmann, Hausdorff & Giladi, 2008), dopaminergic medication

may influence walking and functional activity through both motor and cognitive effects. People with PD rely more on cognitive means of motor control due to deficient automatic motor pathways and also have reduced attention and executive function performance. When available attentional resources are saturated through dual or multi tasking in PD, it is argued that compensatory gait control cannot be maintained and instead reverts back to the deficient basal ganglia circuitry resulting in poor gait performance (O'Shea, Morris & Iansek, 2002; Rochester *et al.*, 2004). The influence on dopaminergic medication on dual task interference remains unclear and has important implications regarding function and safety.

Cues have been shown to reduce dual task interference (Canning, 2005; Rochester *et al.*, 2005; Rochester *et al.*, 2007) and improve gait variability in a dual task in people with PD (Baker, Rochester & Nieuwboer, 2007a). Cues have been argued to reduce the attentional cost of walking accounting for these effects (Rochester et al., 2005) (Rochester et al., 2007). Dual task paradigms allow an estimation of the attentional cost of cueing strategies to be made, as using cues under dual task conditions reveals whether those strategies add to or reduce the competition for attentional resources. This will be developed further in the current study by testing in the more complex home environment.

From a practical point of view, due to the limited efficacy of medication in addressing gait and balance problems in people with PD, there is a clear need for strategies which enhance mobility when on medication to allow functional activity to be maximised. In addition strategies are required which allow a person to move safely

when medication is not working well and movement is most difficult. However, evaluating the application of cues across the medication cycle will also help to establish the underlying mechanisms of cueing in relation to the role of dopamine.

The previous chapters demonstrated that people with PD are able to use both internally and externally generated cues to improve mean spatiotemporal gait parameters. An attentional, or internally generated, strategy and a combination of an attentional strategy with an external auditory cue were equally effective in improving spatiotemporal gait parameters (Baker, Rochester & Nieuwboer, 2007b). However, the combination cue did show an added benefit in its effect on gait variability (Baker, Rochester & Nieuwboer, 2007a). It appears that controlling both spatial and temporal gait parameters with a cue is more effective in improving the stability of the gait pattern. In contrast, although the attentional strategy which instructs the individual to focus on their stride length dramatically improved the parameter at which it was targeted and as a result increased walking speed, it appears that this was at the cost of increasing variability of gait timing. The precise mechanism behind these changes remains unclear.

This study wished to extend these findings by addressing the role of dopaminergic mechanisms on gait control and specifically to determine if the effect of cues is dependent on dopamine. If the hypothesis that compensatory cueing strategies bypass basal ganglia circuitry is accurate then cueing strategies should be effective regardless of medication status. It is also important to consider whether the cognitive influence of dopamine affects the ability to use cue strategies and whether there is a differential

effect of internally and externally generated strategies. In addition subjects were tested in the home environment in order to maximise ecological validity and increase the complexity of the situation.

This home-based study aimed to extend the findings of the laboratory studies discussed in previous chapters. The following research questions were addressed; (1) does medication status influence the effect of internal and external cueing strategies on gait, (2) do cues and dopaminergic medication have different effects on gait, (3) can cues reduce the impact of dual tasks on gait on and off medication?

Chapter 5

5.3. Methods.

Subjects.

A convenience sample of 50 people with idiopathic PD were recruited from a local movement disorders clinic. Ethical consent for the study was granted by Newcastle and North Tyneside Local Research Ethics Committee, UK. All subjects gave informed written consent (see appendices (iii) and (iv) for study information sheet and consent form). Inclusion criteria were: diagnosis of idiopathic PD (by a consultant neurologist with a specialist interest in movement disorders), disease severity of I to IV on the Hoehn & Yahr scale (Hoehn & Yahr, 1967), absence of any other neurological problem or any severe co-morbidity likely to affect gait , absence of dementia (score above 24 on Mini Mental State Examination (Folstein & Folstein, 1975)), adequate sight and hearing with glasses or hearing aid if required, independently mobile indoors without a walking aid, no severe dyskinesias (above 2 on Modified Dyskinesia Scale (Goetz, Stebbins & HM, 1994)) or prolonged off periods and age 80 years or less.

Experimental Design.

A within subjects, repeated measures experimental design compared three cue types under single and dual task conditions and in the ON and OFF phases of the medication cycle. Order and practice effects were controlled for by randomising the order of cue presentation and counterbalancing on and off medication testing. Cueing protocols are described in table 5.1. All testing took place in the subjects' own home and took approximately 1 hour 30 minutes. On medication testing took place around 1 hour

after medication intake. Off medication testing took place before the first daily dose of

medication. In each condition subjects confirmed their on or off status using a visual

analogue scale. The ON and OFF assessments were two weeks apart. Rhythmical

auditory cues were given using a prototype cueing device[a] (see chapter 3, figure 3.3),

which delivered a rhythmical sound set to match preferred stepping frequency,

calculated at a comfortable walking pace during three repetitions of a 6m walk test.

This was calculated separately in both the ON and OFF conditions.

Table 5.1. Experimental protocol for cued and non-cued trials. Non-cued trials were performed before and after the cued trials. The cued trials* were randomised.

Cue Type	Description and instructions
BASELINE – NON-CUED	Baseline. Non-cued walking *Instructions: 'walk at your own comfortable pace'* Performed 3 times
AUDITORY*	External rhythmical auditory cue set at preferred stepping frequency *Instructions: 'as you walk try to step your feet in time to the beat'* Performed twice
ATTENTION*	Instruction to focus on 'walking with big steps' given before each trial *Instructions: 'as you walk try to take big steps'* Performed twice
COMBINATION*	External rhythmical auditory cue set at preferred stepping frequency, associated with 'taking a big step' *Instructions: 'take a big step in time to the beat'* Performed twice
FINAL NON-CUED	Final trial. Non-cued walking completed immediately after cued trials *Instructions: 'walk at your own comfortable pace'* Performed once

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Baseline Measures.

Demographic data were collected in addition to disease duration and severity; scored

with the Hoehn and Yahr scale (Hoehn & Yahr, 1967), Unified Parkinson's Disease

Rating Scale (Fahn & Elton, 1987), Section III (motor subscale) and the Revised

Freezing Of Gait Questionnaire (Nieuwboer et al., 2008).

Cognitive status was tested with the Hayling and Brixton tests of executive function

and the 2 domains of the Test of Everyday Attention (TEA). The Hayling sentence

completion test has two components. In the first part subjects are presented with a

series of 15 sentences which have the last word missing and are asked to respond as

quickly as possible with an appropriate word to complete the sentence. In the second

part subjects again listen to a series of 15 sentences but this time must respond as

quickly as possible with a word that is unconnected in every way to the sentence. The

first part of the test measures response initiation speed while the second measures

response suppression ability, both of which are linked with frontal lobe function

(Burgess & Shallice, 1996; Nathaniel-James, Fletcher & Frith, 1997). The Brixton

test measures the ability to detect rules in a sequence of stimuli, and assesses spatial

anticipation. The TEA tests the separate attentional systems using familiar everyday

materials (Robertson et al., 1994). Two domains of the TEA were used; the

telephone search and the telephone search while counting. The telephone search

involves the subject looking for key symbols while searching a simulated telephone

directory and has been shown to reflect selective attention. The telephone search

while counting uses the same task but the subject must simultaneously count strings

of tones presented on an audio tape which gives a measure of divided attention. There

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are different versions of each of the subtests of the TEA to allow testing on different

occasions with parallel material.

Experimental Protocol.

Subjects completed a functional task which involved walking with and without cues

under two levels of difficulty; walking only and dual tasking (figure 5.1). This was

chosen to reflect a functional, ecologically valid activity which has been used in

previous studies (O'Shea, Morris & Iansek, 2002; Rochester *et al.*, 2004). During the

task the subject walked along an 8m walkway towards a bench, collected a tray with 2

cups of water placed on it, turned through 180 degrees and returned to the start

position, carrying the tray and cups. The level of water in the cups and position of the

cups on the tray was standardised. Subjects were instructed not to prioritise either the

tray carrying or the walking task but rather to concentrate on the task as a whole. The

portion of the test before collecting the tray is described as the single task (walk only)

and the portion after collecting the tray is described as the dual task (walk + carry

tray). Only the central 4m of the walkway in each direction was used to calculate gait

parameters, this removed the acceleration and deceleration at the beginning and end of

the task and also removed the turn and collecting the tray, resulting in a direct

comparison of single versus dual tasking.

During both the ON and OFF assessments, subjects performed 10 trials of the

functional task. Three non-cued baseline trials were performed before the cueing trials

and a final non-cued trial after. Subjects performed two trials with each cue type (table

5.1) in a randomised order.

Figure 5.1. Experimental protocol. Subjects started sitting in the chair, stood and walked along the walkway, picked up the tray from the table, turned through 180° to return to the chair.

Table with tray
2m from finish line

Dual Task Condition
First heel strike over
finish line - Stride
Analyzer switched on

Single Task Condition
Last heel strike over finish
line - Stride Analyzer
switched off

Single Task Condition
First heel strike over
start line - Stride
Analyzer switched on

4 m

Dual Task Condition
First heel strike over
start line – Stride
Analyzer switched off

Subjects started in standing 2
metres back from start line

A Stride Analyzer[b] was used to record gait parameters while walking. This consists of footswitches worn in the subjects own shoes and a microprocessor worn on a belt on the waist (figure 5.2). The footswitches sample at a rate of 500Hz (one sample taken every 2 milliseconds). The Stride Analyzer has been shown to be a reliable means of collecting temporal and spatial gait parameters in people with Parkinson's Disease (Morris *et al.*, 1996; Bilney, Morris & Webster, 2003). This gait analysis system provides a portable means of collecting quantitative gait data which can be used in environments other than the laboratory or clinic. Due to data collection taking place within the home, space was often limited and the minimum length of walkway recommended by the manufacturers of the Stride Analyzer (4m) was used.

Figure 5.2. The Stride Analyzer (reproduced with permission from B&L Engineering).

The stride analyzer was used to record walking speed (m/min), stride amplitude (m) (the distance from one heel contact to the next heel contact on the same foot) and step frequency (steps/min) (a step is defined by heel contact on one foot to heel strike of

the opposite foot). In addition gait variability was measured using the mean and

standard deviation statistics to calculate the coefficient of variation (CV) for stride

time (the time taken for one complete stride or gait cycle shown on figure 5.3) and

double limb support time (DLS) (time spent with both feet in contact with the floor,

marked with the hashed blue areas on figure 5.3). Due to the way in which DLS is

calculated by the Stride Analyzer it was not possible to calculate CV for the total time

spent in double limb support. Instead CV was calculated separately for initial and

terminal double limb support (figure 5.3) and as these both showed the same pattern

of response to medication, task and cues, only initial double support results are

presented to prevent duplication. Left and right foot switch recordings were pooled

for all measures of variability in order to increase the number of data points used.

Figure 5.3. Phases of the gait cycle.
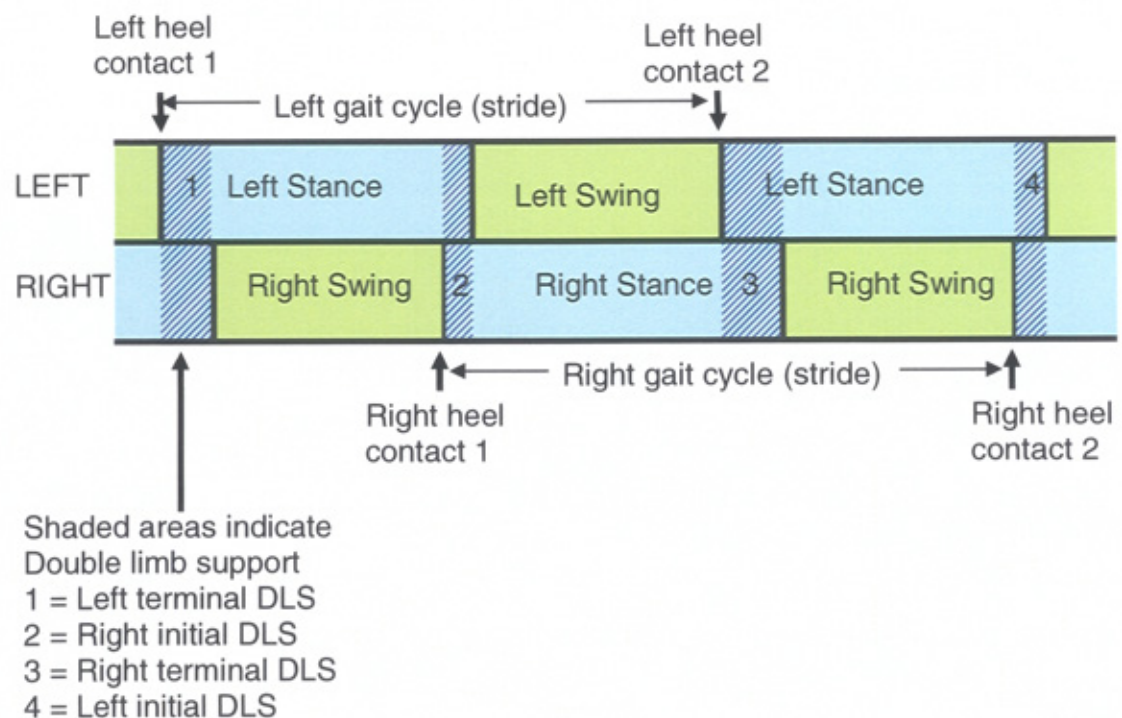
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Data Analysis.

Data were analysed using SPSS for Windows (Version 12)^c. Data were inspected for

distribution using Shapiro-Wilks statistic. All data were normally distributed. A

mixed design repeated measures analysis of variance was used to compare the effects

and interactions of medication (ON and OFF), task type (SINGLE and DUAL) and

cue type (AUDITORY; ATTENTION; COMBINATION). Two-tailed tests with a P

value of 0.05 or less were considered statistically significant for main effects and

Bonferroni adjustments were used to correct for multiple comparisons in post hoc

between trials pair-wise comparisons.

Coefficient of variation for stride and DLS time was calculated in the following way;

$$CV= (SD/mean)*100$$

5.4. Results

The main focus of this study was to confirm the results of the laboratory based study

presented in chapters 3 and 4 in the home environment, to compare the response to

cues on and off medication and to use a dual task paradigm to evaluate the impact of

internal and external cueing strategies on the attentional demand of walking.

Gait performance was assessed with measures of mean spatiotemporal parameters

(walking speed, stride amplitude and step frequency). Variability of stride and DLS

time (coefficient of variation) was calculated from individual footfall data. These

measures are distinct from the mean spatiotemporal gait parameters as they indicate

the stability of the stepping mechanism.

Subject Characteristics.

50 people with idiopathic PD (19 women, 31 men) completed the study, with a mean

age of 69.2 years and a mean 8.7 years since diagnosis (table 5.2). Hoehn & Yahr

ratings (Hoehn & Yahr, 1967) ranged from 2 to 4 when on medication with a median

score of 3 indicating moderate disease severity. All subjects were taking dopamine

replacement therapy, 21 subjects combined this with a dopamine agonist and 12

subjects with a COMT inhibitor. A mean daily equivalent dose of 758.8 mg of

levodopa was calculated according to the method described in detail by Krause et al

2001 (Krause et al., 2001). Item one of the revised Freezing of Gait Questionnaire

(Nieuwboer et al., 2008) which asks the subject to confirm whether they have had any

freezing episodes in the previous month, identified the majority of the sample (n=40)

as freezers and the remainder (n=10) as non-freezers. When asked if they had fallen

in the previous 6 months, 23 subjects reported no falls, 7 subjects reported one fall

and 20 subjects reported more than one fall. The mean score on the Mini Mental State

Examination (Folstein & Folstein, 1975) was 28 with all subjects scoring above the

cut off point of 24, indicating an absence of dementia.

Table 5.2. Subject characteristics for PD subjects (n=50). Values shown are mean and standard deviation unless otherwise stated.

	Mean (SD)
Age (years)	69.22 (6.6)
Disease duration (years)	8.69 (5.19)
MMSE	28.22 (1.57)
Hoehn & Yahr scale	2 subjects rated 2 12 subjects rated 2.5 32 subjects rated 3 4 subjects rated 4
Freezing of gait	40 freezers/10 non-freezers
Falls (self report in last 6 months)	No falls – 23 subjects Single fall – 7 subject Repeat falls – 20 subjects
Medication (Equivalent daily dose of levodopa)	758.8 (333.4) Dopamine replacement: n=17 Dopamine replacement + agonist: n=21 Dopamine replacement + COMT inhibitor: n=12

Effect of dopaminergic medication on baseline physical measures.

Scores on the motor subsection and the gait and posture subsection of the UPDRS

(Fahn & Elton, 1987) significantly increased off medication which indicates a

deterioration in performance (table 5.3). Baseline walking speed, stride amplitude and

stride time variability significantly deteriorated when off medication in both the

single and dual tasks (table 5.3), whereas step frequency and DLS time variability did

not change with medication status.

Table 5.3. Comparison of motor symptoms and non-cued gait on and off medication.
A P value of ≤ 0.05 was considered significant and indicates a significant
deterioration in performance in the off medication compared to the on medication
condition. Values shown are mean and standard deviation unless otherwise stated.
*Balance test scores refer to the number of subjects able to maintain the test for 30
seconds or more

		On medication Mean (SD)	Off medication Mean ± SD	P value (on vs off)
	UPDRS Motor	22.92 (9.16)	34.98 (9.31)	<0.001
	UPDRS Gait & Posture	6.14 (2.61)	8.16 (2.66)	<0.001
	Single leg stance – left*	8	6	0.569
	Single leg stance – right*	7	5	0.543
	Tandem stance – left*	21	12	0.052
	Tandem stance – right*	20	11	0.052
Single Task	Walking speed (m/min)	47.23 (10.92)	41.85 (13.86)	0.034
	Stride amplitude (m)	0.93 (0.25)	0.82 (0.24)	0.029
	Step frequency (steps/min)	102.42 (11.72)	101.84 (12)	0.806
	Stride time CV	4.43 (2.03)	6.12 (2.49)	<0.001
	DLS time CV	6.94 (2.25)	7.73 (2.46)	0.096
Dual Task	Walking speed (m/min)	42.24 (13.21)	36.28 (12.55)	0.023
	Stride amplitude (m)	0.83 (0.22)	0.7 (0.23)	0.009
	Step frequency (steps/min)	101.9 (11.57)	102.12 (11.56)	0.926
	Stride time CV	5.34 (1.39)	6.61 (3.87)	0.033
	DLS time CV	7.66 (3.35)	7.82 (2.07)	0.773

Effect of dopamine on performance of cognitive tests.

Performance on tests of executive function and attention was compared on and off

medication (table 5.4). Scaled scores of 5 on the Hayling test of executive function

are classified as moderate average, while scaled scores of 2-3 on the Brixton are

classified as poor to abnormal. A reduction in the scaled score shows a deterioration

in performance as seen in the off compared to the on medication condition. The

change in the Hayling (P=0.05) and Brixton (P=0.02) score when off medication was

significant with scores deteriorating off mediation. The single task (telephone search)

and dual task (telephone search while counting) components of the test of everyday

attention also showed a deterioration when off medication which was significant for

the dual task component only (P=0.05).

Table 5.4. Scaled scores on tests of executive function and attention on and off medication. A P value of ≤0.05 was considered significant and indicates a significant deterioration in performance in the off medication compared to the on medication condition.

	ON medication	OFF medication	P value (on vs off)
Hayling	5.5 (1.8)	4.82 (1.72)	0.05
Brixton	3.76 (2.23)	2.46 (1.76)	0.02
TEA Single	6.28 (3.03)	4.96 (3.87)	0.06
TEA Dual	7.11 (2.66)	6.74 (3.37)	0.05

Influence of cues.

Main and interaction effects.

There were significant main effects of cues, medication and task for walking speed

and stride amplitude but no interaction effects (table 5.5), suggesting the pattern of

change with cues was the same on and off medication and during single and dual

tasks. Walking speed and stride amplitude were reduced across all trials when off

compared to on medication and during dual compared to single tasks. All cues

increased walking speed and stride amplitude in both single and dual tasks and on and

off medication (figures 5.4 and 5.5). Step frequency showed a significant main effect

of cues but not medication or task (table 5.5) with a reduction in cued trials compared
to non-cued walking.

There were significant main effects of cues, medication and task seen for both stride
time and DLS time variability (table 5.5). There was also an interaction effect of
cues*medication for stride time variability. In the single task, the auditory cue had no
significant effect on medication but reduced stride time variability off medication,
whereas the attentional cue increased variability on but not off medication. The
combination cue reduced variability in both conditions. In the dual task the
attentional cue had no significant effect on or off medication, while the auditory and
combination cues reduced stride time variability in both conditions.

Table 5.5. Main and interaction effects of cues, medication and task. Shaded boxes
indicate significant effects. A P value of ≤ 0.05 was considered significant.

		Walking Speed	Stride Amplitude	Step Frequency	Stride time CV	DLS time CV
Main effects	Cues	F=91.75 P<0.001	F=206.627 P<0.001	F=59.989 P<0.001	F=69.655 P<0.001	F=33.591 P<0.001
	Medication	F=10.413 P=0.001	F=11.087 P=0.001	F=0.604 P=0.438	F=20.742 P<0.001	F=18.463 P<0.001
	Task	F=5.877 P=0.016	F=7.707 P=0.006	F=0.022 P=0.082	F=7.641 P=0.006	F=7.164 P=0.008
Interactions	Cues*Medication	F=0.760 P=0.530	F=1.503 P=0.204	F=0.974 P=0.406	F=4.875 P=0.001	F=2.37 P=0.059
	Cues*Task	F=19.973 P=0.508	F=1.454 P=0.219	F=0.531 P=0.664	F=0.533 P=0.693	F=0.429 P=0.788
	Cues*Medication *Task	F=0.030 P=0.996	F=0.085 P=0.983	F=0.015 P=0.998	F=0.817 P=0.504	F=0.391 P=0.815
	Medication*Task	F=0.003 P=0.954	F=0.035 P=0.852	F=0.032 P=0.858	F=0.219 P=0.641	F=0.207 P=0.650

Effects of cues on mean spatiotemporal gait parameters in the single task.

Table 5.6 shows the cued and non-cued mean spatiotemporal gait parameters in the single task, on and off medication. Figure 5.4 shows the change with cues compared to baseline non-cued trials.

Table 5.6. Mean spatiotemporal gait parameters in the single task: cued and non-cued trials. Shaded boxes indicate significant changes compared to the baseline non-cued trials with the direction of change shown with arrows. A P value of ≤ 0.05 was considered significant.

		Walking speed (m/min)		Stride amplitude (m)		Step frequency (steps/min)	
		Mean	SD	Mean	SD	Mean	SD
ON	Baseline non-cued	47.23	10.92	0.93	0.25	102.42	11.72
	Auditory	50.7 ↑	11.27	1↑	0.27	101.94	14.27
	Attention	54.98↑	17.95	1.17↑	0.31	94.02↓	15.66
	Combination	57.26↑	16.71	1.14↑	0.26	99.8	14.73
	Final non-cued	53.12↑	14.36	1.05↑	0.27	100.72	12.42
OFF	Baseline non-cued	41.85	13.86	0.82	0.24	101.84	12
	Auditory	44.19	14.55	0.86	0.25	101.02	14.14
	Attention	48.96↑	15.85	1.07↑	0.28	91.48↓	13.79
	Combination	51.61↑	16.94	1.06↑	0.29	97.77	15.09
	Final non-cued	45.97↑	13.81	0.94↑	0.26	98.58	11.65

Walking speed.

All cues significantly improved on medication walking speed, with an increase of 7.3% with the auditory cue (P=0.001), 16.4% with the attentional (P<0.001) and 21.2% with the combination cue (P<0.001) (table 5.6, figure 5.4.a). Off medication walking speed was significantly increased with the attentional cue by 17% (P<0.001) and combination cue by 23.3% (P<0.001) (table 5.6, figure 5.4.a). The auditory cue resulted in a smaller increase of 5.6% which did not reach significance. Walking speed remained significantly raised in the final non-cued trial suggesting a short term carry over of effect (figure 5.4.a).

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Stride amplitude.

All cues significantly improved on medication stride amplitude (table 5.6), with an increase of 7.9% with the auditory cue (*P*=0.001), 26.6% with the attentional cue (*P*<0.001) and 22.8% with the combination cue (*P*<0.001) (figure 5.4.b). Off medication stride amplitude was significantly increased by 30.5% with the attentional cue (*P*<0.001) and 29.3% with the combination cue (*P*<0.001) (table 5.6, figure 5.4.b). The increase of 5.2% with the auditory cue was not significant. Stride amplitude remained significantly increased in the final non-cued trial (figure 5.4.b).

Step frequency.

The attentional strategy was the only cue to significantly reduce step frequency (table 5.6) by 8.2% on (*P*<0.001) and 10.2% off medication (*P*<0.001) (figure 5.4.c). There was no difference in step frequency between the baseline and final non-cued trials (figure 5.4.c).

Figure 5.4. Mean percentage change compared to non-cued baseline in mean spatiotemporal gait parameters with cues in the single task. Blue bars represent on medication trials, purple bars represent off medication trials. Error bars show standard deviation. * indicates significant increase compared to non-cued baseline. † indicates significant difference between cues on medication. ▣ indicates significant difference between cues off medication. A P value of 0.05 was considered significant.

a) Walking speed

b) Stride amplitude

c) Step frequency

■ ON
■ OFF
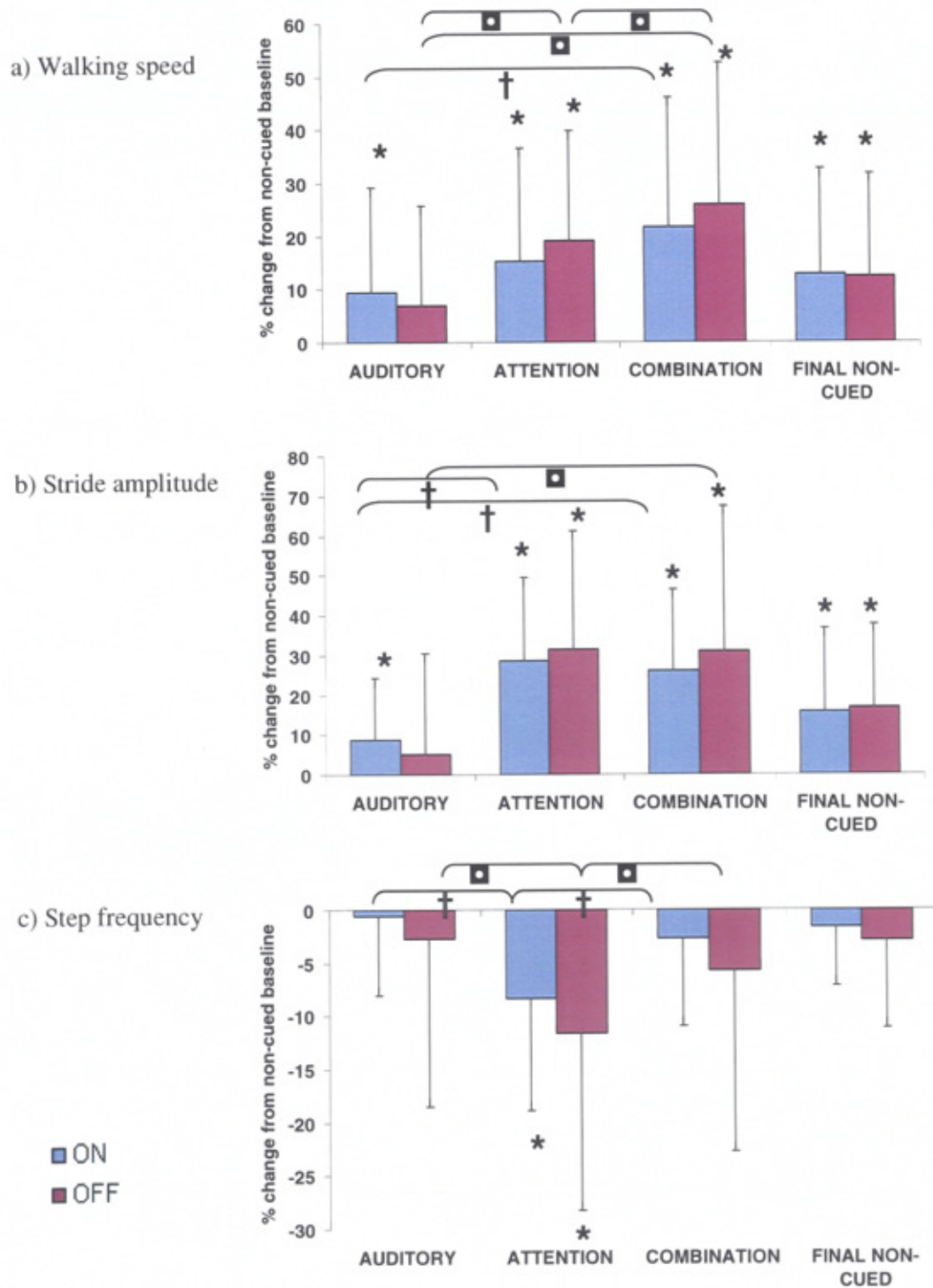
Effect of cues on mean spatiotemporal gait parameters in the dual task.

