Stuart S, Lord S, Hill E, Rochester L.

Gait in Parkinson's disease: a visuo-cognitive challenge.


Copyright:
© 2016. This manuscript version is made available under the CC-BY-NC-ND 4.0 license

DOI link to article:
http://dx.doi.org/10.1016/j.neubiorev.2016.01.002

Date deposited:
24/03/2016

Embargo release date:
07 January 2016

This work is licensed under a
Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International licence

Newcastle University ePrints - eprint.ncl.ac.uk
Gait in Parkinson’s disease: a visuo-cognitive challenge

Samuel Stuart, Sue Lord, Elizabeth Hill, and Lynn Rochester*

Institute of Neuroscience/Newcastle University Institute of Ageing, Clinical Ageing Research Unit, Campus for Ageing and Vitality Newcastle University, Newcastle upon Tyne, United Kingdom

Correspondence to:

Lynn Rochester PhD
Professor of Human Movement Science
Institute of Neuroscience,
Newcastle University Institute for Aging,
Newcastle University
Newcastle upon Tyne
NE4 5PL
Email: lynn.rochester@ncl.ac.uk
Tel: (+44) 0191 208 1291
Email: lynn.rochester@newcastle.ac.uk

Word Count: Abstract (170): 141

Article (Excluding abstract): 5,312

Figure: 1

Tables: 2

*corresponding author
Abstract
Vision and cognition have both been related to gait impairment in Parkinson’s disease (PD) through separate strands of research. The cumulative and interactive effect of both (which we term visuo-cognition) has not been previously investigated and little is known about the influence of cognition on vision with respect to gait. Understanding the role of vision, cognition and visuo-cognition in gait in PD is critical for data interpretation and to infer and test underlying mechanisms. The purpose of this comprehensive narrative review was to examine the interdependent and interactive role of cognition and vision in gait in PD and older adults. Evidence from a broad range of research disciplines was reviewed and summarised. A key finding was that attention appears to play a pivotal role in mediating gait, cognition and vision, and should be considered emphatically in future research in this field.

Highlights
• Impaired vision and cognition contribute independently to gait deficit in PD
• Visual and cognitive interaction during gait has not been robustly examined
• Combined visuo-cognitive processes impact on gait
• Attention plays a pivotal role in visuo-cognitive control of gait in PD

Keywords: Parkinson’s disease, older adults, vision, cognition, gait, saccades, visuo-cognition, attention
Introduction

Parkinson’s disease (PD) is a common neurodegenerative disorder characterised by cardinal motor symptoms such as rigidity, bradykinesia, tremor, postural instability and gait deficit (Jankovic, 2008). Gait impairments in PD include both continuous (constantly present) and episodic (freezing of gait (FOG)) (Nutt et al., 2011). Continuous gait impairment typically manifests as reduced velocity, step length, swing times, arm swing, increased gait variability and reduced automaticity. While episodic impairments emerge with increasing disease severity and are seen as hesitations when turning, a ‘freezing’ block in a small spaces such as doorways and difficulty with gait initiation (Giladi et al., 2013). Gait impairments underpin difficulty walking in real-world environments such as maintaining a straight trajectory during gait (veering) (Davidsdottir et al., 2008), negotiating obstacles (Vitorio et al., 2013), and navigation (e.g. difficulties with narrow spaces such as doorways (Cowie et al., 2010) and misjudgement of object distance (Davidsdottir et al., 2005)). Moreover these problems are common and linked to falls (Paul et al., 2014). Although these problems emphasise the motor complications of PD, it is widely recognised that gait impairment is complex and reflects input from multiple systems that include both motor and non-motor systems (Grabli et al., 2012). For example, there is abundant evidence of the role of cognition in gait and increasing evidence of the role of vision. Understanding their respective contributions is critical in order to inform the mechanisms that drive gait impairment and to contribute to targeted therapeutic development to improve gait, independent mobility and falls risk.

A large body of evidence supports a robust relationship between cognition and gait, highlighting that gait is underpinned by cognitive functions (Lord et al., 2014). Cognitive impairments are common in PD with an estimated 40% of patients presenting with mild cognitive impairment (MCI) at diagnosis (Yarnall et al., 2014) and up to ~75% with dementia at ten years (Aarsland and Kurz, 2010). Previous studies have extensively investigated the relationship between gait and cognition (Amboni et al., 2013) using two methodological approaches. Associative protocols measure gait and cognition as separate behaviours and explore their relationship to identify links between them (Lord et al., 2014). Online protocols on the other hand, manipulate cognition particularly attention during walking through the use of dual-
task protocols which show in real-time the contribution of cognition to gait (Kelly et al., 2012b). Such protocols demonstrate gait deficit such as reduced velocity and step length are associated with impaired cognition (Lord et al., 2014), and exacerbated using dual-tasks in PD (Kelly et al., 2012b).

Visual impairments are also common with up to 75% of people with PD experiencing at least one symptom such as blurred vision (Davidsdottir et al., 2005; Collerton et al., 2012; Urwyler et al., 2013). The relationship between vision and gait in PD has also been investigated either by exploring relationships between separate visual functions and gait or use of online protocols where vision is manipulated during gait (i.e. light or dark rooms) (Azulay et al., 1999; Almeida et al., 2005). Selective gait impairments are associated with deficits in visual functions (Moes and Lombardi, 2009), and exacerbated by visual manipulation in PD (Cowie et al., 2012). Studies have shown that visual functions contribute to gait control in PD (Azulay et al., 1999; Azulay et al., 2002; Khattab et al., 2012).

