Published in final edited form as:

Brain Imaging Behav. 2009 June 1; 3(2): 167–175. doi:10.1007/s11682-008-9059-7.

Relevance of Iron Deposition in Deep Gray Matter Brain Structures to Cognitive and Motor Performance in Healthy Elderly Men and Women: Exploratory Findings

Edith V. Sullivan¹, Elfar Adalsteinsson^{2,3}, Torsten Rohlfing⁴, and Adolf Pfefferbaum^{1,4}

¹ Department of Psychiatry and Behavioral Sciences, School of Medicine, Stanford University, 401 Quarry Road, Stanford, CA 94305-5723, USA e-mail: edie@stanford.edu

² Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge, MA, USA

³ Harvard–MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA, USA

⁴ Neuroscience Program, SRI International, Menlo Park, CA, USA

Abstract

Iron deposition increases in normal aging, has its greatest presence in structures of the extrapyramidal system, and may contribute to functional decline. MR imaging provides a method for indexing iron deposition in brain structures because of iron's ferromagnetic properties, which interact with the MRI environment to cause signal intensity attenuation that is quantifiable by comparing images collected at 1.5 and 3.0 T. We tested functional correlates of an MR-based iron index in 10 healthy, elderly individuals previously reported to have a higher iron burden in the putamen and lower in the thalamus than young individuals. Lower scores on the Dementia Rating Scale and longer reaction times on a two-choice attention test correlated with higher iron estimates in the caudate nucleus and putamen; poorer Mini-Mental State Examination and Digit Symbol scores correlated with lower iron estimates in the thalamus. Further analyses based on multiple regression, which considered regional FDRI estimates and volume measures as predictors of performance, identified iron but not the sampled volume as the unique predictor in each case. These exploratory correlations suggest a substrate of performance degradation in aging and have implications for regional signal darkening in an array of MR-based imaging protocols.

Keywords

Iron; Basal ganglia; Extrapyramidal system; Thalamus; MRI; Cognition; Motor; Age; Aging

Introduction

Myriad changes in brain structure and function accompany aging even in health. Two decades of neuroimaging studies using conventional magnetic resonance imaging (MRI) to quantify brain tissue and cerebrospinal fluid (CSF) filled cavities and spaces, including the ventricular system, fissures, and sulci, consistently reveal shrinkage of brain tissue and expansion of CSF repositories (DeCarli et al. 2005; Good et al. 2001; Jernigan et al. 2001; Pfefferbaum et al. 1994; e.g., Raz et al. 2005; for reviews, Raz and Rodrigue 2006; Sullivan and Pfefferbaum

2007), although the location, extent, and substrate of brain tissue shrinkage remains controversial (Raz et al. 2005, 2007b). Among the elements detectable in vivo in the brain with MRI are the presence, location, and amount of iron because of its ferromagnetic properties, which interact with the MR scanner environment (Bartzokis et al. 2007). MRI evidence for abnormal accumulation of iron abound for neurological conditions affecting striatal structures, including Parkinson's disease, multiple sclerosis, substantia nigra degeneration, multisystems atrophy, Huntington's disease, and Hallervorden-Spatz syndrome (reviewed in Bartzokis et al. 2007; Brass et al. 2006; Haacke et al. 2005), and many studies indicate that the detected iron burden contributes to disease-related functional decline. Fewer studies have measured iron deposition in normal aging (e.g., Bartzokis et al. 2007) or have examined functional correlates of regional iron deposition (Pujol et al. 1992).