The pattern of response to cues was similar in the dual task, with no interaction of

task with cues or medication. Table 5.7 shows the cued and non-cued mean

spatiotemporal gait parameters in the dual task, on and off medication. Figure 5.5

shows the change with cues compared to baseline non-cued trials.

Table 5.7. Mean spatiotemporal gait parameters in the dual task: cued and non-cued trials. Shaded boxes indicate significant changes compared to the baseline non-cued trials with the direction of change shown with arrows. A P value of ≤ 0.05 was considered significant.

		Walking speed (m/min)		Stride amplitude (m)		Step frequency (steps/min)	
		Mean	SD	Mean	SD	Mean	SD
ON	B1	42.24	13.21	0.83	0.22	101.9	11.57
	AUD	46.8↑	15.23	0.91↑	0.25	101.4	14.95
	ATT	49.71↑	16.7	1.06↑	0.3	94.57↓	15.12
	AUD+ATT	52.65↑	14.58	1.07↑	0.24	98.57↓	14.39
	FINAL	48.96↑	15.26	0.97↑	0.29	100.78	11.95
OFF	B1	36.28	12.55	0.7	0.23	102.12	11.56
	AUD	39.92↑	13.92	0.78↑	0.25	101.27	15.09
	ATT	43.56↑	14.44	0.93↑	0.25	92.59↓	11.92
	AUD+ATT	47.16↑	15.43	0.97↑	0.27	97.14↓	13.64
	FINAL	41.64↑	12.89	0.84↑	0.23	98.84↓	12.13

Walking speed.

The pattern of change in walking speed in the dual task was very similar to that in the

single task, with the exception of the auditory cue which significantly increased

walking speed both on ($P=0.01$) and off medication ($P=0.001$) in the dual task (table

5.7), compared to on only in the single task. As in the single task the attentional (on:

$P<0.001$; off: $P<0.001$) and combination cues (on: $P<0.001$; off: $P<0.001$) caused

similar increases in walking speed both on and off medication (figure 5.5.a). Walking

speed remained significantly improved in the final non-cued trial.

Stride amplitude.

Change in stride amplitude was also similar in the single and dual tasks with the exception of the auditory cue which significantly increased amplitude both on (P=0.001) and off medication (P=0.002) in the dual task (table 5.7). As in the single task the attentional (on: P<0.001; off: P<0.001) and combination cues (on: P<0.001; off: P<0.001) caused similar increased in stride amplitude both on and off medication (figure 5.5.b). Stride amplitude remained significantly raised in the final non-cued trial (figure 5.5.b).

Step frequency.

In contrast to the single task, both the attentional and combination cues significantly reduced step frequency both on (attentional: P<0.001; combination: P=0.04) and off medication (attentional: P<0.001; combination: P=0.006) (table 5.7). There was no significant difference in step frequency between the baseline and final non-cued trials (figure 5.5.c).

Figure 5.5. Mean percentage change compared to non-cued baseline in mean spatiotemporal gait parameters with cues in the dual task. Blue bars represent on medication trials, purple bars represent off medication trials. Error bars show standard deviation. * indicates significant increase compared to non-cued baseline. † indicates significant difference between cues on medication. ▫ indicates significant difference between cues off medication. A P value of 0.05 was considered significant.

a) Walking speed

b) Stride amplitude

c) Step frequency

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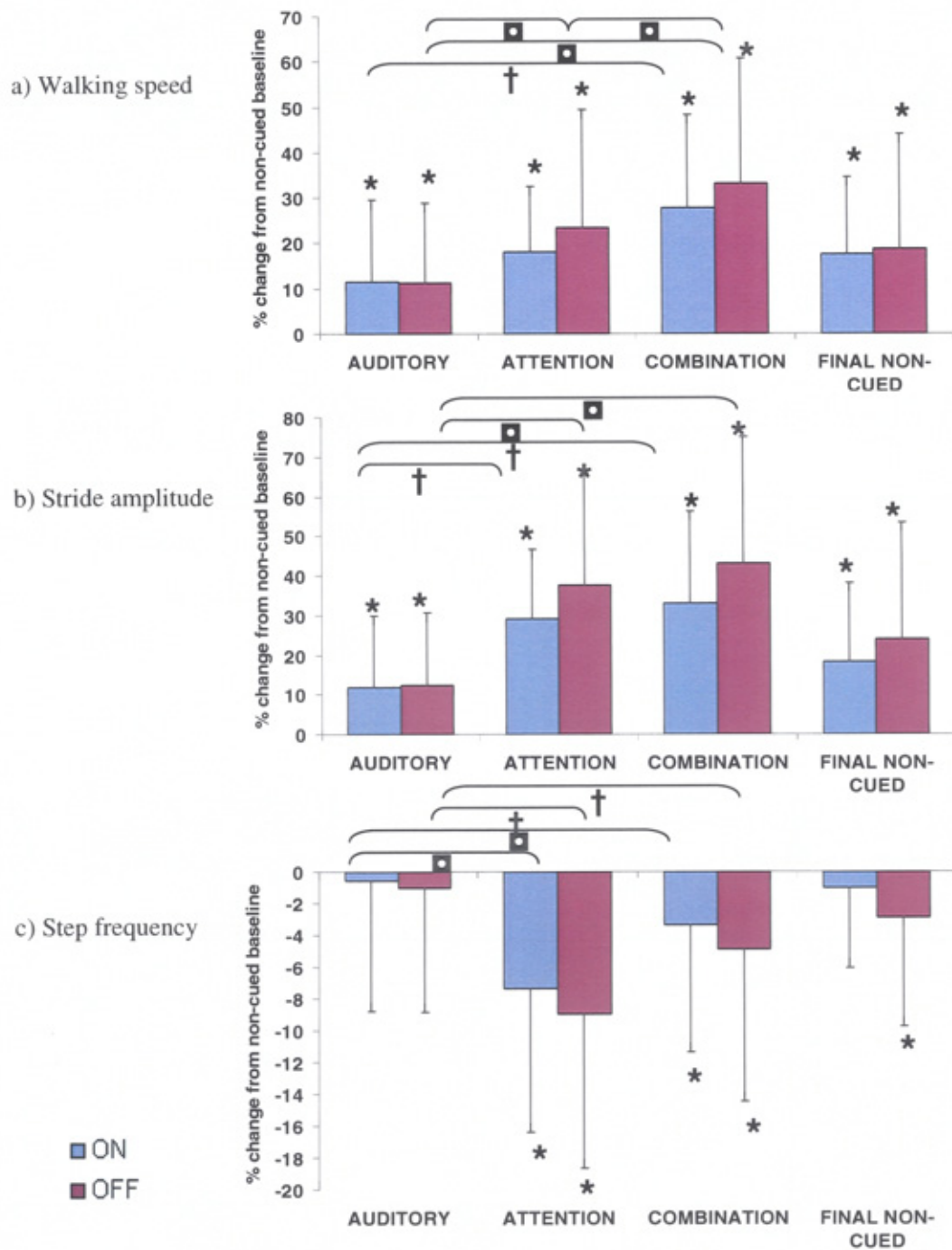
Effect of cues on gait variability in the single task.

Table 5.8 shows the cued and non-cued gait variability measures in the single task, on

and off medication. Figure 5.6 shows the change with cues compared to baseline non-

cued trials.

Table 5.8. Gait variability in the single task: cued and non-cued trials. Shaded boxes
show significant changes compared to non-cued baseline. Arrows show direction of
change. A P value of $\leq$0.05 was considered significant.

		Stride time CV		DLS time CV	
		Mean	SD	Mean	SD
ON	Non-cued baseline	4.43	2.03	6.94	2.25
	Auditory	3.53↓	1.4	6.6↓	2.36
	Attention	5.45↑	1.58	6.96↑	2.44
	Combination	2.64↓	0.87	4.6↓	2.33
	Final non-cued	3.17↓	1.71	5.08↓	3.27
OFF	Non-cued baseline	6.12	2.49	7.73	2.46
	Auditory	4.30↓	2.6	7.06↓	2.95
	Attention	5.26↑	1.31	7.76↑	2.29
	Combination	3.0↓	1.40	5.33↓	2.84
	Final non-cued	4.06↓	1.64	6.92↓	2.07

Stride time variability.

On medication stride time variability was significantly increased with the attentional

cue (P=0.024), and reduced with the combination cue (P<0.001) (figure 5.6.a). The

auditory cue reduced stride time variability but this was not significant (figure 5.6.a).

Off medication, the attentional cue caused a small, non-significant increase in stride

time variability, whereas both the auditory (P<0.001) and the combination cues

(P<0.001) significantly reduced stride time variability (figure 5.6.a). Stride time

variability remained significantly reduced in the final non-cued trial suggesting a

short term carry over effect of cues (table 5.8).

Double limb support time variability.

On medication, DLS time variability was reduced with the auditory cue and increased with the attentional cue but these changes were not significant (figure 5.6.b). The combination cue reduced DLS time variability significantly ($P<0.001$) (figure 5.6.b). Off medication DLS time variability was reduced with the auditory cue and increased with the attentional cue but this was not significant, a significant reduction was seen with the combination cue ($P<0.001$) (figure 5.6.b). DLS time variability remained reduced in the final non-cued trial on but not off medication (table 5.8).

Figure 5.6. Gait variability in the single task; cued and non-cued trials. Blue bars represent the on medication condition, purple bars represent the off medication condition. * indicates significant change compared to non-cued baseline. † indicates significant differences between on medication cued trials. ◘ indicates significant differences between off medication cued trials. A P value of   0.05 was considered significant.

a) Stride time variability

b) DLS time variability

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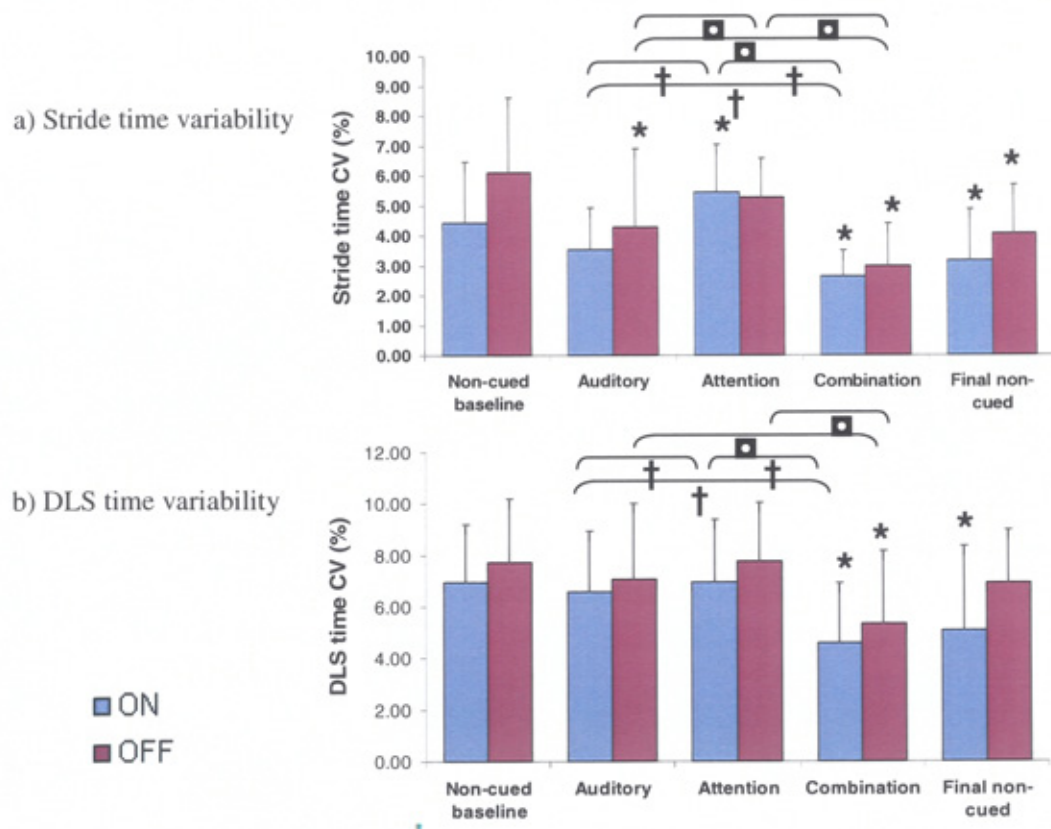
Effect of cues on gait variability in the dual task.

Table 5.9. Gait variability in the dual task: cued and non-cued trials. Shaded boxes show significant changes compared to non-cued baseline. Arrows show direction of change. A P value of ≤ 0.05 was considered significant.

		Stride time CV		DLS time CV	
		Mean	SD	Mean	SD
ON	Non-cued baseline	5.34	1.39	7.66	3.35
	Auditory	3.57↓	1.15	6.88↓	2.75
	Attention	5.66↑	1.61	7.70↑	2.56
	Combination	2.9↓	1.22	4.93↓	2.81
	Final non-cued	3.73↓	2.17	6.05↓	3.03
OFF	Non-cued baseline	6.61	3.87	7.82	2.07
	Auditory	4.83↓	1.87	7.77↓	2.15
	Attention	5.64↓	3.59	7.93↑	2.79
	Combination	3.99↓	1.69	5.65↓	2.78
	Final non-cued	4.45↓	2.48	7.78↓	2.15

Stride time variability.

Stride time variability showed a different pattern of response in the dual compared to the single task with no interaction of cues and medication. The auditory (on: $P<0.001$; off: $P=0.007$) and combination cues (on: $P<0.001$; off: $P<0.001$) reduced stride time variability both on and off medication (figure 5.7.a). The attentional cue had no significant effect on stride time variability on or off medication (figure 5.7.a). Stride time variability remained significantly reduced in the final non cued trial on but not off medication (table 5.9).

Double limb support time variability.

As in the single task, only the combination cue caused a significant change in DLS time variability, causing a reduction both on ($P<0.001$) and off medication ($P=0.001$)

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(figure 5.7.b). No carry over of cueing effect was seen in the final non-cued trial on or

off medication (table 5.9).

Figure 5.7. Gait variability in the dual task; cued and non-cued trials. Blue bars represent the on medication condition, purple bars represent the off medication condition. * indicates significant change compared to non-cued baseline. † indicates significant differences between on medication cued trials. ▪ indicates significant differences between off medication cued trials. A P value of 0.05 was considered significant.

a) Stride time variability

b) DLS time variability

ON
OFF

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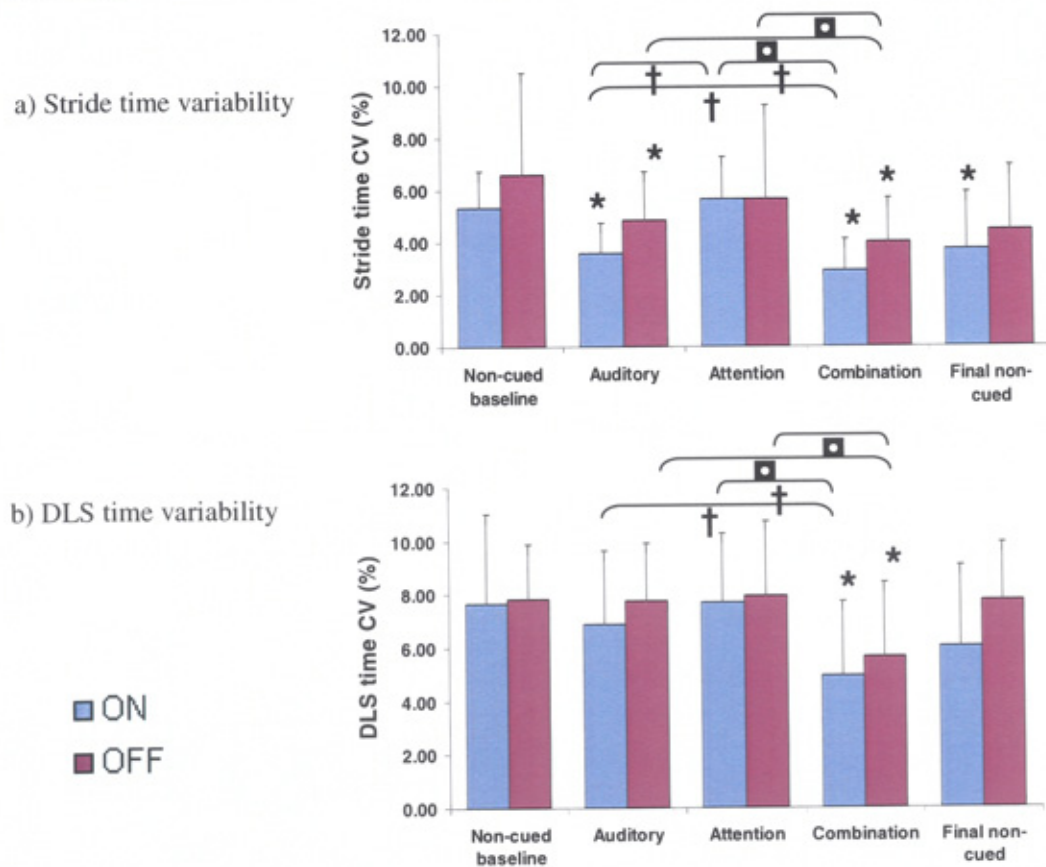
Comparing the effect of medication and cues on gait.

Post hoc tests were carried out to compare the influences of dopaminergic medication
and cues. This involved comparing the improvement in walking seen with medication
only (on medication non-cued walking) and cues only (off medication, cued walking).
T-tests were used to compare non-cued on medication gait measures with cued off
medication gait measures in order to determine how the effects of medication and
cues differed. In addition gait measures with each cue type are compared on and off
medication in order to evaluate the influence of dopamine on the effectiveness of
these strategies. The following description refers to single task walking; the same
pattern of response was observed in the dual task with one exception which is
discussed below.

Walking speed.

Non-cued walking speed was significantly increased by 12.9% with medication
(P=0.034) (table 5.3). Walking speed was increased by 5.6 – 23.3% with cues off
medication (auditory: 5.6%; attention: 17%; combination: 23.3%) compared to non-
cued off medication walking speed (figure 5.8.a). There was no significant difference
in non-cued, on medication walking speed and off medication cued walking speed (all
types), suggesting equal effects of medication and cues (compare the dark blue bar
showing non-cued, on medication walking speed with the light blue bars showing off
medication walking speed with each cue type in figure 5.8.a). Comparing cued trials
on and off medication revealed that a significant difference in walking speed existed
with the auditory cue (P=0.014) (marked by † on figure 5.8.a) with an increase of
5.6% off medication and 21.1% on medication, suggesting a cumulative effect of cues

and medication being observed for this cue type, but not the attention or combination

cues (figure 5.8.a).

Stride amplitude.

Non-cued stride amplitude was significantly increased by 13.4% with medication

(P=0.029). Stride amplitude was increased by 4.9-30.5% with cues off medication

(auditory: 4.9%; attention: 30.5%; combination: 29.3%) compared to non-cued off

medication walking speed (figure 5.8.b. No difference in stride amplitude was seen

between the non-cued on medication condition and off medication with the auditory

cue (figure 5.8b). The attention (P=0.009) and combination (P=0.016) cues caused a

greater increase in stride amplitude than medication (marked by * on figure 5.8.b).

Stride amplitude was significantly greater with the auditory cue on medication with

an increase of 21.9% compared to 4.9% off medication (P=0.01) suggesting a

cumulative effect of cues and medication (marked by † on figure 5.8.b), this was not

seen with the attention and combination cues (figure 5.8.b).

Step frequency.

There was no significant effect of medication on non-cued step frequency. There was

a significant difference between on medication non-cued step frequency and off

medication step frequency with the attentional cue (P<0.001) but not with the

auditory or combination cues (figure 5.6.c). There was no significant difference in

step frequency with any cue between the on and off medication conditions.

Stride time variability.

Non-cued stride time variability was significantly reduced by 27.6% with medication ($P<0.001$). Stride time variability was reduced by 29.7% with the auditory cue and by 51% with the combination cue compared to non-cued off medication stride time variability, while the attentional cue increased variability by 14.1% (figure 5.8.d). There was no significant difference between on medication non-cued stride time variability and off medication with the auditory cue, suggesting an equal effect of medication and this cue type (figure 5.8.d). The attentional cue significantly increased stride time variability off medication compared to non-cued on medication walking ($P=0.017$) (marked by * on figure 5.8.d). The combination cue caused a greater reduction in stride time variability compared with medication ($P<0.001$) (marked by * on figure 5.8.d). Comparing cued trials on and off medication revealed no significant difference in stride time variability with each cue type on and off medication suggesting no cumulative effect of cues and medication (figure 5.8.d). The only difference in the pattern of response seen in the dual task was the influence of medication on cues for stride time variability; comparison of each cue type on and off medication showed significant differences for the auditory ($T=4.072$, $P<0.001$) and combination cues ($T=3.689$, $P<0.001$)

DLS time variability.

Non-cued DLS time variability was reduced by 10.2% with medication, which was not significant. DLS time variability was reduced by 8.7 % with the auditory cue and 31% with the combination cue compared to non-cued off medication variability, while the attentional cue had no effect (figure 5.8.e). Comparing cued trials off

medication with non-cued on medication walking revealed no difference with the
auditory or attention cues. The combination cue caused a greater reduction in DLS
time variability than medication (marked by * on figure 5.8.e). Comparing each cue
type on and off medication revealed no significant differences, with no cumulative
effect of cues and medication.

Figure 5.8. Comparing medication and cueing effects on gait in the single task. Bars
represent mean percentage change compared to off medication, non-cued gait with;
non-cued gait in the on medication condition (dark blue bars), off medication, cued
gait (purple bars) and on medication, cued gait (light blue bars). * indicates a
significant difference between non cued on medication gait and off medication cued
gait; comparing the isolated effects of medication and cues. † indicates a significant
difference between cued trials of the same type on and off medication; examining the
influence of dopamine on each cue strategy.

a) Walking speed.
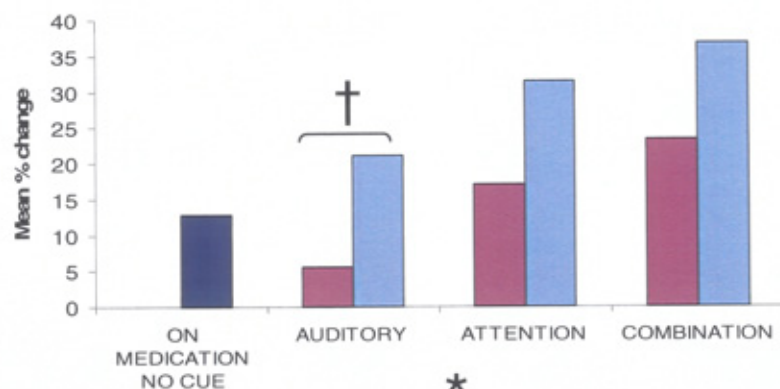
b) Stride amplitude.

Figure 5.8. continued.

c) Step frequency.

d) Stride time variability.

e) DLS time variability.

□ ON
□ OFF

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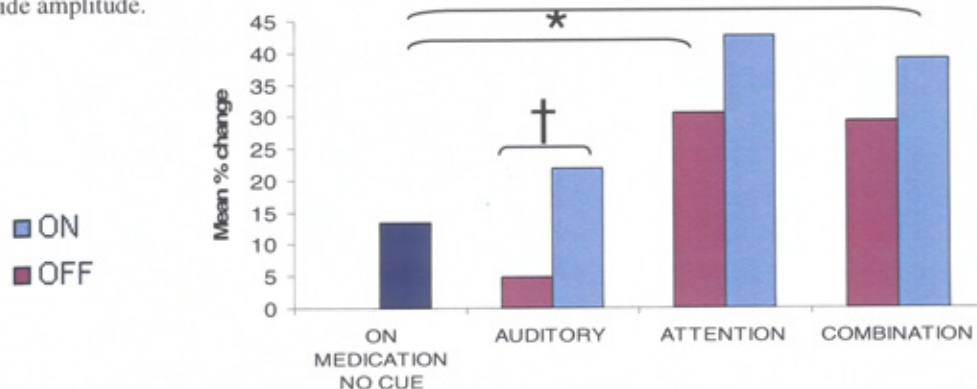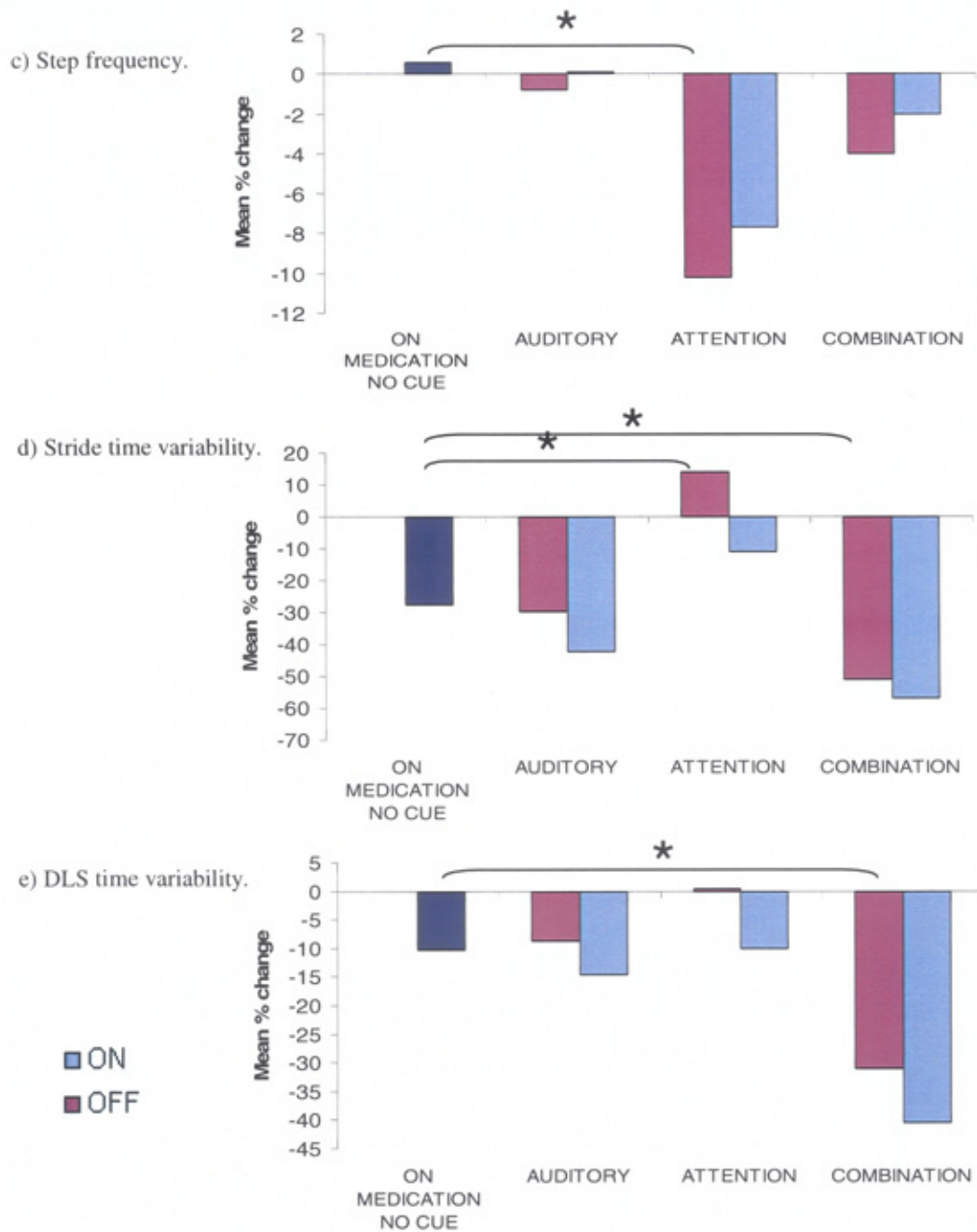
Summary of findings.

