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# The Neural Basis of Central Proprioceptive Processing in Older Versus Younger Adults: An Important Sensory Role for Right Putamen

**Daniel J. Goble,[1,2]* James P. Coxon,[1] Annouchka Van Impe,[1] Monique Geurts,[1] Wim Van Hecke,[3] Stefan Sunaert,[3] Nicole Wenderoth,[1] and Stephan P. Swinnen[1]**

[1]*Motor Control Laboratory, Research Center for Movement Control and Neuroplasticity, Department of Biomedical Kinesiology, K.U. Leuven, Belgium*
[2]*Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, Michigan*
[3]*Department of Radiology, University Hospitals of K.U. Leuven, Belgium*

**Abstract:** Our sense of body position and movement independent of vision (i.e., proprioception) relies on muscle spindle feedback and is vital for performing motor acts. In this study, we first sought to elucidate age-related differences in the central processing of proprioceptive information by stimulating foot muscle spindles and by measuring neural activation with functional magnetic resonance imaging. We found that healthy older adults activated a similar, distributed network of primary somatosensory and secondary-associative cortical brain regions as young individuals during the vibration-induced muscle spindle stimulation. A significant decrease in neural activity was also found in a cluster of right putamen voxels for the older age group when compared with the younger age group. Given these differences, we performed two additional analyses within each group that quantified the degree to which age-dependent activity was related to (1) brain structure and (2) a behavioral measure of proprioceptive ability. Using diffusion tensor imaging, older (but not younger) adults with higher mean fractional anisotropy were found to have increased right putamen neural activity. Age-dependent right putamen activity seen during tendon vibration was also correlated with a behavioral test of proprioceptive ability measuring ankle joint position sense in both young and old age groups. Partial correlation tests determined that the relationship between elderly joint position sense and neural activity in right putamen was mediated by brain structure, but not vice versa. These results suggest that structural differences within the right putamen are related to reduced activation in the elderly and potentially serve as biomarker of proprioceptive sensibility in older adults. *Hum Brain Mapp 33:895–908, 2012.* 

**Key words:** aging; proprioception; kinesthesis; muscle spindle; fMRI; basal ganglia; position sense; DTI

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*Correspondence to: Daniel J. Goble, Department of Physical Medicine and Rehabilitation, University of Michigan, 325 E. Eisenhower Parkway, 300 Suite, Ann Arbor, MI 48108.
E-mail: dgoble@umich.edu

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## INTRODUCTION

Proprioception can be defined as our bodily sense of position and movement in the absence of vision. The importance of proprioception for motor control is now unquestioned in light of several studies involving the motor abilities of individuals lacking proprioceptive sense due to large fiber neuropathy. When vision is unavailable, these individuals exhibit profound deficits in the monitoring of limb position, force control, and the production of coordinated movement sequences such as walking [Lajoie et al., 1996; Rothwell et al., 1982; Sainburg et al., 1995]. Although proprioceptive signals are thought to originate from multiple mechanoreceptor types within the body periphery, there is a general agreement that muscle spindle receptors provide the primary source of information for our proprioceptive sense. The strongest evidence supporting this notion comes from experiments involving the stimulation of muscle spindle afferents using tendon vibration. This manipulation induces perceptual illusions of joint position and motion consistent with lengthening of the vibrated muscle [Cordo et al., 1995; Goodwin et al., 1972; Roll et al., 1989].

Proprioceptive ability is influenced by age [Goble et al., 2009a] and has been linked to performance declines on activities of daily living [Hurley et al., 1998; McChesney and Woollacott, 2000]. Explorations of age-related proprioceptive deficits have been limited to the behavioral domain, and thus, the neural mechanisms underlying poor proprioceptive ability in old age remain largely unknown. Postmortem human and animal studies have suggested that proprioceptive deficits partly originate within the body periphery, as there are reductions in muscle spindle number and responsivity to stretch with increasing age [Liu et al., 2005; Miwa et al., 1995; Swash and Fox, 1972]. Despite this, significant central changes in brain function and structure are a common consequence of old age [Seidler et al., 2010], and therefore, it is possible that proprioceptive declines in older adults also reflect changes to central structures mediating proprioceptive information processing. However, to date, this hypothesis has not yet been tested.

In young adults, experiments over the past half decade have made significant progress in determining the neural basis of central proprioceptive feedback processing. Using functional magnetic resonance imaging (fMRI) and tendon vibration to stimulate muscle spindle afferents, researchers have identified several regions of neural activity related to proprioceptive processing [e.g., Kavounoudias et al., 2008; Naito et al., 2005, 2007; Romaiguere et al., 2003]. Areas of activation included both primary somatosensory and (pre)-motor cortices [i.e., Brodmann area (BA) 2,3,4,6], as well as secondary associative regions such as the parietal opercula and inferior frontal gyri. At higher (3 vs. 1.5 T) magnetic field strengths, evidence of subcortical activation within the basal ganglia has also been provided, including, notably, the putamen [Naito et al., 2007].

The main aim of this study was to elucidate, for the first time, the differences in proprioception-related neural processing that exist between healthy young and older adults. This was accomplished using foot tendon vibration and fMRI, as has been used previously with younger individuals [e.g., Kavounoudias et al., 2008; Naito et al., 2005, 2007; Romaiguere et al., 2003]. Recent studies of sensorimotor coordination from our laboratory have shown greater cortical activation in older adults [Goble et al., 2010; Heuninckx et al., 2005, 2008; Van Impe et al., 2009] with reduced levels of activity in subcortical regions such as the basal ganglia [Coxon et al., 2010; Van Impe et al., 2009]. As these tasks rely to some extent on proprioceptive feedback to monitor performance, we hypothesized that elderly individuals in this study would show similar patterns of overactivation/underactivation during foot tendon vibration. In addition to our primary aim, secondary analyses were performed probing fMRI data for its relationship with brain structure (as measured by the diffusion properties of water molecules) and overt proprioceptive behavior (i.e., an ankle joint position sense test). Here, we hypothesized that the age-dependent neural activity might be differentially related to alterations in brain structure in young and older adults and that there would be a relationship between age-dependent neural activation and a behavioral measure of joint position sense. Ultimately, it was hoped that such correlations between brain activity and structure with proprioceptive ability would provide insight into potential biomarkers of elderly proprioceptive sensibility.