To date the relationship between gait, cognition and vision has received scant attention and is poorly understood. Cognition, vision and gait potentially interact in a selective but overlapping manner in order to plan routes and make ongoing modifications appropriate to changing environments. Static and more recently dynamic test protocols have been used to examine the interplay between cognition and vision. Static protocols range from simple associations between separate cognitive and visual outcomes, to more complex neuro-imaging or computerised saccadic (fast, jump-like) eye-movement assessment. Evidence from static tests supports an interaction between cognition and vision (Lee et al., 2015), and vice versa (Bertone et al., 2007; Toner et al., 2012). This interaction is encompassed by the term visuo-cognition, which is a global descriptor of interaction between cognitive and visual functions across multiple levels of information processing (Antal et al., 1998; Bandini et al., 2002). Visuo-cognition is therefore distinct from limited terms such as visuo-spatial function, which refers to the cognitive ability of the posterior parietal cortex to perceive the spatial relationship of objects (Benton and Tranel, 1993; Possin, 2010). Deficits in visual functions impact visuo-spatial ability due to their interaction (Stoerig and Cowey, 1997), but this exhibits only one aspect of visuo-cognition. Recent technological advances in mobile eye-tracking devices have facilitated measurement of saccadic eye movements during dynamic protocols.
(Land, 2006), which serve as a proxy measure of visuo-cognition during gait in PD (Stuart et al., 2014). To provide a detailed account of the role of vision and cognition during gait in PD there is first a need to understand the relationship and interactions between these two systems, and from these draw inferences about their potential impact on gait.

**Study aims**

A narrative review was undertaken to explore the diverse range of literature which was necessary to inform these complex interactive features. We adopt a model to explore the independent and interacting roles of vision and cognition in gait impairment in PD (Figure 1) and highlight relevant literature pertaining to the role of cognition in gait (Figure 1(A)); the role of vision in gait (Figure 1(B)); the relationship between visual function and cognition (visuo-cognition) (Figure 1(C)); and finally the role of visuo-cognition in gait (Figure 1(D)). We explore evidence in PD and older adults, and make recommendations for future work in this complex and developing area.
A. The role of cognition in gait

Cognition is a multi-dimensional construct represented by interdependent systems, such as those described in Table 1. Attention is one of the most complex cognitive functions and is often considered to have overarching capacity (Lückmann et al., 2014) as a ‘gatekeeper’ or ‘supervisory system’ that allocates resources to competing processes (Posner and Petersen, 1990; Baddeley, 1992; Engle, 2002). Therefore if attentional deficit is present, other cognitive functions are also compromised (Posner and Petersen, 1990). For example, working memory is dependent on attentional processes to determine capacity and allocation (Kane et al., 2006).

Figure 1 - A model of online relationships between vision, cognition and gait in Parkinson’s disease

Four main pathways are involved; A) Cognition and gait, B) Vision and gait, C) Interaction between vision and cognition (visuo-cognition), and finally D) Visuo-cognition (measured through saccades) and gait.

Recognised pathways that have been assessed using both associative and online protocols are represented by black lines.

Unclear pathways that have not been assessed using both associative and online protocols are represented by dashed red lines.
Interpretation is complicated by the lack of a single and clear-cut definition of attention (Yoge-Seligmann et al., 2008). As a result, different theoretical and neuroanatomical models of attention exist which are in turn selectively applied to different areas of research (Posner and Petersen, 1990; Baddeley, 1992; Baluch and Itti, 2011; Petersen and Posner, 2012). However, most neuroanatomical models are consistent in describing attentional processes that originate from the pre-frontal cortex (PFC) which are associated with executive function (Aleman and van't Wout, 2008) and extend to include broader cortical networks including those with BG input (McNab and Klingberg, 2008). Attentional processes are also influenced by subcortical noradrenaline and cholinergic projections (Delaville et al., 2011; Müller and Bohnen, 2013), involving structures such as the locus coeruleus, thalamus, pedunculopontine nucleaus (PPN) and nucleus basalis of Meynert (Bohnen and Albin, 2011; Delaville et al., 2011; Gratwicke et al., 2015; Picillo et al., 2015). Dysfunction in any of these cortical or sub-cortical attentional networks with age or pathology may impact cognitive, visual or gait processes.

Visuo-spatial ability also shares a complex relationship with attention particularly in PD (Crucian and Okun, 2003; Crucian et al., 2010). Standard visuo-spatial assessments require attentional input from an early stage of visual processing to select focal areas of interest (Finton et al., 1998; Baluch and Itti, 2011; White et al., 2013). One study demonstrated that visuo-spatial deficits with PD disappeared when controlling for attention (Bondi et al., 1993), indicating need for a cautious approach to interpretation.