Mean spatiotemporal gait parameters.

- Dopaminergic medication improves walking speed, stride amplitude and gait variability but has no effect on step frequency. In addition improvements are seen in motor and cognitive scores with medication.

- The same pattern of response to cues was seen on and off medication and in single and dual tasks.

- On medication, the combination and the attentional cues were equally effective in improving walking speed, both being more effective than the auditory cue alone. Off medication however the combination cue had a greater effect on walking speed than both the attentional and auditory cues.

- Stride amplitude was equally improved with the attentional and combination cues, both of which had greater effect than the auditory cue alone.

- Step frequency was reduced more with the attentional cue than with the auditory and combination cues in all conditions except the on medication dual task where the combination cue resulted in a similar reduction.

- Short term retention of cueing effect was seen for walking speed and stride amplitude.

Gait variability.

- Dopaminergic medication significantly reduced non-cued stride time but not DLS time variability.

- Cues significantly influenced variability and an interaction of cues*medication was seen for stride time variability. The combination cue reduced stride time variability in all conditions. The auditory cue had no effect in the on medication single task, and significantly reduced stride time variability in all other conditions. The attentional cue increased stride time variability in the on medication single task and had no effect in other conditions.

- DLS time variability was reduced in all conditions with the combination cue and was not influenced by the auditory or attentional cues.

- Short term retention of cueing effect was seen for stride time variability in all conditions except the off medication dual task. DLS time variability remained improved in the on medication single task only.

Comparing medication and cues.

- Cues and medication in isolation were equally effective in improving walking speed.

- The attentional and combination cues had a greater impact on stride amplitude than medication.

- The combination cue was more effective than medication in reducing both stride time and DLS time variability, whereas the auditory cue was equally effective compared with medication.

- Only the auditory cue showed cumulative effects with medication on walking speed and stride amplitude.

5.5. Discussion.

This study has demonstrated that both internal and external cues are able to influence spatiotemporal gait parameters in people with PD both on and off medication. Cues which address the deficit in step amplitude, the attentional and combination cues, were equally effective in improving walking speed and stride amplitude on and off medication. The auditory cue which provided pacing information but no explicit instruction to increase stride amplitude was the only cue type to show a cumulative effect with medication, with the greatest improvement seen with the combination of cues and medication. Gait variability was also influenced by cues both on and off medication, however unlike the spatiotemporal response; there were differences in response of stride time variability to cues depending on medication status. Although the combination cue reduced stride time variability on and off medication, the auditory cue was effective off medication only, whereas the attentional cue increased variability on medication only.

This study confirmed previous reports of the influence of dopaminergic medication on physical and cognitive symptoms in PD (Blin *et al.*, 1991; Pederson, Eriksson & Oberg, 1991; Kulisevsky, 2000; Schaafsma *et al.*, 2003). During non-cued walking at the subject's preferred pace, levodopa caused a significant improvement in walking speed as a result of improvement in stride amplitude, but had no effect on step frequency. This is in agreement with previous research showing a preferential effect of dopaminergic medication on the mean spatial rather than temporal aspects of gait (Blin *et al.*, 1991; Pederson, Eriksson & Oberg, 1991; O'Sullivan *et al.*, 1998). The present study has also confirmed previous findings by showing an increase in stride

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time variability when off medication (Schaafsma et al., 2003), interestingly this did not extend to double limb support time variability.

The primary aim of this study was to determine whether dopaminergic medication influenced the effect of internal and external cueing strategies on gait. There was no interaction of cues and medication status for any of the mean spatiotemporal gait parameters with similar patterns of response on and off medication. This supports the hypothesis that cued movement involves neural pathways not reliant on dopamine. As discussed earlier, imaging studies have shown movement in response to an external trigger preferentially activate parieto-premotor pathways and reduce activity in the basal ganglia- SMA loop (Hanakawa *et al.*, 1999a; Weeks *et al.*, 2001; Debaere *et al.*, 2003). Other studies have reported benefits of visual (Morris *et al.*, 2005) and auditory (McIntosh et al., 1997) cues off medication, suggesting the mechanism of improvement with cues does not rely on dopaminergic pathways.

There was no difference in walking speed, stride amplitude or step frequency with the attentional or combination cues on and off medication, both cues significantly improved walking performance to similar levels regardless of medication status, supporting the view that these cues do not rely on dopaminergic pathways. Another explanation may be that cues which target spatial gait parameters either in isolation or in combination with temporal parameters achieve the maximum speed and amplitude possible and therefore create a ceiling effect, leaving no room for further improvement with medication. The auditory cue had a greater effect on walking speed and stride amplitude on medication, suggesting a cumulative effect of

medication and this cue type, this may be because the cue addresses the temporal

aspect of gait, known to be more resistant to medication, while levodopa acts

primarily on the spatial aspect of gait (Blin *et al.*, 1991; Pederson, Eriksson & Oberg,

1991). Morris reported similar findings with the greatest improvement in stride

amplitude being seen with visual cues and medication (Morris *et al.*, 2005).

Levodopa acts to boost basal ganglia function, whereas cues appear to bypass the

basal ganglia and use alternative compensatory motor pathways (Hanakawa *et al.*,

1999b; Weeks *et al.*, 2001; Debaere *et al.*, 2003).

An interaction of cues and medication status was seen for stride time variability. The

combination cue reduced stride time variability in all conditions, whereas the auditory

cue had no effect in the on medication single task, and significantly reduced stride

time variability in all other conditions and in contrast the attentional cue increased

stride time variability in the on medication single task and had no effect in other

conditions. The auditory cue appeared to improve stride time variability only when

subjects are at their most unstable, off medication and had no effect above the

improvement seen with medication. When comparing cueing and medication effects,

the auditory cue caused equal effects compared to medication for all spatiotemporal

and variability measures. This suggests that either the auditory cue improves gait via

the same mechanism as medication, which seem unlikely when considering the

neuro-imaging evidence regarding changes with medication and in response to

external cues (Hanakawa *et al.*, 1999a; Brooks, 2001; Weeks *et al.*, 2001), or

alternatively medication or the auditory each incompletely address PD gait

dysfunction. Medication acts primarily on bradykinesia and the spatial elements of

movement (Brooks, 2001) whereas the auditory cue provides pacing information but does not influence amplitude and therefore is unable to address the spatio-temporal mismatch.

The combination of an attentional strategy targeted at the spatial component of gait with a rhythmical auditory tone aimed at pacing the temporal components of gait appears to have added benefit over cues which address only one parameter of gait, particularly in relation to gait variability, in agreement with the laboratory based findings (Baker, Rochester & Nieuwboer, 2007a). As discussed in chapter 3 (see discussion) people with Parkinson's disease show disturbance of both the scaling (Morris *et al.*, 1994; Morris *et al.*, 2005), and timing of movement (Rao et al., 1997). There is a mismatch in the relationship between stride amplitude and frequency, which is linear in healthy adults (Winter, 1991). Howe (Howe et al., 2003) demonstrated that although PD subjects were able to up and down regulate their step frequency in response to an auditory cue at a range of frequencies, they did not modify stride amplitude, as would be expected in a healthy adult. This was supported by Almeida (Almeida et al., 2007) who studied PD subjects on and off medication at a range of cueing frequencies and found irrespective of medication status, subjects did not show any change in stride length in response to the altered step frequency imposed by the cue. Other studies, however have shown an increase in stride amplitude with auditory cues in single (McIntosh *et al.*, 1997; Willems *et al.*, 2006; Hausdorff *et al.*, 2007) and dual tasks (Rochester *et al.*, 2005; Rochester *et al.*, 2007) suggesting that some subjects are able to modify stride amplitude in response to a temporal cue without explicit instruction to do so. See chapter 2 for a more detailed

comparison of these studies. There is limited evidence for the impact of auditory cues on gait variability, Hausdorff (Hausdorff et al., 2007), reported an improvement in stride and swing time variability but only when delivered 10% above preferred frequency.

The auditory cue in the present study was delivered at preferred stepping frequency and therefore was not imposing a change in gait pattern. The auditory cue did not influence gait variability on medication, despite significant effects on walking speed and stride amplitude, but resulted in a significant improvement off medication where no change was observed in speed or amplitude. This may suggest a specific effect of the presence of the pacing cue on variability which is only present when gait is at its most unstable, i.e. off medication. In addition, the cue frequency necessary to influence gait variability may be different depending on medication status, as Hausdorff (Hausdorff et al., 2007) found an improvement on medication with a frequency of 10% above preferred stepping frequency, whereas the present study used preferred stepping frequency and saw an improvement off medication. Stability is improved off medication with the auditory cue without improving speed or amplitude, providing further evidence gait variability is a marker of a distinct mechanism to that of mean gait measures. Chapter 6 will explore what factors may contribute to gait variability.

The interaction effect seen was related to an opposing effect seen with the attentional cue, which increased variability on medication and had no effect off medication. Giving instructions to modify only the spatial parameter of gait increased the

mismatch in amplitude and frequency, as subjects increased stride amplitude with the attentional cue, but reduced step frequency in order to achieve this; this may be one reason for the increased variability seen with the attentional cue. As discussed. Almedia found subjects did not alter stride length in response to an auditory cue aimed at changing step frequency and this resulted in increased variability on but not off medication (Almeida et al., 2007). The cueing frequency used in the present study was higher (matched to subject's preferred stepping frequency) than that used in Almeida's study which may explain the difference in findings. It is unclear why variability would be raised on medication only but may be due to the already raised variability when off medication causing a ceiling effect with subjects already being at their most variable. This may also explain why the increase in variability was not seen in the dual task. The increase in variability and reduction in step frequency seen with the attentional cue does not agree with Morris (Morris et al., 1996) who suggests that by correcting stride amplitude, other parameters of gait are also normalised, however her studies did not incorporate measures of gait variability.

The different direction of change seen in stride time variability between cue types is in contrast to the laboratory based study where all cues reduced variability although this was significant for the combination cue only. This may be related to the added complexity of testing in the home environment where any increased competition for attention resources would be more apparent.

In agreement with previous findings (see chapter 3) (Baker, Rochester & Nieuwboer, 2007b) the combination cue was equally effective in improving walking speed and

stride amplitude as the attentional cue and more effective than the auditory cue alone

when on medication. Off medication however the combination cue had a greater

effect on walking speed than both the attentional and auditory cues. Again there

appears to be added benefit of using a cueing strategy which gives both temporal and

spatial information. It may be that the added benefit of the pacing element of the cue

is more apparent when bradykinesia is most severe.

Step frequency was reduced more with the attentional cue than with the auditory and

combination cues in all conditions except the on medication dual task where the

combination cue resulted in a similar reduction. The combination cue significantly

improved walking speed, stride amplitude and gait variability in the on medication

dual task, despite a significant reduction in step frequency, unlike the attentional cue.

This suggests that the improvement seen with the combination cue is not entirely

explained by the kinematic control of temporal and spatial parameters. Cues are

proposed to have an influence on the attentional cost of walking (Rochester *et al.*,

2005; Rochester *et al.*, 2007), with different cognitive demands placed on attentional

resources with internal and external cueing strategies. Imaging studies have shown

that movement which occurs in response to an external stimulus preferentially

activate parieto-premotor pathways with an overall reduction in brain activity

(Hanakawa *et al.*, 1999a; Weeks *et al.*, 2001; Debaere *et al.*, 2003). Although subjects

were able to respond appropriately to the attentional cue, by adapting stride amplitude

as instructed, perhaps having to internally generate the cue requires large amounts of

attentional resource. Stride to stride variability is thought to reflect gait automaticity

and is increased in the presence of basal ganglia dysfunction (Hausdorff et al., 1998),

and it was this measure which differentiated between the attentional and combination cues.

Subjects in the present study performed poorly on tests of executive function and attention, with deterioration off medication, however the combination cue was effective both on and off medication and reduced dual task interference and would therefore appear not to require high levels of attention or executive function. Poor executive function is associated with increased difficulty with dual tasks and increased gait variability (Rochester *et al.*, 2004; Yogev *et al.*, 2005). Rochester et al (Rochester *et al.*, 2005; Rochester *et al.*, 2007) demonstrated a reduction in dual task interference with cues in people with PD, with cues having greater effects during dual than single tasks. The authors proposed greater reliance on external information with increasing task difficulty with cues acting as an attentional biasing signal, allowing the subject to appropriately prioritise the task of gait and removing the need to plan and monitor movement (Rochester *et al.*, 2005; Rochester *et al.*, 2007). This is supported by the improvement in variability being seen with the external cues but not the attentional strategy in the present study.

Variability in the support phases of gait is proposed to reflect dynamic balance control (Gabell & Nayak, 1984). Only the combination cue reduced DLS time variability significantly, with small reductions seen with the auditory cue and no effect with the attentional strategy. This suggests that both the spatial and temporal gait disturbance in PD contribute to instability in walking and both should be addressed in order to improve this component of gait. This has important implications

for the clinical application of cues. In addition to increasing walking speed and stride amplitude, the influence of cues on gait variability and stability should be evaluated to ensure subjects are not compromising safety in order to alter their gait pattern. This finding also supports the hypothesis that stride time and DLS time variability are measuring distinct factors; this will be explored in chapter 6.

Clinical application

The sample in the present study was predominantly of moderate disease severity and showed disturbance of both motor and cognitive function. Farley (Farley & Koshland, 2005) investigated the effect of an attentional strategy similar to that used in the present study and found those with mild disease severity were more able to spontaneously use the strategy to increase speed, whereas more impaired subjects required encouragement to use strategy. This may be related to the level of executive dysfunction and therefore the ability to correctly identify the need to use the attentional strategy. Although this study did not explore the impact on gait variability it may be that attentional strategies are appropriate earlier in the disease with external cues becoming increasingly important with progression of motor and cognitive symptoms.

The improvements in stride time and DLS time variability with the combination cue were present both on and off medication. Despite gait and balance dysfunction being greatest off medication, falls incidence increased when optimally medicated due to increased mobility and activity at these times (Bloem, Steijns & Smits-Engelsman, 2003). Therefore strategies are needed which maximise safe and effective mobility

when on medication and also allow increased independence when off medication.

The combination cue appears to offer some promise as a strategy to address these

issues, influencing both mean spatiotemporal parameters and gait variability in a way

which is easily applied during functional tasks in an ecologically valid environment.

The short term carry over of cueing effect seen in the present study reflects that

reported by others. In the immediate term when cues are removed the increased

attention to gait is retained. However, studies with longer follow up show that this

improvement is not retained (Morris *et al.*, 1994; Rochester *et al.*, 2007), suggesting

a reliance on the presence of the external cue.

Study limitations

Subjects were tested in their own home in order to evaluate gait and functional

activity in an ecologically valid environment. This meant that space was limited and

walkway length reduced. It is accepted that when measuring gait variability, the

greatest possible number of strides should be used to calculate coefficient of

variability with 5 strides being recommended as a minimum (Hausdorff, 2005). In the

current study the median number of strides recorded was 4.5. The sample was heavily

biased towards those with freezing of gait with 40 out of 50 subjects being freezers.

This reduces the generalisation of the results as differential effects of cues have been

shown in freezers and non-freezers in terms of cue delivery (Willems et al., 2006) as

well as differences in measures of gait variability (Hausdorff et al., 2003). Further

investigation is required to determine if freezers and non-freezers do respond

differently to internal and external cues. In addition the design of the functional task

with the incremental increase in complexity from single to dual tasks does not allow

randomisation of task difficulty which may have led to some carry over or learning

effects which would lead to an underestimation of the impact of the dual task. The

secondary motor task was chosen to reflect an everyday, familiar task but did not

allow performance of the task to be measured.

Conclusion.

The present study extended previous work in exploring the effects of internal and

externally generated cue strategies by examining the influence of dopaminergic

medication. Positive effects on gait were seen with and without medication,

suggesting the mechanism of improvement did not rely on dopaminergic pathways.

The present study provides evidence for the effectiveness of cues that are specific

and focussed, in terms of providing information in relation to both the spatial and

temporal parameters of gait both of which are affected in PD.

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Suppliers.
  a. B&L Engineering
  b. TEMEC Instruments Inc, Spekhofstraat 2, 6466 LZ Kerkrade, The Netherlands.
  c. Version 12; SPSS Inc, 233 S Wacker Dr, 11th Fl, Chigago, IL 60606, USA.

Chapter 6

Which clinical characteristics contribute to cued and non-cued gait variability?

6.1. Abstract.

Increased gait variability is thought to reflect disruption in the automatic stepping

mechanism and has been shown in previous chapters to be responsive to cues. This

chapter aimed to explore which clinical characteristics from personal, motor,

cognitive and affective domains contribute to PD subject's gait variability in cued and

non-cued walking. Data collected on 50 people with PD in the study described in

chapter 5 were entered into linear regression models. Increased stride time and DLS

time variability in the single task was associated with increased scores on the UPDRS

III, indicating more severe motor symptoms. The variance seen in stride time

variability in the dual task was more weakly explained by UPDRS III, although this

was still significant. UPDRS III remained the strongest predictor of DLS time

variability in the dual task, but other motor, cognitive and affective characteristics

also contributed. Cued stride time and DLS time variability in the single task was

explained by affective and cognitive characteristics. Regression models were unable

to explain the variance in cued gait variability in the dual task. Differences in which

factors are able to predict gait variability with and without cues support the view that

movement occurring in response to a cue uses different mechanisms of motor control

compared to movement which is internally generated

Chapter 6

6.2. Introduction.

Recent interest in the contribution of non-motor influences on motor control has led

to an increasing appreciation of the relationship between higher level cognitive

function and gait disturbances (Snijders et al., 2007). It is now well accepted that gait

is not a fully automated task, but rather utilises attention and executive functions

(Yogev-Seligmann, Hausdorff & Giladi, 2008) (see chapter 2, section 2.3 and 2.4).

The role of executive function in gait is thought to be in part, to allow a person to

evaluate the demands of a given task or environment, prioritise these demands and

allocate attention where it is needed (Coppin et al., 2006; Yogev-Seligmann,

Hausdorff & Giladi, 2008). The inability to correctly prioritise gait and balance tasks

has been demonstrated to contribute to increased gait variability (Beauchet et al.,

2007) and falls (Faulkner et al., 2007) in older adults.

Falls are related to cognitive as well as gait dysfunction; fallers are thought not to

modify gait appropriately to improve safety (Bloem et al., 2006; Yogev-Seligmann,

Hausdorff & Giladi, 2008). This is supported by the link between falls risk, gait

variability and performance on tests of executive function which has been

demonstrated in older adults (Rapport et al., 1998) and PD subjects (Hausdorff,

Balash & Giladi, 2003).

Regulation of gait variability is normally largely automated, requiring minimal

cognitive input (Hausdorff et al., 1998). Stride time variability is said to reflect the

neural control system's ability to maintain a steady walking rhythm (Gabell & Nayak,

1984). This measure has been found to correlate more closely with measures of executive function than with other gait measures both in older adults and those with neurological deficit (Hausdorff, Balash & Giladi, 2003; Sheridan *et al.*, 2003; Hausdorff *et al.*, 2005; Yogev *et al.*, 2005; Springer *et al.*, 2006). Stride time variability is significantly increased with the addition of a dual task while walking in PD subjects (Hausdorff, Balash & Giladi, 2003; Yogev *et al.*, 2005; Baker, Rochester & Nieuwboer, 2007). In a regression model Hausdorff found that severity of motor symptoms was predictive of increased stride time variability in PD subjects (Hausdorff et al., 1998).

Gait variability is increasingly used as a measure of gait dysfunction, however the causes of increased variability and the validity of the methods used to describe it remain unclear. Variability in the time spent in double limb support (DLS) is thought to reflect dynamic balance mechanisms (Gabell & Nayak, 1984) however this measure has received less attention than stride time variability. There is little indication therefore on the causes of increased DLS time variability.

The previous chapter showed that although an internal (attentional) and an external (the combination of an instruction to increase step size with a rhythmical auditory tone) had similar effects on mean walking speed and stride length, their effect on gait variability was different. The independence of measures of gait variability and mean spatiotemporal parameters has been demonstrated in older adults and PD subjects (Gabell & Nayak, 1984; Blin, Ferrandez & Serratrice, 1990; Schaafsma *et al.*, 2003;

Hausdorff *et al.*, 2005; Yogev *et al.*, 2005; Baker, Rochester & Nieuwboer, 2007). One proposed explanation for the improvement in gait variability with the combination cue only was that the presence of the auditory tone facilitated the allocation of attention to gait, without the subject having to maintain this internally. An alternative explanation is that the combination cue in addressing both spatial and temporal gait parameters is reducing the frequency-amplitude mismatch observed in PD gait.

This study aims to further explore the reasons for the differing responses to the internal and external cueing strategies by examining the clinical characteristics which are associated with gait variability when using each of the cues, on medication. In addition, by comparing the predictors of cued gait with those of non-cued baseline walking we can learn more about the effect of cues on motor control in PD. The relationship between cued and non-cued gait variability and clinical characteristics from person, motor, cognitive and affective domains is explored. These characteristics were chosen because of previous work demonstrating a link to gait variability (see chapter 2, section 2.2).

This study used regression models in order to address the following questions; (1) which clinical characteristics, including personal, motor, cognitive and affective measures, contribute to the increased level of gait variability observed in PD, (2) do different characteristics explain variability of stride time and double limb support time, (3) does task complexity influence the contributory factors for gait analysis, (4)

are the same characteristics associated with cued gait variability, (5) do internal and

external cueing strategies utilise the same or different elements of motor control?

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6.3. Methods.

The experimental protocol used to collect gait variability data has been previously described in chapter 5. Subjects walked with and without cues (see chapter 5, table 5.1 for description of cues) under single and dual task conditions (see chapter 5, figure 5.1 for description of experimental protocol). Although subjects were tested on and off medication, only results from the on medication gait analysis is used in this chapter.

Explanatory characteristics.

14 characteristics were selected which were grouped into four domains as shown below. These were evaluated at home at the same time as the experimental protocol during the on medication assessment.

1. Personal: age.

2. Motor: UPDRS section III measured disease severity; the revised freezing of gait questionnaire was used to identify those subjects who were freezers using a dichotomous score to indicate presence or absence of freezing of gait; total daily intake of dopamine (mg) was used as another measure of disease severity and was normalised to daily equivalent amount of levodopa (mg) and is calculated according to the method described in detail by Krause (Krause et al., 2001); history of falls within the previous 6 months was recorded using a dichotomous score indicating falls or no falls; balance was measured using the single leg and tandem stance tests, again using a dichotomous score for pass

or fail, with subjects passing if they could maintain the test for 30 seconds on either leg.

3. Cognitive: The Hayling and Brixton tests of executive function and the Test of Everyday Attention were used and are described in detail below.

4. Affective: The Mulitdimensional Fatigue Inventory (MFI) is a 20 item questionnaire that evaluates physical and mental fatigue symptoms (Smets *et al.*, 1995). The Hospital Anxiety and Depression Scale (HADS) is screening test which identifies and distinguishes between symptoms of anxiety and depression (Zigmund & Snaith, 1983). The Falls Efficacy Scale (FES) measures confidence in performing a range of activities of daily living without falling.

Hayling and Brixton Tests of Executive Function

The Hayling and Brixton tests have been shown to be valid and reliable measures of dysexecutive function (Burgess & Shallice, 1997). The Hayling sentence completion test has two components. In the first section, participants are read a series of 15 sentences that have the last word omitted and are required to suggest as quickly as possible an appropriate word that completes the sentence. In the second part subjects again listen to a series of 15 sentences but this time must respond as quickly as possible with a word that is unconnected in every way to the sentence. The first part of the test measures response initiation speed while the second measures response suppression ability, both of which are linked with frontal lobe function. The Brixton

test measures the ability to detect rules in a sequence of stimuli, and assesses spatial anticipation.

The Test of Everyday Attention (TEA)

The TEA tests the separate attentional systems using familiar everyday materials making it plausible and acceptable to patients (Robertson et al., 1994). Two domains of the TEA were used; the telephone search and the telephone search while counting. The telephone search involves the subject looking for key symbols while searching a simulated telephone directory and has been shown to reflect selective attention. The telephone search while counting uses the same task but the subject must simultaneously count strings of tones presented on an audio tape which reflects divided attention. There are different versions of each of the subtests of the TEA to allow testing on different occasions with parallel material.

Data Analysis.

Bivariate correlations were used to inspect the relationship between each of the predictors and the outcome variables; stride and DLS time variability at baseline and with the attentional and combination cues.

Multiple linear regression analysis explored the importance of 14 clinical characteristics to cued and non-cued variability (coefficient of variation of stride time and DLS time) in single and dual tasks. For each gait variability measure in each condition, an exploratory multiple linear regression model was fitted by forcing all 12

explanatory variables into the model. Beta coefficients were inspected and only those with P values of ≤ 0.2 were entered into a second model. Part correlation coefficients and their R2 are reported for each variable in the model to describe their unique contribution to the measure of gait variability.

All assumptions of linear regression models were met; all predictor variables were quantitative or categorical, displayed non-zero variance, absence of perfect multicollinearity (identified with eigenvalues), absence of autocorrelation (using the Durbin-Watson statistic, all with values less than 3), lack of homoscedasticity, independent normally distributed errors.(Field, 2005) Outliers were identified but did not exceed 5% of the sample in any of the models and no change to the outcome of the model resulted if they were removed, therefore the whole sample was included in the regression models. The alpha level was set at 0.05.

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6.4. Results.

Subject characteristics.