## MATERIALS AND METHODS

### Participants

A sample of 20 young (mean age = 26.1 years; range = 19.9–32.4 years) and 20 older (mean age = 68.9 years; range = 62.3–81.3 years) adults was recruited from the local community. The young and older groups were matched for gender (12 females and 8 males) and were right handed and right footed as determined by the Edinburgh Handedness Inventory of Oldfield [1971]. Participants exhibited no evidence of neuromuscular impairment at the time of testing and were not using psychoactive or vasoactive medications. Participants were generally physically active and scored high (i.e., 27+) on the Mini-Mental State Examination [Folstein et al., 1975]. Prior to testing, written informed consent was obtained. All procedures were carried out according to the established guidelines of the Ethics Committee of Biomedical Research at the Katholieke Universiteit Leuven, and the procedures were aligned with the Code of Ethics laid down by the World Medical Association (Declaration of Helsinki).

### Mapping of Brain Regions Showing Neural Activity During Proprioceptive (Muscle Spindle) Stimulation: Foot Tendon Vibration During fMRI

The primary aim of this study was to quantify age-related brain activity during stimulation of key proprioceptors (i.e.,

the muscle spindles). To accomplish this, a muscle tendon vibration paradigm within an fMRI environment was used, similar to the paradigm used previously for young adults [e.g., Kavounoudias et al., 2008; Naito et al., 2005, 2007; Romaiguere et al., 2003]. Participants were placed head first and supine into the fMRI scanner with arms resting comfortably at the sides of their body. The lower limbs were supported in a slightly flexed position at the hip and knee, with the feet elevated and hanging freely at ~10 cm above the scanner bed. Subjects removed their socks and rolled their pant legs to above the knees.

Custom-made pneumatic vibration devices (Mag Design and Engineering, Sunnyvale, CA) were placed across the long tendons of the lesser toes (TENDON) and the crest of the lower portion of the tibia (BONE). During TENDON vibration, it was assumed that both muscle spindle and vibrotactile cutaneous receptors were stimulated. For BONE vibration, it was assumed that only vibrotactile receptors were stimulated. In this way, TENDON > BONE fMRI contrasts (described later) were assumed to reveal neural activations related specifically to muscle spindle stimulation. Vibration devices were held flat to the skin surface (contact area = ~8 $cm^2$) via elastic straps to prevent transmission of vibration to adjacent structures [Montant et al., 2009]. Vibration frequency was ~80 Hz, with 0.2–0.5 mm amplitude. These stimulation parameters have been shown to provide optimal stimulation of muscle spindle receptors, as evidenced by both microneurographic measures and the experience of proprioceptive illusions consistent with lengthening of the vibrated muscle [Goodwin et al., 1972; Roll and Vedel, 1982; Roll et al., 1989]. In this study, most (35 of 40; 17 older and 18 young adults) participants experienced proprioceptive illusions of toe flexion and/or ankle plantar flexion when TENDON, but not BONE, was vibrated. The duration of illusions was quantified in the scanner by having subjects use a modified computer mouse. Subjects held down the left button with their right index finger when they felt an illusion, and the right button with their right middle finger when no illusion was present. This monitoring system helped to assure that subjects remained alert throughout the testing session. Information regarding illusion duration was also used in the modeling of fMRI data to account for group and individual differences related to the experience of proprioceptive illusions.

While undergoing fMRI, participants experienced alternating 21s blocks of three vibration conditions: (1) TENDON, (2) BONE, and (3) REST (i.e., no vibration). Subjects kept their eyes closed throughout the testing. The vibration devices were triggered via custom software developed within the LabVIEW environment (National Instruments, Austin, TX). Image acquisition was performed on a 3-Tesla Magnetom Trio MRI scanner (Siemens, Erlangen, Germany) with a standard head coil. Scanning sessions included a high-resolution T1-weighted image (MPRAGE; TR = 2,300 ms; echo time = 2.98 ms; 1 mm × 1 mm × 1.1 mm voxels, field of view 240 × 256; 160 sagittal slices) for anatomical detail. fMRI data were acquired over four time series (i.e., runs) with an interleaved echo planar imaging pulse sequence for T2*-weighted images (repetition time = 3,000 ms; echo time = 30 ms; flip angle = 90°; 50 oblique slices = 2 mm thick; interslice gap = 0.028 mm; in-plane resolution = 2.5 mm × 2.5 mm; 80 × 80 matrix). Two runs were performed on the left side of the body and two runs on the right, with presentation of body side randomly and evenly distributed across subjects and groups. Three dummy scans at the beginning of each run were discarded from analysis to allow for scanner equilibration. Each run consisted of 147 scans, with seven blocks of the three task conditions whereby each condition lasted seven whole brain images (i.e., 21 s). The order of conditions was randomized across time series, and rest periods were inserted between all runs (~3 min). Within the week prior to testing, subjects were given 20 min of practice in a "dummy scanner" to ensure familiarity with the tasks and scan environment.

Analyses of fMRI data were performed using SPM 5 (Wellcome Department of Imaging Neuroscience, London, UK) implemented with Matlab 7.4 (Mathworks, Natick, MA). To preprocess the data prior to running statistics, T2*-weighted images were realigned to the first image of the time series, and a mean image was created from the realigned volumes. From the realigned data, it was verified that no subject had head movement larger than 2 mm in any direction during any of the functional runs. In addition, the realigned images underwent an "unwarp" procedure to remove a portion of unwanted movement-related variance independent of variance related to the task conditions [Andersson et al., 2001]. The resulting images from these analyses were then normalized to a standard template based on the Montreal Neurological Institute (MNI) reference brain in Talairach space [Talairach and Tournaux, 1998] and subsampled at 2 mm × 2 mm × 2 mm. Lastly, an isotropic 3D Gaussian smoothing kernel (10 mm full width at half maximum) was applied to the normalized data.

## Age-Dependent Activation Relationship to Brain Structure: Fractional Anisotropy Calculated From DTI

As a corollary to the fMRI protocol described above, DTI (single shot spin echo; slice thickness = 2.9 mm; repetition time = 7,200; echo time = 81; number of diffusion directions = 64; diffusion sensitivity = 1,000; number of sagittal slices = 56; in-plane resolution = 2.2 mm × 2.2 mm) was performed on each participant in the same magnetic resonance scanner. Processing of DTI data included corrections for subject motion and eddy current-induced geometrical distortions [Leemans and Jones, 2009; Van Hecke et al., 2007]. Fractional anisotropy (FA) maps were determined from the DTI data using the Explore DTI toolbox [Leemans et al., 2009] with a nonlinear regression

procedure [Jones and Basser, 2004]. For a direct comparison of FA and fMRI data in common space, diffusion images were warped into a subpopulation atlas space [Van Hecke et al., 2008]. The atlas image was subsequently normalized to the DTI-81 FA template image (International Consortium for Brain Mapping), and the warping parameters generated from this step were then applied to each individual's FA image to register them in MNI space.