**Cognition in Parkinson’s disease**

Cognitive impairment in PD is diverse, with severity and progression to dementia (classified according to criteria from the Movement Disorders Society taskforce (Litvan et al., 2012)) selective to PD phenotype (Pagonabarraga and Kulisevsky, 2012). Cognitive deficits most commonly present in attention, executive function, working memory and visuo-spatial ability (Caccappolo and Marder, 2010) (summarised in Table 1), whereas other processes such as language are usually less affected (Barone et al., 2011). Such deficits occur early and insidiously (Pfeiffer et al., 2014; Yarnall et al., 2014), and are dominated by attentional impairment (Taylor et al., 2008; Svenningsson et al., 2012).
Progression of cognitive impairment relates to genetic factors and pathological changes in different substrates (Svenningsson et al., 2012), such as fronto-striatal (Jokinen et al., 2013) and posterior-cortical dysfunction (Pagonabarraga and Kulisevsky, 2012). Dopaminergic fronto-striatal deficits relate to slow cognitive decline (Emre et al., 2014), and primarily impact attention, executive function and working memory. Whereas posterior-cortical deficits relate to rapid cognitive decline, perhaps determined by degeneration of cholinergic projections from the basal forebrain (Pagonabarraga and Kulisevsky, 2012). Age-related cognitive deficits (Table 1) which are typically more amnestic and represent increased cholinergic burden also contribute to PD cognitive impairment (Petersen et al., 1999; Bohnen et al., 2006), especially in more advanced disease (Bohnen and Albin, 2011).

**Cognition and gait**

The relationship between gait and cognition in PD (Figure 1(A)) is particularly strong and supported by mechanistic and imaging work (Grabli et al., 2012; Maillet et al., 2012). Various relationships between selective gait characteristics and cognitive functions have been found, however attention has a central role in gait in PD (Yogevesligmann et al., 2008).

Recent work from our group examined the association between gait and cognition in older adults and PD (Lord et al., 2014), using a comprehensive battery of cognitive and gait measures. We found a strong relationship between attention and the ‘pace’ domain of gait (comprising gait velocity, step length and step time). Similarly, online studies utilising dual task protocols which manipulate attention in real-time demonstrate an increase in gait variability, reduced velocity, swing time and step length in older adults (Hollman et al., 2007; Verghese et al., 2007; Hausdorff et al., 2008) and PD (Yogevesligmann et al., 2005; Rochester et al., 2008; Kelly et al., 2012a). However dual task interpretation is challenging because of the complex intertwined nature of attention, executive function and working memory (Yogevesligmann et al., 2008; Rochester et al., 2014), which have overlapping influences on dual task performance (Kelly et al., 2012b).

Executive dysfunction is related to gait deficit in PD, particularly in those who report FOG (Amboni et al., 2008; Heremans et al., 2013) and people with the Postural Instability and Gait Disturbance (PIGD) phenotype (Lord et al., 2014), who present
with greater frontal impairment (Burn et al., 2006; Maidan et al., 2015). Associations between gait and cognition have shown that executive dysfunction is related to reduced gait velocity, increased variability, step time and swing time in older adults (Ble et al., 2005; Springer et al., 2006; van Iersel et al., 2008; Liu-Ambrose et al., 2010; Holtzer et al., 2012) and PD (Plotnik et al., 2009; Lord et al., 2010; Lord et al., 2014). Interpretation is complicated by the intimate relationship between executive function and attention (Kudlicka et al., 2011), which has prompted these functions to be discussed both separately and as a unitary domain (i.e. executive-attention) (Holtzer et al., 2006; Verghese et al., 2008; MacAulay et al., 2014). Discerning their individual role in gait is therefore challenging, and highlights a need for precise cognitive assessment and outcome reporting.

As another closely related cognitive function, working memory is also associated with gait deficit in older adults, for example with gait velocity (Holtzer et al., 2006; Soumare et al., 2009), step time (Holtzer et al., 2012), step time variability, double support time and step length (Holtzer et al., 2006; Martin et al., 2013). The relationship in PD is less clear with research showing contradictory results (Amboni et al., 2012; Lord et al., 2014; Stegemoller et al., 2014). Inconsistencies in PD associations are possibly due to the use of subtly different working memory assessments (i.e. digit span forward or backward, or Rey Auditory Verbal Learning Test) and limited consideration for features that potentially sensitise the relationship such as disease phenotype, as reported by Lord et al. (2014).

Visuo-spatial ability has been related to Parkinsonian gait, possibly due to impairment of attentional networks common to visuo-spatial function and gait control (Menant et al., 2014). Amboni et al. (2012) reported an association in PD between impaired visuo-spatial ability and deficits in their ‘stability’ gait domain. Correspondingly, deficits are implicated in falls in older adults (Reed-Jones et al., 2013) and PD (Davidsdottir et al., 2005; Allen et al., 2013). Visuo-spatial impairment with age and PD also relates to reduced step length (Nadkarni et al., 2010), gait velocity (Beurskens and Bock, 2011), and increased double support time, stride time variability (Menant et al., 2014), step length variability (Martin et al., 2013) and reduced timed up and go speed (Donoghue et al., 2012). Findings are however contradictory (Soumare et al., 2009; Plotnik et al., 2011), at least partly due to lack of comprehensive and rigorous visuo-spatial assessment (Lord et al., 2014). Again, the
relationship may also depend on disease severity, as reported previously for the PIGD phenotype (Domellof et al., 2011) and in those who experience FOG (Nantel et al., 2012; Heremans et al., 2013) (Table 1). A recent study involving a large number of people with PD (n=783) found that visuo-spatial ability was significantly related only with FOG severity (Kelly et al., 2015), possibly due to greater frontal and right posterior-parietal cortex deficits in those with FOG (Velu et al., 2013; Handojoseno et al., 2015). Understanding of visuo-spatial contribution to gait is further limited by lack of online studies (Kelly et al., 2012b). For example, a recent study by Ricciardi et al. (2014) manipulated visuo-spatial ability during gait in a small cohort of PD using a dual task (i.e. completion of a visuo-spatial assessment shown on a projector screen while walking), but did not report gait characteristics during the task which limited findings. Test paradigms are not always considered with respect to other cognitive (i.e. attention) and visual functions which are not routinely assessed. A further issue is that laboratory manipulations may also be unrepresentative of real-world environments (Dowiasch et al., 2015; Ottosson et al., 2015).