Half a century ago, Hallgren and Sourander (1958) published an extensive, systematic study of the distribution of non-heme iron deposition throughout the brain across the entire life span, from birth to 100 years of age. Care was taken to exclude cases with cerebrovascular and neuropsychiatric disorders to reduce the likelihood that measured iron was not reflective of hemoglobin iron, that is, from blood, suggestive of hemorrhagic stroke. Further case exclusion followed examination for excessive edema. The highest iron values were located in structures of the extrapyramidal system, including globus pallidus, red nucleus, substantia nigra, putamen, and caudate nucleus; the dentate nucleus of the cerebellum also had high values. By contrast, iron content in the cortex, thalamus, and frontal white matter was considerably lower. The pattern of iron distribution in the otherwise nonpathological brain reported in this landmark postmortem study has been replicated with in vivo methods using MRI (e.g., Bartzokis et al. 2007). Considering the loci of greatest concentration, later studies, notably those using in vivo MRI, focused on iron deposition as contributing to classical movement disorders, although studies using cognitive as well as motor tests in normal healthy individuals identified cognitive correlates of MRI measures of brain iron (Pujol et al. 1992).

Iron deposition in brain tissue causes signal intensity loss, the measurement of which depends on the choice of image acquisition protocol (e.g., diffusion weighted imaging Pfefferbaum et al. 2008) and MR field strength. Ferromagnetic properties of iron deposits become increasingly apparent when subjected to a strong magnetic field, and the stronger the field (e.g., from 0.5 to 1.5 to 3.0 T), the greater the signal loss. In the MR context, iron causes protons in nearby water molecules to lose their coherence, thereby disrupting signal intensity more quickly than in locations without iron deposition. The iron affects transverse relaxation time, T_2 , or the corresponding rate, $R_2=1/T_2$, that characterizes the time during which the proton spins interact with each other (spin-spin interactions) and the signal in the transverse plane is lost. Several methods have been developed to measure iron in the brain (e.g., Bartzokis et al. 1993, 1994; Bizzi et al. 1990; Haacke et al. 2005). A robust approach requires acquisition of MRI at two or more field strengths, which takes advantage of iron's differential effect on transverse relaxation rates (R_2) at different field strengths (Bizzi et al. 1992; Gomori and Grossman 1993; Majumdar et al. 1989). Brain iron, which is in ferritin molecules, increases R_2 linearly with increases in MR field strength (but see Bizzi et al. 1990) and can be quantified as the field-dependent R_2 increase (FDRI) per unit Tesla, where higher FDRI indexes greater local concentration of iron (Bartzokis et al. 1993, 1994, 2007).

The local inhomogeneity caused by iron particles increases transverse relaxation rates contributing to signal darkening on conventional spin-echo MRI, notable in structures of the basal ganglia (Raz et al. 2007a). Quantitative studies using the FDRI metric have shown that, after adolescence (e.g., Thomas et al. 1993), iron is present in the globus pallidus relatively uniformly across the adult age range; however, with advancing age, iron increases in amount and distribution in the caudate nucleus and putamen (Bartzokis et al. 2007).

Recently, we observed this pattern of iron's effect on signal intensity, especially in the putamen of elderly (65 to 79 years) compared with young adults (22 to 37 years), whereas the thalamus was free of evidence for iron and, unlike basal ganglia structures, FDRI estimates in the thalamus were lower in older than younger healthy adults (Pfefferbaum et al. 2008). The aim of the present analysis was to examine whether the amount of iron estimated with the FDRI approach had functional ramifications. Accordingly, we tested correlations between motor and cognitive data, collected concurrently with collection of 1.5 T imaging data, and regional FDRI estimates. To test the selectivity of identified correlations, we then examined whether the iron estimate or the underlying tissue volume examined was a unique predictor of performance level. Given the small sample, the analyses should be considered exploratory.

Methods

Participants

The 10 elderly subjects, five men and five women (mean age=72.2 years, range=65 to 79 years and 16.3 years of education, range=12 to 18 years), who participated in the previous report (Pfefferbaum et al. 2008) on iron measurement in the basal ganglia, had been administered a short battery of neuropsychological tests. These participants were recruited from a larger ongoing study of normal aging, underwent extensive neuropsychiatric and medical screening, and scored well within the normal range on two dementia screening tests: Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) (mean=28.9, range= 27 to 30 out of 30) and the Dementia Rating Scale (Mattis, 1988) (mean=140.1, range=138 to 143 out of 144). Appropriate approval and procedures were used concerning human subjects.