Demographic data for the sample of 50 subjects with idiopathic PD are described in

detail in chapter 5. Clinical characteristics which were used as explanatory variables

in the regression model are shown in table 6.1. Motor characteristics indicate

moderate disease severity, with 80% of the sample being categorised as freezers and

slightly more than half of the sample categorised as fallers. Cognitive tests revealed

moderate average scores on the Hayling test and poor performance on the Brixton test

of executive function. Mean scores on both the single and dual task components of

the TEA were at the lower end of normal range. Affective characteristics revealed

below average confidence not to fall with the FES, while the HADS scale revealed

the presence of both anxiety and depression in the sample.

Table 6.1. Clinical characteristics of PD subjects (N=50) as tested on medication.
Mean and standard deviation (SD) or are reported, except for dichotomous data for
which numbers are presented.

		Mean (SD)	Number
Personal	Age	69.2 (6.6)	
Motor	UPDRS III	35 (9.3	
	Freezers/non-freezers		40/10
	Fallers/non-fallers		27/23
	Single leg stance pass/fail		10/40
	Tandem stance pass/fail		21/29
Cognitive	Hayling	5.5 (1.8)	
	Brixton	3.8 (2.2)	
	TEA Single	6.3 (3)	
	TEA Dual	7.1 (2.7)	
Affective	HADS Depression	7.1 (3.6)	
	HADS Anxiety	7.9 (3.6)	
	MFI	14.4 (9.5)	
	FES	6.6 (2)	

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Table 6.2. shows stride time and DLS time variability in the single and dual task.

Stride time variability was significantly raised in the dual task compared to the single

task during non-cued walking (T=2.630, P=0.01). There was no significant difference

found between single and dual task DLS time variability.

Table 6.2. Non-cued baseline gait variability in the single and dual task. Values
shown are mean (SD).

	Single task Mean (SD)	Dual task Mean (SD)
Stride time CV (%)	4.43 (2.03)	5.34 (1.39)
DLS time CV (%)	6.94 (2.25)	7.66 (3.35)

Baseline gait variability.

Single task.

Table 6.3 shows the bivariate analysis of the 15 explanatory variables with stride time

and DLS time variability in the single task. A correlation stronger than $P \leq 0.2$ existed

between stride time variability and scores on the Hayling, Brixton, HADS Anxiety

and UPDRS III and age. HADS anxiety and UPDRS III correlated with DLS time

variability. Exploratory variables with a P value ≤ 0.2 were taken forward into a

second model.

Table 6.3. Bivariate analysis of explanatory variables for stride time and double limb support time variability during non-cued baseline walking in the single task. Unstandardised regression coefficients (B), standard errors (SE), standardised regression coefficients (β) and P values are reported.

			B	SE	β	P
Stride time CV	Personal	Age	0.07	0.05	0.22	0.17
	Motor	UPDRS III	0.15	0.05	0.7	<0.001
		FOGQ	-0.3	0.84	-0.06	0.72
		Falls	-0.14	0.89	-0.03	0.88
		Single leg stance	0.54	0.9	0.11	0.55
		Tandem stance	0.41	0.75	0.1	0.59
		Medication	0	0	-0.02	0.89
	Cognitive	Hayling	0.27	0.19	0.24	0.16
		Brixton	0.27	0.15	0.3	0.09
		TEA Single	0	0.11	0	0.98
		TEA Dual	-0.04	0.15	-0.05	0.79
	Affective	HADS - Anxiety	-0.23	0.12	-0.42	0.06
		HADS - Depression	0.13	0.1	0.22	0.23
		MFI - Total	0.07	0.08	0.25	0.36
		FES	-0.02	0.01	-0.22	0.25
DLS time CV	Personal	Age	-0.02	0.04	-0.06	0.6
	Motor	UPDRS III	0.2	0.04	0.87	<0.001
		FOGQ	-0.67	0.65	-0.12	0.31
		Falls	-0.1	0.68	-0.02	0.89
		Single leg stance	0.49	0.69	0.09	0.48
		Tandem stance	0.04	0.58	0.01	0.95
		Medication	0	0	-0.13	0.28
	Cognitive	Hayling	0.1	0.15	0.09	0.48
		Brixton	0.08	0.12	0.08	0.5
		TEA Single	-0.07	0.08	-0.09	0.42
		TEA Dual	0.06	0.11	0.07	0.61
	Affective	HADS - Anxiety	0.16	0.09	0.27	0.09
		HADS - Depression	-0.07	0.08	-0.1	0.42
		MFI - Total	-0.02	0.06	-0.07	0.73
		FES	0	0.01	-0.02	0.86

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Single task baseline non-cued stride time variability.

Five characteristics from personal (age), motor (UPDRS III), cognitive (Hayling and

Brixton) and affective (HADS Anxiety) domains were forced into a second regression

model with non-cued single task stride time variability as the outcome variable. 55%

of the variance associated with non-cued single task stride time variability was

explained by the model but only one motor characteristic, UPDRS III, was significant

and the unique contribution of this variable accounted for 26% of the variance (table

6.4). The association between UPDRS III and stride time variability is shown in

figure 6.1.a, with greater variability seen in those with higher UPDRS III scores

indicating more severe disease symptoms.

Single task baseline non-cued DLS time variability

Two characteristics from motor (UPDRS III) and affective (HADS Anxiety) domains

were forced into a second model with non-cued DLS time variability in the single

task as the outcome variable. 62% of the variance associated with non-cued DLS time

variability in the single task was explained by the model with only UPDRS III being

significant, with a unique contribution of 57% (table 6.4). DLS time variability was

greatest in subjects with higher UPDRS III scores (figure 6.1b).

Table 6.4. Non-cued baseline variability in the single task; regression coefficients of the variables entered into the final model Standardised regression coefficients (β) and P values are reported with explanatory variables which significantly contribute to the model indicated by an *. Part correlations and R^2 values are reported for each explanatory variable representing the unique contribution to the model. R^2 and F change are given for each model.

		B	P value	Part Correlation	R^2 Part Correlation
Stride time CV (%)	Hayling	0.14	0.32	0.13	0.02
	Brixton	0.23	0.13	0.2	0.04
	Age	0.21	0.11	0.2	0.04
	HADS - Anxiety	-0.06	0.62	-0.06	0
	UPDRS III	0.57	<0.001*	0.51	0.26
	R^2=0.547; Significant F Change=0.006				
DLS time CV (%)	HADS - Anxiety	0.12	0.19	0.12	0.01
	UPDRS III	0.76	<0.001*	0.75	0.57
	R^2=0.616; Significant F Change<0.001				

Figure 6.1. Relationship between gait variability during non-cued baseline single task walking and scores on the UPDRS III.

a) Stride time variability   b) DLS time variability
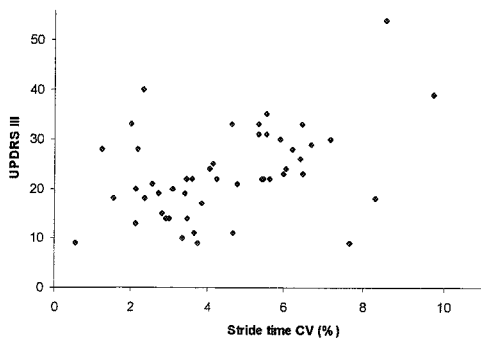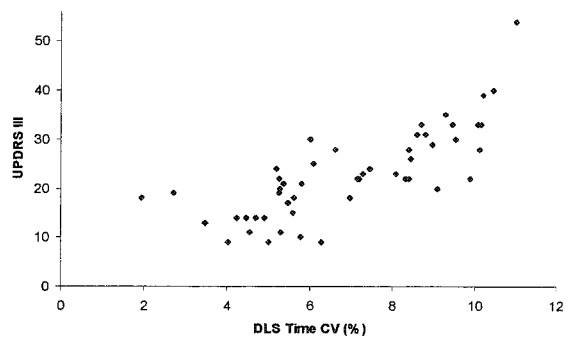
Dual task.

Table 6.5. Bivariate analysis of explanatory variables for stride time and double limb support time variability during non-cued baseline walking in the dual task. Unstandardised regression coefficients (B), standard errors (SE), standardised regression coefficients (β) and P values are reported.

			B	SE	β	P
Stride time CV	Personal	Age	0.04	0.03	0.17	0.28
	Motor	UPDRS III	0.07	0.03	0.49	0.03
		FOGQ	-0.21	0.58	-0.06	0.72
		Falls	0.2	0.61	0.07	0.75
		Single leg stance	-0.32	0.62	-0.09	0.61
		Tandem stance	0.27	0.52	0.09	0.61
		Medication	0	0	-0.21	0.21
	Cognitive	Hayling	0.1	0.13	0.12	0.47
		Brixton	0.08	0.1	0.14	0.43
		TEA Single	0.02	0.07	0.04	0.79
		TEA Dual	-0.07	0.1	-0.13	0.49
	Affective	HADS - Anxiety	-0.07	0.08	-0.19	0.38
		HADS - Depression	0.09	0.07	0.22	0.24
		MFI - Total	0.05	0.05	0.27	0.32
		FES	0	0.01	0	0.98
DLS time CV	Personal	Age	-0.05	0.04	-0.1	0.18
	Motor	UPDRS III	0.28	0.04	0.76	0
		FOGQ	1.39	0.64	0.16	0.04
		Falls	0.8	0.67	0.12	0.24
		Single leg stance	-0.45	0.68	-0.05	0.52
		Tandem stance	1.03	0.57	0.15	0.08
		Medication	0	0	-0.06	0.42
	Cognitive	Hayling	0.03	0.14	0.02	0.83
		Brixton	0.19	0.11	0.13	0.1
		TEA Single	-0.18	0.08	-0.16	0.03
		TEA Dual	-0.12	0.11	-0.09	0.31
	Affective	HADS - Anxiety	-0.02	0.09	-0.02	0.81
		HADS - Depression	-0.01	0.08	-0.01	0.93
		MFI - Total	0.01	0.06	0.03	0.83
		FES	0.01	0.01	0.06	0.47

Table 6.5 shows the bivariate analysis of the 15 explanatory variables with stride time

and DLS time variability in the dual task. A correlation stronger than $P\leq0.2$ existed

between stride time variability and UPDRS III score only. Brixton, FOGQ, TEA

single, UPDRS III, tandem stance scores and age correlated with DLS time

variability. Exploratory variables with a P value ≤ 0.2 were taken forward into a

second model.

Dual task baseline non-cued stride time variability

Only UPDRS III was correlated strongly enough with dual task stride time variability

to be entered into the second model. 18% of the variance associated with non-cued

dual task stride time variability was explained by UPDRS III score (table 6.6). Higher

UPDRS III scores were associated with higher levels of stride time variability.

Dual task baseline non-cued DLS time variability

Six characteristics from personal (age), motor (UPDRS III, FOGQ and tandem

stance), cognitive (Brixton and TEA single) were forced into a second model. 87% of

the variance associated with non-cued dual task DLS time variability was explained

by the model (table 6.6). All predictors except age significantly contributed to the

model. Examining the unique contribution of each variable (table 6.6) UPDRS III

most strongly contributes to DLS time variability, with the unique contribution

explaining 54% of the variance. As in the single task, higher UPDRS III scores (more

severe motor symptoms) was associated with higher stride time and DLS time

variability in the dual task.

Table 6.6. Non-cued baseline variability in the dual task; regression coefficients of the variables entered into the final model Standardised regression coefficients (β) and P values are reported with explanatory variables which significantly contribute to the model indicated by an *. Part correlations and R^2 values are reported for each explanatory variable representing the unique contribution to the model. R^2 and F change are given for each model.

		B	P value	Part correlation	R^2 Part Correlation
Stride time CV (%)	UPDRS III	0.43	<0.001*		
R^2=0.183; Significant F Change=0.002					
DLS time CV (%)	Brixton	0.14	0.03*	0.12	0.02
	Age	-0.07	0.24	-0.07	0
	FOGQ	0.12	0.04*	0.12	0.01
	TEA_Single	-0.19	<0.001*	-0.18	0.03
	UPDRS III	0.87	<0.001*	0.74	0.54
	Tandem stance	0.13	0.04*	0.12	0.01
R^2=0.874; Significant F Change<0.001					

Cued gait variability.

Single task.

Table 6.7 shows the bivariate analysis of the 15 explanatory variables with cued

stride time and DLS time variability in the single task. Exploratory variables with a P

value ≤ 0.2 were taken forward into a second model.

Table 6.7. Bivariate analysis of explanatory variables for stride time and double limb support time variability during cued trials, using the attention and combination cue strategies in the single task. Unstandardised regression coefficients (B), standard errors (SE), standardised regression coefficients (β) and P values are reported.

			Attention				Combination			
			B	Std. Error	Beta	P	B	Std. Error	Beta	P
Stride time CV	Personal	Age	-0.01	0.04	-0.05	0.78	0	0.02	-0.02	0.9
	Motor	UPDRS III	-0.01	0.04	-0.07	0.78	0	0.02	0.04	0.88
		FOGQ	0.9	0.74	0.22	0.24	0	0.4	0	0.99
		Falls	0.3	0.78	0.09	0.7	-0.03	0.43	-0.02	0.95
		Single leg stance	0.03	0.8	0.01	0.97	-0.21	0.43	-0.1	0.63
		Tandem stance	-0.1	0.67	-0.03	0.88	-0.08	0.36	-0.04	0.83
		Medication	0	0	-0.01	0.94	0	0	0.05	0.79
	Cognitive	Hayling	0.28	0.17	0.31	0.11	0.02	0.09	0.04	0.82
		Brixton	-0.02	0.13	-0.03	0.88	0.15	0.07	0.39	0.05
		TEA Single	0.19	0.09	0.35	0.05	0	0.05	0	0.99
		TEA Dual	-0.21	0.13	-0.35	0.11	-0.01	0.07	-0.02	0.94
	Affective	HADS - Anxiety	-0.23	0.1	-0.52	0.04	-0.04	0.06	-0.17	0.48
		HADS - Depression	0.1	0.09	0.21	0.31	-0.03	0.05	-0.11	0.6
		MFI - Total	0.11	0.07	0.48	0.11	0.08	0.04	0.66	0.03
		FES	0.01	0.01	0.23	0.28	0.01	0.01	0.24	0.25
DLS time CV	Personal	Age	-0.01	0.06	-0.03	0.82	0.01	0.07	0.03	0.88
	Motor	UPDRS III	0.06	0.05	0.22	0.31	-0.06	0.06	-0.24	0.35
		FOGQ	1.1	0.94	0.19	0.25	0.25	1.1	0.04	0.82
		Falls	-1.43	0.99	-0.31	0.16	0.49	1.16	0.1	0.68
		Single leg stance	0.11	1	0.02	0.91	-0.41	1.17	-0.07	0.73
		Tandem stance	0.76	0.84	0.16	0.38	0.19	0.99	0.04	0.85
		Medication	0	0	-0.29	0.07	0	0	0.09	0.63
	Cognitive	Hayling	-0.21	0.21	-0.16	0.32	0.34	0.25	0.26	0.18
		Brixton	0.01	0.17	0.01	0.96	-0.2	0.2	-0.2	0.32
		TEA Single	-0.25	0.12	-0.32	0.04	-0.03	0.14	-0.04	0.84
		TEA Dual	0.35	0.16	0.4	0.04	-0.17	0.19	-0.2	0.37
	Affective	HADS - Anxiety	-0.13	0.13	-0.2	0.33	0.19	0.15	0.29	0.23
		HADS - Depression	-0.22	0.12	-0.34	0.06	-0.17	0.14	-0.26	0.21
		MFI - Total	0.16	0.09	0.47	0.08	0.12	0.1	0.34	0.27
		FES	0.03	0.02	0.29	0.11	0.02	0.02	0.27	0.2

Chapter 6

Single task cued stride time variability.

Attention: Six characteristics from motor (single leg stance and tandem stance),

cognitive (Hayling and TEA single) and affective (HADS anxiety and MFI) domains

were forced into a second regression model. 19% of the variance associated with

single task stride time variability with the attentional cue was explained by the model

with MFI and HADS anxiety being significant, their unique contribution explaining

11% and 9% respectively, however overall the model's F change score was not

significant (table 6.8).

Combination: Two characteristics from cognitive (Brixton), and affective (MFI)

domains were forced into a regression model. 25% of the variance associated with

single task stride time variability with the combination cue was explained by the

model with both Brixton and MFI scores being significant, their unique contribution

explaining 16% and 12% of the variance respectively (table 6.8). Higher scores on

both the Brixton test and MFI were associated with greater stride time variability

when using combination cue.

Single task cued DLS time variability.

Attention: Seven characteristics from motor (falls and medication), cognitive (TEA

single and TEA dual) and affective (MFI, HADS Depression, and FES) domains were

forced into a second regression model. 36% of the variance associated with single

task DLS time variability with the attention cue was explained by the model with

cognitive (TEA single, TEA dual) and affective (MFI, HADS Depression)

characteristics being significant (table 6.8). The largest unique contribution was made

by HADS Depression which explained 14% of the variance, while MFI, TEA single

and dual and medication explained 8-9% each (table 6.8). Higher scores on each of

the scales were associated with higher variability with the attention cue.

Combination: Two characteristics from cognitive (Hayling) and affective (FES)

domains were forced into a regression model. The model was not able to explain the

variance associated with single task DLS time variability with the combination cue.

Table 6.8. Cued gait variability in the single task; regression coefficients of the variables entered into the final model. Standardised regression coefficients (β) and P values are reported with explanatory variables which significantly contribute to the model indicated by an *. Part correlations and R^2 values are reported for each explanatory variable representing the unique contribution to the model. R^2 and F change are given for each model.

		β	P	Part correlation	R^2 part correlation
Stride time CV (%) with attention cue	Hayling	0.20	0.21	0.18	0.03
	MFI	0.51	0.02*	0.34	0.11
	HADS - Anxiety	-0.44	0.04*	-0.3	0.09
	TEA Single	0.22	0.15	0.21	0.04
	Single leg stance	0.05	0.77	0.04	0
	Tandem stance	-0.05	0.80	-0.04	0
	R2=0.185; Significant F Change=0.197				
Stride time CV (%) with combination cue	Britxon	0.40	<0.001*	0.4	0.16
	MFI	0.34	0.01*	0.34	0.12
	R2=0.250; Significant F Change=0.001				
DLS time CV (%) with attention cue	FES	0.26	0.13	0.20	0.04
	MFI	0.44	0.03*	0.28	0.08
	HADS - Depression	0.47	0.01*	-0.38	0.14
	TEA Single	0.34	0.03*	-0.3	0.09
	TEA Dual	0.32	0.03*	0.28	0.08
	Medication	-0.31	0.03*	-0.29	0.09
	Falls	-0.16	0.27	-0.14	0.02
	R2=0.355; Significant F Change=0.011				
DLS time CV (%) with combination cue	Hayling	0.13	0.39	0.13	0.02
	FES	0.01	0.93	0.01	0
	R2=0.016; Significant F Change=0.677				

Dual task.

Table 6.9. Bivariate analysis of explanatory variables for stride time and double limb support time variability during cued trials, using the attention and combination cue strategies in the dual task. Unstandardised regression coefficients (B), standard errors (SE), standardised regression coefficients (β) and P values are reported.

			Attention				Combination			
			B	SE	β	P	B	SE	β	P
Stride time CV	Personal	Age	0.03	0.05	0.11	0.6	-0.02	0.03	-0.11	0.56
	Motor	UPDRS III	0	0.05	-0.01	0.97	0	0.03	-0.03	0.92
		FOGQ	-0.34	0.83	-0.09	0.68	-0.14	0.57	-0.05	0.81
		Falls	0.25	0.87	0.08	0.77	0.23	0.61	0.1	0.71
		Single leg stance	0.62	0.89	0.16	0.49	-0.31	0.61	-0.11	0.62
		Tandem stance	-0.13	0.74	-0.04	0.87	-0.33	0.52	-0.14	0.53
		Medication	0	0	0.05	0.8	0	0	0.01	0.95
	Cognitive	Hayling	0.05	0.19	0.05	0.8	-0.06	0.13	-0.1	0.64
		Brixton	0.01	0.15	0.01	0.95	0.13	0.1	0.27	0.21
		TEA Single	0.07	0.1	0.14	0.5	-0.09	0.07	-0.23	0.23
		TEA Dual	-0.04	0.14	-0.07	0.77	0.07	0.1	0.17	0.48
	Affective	HADS - Anxiety	-0.14	0.12	-0.33	0.22	0.01	0.08	0.03	0.9
		HADS - Depression	-0.03	0.1	-0.07	0.76	-0.07	0.07	-0.23	0.3
		MFI - Total	0.07	0.08	0.31	0.36	0.04	0.05	0.27	0.41
		FES	-0.01	0.01	-0.15	0.53	0.01	0.01	0.17	0.46
DLS time CV	Personal	Age	-0.03	0.08	-0.08	0.69	0	0.08	0.01	0.96
	Motor	UPDRS III	0.01	0.08	0.06	0.85	-0.07	0.08	-0.23	0.4
		FOGQ	0.14	1.31	0.02	0.91	0.52	1.37	0.07	0.71
		Falls	0.12	1.38	0.03	0.93	-0.3	1.45	-0.05	0.84
		Single leg stance	-0.94	1.4	-0.16	0.51	-1.29	1.47	-0.19	0.38
		Tandem stance	-0.11	1.17	-0.02	0.92	-0.21	1.23	-0.04	0.87
		Medication	0	0	0.01	0.97	0	0	-0.07	0.72
	Cognitive	Hayling	-0.01	0.3	-0.01	0.96	0.31	0.31	0.2	0.33
		Brixton	0.1	0.24	0.1	0.66	-0.23	0.25	-0.19	0.35
		TEA Single	0.09	0.17	0.11	0.6	-0.02	0.17	-0.03	0.89
		TEA Dual	0.03	0.23	0.03	0.89	-0.04	0.24	-0.04	0.86
	Affective	HADS - Anxiety	-0.13	0.18	-0.19	0.49	-0.06	0.19	-0.08	0.75
		HADS - Depression	0.07	0.16	0.09	0.69	-0.06	0.17	-0.08	0.72
		MFI - Total	0.07	0.12	0.2	0.57	0.21	0.13	0.52	0.11
		FES	0.02	0.02	0.24	0.32	0.05	0.02	0.43	0.06

Chapter 6

Stride time variability.

No characteristics were correlated strongly enough with dual task stride time

variability with either cue to enter into a final regression model and therefore the

variance in cued stride time variability in the dual task was not explained.

DLS time variability

Attention: No characteristics were correlated strongly enough with dual task DLS

time variability with the attentional cue to enter into a final regression model and

therefore the variance in this parameter was not explained.

Combination: Two affective characteristics (FES and MFI) were forced into a final

regression model. 12% of the variance associated with dual task DLS time variability

with the combination cue with both FES and MFI being significant (table 6.10). The

unique contribution of FES explained 8% and MFI 10% of the variance. Higher

scores on both the FES (greater fear of falling) and MFI (higher levels of fatigue)

were associated with greater DLS time variability with the combination cue in the

dual task.

Table 6.10. Cued gait variability in the dual task; regression coefficients of the
variables entered into the final model. Standardised regression coefficients (β) and P
values are reported with explanatory variables which significantly contribute to the
model indicated by an *. Part correlations and R^2 values are reported for each
explanatory variable representing the unique contribution to the model. R^2 and F
change are given for each model.

		β	P	Part correlation	R^2 part correlation
DLS time CV with the	FES	0.35	0.04	0.29	0.08
combination cue	MFI	0.39	0.02	0.32	0.10
	R2=0.119; Significant F Change=0.05				

Chapter 6

Summary of findings.

- Subjects scored below average on tests of executive function and attention and fell outside of normal range on measures of affective symptoms including depression, anxiety and fatigue

- Physical tests revealed moderate disease severity with freezing of gait in 40 out of 50 of the subjects and more than half of the sample categorising themselves as fallers.

- In the single task, the variance seen in stride time variability (55%) and DLS time variability (62%) was explained by UPDRS III, with more severe motor symptoms being associated with greater single task baseline variability.

- In the dual task, the variance seen in stride time variability was more weakly explained by UPDRS III score (18%). UPDRS III remained the strongest predictor of DLS time variability in the dual task, but scores on the Brixton, FOGQ, TEA single and tandem stance also significantly contributed to a model which explained 87% of the variance seen in DLS time variability.

- In the single task, MFI and HADS anxiety scores were found to be predictive of stride time variability with the attention cue (19% of variance explained), whereas Brixton and MFI scores predicted stride time variability with the combination cue (25% of variance explained). DLS time variability with the attentional cue was predicted by MFI, HADS Depression, TEA Single and TEA dual scores (36% of variance explained). DLS time variability with the combination cue was not explained by any of the predictors.

- In the dual task, none of the explanatory variables significantly predicted stride

  time variability during walking with either the attentional or combination cues.

  This was also true for DLS time variability with the attention cue. FES and MFI

  explained 12% of DLS time variability with combination cue in the dual task

  with higher scores associated with higher variability

6.5. Discussion.

This study aimed to address the question of which clinical characteristics explain the increased variability observed in the gait of PD subjects and whether internal and external cueing strategies change the relative predictive power of these variables. In agreement with other studies (Brown & Marsden, 1988; Hayashi, Hanyu & Tamaru, 1998; Dujardin *et al.*, 1999), PD subjects performed poorly on tests of executive function and attention. In addition, measures of affective symptoms revealed depression, anxiety and fatigue scores which fell outside of normal range (Zigmund & Snaith, 1983; Smets *et al.*, 1995). Physical tests revealed moderate disease severity, with freezing of gait in 40 out of 50 of the subjects and more than half of the sample categorising themselves as fallers.

Contributors to baseline gait variability in the single task.

Linear regression models were able to significantly explain baseline non-cued gait variability in the single task. Increased stride time variability was associated with increased scores on the UPDRS III, indicating more severe motor symptoms. This agrees with Hausdorff who examined the role of the basal ganglia in regulating gait stability by studying two basal ganglia disorders, PD and Huntington's disease (HD), and found greater variability was correlated with disease severity in both groups (Hausdorff et al., 1998). In addition this increased gait variability was not attributed to walking speed, as PD subjects walked more slowly than HD subjects, but variability was higher in HD (Hausdorff et al., 1998).

Similarly DLS time variability was highly explained by the UPDRS III score; subjects with more severe motor symptoms having greater variability. DLS time variability is thought to reflect dynamic balance control (Gabell & Nayak, 1984) and as increasing dysfunction of balance control is seen with disease progression, this would perhaps be expected. Unlike other balance outcomes which tend to measure static balance control, DLS time variability may be a promising measure of balance which reflects more closely instability during functional activity.

Contributors to baseline gait variability in the dual task

Differences in explanatory characteristics in single and dual task gait are presumed to be due to the increased attentional demand of the more complex task. Linear regression models were able to significantly explain baseline non-cued gait variability in the dual task. In contrast to the single task, the variance seen in stride time variability in the dual task was more weakly explained by UPDRS III score, although this was still significant. Previous studies have found greater association of cognitive rather than physical measures with gait variability when dual tasking (Hausdorff, Balash & Giladi, 2003; Sheridan *et al.*, 2003; Hausdorff *et al.*, 2005; Yogev *et al.*, 2005; Springer *et al.*, 2006; Beauchet *et al.*, 2007). The involvement of executive function and attention in models of dual task walking, suggests that gait control is not wholly automatic, but rather requires ability to recognise changes in task or environment, make necessary adjustments, prioritise and allocate attention particularly during functional activity (Rochester *et al.*, 2004; Yogev *et al.*, 2005; Holtzer *et al.*, 2006; Rochester *et al.*, 2008; Yogev-Seligmann, Hausdorff & Giladi,

2008). It is therefore surprising that the cognitive measures in the current study were not retained in the model predicting variability of stride time in the dual task. The much smaller amount of the variance of stride time variability explained by the UPDRS III in the dual task compared to the single task suggests that there must be other factors contributing, however none of the clinical characteristics included as predictors in the current study were explanatory.

