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BRAIN RESEARCH

Research Report

MRI- and MRS-derived hippocampal correlates of quantitative locomotor function in older adults

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ABSTRACT

Gait measures have been shown to predict cognitive decline and dementia in older adults. Investigation of the neurobiology associated with locomotor function is needed to elucidate this relationship with cognitive abilities. This study aimed to examine magnetic resonance imaging (MRI; hippocampal volume)- and proton magnetic resonance spectroscopy (MRS; N-acetylaspartate to creatine (NAA/Cr) ratios)-derived hippocampal correlates of quantitative gait function (swing time (seconds), stride length (cm), and stride length variability (standard deviation)) in a subset of 48 nondemented older adults (24 males; mean age=81 years) drawn from the Einstein Aging Study, a community-based sample of individuals over the age of 70 residing in Bronx, New York. Linear regression analyses controlling for age were used to examine hippocampal volume and neurochemistry as predictors of gait function. We found that stride length was associated with hippocampal volume (β=0.36, p=0.03; overall model R^2=0.33, p=0.01), but not hippocampal neurochemistry (β=0.09, p=0.48). Stride length variability was more strongly associated with hippocampal NAA/Cr (β=−0.38, p=0.01; overall model R^2=0.14, p=0.04) than hippocampal volume (β=−0.33, p=0.08). Gait swing time was not significantly related to any neuroimaging measure. These relationships remained significant after accounting for memory and clinical gait impairments. These findings suggest that nondemented older adults exhibit increased stride length variability that is associated with lower levels of hippocampal neuronal metabolism, but not hippocampal volume. Conversely, decreased stride length is associated with smaller hippocampal volumes, but not hippocampal neurochemistry. Distinct neurobiological hippocampal substrates may support decreased stride length and increased stride length variability in older adults.

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Abbreviations: MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA/Cr, N-acetylaspartate to creatine ratio; EAS, Einstein Aging Study; FCSRT-IR, free and cued selective reminding test-immediate recall; BIMC, Blessed information-memory-concentration test; LTP, long-term potentiation

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1. Introduction

The number of adults over the age of 65 is projected to represent a rising proportion of the general population in the coming years (Wan et al., 2005). As the population ages, it is increasingly important to characterize the biological, cognitive, and motor manifestations of the aging process. The extant literature demonstrates that advancing age is associated with declining brain function in both motor and cognitive domains (Anstey and Low, 2004; Christensen, 2001; Fratiglioni et al., 1999) and that gait dysfunction (Camicioli et al., 1998; Verghese et al., 2002, 2007) and poor performance on cognitive tests (DeCarli et al., 2004; Grober et al., 2000) are associated with increased risk of cognitive decline and dementia. While the neuroimaging correlates of cognitive dysfunction have been extensively examined using measures of hippocampal volume (Jack et al., 1999; Killiany et al., 2000) and neuronal metabolism (Chao et al., 2005; Modrego et al., 2005; Zimmerman et al., 2008), brain based correlates of locomotor abilities require additional investigation.

The objective of the present study was to examine the cross-sectional relationship between MR-derived measures of hippocampal structure and function and quantitative indices of locomotion in nondemented older adults. Previously, (Verghese et al., 2007) we performed a factor analysis on eight different quantitative gait variables in a community-based sample. We found three gait factors (pace, rhythm, and variability) that were predictors of risk of cognitive decline and dementia in that sample. For the current study, we selected the quantitative gait measures that loaded most strongly on each of the three previously determined gait factors (stride length, swing time, and stride length variability, respectively) as our primary gait indices of interest. Stride length is the distance between the heel points of two successive footfalls of the same foot. Swing time, a marker of gait stability, is the amount of time when the foot is in the air from toe off to heel strike of the same foot. Stride length variability is the standard deviation of the variability in length between strides.

Structural magnetic resonance imaging (MRI) is an important neuroimaging tool that promotes the characterization of brain structures that may be involved in pathological processes and provides an important context in which to consider both neurochemical and neurofunctional findings. MRI was used in the current study to obtain measures of hippocampal volume. Magnetic resonance spectroscopy (MRS) is a neuroimaging technique that permits investigation of neuronal cellular chemical activity through examination of neurotransmitters and amino acids. MRS provides a measure of cerebral metabolic change which may reflect pathological insults to brain integrity. Although several different chemical compounds (e.g., choline, myo-inositol) have been examined in older individuals, decreased hippocampal N-acetylaspartate (NAA) and its ratio to creatine (Cr) has been a particularly robust age-associated finding (Angelie et al., 2001; Driscoll et al., 2003; Schuff et al., 1999). NAA is primarily located in neurons and is thought to be a marker of neuronal viability (Pettegrew et al., 2000), while Cr reflects biochemical energy reserves of glia and neurons and is presumed to be stable in the context of pathologic processes (Narayana, 2005). MRS was used in the current study to obtain measures of hippocampal NAA/Cr.

Previous studies examining neuroimaging correlates of gait dysfunction have focused on subcortical white matter lesions and ventriculomegaly (e.g., see Rosano et al., 2007b, 2005) and gray matter volumes (Rosano et al., 2007a). In addition to these brain substrates, several lines of evidence provide support for the role of the hippocampus in locomotion: 1) Animal models of hippocampal lesions reveal behavioral abnormalities that include impairments in learning and memory as well as abnormalities in gait, balance, and motor coordination (e.g., see Ferguson et al., 2000; Paylor et al., 2001); 2) Numerous animal models demonstrate a link between hippocampal neurophysiology and both voluntary and wayfinding locomotor function (e.g., see Bland, 2004; Oddie et al., 1996); 3) In our community-based sample, we previously reported that disruptions in gait function in nondemented older adults are an early predictor of the development of memory decline and dementia (Verghese et al., 2007). We have also shown that smaller hippocampal volume and lower hippocampal metabolism are related to memory difficulties in nondemented older adults (Zimmerman et al., 2008). Thus, our hypothesis that locomotor function in older adults is associated with neuroimaging measures of hippocampal volume and hippocampal NAA/Cr is supported by collective consideration of findings from animal studies as well as our own work with locomotion, neuroimaging markers, and memory function in older adults. Investigation of the underlying hippocampal neurobiology associated with gait dysfunction may enhance understanding of the preclinical onset of cognitive decline in elderly adults.

2. Results

2.1. *Sample characteristics*

Sample demographics, quantitative gait performance, and hippocampal measurements are presented in Table 1. Sex and ethnicity characteristics were consistent with those of both the larger Einstein Aging Study (EAS) cohort and the U.S. Census Bureau data for Bronx County. Global cognitive status and memory performance were similar between the MRI subsample and the larger EAS cohort. There were no education, sex, or ethnicity differences on the MR-derived or gait variables of interest, with the exception of men exhibiting a longer stride length than women ($t=2.20$, $p=0.03$). The effect of gender was considered in all subsequent analyses examining stride length. MRI-derived hippocampal volumetric and midsagittal area measurements were available for 39 and 36 individuals due to scan acquisition limitations. There were no differences in age, education, sex, global cognitive status, memory performance, or hippocampal NAA/Cr between those participants who had hippocampal volumetric data and those that did not.

2.2. *Clinical gait characteristics*

Data for self-reported history of neurological disorders associated with gait impairment were available for 47 individuals.