

the results of standardized  $z$ -scores in this study sample. NCSS statistical software ([www.ncss.com](http://www.ncss.com)) was used for the analyses.  $P < .05$  was taken as statistically significant.

In 2003, the average age  $\pm$  standard deviation was  $75 \pm 4$  in both groups ( $P = .30$ ). In 1974, men in the high-risk group had significantly higher body mass index, blood pressure, cholesterol, and triglycerides than the low-risk group. Except for the more-frequent history of diabetes mellitus in the high-risk group ( $P = .04$ ), there were no significant differences in the history of diseases after 1974 between the groups. The mean summary  $z$ -scores of the neuropsychological assessment in 2003 are shown in the Figure 1. The cross-sectional study of Vogels et al.<sup>1</sup> showed that neuropsychological status in general was best in healthy controls, worse in cardiac patients, and worst in patients with CHF. The longitudinal Helsinki Businessmen Study gives perspective to this result by showing that higher cardiovascular risk factor status in healthy middle-aged men predicted worse cognitive function 29 years later, in old age. This result in a socioeconomically homogenous cohort is in accordance with other studies showing long-term adverse effects of vascular risk factors on the development of dementia.<sup>3</sup> The prevention of cognitive decline should thus be started early.

*Kirsi Rantanen, MD  
Raija Ylikoski, PhD  
Olli Häppölä, MD, PhD  
Department of Neurology  
Helsinki University Central Hospital  
Helsinki, Finland*

*Timo E. Strandberg, MD, PhD  
Department of Public Health Science and General Practice  
University of Oulu and University Hospital  
Unit of General Practice  
Oulu, Finland*

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## DOES IMPAIRED CEREBELLAR FUNCTION CONTRIBUTE TO RISK OF FALLS IN SENIORS? A PILOT STUDY USING FUNCTIONAL MAGNETIC RESONANCE IMAGING

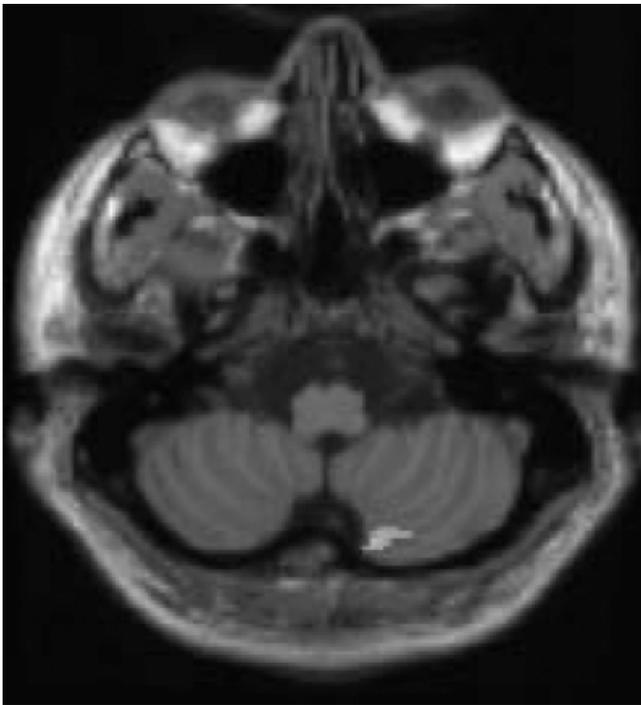
*To the Editor:* Falls are a well-recognized geriatric syndrome. One of the key factors contributing to falls is cognitive dysfunction. Recent evidence indicates that even mild cognitive decline is a risk factor for falls.<sup>1</sup> In seniors with Mini-Mental State Examination (MMSE) scores greater than 24 out of 30, baseline cognitive performance was found to be linearly and inversely associated with rate of falling over 8 years.<sup>1</sup>

What aspects of cognition contribute to falls? Within the multiple domains of cognitive function, impaired executive functioning—the ability to concentrate, to attend selectively, to plan and strategize—is associated with falls in seniors<sup>1,2</sup> and injurious falls.<sup>3</sup> Impaired executive functioning is prevalent even in healthy, community-dwelling seniors without cognitive impairment (MMSE score  $\geq 24$ ),<sup>4</sup> although the neural basis underlying impaired executive functioning and falls among this population remains unclear.