As the complexity of the task or environment within which walking takes place increases, the role of cognitive functions such as attention and executive function is thought to become more important (Snijders et al., 2007). Rochester (Rochester et al., 2008) found similar characteristics were predictive of PD walking speed in single and dual tasks, but the relative contribution of these variables changed according to task. In contrast to the current results with variability, the contribution of UPDRS III to walking speed was relatively small in the single task and greater in the dual task. Rochester proposes this is due to the ability to use compensatory motor control to regulate walking speed in the single task, but due to the attentional cost of such strategies, subjects were unable to maintain this in the dual task. As gait variability is said to be a more sensitive measure and more closely related to gait automaticity it is possible that although subjects are able to use cognitive gait control to maintain walking speed in the single task, this increased attentional effort results in greater variability. In the dual task competition for attentional resources relegates gait control to subcortical structures and therefore other mechanisms may be responsible for the increased gait variability.

Hausdorff and colleagues (Hausdorff et al., 2005) supported the view that gait is a relatively complex motor task requiring executive function. Comparison of gait performance with a simple finger tapping task and a more complex upper limb catching task which required estimation, planning and real time adjustments in older adults found gait performance correlated strongly with the latter. Poor performance in the Stroop test which examines the ability to switch attention and adapt to changing demands was predictive of increased gait variability. The authors proposed that subtle changes in the motor control and sensory feedback systems lead to reduced automaticity of gait which in turn makes it necessary to employ cognitive strategies in order to integrate sensory information and regulate gait and balance. This in effect means that the person is carrying out a multi task while walking, requiring executive functions, specifically the ability to appropriate allocate attention. It is also assumed that this compensatory cognitive control of gait is less efficient and therefore leads to increased gait variability.

UPDRS III remained the strongest predictor of DLS time variability in the dual task, but executive function, attention, affective and other physical measures including balance and freezing of gait also significantly contributed to a model which explained 87% of the variance seen in DLS time variability in the dual task. However, the relative contribution of these predictors, although significant were much smaller than that of the UPDRS III. Although increased variability of the support phases of gait are proposed to reflect disruption of dynamic balance

mechanisms little is known about the clinical contributors of this parameter. Interestingly, the regression models in the present study were able to explain a larger proportion of the double limb support time variability than was the case with stride time variability, particularly in the dual task.

Previous studies have found that PD subjects show increased time spent in double limb support, and this is proportional to disease severity (Morris *et al.*, 1999; Sofuwa *et al.*, 2005). DLS time variability was found in one study to be twice that of controls (Hausdorff et al., 1998). One measure of static balance (tandem stance) was retained in the DLS time variability models which supports the proposal that this parameter reflects balance control. Also included in the model was freezing of gait classification, with the presence of freezing being predictive of increased DLS time variability in the dual task, agreeing with previous findings (Hausdorff *et al.*, 2003). Freezing of gait is strongly associated with falls in PD (Bloem et al., 2004). Incidence of falls was not retained in any of the regression models explaining either stride or DLS time variability. This is a surprising finding due to the strong association found between risk of falls and increased gait variability in older adults and PD subjects (Hausdorff, Balash & Giladi, 2003; Sheridan *et al.*, 2003; Hausdorff *et al.*, 2005; Yogev *et al.*, 2005; Springer *et al.*, 2006). Measure of falls in the present study was based on self-report and used a simple dichotomous score of faller or non-faller which may have been an insensitive measure.

Chapter 6

Contributors to cued gait variability in the single task.

The clinical characteristics predicting gait variability during cued walking were compared to those predicting baseline variability. In addition, by comparing gait variability predictors when walking with an internal and an external cueing strategy, inferences could be made as to whether these strategies use similar or separate mechanisms.

Less of the variance associated with cued stride and DLS time was explained by the regression models than during non-cued walking. UPDRS III, although strongly associated with non-cued gait variability, was not predictive of cued variability. This suggests that both internal and external cueing strategies reduce the influence of disease severity on gait variability. Previous studies have found differing effects of disease severity on the outcome of physical therapy. Nieuwboer et al found that disease severity was negatively associated with the outcome of a programme of physical therapy using primarily attentional (internal) cueing strategies (Nieuwboer et al., 2002), whereas when examining the clinical characteristics of subjects who had undergone a 3 week programme of cueing therapy based on rhythmical external cues, it was found that those with more severe motor symptoms showed greater improvement in posture and gait scores (Willems et al., 2006). Neither of these studies reported effect on gait variability. The present study looked at immediate responses to cues only and therefore comparison with studies concerned with a period of training is limited.

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Stride time variability in the single task was associated with fatigue and anxiety scores when walking with the internal (attentional) strategy. Fatigue was also retained in the model for stride time variability with the combination cue in addition to score on the Brixton test of executive function. DLS time variability with the internal (attention) cue was associated with fatigue, depression scores and performance on tests of sustained and divided attention, although none of these associations were particularly strong. None of the clinical characteristics were able to explain DLS time variability with the combination cue. This is again in contrast to non-cued DLS time variability which was strongly associated with disease severity in addition to other motor and cognitive measures.

Differences in the clinical characteristics contributing to gait variability with and without cues supports the view that movement occurring in response to a cue uses different mechanisms of motor control compared to movement which is internally generated. Imaging studies using upper limb tasks have shown that externally triggered movements produce significantly less activation of the frontal cortex than self initiated movements and the SMA is less active (and is activated later) when movement occurs in response to a trigger as it's role in preparation of movement is less necessary (Jueptner et al., 1996; Jenkins et al., 2000; Weeks et al., 2001; Cunnington et al., 2002). Therefore there is greater frontal lobe activity involved in internally generated movement whereas externally cued movements are more reactive with motor preparation being minimised (Weeks et al., 2001).

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Different clinical characteristics were associated with gait variability with internal (attention) and external (combination) cues compared to non-cued walking. This might suggest that not only do external cues result in motor control being re-routed via more cortical brain pathways, but simply attending to the desired movement may result in similar changes. However this must be interpreted alongside the performance data presented in chapter 5 which clearly demonstrates that although both strategies were equally effective in improving the mean spatiotemporal parameters of gait, only the combination cue improved variability. This may suggest that the combination cue not only increases attention to movement by acting as a prompt, but also has some specific influence which is reliant on the rhythmical nature of the cue. Hausdorff (Hausdorff et al., 2007) also demonstrated an improvement in gait variability with the application of a rhythmical external cue which was not found to be a simple by-product of improving speed or stride length. The authors proposed that the rhythmical external cue may have specific influence on neural circuitry, possibly involving areas such as the cerebellum (Hausdorff et al., 2007). As proposed in chapter 5 the combination cue addressing both temporal and spatial gait parameters may improve the temporo-spatial relationship in parkinsonian gait.

Contributors to cued gait variability in the dual task

The regression models were unsuccessful in explaining the variance in stride time variability with either the internal or the external cueing strategy in the dual task. DLS time variability was weakly predicted by confidence not to fall and fatigue with the external (combination) cue but not the internal (attention) strategy. This again

shows that not only is variability altered with combination cue, but also the clinical characteristics which contribute to the variability are very different in the presence of cues.

Limited conclusions can be drawn from the regression models presented here as to the distinct mechanism of control between internal and external cueing strategies due to the limited ability of the models to account for variability. Further work is now indicated to explore these issues in both healthy and patient populations. .

Limitations of the study

Gait variability is a relatively new gait parameter reported in the literature and therefore the present study was highly exploratory; the choice of a wide range of clinical characteristics entered into the regression model reflects this. The limited number of subjects and the inclusion criteria for the study may limit the ability to generalise the findings; subjects were selected to be able to complete the walking tests in the off condition and therefore those with severe walking difficulties were not included. Also, the sample were predominantly freezers and previous work has shown that freezers and non-freezers respond differently to cues (Willems et al., 2006). As discussed in chapter 5 the gait variability data was collected in the home and therefore calculated over a limited distance which represents a more ecologically valid context within which to observe gait. More work is needed to establish minimum standards for the collection of reliable gait variability data.

Chapter 6

Clinical implications and conclusions

It is becoming increasingly recognised that assessment of walking without consideration for non-motor domains such as cognition and affective symptoms has limited functional translation due to the increasing evidence linking neuro-cognitive parameters with a person's walking and functional ability (Snijders et al., 2007). The home environment is complex due to different lighting, floor coverings, cluttered environments and obstacles, therefore even everyday mobility can become an attentionally demanding task for those with reduced attentional capacity (Lord et al., 2006) and more so in people with PD who are utilising cognitive control for movements due to deficient basal ganglia function.

By identifying the characteristics which predict not only normal walking, but also walking under the influence of specific interventions, we can be increasingly targeted in our approach to treating the complex gait problems presented in PD. By increasing this knowledge we will ultimately be able to develop specific guidelines for the use of an intervention and the most appropriate time to implement it. This may also encourage the option of specific physical therapy strategies to be exploited in order to maximise the effectiveness of pharmacological or surgical interventions. It may be that it is a combination of approaches which is most appropriate in PD.

Chapter 6

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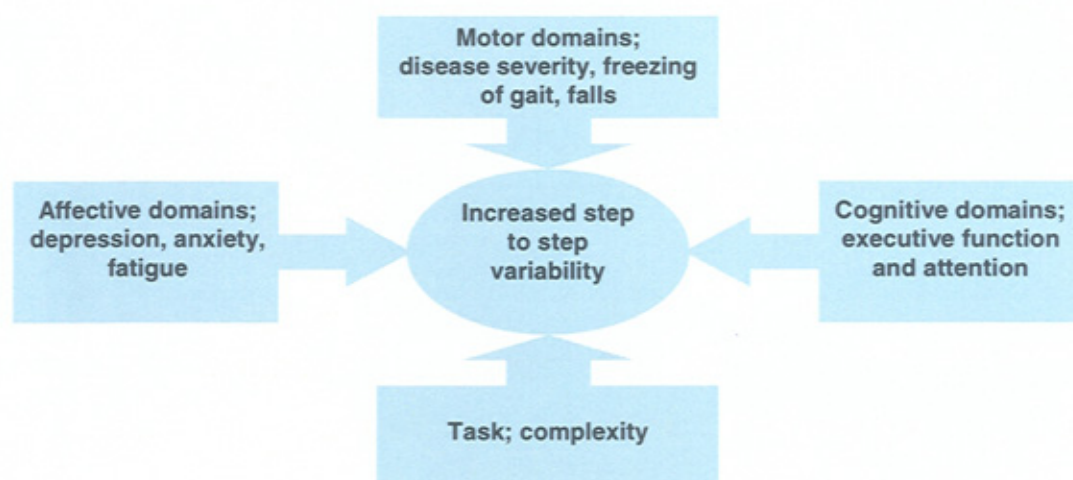
Chapter 7

Overall discussion.

Chapter 2 introduced key themes which formed the background to work presented in this thesis; the origin of the movement disorder and gait dysfunction in PD, cognition and dual tasking studies, cueing studies and gait analysis. This chapter will revisit these themes, integrating the findings of the four studies presented in the thesis and present some additional areas of interest which have emerged through the research in addition to suggesting some future areas of research.

7.1. Motor control and gait dysfunction in PD.

Gait variability has been described as a measure of gait control which is sensitive to disease severity (Blin, Ferrandez & Serratrice, 1990; Hausdorff *et al.*, 1998; Baltadjieva *et al.*, 2006), changes in cognitive load (Hausdorff, Balash & Giladi, 2003; Yogev *et al.*, 2005; Baker, Rochester & Nieuwboer, 2007) and medication status (Hausdorff *et al.*, 2003; Schaafsma *et al.*, 2003) in PD subjects and has been a particular focus throughout this thesis.

Figure 7.1. Contributors to increased step to step variability.

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Chapter 5 results showed an improvement in gait variability with dopaminergic

medication in agreement with others (Hausdorff *et al.*, 2003; Schaafsma *et al.*, 2003).

When considering the domains known to influence gait variability (figure 7.1) it is

likely that medication improves gait variability via the influence on motor domains.

The relationship between step amplitude and step frequency is known to improve

with medication (figure 7.2) but as with the improvement in gait variability is not

normalised. SMA activity is increased with dopaminergic medication which reduces

the underscaling of movement (Haslinger *et al.*, 2001) but has less effect on temporal

gait parameters. An important output from the basal ganglia circuitry is to the

pedunculopontine nucleus (PPN) which has a role in rhythmical lower limb

movements. The PPN influences movement via the globus pallidus, vestibular nuclei

and reticular areas and is mediated predominantly by acetylcholine (Lundy-Ekman,

2007). This may explain why movement timing is deficient in PD and is not

addressed by dopaminergic medication.

The step frequency/amplitude mismatch seen in PD may be as a result of an

imbalance between two systems, one dopaminergic and the other cholinergic. Morris

et al (2005) suggest that the mismatch comes from a deficiency between cortically

selected and actual movement amplitude (Morris *et al.*, 2005), emphasising the

importance of the spatial over the temporal elements of gait. However, temporal

parameters of gait including step frequency and gait variability also show change in

PD, particularly when correcting for the reduced walking speed. It seems therefore

that the mismatch results from changes in both domains. The possibility of this

premature 'break point' being a postural control mechanism to prevent a size of step

beyond safe limit in view of deficient balance responses should also be considered.

The 'break point' refers to the step frequency at which no further increase in step

amplitude is possible, this is reduced in PD and improved but not normalised with

dopaminergic medication (Morris *et al.*, 1998).

Figure 7.2. The relationship between step amplitude and step frequency in healthy
adults and people with PD on and off medication.
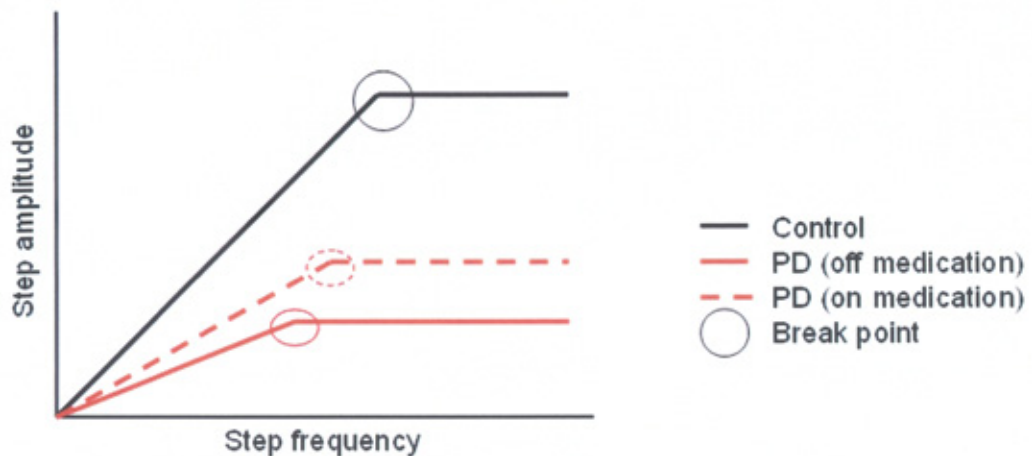
A strong link between gait variability and cognition, particularly attention and

executive function, has been established in previous studies (Hausdorff, Balash &

Giladi, 2003; Hausdorff *et al.*, 2005; Yogev *et al.*, 2005). A reduction in activity of

the anterior cingulate and the DLPFC is seen in PD subjects when off medication

compared to when on medication, these areas have substantial input to the pre-SMA

and also contribute to the cognitive abnormalities seen in PD (Cunnington *et al.*,

2002). Therefore there may also be a dopaminergic influence on gait variability via

the effect on cognition. The regression models presented in chapter 6 failed to show

the link between non-cued gait variability and measures of executive function and

attention, however there was a strong association with severity of motor symptoms.

Cognitive symptoms are known to worsen with disease progression and show a close

association with motor progression (Hayashi, Hanyu & Tamaru, 1998). It may be

therefore that the cognitive tests used were not sensitive enough to detect any

influence beyond that which would correlate with motor symptom severity.

The results of these studies are unable to determine whether the increased gait

variability seen in PD is as a result of reduced automaticity and therefore increased

cognitive demand of walking, or rather due to the alteration of both temporal and

spatial kinematics. In light of the complex range of factors known to contribute to

gait variability (figure 7.1) and the multi-factorial nature of gait control in PD

(Rochester *et al.*, 2008), it seems sensible to assume a role of both of these

mechanisms and further work is now indicated to explore this in more detail.

7.2. Implications of cognition and dual tasking.

The anterior cingulate and dorsolateral prefrontal cortex have specific roles in

response monitoring and attention, and are both influenced by dopamine (Brown &

Marsden, 1991; Dalrymple-Alford *et al.*, 1994). The dual task used in these studies

was chosen to reflect a familiar, functional task and no specific instruction was given

regarding prioritisation of task, in order to observe any influence of the cue in

prioritising gait.

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Psychological studies of healthy younger and older adults examined the ability to

train attentional control in dual tasks and found that improvement in dual task

performance lead to an improvement in dual task processing skills which also

enhanced performance of non-trained novel dual tasks (Kramer, Larish & Strayer,

1995; Erickson *et al.*, 2007). This suggests an improved ability to allocate attention.

More research is now needed to determine whether this training effect is seen in

people with executive dysfunction and specific dual task difficulty. Specific

instruction regarding attentional focus was thought to be particularly important to the

success of the training (Kramer, Larish & Strayer, 1995). The combination cue used a

specific instruction in order to alter the response to a rhythmical cue. The association

of a specific instruction with the tone may also have improved the allocation of

attention towards gait.

Other studies have shown improvement in motor performance with dual task training.

Elderly adults with balance impairment improved performance of a dual task balance

task only when training focussed on performance of dual tasks (Silsupadol *et al.*,

2006). An exploratory study has shown that in people with mild to moderate PD, a 3

week training programme where subjects walked with various additional tasks of

increasing complexity improved dual task gait performance (Canning, Ada &

Woodhouse, 2008). This provides promising evidence that dual task performance can

be improved even in populations with defective automatic motor control and

executive dysfunction. Cues are known to improve dual task performance in PD

(Rochester *et al.*, 2005; Rochester *et al.*, 2007). Further research is needed to explore

the potential to retrain functional activity in PD and also to explore the possibility of

using cues to facilitate improvement in dual tasks.

7.3. Cueing mechanisms.

Differences in the neural networks involved in internally and externally driven

movement have been clearly demonstrated in younger adults, with a clear distinction

in processing between the two (Jueptner et al., 1996; Weeks et al., 2001; Debaere et

al., 2003). In older adults however, this distinction appears to be lost. Using a

hand/foot coordination task, Heuninckx et al (Heuninckx, Wenderoth & Swinnen,

2008) demonstrated the disassociation of areas activated by internally and externally

driven movement in younger subjects. In elderly subjects however not only were

more extensive brain areas activated in both conditions, but the difference between

the two on imaging was lost despite an improvement in performance in the externally

guided condition. The external cue in this study was visual feedback generated by the

movement of the subjects themselves and therefore may not generalise to conditions

where the cue is presented irrespective of performance.

This has interesting implications for understanding the mechanism of cueing in PD,

as it is accepted that people with PD use more external guidance and this has been

thought to be a compensatory mechanism used in order to 'bypass' the basal ganglia

circuitry. However if the lack of dissociation between internally and externally driven

movement applies to PD, as it is likely to given the age of the population, then this is

likely to be a gross oversimplification. It maybe that cues improve the efficiency of

these more diverse pathways rather than utilising different pathways altogether. A recent review suggests caution in interpreting imaging studies using upper limb tasks as there is little agreement in the imaging methods and tasks used (Witt & Laird, 2008). Current paradigms may fully illustrate the networks needed for more complex activity and the transfer from upper limb to lower limb tasks including gait may be limited.

Using regression models, chapter 6 demonstrated that different characteristics explained cued and non-cued gait variability, which may also support the argument that different mechanisms of motor control are utilised by internally and externally generated movements. Disease severity was found to be explanatory of non-cued but not cued gait variability. This may be due to the fact that cued walking is not reliant on the dysfunctional basal ganglia and therefore less influenced by PD pathology, however this is likely to be an oversimplified explanation. As much less of the variance associated with cued gait variability was explained by the models, further work is needed to explore the relationship between gait variability and a wider range of measures.

The combination cue had particular benefit in reducing variability of stride and double limb support time and this was felt to reflect two mechanisms; the reduction in mismatch between stride amplitude and frequency in order to increase walking speed appropriately and the reduced attentional demand when walking with an external cue. Dubost (Dubost et al., 2006) reported that gait variability was influenced

by walking speed and task complexity which supports this hypothesis. As discussed

earlier in relation to the influence of dopaminergic medication on gait variability, it

seems likely that both attentional and kinematic factors associated with cueing are

implicated in the improvement seen in stride to stride variability. It may be that

although the pathways involved are to a large extent distinct, there is some overlap in

effect of cues and medication which is supported by the similar levels of

improvement seen with medication and cues described in chapter 5.

Hanakawa (Hanakawa *et al.*, 1999) showed gait disturbance in PD is associated with

underactivity in BG/SMA loop and also in the cerebellum. Dopaminergic medication

works largely on the BG/SMA loop, whereas rhythmical cueing may also target the

cerebellum. Thaut (Thaut *et al.*, 1999) describes the auditory system as an extremely

fast processor of sensory information with vast interaction with the motor systems.

Cortical and subcortical pathways are involved in rhythm processing and

synchronising motor output with a central role of the cerebellum (Thaut, 2003). This

may add further explanation of the added benefit of the combination cue, with its

rhythmical component, over the attentional cue in terms of improvement in gait

variability.

In a study by Ballenger (Ballenger *et al.*, 2008) PD subjects carried out an upper

limb task under self initiated, externally cued and 'urgent' externally cued conditions

where greater stress and urgency was associated with the cue. No detectable

difference in response was seen between the self initiated and externally cued

condition, but the urgent external cue was associated with recruitment of the

contralateral cerebellum to a greater extent in PD than controls. The cerebellum is a

key component of accessory motor circuitry typically recruited to compensate for BG

dysfunction (Ballenger *et al.*, 2008) and is perhaps enhanced by the presence of a

rhythmic cue as seen in the present gait studies.

Figure 7.3. describes the hypothetical link between cues and the attentional cost and

executive demands of walking. Previous research has suggested that cues reduce the

attentional demand of walking in PD (Rochester *et al.*, 2005; Rochester *et al.*, 2007).

In the current studies dual task performance was improved with cues, supporting this

argument, however regression models did not successfully explain which clinical

characteristics contributed to cued gait under these dual task conditions and therefore

it is difficult to draw firm conclusions regarding an influence on underlying

attentional mechanisms.

Figure 7.3. Theoretical impact of specific domains of executive function on PD gait (adapted from Yogev-Seligmann et al (Yogev-Seligmann, Hausdorff & Giladi, 2008)) and proposed influence of cues.
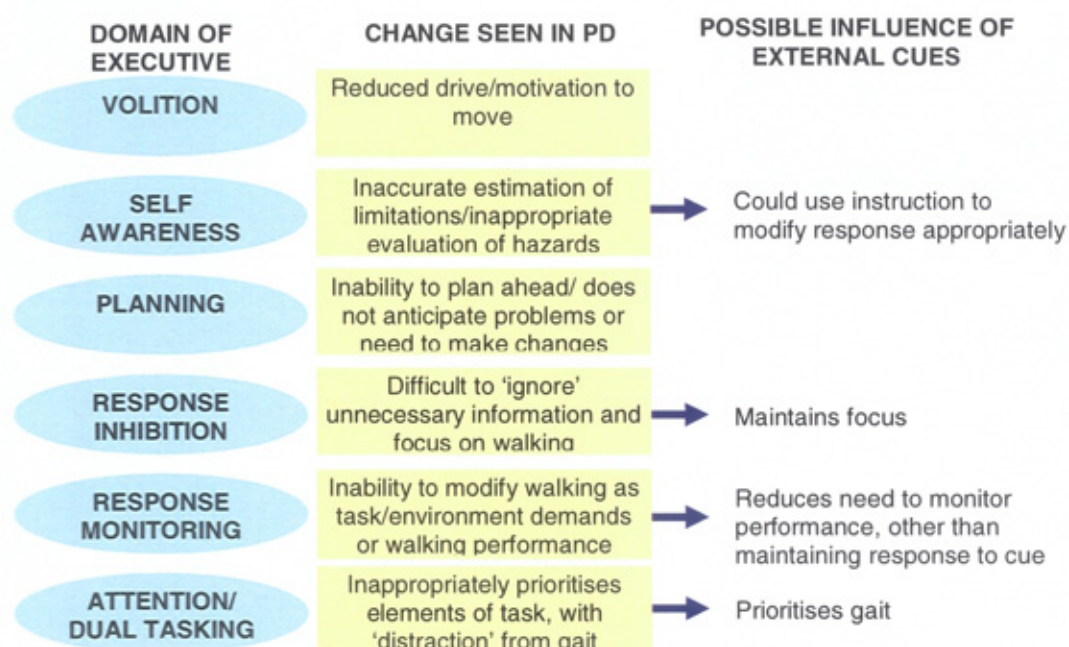
7.4. Application of cues.

Table 7.1 describes the ways in which cues can be applied and how the modality, parameter and instruction can be manipulated in order to achieve a specific response. As described in chapter 2 (section 2.5) previous cueing studies have targeted either temporal or spatial gait parameters, with the exception of two studies which combined external cue types but found no additional benefit compared to single modality cues (Suteerawattananon et al., 2004; Arias & Cudeiro, 2008). The combination cue described throughout the thesis used modification of instruction to address both spatial and temporal gait parameters, rather than presenting two external sources of information.

Table 7.1. Modalities and parameters of cueing strategies.

MODALITY
 	
Mode of delivery
	EXTERNAL (rhythmic or non-rhythmic)
	  Auditory
	  Visual
	  Somatosensory
		Feed-back response Utilising parieto-premotor pathways

	INTERNAL Focus/concentration	Feed-forward response Utilising cognitive control mechanisms

PARAMETER
 	
Settings/specificity of information
	TEMPORAL
	  Step frequency
	  Consistency of
	  stepping rate
		Facilitating stable rhythm of stepping

	SPATIAL
	  Step amplitude
	
	COMBINATION
	  Temporal and
	  spatial information
	  together
		Correcting mismatch in cortically selected and actual amplitude of steps
		
		Potential correction of step frequency-amplitude relationship

INSTRUCTION	Used to change focus/emphasis in order to adapt response	

The attentional cue was effective in improving both walking speed and step amplitude but this was at the cost of increased gait variability. This may have been due to the sample being predominantly of moderate disease severity. Attentional cues may play an important role in the management of gait dysfunction but may be more appropriate at earlier disease stages when any cognitive and balance changes are less severe. As the clinical picture of a person with PD changes dramatically with disease progression, it is likely that different management strategies will be appropriate at different stages, emphasising the need for clinically graded guidelines and constant

review of any strategies put in place. Cues should be used in the context of a wider management programme addressing factors such as cardiovascular fitness, strength, range of movement, posture and balance. Such comprehensive approaches must also take into account the impact of PD not only on specific body functions but should translate this to levels of activity and participation.