The FA images had values ranging from 0 to 1, such that values closer to 1 represented greater anisotropic diffusion of water molecules. While it should be noted that the interpretation of FA is not always straightforward [Beaulieu, 2002; Le Bihan, 2003], it is generally believed that increased anisotropy represents increased integrity of brain tissue (i.e., greater cell density, more coherent organization, and/or increased degree of myelination). Traditionally, FA has been used to assess white matter in human brain. However, there is now a growing contingent of work demonstrating the usefulness of this measure in brain regions consisting primarily of gray matter such as the basal ganglia [Bhagat and Beaulieu, 2004; Boska et al., 2007; Chan et al., 2007; LeBel et al., 2008; Snook et al., 2005; Vaillancourt et al., 2009; Yoshikawa et al., 2004]. In this study, group-level DTI analyses were driven by age-related differences in neural activity (i.e., based on fMRI analyses). As such, FA values presented here are presumed to reflect, primarily, alterations in gray matter structure.

## Behavioral Assessment of Proprioceptive Acuity: Test of Ankle Joint Position Sense

On a separate day, the same subjects who participated in the neuroimaging aspect of this study also performed a behavioral test aimed at quantifying ankle joint proprioceptive acuity to serve as a corollary to the main fMRI experiment. For this assessment, subjects were blindfolded and seated with either the left or right lower limb secured to a custom-made manipulandum device. This device allowed for ankle rotation in the sagittal plane through either passive displacement by the experimenter or active movement of the subject. The device was counter weighted to reduce the amount of muscle force required to produce ankle rotation. A potentiometer, accurate to less than 0.1°, recorded ankle joint position in real time to a desktop computer.

Joint position sense testing consisted of 10 right ankle and 10 left ankle matching trials with the order of presentation randomized and balanced across individuals and age groups. Each trial was composed of a two-phase (reference and matching) procedure. In the reference phase, the experimenter passively rotated the ankle from its resting position to a position that was between 25 and 75% of the subject's active range of dorsiflexion or plantarflexion. This joint angle was maintained for 5 s and then returned to the resting position. Following a short delay (~1 to 2 s), the matching phase of the task was initiated. In this phase, subjects were given a verbal cue (i.e., "Match"), which prompted them to return the ankle to the previously experienced ankle position. This position was held for several seconds before the subject was prompted to "relax" and return to the resting position.

For each trial, a measure of total error (TE) was calculated according to the method of Henry [1974]. This measure is an idealized combination of matching bias (i.e., constant error) and matching variability (i.e., variable error) and is well suited to tests of joint position sense [e.g., Goble et al., 2009c]. Reference and matching joint angles were quantified offline from the recorded potentiometer data using a threshold algorithm that determined the last point in time when joint velocity was within two standard deviations of the baseline (premovement) value. To account for the effects of target amplitude [Goble and Brown, 2008b; Goble et al., 2006], TE was normalized to the reference ankle position. Consequently, this variable is expressed as a percentage of the reference angle.

## Statistical Analyses

Statistical analyses for fMRI data were performed with SPM 5 in accordance with the general linear model [Friston et al., 1995]. For each subject, a first-level model was specified with boxcar regressors for the TENDON and BONE conditions, while rest was implicitly modeled. Regressors were subsequently convolved with the canonical hemodynamic response function provided in SPM. Data were high-pass filtered (1/128 Hz) to remove low-frequency drifts of the scanner signal. To account for temporal autocorrelations, an autoregressive, AR(1), model was fit to the residuals of the fMRI time series.

### *Areas of neural activation during stimulation of muscle spindles*

First-level (i.e., individual subject) contrast images for TENDON > BONE were initially calculated to reveal neural activations related to muscle spindle stimulation in the absence of a cutaneous, vibrotactile response. These images were then entered into a second-level ANOVA with the factors "group" (YOUNG, OLD) and "side" (LEFT, RIGHT). In this ANOVA, cluster-wise significance was determined at the level of $P < 0.05$ corrected for family-wise error (FWE), following voxel-level thresholding at $P < 0.001$ (uncorrected). In addition, a constrained search [Friston et al., 2006] was performed to help restrict analyses to voxels with significant activation (rather than deactivation). Specifically, a binary mask image was created from the union (i.e., global conjunction) of voxels demonstrating significant activation ($P < 0.001$ uncorrected) for any group or body side condition in an independent, second-level ANOVA, testing TENDON > REST first-level contrast images, with a correction for differences in illusion duration (i.e., this variable was added as a covariate of no interest). It is worth noting

that even when explored at relatively low threshold (i.e., $P < 0.01$ uncorrected), the illusion regressor did not explain significant variance, that is, activation was similar regardless of whether subjects did or did not experience proprioceptive illusions.

### *Relationship between neural activation, brain structure, and proprioceptive acuity*

In clusters showing significant age-related differences in neural activation, we calculated the mean percent signal change (PSC) of the fMRI bold oxygen level-dependent signal and the mean FA value for each individual. PSC was quantified according to the methods proposed by Brett et al. [2002] using the Marsbar toolbox. Mean FA values were determined as the average FA across all voxels falling within a mask of the cluster of interest. Where appropriate, group comparisons of these variables were made using two-sample *t*-test procedures. Additionally, the relationship between PSC, FA, and TE was explored using Pearson correlation tests and/or partial correlation methods where appropriate. These statistical tests were carried out using SPSS (SPSS Inc., Chicago, IL) with an $\alpha = 0.05$.

## RESULTS

All participants tested were successful in completing the entire experimental procedure. Below, we first describe age-independent and age-dependent areas of neural activity resulting from our primary analysis of muscle spindle stimulation during fMRI. We then explore the relationship between age-dependent neural activation, brain structure (i.e., FA), and proprioceptive acuity (i.e., TE from the test of joint position sense).