Evidence from imaging

Imaging the brain while walking is impossible as the head has to remain still. To overcome this, protocols have used motor imagery or assays of gait in an attempt to understand the neural correlates of gait. Imaging studies generally demonstrate that gait involves a widely distributed neural network (Maillet et al., 2012; Bohnen and Jahn, 2013; Herman et al., 2013; Holtzer et al., 2014). Although most studies have focussed on motor control, more recent work demonstrates overlap with neural networks associated with cognitive function such as the pre-frontal and frontal cortex (Seidler et al., 2010; Shine et al., 2013a). More recent work has used techniques such as functional near infra-red spectroscopy (fNIRs) that allow activity in the frontal cortex to be measured while a person is walking (Ferrari and Quaresima, 2012). These studies have shown that episodic gait impairment and postural control in PD are associated with online changes in frontal cortex activation (cerebral oxygenation: HbO2) levels (Mahoney et al.; Maidan et al., 2015). Similarly, fNIRs studies have shown increased PFC activation during dual task gait in older adults (Holtzer et al., 2011; Doi et al., 2013; Beurskens et al., 2014). Also, studies exploring network functions and connectivity have shown a breakdown in connectivity between regions related to gait, attention, executive function (Fasano et al., 2015; Sarasso et al., 2015).
and visuo-spatial ability (Nantel et al., 2012), accompanied by greater right hemisphere dysfunction (Tessitore et al., 2012; Fling et al., 2013; Shine et al., 2013b; Peterson et al., 2014). To date, limitations to this emerging area of research include recruitment of mostly advanced cohorts and test protocols using techniques such as motor imagery or virtual reality, which may only partially represent online execution and therefore require cautious application (Cohen et al., 2011).
<table>
<thead>
<tr>
<th>Cognitive Function</th>
<th>Definition/Background</th>
<th>Older adults</th>
<th>Parkinson’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention</strong></td>
<td>An overarching cognitive function (Lückmann et al., 2014). Ability to focus, select information (inhibition) and mediate parallel processes, allocating limited central processing capacity where relevant (Noudoost et al., 2010).</td>
<td>Declines more rapidly than other cognitive functions (Sweeney et al., 2001)</td>
<td>Commonly impaired even in those without dementia (Palavra et al., 2013)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deficits impact various aspects of attentional control such as inhibition seen in a number of tests such as the Stroop test (West and Alain, 2000)</td>
<td>Relates to dysfunctional fronto-striatal and fronto-parietal pathways (Gerrits et al., 2015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Declines with age</td>
<td>Cholinergic dysfunction is also involved via nucleus basalis of Meynert and pedunculo-pontine nucleus input to the thalamus and cerebral cortex (Yarnall et al., 2011)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Declines more rapidly than other cognitive functions</td>
<td>Shown via neuropsychological tests and prolonged P3 latencies (Suna et al., 2014) which increase with disease severity (Lopes et al., 2014; Tang et al., 2015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Impaired</td>
<td>• Commonly impaired even in those without dementia (Palavra et al., 2013)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Declines more rapidly than other cognitive functions</td>
<td>• Relates to dysfunctional fronto-striatal and fronto-parietal pathways (Gerrits et al., 2015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Deficits impact various aspects of attentional control such as inhibition seen in a number of tests such as the Stroop test (West and Alain, 2000)</td>
<td>• Cholinergic dysfunction is also involved via nucleus basalis of Meynert and pedunculo-pontine nucleus input to the thalamus and cerebral cortex (Yarnall et al., 2011)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Declines with age</td>
<td>Shown via neuropsychological tests and prolonged P3 latencies (Suna et al., 2014) which increase with disease severity (Lopes et al., 2014; Tang et al., 2015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Impaired</td>
<td>• Commonly impaired even in those without dementia (Palavra et al., 2013)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Declines more rapidly than other cognitive functions</td>
<td>• Relates to dysfunctional fronto-striatal and fronto-parietal pathways (Gerrits et al., 2015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Deficits impact various aspects of attentional control such as inhibition seen in a number of tests such as the Stroop test (West and Alain, 2000)</td>
<td>• Cholinergic dysfunction is also involved via nucleus basalis of Meynert and pedunculo-pontine nucleus input to the thalamus and cerebral cortex (Yarnall et al., 2011)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Declines with age</td>
<td>Shown via neuropsychological tests and prolonged P3 latencies (Suna et al., 2014) which increase with disease severity (Lopes et al., 2014; Tang et al., 2015)</td>
</tr>
<tr>
<td><strong>Executive Function</strong></td>
<td>Ability to plan and execute goal-directed behaviours (Ding et al., 2015).</td>
<td>Linked to age-related frontal-striatal deterioration (Buckner, 2004)</td>
<td>Impaired</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impairments impact on intention, initiation, inhibition and switching performance (Hull et al., 2008)</td>
<td>• Early impairment which primarily involves the pre-frontal cortex and fronto-striatal pathway (Zgaljardic et al., 2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Declines with age</td>
<td>• Reflected by impairment in a range of cognitive skills such as poor inhibitory response (Ding et al., 2015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Declines with age</td>
<td>• Linked to increased motor slowing and difficulties in planning (Weintraub et al., 2005)</td>
</tr>
<tr>
<td><strong>Working Memory</strong></td>
<td>Ability to maintain and manipulate information over short time periods, which is linked to attentional control (Baddeley, 1992; Awh et al., 2006).</td>
<td>Decline related to deterioration of attention (Gazzaley et al., 2005)</td>
<td>Impaired</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Related to inhibition and decreased functional connectivity within large-scale brain networks (Fabiani et al., 2015)</td>
<td>• Not always apparent without the use of sensitive neuropsychological tests (Posnin et al., 2008)</td>
</tr>
<tr>
<td><strong>Visuo-spatial ability</strong></td>
<td>Ability to visually perceive the spatial relationships of objects. It is linked to attention and memory (Richards et al., 1993).</td>
<td>Declines more than verbal cognitive tasks (Jenkins et al., 2000)</td>
<td>Impaired</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Declines related to changes in underlying neural mechanisms (Klencklen et al., 2012), which involve altered fronto-parietal projections (Drag et al., 2015)</td>
<td>• Associated with increased motor severity and freezing of gait (Nantel et al., 2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Declines with age</td>
<td>• Related to frontal and parietal lobe deterioration (Biundo et al., 2013), with right hemisphere dysfunction implicated (Karádi et al., 2015; Seichepine et al., 2015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Declines more than verbal cognitive tasks (Jenkins et al., 2000)</td>
<td>• Underlying structural changes of grey matter in frontal and temporal-parietal cortices impact this function (Pereira et al., 2009; Rektorova et al., 2014)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Declines related to changes in underlying neural mechanisms (Klencklen et al., 2012), which involve altered fronto-parietal projections (Drag et al., 2015)</td>
<td>(Unless otherwise stated reported older adult impairments relate to comparison between older adults (&gt;50 years old) and either younger adults or pathological groups, and reported Parkinson’s disease impairments relate to comparison to a control group)</td>
</tr>
</tbody>
</table>