The studies presented in this thesis have established the feasibility of combining cues, subjects were able to increase step amplitude while responding to the rhythmical cue. This addresses the limitations of previous cueing studies which have used single modality cues to target a single parameter of gait. One aim of these studies was to exploit the large effects seen with attentional spatial cues (Morris *et al.*, 1996b; Behrman, Teitelbaum & Cauraugh, 1998; Canning, 2005) and also the practicality and functional application of rhythmical auditory cues (Thaut *et al.*, 2001; Howe *et al.*, 2003; Rochester *et al.*, 2005; Willems *et al.*, 2006; Hausdorff *et al.*, 2007; Nieuwboer *et al.*, 2007; Rochester *et al.*, 2007) in order to develop an optimised cue strategy. This allowed both spatial and temporal parameters of gait to be targeted in an attempt to restore the relationship between step amplitude and frequency which is disrupted in PD (Morris et al., 1998).

It was important to determine that this dual parameter combination cue was not too demanding for subjects. This is especially important for those people who have reduced automatic gait control and therefore greater reliance on cortical means of gait control and also where executive function and attentional performance is below

normal (Dalrymple-Alford et al., 1994), as in PD. Dual tasks have been shown to

cause interference with gait in PD (Camicioli *et al.*, 1998; Bond & Morris, 2000;

Bloem *et al.*, 2001; Rochester *et al.*, 2004; Yogev *et al.*, 2005; Canning, Ada &

Woodhouse, 2008) and this is associated with increased risk of falls (Ashburn *et al.*,

2001; Bloem, Steijns & Smits-Engelsman, 2003). The ability to use the cue during a

dual task confirmed that subjects were not using large amounts of attentional

resource to respond to the cue. In contrast dual task performance improved with cues

which may reflect reduced attentional cost compared to non-cued walking (Rochester

et al., 2005; Rochester *et al.*, 2007). Performance of the secondary task was not

directly measured but none of the subjects spilt water or dropped the tray, reflecting

no significant increase in difficulty performing the task. No instruction was given to

prioritise the gait element of the dual task. Bloem et al (Bloem et al., 2006) suggests

that PD subjects tend to prioritise the secondary task and show deterioration in gait

performance. The use of cues appears to facilitate prioritisation of gait performance

which is particularly beneficial in people with poor executive function and difficulty

therefore with task prioritisation, as seen in PD (Yogev-Seligmann, Hausdorff &

Giladi, 2008) (figure 7.3).

The limitation of dopaminergic therapy in addressing gait problems in PD highlights

the need for effective rehabilitation strategies which can be used throughout the

medication cycle. The majority of studies of cueing in PD have been conducted when

subjects were optimally medicated as this is the most stable phase of the medication

cycle (Morris et al., 1996a). However it is when off medication that individuals have

most difficulty with movement and therefore have more need of strategies to improve gait. Falls, however, are more likely to occur in the 'on' phase of the medication cycle, as individuals are more active at this time and this may also be associated with dyskinesia (Ashburn et al., 2001). Rehabilitation strategies should therefore be flexible, allowing the individual to maximise the effect of medication in the 'on' phase to increase function, improve safety and perhaps offer the chance to exercise, whereas in the 'off' phase the emphasis changes to improving movement to a level to allow unavoidable functional activities to be carried out and the effort involved minimised. Morris (Morris, 2006) emphasises the importance of tailoring rehabilitation approaches to the individual with PD, taking into account factors such as disease stage, freezing, and other characteristics which may include cognition.

The subjects involved in both studies in this thesis were predominantly of moderate disease severity which is also true for most studies of cueing in PD. More research is needed into effects of cues in people with very early, mild disease, to establish any potential for cueing strategies to be incorporated into a physical approach aimed at delaying gait problems, as suggested by Farley (Farley et al., 2008). In addition people with more advanced disease tend not to be studied due to the inherent complications when dealing with this population. This means, however, that there is very little guidance on the management of these complex patients. The needs of the patient at these different stages of the disease are likely to be quite diverse and therefore management strategies are needed which can be adapted to meet these changing demands.

The studies in this thesis have examined the immediate response to different types of cue. Studies have shown that a period of training with rhythmical cues improves walking in people with PD. A multi-centre RCT found improvement in gait and balance with a three week therapy programme based on cues delivered in the home (Nieuwboer *et al.*, 2007). A similar response was seen in a study where subjects performed daily exercises with or without rhythmical cues for 3 weeks; the cued group showed greater improvements in walking speed and stride amplitude (Thaut et al., 1996). Both studies tested subjects before and after training, without cues, suggesting some carry over effect. However long-term follow up has shown these effects diminish with time when training is discontinued (Nieuwboer *et al.*, 2007). Fernandez del Olmo (Fernandez del Olmo et al., 2006) showed that improvements in gait seen after training with cues were associated with increased activity in the dentate nucleus of the cerebellum and the parietal and temporal lobes, suggesting some influence of cues on the underlying motor control mechanisms.

Training with attentional strategies has received less attention. One study of a 4 week training programme of exercises and functional activities with instructions to concentrate on increasing movement amplitude showed improvements in walking speed and stride amplitude after training (Farley & Koshland, 2005). Retention of these improvements was found to depend on disease severity with more severe subjects reverting back to baseline measures soon after training stopped (Farley & Koshland, 2005), suggesting patients with more advanced disease did not continue to

use the attentional strategies when there was no perceived need to do so. This agrees

with Morris et al (Morris et al., 1996b) who found that subjects who had successfully

used an attentional strategy to improve walking reverted back to pre-training

performance when gait was measured covertly.

In addition a recent exploratory study in people with early mild to moderate PD

showed a three week training programme of walking with various additional tasks of

increasing complexity improved dual task training (Canning, Ada & Woodhouse,

2008). This suggests that cueing is one strategy to improve functional activity in PD

but could be used alongside other approaches. The decision of which approach is

appropriate will depend on factors such as disease severity, degree of gait impairment

and cognitive status as well as the lifestyle and expectations of the individual.

Farley et al (Farley *et al.*, 2008) describes a programme based around cognitive

cueing which was originally developed for maintaining volume in speech and has

been adapted for amplitude in gait, relearning ability to 'recalibrate' amplitude. The

traditional problem based/compensatory approach has assumed that neurophysiologic

changes are no longer possible, and therefore does not address issues of counteracting

of disease pathology or the potential for motor learning. There is increasing evidence

emerging for the influence of exercise on neuroplasticity and studies of patients

following stroke and SCI have emphasised particular requirements of therapeutic

programmes hoping to drive neuro-plasticity (Shepherd, 2001; Smith & Zigmond,

2003; Behrman, Bowdern & Nair, 2006) but the potential in PD remains unclear.

Chapter 7

Farley et al (2008) proposed a theoretical framework for a therapeutic programme using cueing principles which would be available at diagnosis. Using these requirements Farley et al have suggested ways in which retraining of normal amplitude in PD may enhance activation of damaged BG pathways and therefore affect the underlying pathology (Figure 7.4). This framework is highly hypothetical but provides an interesting basis for further research into the potential of cues.

Figure 7.4. A theoretical framework for the use of cueing strategies to drive motor learning in PD. Based on Farley et al (Farley *et al.*, 2008).

REQUIRED ELEMENT OF TRAINING PROGRAMME	RECOMMENDATIONS FOR CUEING THERAPY	CHALLENGES IN PD
TIMING	Train/educate early before function is compromised. Increase awareness and ability to self correct	Physical changes subtle in early disease. May have reduced awareness of need for physiotherapy
COMPLEXITY	Gradually integrate complexity into training. Retrain ability to maintain desired gait pattern during functional tasks	Difficulty with complex multi tasks due to reduced automaticity. Maintaining safety should be priority.
INTENSITY	Intensive therapy sessions with home exercises to increase carry over. Should be able to integrate into daily life.	Intensive exercise difficult due to poor CV fitness and non-motor symptoms such as fatigue, depression.
AVOID INACTIVITY	Educate early. Everyday activities as exercise. Maintain participation.	Inactivity may occur before recognition of need to exercise. Requires motivation.
SALIENCY	Use familiar, functional activities and integrate cueing therapies.	Reduced awareness of need/benefit.

Even in the absence of a direct effect on BG function, training may have an effect by improving the efficiency of the compensatory motor system. This was described by Hallett (Hallett, 2008) who showed that PD subjects were able to achieve

'automaticity' of a simple task as measured by dual task performance but this behavioural change was not reflected by changes on brain imaging. It seems that patients were using the same pathways pre and post training but became more efficient at doing so and therefore behavioural performance was improved. Interestingly the improvement was not seen to the same extent in a more complex task which may have required more intensive and prolonged training.

Nieuwboer et al recently carried out a review of cueing evidence based on the International Classification of Functioning (ICF) (World Health Organisation 2001) (Figure 7.5) which aimed to demonstrate which domains had responded to cueing training (Nieuwboer, Rochester & Jones, 2008). Evidence for cues is very strong at impairment (body function and structures) level of the ICF because of the immediate corrective effect (Rubinstein, Giladi & Hausdorff, 2002; Lim *et al.*, 2005) enhancing size or timing of steps depending on the modality and parameter chosen (see table 7.1) and can be used as a problem solving strategy for episodic problems such as freezing (Nieuwboer, 2008). Cues can also be used to facilitate gait over longer periods in order to maintain the desired pattern whereby through training therapy is targeted at activity level of ICF. Studies of training with cues are limited but have shown improvements in gait, ADL's and motor symptoms (Thaut *et al.*, 1996; Marchese *et al.*, 2000; Nieuwboer *et al.*, 2007). The Rescue project, a large RCT showed effects of a home based cueing programme at body function and activity levels with improvements in gait and balance and improved confidence in walking with reduced fear of falling (Nieuwboer *et al.*, 2007). No change was seen in ADL's or at the level of participation, which suggests a need to further develop cueing

methods which are effective and applicable in a range of settings. A qualitative study

explored the challenges experienced by people with PD when walking in the real

world setting, which included walking while doing something else or in different

environments, termed 'walking plus' (Jones *et al.*, 2008) again emphasising the need

for interventions which can be integrated into function.

Figure 7.5. Gait and mobility problems in PD with potential application of cues
across domains of the International Classification of Functioning (based on
Nieuwboer et al 2008).
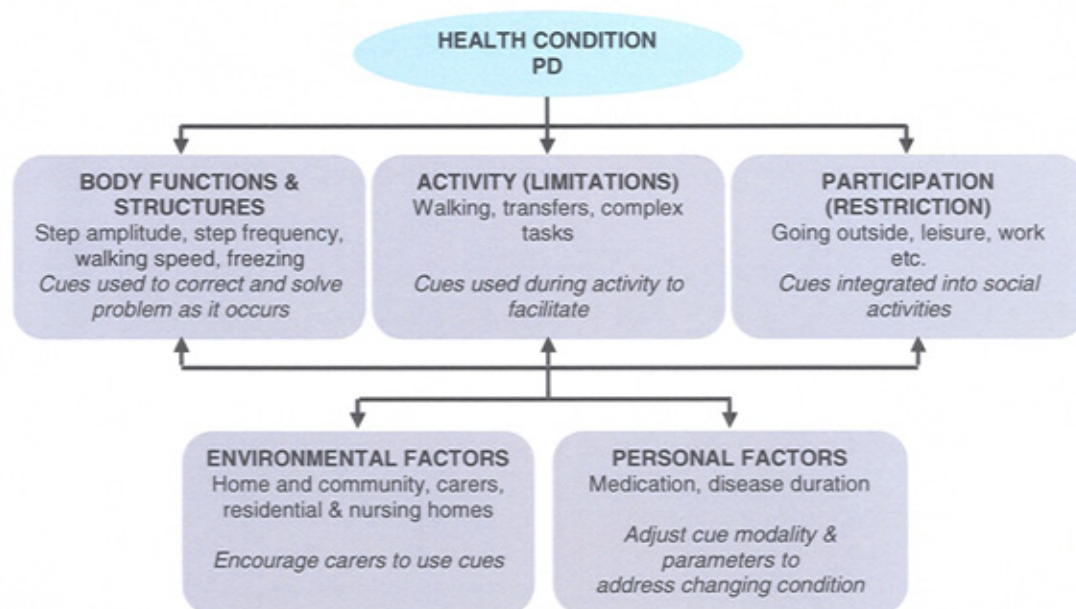
7.5. Future directions of cueing research.

After considering the results presented in this thesis there are a number of ways this

area of research could be taken forward in addition to those already mentioned. It is

now warranted to examine the effects of training with the combination cue to evaluate

whether the response could be further enhanced. It would also be interesting to study

generalisation of cueing effect more closely, perhaps through activity monitoring to

determine whether individuals are able to utilise the improvements seen in gait to enhance activity and participation.

As gait variability has proven to be a sensitive measure of change in PD, further investigation is now needed to assess its merit as an outcome measure. There may be potential for using such measures in addition to more traditional gait outcomes to determine optimal pharmocological control for example. The ability of gait variability to identify those at risk of falls is already well documented (Hausdorff *et al.*, 1997; Maki, 1997; Hausdorff *et al.*, 2001; Hausdorff, Rios & Edelberg, 2001; Schaafsma *et al.*, 2003; Hausdorff *et al.*, 2004; Beauchet *et al.*, 2007) and due to the profound impact of falls on people with PD (Ashburn et al., 2001) tools are needed to identify those at risk in order to minimise risk. Advances in technology are making gait analysis increasingly accessible and portable meaning the practical limitations of such screening are less of a barrier, but more work is needed to establish the reliability of such equipment in measuring variability. However, before these measures can be used to inform clinical decisions, databases of 'normal' values are needed to allow assessment of what is 'abnormal'.

Increased gait variability has been described in other patient groups including stroke, Alzheimers disease, Huntingdon's disease and affective disorders (Hausdorff *et al.*, 1998; Sheridan *et al.*, 2003; Hausdorff *et al.*, 2004). Due to the specific benefit in addressing gait variability seen with the combination cue, there may be application in these groups.

More understanding of the relationship between step frequency and step amplitude would allow better interpretation of reasons for this relationship to be lost and to discover ways of restoring it. Systematic manipulation of both parameters in healthy subjects as well as those with PD would provide an insight into these mechanisms and may help determine whether this relationship is an important factor in the variability of gait.

Chapter 7

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APPENDICES

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CONSENT FORM

Title of Project: The attentional cost of walking and functional activity in people with Parkinson's disease: measurement and therapeutic strategies.

Name of Researchers: Dr Lynn Rochester, Katherine Baker and Vicki Hetherington

Patient Identification Number for this trial:

Please initial box

1. I confirm that I have read and understand the information sheet dated for the above study ☐ and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, ☐ without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by the named ☐ researchers where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study.   Test One   ☐

                                                 Test Two   ☐

_____   _____   _____
Name of Patient   Date   Signature

_____   _____   _____
Researcher   Date   Signature

1 copy for patient; 1 for researcher:

northumbria
UNIVERSITY

CONSENT FORM

Optimising cueing to improve walking and functional activities in people with Parkinson's disease in the home, while on and off medication.

Name of Researchers:
Dr Lynn Rochester, Katherine Baker, Dr David Burn.

Patient Identification Number:

Please initial box

1. I confirm that I have read and understand the information sheet dated for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I agree to take part in the above study.

4. I agree to be video taped during the study procedure.

_____   _____   _____
Name of Patient   Date   Signature

_____   _____   _____
Researcher   Date   Signature

1 copy for patient; 1 for researcher:

P=0.007). However, the two WGA SNPs in HIVEP3 were not significant. Our failure to replicate the LOC20008 findings supports the negative results of three recent replicate studies for this gene. It is encouraging that HIVEP3 was found to be significantly associated with PD in two independent studies, implying HIVEP3 as a strong candidate for PARK10. Further testing of HIVEP3 by other PD research groups to replicate this gene is encouraged.

P814

A UK comparison of Sniffin' Sticks (SS) and University of Pennsylvania (UPSIT) Smell identification tests in Parkinson's disease
L. Silveira-Moriyama, D. R. Williams, A. H. Evans, R. Katzenchlager, H. Watt, A. J. Lees (London, United Kingdom)

Objective: To compare 2 different smell identification tests in Parkinson's disease (PD).

Background: Hyposmia is frequent in PD and might prove to be useful in the differential diagnosis of parkinsonism. Two commercially available tests of smell identification have been widely used in research but they are not routinely used in clinical neurology. We have determined the practical applicability of the UPSIT and SS tests in routine neurological practice.

Methods: Twenty-seven patients with PD were assessed with the UPSIT and SS smell test kits.

Results: The Pearson correlation coefficient between the two tests was 0.752 (p<0.001). The mean scores were 18.85 (out of 40) for the UPSIT and 7.03 (out of 16) for the SS.

Conclusions: Performance of patients in both tests was notably below previously published normative data in North Americans (1) (for the UPSIT) and mainly Germans (2) (for the Sniffin Sticks). There was a strong correlation between the two tests indicating that both can be used in clinical practice with similar applicability. The Sniffin Sticks is a cheaper and quicker test and can be done during a routine consultation by the physician. The UPSIT takes longer but can be self-administered. However, even after careful explanation by the physician approximately 5% of patients are unable to self-administer the test correctly.

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P815

Genome-wide SNP typing as a tool to identify structural alterations in the genome of PD patients
J. Simon-Sanchez, S. Scholz, F. Hon-Chung, M. Matarin, D. Hernandez, R. Gibbs, A. Britton, F. Wavrant De Vrieze, A. Singleton (Bethesda, MD, USA; Valencia, Spain)

Objective: To identify genomic structural alterations related to the development of Parkinson's disease (PD).

Background: Since 1997 mutation in five genes, SNCA, PRKN, DJ1, PINK1 and LRRK2 have been unequivocally linked to rare familial forms of parkinsonism. Missense mutations have been identified in all five of these genes, and to date large genomic deletion and multiplication mutations have been found in SNCA, PRKN, DJ1 and PINK1. There is not known genetic basis for the remaining PD cases, which are mostly sporadic in nature.

Methods: In order to identify new variants involved with the development of sporadic PD, we embarked on a whole-genome SNP genotyping study using the Infinium 317K SNP chip (Illumina Inc., San Diego, CA) in cohorts of 276 PD cases and 276 controls. In the course of analyzing the results obtained with this approach we observed that, not only is the data obtained useful for case-control type association studies, but also for the direct identification of structural genomic variation. Since structural aberrations have previously been related to the appearance of certain variants of PD we accurately analyzed the data obtained using the Genotyping and LOH-PLUS modules within the version 2.3.25.17261 of BeadStudio software (Illumina Inc, Sand Diego, CA).

Results: Of the 276 neurologically normal control subjects assessed 119 control samples presented data consistent with 167 heterozygous multiplications and these were identified in all chromosomes. 90 control samples

presented data consistent with 119 heterozygous deletions and 21 heterosomic deletions.

Of the 276 PD cases assayed, 128 DNA samples were found to be harbor 179 heterozygous multiplications, 112 revealed 158 heterozygous deletions and 39 showed 54 heterosomic deletions.

Conclusions: In comparing genomic regions affected by multiple structural alterations we identified several loci where deletion or duplication was more common in cases than controls. This included loci on chromosomes 2, 3, 5, 11 and X. Follow up studies are currently being performed in different cohorts.

P816

The attentional demands of walking in PD: Effect of cue modality on gait variability
K. Baker, L. Rochester, A. Nieuwboer (Newcastle Upon Tyne, United Kingdom; Leuven, Belgium)

Background: People with PD have difficulties performing dual tasks. External rhythmical cues have been shown to improve gait performance during a dual task argued to be through reduced attentional demand.

Objective: to investigate if internally generated (attentional) cueing strategies would show greater gait variance than externally cued strategies due to the increased cognitive demand.

Methods: Fifteen participants with idiopathic PD, mean age 68.83 (3.30) and 12 age/sex matched controls, mean age 71.50 (2.58) were evaluated. Gait was measured in a laboratory using a dual task paradigm. Two task types were tested: walking (single task) and walking while carrying a tray (dual task). Cueing trials were completed for both task types; (1) synchronising steps to an auditory tone, (2) using an attentional strategy to think about taking a big step and (3) synchronising steps to an auditory tone while thinking about taking a big step .Cue modalities were presented in a random order. Cueing was delivered at 10% below preferred step frequency. PD subjects were 'on' medication. Gait variance was measured using the CV of step length and step time. Data were analysed using repeated measure ANOVA.

Results: There was a significant difference in variance of step length for cue modality in PD and control subjects (F=2.642; P=0.035), but not between single and dual tasks or between PD and control subjects. Variance in step length was significantly lower when performing single and dual task walking with cue type 3 (auditory + attentional strategy) (P= 0.009) compared to baseline (no cues). There was no significant difference in step time variance. No significant differences in variance were seen with different cue modalities in the control group.

Conclusions: Association of an external cue with an attentional strategy (to increase step size), resulted in decreased variance in step length suggesting improved gait symmetry and a more stable gait pattern. This cue strategy may be less attentionally demanding than cueing at speeds below preferred cadence and using internally generated strategies and has implications for rehabilitation.

P817

Substantia nigra hyperechogenicity in transcranial sonography preceding reduced striatal uptake in [123I]FP-CIT SPECT in Parkinson's disease: A report of three cases
S. Schmidt, K. Schepp, P. Maaser, I. Reuter, M. Kaps (Giessen, Germany)

Objectives: In idiopathic Parkinson's disease transcranial ultrasound represents a new method to verify clinical diagnosis in early stage of disease. Several studies demonstrated increase in Substantia nigra (SN) echogenicity in 95% of patients, but only in up to 9% healthy adults. It has been proposed to use TCS complementary to [123I]FP-CIT SPECT, an imaging technique of dopamine reuptake transporters with high sensitivity for IPD diagnosis. TCS shows pathomorphological alterations in SN probably even before onset of IPD. We present data of 3 IPD pat. in whom SN hyperechogenicity preceded SPECT alterations.

Methods: TCS was done using a Philips Sonos 5500. In 110 IPD pat.(UK brain bank crit.)aged 65.6±6.3(H&Y 1-4)and age matched controls area of SN hyperechogenicity was measured. SPECT was performed using [123I]FP-CIT SPECT.

Results: We found a significant difference in SN hyperechogenicity in IPD pat. ($0.31 \pm 0.07 cm^2$) and controls ($0.13 \pm 0.06 cm^2$). 4.4% of IPD pat. did not show an increased SN while that was seen in 7% of controls.

Three pat., 2male,1fem.,aged 59,62,68,H&Y1-2, revealed a normal SPECT ratio (right/left:3.2/3.2;3.0/3.2:2.9/2.9) but showed a significant SN hyperechogenicity in TCS ($[cm^2]0.3/0.32;0.29/0.28;0.25/0.29$). When SPECT was repeated 24 months later a pathological pattern with asymmetric reduced FP-CIT uptake was found (2.2/2.9;2.1/2.9;1.8/2.9).

Conclusions: The findings underline the high sensitivity of TCS in early diagnosis of IPD where it might even precede alterations in SPECT. These results are in correspondence with previous data proposing SN hyperechogenicity as predisposing factor in IPD. Whereas SPECT is based on alterations of presynaptic dopaminergic nerve terminals SN hyperechogenicity in TCS is a static parameter caused by structural changes due to iron accumulation not depending on disease severity or duration. Although in early IPD dopamine transporter mRNA downregulation has been shown there might be other compensatory mechanisms influencing FP-CIT-binding in early stage of IPD. Therefore when the diagnostic workup reveals pathological TCS and normal SPECT it might be worth to repeat the latter some months later.

P818

Quantitative analysis of movement smoothness in Parkinson's disease
J. Gracies, S. J. Fried, E. A. Kappos, K. Fung, W. Tse, D. J. Weisz (New York, NY, USA)

Objective: Movements in Parkinson's Disease (PD) lack speed (bradykinesia), and they also lack smoothness, although this feature has not been well characterized. We have tested methods to quantify movement smoothness in PD by comparison with normal movement and voluntary slow movement.

Methods: Eight PD patients and 12 controls performed rapid alternating elbow flexion-extension movements over small and large ranges. Six controls were also instructed to perform the same movements matched for speed with those of the PD patients. Angle displacement was monitored using a potentiometer. We analyzed: (1) Normalized average rectified jerk (NARJ), a measure of the rate of change in acceleration; (2) Fourier power spectrum of the acceleration profile. Specifically, we calculated the ratio of the power at frequencies faster than the movement frequency to the power at the movement frequency (FF/MF ratio), which is another measure reflecting the variability in the acceleration profile.

Results: The table below displays the mean values of these two parameters in PD (more affected hand) as percentage of those in controls (dominant hand) and indicates the significance of differences (ANOVA): Both NARJ and FF/MF correlated with time since diagnosis.

Conclusions: Movements in PD not only lack speed, they also lack smoothness. We suggest two measures to quantify the irregularity of the acceleration profile, which may also distinguish voluntary normal slowness from parkinsonian slowness.

	% of control value		% controls matched for speed	
	Large	Small	Large	Small
NARJ	189% (p=.007)	144% (p=.001)	151% (p=.001)	139% (p=.032)
FF/MF	277% (p=.028)	613% (p=.001)	208% (p=.032)	247% (p=.001)

TABLE 1 (P818).

P819

Disability profile at various stages of Parkinson's disease evaluated by a novel instrument: The ADL taxonomy
G. Hariz, M. Edström, E. Lindmark, M. Lindberg, L. Forsgren (Umeå, Sweden)

Objective: To evaluate the profile of ADL of patients with Parkinson's disease (PD) at different stages of the illness using the ADL taxonomy.

Background: Parkinson's disease (PD) results in various degrees of disability in everyday life, depending on the stage of disease and on individual factors in each patient. The ADL part of the UPDRS is a mixture of impairment and disability items, and it is not sufficient to illustrate in detail the profile of the patients activity limitation in ADL. A novel occupational therapy instrument, the ADL taxonomy, is now investigated in this group of patients.

Methods: Fifty-five consecutive newly diagnosed patients, and an age and sex-matched control group of 24 healthy volunteers were evaluated. Evaluations were conducted at baseline, at 6 months, and at 12 months. Additionally, 33 patients with more advanced disease (14 tremor dominant patients with a 9 year history of PD, and 19 fluctuating patients with 13 year history of PD), subjected to surgery were also evaluated. The ADL taxonomy addresses in detail following activities: eating and drinking, mobility, going to the toilet, dressing, hygiene, grooming and communication, which are scored on a five graded scale: without difficulties, with some effort, with major effort, need some help or need all help.

Results: Newly diagnosed PD patients showed some limitations in mobility and communication. At 6 and 12 months, there was deterioration mainly in writing, pedicuring and transfer in bed. In comparison, patients with long-standing tremor-dominant PD showed major effort in writing and pedicuring while patients with fluctuations and dyskinesias showed major effort in performance of most listed activities.

Conclusions: The impact of PD on ADL and the profile of disability are well scored by the ADL taxonomy, allowing for a better purposeful and individualized rehabilitation program for patients. It is also a comprehensive evaluation tool for medical and surgical treatment.

P820

Optimising cueing to improve walking and functional activities in people with PD
K. Baker, L. Rochester, A. Nieuwboer (Newcastle upon Tyne, United Kingdom; Leuven, Belgium)

Background: Visual cues are effective in increasing step size and normalising gait whereas rhythmical auditory cues are effective in increasing walking speed through increased step frequency. The type of cue and instruction given seems to focus the individual on a specific parameter of gait.

Objective: To see if a cueing method which addresses 2 parameters of gait is more effective than single parameter cue methods. To see if dual parameter cueing is stable under dual task conditions.

Methods: Fifteen participants with PD and 12 age-matched controls were evaluated using a repeated measures design. Gait parameters were recorded during 2 conditions: walking only and walking while carrying a tray (dual task). In each condition participants walked with and without cues. The cueing trials were (a) stepping in time to an auditory tone (AUD), (b) responding to an attentional command to increase step length (ATT) and (c) stepping in time to an external pacing cue (auditory) which they were instructed to associate with a big step (AUD+ATT) presented in a random order. Cueing was delivered at 10% below preferred stepping frequency. All subjects were 'on' medication.