### Common Brain Activity for Young and Older Adults During Muscle Spindle Stimulation

Neural activation revealed by fMRI during muscle spindle stimulation (i.e., TENDON > BONE contrast) was present in an expanded network of brain areas for both young and older individuals (Fig. 1 and Table I). With respect to body side, only the primary sensorimotor cortices (peak activation in BA 4 and extending into BA 3a: foot regions) showed limb-specific activity with contralateral (i.e., hemisphere opposite to the stimulated body side) activation noted for the right (ANOVA model: RIGHT > LEFT; $P < 0.05$ FWE) and left (ANOVA model: LEFT > RIGHT; $P < 0.05$ FWE) foot stimulation conditions. In contrast, all other active regions for the TENDON > BONE contrasts were non-limb specific. A conjunction analysis was, therefore, conducted testing for significant clusters of activation in OLD and YOUNG groups for the average effect of left and right stimulation (ANOVA model: OLD LEFT and OLD RIGHT conjoined with YOUNG LEFT and YOUNG RIGHT; $P < 0.05$ FWE). This analysis revealed activity in the bilateral inferior parietal cortex (BA 40) and in the bordering primary somatosensory area (BA 2). Regions of activation were also seen in bilateral inferior frontal gyri (pars opercularis: BA 44; pars triangularis: BA 45), bilateral anterior insular cortex, supplementary motor area (SMA: BA 6), preSMA (BA 6), bilateral basal ganglia (putamen/palladium), and thalamus. Lastly, a number of regions showed activation in only the right hemisphere including ventral premotor cortex (BA 6), orbitofrontal cortex (BA 47), dorsolateral prefrontal cortex (BA 46) and the dorsal anterior cingulate cortex (BA 32). Although a direct assessment of laterality was beyond the scope of this experiment, it is worth noting that these results align well with Naito et al. [2005, 2007], who found right-hemisphere dominance in similar regions when assessing muscle spindle feedback processing in young adults.

### Differences in Neural Activity Between Young and Older Adults During Muscle Spindle Stimulation

Muscle spindle-related neural activity was largely overlapping for young and older adults. However, a significant age-related difference was seen for a cluster of voxels within the right putamen (Fig. 2; ANOVA model: YOUNG LEFT and YOUNG RIGHT > OLD LEFT and OLD RIGHT; $P < 0.05$ FWE). The activated cluster had an extent of 371 voxels and two significant activation peaks ($x = 24$; $y = 14$; $z = -4$; $x = 32$; $y = 4$; $z = 10$). Using PSC as a measure of the fMRI signal response to muscle spindle stimulation (Fig. 2A), the group difference in right putamen was found to be one of greater activation for younger versus older adults (two-sample *t*-test: OLD versus YOUNG PSC; $P = 0.0009$).

### Relationship Between Age-Dependent Neural Activation, Brain Structure, and Joint Position Sense

Within the cluster of right putamen voxels showing greater neural activation for young versus older individuals, there was no age-related difference in brain structure as measured by mean FA (Fig. 2B; two-sample *t*-test: OLD versus YOUNG; $P > 0.05$). Despite this, the PSC of neural activity within this cluster was significantly correlated with mean FA for older adults (Pearson correlation: OLD PSC with mean FA; $r = 0.51$; $P = 0.02$), but not for young adults (Pearson correlation: YOUNG PSC with mean FA; $r = 0.06$; $P > 0.05$). As demonstrated in Figure 2C, older adults who had higher mean FA values showed increased activation of the right putamen during muscle spindle stimulation.

Our behavioral measure of proprioceptive acuity (i.e., test of ankle joint position sense) did not differ between the left (mean ± SE TE = 18.4% ± 1.7%) and right (mean ± SE TE = 17.2% ± 1.5%) lower limbs (two-sample *t*-test: LEFT versus RIGHT TE; $P > 0.05$). In addition, there was no difference in matching accuracy across feet between the

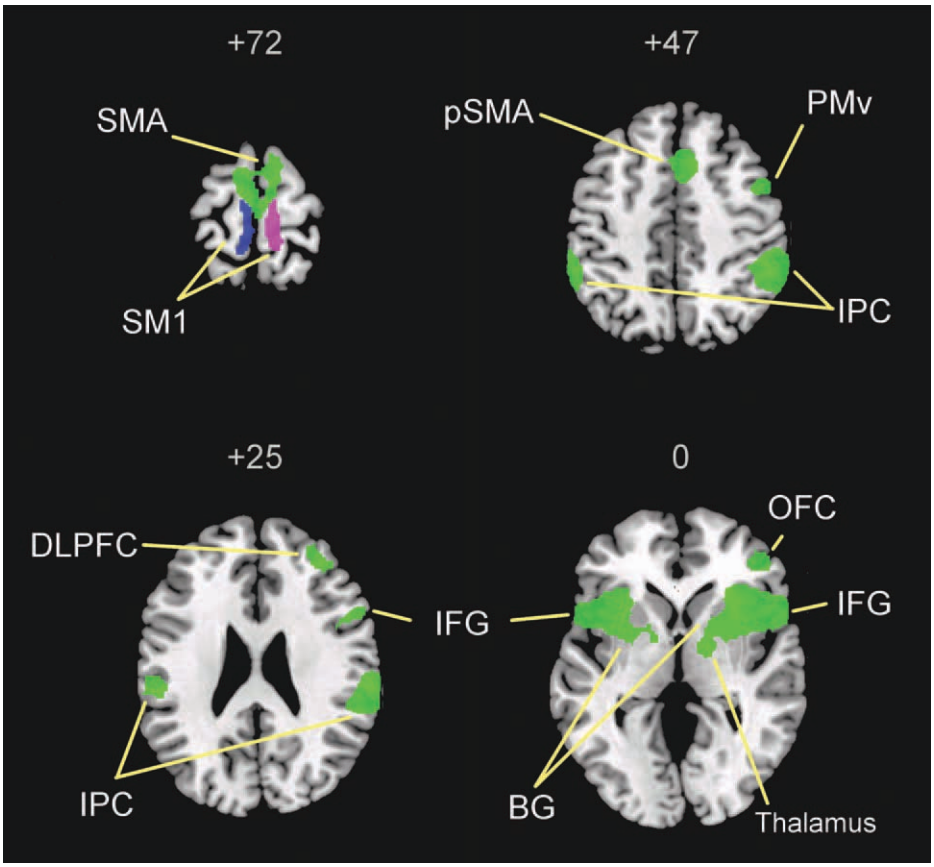


**Figure 1.**

Common areas of neural activity seen in younger and older adults during muscle spindle (i.e., TENDON > BONE) stimulation. Results displayed on a template brain image in neurologic orientation. Blue = right foot only; magenta = left foot only; green = both right and left feet. SMA, supplementary motor area; SM1, primary sensorimotor cortex; pSMA, presupplementary motor area; PMv, ventral premotor cortex; IPC, inferior parietal cortex; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus (pars opercularis and pars triangularis); BG, basal ganglia (putamen and pallidum); OFC, orbitofrontal cortex. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