MRI acquisition protocol

As described in our original report (Pfefferbaum et al. 2008), the 3-T MRI data were acquired on a General Electric (Milwaukee, WI) Signa human MRI scanner (gradient strength=40 mT/m; slew rate=150 T/m/s; software version VH3). Four axial sequences were collected: (1) Structural Fast Spin Echo (FSE; FOV=24 cm, TR=10,000 ms TE=14/98 ms, ETL=8, thick=2.5 mm, skip=0 mm, slices=62, refocusing flip angle for echoes 1, 2, 3–8=173.9°, 158.3°, 160.1°); (2) Inversion Recovery Prepared SPoiled Gradient Recalled echo (IRPrepSPGR; FOV=24 cm, TI=300 ms, TR/TE=6.5/1.54 ms, thick=1.25 mm, slices=124); (3) Fieldmap (FOV=24 cm, multislice, dual echo, multi-shot (16) spiral acquisition, x -dim=128, y -dim=128). The SPGR data were aligned such that adjacent pairs of 1.25 mm thick SPGR slices subtended each 2.5 mm thick FSE using custom scanner prescription software, which computed precise slice locations. The data from the spiral acquisition for each echo were gridded and Fourier transformed, and a fieldmap was estimated from a complex difference image between the two echoes (Glover and Lai 1998; Pfeuffer et al. 2002).

The 1.5 T structural data, acquired on a General Electric human MRI scanner, used for this analysis were coronally-acquired FSE images (FOV=24 cm, TR=7,500 ms TE=14/98 ms, ETL=8, thick=4.0 mm, skip=0 mm, slices=47, echo-train flip angle=180°). The 1.5- and 3-T MRI acquisition sessions were separated by 20 to 389 days (mean $\pm$ SD=171.4 $\pm$ 123.1).

Image registration

Voxel-by-voxel maps of R_2 estimates were calculated by two-point log fit for the 3- and 1.5-T FSE data separately. Because these maps were based on FSE rather than true spin echo data, we refer to this measure as an R_2 estimate. Within each subject, the late echo FSE data were registered to the SPGR data (Rohlfing and Maurer 2003). Each subject's SPGR data were then registered to the SPGR channel of the SRI24 atlas (Rohlfing et al. 2008) with non-rigid registration. These transformations were aggregated by concatenation and applied to the early- and late-echo FSE and SPGR data for each subject and all were reformatted, each with a single

tri-cubic interpolation, into 1 mm isotropic data sets in atlas space. R_2 estimates were computed directly in atlas space from the early and late echoes. The 1.5-T late-echo FSE data were registered to the 3-T late-echo FSE data, the transformation added by concatenation to the above transformation train, and early and late echoes reformatted, each with a single tri-cubic interpolation, into 1 mm isotropic data sets in atlas space. R_2 estimates for the 1.5-T data were also computed directly in atlas space from the early and late echoes.

Region of interest volume determination and FDRI calculation

Bilateral caudate, globus pallidus, putamen, and thalamus regions of interest (ROI) were drawn (by A.P.) on the SRI24 atlas presented in the coronal plane. The globus pallidus, putamen, and caudate were drawn on 10 contiguous 1 mm thick slices at an anterior-posterior location that maximized the presence of all three basal ganglia structures (see Fig. 1). The thalamus was drawn on the next 10 contiguous slices posterior to the basal ganglia. The caudate ROI was eroded one pixel and the thalamus ROI was eroded two pixels on a slice-by-slice basis to avoid partial voluming of CSF. Tissue volumes and FDRI were determined for each manually delineated ROI.