Results: Repeated measures analysis of variance was used to compare walking speed, step length and step frequency for the effect of task (walk and dual task), the effect of cue type (AUD; ATT; AUD+ATT). During walk and dual task the ATT strategy and the AUD+ATT strategy increased step length of PD participants (p<0.002) to that of controls walking at baseline, i.e. step length was normalised. During walking the ATT strategy caused a significant increase in PD velocity (p=.018) compared to baseline and AUD cue only. In the dual task condition the AUD+ATT strategy significantly increased PD velocity compared to the AUD cue alone (p=0.08).

Conclusions: Associating an external pacing cue with an attentional command was equally as effective in normalising gait in PD as the attentional strategy. The external pacing cue may act as a prompt which requires reduced attentional demands compared to internally generated cueing strategies and could be useful in functional situations to improve gait in PD.

ORIGINAL ARTICLE

The Immediate Effect of Attentional, Auditory, and a Combined Cue Strategy on Gait During Single and Dual Tasks in Parkinson's Disease

Katherine Baker, BSc, Lynn Rochester, PhD, Alice Nieuwboer, PhD

ABSTRACT. Baker K, Rochester L, Nieuwboer A. The immediate effect of attentional, auditory, and a combined cue strategy on gait during single and dual tasks in Parkinson's disease. Arch Phys Med Rehabil 2007;88:1593-600.

Objective: To compare the effect of rhythmic auditory and attentional cues, and a combination of both cues on gait, in people with Parkinson's disease (PD) during single and dual tasks.

Design: A repeated-measures study requiring participants to perform single and dual-motor tasks under different cueing conditions.

Setting: Human movement analysis laboratory.

Participants: Fifteen participants with idiopathic PD and a comparison group of 12 healthy participants.

Interventions: Three cueing strategies were compared: a rhythmic auditory cue (walking in time to a metronome beat), an attentional strategy (asked to focus on taking big step), and a combination cue (asked to walk in time to a metronome beat while taking big steps).

Main Outcome Measures: Walking speed, step amplitude, and step frequency.

Results: Walking speed of PD participants improved significantly compared with noncued walking in the single- and dual-task condition with the attentional ($P<.001$, $P=.037$) and combination cue strategies ($P=.013$, $P=.028$). Step amplitude also increased significantly with the attentional and combination cue strategies in single- ($P<.001$, $P<.001$) and dual-task ($P<.001$, $P<.001$) conditions. Step frequency was reduced significantly with the attentional strategy ($P=.042$) in the single and dual tasks ($P<.001$) and combination cue strategy ($P=.009$) in the dual task. The rhythmic auditory cue alone did not alter significantly any parameter of gait in the single or dual tasks.

Conclusions: The attentional strategy and the combination of a rhythmic auditory cue with an attentional strategy were equally effective, and improved walking speed and step amplitude significantly during both single and dual tasks. The combination cue, however, may still be a useful alternative in situations of increased attentional demand, or where problems exist with executive function.

Key Words: Attention; Cues; Gait; Parkinson disease; Rehabilitation.

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GAIT DISTURBANCE IN Parkinson's disease (PD) is characterized by reduced speed and step amplitude, increased stepping frequency and, in some cases, festination and freezing.[1] The primary gait deficit in PD, however, has been described as an inability to generate sufficient amplitude of movement.[1] Morris et al[1] advocate that increasing step amplitude should therefore be the primary goal of therapy intended to normalize gait.

Cueing strategies have improved gait in people with PD,[2-16] and are argued to bypass the defective basal ganglia by using alternative pathways unaffected by PD to improve motor performance.[17] External cues provide temporal or spatial stimuli associated with the initiation and facilitation of a motor activity and can be delivered using different modalities (auditory, visual, somatosensory) that address single parameters of gait, such as step frequency or step amplitude.[10] Attentional strategies, such as instructions to increase step length, offer an alternative to external cues; they rely more on cognitive mechanisms of motor control and are internally generated.[9,18-21]

Research has generally focused on using a single cue modality. Visual and attentional strategies appear to have a greater effect on step amplitude and walking speed than do rhythmic auditory cues when they are tested in a laboratory situation with subjects doing simple tasks.[1,6,9,18-22] Not withstanding the benefits of using cues to facilitate gait, their use in facilitating the performance of functional activities and in complex environments has received less attention.

People with PD have difficulty performing dual tasks, argued to result from attentional overload and inability to use automatic movement control.[23-26] Morris et al[9] found that constant monitoring was required for attentional strategies to retain their effectiveness, which is difficult to do in the real world and during dual-task performance. Canning,[22] however, found that attentional strategies were effective during dual tasks when subjects were given explicit instructions to direct their attention to gait. In contrast, rhythmic auditory cues improve gait during dual and multiple tasks involving both motor and cognitive tasks conducted in the home environment,[12] possibly because they impose less attentional demand. Deficits in executive function in PD subjects may exacerbate dual-task difficulties because they will have an effect on the appropriate allocation of attention to gait during dual- and multi-tasks.[26,27] Cueing strategies therefore must be effective under dual-task conditions in the context of complex environments where attentional demands increase,[12] and must take into consideration cognitive difficulties.

Combining a rhythmic auditory cue to prompt step frequency with a spatial cue to normalize step amplitude so to

address both the temporal and spatial components of gait in people with PD may provide an alternative to address issues of generalization.[12] The external cue may reduce the need for constant monitoring by prompting a person to focus on step amplitude, thus overcoming limitations of executive function and increased attentional requirements.

In this exploratory study, we asked the following questions: (1) can people with PD effectively combine a rhythmic auditory cue with an attentional strategy; (2) does the combination cue provide greater benefits than the attentional strategy alone; and (3) can these cues be used to improve gait when performing a dual task?

METHODS

Participants

We used a convenience sample of 15 people with idiopathic PD (PD group) (6 men, 9 women; mean age, 68.83±3.30y) and a control group of 12 healthy participants (5 men, 7 women; mean age, 71.50±2.58y) matched for age (table 1). The Sunderland local research ethics committee in the United Kingdom granted ethical consent for the study, and all participants gave their informed written consent. We used the following criteria to recruit the PD group: diagnosis of idiopathic PD (by a consultant neurologist with a specialist interest in movement disorders), absence of any other neurologic problem, absence of dementia (score >24 on Mini-Mental State Examination [MMSE]),[28] absence of any severe comorbidity likely to affect gait, adequate sight and hearing with glasses and hearing aid, if required (determined informally by ensuring that the subject could read the study information sheet and hear the cueing device), independently mobile indoors without a walking aid, no severe dyskinesias (score >2 on the Modified Dyskinesia Scale),[29] or prolonged off periods, and age 80 years or less. Participants who scored greater than or equal to 1 on item 3 of the Freezing of Gait Questionnaire (FOGQ)[30] were considered to have freezing as a symptom of PD. The control group participants were fit and well, with no severe comorbidity, an MMSE score of 24 or higher, adequate vision and hearing, and aged 80 years or less.
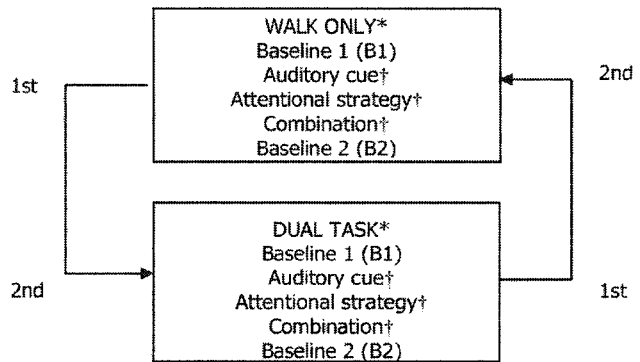
Experimental Design

We used a repeated-measures experimental design that compared 3 different cue types under single- and dual-task conditions. We controlled order and practice effects by counterbal-

Table 1: Participant Characteristics for PD (n=15) and Control (n=12) Participants

Characteristics	PD	Control	P
No. of subjects	15	12	
Mean age (y)	68.8±3.3	71.5±2.6	.045*
Height (cm)	165.9±10.9	165.4±8.3	.67
MMSE score	27.9±2.17	28.6±1.8	.037
Sex (men/women)	6/9	5/7	
Disease duration (y)	6.5±3.2	NA	NA
UPDRS motor score	23.4±9.2	NA	NA
Hoehn & Yahr stage	2-3		
	2.5-4	NA	NA
	3-8		
Freezers/nonfreezers	10/5	NA	NA

NOTE. Values are mean ± standard deviation (SD) or n.
Abbreviations: MMSE, Mini-Mental State Examination; NA, not applicable; UPDRS, United Parkinson's Disease Rating Scale.
*P≤.05 was considered significant.

Fig 1. Experimental design. *Counterbalanced; †randomized.

ancing the walking alone and dual-task conditions,. and by randomizing the order of cue presentation (fig 1).

Primary Outcome Measures

We used the GAITRite mat[a] to collect walking speed (in cm/s), step amplitude (in centimeters), and step frequency (in steps/min).

Baseline Measures

The participants' demographic data included sex, age, height, and weight. For the PD group, disease, duration, and severity were recorded and scored with the Hoehn and Yahr Scale, which rates disease progression on a scale of 1 to 5[31]; the Unified Parkinson's Disease Rating Scale, section III (motor examination), which scores the motor signs of PD including speech, facial expression, tremor, rigidity, bradykinesia, balance, and gait[32]; the FOGQ, which rates the symptom of freezing according to frequency; situations that cause freezing and severity of freeze[30]; and the Modified Dyskinesia Scale, which scores the symptom of dyskinesia on a scale of 0 to 4 according to interference with motor tasks.[29]

Cueing Types

Three different cue types were compared:
1. Rhythmic auditory cue:
   Instructions: "As you walk try to step your feet in time to the beat."
2. Attentional cue strategy, participants had to think about taking big steps:
   Instructions: "As you walk try to take big steps."
3. Combination cue-rhythmic auditory cue associated with taking a big step each time the tone is heard:
   Instructions: "Take a big step in time to the beat."
   Rhythmic auditory cues were given using a prototype cueing device[b] that delivered a rhythmic sound set at 10% below preferred stepping frequency. We calculated each participant's preferred stepping frequency using the mean of 3 repetitions of a 10-meter walk test. The choice of cueing frequency was made to enable the participants to synchronize with the cue during both the single and dual tasks and also to allow time for a larger step. A previous study[10] showed improvements in gait at 10% below preferred stepping frequency.

Cueing Conditions

A functional task was performed with and without cues in which participants walked under 2 different conditions:
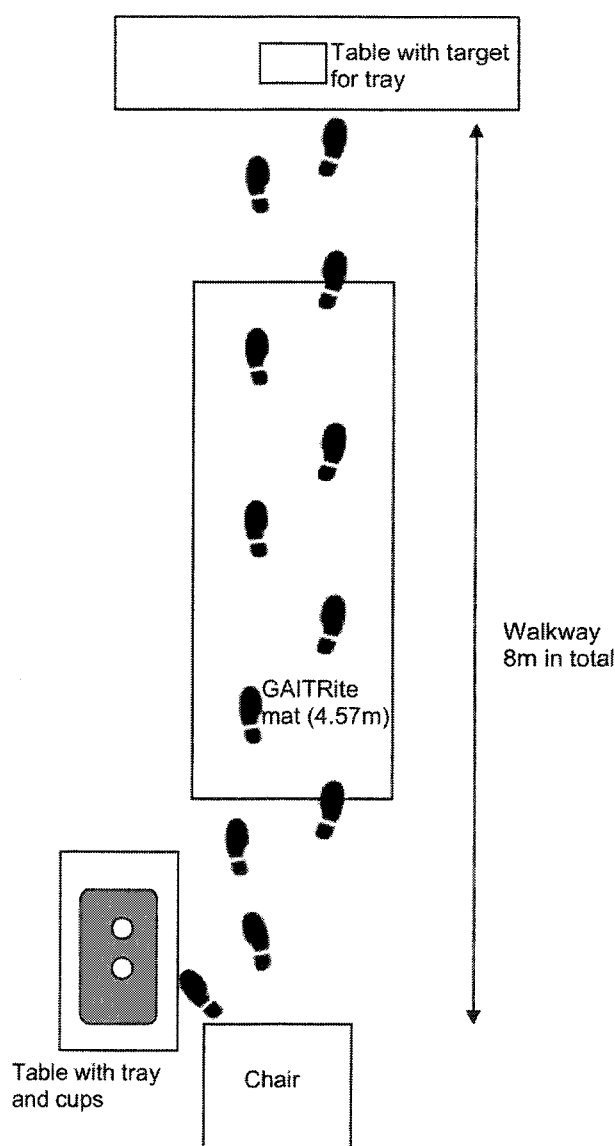
Fig 2. Experimental protocol.

mately 45 minutes, during which the PD group was in the on phase of the medication cycle (1h after medication intake), confirmed through the use of a visual analog scale with which the participants rated their current status on a scale of from "on" to severely "off."

Participants performed 10 trials in both the single- and dual-task conditions (see fig 1), with the order of the tasks being counterbalanced. Three noncued baseline trials (B1) preceded the cueing trials (see fig 1), with a final noncued baseline trial performed after the cueing trials so as to examine the short-term carry-over effects of cue use. Participants performed 2 trials with each cue type in a randomized order.

For each trial, participants walked a distance of 8m over a GAITRite mat, which recorded these gait parameters: walking speed, step frequency, and step amplitude, which measures the distance from the center of the heel on 1 foot to the center of the heel of the opposite foot. The mat was positioned in the middle section of the walkway to record the most stable phase of each walk and reduce the effects of acceleration and deceleration. The GAITRite system is a flexible electronic walkway that provides an automated means of measuring the spatial and temporal parameters of gait by using a carpet embedded with sensors that detect footfalls. It has been shown to provide valid and reliable data.[33-35] The carpet is 457cm long, with an active (data recording) area of 366cm, at a data sampling rate of 32.2 to 38.4Hz.

Data Analysis

We used SPSS[c] to analyze the data, which were examined for distribution using the Shapiro-Wilk W test. All data were normally distributed and therefore we used parametric statistics for analysis. We used a mixed-design, repeated-measures analysis of variance to compare walking speed, step amplitude, and step frequency for the effect of participant type (PD, control), cue type (auditory, attentional, combination), and task type (single, dual task).

We described the data as the mean values for each trial type. In addition, we calculated the interference effect on gait of a dual task with and without cues. This was expressed as the mean percentage difference between single and dual tasks for each trial type, as shown in the equation:

$$\left(\frac{\text{dual task} - \text{single task}}{\text{single task (baseline 1)}} \right) \times 100 = \text{Interference}$$

For walking speed and step amplitude, a negative response indicates reduced performance during the dual-task condition and a positive response indicates improved performance; this is reversed for step frequency.

We used pairwise comparisons with Bonferroni adjustments to identify significant differences between trials. Two-tailed tests with a P value of .05 or less were considered statistically significant.

RESULTS

PD and control participants were matched for height ($P=.67$) and sex, however, there was a small but significant difference between the ages of the groups ($P=.045$), with the control participants being a mean of 2.67 years older than the PD subjects. There was no significant difference in scores on the MMSE ($P=.37$), with all participants scoring above the cutoff of 24, which indicates an absence of dementia. The mean duration of the PD group's disease was 6.15 ± 3.16 years; Hoehn and Yahr ratings are presented in table 1 and indicate mild-to-moderate disease severity.

(1) single task (walking alone), and (2) dual task (walking and carrying a tray on which there were 2 cups of water). This task was chosen to reflect a functional, ecologically valid activity, and has been used in previous studies.[22,24,26]

Single task. Participants were seated in a chair, then stood and walked along an 8-m walkway, stopping when they touched a designated point on a table (fig 2).

Dual task. Participants were seated in a chair, stood, collected a tray with 2 cups of water placed on it from a table beside the chair, walked along the 8-m walkway carrying the tray and stopped when they placed the tray on a designated point on a table (see fig 2). The water levels in the cups and the positions of the cups on the tray were standardized.

Experimental Protocol

All testing took place in the human movement analysis laboratory at Northumbria University. Testing lasted approxi-

Table 2: Descriptive Data for PD (n=15) and Control Subjects (n=12) for Noncued and Cued Trials and Single- and Dual-Task Conditions (1–2)

Variable	Subject Type	Condition	Single Task	Dual Task	Interference Effect (%)
Walking speed (cm/s)	PD	B1	101.1±18.3	92.8±16.8	−7.6±9.6
		AUD	98.4±18.1	91.1±19.5	−6.8±9.8
		ATT	111.8±20.9*	101.3±21.2*	−10.2±8.6
		AUD+ATT	110.9±21.8*	102.6±20.9*	−8.1±6.5
		B2	102.8±14.1	96.3±16.7	−6.8±6.7
	Control	B1	127.3±12.4	110.8±8.4	−12.7±5.6
		AUD	117.2±17.8	106.3±13.0	−8.5±8.0
		ATT	139.1±14.1*	127.1±19.0*	−9.8±9.1
		AUD+ATT	138.5±21.9*	125.5±21.2	−10.2±8.5
		B2	126.3±12.0	115.7±9.5	−8.2±9.1
Step amplitude (cm)	PD	B1	57.7±7.0	52.4±6.2	−9.0±6.5
		AUD	59.1±6.1	53.7±6.4	−9.2±6.8
		ATT	68.2±8.5*	62.9±7.7*	−9.0±7.0
		AUD+ATT	67.5±8.3*	61.5±7.5*	−10.4±8.1
		B2	60.1±6.7	55.8±6.7	−7.4±5.6
	Control	B1	66.4±6.4	58.0±4.6	−12.5±4.8
		AUD	66.9±6.6	60.4±5.7	−9.7±6.5
		ATT	81.5±8.3*	75.0±8.5*	−10.0±7.0
		AUD+ATT	81.0±8.3*	74.9±7.8*	−9.3±6.2
		B2	69.1±7.1	62.29±5.52*	−10.1±5.3
Step frequency (steps/min)	PD	B1	104.6±11.9	106.2±11.9	1.7±5.7
		AUD	99.5±12.4	101.4±14.1	2.0±8.4
		ATT	98.4±13.1*	96.6±14.3*	−1.7±4.9
		AUD+ATT	98.6±14.7	100.4±14.5*	1.7±4.5
		B2	103.1±10.0	103.6±12.4	0.4±4.9
	Control	B1	115.4±5.8	114.6±4.6	−0.6±2.6
		AUD	104.9±8.8	105.4±7.0	0.5±4.3
		ATT	102.6±7.2*	101.6±8.9*	−0.7±6.2
		AUD+ATT	102.3±9.4*	100.2±10.3*	1.8±4.6
		B2	110.4±8.2	111.6±7.5	1.0±5.6

NOTE. Values are mean ± SD. The interference effect refers to the mean percentage difference between single- and dual-task trials and is calculated as follows for each parameter in each of the noncued and cued trials: ([dual task − single task]/single task B1) × 100.
Abbreviations: ATT, attentional cues; AUD, rhythmical auditory cues; AUD+ATT, combination cues; B1, baseline.
*Significant differences compared with B1 in the single and dual tasks.

Comparison of PD and Control Group

There was a significant main effect of participant type in walking speed (F=$_{25.65}$, $P<.001$), step amplitude (F=$_{29.13}$, $P<.001$), and step frequency (F=$_{4.18}$, $P=.046$), with the PD group walking consistently slower, with smaller steps, and a reduced step frequency across all conditions. There was no interaction effect of participant type and cue type between the 2 groups, which suggests that although PD participants walked away more slowly and with smaller steps, they responded in a similar way to cue types and conditions. Therefore, the following description of the results will only refer to the PD group unless otherwise stated. Table 2 lists the values for the controls for comparison purposes.

Comparison of Cue Modality

There was a significant main effect of cue type for all parameters (walking speed, F=$_{48.70}$, $P<.001$; step amplitude, F=$_{232.60}$, $P<.001$; step frequency, F=$_{44.21}$, $P<.001$), which indicates that cue modalities differed significantly from each other. Figure 3 shows the changes in each parameter relative to the noncued B1 trial (expressed as the percentage mean difference). For walking speed and step amplitude, a negative value indicates that gait performance is reduced with the cue, compared with the noncued trial; a positive response indicates that walking improves with the cue. A negative value for step frequency indicates an improvement.

Walking speed. During the single-task condition, the attentional cue type resulted in a significant increase in speed compared with baseline ($P<.001$) of 10.68cm/s, which represents a 9.5% improvement compared with noncued gait. The combination cue type was equally effective ($P=.013$), but showed no further increase from the addition of the rhythmic auditory cue (fig 3A). The auditory cue reduced speed during single-task gait but this change was not significant. In the dual-task condition, there were similar significant increases for attentional ($P=.037$) and combination ($P=.028$) cue types, with an increase in speed of approximately 8.5 to 10cm/s. The auditory cue type increased speed by about 2%, which was not significant.

Step amplitude. During the single-task condition, there was a significant increase in step amplitude of approximately 10cm, representing a 15% increase, for the attentional and combination cue types ($P<.001$, $P<.001$) (fig 3B), with no differences between them. Although the auditory cue caused a small increase in step amplitude, it was not significant. The same response was seen in the dual-task condition, with significant increases in step amplitude of 9 to 10cm, an improvement of 15% to 17% for the attentional and combination cue types ($P<.001$, $P<.001$), and a small nonsignificant increase for the auditory cue type.

Step frequency. During the single-task condition, only the attentional cue type caused a significant ($P=.042$) reduction in
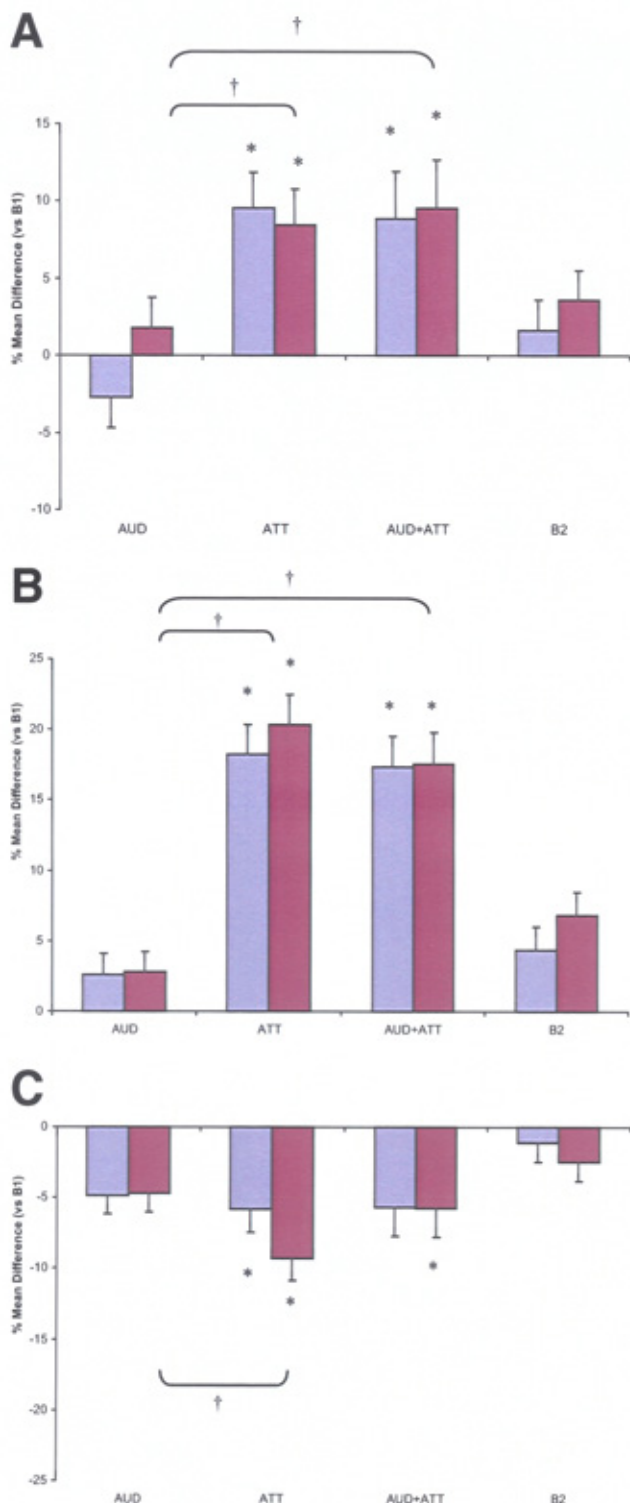
Fig 3. Bars represent percentage change of the PD group in (A) walking speed, (B) step amplitude, and (C) step frequency in each cued condition and baseline 2 compared with baseline (B1; noncued gait). Lighter bars represent single task, darker bars represent dual task. Abbreviations: ATT, attentional cues; AUD, rhythmical auditory cues; AUD+ATT, combination cues; B2, final noncued trial. *Significant changes compared with baseline (B1) in the PD group; †significant differences between cue types.

step frequency of 6.15 steps/min or 6% (fig 3C). The combination and auditory cue types caused a slightly smaller reduction of about 5 steps/min, which was not significant. In the dual-task condition; however, both the attentional and combination cue types caused significant reductions of 6%, to 10 steps/min—a decrease of about 6% to 10% ($P<.001$, $P=.009$). The auditory cue type again caused a nonsignificant reduction of about 5 steps/min.

Interference Effect on Gait

There was a significant main effect of task type on walking speed and step amplitude ($F=_{5.47}$, $P=.023$; $F=_{11.49}$, $P=.001$), with dual-task performance always being significantly reduced compared with single-task performance (see table 2). This was not so with step frequency, where there was no significant difference between single and dual tasks. There was no significant interaction effect of task type (single, dual task) by cue type, indicating that the pattern of response during cued and noncued trials for each condition (single, dual task) was the same for all gait variables (speed, step amplitude, step frequency).

Cues reduced the interference between a single and a dual task in speed, step amplitude, and step frequency when compared with noncued trials (see table 2, interference effect), which was approximately a 7% to 9.5% reduction in all parameters; however, the reduction was not significant.

Do Cues Normalize Gait to Control Levels?

To see if gait parameters of the PD group were normalized to control values in the single and dual tasks, we compared each cue modality for the PD group with the controls' baseline values (walking at preferred speed without cues in the single and dual tasks) (see table 2). Walking speed was normalized with the attentional ($P=.13$) and combination ($P=.183$) cue types to the level of the control group at baseline in the dual-task condition only. Step amplitude, however, was normalized in both the single- and dual-task conditions with the attentional ($P=.566$, $P=.063$) and combination ($P=.707$, $P=.175$) cue types. Step frequency did not differ significantly from control subjects and this did not change with cues.

Immediate Carry-Over Effects of Cueing

When cues were removed in the final (B2) noncued trial (see fig 3), a small improvement remained in all gait parameters in the single and dual tasks. This was significant for step amplitude in the dual task, which remained increased compared with B1 ($P=.038$) and indeed, was normalized to control values.

DISCUSSION

Our main findings in this study were that subjects could use an attentional strategy to increase step amplitude during both a single and a dual task and this strategy also normalized walking speed. In addition, they could combine a rhythmic auditory cue with an attentional strategy during single and dual tasks and this was as effective as the attentional strategy alone, but not more so. The attentional strategy and the combination cue resulted in large improvements in both walking speed ($\approx$10% improvement) and step amplitude ($\approx$15% improvement), considerably higher than the 1.03cm/s improvement in walking speed and 2cm improvement in step amplitude suggested to have a clinical effect above the normal variance in gait of people with PD.[36] The rhythmic auditory cue, when delivered on its own at 10% below preferred stepping frequency, improved step amplitude but the improvement was not significant.

