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Gait and cognition in Parkinson's disease: implications for rehabilitation

Abstract: An increasing awareness of the interaction between gait and cognition has occurred over recent time. This interaction is even more prominent in Parkinson's disease (PD), where the alteration of striatal dopamine deficiency places a greater emphasis on cognition to compensate for the gait disturbances seen in PD. This dissertation aims to provide an insight into this interaction in PD and demonstrate how normal gait control mechanisms are altered in PD to more cognitive control. Evidence will be provided which demonstrates a shift between attention and automatic gait control mechanisms toward attention. In addition, it will be demonstrated that, because of the cognitive dysfunction that also occurs in PD, the capacity to normalize gait still remains impaired and becomes more subject to the effects of external environmental influences. Further, a rationale will be provided to utilize this interaction in a more beneficial manner, to assist the attention control mechanisms to return gait towards normal. This latter approach is applicable to all aspects of gait disorders in PD and forms a basis for possible intervention therapies.

Keywords: attention; basal ganglia; cognition; gait; Parkinson's disease.

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Introduction

The interaction between gait and cognition has assumed an increased scientific awareness over recent years, with an exponential increase in publications and specialist meetings on this topic. The basis for this interaction lies in central gait control mechanisms that normally regulate gait, in a constantly changing environment. In Parkinson's disease (PD), this interaction with the environment is exaggerated, due to malfunction of the basal ganglia, resulting in cognitive processes playing a much larger role in gait regulation than normal. This review will present a theoretical basis for the impact of cognition on gait in PD, based on an understanding of normal gait control mechanisms and how malfunction in PD shifts control of gait to cognitive processes. This increased dependency on cognition to improve gait in PD, makes gait more vulnerable to external influences. The impact of worsening cognition, brought about by the disease process itself, erodes compensatory effects. Our focus will therefore be on normal gait control mechanisms, their malfunction in PD and the impact of change in cognitive function. A detailed explanation of cognitive problems in PD will illustrate how this compensatory capacity can be eroded and how gait deteriorates. Finally, clinical examples will be used to demonstrate how focused attention can improve gait, but at the expense of concurrent tasks.

Normal gait control mechanisms

Central gait control mechanisms are involved in the programming of gait for the specific environment and task at hand. Gait control mechanisms are 2-fold and include attention and automation (Bernstein, 1967). Their selection is dependent on the intention for gait, which in turn is regulated by the environment in which walking should take place and the individual's requirements within that environment (e.g., Yogev-Seligmann et al., 2008). Attentional control of gait utilizes a number of cortical motor areas, which include the pre motor (PMA), the cingulate motor areas (CMA), the dorsal frontal premotor area and the precuneus (e.g., Wu et al., 2004, 2010). The second control mechanism involves automation of gait. This utilizes the basal ganglia (BG)-supplementary motor area (SMA) interaction, which translates the intention of the individual into automation and maintains that intention in automation, until a change in intention occurs (Wu et al., 2004; Wu and Hallett, 2005). Imaging studies have verified the role of the BG-SMA interaction in this process

(e.g., Deiber et al., 1991; Wu et al., 2004). Automatic gait does not require attention resources, when walking within environments that are unencumbered. Alternatively, a change in the environment may engage attention and executive functioning to modulate the stepping pattern.

Once the command has been delivered from either control mechanism, it is contingent for its execution on the mesencephalic and spinal gait control mechanisms. These include the cerebellum, midbrain, pons and spinal cord. The role of the executive system is to adjust the peripheral neuromuscular apparatus to achieve the higher order command (Yogev-Seligmann et al., 2008). The executive system enables flexible adaptation of gait, to accommodate unforeseen environmental perturbations or changes. Examples include the necessity to walk up a hill, against a strong wind or even temporarily through water. In automatic gait, once the intended stride length has been programmed by the BG-SMA interaction, it needs to engage the stride length-cadence relationship, in order to obtain an appropriate cadence. The stride length-cadence relationship is a fixed entity with a wide range that has been shown to be age stable (Egerton et al., 2011). Recent evidence suggests stride length may be cortically controlled and cadence controlled via brainstem connections (de Laat et al., 2011; Snijders et al., 2011; Thevathasan et al., 2012). Past studies have suggested that cholinergic projections may be important in gait regulation and cognition. While the latter suggestion has considerable evidence to support the concept, little direct evidence exists to support its role in gait control, other than by association (Bohnen et al., 2009; Shin et al., 2012).

