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Structural neural correlates of impaired mobility and subsequent decline in executive functions: a 12-month prospective study

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ABSTRACT

Impaired mobility, such as falls, may be an early biomarker of subsequent cognitive decline and is associated with subclinical alterations in both brain structure and function. In this 12-month prospective study, we examined whether there are volumetric differences in gray matter and subcortical regions, as well as cerebral white matter, between older fallers and non-fallers. In addition, we assessed whether these baseline volumetric differences are associated with changes in cognitive function over 12 months. A total of 66 community-dwelling older adults were recruited and categorized by their falls status. Magnetic resonance imaging occurred at baseline and participants' physical and cognitive performances were assessed at baseline and 12-months. At baseline, fallers showed significantly lower volumes in gray matter, subcortical regions, and cerebral white matter compared with non-fallers. Notably, fallers had significantly lower left lateral orbitofrontal white matter volume. Moreover, lower left lateral orbitofrontal white matter volume at baseline was associated with greater decline in set-shifting performance over 12 months. Our data suggest that falls may indicate subclinical alterations in regional brain volume that are associated with subsequent decline in executive functions.

1. Introduction

Worldwide, the number of individuals aged 60 years or over is expected to more than double, from 841 million people in 2013 to >2 billion in 2050 (United Nations, 2013). Consequently, geriatric syndromes such as cognitive impairment and impaired mobility will place increasing demand on the public health system. Both geriatric syndromes are associated with institutionalization, reduced quality of life, disability, and death (Scott et al., 2010). Current evidence suggests that cognitive impairment and impaired mobility are associated and often co-exist among older adults (Montero-Odasso et al., 2012). Notably, there is growing recognition that clinical gait abnormalities and falls are early biomarkers of cognitive impairment and dementia (Verghese et al., 2002). For example, with data from the Health, Aging and Body Composition Study, Inzitari and colleagues (Inzitari et al., 2007) showed that slower gait speed at baseline was predictive of subsequent cognitive decline over approximately one decade. Others have shown that gait speed begins to decline more precipitously approximately one decade before the diagnosis of mild cognitive impairment (Buracchio et al., 2010). A recent 12-month prospective study of 125 cognitively normal, community-dwelling older adults demonstrated that higher levels of Pittsburgh compound B retention – a biomarker for greater amyloid deposition – and Alzheimer's disease (AD) related cerebrospinal fluid biomarkers were associated with a faster time to first fall (Stark et al., 2013).

Consistent with these links between mobility and cognition, evidence from neuroimaging studies suggests that slower gait speed or a history of falls is associated with subclinical alterations in both brain structure and function (Rosano et al., 2008; Hsu et al., 2014; Rosso et al., 2014). With respect to structure, in a cross-sectional study of 220 community-dwelling older adults, Rosano and colleagues (Rosano et al., 2008) demonstrated that lower gray matter volume in the sensorimotor regions and frontoparietal regions were associated with impaired gait (i.e., shorter steps and longer double support times). In another cross-sectional study of 112 community-dwelling older adults, Ezzati and colleagues (Ezzati et al., 2015) reported that lower gray

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matter and hippocampal volumes were associated with slower gait speed. Hippocampal atrophy over 2.5 years was associated with concurrent gait speed decline among 225 older adults between age of 60 to 86 (Callisaya et al., 2013). These brain-mobility associations found in gray matter and subcortical structures are highly relevant within the context of cognitive aging as studies have consistently demonstrated the contribution of total gray matter and hippocampal volumes to cognitive performance in late life (Mungas et al., 2005; Jagust et al., 2006; Persson et al., 2006). Thus, impaired mobility may be an overt biomarker for covert gray and subcortical neural degeneration that predicts subsequent cognitive decline.

In terms of brain function, our own work demonstrated that compared with their non-faller counterparts, older adults with a history of multiple falls (i.e., ≥2 non-syncope falls in the previous 12 months) showed aberrant neural network functional connectivity – a measure of synchronous brain activity (Hsu et al., 2014). Notably, the aberrant network connectivity demonstrated by fallers was independently associated with greater decline in both executive functions and mobility over a 12-month period after accounting for relevant covariates (Hsu et al., 2014). Hence, a recent history of multiple falls among older adults without a diagnosis of dementia may indicate sub-clinical changes in brain function and increased risk for subsequent decline.

However, more evidence generated from longitudinal studies is needed to establish falls as a biomarker of covert neural degeneration as well as to evaluate the significance of these changes in relation to subsequent decline in cognitive function among otherwise healthy community-dwelling older adults. Moreover, the contribution of regional cerebral white matter volume to mobility has not been explored extensively to date. Yet, significant age-related reduction in cerebral white matter volume co-occurs with gray matter loss (Bartzokis et al., 2003; Allen et al., 2005), particularly in the frontal and parietal regions (Resnick et al., 2003). Reduced white matter volume is also associated with cognitive impairment and dementia (Salat et al., 2009).

