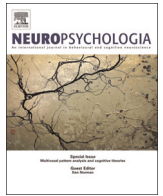




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Virtually-induced threat in Parkinson's: Dopaminergic interactions between anxiety and sensory–perceptual processing while walking

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ABSTRACT

Research evidence has suggested that anxiety influences gait in PD, with an identified dopa-sensitive gait response in highly anxious PD. It has been well-established that accurate perception of the environment and sensory feedback is essential for gait. Arguably since sensory and perceptual deficits have been noted in PD, anxiety has the potential to exacerbate movement impairments, since one might expect that reducing resources needed to overcome or compensate for sensory–perceptual deficits may lead to even more severe gait impairments. It is possible that anxiety in threatening situations might consume more processing resources, limiting the ability to process information about the environment or one's own movement (sensory feedback) especially in highly anxious PD. Therefore, the current study aimed to (i) evaluate whether processing of threat-related aspects of the environment was influenced by anxiety, (ii) evaluate whether anxiety influences the ability to utilize sensory feedback in PD while walking in threatening situations, and (iii) further understand the role of dopaminergic medication on these processes in threatening situations in PD. Forty-eight participants (24 HC; 12 Low Anxious [LA-PD], 12 Highly Anxious [HA-PD]) completed 20 walking trials in virtual reality across a plank that was (i) located on the ground (**GROUND**) (ii) located above a deep pit (**ELEVATED**); while provided with or without visual feedback about their lower limbs (+VF; –VF). After walking across the plank, participants were asked to judge the width of the plank they had just walked across. The plank varied in size from 60–100 cm. Both ON and OFF dopaminergic medication states were evaluated in PD. Gait parameters, judgment error and self-reported anxiety levels were measured. Results showed that HA-PD reported greater levels of anxiety overall ($p < 0.001$) compared to HC and LA-PD, and all participants reported greater anxiety during the ELEVATED condition compared to GROUND ($p = 0.01$). PD had similar judgment error as HC. Additionally, medication state did not significantly influence judgment error in PD. More importantly, HA-PD were the only group that did not adjust their step width when feedback was provided during the GROUND condition. However, medication facilitated a reduction in ST-CV when visual feedback was available only in the HA-PD group. Therefore, the current study provides evidence that anxiety may interfere with information processing, especially utilizing sensory feedback while walking. Dopaminergic medication appears to improve utilization of sensory feedback in stressful situations by reducing anxiety and/or improving resource allocation especially in those with PD who are highly anxious.

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1. Introduction

Anxiety in Parkinson's disease (PD) is drastically understudied considering the ominous influence that anxiety has demonstrated over movement symptoms (e.g. gait behavior) and quality of life in those with PD (Ehgoetz Martens et al., 2014b; Hanna and Cronin-Golomb, 2012; Nuti et al., 2004). Although the pathophysiology of

anxiety in PD remains unclear, neuroimaging research suggests that anxiety in PD is likely related to dopamine depletion within the striatum of the basal ganglia (nucleus accumbens-NAcc), and also reduced dopaminergic innervation to the amygdala (Benke et al., 1998; Tessitore et al., 2002). It has been hypothesized that interconnections between the limbic and motor circuits within the basal ganglia (NAcc) provide means for anxiety to influence motor outputs, especially in stressful situations, since integrated processing across different basal ganglia circuits has been suggested to be modulated by striatal dopamine (Balaban and Thayer, 2001; Bracs et al., 1984; McCullough et al., 1993; Valenti and Grace,

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2010). Lending support to this notion, anxiety has been found to be more prevalent in the OFF dopaminergic state (Nissenbaum et al., 1987; Racette et al., 2002; Siemers et al., 1993) and dopaminergic treatment has been shown to improve anxiety and emotional processing impairments in PD (Funkiewiez et al., 2006; Maricle et al., 1995a, 1995b; Stacy et al., 2010; Tessitore et al., 2002; Witjas et al., 2002). Interestingly, recent research has identified that anxiety profiles (high and low trait levels in PD) show different responses to medication. That is, dopaminergic medication selectively improved gait behavior (surprisingly even step-to-step variability which is not usually dopa-responsive) when walking in anxiety-provoking environments, but only in those with PD who are highly anxious (Ehgoetz Martens et al., 2015). It was hypothesized that these gait improvements result from dopaminergic medication, improving the basal ganglia's capacity to process incoming information (emotional, sensory, etc.), and/or possibly reducing the "load" of anxiety.

Notably, gait changes that occur when walking in a threatening environment (in healthy older adults (HC) and PD) resemble the typical response when distracted by a dual task (i.e. slower and more variable gait) (Hausdorff et al., 2003; Rochester et al., 2014; Yogev et al., 2005). Dual-tasking has been shown to interfere with PD participants' ability to adopt a larger step width to increase stability in order to reduce their risk of falling (Rochester et al., 2014). In fact, gait impairments are exacerbated in those with PD who are highly anxious, resulting in even greater increases in their step time variability and notable reductions in step width (instead of increases like HC) when walking in threatening situations (Ehgoetz Martens et al., 2015). Thus, anxiety in PD may contribute to an overload in a similar way that a dual-task does, which might explain *how* an anxiety-provoking environment exacerbates gait impairments in PD.