(Unless otherwise stated reported older adult impairments relate to comparison between older adults (>50 years old) and either younger adults or pathological groups, and reported Parkinson’s disease impairments relate to comparison to a control group)
B. Role of vision in gait

Vision is a complex sensory system, involving integration of multiple structures and levels of information processing (Kaas, 2008). Critically vision relies on creation of various components (i.e. form, colour and movement) to allow interpretation of complex visual scenes (Cavanagh, 2011). Visual processes begin at the retina where photoreceptors absorb light and visual functions begin to break down the retinal image into its components (Itti and Koch, 2001) before sending the information to high-level areas for further processing (Wolfe, 1994) (Table 2). Integrity of these low-level visual functions is therefore vital for adequate vision.

Visual function in Parkinson's disease

Visual impairment is common in PD and is associated with gait dysfunction, although methodological issues (summarised in Table 2) necessitate cautious interpretation. The impact of visual impairment on gait has primarily been investigated in healthy young and older adults, with limited evidence in PD. Such studies demonstrate that age-related deficit in visual function is associated with reduction in activities of daily living, quality of life, mobility and is an independent risk factor for falls (Reed-Jones et al., 2013; Uiga et al., 2015). Visual pathology, such as glaucoma, cataracts and macular degeneration are a common and often under-reported problem in older adults. However these visual problems are seen in PD along with a wide range of other visual impairments, from impairment of basic functions such as visual acuity (VA) and contrast sensitivity (CS) to more complex processes such as depth perception, motion perception and optic flow (Armstrong, 2011), as shown in Table 2. Associations between visual impairments and gait in older adults may be stronger in PD especially as visual deficits increase with disease progression.

Vision and gait

Paradigms that explore the association between visual function and gait characteristics or manipulate vision in real-time while the participant is walking (e.g. navigating narrow doorway, lines on the floor, light and dark rooms) provide some understanding of the contribution of vision to gait in PD, as depicted in Figure 1(B). Impaired visual functions such as VA have been associated in PD and older adults with reduced step length (Spaulding et al., 1994; Hallemans et al., 2010) and gait velocity (Shin et al., 2015), although this finding is not consistent (Klein et al., 2003).
In PD, VA is the most commonly and often only assessed visual function. Changes in vision may not be adequately represented by VA alone (Geldmacher, 2003). CS is considered more applicable to real-world vision during gait, where the contrast of light and shade is critical. Indeed, impaired CS has been associated with reduced step width (Wood et al., 2009), step length (Wood et al., 2009; Swigler et al., 2012), gait velocity (Moes and Lombardi, 2009; Wood et al., 2009), physical activity levels (Black et al., 2011), and fear of falling (Wang et al., 2012). Other functions related to real-world vision such as dynamic VA have also been associated with falls (Honaker and Shepard, 2011). This indicates a need for comprehensive visual function assessment and more stringent methodological consideration. More complex assessments involving depth perception have been associated with increased obstacle contacts during gait (Menant et al., 2010), likely due to impairment of obstacle height perception (Yamaji et al., 2011). Motion perception (described in Table 2) has been associated with reduced functional task (e.g. driving) performance (Owsley, 2011), however despite obvious ties to gait it has largely been overlooked (Armstrong and Kergoat, 2015).