Thus, we conducted a 12-month prospective study to determine whether there are differences in brain structure between otherwise healthy community-dwelling older adults with and without a recent history of multiple falls, and to evaluate the significance of these differences in relation to subsequent changes in cognitive function – with a focus on executive function. Given our emphasis on executive functions, our specific aims were to examine whether: 1) community-dwelling older adults with a recent history of multiple falls have lower regional frontal and parietal gray matter, frontal and parietal cerebral white matter, and subcortical volumes compared with their non-falling counterparts; and 2) whether baseline volumetric differences are independently associated with change in cognitive functions over 12 months. Importantly, this research may lead to the early identification of those at risk for cognitive decline, and thereby facilitate the timely implementation of effective prevention strategies.

2. Material and methods

2.1. Study design and participants

We conducted a 12-month prospective exploratory study with 66 older adults. Participants were recruited from metropolitan Vancouver via newspaper advertisements. Individuals were eligible if they: 1) were aged 70 to 80 years; 2) scored ≥24/30 on the Mini-Mental State Examination (MMSE) (Cockrell and Folstein, 1988); 3) were right hand dominant as measured by the Edinburgh Handedness Inventory (Oldfield, 1971); 4) were living independently in their own homes; 5) had visual acuity of at least 20/40, with or without corrective lenses; and 6) provided informed consent. We excluded those who: 1) had a neurodegenerative disease, stroke, dementia (of any type), or psychiatric condition; 2) had clinically significant peripheral neuropathy or severe musculoskeletal or joint disease; 3) were taking psychotropic medication; 4) had a history indicative of carotid sinus sensitivity; 5) were living in a nursing home, extended care facility, or assisted-care facility; or 6) were ineligible for MRI scanning.

Based on their falls history in the 12 months prior to study entry, participants were classified as a faller or non-faller (see 2.1.1 and 2.1.2). Ethics approval was obtained from the Vancouver Coastal Research Health Institute and University of British Columbia's Clinical Research Ethics Board. All participants provided written consent.

2.1.1. Specific inclusion criterion for fallers

An individual must have experienced ≥2 minimal displacement non-syncopal falls in the previous 12 months, with one of the falls occurring in the last 6 months (Delbaere et al., 2010a). This was determined from two sources: 1) participant recall and 2) participant's immediate family member or friend recall. Falls were defined as "unintentionally coming to rest on the ground, floor, or lower level" (Hauer et al., 2006).

2.1.2. Specific inclusion criterion for non-fallers

An individual must not have experienced >1 displacement falls (with or without syncope) in the previous 12 months. This was determined based on two sources: 1) participant recall and 2) participant's immediate family member or friend recall. We highlight that individuals with one fall (non-injurious) in the previous 12 months resemble the physiological profile of non-fallers (Nevitt et al., 1989; Lord et al., 1991). Specifically, a prospective study found that single fallers had similar physical and mental status compared with non-fallers, while multiple fallers showed significant musculoskeletal and neurological deficits (Nevitt et al., 1989).

2.2. Measurement

All measures, with the exception of neuroimaging, were assessed at baseline and 12 months. All assessors were trained and standardized protocols were used. Neuroimaging data were acquired at baseline only.

2.2.1. Global cognition and current physical activity level

Global cognition was assessed using the MMSE (Cockrell and Folstein, 1988) and the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). The MoCA is a 30-point test that covers multiple cognitive domains. The MoCA has been found to have good internal consistency and test-retest reliability and was able to correctly identify 90% of a large sample of individuals with mild cognitive impairment from two different clinics with a cut-off scores of <26/30 (Nasreddine et al., 2005). Current level of physical activity (i.e., last 7 days) was determined by the Physical Activities Scale for the Elderly (PASE) self-report questionnaire (Washburn et al., 1999).

2.2.2. Comorbidity and depression

Comorbidities were assessed with the Functional Comorbidity Index (FCI) (Groll et al., 2005), an 18-item questionnaire that calculates the total number of comorbidities associated with physical functioning (Groll et al., 2005). We used the 15-item Geriatric Depression Scale (GDS) (Yesavage et al., 1982; Yesavage, 1988) to indicate the presence of depression; a score ≥5 indicates depression (van Marwijk et al., 1995).

2.2.3. Physiological falls risk

Physiological falls risk was assessed using the short form of the Physiological Profile Assessment (PPA). The PPA is a valid (Lord et al., 1991; Lord et al., 1994) and reliable (Lord and Castell, 1994) measure of falls risk. Based on a participant's performance in five physiological domains – postural sway, reaction time, strength, proprioception, and vision – the PPA computes a falls risk score (standardized score) that has a 75% predictive accuracy for falls among older people (Lord et al., 1991; Lord et al., 1994). A PPA Z-score ≥ 0.60 indicates high physiological falls risk (Delbaere et al., 2010b).