The iron concentration was estimated by comparing the R_2 estimates across the two field strengths (1.5 and 3 T) for each ROI (Bartzokis et al. 2007). After maps of the R_2 estimates were constructed, the median R_2 estimate for each ROI for each field strength was computed. The iron estimate (FDRI) was computed as $(R_2 \text{ at } 3 \text{ T} - R_2 \text{ at } 1.5 \text{ T})/1.5$, and yielded a numerical range across all subjects of 0.07 to 4.1 s^{-1} .

Neuropsychological tests

The 10 elderly participants completed neuropsychological tests assessing cognitive and motor performance collected within 1 week of the 1.5-T MRI session. Cognitive status was tested with the *Mini-Mental State Examination* (Folstein et al., 1975) and the *Mattis Dementia Scale* (Mattis, 1988), composed of five subtests: memory, arithmetic, construction, conceptualization, and initiation/perseveration. The *Digit Symbol* substitution test of the Wechsler Adult Intelligence Scale (Wechsler 1981), assessing cognitive-motor speed, required speeded scribing of symbols matched to single-digit numbers; this test was scored in two ways: number of correct symbols written in boxes in 90 s and time to complete filling in all 93 boxes (Sassoon et al. 2007).

Motor ability was assessed with tests of upper limb speed. The *Fine Finger Movement Test* required subjects to turn a knurled rod with their forefinger and thumb, unimanually and then bimanually (Corkin et al. 1986); three, 30-s trials for each condition were administered with the scores being the number of rotations. The *Two-Choice Task* (Cahn et al. 1998) consisted of a box displaying three buttons. A warning tone preceded a light that illuminated above the left or right button. Subjects pressed the button under the light as quickly as possible. Each trial started with the subject pressing down the middle button (start position). Reaction time (time to remove finger from the start position) and movement time (time to press the left or right button minus reaction time) were recorded.

Statistical analysis

Pearson product-moment correlations tested relations between FDRI estimates and performance measures. Because of the small sample size, these parametric correlations were confirmed with nonparametric Spearman Rank Order tests. The analyses tested whether FDRI estimates had functional correlates. We assumed that *higher* FDRI in the basal ganglia structure—caudate, putamen, and globus pallidus—should predict poorer performance because we showed previously that the elderly group had significantly higher FDRI in these structures than did a young healthy group. By contrast, *lower* FDRI in the thalamus should predict poorer

performance, because the elderly group had been observed to have lower FDRI in the thalamus than the younger group.

Results

All bivariate correlations reaching or approaching significance are presented in Fig. 2 for motor test performance relations with FDRI estimates and in Fig. 3 for cognitive test performance with FDRI estimates.

Cognitive test performance correlations with regional FDRI estimates

For basal ganglia structures, higher FDRI estimates in the caudate nucleus were predictive of lower total scores of the Dementia Rating Scale ($r=-0.70$, $p=0.0232$; $Rho=-0.56$, $p=0.0944$). Lower arithmetic scores on the Dementia Rating Scale correlated with higher FDRI estimates in the caudate ($r=-0.64$, $p=0.0481$; $Rho=-0.70$, $p=0.0359$) and putamen ($r=-0.78$, $p=0.0077$; $Rho=-0.65$, $p=0.0495$). As anticipated, correlations between thalamic FDRI and cognitive tests were in the opposite direction to those based on basal ganglia structures. Specifically, thalamic FDRI estimates were predictive of Digit Symbol output ($r=0.77$, $p=0.0088$; $Rho=0.57$, $p=0.0865$), time taken to complete the test ($r=-0.79$, $p=0.0069$; $Rho=-0.56$, $p=0.0909$), and the Mini-Mental State Examination scores ($r=0.66$, $p=0.0397$; $Rho=0.47$, $p=0.1611$) (Fig. 2).