Optic flow is a similar concept to motion perception, and has predominantly been studied using online manipulation. Manipulation of optic flow while walking is carried out using video or projection based visual input (i.e. projected dots on a screen) shown at varying velocities to provide a sense of depth. In PD, significant gait impairments are found in velocity and step length (Lebold and Almeida, 2010) as well as increased veering (Davidsdottir et al., 2008), with dysfunction of the right parietal cortex implicated (Davidsdottir et al., 2008; Putcha et al., 2014). Optic flow protocols however require intact depth perception (Simpson, 1993) and a limitation of these studies is that they do not control for visual deficits, as noted in Table 2. As a consequence it is unclear if gait impairment is a result of impaired depth perception (Lord et al., 2002; Menant et al., 2010) or indeed optic flow as suggested. Lack of an appropriate control group (older adults) in optic flow studies in PD (Lebold and Almeida, 2010; Almeida and Bhatt, 2012) and use of attentional tasks (such as lines on the floor to step on) which alter optic flow without consideration of cognitive processes further confound interpretation of findings.

Other studies with simple visual manipulations such as doorways (Cowie et al., 2010; Cowie et al., 2012) have shown reduction in gait velocity and step length, and
increased step time in PD (Lebold and Almeida, 2010; Pieruccini-Faria et al., 2014). These studies suggest that people with PD become reliant on vision for gait (Azulay et al., 1999; Azulay et al., 2002; Khattab et al., 2012). However many previous studies have involved visual occlusion (e.g. walking in a dark room) (Azulay et al., 1999; Adamovich et al., 2001; Almeida et al., 2005), which merely provides a comparison of the contribution of proprioception compared to vision during gait (Stuart et al., 2014). When vision is occluded, visual processing still occurs with visuo-spatial information obtained from working memory (Jackson et al., 1995), which adds unnatural cognitive load during gait. Mimicking real-world environments with more subtle visual manipulations (such as adding a doorway) may provide insight into real-world impairments (Jackson et al., 1995).
### Table 2 – Brief overview of Visual Deficits in Parkinson’s disease and Older Adults

<table>
<thead>
<tr>
<th>Visual Function</th>
<th>Definition</th>
<th>Older adults</th>
<th>Parkinson’s disease</th>
<th>Key Issues</th>
<th>Methodological Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity (VA)</td>
<td>The ability to distinguish small details and shapes of objects (Kaiser, 2009).</td>
<td>Declines with age</td>
<td>Associated with subjective reports of blurred vision (Jones et al., 1992; Archibald et al., 2011; Armstrong, 2011)</td>
<td>Linked to dopamine depletion in the retina (Archibald et al., 2009)</td>
<td>Often non-significant impairment in PD compared to controls reported due to small sample sizes e.g. Galna et al. (2012).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Susceptible to decline from changes in ocular media (Sjostrand et al., 2011), and changes in neural processing (Hennelly et al., 1998)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast sensitivity (CS)</td>
<td>The ability to differentiate between objects and their background (Evans and Ginsburg, 1985).</td>
<td>Declines with age</td>
<td>Seen via standard visual chart assessment (Galna et al., 2012)</td>
<td>Specific losses for spatial frequencies (Bodis-Wollner et al., 1987; Price et al., 1992; Swigler et al., 2012)</td>
<td>Often non-significant impairment in PD compared to controls reported due to small sample sizes e.g. Galna et al. (2012).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Susceptible to decline from changes in ocular media (Ross et al., 1984), and changes in neural processing (Sloane et al., 1988)</td>
<td></td>
<td>Significant deficit in orientation discrimination for horizontal but not for vertical gratings (Mestre et al., 1990)</td>
<td></td>
</tr>
<tr>
<td>Dynamic visual acuity</td>
<td>The ability to perceive an object when there is motion between the observer and the target (Ishigaki and Miyao, 1994).</td>
<td>Declines with age</td>
<td>Under all luminance, velocity, and duration conditions (Long and Crambert, 1990)</td>
<td>Under all luminance, velocity, and duration conditions (Uc et al., 2005; Taweekarn et al., 2009)</td>
<td>Not often assessed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Under all luminance, velocity, and duration conditions (Long and Crambert, 1990)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth perception</td>
<td>The ability to perceive the world in three dimensions (3D) and the distance of an object (Omoto et al., 2010).</td>
<td>Declines with age</td>
<td>Common in drug naïve patients (Kim et al., 2011)</td>
<td>Linked to reduction in gray matter volume in the right extra-striate visual cortex (Koh et al., 2013)</td>
<td>Some studies limited by not assessing for nor excluding patients with vision affecting eye conditions e.g. Goodale and Haffenden (1998).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Common in the absence of ocular morbidity (Wright and Wormald, 1992)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motion perception</td>
<td>The process of inferring the speed and direction of elements in a scene (Ehrenstein, 2003).</td>
<td>Declines with age</td>
<td>Motion perception thresholds significantly elevated (Trick et al., 1994)</td>
<td>Linked to VA and CS impairment (Uc et al., 2005)</td>
<td>Not often assessed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Motion perception thresholds shown to be approximately two times higher in those 70-80 years old than individuals under thirty (Trick and Silverman, 1991)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic flow</td>
<td>Refers to the motion of the environment projected on the retina during movement in the world (Kelly et al., 2005).</td>
<td>Declines with age</td>
<td>Linked to gait impairments such as veering and navigation issues (Davidsdottir et al., 2008; Lin et al., 2014) Relates to impaired neural processing in visuo-vestibular (Putcha et al., 2014) and feed-forward visuo-motor regions (van der Hoom et al., 2014)</td>
<td></td>
<td>Many studies use artificial assessment devices which require depth perception, but do not control for or exclude based on depth perception deficits.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decline in ability to localise and detect optic flow patterns (Berard et al., 2009) Affects navigation and steering control (Berard et al., 2011)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Unless otherwise stated reported older adult impairments relate to comparison between older adults (>50 years old) and either younger adults or pathological groups, and reported Parkinson’s disease impairments relate to comparison to a control group)
C. The interaction between visual and cognitive function: Visuo-cognition

To date the interaction between visual and cognitive functions (Tables 1 and 2) during gait has not been considered in PD or older adults, but are instead distinguished from each other (Figure 1(C)). This distinction is somewhat contrived, given that evidence from static studies indicate an association between each function (Harris, 1998; Lin et al., 2004) and gait in older adults and PD.