Identifying the relevant neural correlates of executive functioning in fallers is important from a mechanistic perspective (i.e., understanding pathophysiology) and because it could increase the capacity to refine falls risk screening. Therefore, functional magnetic resonance imaging (fMRI) was used to examine the neural basis for the association between impaired executive functioning and falls, a methodology allowing localized changes in hemodynamic brain activity to be tracked during cognitive task performance. Specifically, a 2-month prospective observational pilot study was conducted to ascertain whether there were differences in cortical activation during an executive task between community-dwelling senior women without cognitive impairment (MMSE score  $\geq 24$ ) who fell and those who did not fall.

The pilot study consisted of 83 community-dwelling senior women aged 65 to 75. During fMRI scanning, participants performed a modified Ericksen flanker task<sup>5</sup>—a task that engages selective attention and response inhibition. On each trial, participants viewed a visual display that contained five arrows and were asked to indicate the direction the central arrow was pointing (left vs right) while ignoring the two flanking arrows on each side. On half the trials, the flanking arrows pointed in the same direction as the central arrow cue (e.g., <<<<<; referred to as the congruent condition), and on the other half of the trials, the flanking arrows pointed in the opposite direction (e.g., >><>>; referred to as the incongruent condition). In this paradigm, the primary measure of executive cognitive function stems from comparing behavioral and neural responses of incongruent and congruent trials, because the former condition requires engaging selective attention and response inhibition to ignore the flanking distractors that engender a response incompatible with the required target response.

Falls were documented during the 2-month observational period using monthly calendars. Fourteen women fell and contributed 15 falls during the 2-month observation period. One fall caused a hip fracture; eight caused mod-



**Figure 1.** Activation of the posterior lobe of the right cerebellum. Montreal Neurological Institute anatomical template provided with spm2, shown at slice  $z = -50$ . This shows activation of the posterior lobe cerebellum during functional magnetic resonance imaging averaged across all participants ( $N = 83$ ).

erate injuries (sprains and bruises). Across all participants, regions showing increases in the hemodynamic response on incongruent relative to congruent trials included bilateral inferior and middle frontal gyri, anterior cingulate cortex, bilateral precuneus, and the right cerebellum, but in fallers, the posterior lobe of the right cerebellum had a significantly lower hemodynamic response than in nonfallers ( $P = .05$ ) (Figure 1).

The data thus implicate the right cerebellum as a potential region of interest in falls. Although the cerebellum has long been associated with key aspects of normal motor function, recent evidence indicates that the cerebellum contributes to non-motor functions as well,<sup>6</sup> including executive functions<sup>7</sup> and spatial navigation,<sup>8,9</sup> both of which are integral to safe movement through the physical environment. Indeed, the existence of a “cognitive affective syndrome” arising from cerebellar lesions has been proposed.<sup>10</sup> Neuropsychological evidence has shown that individuals with cerebellar lesions have pronounced systematic impairments in cognitive, executive, and affective functioning<sup>10</sup>—a model consistent with the current study’s finding that fallers show hypofunctioning in the cerebellum during executive functioning tasks. These findings also suggest that greater falls risk in seniors may be associated with impaired functioning of a specific, localized brain region, rather than a network of regions.

In conclusion, this pilot study had limitations; because of the short observation period and small sample size, the number of fallers and fall events observed was small, but this was pilot study designed a priori and to the authors’ knowledge, the largest fMRI study in seniors to date.

*Teresa Y. L. Liu-Ambrose, PhD, PT*  
*Lindsay S. Nagamatsu*  
*Todd C. Handy, PhD*  
 Centre for Hip Health  
 Vancouver Coastal Health Research Institute  
 University of British Columbia  
 Vancouver, BC, Canada

*Teresa Y. L. Liu-Ambrose*  
 Department of Physical Therapy  
 University of British Columbia  
 Vancouver, BC, Canada

*Teresa Y. L. Liu-Ambrose*  
*Todd C. Handy*  
 Brain Research Centre  
 University of British Columbia  
 Vancouver, BC, Canada

*Lindsay S. Nagamatsu*  
*Adil Leghari*  
*Todd C. Handy*  
 Department of Psychology  
 University of British Columbia  
 Vancouver, BC, Canada

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## NOCTURIA IN ELDERLY PEOPLE WITH HYPERTENSION—NO INFLUENCE OF LOW-DOSE THIAZIDE ADDED TO LOSARTAN

*To the Editor:* Most guidelines recommend thiazide-type diuretics as the preferred initial drugs for the treatment of hypertension. Thiazides, used in lower doses in elderly people with hypertension, are useful especially when used with an angiotensin II receptor blocker (ARB), which can antagonize the potassium-excreting effect of thiazides. It is also reported that drug-related adverse reactions are lower when thiazide-type diuretics are added to ARB monotherapy than with other combinations.<sup>1,2</sup> However, in these studies, consideration of the influence of thiazides on the geriatric syndrome is lacking. There could be a particular concern with regard to nocturia, a component of the geriatric syndrome that influences general health and quality of life (QOL) in elderly patients.<sup>3</sup> Some epidemiological studies have reported that diuretics are one of the risk factors for urinary problems in elderly people.<sup>4</sup> With this in mind, the effect of low-dose thiazide added to losartan monotherapy on nocturia in elderly hypertensives was examined.