BG function

The role of the BG in movement control can be understood if examined in global terms, rather than in specific terms of inter-nuclear functions, as commonly delineated in the literature (e.g., Alexander et al., 1986). In particular, the BG needs to be seen in the correct context of the movement control hierarchy. In this regard, it is involved with higher order control and programming of automatic movements. Anatomically it is connected to the SMA and functionally it interacts with the SMA to run complex sequences of movements in automatic mode (Wu et al., 2010). Investigators have used cerebral blood flow studies, single cell recordings in animals, functional MRI and pre-movement potential measures to demonstrate this interaction between the BG and SMA (Fukuyama et al., 1997; Cunnington et al., 1999, 2002; Wu et al., 2004). The BG interacts with the SMA in two distinct ways. The first is to maintain a motor set during automatic running of a cortically preselected motor plan (Wu et al., 2004). The maintenance of a motor set ensures that the correct amplitude of movement for the preselected plan is maintained during automation. At a neuronal level set manifests as sustained tonic neuronal activity (Brotchie et al., 1991). The second form of interaction relates to the provision of internal timing cues (e.g., Cunnington et al., 1995). These cues are related specifically to each sub-movement of the preselected plan and enable the components to connect temporally in a correct and appropriate manner, so that the whole movement is performed rapidly and correctly, without need of attention (Brotchie et al., 1991). This function is represented at a neuronal level as phasic discharge. This phasic activity is generated in BG neurons at the end of a sub-movement. This information is derived from cortical discharge for the execution of the previous sub-movement, however, the phasic activity is used to release the current sub-movement and to initiate the preparatory activity, in the SMA, for the next sub-movement (Cunnington et al., 1999). This is an online process, in which temporal cues are generated as the sub-movements are sequentially generated.

BG malfunction in PD

In PD, there is malfunction of the BG-SMA interaction, due to the reduction in striatal dopamine (Cunnington et al., 1996). Disruption to BG function causes automatic movements to become impaired, however, attention control of movement remains intact (Morris et al., 1994). There is a shift from automatic control to attention control that can be viewed as a compensatory mechanism. This shift has been well documented in numerous studies that have examined cerebral blood flow or oxygen consumption during movement in PD (e.g., Deiber et al., 1991).

During automatic movements in PD, there is a mismatch between intention and automation, so that the amplitude of the movement is reduced compared to the pre-planned or intended movement. The degree of this discrepancy is directly related to the striatal dopamine loss (Morris et al., 2005). In addition, internal cue generation may become corrupted, leading to a gradual reduction in sub-movement amplitude performed down a sequence of movements (sequence effect) (Iansek et al., 2006). These two deficits are present in all movements, which include handwriting (McLennan et al., 1972), speech (Ho et al., 1999) and gait (Morris et al., 1994). These deficits occur

without an awareness of their existence, unless an external reference is provided, usually of a visual nature. Ho et al. (1999) clearly demonstrated this deficit in internal referencing of automatic movement for speech volume. The mechanism of internal movement reference has been alluded to in numerous reports that examine sensory deficits in PD, and have been attributed to disturbance in corollary discharge. These changes in automatic movement control in PD will now be applied to the varying deficits that occur in gait.