young (mean ± SE = 17.8% ± 1.8%) and older (mean ± SE = 17.7% ± 1.1%) age groups. Despite this, there was a significant relationship between joint position matching TE averaged across lower limbs and the amount of right putamen neural activity induced by stimulation of the muscle spindles (Pearson correlation: YOUNG and OLD PSC with TE; $r = -0.39$; $P = 0.04$). As shown in Figure 3A, this relationship was such that increased neural activity was associated with smaller TE (indicating better proprioceptive acuity).

Mean FA of the right putamen cluster showing age-dependent activation was also associated with joint position sense averaged across the two limbs (Fig. 3B). However, this was only the case for older individuals, where higher mean FA values were strongly correlated (Pearson correlation: OLD mean FA with TE; $r = -0.77$; $P = 0.00007$) with lower TE. A partial correlation analysis was conducted to determine the relationship between PSC and elderly joint position sense (i.e., TE) when corrected for brain structure (i.e., FA) is accounted for and vice versa. This analysis demonstrated that the correlation between PSC and TE was mediated by structural factors (i.e., the correlation was not significant when mean FA was accounted for; partial correlation: OLD PSC and TE corrected for mean FA; $r = 0.01$, $P > 0.05$), whereas mean FA remained significantly correlated with TE (partial correlation: OLD mean FA and TE corrected for PSC; $r = -0.72$, $P = 0.0005$), even when variance accounted for by PSC was removed.

## DISCUSSION

This study provided novel results regarding the age-related central processing of proprioceptive information and its relationship with measures of brain structure and

**TABLE I. Neural activation during muscle spindle stimulation (i.e., TENDON > BONE contrast) common to both YOUNG and OLD**

| Activation peak location | Side | *X* | *Y* | Z | *t*-value |
|---|---|---|---|---|---|
| CLUSTER#1: 4205 voxels | | | | | |
| Inferior frontal gyrus (p tri, BA 45) | R | 54 | 16 | −2 | 5.78 |
| Inferior frontal gyrus (p oper, BA 44) | R | 52 | 16 | 16 | 4.97 |
| Anterior insular lobe (BA 48) | R | 28 | 20 | −8 | 5.63 |
| Precentral gyrus (PMv, BA 6) | R | 50 | 10 | 38 | 5.44 |
| | R | 48 | 4 | 46 | 4.73 |
| | R | 50 | 6 | 48 | 4.73 |
| Orbitofrontal cortex (BA 47) | R | 44 | 22 | −14 | 5.07 |
| | R | 48 | 42 | −4 | 4.15 |
| Basal ganglia (pallidum) | R | 18 | 0 | 0 | 4.8 |
| | R | 22 | 0 | 2 | 4.75 |
| Basal ganglia (putamen) | R | 34 | 10 | −4 | 4.74 |
| Thalamus | R | 14 | −8 | 0 | 4.49 |
| CLUSTER#2: 2142 voxels | | | | | |
| Supramarginal gyrus (BA 40) | R | 60 | −42 | 42 | 6.10 |
| Supramarginal gyrus (BA 40/2) | R | 64 | −38 | 40 | 6.08 |
| | R | 64 | −34 | 30 | 5.57 |
| Inferior parietal cortex (BA 40) | R | 60 | −44 | 48 | 5.88 |
| CLUSTER#3: 2123 voxels | | | | | |
| Inferior frontal gyrus (p oper, BA 44) | L | −50 | 10 | 12 | 5.31 |
| | L | −50 | 12 | 4 | 4.96 |
| Anterior insular lobe | L | −30 | 20 | 4 | 5.2 |
| | L | −32 | 20 | −6 | 4.94 |
| | L | −34 | 18 | −8 | 4.94 |
| Inferior frontal gyrus (p tri, BA 45) | L | −48 | 16 | −2 | 5.2 |
| Basal ganglia (putamen) | L | −24 | 0 | 8 | 4.38 |
| | L | −26 | 2 | 6 | 4.35 |
| Basal ganglia (pallidum) | L | −16 | 2 | 2 | 3.79 |
| Thalamus | L | −20 | −6 | 8 | 4.14 |
| CLUSTER#4: 1809 voxels | | | | | |
| Pre SMA (BA 6) | R | 8 | 14 | 58 | 5.49 |
| | R | 8 | 10 | 60 | 5.44 |
| | L | −10 | 2 | 70 | 4.18 |
| | L | −4 | 10 | 58 | 3.97 |
| SMA (BA 6) | R | 10 | −4 | 70 | 4.71 |
| | R | 2 | −20 | 72 | 4.22 |
| | L | −10 | −4 | 78 | 4.33 |
| | L | −14 | −6 | 70 | 4.18 |
| | L | −10 | −12 | 74 | 4.09 |
| | L | −6 | −6 | 64 | 3.85 |
| Dorsal anterior cingulate (BA 32) | R | 6 | 22 | 48 | 5.27 |
| | R | 8 | 26 | 34 | 4.61 |
| CLUSTER#5: 938 voxels | | | | | |
| Inferior parietal cortex (BA 40) | L | −62 | −48 | 40 | 5.31 |
| | L | −60 | −48 | 44 | 4.95 |
| | L | −58 | −44 | 50 | 4.81 |
| | L | −56 | −46 | 52 | 4.4 |
| | L | −60 | −58 | 34 | 3.65 |
| Supramarginal gyrus (BA 40/2) | L | −64 | −44 | 36 | 4.81 |
| | L | −66 | −36 | 32 | 4.04 |
| | L | −60 | −30 | 46 | 3.93 |
| Supramarginal gyrus (BA 2) | L | −56 | −24 | 30 | 4.37 |
| | L | −56 | −28 | 30 | 4.36 |
| CLUSTER#6: 422 voxels | | | | | |
| Middle frontal gyrus (DLPFC, BA 46) | R | 28 | 50 | 20 | 4.49 |
| | R | 38 | 40 | 34 | 4.23 |