Motor test performance correlations with regional FDRI estimates

Regional FDRI estimates correlated with manual speed in the two-choice test. Specifically, higher FDRI estimates in the caudate correlated with longer reaction time by the left ($r=0.56$, $p=0.0918$) and right ($r=0.79$, $p=0.0062$) hands. In addition, higher FDRI estimates in the globus pallidus correlated with longer reaction time by the right hand ($r=0.65$, $p=0.0421$). Finally, higher FDRI estimates in the putamen correlated with longer movement time by the left ($r=0.70$, $p=0.024$) hand (Fig. 3). Fine finger movement speed showed no significant relationship with FDRI estimates in any region examined. Motor performance per se did not correlate with FDRI estimates in the thalamus.

To examine the potential effect of lag between MRI acquisitions on these correlations, we re-assessed the relations between performance and FDRI estimates with multiple regression analysis and entered as predictors of performance lag time and regional FDRI estimate. In each and every case, lag time made an insubstantial contribution to the variance (p -values ranged between 0.341 and 0.850), and regional FDRI estimates endured as predictors of performance with virtually the same levels of significance observed in the simple correlations.

Selectivity of the FDRI-performance correlations

We used multiple regression analysis to examine different aspects of the selectivity of the FDRI-performance correlations observed with bivariate analysis. In the first analysis, FDRI estimates in the caudate and thalamus were entered as simultaneous predictors of two-choice reaction time of the right (preferred) hand. Together these variables accounted for 82% of the variance but only the caudate iron measure endured as a unique predictor ($p=0.0077$) of reaction time over thalamic iron ($p=0.408$). When the same variables were used as predictors of time to complete the Digit Symbol grid, 80% of the variance was accounted for, but in this case low thalamic iron ($p=0.0096$) was a unique predictor of performance over the caudate iron measure ($p=0.5192$).

A second set of multiple regression analyses tested the contribution of each ROI volume measure to the 10 significant FDRI-performance correlations (Figs. 2 and 3). In short, these analyses revealed that in no case was region-of-interest volume a significant predictor of

performance over and above the FDRI estimate for that tissue sample. In only three cases did the unique contribution of FDRI decline in strength after taking volume into account (Table 1).

Finally, age did not correlate significantly with any cognitive or motor measure in the elderly group. Further, when age was entered as a potential contributor to the performance-FDRI regressions, we found that age did not add significantly and uniquely to the variance explaining the observed relations in this elderly group.

Discussion

This exploration of functional correlates of subcortical FDRI estimates revealed that a greater presence of iron, as indicated by high FDRI estimates in the caudate nucleus, was related to lower total scores on the Dementia Rating Scale, a measure of general cognitive status and screening tool for dementia. None of the elderly participants met criteria for dementia, yet the range on this scale was adequate to produce at least a modest correlation with the implication that the caudate nucleus can influence cognitive ability and be negatively affected by iron deposition. Further, the arithmetic subtest of this dementia scale showed similar negative correlations, whereby better performance related to lower iron deposition estimates in the caudate nucleus and putamen. In our earlier study of this small cohort (Pfefferbaum et al. 2008), of all the structures examined, the putamen had shown the greatest evidence for higher iron deposition with older age.

The fine finger movement test, a speeded task requiring little cognitive input and known to be impaired in patients with motor rigidity caused by Parkinson's disease (Cooper et al. 1991), showed no relation with the iron index in any regions examined. By contrast, longer reaction times in a two-choice test of attention correlated with higher FDRI estimates in the caudate and globus pallidus. Similarly, the time to move one's finger from one target to the other after reacting to the target onset related to higher FDRI in the putamen. Despite the lack of selectivity in relating motor function to only a single brain structure, the motor components of the two-choice test showed relationships with iron deposition in the three subcortical structures known to subserve different aspects of motor function but not in the thalamus, which is known to support different components of cognitive processes, including episodic memory (Aggleton and Sahgal 1993; Harding et al. 2000).