Fifteen elderly patients with hypertension (mean age  $\pm$  standard deviation =  $76 \pm 8$ , female/male = 6/9) who had been receiving losartan monotherapy (50 or 100 mg/d) for more than 1 month and had systolic blood pressure (BP) of 140 mmHg or greater or diastolic BP of 90 mmHg or greater were enrolled. They did not have any history of heart failure or other cardiovascular disease. Hydrochlorothiazide (HCTZ) at 12.5 mg/d was added to losartan and maintained for 3 months. Other medication was unchanged during the study; four patients were taking a statin, one was taking a sulfonyleurea, but no patient was taking medication for gout or an overactive bladder. BP was measured at home and in the doctor's office early in the morning. Laboratory tests were performed in the morning after an overnight fast, and questionnaires on nocturia and health-related QOL were given to all patients.

As shown in Table 1, addition of low-dose HCTZ significantly reduced office BP after 1 month. The BP-lowering effect was sustained at 3 months and confirmed by morning home BP. No patient experienced worsening of nocturia during the study. On average, the frequency of nocturia was less at 1 month. At 3 months, the frequency of nocturia was similar to that at baseline. The result was unchanged if the subjects without nocturia were excluded from the analysis ( $1.3 \pm 0.6$  episodes/night at baseline to  $1.2 \pm 0.6$  episodes/night after 3 months;  $n = 11$ ,  $P = .17$ ). In the QOL questionnaire (visual analog scale graded 0–5), sufficiency of sleep ( $3.4 \pm 1.5$  to  $3.3 \pm 1.6$ ) and satisfaction with health ( $3.1 \pm 1.0$  to  $3.2 \pm 0.9$ ) did not change significantly during the study period. Although serum creatinine and uric acid were significantly higher after 3 months, the changes were slight, and no subject showed an abnormal rise beyond

**Table 1. Changes in Blood Pressure (BP), Serum Parameters, and Nocturia After Addition of 12.5 mg/Day of Hydrochlorothiazide to Losartan**

Parameter	Baseline	After 1 Month	After 3 Months
	Mean $\pm$ Standard Deviation		
Office systolic BP, mmHg	153 $\pm$ 17	140 $\pm$ 18 <sup>†</sup>	137 $\pm$ 18 <sup>†</sup>
Office diastolic BP, mmHg	87 $\pm$ 9	81 $\pm$ 10*	75 $\pm$ 10 <sup>†</sup>
Home systolic BP, mmHg	144 $\pm$ 11	—	132 $\pm$ 11 <sup>†</sup>
Home diastolic BP, mmHg	81 $\pm$ 9	—	77 $\pm$ 8
Glucose, mg/dL	107 $\pm$ 14	—	107 $\pm$ 13
Creatinine, mg/dL	0.82 $\pm$ 0.13	—	0.88 $\pm$ 0.15*
Uric acid, mg/dL	5.3 $\pm$ 1.2	—	6.1 $\pm$ 1.8*
Potassium, mEq/L	4.3 $\pm$ 0.3	—	4.2 $\pm$ 0.2
Nocturia, times per night	0.97 $\pm$ 0.81	0.67 $\pm$ 0.82*	0.87 $\pm$ 0.74

$P < .01$ , \*.05 vs baseline according to paired *t*-test.

— = not determined.

the normal range. Fasting plasma glucose, serum total cholesterol, triglycerides, urea nitrogen, and potassium did not change significantly (Table 1 and data not shown).

This study is preliminary in terms of its size and non-controlled design, but the results suggest that addition of low-dose HCTZ to losartan monotherapy effectively inhibits BP without worsening of nocturia in elderly people with hypertension. Because an ARB/thiazide combination is one of the most frequently prescribed regimens, the findings of the present study may provide useful information on urinary problems in elderly people with hypertension.

Taro Kojima, MD  
Masahiro Akishita, MD, PhD  
Katsuya Iijima, MD, PhD  
Masato Eto, MD, PhD  
Yasuyoshi Ouchi, MD, PhD  
Department of Geriatric Medicine  
Graduate School of Medicine  
University of Tokyo  
Tokyo, Japan

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