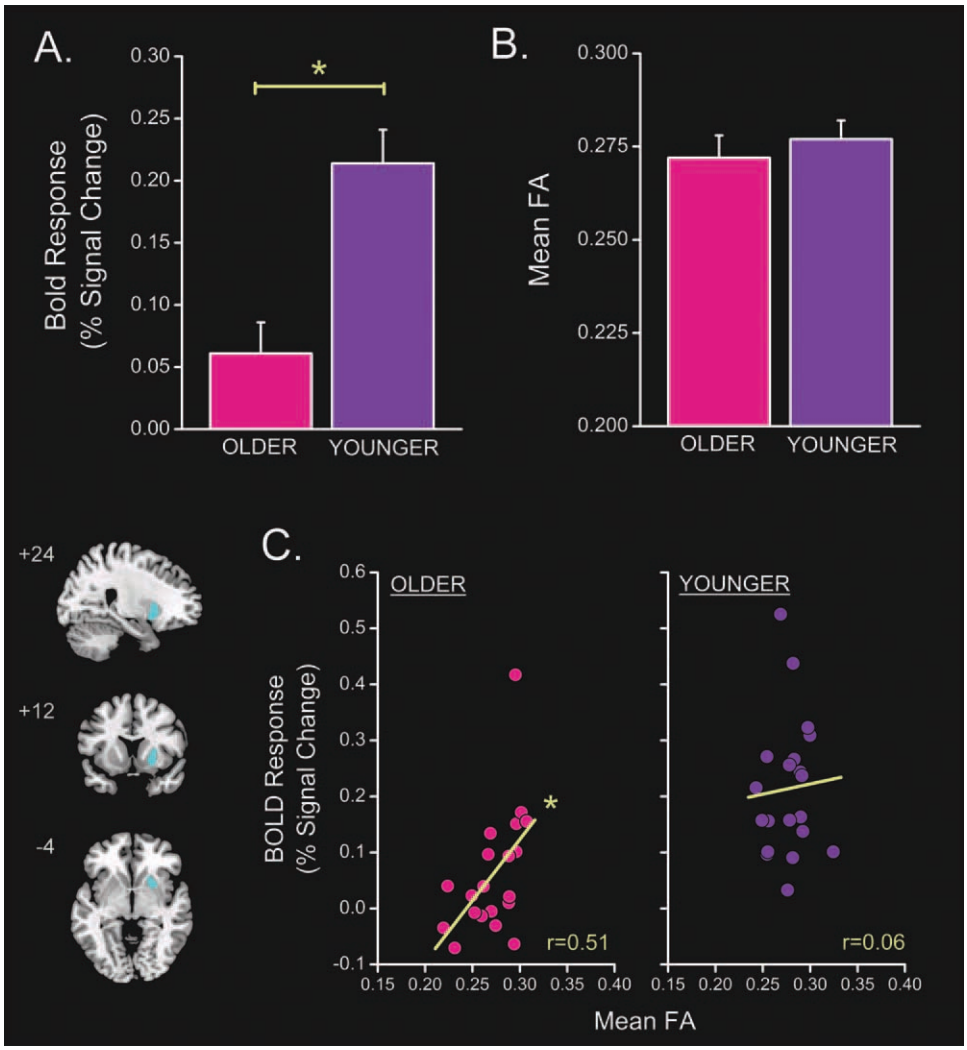


**Figure 2.**
Older and younger adult mean ± SE PSC (**A**), mean ± SE FA (**B**), and the correlation between PSC and mean FA (**C**) in a cluster right putamen voxels demonstrating age-dependent neural activity. Cluster rendered on a standard template brain in neurologic orientation (bottom left). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

joint position sense. Our primary aim was to map regions of the aging brain that were active during stimulation of key proprioceptors (i.e., the muscle spindles) by using the combination of tendon vibration and fMRI. We found a significant reduction in neural activity in the right putamen of older adults when compared with younger adults. In addition, secondary correlational analyses revealed links between age-dependent right putamen neural activation, brain structure (measured as mean FA), and performance on a proprioceptive joint position sense test. Correlations differed for the two age groups with both young and older individuals showing significant associations between increased neural activity and greater proprioceptive acuity, while only the older group had a significant correlation between higher mean FA and increased neural activity. Based on partial correlation analysis, it was revealed that the relationship between neural activity and proprioceptive ability in the elderly was largely mediated by brain structure (i.e., mean FA). This finding provides some insight that for older adults, the structure of right putamen may serve as a biomarker of proprioceptive sensibility.

## Central Components of the Aged Proprioceptive Processing Network

Elderly (and young) individuals demonstrated a broad array of neural activations in response to the stimulation of muscle spindles. The base network of proprioception-