A recent review by Archibald et al. (2009) supported the notion that cognitive and visual functions interact in PD. Indeed, foveal retinal dopaminergic depletion (Bodis-Wollner, 2009) and structural changes (Bodis-Wollner, 2013) such as retinal thinning (Adam et al., 2013; Bodis-Wollner et al., 2013) can distort signals from visual functions which in turn influence subsequent cognitive processes. Abnormal visual processing within BG loops is also suggested to cause people with PD to become reliant on attentional compensation (Redgrave et al., 2010). Imaging data demonstrates that attention can compensate for visual function deficits in healthy adults (Meppelink et al., 2009), a mechanism which may be intact in early PD. Attention has been shown to influence stimulus appearance (Carrasco et al., 2004) which can improve spatial resolution (Yeshurun and Carrasco, 1998; Carrasco et al., 2002), and enhance contrast (Carrasco et al., 2000; Pestilli and Carrasco, 2005; Carrasco, 2006) and salience via V4 neurons by up to 51% (Reynolds et al., 2000). Attention is also related to increased visual processing speed in neurons as early as V1 (Carrasco and McElree, 2001; Pestilli and Carrasco, 2005). However, despite attentional compensation and the ability for levodopa to sustain dopamine within the retina (Archibald et al., 2009) visual deficits such as slow visual processing persist in PD (Woollacott and Shumway-Cook, 2002). Importantly, compensation via attention is constrained because it is also impaired due to pathology, as noted above. Of further interest is the attenuation of visual control during gait when attentional demands increase, for example when walking under dual task conditions.

Cognitive and visual functions share the same neural resources and BG-cortical loops, and these overlap in striatal regions that have greater dopaminergic activity (e.g. ventral striatum) (Helmich et al., 2010), which further implicates a role for PD pathology in visuo-cognitive interactions during gait. However, these interactions in PD are complex and the processes that underpin them remain unclear (Figure 1(C)). Cognitive functions, particularly attention activate and inhibit many structures during
visual processing (Buhmann et al., 2015), giving rise to an internal priority (saliency) map (Baluch and Itti, 2011). Executive processes at the PFC signal an initial ‘estimate’ at the main visual priority (based on task goals) and project back via attentional circuits to the temporal cortex where selection is integrated into further automatic visual processing (Bar et al., 2006). Therefore early cognitive biasing of visual input selection occurs before the automatic (bottom-up) visual processing cascade (Baluch and Itti, 2011), and would indicate that even though the two systems (vision and cognition) work in unison, cognitive functions may underpin basic visual functions (Borji et al., 2011), especially during goal-orientated tasks such as gait.

Saccades during static tasks

Investigation of saccades during static tasks is one methodology that has allowed study of visuo-cognition in older adults and PD (van Stockum et al., 2012). Saccades provide an online behavioural measure of visuo-cognition (Land, 2006) due to their links to both visual (Bridgeman et al., 1981; Hernandez et al., 2008) and cognitive functions, particularly attention (van Stockum et al., 2011) (Figure 1). Saccades are integral to accurate task completion, as they align areas of interest in the environment with our fovea to produce high quality visual information (Bodis-Wollner, 2013; Bodis-Wollner et al., 2013) for further cognitive processing.

Visuo-cognitive deficits in older adults are evidenced by ineffective visual search strategies (Becic et al., 2008) and impaired saccades (Ridderinkhof and Wijnen, 2011) during static testing. Similarly people with PD demonstrate saccadic impairment when compared to older adults (Chan et al., 2005; Mosimann et al., 2005), with impaired voluntary (cognitively activated) and to a lesser extent reflexive (visual stimuli activated) saccades (Terao et al., 2013). Voluntary saccades have been shown to be impaired more in advanced PD than early or moderate PD (Blekher et al., 2000). Similarly Briand et al. (2001) and Terao et al. (2013) demonstrated that reflexive saccades are relatively preserved in early PD but worse in advanced PD. Other specific PD saccadic impairments have been highlighted in several recent reviews (Anderson and MacAskill, 2013; Srivastava et al., 2014; Antoniades and Kennard, 2015), such as; hypometric saccades, initiation deficits including increased errors during anti-saccade tasks, reduced gain, increased
latency of voluntary saccades, reduced latency of reflexive saccades and abnormal facilitation during inhibition of return tasks.