Evidence from non-Parkinsonian clinical anxiety literature has shown that anxiety does influence information processing, primarily perception (Eysenck et al., 1987), since highly anxious individuals allocate greater amounts of attentional resources to threatening stimuli and are often more sensitive to threatening content. Neuroimaging and ERP studies have both shown that levels of anxiety (most often trait anxiety) can modulate cortical and subcortical functions while patients perform attentional tasks including emotional items (Bishop et al., 2004; Bishop, 2007; Carretie et al., 2004; Etkin et al., 2004; Small et al., 2003). This abnormal distribution of attention has been investigated in detail, but has found inconsistent results. Some research suggests that anxious people orient their attention to threat during early stages of processing, but then subsequently attend away from threat (avoid) during stages of elaborated processing as a strategy to reduce affective distress (Koster et al., 2005; Mercado et al., 2009). However, this behavior has been argued to hinder detailed perception of their environment due to inadequate processing (Mogg et al., 1997). In contrast, other research has demonstrated that anxious individuals dedicate resources to threatening stimuli, leaving them unable to disengage attention, instead of avoiding the threat (Fox et al., 2007, 2008). This type of behavior has been shown to facilitate sensory processing (mainly in the visual domain) since it enhances the amount of attentional resources devoted to it.

In general, accurate processing of both the environment and self-motion are essential in order to properly navigate through an environment, especially a threatening one (Ehgoetz Martens et al., 2014a). Compromising either of these processes could lead to impaired gait behavior that is seen when walking through anxiety-provoking environments. Arguably since sensory and perceptual deficits have been identified in PD (Almeida and Lebold, 2010; Ehgoetz Martens et al., 2014a, 2013a; Johnson et al., 2004; Martens and Almeida, 2012; Patel et al., 2014), it is likely that resources are

already dedicated to compensating for these impairments. Thus, the impact anxiety has on overloading information processing capacity may be greater in PD, resulting in even more severe gait impairments.

The current study aimed to investigate *how* anxiety influences walking in PD. By using virtual reality (VR), we contrasted walking along a plank in threatening and non-threatening environments while plank size and self-motion feedback was manipulated. There were three main objectives. The first one was to evaluate whether processing of threat-related aspects of the environment (plank size) was influenced by anxiety. The second objective was to evaluate whether processing of online self-motion feedback was influenced by anxiety, and the third was to further understand the role of dopaminergic medication on information processing in threatening situations in PD. It was hypothesized that if anxiety interferes with information processing (e.g. plank size or self-motion feedback) while walking, then PD participants may demonstrate inaccurate plank size judgments and visual feedback about their lower limbs may not influence gait while walking in the threatening environment. However, while walking in a non-threatening environment we might expect those with PD (especially those who are highly anxious) to demonstrate more accurate plank size judgments and improvements to spatiotemporal aspects of gait when visual feedback about their lower limbs is available. Finally, if dopaminergic treatment reduces anxiety and facilitates more information processing, then PD participants (especially those who are highly anxious) may demonstrate improvements in judgment accuracy and utilization of sensory feedback to adapt gait when tested in their ON dopaminergic state, specifically when walking in a threatening environment.

2. Material and methods

2.1. Participants

Fifty-nine participants (25 HC, 34 PD) were recruited for participation in the current study, however only 24 healthy age-matched control participants and 24 PD participants were able to complete the full study. The Unified Parkinson's Disease Rating Scale motor section (UPDRS-III) (Goetz et al., 2007) was administered by a certified clinician and used to assess disease severity in those with PD. Additionally, all participants completed the Modified Mini Mental State Exam (Teng and Chui, 1987), State and Trait Anxiety Inventory (Spielberger, 1987) assessing baseline levels of anxiety, Geriatric Depression Scale (Yesavage et al., 1983), and the SCOPA-AUT questionnaire (Visser et al., 2004). Participants also rated their fear of heights on a 1–10 scale, and reported the number of falls they had experienced in the past year. Finally, a simulator sickness questionnaire was completed once before the experiment and then again after the experimental walking trials to quantify any adverse effects as a result of the virtual reality (VR) protocol. Table 1 shows the demographic characteristics and clinical details of participants. Previous research has demonstrated that highly anxious PD are especially impacted when walking in threatening situations, and dopaminergic treatment selectively improves walking in only in those PD who are highly anxious. Thus, the current study split the PD group into highly anxious (HA-PD) and low anxiety (LA-PD) subgroups. These two groups were created by performing a median split based on PD participants' off state Trait anxiety score (similar to many previous studies (Bishop, 2009; Broadbent and Broadbent, 1988; Eysenck et al., 1987; MacLeod and Mathews, 1988; Mathews, 1990; Mogg and Bradley, 1998). It is important to note that the median within our sample ($M=35.5$) was similar to previous studies who performed this method ($M=35$) (Broadbent and Broadbent, 1988; Ehgoetz

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