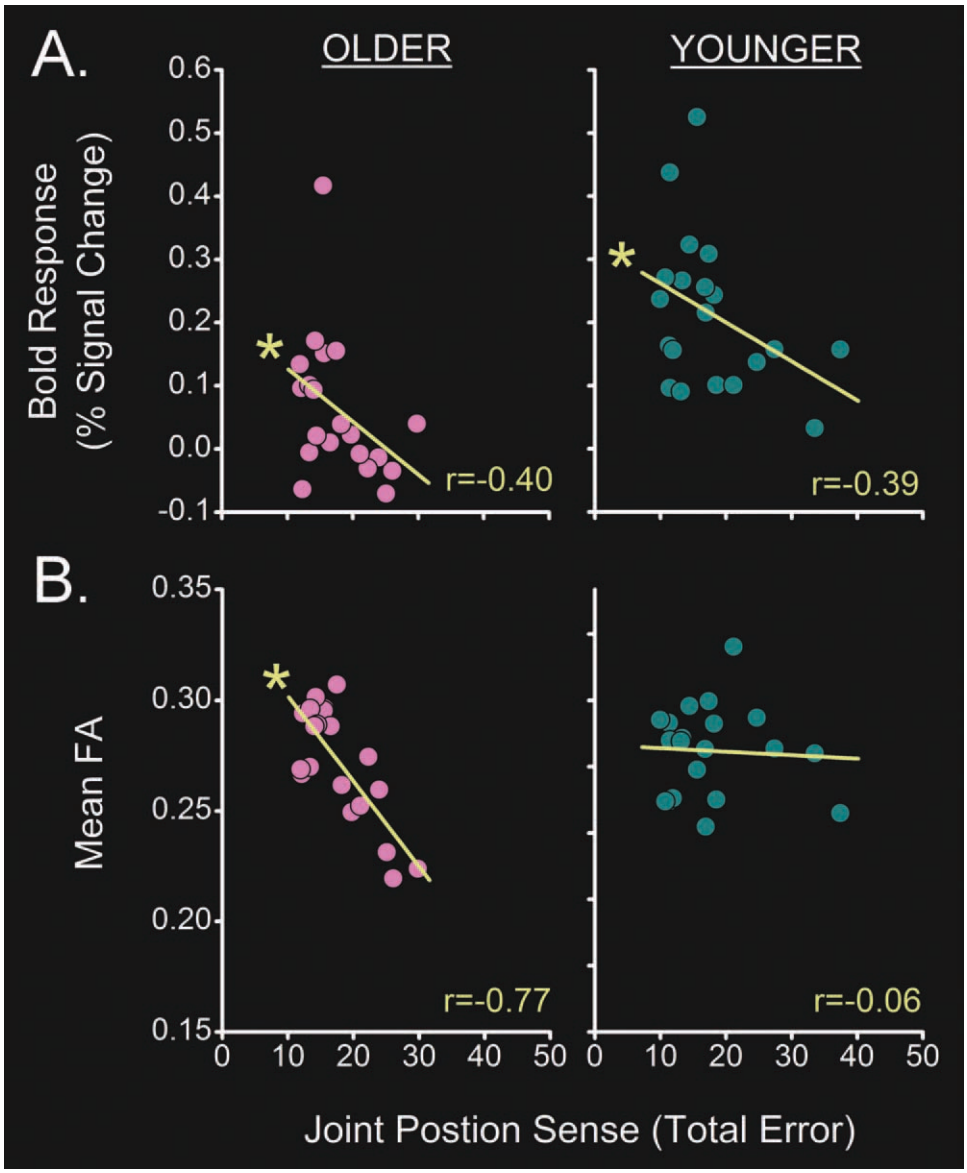


**Figure 3.**
Correlations between PSC (**A**) and mean FA (**B**), with the ankle joint position sense of younger and older adults in the age-dependent cluster of right putamen voxels rendered in Figure 2. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

related activity is in good agreement with previous imaging studies involving young subjects where either tendon vibration [Kavounoudias et al., 2008; Naito et al., 2005, 2007; Romaiguere et al., 2003] or passive limb displacement [Mima et al., 1999; Weiller et al., 1996] were used to stimulate proprioceptors. Not surprisingly, activations were found in primary sensorimotor cortices contralateral to the side of stimulation. The peak of this activity was in primary motor cortex (BA 4 – foot area) and it spread to adjacent BA 3a. The role of the motor cortex in kinesthetic processing has been well established [see for review, Naito, 2004] and partly relates to the perception of limb movement during proprioceptive illusions [Romaiguere et al., 2003]. Activity in this region cannot be explained by the low levels of muscle activity associated with the tonic vibration reflex [Naito et al., 2007]. Rather, it is likely that this activation is the result of afferent input from the dorsolateral medial-lemniscal proprioceptive pathway to BA 4, via the thalamus [Lemon and van der Burg, 1979; Wong et al., 1978]. With respect to the activation of BA 3a, it is worth noting that this primary somatosensory region is most responsive to muscle spindle stimulation, whereas BA 3b is

more representative of cutaneous stimulation [Phillips et al., 1971; Tanji and Wise, 1981]. In this case, our activity in BA 3a, but not BA 3b, suggests that the effects of vibrotactile/cutaneous stimulation were well controlled by contrasting the TENDON and BONE conditions.

The remaining areas of neural activation during muscle spindle stimulation were body side independent. We found bilateral activity in midline brain structures (i.e., SMA and preSMA), which have been previously shown to respond to both passive joint movement and vibration-induced stimulation of the muscle spindles [e.g., Naito et al., 2005, 2007; Weiller et al., 1996]. Bilateral activity in inferior parietal cortex (BA 40) and bordering primary somatosensory cortex (BA 2) was also evident and is in line with converging evidence, suggesting that these interconnected regions use proprioceptive information to form a coherent body representation [Daprati et al., 2010]. Muscle spindle stimulation additionally activated bilateral anterior insular cortex and regions of the lateral (pre)frontal cortex. These activations are almost certainly involved in higher order perceptuo-proprioceptive processes such as corporeal awareness and attention. For example, it has been proposed by Corbetta and Shulman [2002] that salient, stimulus-driven shifts of attention (such as those likely induced by illusory tendon vibration) are accomplished by activations in the right temporoparietal junction, inferior frontal gyrus (BA 44, BA 45), dorsolateral prefrontal cortex (BA 46), anterior insula, and the cingulate/preSMA. All these areas were active in this study.

In addition, we found right-sided activation in ventral premotor cortex, an area that has been recently shown to modulate the primary somatosensory cortex [Christensen et al., 2007], and activation of right orbitofrontal cortex (BA 47), which might represent anticipatory activity related to the expected sensory consequences of tendon vibration [Schoenbaum et al., 2009]. Overall, greater involvement of right hemisphere regions for the processing of proprioception-related information has been previously described in detail [Naito et al., 2005, 2007] and has been hypothesized to underlie contralateral left arm accuracy advantages on tests of upper limb joint position sense [Goble et al., 2005, 2006, 2009b; Goble and Brown, 2007, 2008a,b, 2009, 2010; Goble, 2010].

A relatively novel finding compared with previous proprioceptive mapping studies was that bilateral regions of the basal ganglia (putamen/pallidum) were active during tendon vibration. This finding may reflect our use of a more sensitive, 3-Tesla scanner [Naito et al., 2007]. Although the basal ganglia have been traditionally ascribed with a series of "motor" functions, prior work on human and animals has brought to light a role for the basal ganglia as a "sensory analyzer," particularly for proprioceptive feedback processing [Lidsky et al., 1985]. For example, single-cell recording studies involving monkeys have shown that neurons in putamen [Crutcher and DeLong, 1984] and, to a lesser extent, globus pallidus [DeLong et al., 1985] code for passive joint displacement. Such responses likely originate from muscle spindle input signals directed to the putamen through densely connected portions of the primary somatosensory and motor cortices [Kunzle, 1975, 1977]. These results suggest that the processing role served by the basal ganglia falls somewhere on the continuum between lower level primary somatosensory and higher order secondary-associative cortical regions.