Gait disturbances in Parkinson's disease

Reduction in the amplitude of step size (hypokinesia) is a regular feature of PD. Morris et al. (1994) clearly demonstrated that the basic problem in PD gait is stride length (SL) regulation with normal cadence control. Morris et al. (1994) also showed that SL could be normalized with the use of attention control of gait, once the correct SL was visually demonstrated. In addition, they demonstrated that attention control compensates for disturbed automatic control in PD, by enabling the use of a larger SL, even without visual information on correct SL. An inverse relation between the severity of PD, measured using the Unified Parkinson's Disease Rating Score motor section (UPDRS III) and SL, has been documented by both Morris et al. (2005) and Shoushtarian et al. (2011). A higher score on the UPDRS was demonstrated to be associated with a smaller SL. Other gait disturbances occurring in PD include the progressive decrease in size of consecutive footsteps (sequence effect), which may lead to a sudden unplanned stop (freeze or motor block) (Iansek et al., 2006). The sequence effect steps, despite becoming increasingly smaller, may appear to paradoxically accelerate (festination). Difficulty with gait initiation, or ignition failure, is another disturbing gait disorder affecting a small but significant number of people with PD (PwP) (Schaafsma et al., 2003). Gait initiation difficulty presents clinically as repeated, but failed attempts to take the first step. In some individuals, the gait initiation failure is associated with a tendency to fall forward and if the step cannot be initiated, then the person falls (anticipatory postural adjustment uncoupling). The imminence of the fall results in a repeated but ineffective movement of the feet (trembling in place) (Schaafsma et al., 2003). Freezing of gait (FOG) may manifest all, or only some types of gait disturbance described (Schaafsma et al., 2003).

Cognitive profile of PD

Parkinson's disease is associated with deficits in a number of cognitive domains and processes. Most commonly, there are difficulties with the executive functions, attention, visuospatial abilities and memory (see Caccappolo and Marder, 2010 for review). Language is relatively preserved. These impairments begin insidiously, progress gradually (Emre, 2010) and may lead to PD dementia (Emre et al., 2007), where more than one domain is impaired and functional abilities are affected. The concurrent presence of Alzheimer's pathology also needs to be considered.

Executive dysfunction is usually the most prominent cognitive deficit early in the course of PD and involves impairment of working memory, sequencing, planning, initiation, impulse inhibition, reasoning and set-shifting (Caccappolo and Marder, 2010). These culminate in difficulties solving novel and unstructured problems and flexibly adapting behavior to be contextually appropriate and productive (e.g., Luria, 1980). Typically this manifests in dysfunction of instrumental activities of daily living, such as driving, shopping, paying bills and handyman repairs. Its basis may represent non-motor BG malfunction of set maintenance and sequencing.

In PD, there are deficits of divided, selective, sustained and shifting attention, as well as distractibility (Stam et al., 1993; Machado et al., 2009). These relate to the central executive component of working memory (Baddeley, 1986). It is difficult to know if these deficits represent normal attention processes, which are used to compensate for the executive dysfunction, but are over loaded and thus appear to malfunction, or whether a primary malfunction exists, or both. In PD dementia, there are fluctuating levels of cognition and attention (Ballard et al., 2002), decreased automatic stimulus detection (Brønnick et al., 2010) and mental slowing (Brønnick, 2010).

Visuospatial impairment in PD can manifest as difficulties with basic visual perception or with constructional difficulties, such as copying complex figures or block assembly (Mosimann et al., 2004). Constructional abilities are typically affected early in the course of PD (Stella et al., 2007), whereas visual-perceptual difficulties are evident in PwP with dementia (Mosimann et al., 2004).

The prototypical memory profile in PD is characterised by inefficient acquisition and encoding of information and difficulties with spontaneous retrieval (Weintraub et al., 2004). These difficulties are often secondary to impairments of attention and executive function (Bondi et al., 1993; Higginson et al., 2003) and may

represent markedly decreased working memory, with limited temporary storage capacity. Shifting attention, to maintain multiple cognitive tasks in readiness, can prove difficult to sustain. Functionally, the person with PD may appear to have poor memory as they misplace objects, forget what they were looking for, or forget to take their medication. However, it is not typical to see accelerated forgetting over a 30-min delay, as is characteristic of primary amnestic conditions such as Alzheimer's disease (Helkala et al., 1988). Memory may be facilitated via prompts and cues (Weintraub et al., 2004), implicating a deficit of retrieval.

