Brain and Cognition 125 (2018) 14–22

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

The effect of diabetes on prefrontal cortex activation patterns during active walking in older adults

Roee Holtzer[a,b,*], Claudene J. George[a], Meltem Izzetoglu[c], Cuiling Wang[a]

[a] Albert Einstein College of Medicine Bronx, New York, USA
[b] Yeshiva University Bronx, New York, USA
[c] Villanova University, Electrical and Computer Engineering, Villanova, PA, USA

ARTICLE INFO

Keywords:
Diabetes
Locomotion
Prefrontal cortex
Aging
fNIRS
Executive functions

ABSTRACT

Background: Gait alterations were documented in diabetic patients. However, the effect of diabetes on cortical control of gait has not been reported. We evaluated the effect of diabetes on prefrontal cortex (PFC) Oxygenated Hemoglobin (HbO_2) levels during active walking in older adults.

Methods: Of the total sample (n = 315; mean age = 76.84 ± 6.71ys; % female = 56.5) 43 participants (13.7%) had diabetes. The experimental paradigm consisted of two single tasks: Normal-Walk (NW); and Cognitive Interference (Alpha); and one dual-task condition consisting of the two single tasks, Walk-While-Talk (WWT). Functional Near-Infrared-Spectroscopy (fNIRS) was used to quantify PFC HbO_2 levels.

Results: Older adults without diabetes showed higher PFC HbO_2 levels in WWT compared to both NW and Alpha. HbO_2 levels during NW were not different between the two groups. Consistent with *Neural Inefficiency,* older adults with diabetes exhibited higher HbO_2 levels during Alpha while performing significantly worse than those without diabetes. Moreover, the presence of diabetes was associated with attenuated HbO_2 levels during WWT. This pattern is consistent with *Capacity Limitations* suggesting a failure to recruit brain resources vis-à-vis the more cognitively challenging WWT condition.

Conclusions: A distinct functional neural signature of diabetes was established during active and attention demanding walking among older adults without overt neurological disease.

1. Introduction

Diabetes is common in the general population, notably among older adults (CDC, 2014). A recent cohort study reported a 9.3% prevalence of confirmed diabetes among individuals age 72 years and older (Palta et al., 2017). The presence of diabetes is associated with numerous adverse health outcomes (Nolan, Damm, & Prentki, 2011). While the literature concerning the effect of diabetes on locomotion is relatively limited, a few studies observed the presence of gait alterations in diabetic patients (Allet et al., 2008). A population study of middle aged and older adults revealed that individuals with diabetes performed worse on quantitative gait parameters compared to those without diabetes (Maksimovic et al., 2016). A large cohort study of older Catholic clergymen and women who were free of dementia and Parkinson disease at baseline, found that the presence of diabetes was associated with decline in gait and worsening rigidity (Arvanitakis et al., 2004). A few investigations began to shed light on factors that might explain the negative effect of diabetes on mobility outcomes (Rucker, McDowd, & Kluding, 2012). For instance, diabetes was associated with reduced gait speed, shorter step length, wider and longer stance, in a sample of ambulatory older adults who participated in the Cardiovascular Health study (Brach, Talkowski, Strotmeyer, & Newman, 2008). Notably, this association was explained, in part, by performance on measures of executive functions as well as measures of global cognition, depressive symptoms and demographic variables. Gait alterations were observed in patients with diabetes compared to controls irrespective of the presence of polyneuropathy (Sawacha et al., 2009). However, in the same study, reduced ranges of motion were recorded among patients with diabetes who also had polyneuropathy. Finally, a recent review pointed to associations between diabetic neuropathy and mobility outcomes including gait and falls (Alam et al., 2017). The ability to ambulate effectively is critical for functional independence and wellbeing. Among older adults, slower walking speed predicts increased risk of incident disability, morbidity and mortality (Studenski et al., 2011). Hence, identifying factors that influence gait decline and impairment among older adults with diabetes has important clinical and public health implications.

There is unequivocal evidence that locomotion and cognition,

* Corresponding author at: 1225 Morris Park Avenue, Van Etten Building, Bronx, NY 10461, USA.
E-mail address: roee.holtzer@einstein.yu.edu (R. Holtzer).

https://doi.org/10.1016/j.bandc.2018.03.002
Received 5 December 2017; Received in revised form 5 February 2018; Accepted 6 March 2018

executive functions in particular, and their underlying brain substrates are interrelated in older adults (Holtzer, Verghese, Xue, & Lipton, 2006; Holtzer, Wang, & Verghese, 2014; Rosso et al., 2013). Dual-task methodology provides a framework for evaluating the effect of divided attention, a facet of executive functions (Miyake et al., 2000), on walking. Specifically, the decline in gait speed in dual compared to single walking task conditions is causally linked to attention resources (Holtzer, Wang et al., 2014). Executive functions (Koechlin, Ody, & Kouneiher, 2003) and dual-tasking (Filmer, Mattingley, & Dux, 2013) are subserved by the prefrontal cortex (PFC). However, relatively little is known about the functional brain correlates of locomotion because active walking cannot be assessed in MRI and PET scanners. A review of neuroimaging studies of locomotion in aging emphasized the paucity of research in this area but identified the PFC and related circuits as key brain regions involved in higher order control of locomotion, especially under attention-demanding conditions (Holtzer, Epstein, Mahoney, Izzetoglu, & Blumen, 2014). Further, a recent review suggested that fNIRS provides a promising approach to identifying neural activity during locomotion in normal and disease populations (Gramigna et al., 2017). Indeed, studies using fNIRS provided converging evidence that PFC oxygenation levels, assessed during active walking, increased in dual compared to single task conditions in older adults (Holtzer et al., 2015; Holtzer, Schoen, et al., 2017; Holtzer, Verghese, et al., 2016; Holtzer, Yuan, et al., 2017; Mirelman et al., 2017). This effect was also observed in patients with Multiple Sclerosis (Hernandez et al., 2016) and Parkinson's disease (Maidan, Bernad-Elazari, Giladi, Hausdorff, & Mirelman, 2017; Maidan et al., 2016). Dual-task walking is designed to better approximate real world conditions and may thus have greater ecological validity. For example, poor dual-task walking performance predicted increased risk of incident falls (Ayers, Tow, Holtzer, & Verghese, 2014) as well as frailty, disability and mortality in older adults (Verghese, Holtzer, Lipton, & Wang, 2012). Moreover, differences in PFC activation levels, as assessed with fNIRS during dual-task walking, predicted incident falls among healthy older adults (Verghese, et al., 2016).