Static studies have provided insight into underlying mechanisms involved in saccadic impairment in PD. Voluntary saccades are controlled by interaction between the frontal cortex, BG and brain stem (Javaid et al., 2012; Matsumoto et al., 2012). Recent investigations have shown that frontal pathology rather than motor severity is linked to saccadic deficits in PD (Perneczky et al., 2011; Macaskill et al., 2012; Tommasi et al., 2015). However, dysfunction of the BG in PD also causes deficits in voluntary (top-down) saccades due to impairment of cortico-BG loops (Tommasi et al., 2015). The BG inhibit and disinhibit information based on attentional signals from the PFC. Excessive inhibition on the superior colliculus (SC) by the BG with PD can impair voluntary and reflexive (bottom-up) saccades, as seen by increased errors in pro and anti-saccade tasks (Armstrong, 2011). Reflexive saccades are primarily controlled by the parietal cortex (posterior-parietal cortex and posterior eye-field) and the brain stem cholinergic system rather than the dopaminergic reward system (Terao et al., 2013), and as such they are relatively spared in early PD. However the ability to inhibit reflexive saccades degrades with PD progression. In early disease, BG impairment can be circumvented with inhibition elicited via direct top-down influence from the PFC to the SC (Pierrot-Deseilligny et al., 2004). Progressive dopamine depletion in the striatum with PD reduces the PFC inhibitory effect (Tommasi et al., 2015). Therefore reduced PFC activity and disruption of the BG-thalmo-cortical loops results in an inability to suppress reflexive saccades (Deijen et al., 2006). Combined voluntary saccade impairment and increased distractibility in PD during static tasks has implications for gait, as such visuo-cognitive impairment likely impacts gait control.

D. The role of visuo-cognitive processes in gait

As noted above, investigation of the role of vision and cognition as separate entities with respect to gait has led to some understanding of the mechanisms involved (see Figure 1 (A&B)). However because vision and cognition interact (Figure 1(C)) this is likely to have important implications for gait in PD (Figure 1(D)). Knowledge of visuo-cognitive processes during gait is therefore important and critical to fully understand mechanisms underlying gait impairment.
Saccades during gait and other real-world tasks

Visuo-cognitive processes during gait in PD have largely been investigated by monitoring saccades during gait (Figure 1). Only one previous study (Galna et al., 2012) explored the association between vision, cognition and saccades, finding that saccade frequency during gait had greater association with attention than visual functions (VA and CS). To date no one has examined the relationship between saccadic and gait characteristics in PD (Figure 1(D)), but online studies have revealed important findings.

A recent structured review (Stuart et al., 2014) summarised studies that report deficits in saccades and fixations (pauses between saccades) in PD during real-world tasks (i.e. gait, reaching, obstacle crossing etc.), which indicated the task-dependent nature of saccadic impairments. For example; during gait a reduction in saccadic frequency was found in PD compared to older adults, which although did not reach significance (Galna et al., 2012), suggests impairment of voluntary saccadic initiation caused by dopaminergic depletion (van Stockum et al., 2011). In contrast, saccade frequency was increased in PD during turning in place (Anastasopoulos et al., 2011; Lohnes and Earhart, 2011), which may reflect impairment of smooth pursuit in PD and use of ‘catch up’ saccades to compensate (Helmchen et al., 2012). Several other studies have also showed reduction in saccade and fixation activity during real-world tasks in PD (Uc et al., 2006; Heremans et al., 2012), including increased fixation durations (Sacrey et al., 2009; Sacrey et al., 2011) and reduced saccade latencies (Anastasopoulos et al., 2011; Lohnes and Earhart, 2011). Similar differences in saccadic activity during gait in older adults are suggested to reflect compensatory adaptations (Uiga et al., 2015), and the same could be true for those with PD. For example; a change in saccadic activity may help maintain online control of real-world tasks despite visual and cognitive impairment.

Saccadic activity differences during gait could also be an attempt to compensate for underlying visual, cognitive and motor deficits associated with PD. For example; reduced saccade latencies and longer fixation durations during gait in PD (Anastasopoulos et al., 2011; Lohnes and Earhart, 2011) may be needed due to increased visual processing time required for motor programming, which attention is unable to expedite due to resources being preferentially allocated to maintaining gait
(Lee et al., 2003). However such differences are possibly due to a number of underlying visuo-cognitive interactions yet to be fully investigated, such as; imbalance between dopaminergic and cholinergic systems, abnormal frontal processes involved in saccade facilitation influencing the SC, fluctuations of inhibitory mechanisms or facilitation from other regions such as the frontal and supplementary eye-fields (Terao et al., 2011; van Stockum et al., 2011; van Stockum et al., 2012; Terao et al., 2013; van Stockum et al., 2013). Further investigation is required to understand specific saccadic impairments, and how these relate to cognitive function, visual function, and gait in PD.

Limitations
Given the broad topic of inquiry and the exploratory nature of this review which drew on inter-related but independent areas of research, we choose a narrative rather than a structured review process. As such, our critique of the literature was confined. However, this review was able to identify and draw attention to a research area that is currently not considered within gait research.

Summary and Conclusions
This narrative review covered a substantial body of literature and used a theoretical model to explore the contribution of vision, cognition and visuo-cognition to gait in PD. The use of associative and online protocols revealed a complex interdependence of these functions with evidence suggesting that attention may play a pivotal role. Exacting research is required to illuminate the field of inquiry and enhance our understanding of this relationship. This consolidated knowledge will then be used to optimise the management of gait dysfunction in PD, and thereby enhance overall function and quality of life.

With this in mind we make the following recommendations for future research:

- Assess vision, attention and cognition separately for independence and interaction
- Static and dynamic test protocols yield different but complimentary information
- A combination of methodological approaches (associative and online) provide a comprehensive understanding of the relative contribution of vision, cognition and visuo-cognition to gait impairment in PD
Acknowledgements
This research is supported by the National Institute for Health Research (NIHR) Newcastle Biomedical Research Unit (BRU) and centre (BRC) based at Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University. The research was also supported by NIHR Newcastle CRF Infrastructure funding. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflicts of Interest
No conflicts of interest are declared.

References