Pathophysiology of cognitive impairment in PD

The pathophysiological basis of cognitive impairment in PD remains incompletely defined, although there are multiple theories that reflect non-motor BG malfunction, or extra BG dysfunction. These include disruption of fronto-striatal circuits by impaired dopamine metabolism (Owen, 2004), and cholinergic (Bohnen et al., 2006) and noradrenergic deficit (Kehagia et al., 2010).

Clinical pathological studies focusing on dementia in PD have most commonly shown cortical Lewy bodies (e.g., Hughes et al., 1993; Mattila et al., 2000), although additional changes including Alzheimer-type changes (Hughes et al., 1993) and neuronal loss in the medial part of the substantia nigra (Rinne et al., 1989) have also been described. Progressive deterioration of dopamine metabolism (Piggot and Perry, 2010) may also contribute to worsening cognition. Regional Lewy body pathology in the parahippocampal gyrus, anterior cingulate, amygdala and inferior temporal cortex is related to overall severity of dementia in PD (see Revuelta and Lippa, 2010 for a review).

In summary, BG motor malfunction in PD results in reduced amplitude of movements and difficulty sequencing movements in automatic mode. In a similar manner, non-motor BG malfunction results in difficulty in maintenance of cognitive tasks in readiness and difficulty in sequencing task components. The shift to attention control to compensate for motor and non-motor deficits highlights the difficulty in divided attention with de-compensation, if more than one task is performed simultaneously. In extra BG pathology, further deficits with memory impairments, reduced functional reserve and the need for medication, can lead to neuropsychiatric disturbances and impair gait irreversibly.

Cognition and gait in PD

The reduced working memory noted could be explained by inability to run cognitive processes in automation, in a similar manner to running automatic movements. Compensation utilizes attention, but the capacity to divide attention is limited and the running of multiple automatic tasks in PD is difficult. People with PD use attention to compensate for the reduced amplitude of SL. Self-initiated tasks, but not externally cued tasks, are reduced in amplitude and velocity (Werheid et al., 2007). When complex dual tasks are performed while walking, step length and gait speed are reduced when compared to healthy controls (Bond and Morris, 2000). However, dual task performance reveals that attention is able to improve SL, as dual tasking has an even greater detrimental effect on walking. In general terms, attention improves SL in PwP, as long as they concentrate on walking. If attention is diverted from walking, a reduction in SL takes place. This impact of attention on SL in PD is nonspecific and never returns the SL to normal. Similarly, PwP can increase SL and velocity if instructed to walk faster and faster (Morris et al., 1994). However, these increments never return the SL or velocity to normal, because it still utilizes an abnormal SL cadence relationship, which in PD is shifted to the right (Morris et al., 1998). The only way PwP can normalize SL is by visual information regarding the correct SL. If this is known, then attention can be used to normalize SL. Its normality, however, is still dependent on attention to control gait. Diversion of attention will return SL to the reduced level maintained by the malfunctioning BG (Bond and Morris, 2000).

Attention plays a very important role in regulating gait in PD. However, medication used to return striatal dopamine level to normal, can impact on attention resources in PD in a number of ways. The first involves the development of dyskinesia. Clinically, this is usually associated with difficulty in focusing attention and concentrating on only one task, with any new event drawing the person's attention away from their walking. In this context, attention cannot be used effectively to control gait, resulting in a return to smaller steps, despite adequacy of medication. Adjustment of medications to minimize dyskinesia can therefore lead to improvement in gait by improving the person's ability to focus their attention. Medication can also lead to confusion in susceptible PwP, particularly in those with cognitive decline and early dementia. Drug-induced confusion will make it difficult to utilize attention effectively, however, with reorganization of

the drug regime, confusion can be minimized and gait improved.