## Differences in Neural Activation Between Young and Old Adults and Their Unique Relation to Brain Structure and Proprioceptive Ability Within Age Groups

We found reduced activation in a cluster of right putamen voxels for older adults during muscle spindle stimulation conditions, and the activity in this cluster was correlated with brain structure (i.e., PSC increased with increased mean FA). The putamen (along with the substantia nigra and caudate) is an integral part of the nigrostriatal system and is highly reliant on dopaminergic neurotransmission. Studies of the aging brain have shown that dopamine regulation is significantly reduced in old age via structural degradation including neuronal loss, fewer neuroreceptor sites, and a lack of transporter molecules [Kaasinen and Rinne, 2002]. These declines have led some to suggest that the aging brain lies somewhere on a preclinical continuum of Parkinson's disease. Here, it is noteworthy that a substantial body of literature exists that demonstrates proprioceptive deficits in individuals with Parkinson's disease [Konczak et al., 2009]. Indeed, such studies have commonly found deficits in both joint position sense [Maschke et al., 2003; Zia et al., 2000, 2002] and/or targeted reaching in the absence of vision [Adamovich et al., 2001; Swinnen et al., 2000].

Right putamen activity was also significantly correlated with increased performance on a test of ankle position sense, and this effect was seen regardless of age. This finding provides the best evidence to date supporting a link between a measure of neural activation and overt performance on a test of proprioceptive sensibility. The right-sided nature of the cluster may reflect both right hemisphere dominance for proprioceptive processing [Naito et al., 2005, 2007] and or right lateralized higher order perceptuo-proprioceptive functions such as attention to, and/or the awareness of, relevant proprioceptive stimuli [Corbetta and Shulman, 2002]. With respect to this latter hypothesis, it is interesting to note that the age-dependent activation difference was relatively located in the anterior putamen, which has been shown to have stronger connections with preSMA versus SMA, premotor or primary sensorimotor cortices [Lehericy et al., 2004]. Additionally, in a case report, Halligan et al. [1993] described an individual with right basal ganglia damage due to stroke who showed disturbances in the normal experience of body schema including supranumerary phantom limb. There were no age-related differences within primary sensorimotor

regions. We believe that this null finding may be due to the relative sparing of primary sensorimotor cortex with age when compared with the known vulnerability of structures like the putamen and ventrolateral prefrontal cortex [Fjell et al., 2009].

Neural activation in response to stimulation of muscle spindles within the age-dependent right putamen cluster was also greater for older adults who had higher mean FA values. Higher FA was further associated with joint position sense in the elderly, and partial correlation analyses showed that brain structure (i.e., mean FA) was an important mediating factor in the correlation between elderly neural activity and joint position sense (TE). Although the meaning of FA in regions of the brain primarily subserved by gray matter is not entirely clear [Beaulieu, 2002], the relationship between this measure, neural activation and behavior, in this study suggests that FA may be a useful biomarker of structural integrity for key proprioceptive structures such as the putamen in the elderly. Similar suggestions have been made with respect to other basal ganglia structures (e.g., substantia nigra) in the diagnosis of individuals with Parkinson's disease [Vaillancourt et al., 2009; Yoshikawa et al., 2004]. For example, Vaillancourt et al. [2009] were recently able to predict with 100% sensitivity and specificity the existence of early stage Parkinson's disease on the basis of reduced FA within the caudal portion of the substantia nigra. In this case, reductions in FA were assumed to reflect, primarily, neuronal loss and an increase in extracellular fluid.

Our findings of lower FA correlating with less activation and poorer proprioceptive performance in older adults, although in agreement with studies of individuals with basal ganglia dysfunction, are less in line with several studies in the aging domain that have noted an increase in putamen FA with age [Abe et al., 2008; Bhagat and Beaulieu, 2004; Pfefferbaum et al., 2010; Wang et al., 2010; Zhang et al., 2010]. To this point, it is important to note that these previous studies have largely used a linear regression approach assessing FA across the lifespan (from 20 years to old age), which has been the subject of some criticism [Hasan, 2010]. Indeed, increases in FA with age are at least partly due to maturation of the putamen which occurs until approximately 25 years [LeBel et al., 2008], rather than any increased FA in old age. It is, therefore, important to note that in this study, the majority of young subjects tested (16/20) were at least 25 years of age.

An alternative explanation for the rise in mean putamen FA with age was recently brought forth by Pfefferbaum et al. [2010]. These researchers demonstrated using field-dependent relaxation rate increase indices that a rise in FA could be the result of accumulating iron deposits within the aging putamen. Based on this finding, it is tempting to speculate that the lack of mean group FA differences in this study might reflect the good general health of the elderly group tested and/or a lack of age-related differences in iron accumulation. Additionally, we assessed FA in voxels within the putamen that were known to be active at the group level during the fMRI experiment. This may have increased the likelihood that primarily gray matter was assessed.

As a group, our elderly subjects did not differ from young individuals on our test of proprioceptive sensibility (i.e., joint position sense). Although at first this result may appear somewhat surprising, we believe that this may simply reflect the high-functioning nature of the elderly individuals in this study. Indeed, many of our subjects engaged in sport or competitive fitness programs three or more times per week. Despite this, the lack of overall age differences in this study and the intuitive nature the elderly results regarding a correlation between position sense and brain structure/function remain intriguing. Indeed, it is expected that further probing of this effect with a group of even older and, perhaps, frail older adults would only provide more substantive evidence of a relationship between position sense, right putamen activation, and right putamen mean FA.

## CONCLUSIONS

This study uncovered regions of the elderly brain involved in central processing of proprioceptive feedback. In contrast to recent studies involving the neural correlates of motor tasks [Goble et al., 2010; Heuninckx et al., 2005, 2008; Van Impe et al., 2009; Ward and Frackowiak, 2003; Ward et al., 2008; Wu and Hallett, 2005], which typically have shown cortical overactivation, we found only a localized underactivation of the right putamen [Coxon et al., 2010; Van Impe et al., 2009]. Our results, therefore, indicate that proprioceptive processing in the elderly is influenced by structural differences that limit activation within subcortical regions (i.e., putamen). These differences, in turn, can be related to overt proprioceptive function as assessed by tests of joint position sense.

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