Basal ganglia structures and circuitry are more likely to subserve mnemonic procedures (Pascual-Leone et al. 1993; Saint-Cyr et al. 1988) and habits (Yin and Knowlton 2006) than the thalamus. Further to this process distinction, greater iron deposition in the thalamus, but not basal ganglia structures, was predictive of Digit Symbol speed and accuracy of performance as well as the test of general cognitive status, the Mini-Mental State Examination. In support of this process distinction is the identification of a double dissociation. Specifically, FDRI estimates in the caudate and thalamus accounted for 82% of the variance in two-choice reaction time of the right (preferred) hand. Yet only the caudate iron measure endured as a unique predictor of reaction time over thalamic iron. When the same variables were used as predictors of time to complete the Digit Symbol grid, considered to involve associative learning (Lezak et al. 2004), 80% of the variance was accounted for, but in this case low thalamic iron was a unique predictor of performance over the caudate iron measure. Further support for the selectivity of the iron estimate as contributing to performance levels derives from the assessment of unique variance accounted for by FDRI compared with volume measures of a particular region of interest. In none of the 10 relations identified with simple iron-performance correlations did the volume measure make a significant unique contribution to the overall variance. By contrast, the FDRI estimate endured in contributing uniquely to predicting

performance. Thus, the amount of iron in striatal tissue was a better predictor of performance than the amount of tissue per se.

The retrospective nature of this study imposes certain limitations. In particular, the sample of healthy elderly subjects with neuropsychological and MR imaging data at two field strengths was small, thus limiting our conclusions. The FDRI estimates were based on FSE sequences, which underestimated the classical FDRI index of brain iron. Under ideal conditions of excitation homogeneity, the estimates of R_2 can be made efficient by encoding FSE images with a train of refocusing pulses in a dual-echo sequence, and at 1.5 T, B1 excitation homogeneity is typically excellent on current clinical scanners. At higher field strengths, such as 3 T, there is greater spatial variation in the excitation B1 fields, and power deposition limits for in vivo scanning at high field are more likely to constrain the acquisition prescription than at 1.5 T. For the FSE at 3 T, refocusing trains may be implemented with flip angles lower than 180° , which substantially reduce peak and average power but introduce a bias to the resulting R_2 estimate. The bias term is more pronounced at the periphery of the axial slices of interest, whereas medial regions, such as the central gray matter structures reported herein, are less affected. Thus, the imaging parameters and data quality reported here were adequate to detect robust and regionally differential effects of subcortical iron.

Validation of our MRI iron estimate as an index of the health of aging striatal structures comes from two sources. Firstly, the relations identified between neuropsychological performance and regional iron but not volume measures provide support for the physiological meaningfulness of the FDRI estimate. Secondly, following the lead of Bartzokis et al. (2007), we correlated our regional FDRI estimates with postmortem measurements of iron published in autopsy 52 to 58 cases of nonpathological brains (Hallgren and Sourander 1958). Replicating the observation by Bartzokis et al., the correlation ($r=0.99$, $p=0.01$) was high and provides convergent validation for our in vivo iron estimate as comporting with the postmortem gold standard (Fig. 4).

Bartzokis et al. (2007) had speculated that age-related decline in the ferritin iron index of white matter and thalamus, which contains significant myelin, should be accompanied by myelin breakdown owing to oxidative stress caused by iron release. Although our previous report (Pfefferbaum et al. 2008), on which the current one is based, did not support this speculation with relevant data from MR diffusion tensor imaging (DTI), we did show correlations between FDRI estimates and transverse diffusivity, a diffusion index of myelin degradation yielded with DTI. High FDRI estimates, however, did relate to low diffusion-weighted imaging signal intensity in the thalamus and putamen, likely reflecting signal attenuation from iron.