The episodic reduction in SL manifests more frequent and prominent symptoms in subjects who experience FOG (Camicioli et al., 1998). This suggests PwP and FOG have an even greater dependency on attention when walking compared to PwP who do not have FOG. The main reason is that motor arrest occurs when the background SL is reduced to a sufficient level to approximate the sequence effect SL (Chee et al., 2009). The other manifestation, that may or may not be present in all subjects who experience FOG, includes gait initiation difficulties. The combination has devastating effects on individuals. Numerous factors that can impinge on attention will lead to a reduction in SL and if the SL is small enough, the risk of a freezing episode is increased. Some of these factors include visual distracters, such as doorways, talking while walking, or walking in restricted space (Schaafsma et al., 2003). Normal biomechanical requirements during a directional change also result in a reduction in step length during the turn, and for PwP with a reduced background SL, this mandatory decrease in step length may lead to an increased risk of a FOG episode (Huxham et al., 2008). The reduction of step length when turning may explain why attention focused on the turn may fail to prevent FOG. Strategies that minimize the need to reduce step length during a turn, such as turning in a wide arc, are commonly used to reduce the risk of a FOG episode (Morris, 2000). Subjects who experience gait initiation difficulties may have disturbed preparatory pre-movement activity from the supplementary motor area (Shoushtarian et al., 2011), so that the ability to initiate gait in automatic mode is disturbed. Typically, these subjects do respond to L-dopa with improvement in gait initiation, if on appropriate doses of medication (Schaafsma et al., 2003). Focus of attention on initiation does not result in an improvement, as this focus is nonspecific. However, if a visual size of the step is provided and attention is directed to the appropriate step size, then initiation becomes possible. Some PwP who experience gait initiation difficulties may not respond to medication (Schaafsma et al., 2003). One explanation may be a block to communicating the command regarding SL to the cadence control center in the region of the pedunculopontine nucleus in the upper brainstem (Snijders et al., 2011). Although attention control with a visual image of the correct step length may overcome the initiation disturbance initially, as the condition progresses, this compensatory mechanism becomes ineffective.

Management principles for rehabilitation for gait disorders in PD

This overview has provided a basis for understanding the theoretical framework on which strategies to normalize gait disorders in PD are based. The capacity of strategies to improve gait, depends on the ability of the individual to utilize attention and mental imagery, which in turn is dependent on cognitive capacity. The optimization of medical management is of the utmost importance in order to minimize fluctuations, dyskinesia and neuropsychiatric side effects (Olanow et al., 2009). The use of strategies utilizes the pre-existing interplay between attention and automatic control of gait and requires the provision of information regarding correct movement amplitude or speed, to overcome the internal disruption of movement referencing (Hallett, 2008). Strategies to achieve this include visual or auditory cues. Focus of attention to the correct parameter, such as step length, will then enable normal performance of the movement, as long as attention is maintained and dual tasks and distractions avoided (O'Shea et al., 2002). The requirement of single task performance limits this approach, as activities of daily life involve multitasking. To address this limitation, alternative approaches to improve gait have included entrainment to rhythmical cues, using various modalities such as visual, auditory or somatosensory devices (e.g., Rochester et al., 2007). Although these techniques have some basis in BG malfunction, they fail to understand the disturbed internal movement-referencing present in PD and as such, do not return gait back to normal, but rather improve the gait disturbance to a minimal degree (Rochester et al., 2007). Interventions that aim to improve strength, postural control, range of motion and endurance training, do not deal with the basic disturbances in automatic control of gait, and any improvement in SL is again minor (Kwakkel et al., 2007).

In summary, the cognitive status of a person with PD is an important contributor to the person's capacity to walk at their best. This disturbed cognitive spectrum in PwP, not only can mimic that of the motor domain, but also becomes irreparably impaired in the context of dementia and extra BG pathology. This is further compounded by attention disturbance, which can become overloaded, with a resultant difficulty in multi-tasking. Understanding the basis for the interaction between gait and cognition and how this is shifted towards attention control in PD, assists in utilizing attention to actually improve gait with movement strategy training.

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