Effect of Cue Modality During Walking (single task)

As expected, the attentional strategy resulted in significant improvements in walking speed, step amplitude, and step frequency in the single task, normalizing gait parameters of the PD group. This supports previous findings that people with PD can effectively modify their gait pattern during a single task when given appropriate instruction to do so.[9,18-22] Our main purpose in this study was to determine whether people with PD could combine a rhythmic auditory cue with an attentional strategy, and to see if the combination was as, or more, effective as the attentional strategy. Our results show that participants successfully combined the cue types and it was equally effective in normalizing walking speed and step amplitude, but it was not superior. This is in contrast to results of a previous study[14] that investigated the effect of combining a rhythmic auditory cue at 25% above preferred stepping frequency with a visual cue (stripes on the floor) and found that the significant improvement in step amplitude with the visual cue alone was lost when the cue types were combined. We suggest that the attentional demand of using 2 different external cue types together resulted in gait interference. Interestingly, we did not find this, which suggests there was no increased attentional demand when this combination of cues was used.

The combined cues did not provide additional benefit over the use of the attentional strategy alone. The choice of a cueing frequency of 10% below preferred stepping rate might be important here. While the rhythmic auditory cue caused a small increase in step amplitude and a small reduction in both walking speed and step frequency, none of these changes reached significance. We chose this cue frequency because subjects had to synchronize with the cue during a dual task as well as while walking alone; therefore, safety was a consideration. When rhythmic auditory cues are delivered at baseline or higher, there are improvements in walking speed,[12] but not in step amplitude.[1,3,5,14] Although the effect of the combination cue was not greater than the attentional strategy alone, the effect of increased cueing frequency to baseline or above may be that it results in additional benefits. The effect of cue frequency on the combination cue and the identification of the optimal cue frequency for dual-task activity therefore require investigation.

Effect of Cue Modality During a Dual Task

A range of secondary tasks have been used in dual-task studies that include secondary cognitive or motor tasks.[9,22,26,37] We chose a task that was both functional and familiar to the participants and therefore had greater ecologic validity. O'Shea et al[25] suggested there is a critical level of task complexity that must be met for interference to occur. The relatively simple dual-motor task we used resulted in a significant deterioration in walking speed and step amplitude in the PD group during the noncued baseline trials and therefore it can be said to have reached a critical level of difficulty. This also agrees with previous studies that have reported an interference effect on gait of a secondary motor task.[23-26,38] Furthermore, none of the cue strategies significantly increased gait interference, which indicates that subjects could attend to both the task and the cue without further deterioration in gait, suggesting the cues did not increase attentional demands further.

The attentional strategy resulted in significantly improved walking speed and step amplitude and normalized gait in the PD group in the dual task. Previous studies have reported reduced effectiveness of attentional strategies during dual tasks because constant vigilance is required.[9] Canning[22] found that when participants were asked to direct attention to a specific aspect of gait, attentional strategies were effective during a

tray-carrying task similar to the task in our study. Importantly, however, the measurement of gait by Morris et al[9] was covert and the participants perceived no need to remain vigilant to the attentional strategy, which perhaps is more reflective of a functional situation. In the present study, participants knew that their gait was being measured, which may have heightened their arousal and made it more likely that they continued to use the attentional strategy during the dual task.

The effect of executive dysfunction on cue use during dual tasks is unknown. It is possible, however, that the combination cue may provide a prompt that a person simply responds to by directing attention to gait without the need for constant vigilance. This method might be a practical alternative for patients who find attentional strategies difficult to use in a functional setting because of distractions in the environment, or problems with executive function.

The rhythmic auditory cue improved gait during the dual task, but this was not significant. This is in contrast to results of previous studies by our group, where there were significant increases in step amplitude with rhythmic auditory cues during dual and multitask performances in the home.[12] This, however, may have been the result of the cue frequency we used, as discussed previously.

The present study tested the immediate response to cues and also showed a short-term carryover effect on step amplitude in the dual task. A period of training with rhythmic auditory cues has been shown to improve walking performance.[2,7,22,39-42] Retention of the effect of an attentional strategy that instructs subjects to increase step size depends on disease severity, with more severe subjects reverting back to baseline measures despite significant improvements made at the time of training with the strategy.[19] This may be the result of increased executive and attentional dysfunction that is seen in more severe disease stages, which may make it less likely that subjects will remember to use the strategy they have been taught if they are not prompted to do so. This may be a promising role for strategies such as the combination cue, which has the external element to aid its use in more functional settings. The effect sizes seen here with the attentional strategy and the combination cue suggest a potential for further improvement with training; the question remains whether the effects of either cue type can be sustained.

Study Limitations

This study involved a small sample of PD and control participants, which limits the ability to generalize its results to a wider population. There was a small but significant difference in the ages of the 2 groups, with the controls being just over 2 years older. This fact may reduce the differences between the groups inasmuch as walking speed and step amplitude are known to be reduced with normal aging, as does dual-task ability; this, in addition to the small number of people studied, should lead to a cautious interpretation of the data. The small number of people with PD also prevented further subgroup analysis, for example, discriminating freezers from nonfreezers. Although no participants experienced freezing during the phase of the walk that was analyzed, freezing may still be a factor that alters response to cues.

The testing environment of the laboratory also reduces transfer of these findings. A more complex dual task would have made it possible for us to more fully evaluate the attentional cost of the cueing strategies because the task we used does not necessarily transfer to more complex tasks such as crossing a busy street. All participants were tested in the on phase of their medication and little is known about the effects of cues on gait in the off medication phase. A planned further study will

involve a larger sample in the home environment, which should address these issues. This study presents the effect of cues on mean gait values. There is increasing evidence that variability of gait parameters also needs to be investigated to fully evaluate the attentional cost of cues.[43]

CONCLUSIONS

This study has extended the findings of previous work by demonstrating that an attentional strategy and a combination cue strategy were equally effective in improving walking speed and step amplitude during both single and dual tasks. The combination cue strategy appears to offer an effective and practical alternative for managing gait deficits in Parkinson's disease, in addition to the use of rhythmic auditory cues or attentional strategies alone. Perhaps it has potential for use in situations of increased attentional demand, or where there are problems of executive dysfunction.

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Suppliers

ELSEVIER

The effect of cues on gait variability—Reducing the attentional cost of walking in people with Parkinson's disease

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Abstract

Parkinson's disease (PD) subjects have increased gait variability, reflecting greater attentional demand during walking. This study aimed to investigate the attentional cost of three cueing strategies by examining their effect on gait variability. Fourteen PD and 12 age matched control subjects were studied under single and dual walking tasks. Gait variability of PD subjects tended to reduce with all cues, the most consistent reductions in variability seen with a combination of an attentional strategy (focussing on big steps) and a rhythmical auditory cue. The reduction in gait variability of PD subjects with cues, suggests they may reduce the attentional cost of walking.
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1. Introduction

People with Parkinson's disease (PD) have increased gait variability compared to age matched controls, thought to reflect reduced automatic control of walking [1]. This is supported by the fact that in healthy young and older adults variability remains consistent under dual task conditions [2–4], but increases in PD [4,5]. People with executive dysfunction, of which attention is a component, display increased gait variability [4,6,7]. Gait variability is a sensitive gait parameter and is predictive of falls in the elderly [7–9]. Variability of step or stride time is said to reflect a disturbance of the gait patterning mechanism [2,4] whereas variability in the support phases of the gait cycle (e.g. stance time and double limb support time) has been attributed to dynamic balance mechanisms [2,4].

Defective functioning of the basal ganglia results in increased cortical involvement in motor control in people with PD leading to increased difficulty with dual tasks [10–12]. It is also known that the ability to appropriately prioritise gait and balance during dual task activities is impaired in PD, likely due to deterioration in executive processes [11,13] and this is correlated with increased gait variability [4,6,7]. PD subjects show an increase in gait variability in response to dual tasks which place increased demands on attentional resources [4,5].

Cues improve gait in people with PD [14,15]. External cues provide temporal or spatial stimuli associated with the initiation and facilitation of a motor activity [15]. Attentional strategies rely more on cognitive, internally generated mechanisms of motor control. The effect of cues on gait variability remains uncertain. In PD, visual cues in the form of stripes on the floor reduce stride length variability [16], whereas step length and stride time variability increase when walking in time to a metronome beat set at 20% below preferred stepping frequency [17]. Clearly the frequency at which external rhythmical cues are delivered may have an impact on gait but at the present time the influence of cues on gait variability remains unclear. One study of early stage PD found that an auditory cue delivered at 7.5% and 15% above preferred stepping frequency significantly improved walking speed but had no effect on stride length [18]. Willems et al. found differential effects on stride length, with an increase in non-freezers seen at preferred stepping frequency, however freezers

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benefited from a reduction of 10% below preferred stepping frequency [19].

Previous work suggested that external cues may be less attentionally demanding than internally generated strategies and are effective during dual tasks [20,21]. Attentional strategies have also been shown to be difficult to use during dual tasks [14]. This study aimed to investigate the difference between internally generated cues and externally delivered cues on gait variability. An external rhythmical cue, an attentional strategy and a combination of the two were compared and cues were tested under single and dual task conditions in order to test the effects of increased attentional demands on cue use. A previous study examined the spatio-temporal gait responses to the three cue types and found that both the attentional and combination cues were effective in improving walking speed and step amplitude [22], this study sought to investigate whether this was at the cost of gait stability.

The following research questions were addressed: firstly, is there a difference between cue types in their effect on different aspects of gait variability and is this response different in PD and healthy subjects? Secondly do cues reduce gait variability under dual task conditions? Finally, is there any short-term carry over of the effect of cues when they are removed?

2. Methods

2.1. Subjects

Fourteen people with idiopathic PD, 5 men, 9 women, mean age 69.3 (3.4) years and a comparison group of 12 age matched healthy subjects mean age 71.5 (2.6) years were studied (Table 1). Ethical consent for the study was granted by Sunderland Local Research Ethics Committee, UK. All subjects gave informed written consent. Inclusion criteria for PD subjects were: diagnosis of idiopathic PD (by a consultant neurologist with a specialist interest in movement disorders), disease severity of I–IV on the Hoehn and Yahr scale [23], absence of other neurological problems or severe co-morbidities likely to affect gait, absence of dementia (score above 24 on Mini Mental State Examination [24]), adequate sight and hearing with glasses or hearing aid if required, independently mobile

Table 1
Participant characteristics for PD ($n = 14$) and control ($n = 12$) participants

	PD	Control	P-value
Number of subjects	14	12	
Age (years)	69.29 (3.36)	71.50 (2.58)	0.075
Sex (men/women)	5/9	5/7	
Height (cm)	165.57 (11.27)	165.42 (8.33)	0.969
MMSE score	27.71 (2.16)	28.58 (1.83)	0.285
Hoehn and Yahr (median)	2 × 2, 4 × 2.5, 8 × 3 (3)		
Disease duration	6.64 (3.25)		
UPDRS motor score	22.86 (9.26)		
Freezers/non-freezers	9/5		

No differences were found in age, height and MMSE score between PD and control subjects with a P-value of $\leqslant 0.05$ being considered significant. Values shown are mean and standard deviation unless otherwise stated Hoehn and Yahr and UPDRS scores were measured when subjects were ON medication.

Table 2
Non-cued and cued trials

Cue type	Description and instructions
Baseline—non-cued (B)	Baseline. Non-cued walking *Instructions: 'walk at your own comfortable pace'* Performed three times
AUD[a]	External rhythmical auditory cue set at 10% below preferred stepping frequency *Instructions: 'as you walk try to step your feet in time to the beat'* Performed twice
ATT[a]	Instruction to focus on 'walking with big steps' *Instructions: 'as you walk try to take big steps'* Performed twice
AUD + ATT[a]	External rhythmical auditory cue set at 10% below preferred stepping frequency, associated with 'taking a big step' *Instructions: 'take a big step in time to the beat'* Performed twice
Final non-cued	Final trial. Non-cued walking completed immediately after cued trials *Instructions: 'walk at your own comfortable pace'* Performed once

Non-cued trials were performed before and after the cued trials.
[a]The cued trials were randomised and performed under single and dual task conditions. The order of the single and dual tasks was counterbalanced.

indoors without a walking aid, no severe dyskinesias (above 2 on Modified Dyskinesia Scale [25]) or prolonged off periods and age 80 years or less. The control group subjects were fit and well with no severe co-morbidity, MMSE score of $\geqslant 24$, adequate vision and hearing and aged 80 years or less.

2.2. Experimental design

A within subjects, repeated measures experimental design compared three cue types under single and dual task conditions. Order and practice effects were controlled for by counterbalancing the walking alone and dual task conditions and randomising the order of cue presentation (Table 2). Cueing strategies are described in Table 2. All testing took place in a gait laboratory and took approximately 45 min, during which time PD subjects were in the ON phase of the medication cycle (1 h after medication intake) confirmed using a visual analogue scale with which the participants rated their current status on a scale from 'ON' to severely 'OFF', patients were accepted as being ON if they rated themselves in the top quarter of the scale.

2.3. Baseline measures

Demographic data were collected for subjects including: gender, age (years), height (m) and weight (kg). For PD subjects disease duration and severity were recorded, scored with the Hoehn and Yahr scale [23], Unified Parkinson's Disease Rating Scale [26], Section III (motor subscale) and the Freezing Of Gait Questionnaire [27].

Rhythmical auditory cues were given using a prototype cueing device,[1] which delivered a rhythmical sound set at 10% below preferred stepping frequency, calculated at a comfortable walking pace during three

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[1]TEMEC Instruments Inc., Spekhofstraat 2, 6466 LZ Kerkrade, The Netherlands.

repetitions of a 10 m walk test. The choice of cueing frequency was made to enable the subjects to safely synchronise with the cue during both the single and dual task. A previous study has shown improvements in gait at 10% below preferred stepping frequency in people with PD with freezing of gait [19]. As the current exploratory study uses a small sample it is not practical to separate freezers and non-freezers into discreet groups, therefore a cueing frequency of 10% below preferred stepping frequency was used as we hoped to increase step amplitude and needed to ensure the subjects were able to safely synchronise with the cue during both a single and dual task.

2.4. Experimental protocol

Subjects walked with and without cues under two different conditions chosen to reflect a functional, ecologically valid activity which has been used in previous studies [11,28,29].

1. Single task—walk only: The subjects were seated in a chair, then stood up and walked along an 8 m walkway stopping when they touched a designated point on a bench.
2. Dual task: The subjects were seated in a chair, stood, collected a tray with two cups of water placed on it from a table beside the chair, walked along the 8 m walkway carrying the tray and stopped when they placed the tray on a designated point on a bench. The level of water in the cups was kept constant by filling to a pre-marked line 2.5 cm below the rim and position of the cups on the tray was standardised. No measure of performance of the task (i.e. the amount of water spilled) was used as this was not a primary outcome of the study.

Subjects were not instructed to prioritise either the walking or tray carrying task. In each condition, subjects performed 10 trials as described in Table 2 under single and dual task conditions. Non-cued baseline trials were performed immediately before and after the cueing trials. Subjects performed two trials with each cue type (Table 2) in a randomised order.

For each trial subjects walked a distance of 8 m over a GAITRite mat[2] which recorded walking speed (cm/s), step time (s) and double limb support time (s). The mat was positioned in the middle section of the walkway in order to record the most stable phase of each walk, reducing the effects of acceleration and deceleration. The GAITRite system[2] is a flexible electronic walkway providing an automated means of measuring the spatial and temporal parameters of gait using a carpet embedded with sensors which detect footfalls. It has been shown to give valid and reliable data [30,31]. The carpet is 457 cm long with an active area of 366 cm, the sampling rate is 32.2–38.4 Hz.

2.5. Data analysis

Data were analysed using SPSS for Windows (Version 12).[3] Data were inspected for distribution using Shapiro–Wilks statistic and all were normally distributed.

Within each condition, repetitions of trials using the same cue for each subject were pooled in order to increase the number of steps used (left and right steps were pooled), this led to a range of 5–20 steps being used to calculate the coefficient of variability (CV) for step time and double limb support time:

$$CV = 100 \times \frac{\text{standard deviation}}{\text{mean}}$$

A mixed design repeated measures analysis of variance was used to compare the effect of subject type (PD and control) and cue type (AUD, ATT, and AUD + ATT) in the single and dual task conditions. Two-tailed tests with a P-value of 0.05 or less were considered statistically significant

for main effects and Bonferroni adjustments were used to correct for multiple comparisons in post hoc between trials pair-wise comparisons.

3. Results

PD and control subjects were matched for age ($P = 0.075$), height ($P = 0.969$) and sex (Table 1). There was no significant difference in scores on the MMSE ($P = 0.285$) with all subjects scoring above the cut off of 24, indicating an absence of dementia. The PD group had a mean disease duration of 6.6 (3.3) years and a median Hoehn and Yahr rating of 3 indicating mild to moderate disease. Walking speed data is included for reference in Table 3 and is discussed in detail elsewhere [22].

3.1. Baseline differences between groups

3.1.1. Single task
Step time variability was significantly higher in PD subjects than the control group ($T = 3.18$, $P = 0.004$) (Table 3). DLS time variability was also significantly higher in PD subjects ($T = 2.331$, $P = 0.028$) (Table 3).

3.1.2. Dual task
Step time variability was significantly higher ($T = 3.465$, $P = 0.002$) in the PD group compared to controls but no significant difference was seen in DLS time (Table 3). PD subjects significantly increased step time variability at baseline in the dual task compared to the single task ($T = 2.42$, $P = 0.023$) as did control subjects ($T = 2.485$, $P = 0.021$). No significant difference was observed in either group for DLS time variability between the single and dual tasks.

3.2. Effect of cues during the single task

A significant interaction between cue type × subject type ($F = 3.087$, $P = 0.019$) was found for step time variability, indicating that variability showed a trend of reducing with all cue types in PD subjects and increasing in control subjects. In PD subjects further analysis showed the reduction in step time variability was significant with the AUD + ATT cue type by 32% compared to baseline values ($P = 0.02$) (Table 3). While cues tended to increase step time variability in controls, this was not significant for any cue type.

A significant main effect of cue type ($F = 5.57$, $P = 0.003$) and subject type ($F = 4.526$, $P = 0.04$) was seen for DLS time variability but no interaction effects were found. All subjects tended to reduce DLS time variability with cues with the exception of the control subjects when using the attentional strategy. Further analysis showed that in PD subjects there were significant reductions in DLS time variability with the ATT ($P = 0.001$) and AUD + ATT ($P < 0.001$) cue types compared to baseline (Table 3). There were no significant

Table 3
Measures of gait variability in the single task and dual task conditions for PD and control participants

		PD			Control		
		Walking speed cm/sec	Step Time CV %	DLS Time CV %	Walking speed cm/sec	Step Time CV %	DLS Time CV %
SINGLE TASK	B Non-cued	101.07 (8.29)	5.86 (1.70)	11.46 (1.61)	127.31 (12.41)	3.97 (1.17)	9.96 (1.68)
	AUD	98.43 (18.11) P=1.00	5.08 (1.60) P=1.00	9.06 (2.38) P=0.098	117.21 (17.82) P=0.161	6.15 (1.59) P=0.61	9.59 (2.01) P=1.00
	ATT	111.75 (20.87) P=0.003	5.43 (1.66) P=1.00	8.38 (1.59) P=0.001	139.06 (14.11) P=0.034	5.78 (2.02) P=0.13	10.81 (2.75) P=1.00
	AUD +ATT	110.87 (21.76) P=0.013	4.01 (1.06) P=0.019	7.43 (1.73) P<0.001	138.50 (21.89) P=0.241	4.79 (1.76) P=1.00	8.93 (2.43) P=1.00
	FINAL Non-cued	102.79 (14.08) P=1.00	4.89 (2.26) P=1.00	6.82 (4.42) P=0.023	126.28 (12.03) P=1.00	4.27 (1.84) P=1.00	8.38 (3.70) P=1.00
DUAL TASK	B Non-cued	92.78 (16.83)	6.34 (1.25)	11.75 (2.24)	110.79 (8.44)	5.07 (1.00)	10.74 (1.89)
	AUD	91.14 (19.48) P=1.00	5.33 (1.49) P=0.322	9.24 (3.45) P=0.313	106.28 (12.98) P=0.977	5.10 (1.05) P=1.00	9.78 (2.83) P=1.00
	ATT	101.33 (21.17) P=0.037	5.88 (1.43) P=1.00	9.64 (2.90) P=0.206	127.05 (19.01) P=0.018	5.48 (1.93) P=1.00	10.77 (3.91) P=1.00
	AUD +ATT	102.61 (20.90) P=0.028	4.65 (1.29) P=0.025	9.21 (3.03) P=0.096	125.5 (21.18) P=0.085	4.49 (04 3) P=0.297	11.42 (3.32) P=1.00
	FINAL Non-cued	96.27 (16.68) P=488	5.60 (1.67) P=1.00	6.83 (3.96) P=0.001	115.73 (9.51) P=0.669	5.08 (2.35) P=1.00	10.63 (4.68) P=1.00

Boxes shaded grey indicate a significant reduction in variability in comparison to the non-cued baseline (B). P-values shown refer to the post hoc tests comparing the cued and final non-cued trials with the non-cued baseline (B).

changes in DLS time variability in the control group with cues.

3.3. Effect of cues during the dual task

A significant main effect of cue type was found for step time variability in the dual task condition ($F = 2.639$, $P = 0.048$) but no significant effect of subject type or interaction effects. All cue types tended to reduce variability compared to baseline in the PD group and this was significant with the AUD + ATT cue ($P = 0.025$) (Table 3). No significant changes were seen in the control group with cues.

Double limb support time variability showed a significant effect of cue type ($F = 2.831$, $P = 0.029$) but no significant effect of subject type or interaction effects. There were no significant reductions in variability compared to baseline with any cue type for PD or control subjects (Table 3).

3.4. Short-term carry over effect (final un-cued trial)

In the single task condition, there were no significant difference between the B_1 and the final un-cued trial for step time variability in either PD or control subjects. Double limb support time variability however, remained significantly reduced in the PD group from B_1 to the final un-cued trial ($P = 0.023$) (Table 3) but not in the control group. In the dual task condition, there were no significant differences in step time variability between the B_1 and the final un-cued trial condition for either the PD or control

group. Double limb support time variability however, remained significantly reduced for PD subjects from B_1 to the final un-cued trial, ($P = 0.003$) (Table 3).

4. Discussion

The main finding of this study was that there was a marked difference in the response to cues which decreased variability in PD subjects and increased variability in controls particularly in terms of step time variability. There were differences between the cue types in PD subjects with the combination cue most consistently reducing variability, in both single and dual tasks.

4.1. Effect of cues on gait variability in the single task condition

PD subjects tended to reduce step time variability compared to baseline values with all cue types, in contrast control subjects tended to show an increase with all cue types. It seems that in healthy adults, cues disrupt the normal gait pattern, possibly through increased attentional demand or motor adjustments having to be made to follow the cue. PD subjects rely more on external input to guide movement [32] and seemed to gain benefit from the presence of cues.

While PD subjects step time variability reduced with all cues, this was significant only for the combination cue and the attentional strategy had least impact. This raises two issues, firstly the ability of cues to reduce step time variability and secondly the difference between cues in

achieving this. Addressing the first issue, step time variability may simply have been reduced through an increase in walking speed or step amplitude as suggested by others [33,34]. This group previously showed walking speed and step amplitude increased significantly with both the attentional and combination cue types [22], however only the combination cue resulted in a significant reduction in step time variability. This argues against the reduction in step time variability resulting from an increase in walking speed or step amplitude. With regard to the second issue, we propose that the relative attentional demands of cues that are generated internally may be greater as they impose executive demands to plan and prepare the movement [21]. An external cue may provide an executive function, acting as a constant prompt and pace maker, reducing attentional cost.

The rhythmical auditory cue alone had less effect on step time variability than the combination cue. This may be partly explained by the cueing frequency (10% below baseline). Another study using a cue delivered at 20% below preferred stepping frequency found increased variability of both step length and step time [17]. Manipulation of gait speed led to a reduction in variability in one study with the use of a treadmill, the authors arguing the treadmill acts as an external pacemaker in the manner of a cue [35], interestingly as with the present study, effects on variability of gait timing were observed in PD subjects but not controls. Visual cues have been shown to significantly reduce variability of step length (a spatial parameter) only and not the temporal parameters of cadence [16], suggesting some specificity of effect of the cue type on variability. This highlights that more work is indicated in order to determine the optimal delivery of external rhythmical cues.

In support of this DLS time variability was reduced significantly with the attentional and combination cues for PD subjects. This parameter of variability may be influenced more by step length, which was targeted by the attentional and combination cues and not the auditory cue, which had the least effect on double limb support compared to the other two cue types. As variability of the support phases of gait is said to reflect balance mechanisms [2,4] this is a positive finding. Further study needs to clarify if cues improve stability and potentially safety in PD subjects.

4.2. Effect of cues on gait variability in the PD and control group during the dual task

PD subjects have impaired executive functions [36,37] and also show increased gait variability increases during dual tasks [2–6,38] thought to be due to an inability to appropriately allocate attention [11]. In the present study, in PD subjects the influence of cues was reduced compared to the single task for DLS variability but remained the same for step time variability. Previous studies have shown that cues can be effective at improving walking in PD

subjects during dual tasks [20,29], possibly by freeing up cognitive resources and reducing attentional cost. PD subjects significantly reduced step time variability with the combination cue possibly due to reduced attentional cost supporting these findings. The effect on balance control may have been limited by the tray carrying task.

4.3. Short-term carry over effect of cues

We found a significant short-term improvement in DLS time variability when cues were removed in both single and dual tasks. Conclusions that can be drawn from this are limited due to the very short time between trials. However, it does suggest that the benefits of cues are in part retained and this warrants further investigation. Previous investigation involving training with cues found a reduction in variability of stride time associated with increased activity in the dentate nucleus of the cerebellum and the parietal and temporal lobes [39], which are associated with time keeping of rhythmical movements.

This exploratory study used a small convenience sample. The experimental protocol and method of data collection allowed a limited number of steps to be recorded (on average around 12) and the sampling rate of the GAITRite mat^2 may have reduced sensitivity. Although Hausdorff [40] comments on the absence of standards and reference values for the study of gait variability it is generally accepted that larger numbers of steps are desirable [41–43]. Previous studies have reported coefficient of variation values of around 5–6% in PD populations when calculated over hundreds of steps [40] and the present study found comparable levels of variability. Another limitation of the present study is that due to the small sample it was not possible to separate freezers and non-freezers and this may have important implications on the response to cues, also the number of freezers in the sample of mild to moderate PD (64%) may have been disproportionate to the incidence of freezing in the PD population. A review by Bloem et al. found that reports of the incidence of freezing of gait in patients with more advanced disease ranged from 20% to 60% [44]. The MMSE was used to screen for cognitive dysfunction (dementia) as this was a small exploratory study. Follow-up studies have incorporated a broader range of psychological outcomes related to executive function and attentional deficits.

5. Conclusion

Overall cues appear to reduce variability in PD and the combination cue strategy was most consistent in this small sample. The effect of cues on gait variability differs between PD and control subjects and appears to highlight the benefits obtained in PD subjects through the use of cues also sustained during a dual task. All cues showed a tendency to reduce variability in PD; however, the combination cue was the most effective for both parameters of variability. These results are interesting considering that a combination of cues

which give two discreet types of information (temporal and spatial) may have been thought to require more attention than a simple cue. These preliminary results however suggest this is not the case. This highlights interesting questions regarding the mechanism of action of cues that are generated externally or internally, the application of different cueing strategies and their generalisation to more complex activities of daily living.

Acknowledgements

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