In contrast to the limited literature concerning the relationship between diabetes and locomotion, evidence for the effect of the former on cognition and brain structure and function is robust. A recent meta-analytic study revealed poor performance in executive functions and memory in patients with diabetes compared to controls (Sadanand, Balachandar, & Bharath, 2016). Cross-sectional studies (Brundel, van den Heuvel, de Bresser, Kappelle, & Biessels, 2010; den Heijer et al., 2003; Manschot et al., 2007; Moran et al., 2013) reported greater gray matter atrophy and white matter loss in temporal and frontal regions in patients with type 2 diabetes compared to controls. Longitudinal studies (de Bresser et al., 2010; Kooistra et al., 2013; van Elderen et al., 2010) found that the presence of type 2 diabetes was associated with accelerated brain atrophy and white matter loss. The association between brain function and structure and cognitive performance in individuals with diabetes, however, remains equivocal (Moheet, Mangia, & Seaquist, 2015). Critically, the effect of diabetes on higher order control of locomotion and its underlying brain substrates has not been reported, notably when gait is evaluated under cognitively demanding conditions.

1.1. Current study

The current study was designed to evaluate the effect of diabetes on cortical control of locomotion. We used fNIRS to measure PFC HbO_2 levels during active walking under Normal-Walk (NW), cognitive interference task (Alpha) and Walk-While-Talk (WWT) conditions in a cohort of community residing non-demented older adults. The focus on the PFC as a region of interest was based on previous literature, in particular studies that involved gait and fNIRS (for review see (Gramigna et al., 2017)). We hypothesized that, among older adults, the presence of diabetes would have a distinct effect on brain activation patterns during walking. Specifically, two models provided a conceptual framework for evaluating the effect of diabetes on brain function, operationalized as PFC HbO_2 levels, during two single tasks and one dual-task walking conditions. The *Capacity Limitations* hypothesis (Reuter-Lorenz et al., 2000) proposes that in the context of cognitively challenging tasks or when comparing tasks that increase in terms of difficulty or complexity the presence of brain pathology would be associated with attenuated brain activation patterns. *Neural Inefficiency*, (Rypma, Berger, & D'Esposito, 2002; Zarahn, Rakitin, Abela, Flynn, & Stern, 2007) on the other hand, exists when higher brain activations are associated with equivalent or worse task performance. This latter model suggests that due to compromised structure and/or function the brain does not efficiently allocate resources to support cognitive task demands. It is noteworthy that the two models are not mutually exclusive as differences in activation patterns across groups may vary as a function of task type and complexity. We also evaluated the effect of diabetes on stride velocity and cognition during single and dual-task conditions.

2. Methods and procedures

2.1. Participants

Participants were community residing older adults (age ≥ 65 yrs) enrolled in "Central Control of Mobility in Aging" (CCMA), a cohort study designed to determine cognitive and brain predictors of mobility as previously described (Holtzer, Mahoney, & Verghese, 2014). Briefly, structured telephone interviews were administered to obtain verbal assent and determine initial eligibility. Individuals deemed study eligible based on the telephone interview were invited to two annual study visits during which trained research assistants administered comprehensive neuropsychological, psychological, and mobility assessments. The fNIRS dual-task walking paradigm was administered during the first day of testing. The study physician conducted structured neurological examinations, which included review of medical history. Cognitive status was determined via established consensus diagnostic case conference procedures (Holtzer, Verghese, Wang, Hall, & Lipton, 2008). Exclusion criteria were: current or history of severe neurological or psychiatric disorders, inability to ambulate independently, significant loss of vision and/or hearing that threatened the validity of the testing procedures, and recent or anticipated medical procedures that may affect ambulation. A total of 315 participants who completed the two-day in-person baseline annual assessments between June of 2011 and January of 2014 were included in this study. The Review Board of Albert Einstein College of Medicine approved this study. Written informed consents were obtained in-person from all participants.

2.2. Diabetic status

Study physicians determined the presence of diabetes during a structured in-person interview assessing medical history and current medications usage. Confirmation of diabetes required a positive self-report by study participants as well as evidence based on current medications known to be prescribed to patients with diabetes only, specifically, oral hypoglycemic agents or insulin. Based on the medical history, age and medications, participants were diagnosed with type 2 diabetes, though glucose blood levels were not available to confirm the diagnosis and type of diabetes. Neuropathy, in general, or diabetic neuropathy did not serve as exclusion criteria but clinical gait subtyping, which included neuropathic gait served as a covariate (see covariates section for details).

2.3. Quantitative gait assessment

Zenometrics. A 4×14 foot Zeno electronic walkway using ProtoKinetics Movement Analysis Software (PKMAS) was utilized to