In conclusion, the present brain structure-function results, which were based on our prior study of age-related iron deposition estimates in subcortical structures, were founded on correlations, which, by definition, cannot connote causality. In the aggregate, nonetheless, these correlations along with the differential presence of iron in subcortical gray matter structures have significant implications for regional differences in an array of MR-based imaging protocols. For example, alterations in MR signal relaxivity related to local iron deposition may contribute to signal heterogeneity in the gray matter spectrum of intensities and consequently add to the challenges of automated segmentation routines in differentiating gray matter from white matter, which is especially difficult to achieve in subcortical regions. The subcortical concentration of iron deposition may also attenuate or accentuate the T_2^* , or Blood Oxygenated Level Dependent (BOLD), effect on which functional MRI (fMRI) studies are based, on tasks invoking iron-laden brain structures. The BOLD effect is a physiological measure between oxygenated and deoxygenated hemoglobin levels; oxygenated hemoglobin concentration is thought to be greatest in brain regions involved in performing a particular cognitive, sensory, or motor task. The systematic and differential increase in iron deposition in basal ganglia structures dependent

on age in striatal and other subcortical structures could affect the BOLD signal without actually affecting a functional neural substrate of an fMRI task. Further, we have already demonstrated the severe signal attenuation by local iron on MR diffusion-weighted imaging (Pfefferbaum et al. 2008). Finally, given the exploratory yet predictable correlations reported here, an excess of iron deposition may be a relevant, noninvasive early marker for the detection of certain neurodegenerative conditions (Killiany 2006).

Acknowledgments

This work was supported by U.S. National Institutes of Health grants AG17919 and AA05965.

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Fig. 1.

Top to bottom: Structural SPGR MR image, T2 image FSE at 1.5 T, T2 image at 3.0 T, and iron image as estimated by FDRI from group averages in common anatomical space constructed for elderly participants. These mid-coronal images are at the same location and level that includes caudate nucleus, globus pallidus, and putamen. The caudate nucleus, globus pallidus, and putamen regions of interest are outlined in white on the SPGR images; the slices containing the thalamus region of interest are posterior to this slice

COGNITIVE TESTS

Fig. 2.
Significant correlations between regional FDRI and cognitive measures

MOTOR TESTS

Fig. 3.
 Significant correlations between regional FDRI and motor measures

Fig. 4.

Correlation between postmortem iron concentrations (mg iron/100 g wet brain) measured in the four structures of interest in 52 to 58 cases and in vivo FDRI estimates in the same subcortical structures of our 10 elderly participants. *Horizontal error bars* standard deviation of the postmortem cases; the *vertical error bars* standard deviation of the in vivo data

Table 1

Multiple regression for regional FDRI and volume as predictors of performance

ROI	Test		FDRI	Volume
Globus pallidus	Reaction time (right hand)	Partial F	3.327	0.038
		p	0.110	0.851
		Total R^2	0.65	–
Caudate	Dementia Rating Scale			
		Partial F	4.879	0.286
		p	0.063	0.609
		Total R^2	0.65	–
	Arithmetic	Partial F	4.879	0.286
		p	0.063	0.609
		Total R^2	0.65	–
	Total	F	14.869	7.578
		p	0.006	0.028
		Total R^2	0.87	–
	Reaction time (left hand)	Partial F	3.227	0.124
		p	0.116	0.735
		Total R^2	0.57	–
Putamen	Reaction time (right hand)	Partial F	11.877	0.011
		p	0.011	0.920
		Total R^2	0.79	–
	Dementia Rating Scale			
		Partial F	11.911	0.554
		p	0.011	0.481
		Total R^2	0.80	–
	Arithmetic	Partial F	11.911	0.554
		p	0.011	0.481
		Total R^2	0.80	–
	Movement time (left hand)	Partial F	5.950	0.011
		p	0.045	0.918
		Total R^2	0.70	–
Thalamus	MMSE	Partial F	6.045	1.154
		p	0.044	0.318
		Total R^2	0.71	–
	Digit Symbol Test			
		Partial F	10.580	0.161
		p	0.014	0.700
		Total R^2	0.78	–
	Number correct	Partial F	10.580	0.161
		p	0.014	0.700
		Total R^2	0.78	–
	Completion time	Partial F	11.838	0.298
		p	0.011	0.602
		Total R^2	0.80	–

Multiple regression partial F s and associated p -values for each brain–behavior relation previously identified with bivariate correlations