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Associations between age, motor function, and resting state sensorimotor network connectivity in healthy older adults

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ABSTRACT

Aging is associated with impaired motor performance across a range of tasks. Both primary neural representations of movement and potential compensatory cognitive mechanisms appear to be disrupted in older age. Here we determined how age is associated with resting state sensorimotor functional connectivity, and whether connectivity strength is associated with motor performance. We investigated the association between age and resting state functional connectivity of several sensorimotor networks in 191 healthy older, right-handed individuals. Regions of interest were defined in the left motor cortex, left putamen, and right cerebellar lobules V and VIII. Analyses were adjusted for head motion, gray matter volume, diastolic blood pressure, and smoker status; we then evaluated whether connectivity is associated with participants' manual motor performance. We found both increased and decreased connectivity within portions of the motor cortical and cerebellar networks after adjusting for covariates. We observed that connectivity increased with age for the motor cortex and cerebellar lobule VIII with the putamen, providing evidence of greater interactivity across networks with age. Higher tapping frequency and greater grip force were associated with stronger connectivity between the motor cortex during resting state, putamen, cerebellar lobule VIII and the insular cortex, suggesting that greater network interactivity may protect against age declines in performance.

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Introduction

Aging is associated with degeneration of the central nervous system and decreases in motor performance (Seidler et al., 2010). Although task-based fMRI studies have provided important knowledge regarding the aging brain and sensorimotor control (Mattay et al., 2002; Noble et al., 2011; Ward and Frackowiak, 2003; Ward et al., 2008), examining resting state functional connectivity strength also has the potential to provide key insights into motor declines in healthy aging. Resting state functional connectivity MRI (rs-fcMRI) involves acquiring functional images across several minutes while participants are not performing a task (Biswal et al., 1995). Resting state activity can be seen as a kind of starting or reference point from which task-related activation emerges. Since its first application, rs-fcMRI has been used to investigate age differences in a variety of brain networks, including sensorimotor networks (Bernard et al., 2012; Bernard et al., 2013; Biswal et al., 1995; Fling et al., 2011; Fling et al., 2012; Langan et al., 2010). Several studies have reported altered resting state connectivity in both healthy aging (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008) and disease (Greicius et al., 2004; Sorg et al., 2007; Wang et al, 2007), but most have studied the default mode network. Far fewer have examined sensorimotor network connectivity in healthy older adults (Roski et al., 2013; Wu et al., 2007), and whether sensorimotor network connectivity strength is associated with motor performance (Bernard et al., 2013; Fling et al., 2012; Langan et al., 2010). Our work and that of others suggests that age is associated with both increased and decreased connectivity strength within several sensorimotor networks, including the motor cortical network, the corticostriatal and the corticocerebellar networks (Bernard et al., 2013; Langan et al., 2010; Roski et al., 2013; Tomasi and Volkow, 2012; Wu et al., 2007), with greater resting state connectivity between the two motor cortices in older versus young adults (Langan et al., 2010), and decreased cortico-cerebellar connectivity (Bernard et al., 2013).

Several previous studies have found connectivity strength to be positively associated with motor performance in older adults,

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suggesting that it may serve as a biomarker of brain health and functional performance (Langan et al., 2010). However, the studies that have related connectivity strength to motor performance in older adults have used small sample sizes, ranging from 10 – 30 participants. In the current study, we applied rs-fcMRI to investigate connectivity strength in several sensorimotor networks in a large sample (nearly 200 participants) of healthy older adults. We investigated motor cortical connectivity, motor corticostriatal connectivity, and motor corticocerebellar connectivity. Based on the existing literature, we hypothesized that: 1. Participants with advanced age would demonstrate reduced sensorimotor network connectivity, similar to what has been observed with default mode network connectivity in older adults (cf. Andrews-Hanna et al., 2007). Further, we hypothesized that: 2. When controlling for age and other confounding variables, better motor performance would be associated with stronger sensorimotor network connectivity, supporting the notion that maintained brain functional connectivity with age is important for sensorimotor function.

Methods

Participants

We included 193 subjects from the first time point of the longitudinal Healthy Aging Brain (LHAB) database study, an ongoing longitudinal project at the International Normal Aging and Plasticity Imaging Center (INAPIC) at the University of Zurich (Zollig et al., 2011) who had complete data for rs-fcMRI and all covariates (i.e., head motion, gray matter volume, smoker status and electronic measurement of diastolic blood pressure (Omron, Model: M6 HEM-7211-E)). Participants were older than 64 years old, right handed, native German speakers, had a mini-mental status examination (MMSE) score >26 (Folstein et al., 1975) and passed the MRI safety standards (e.g., no metallic implants). In addition, participants had no history of neurological diseases (e.g., Parkinson Disease, Alzheimer's Diesease), mental disorders (e.g., depression), diseases of the hematopoietic system (e.g., Anemia, Leukemia), traumatic brain injuries in the last 2 years, and did not suffer from diabetes or tinnitus. After preprocessing, two participants were excluded because of excessive head motion inside the scanner (>2 mm), thus leading to a final sample size of N = 191 (89 males and 102 females, mean age 70.3 ± sd 4.8).

Sensorimotor Assessments

We used a sensory-motor test battery that includes tests of right and left hand motor tapping (Schatz, 2010), right and left hand maximum grip force (Podell, 2010), bimanual visual-motor control (Schufried, 2011) and right and left hand grooved pegboard performance (Merker and Podell, 2010), yielding the following outcome measures: a) maximum grip force, b) taping frequency, c) bimanual visuo-motor coordination (duration in seconds to finish the track, duration off track and duration off track as percentage of the total duration), and d) manual dexterity (duration in seconds). Scores on sensorimotor tests were compared mutually by means of their significance of correlation with age and with each other (see, Table 1). Due to high correlation between several of the motor measures, we chose to include only right hand maximum grip force and right hand motor tapping measures in our fMRI analyses. Tapping speed has been linked primarily to the motor cortex and cerebellum (Lutz et al., 2005), while control of grip force has been linked to these regions as well as the supplementary motor cortex and basal ganglia nuclei (cf., Spraker et al., 2007). Thus we ended up with two tasks that rely on partially overlapping yet distinct motor circuits.

Grip force was measured using a hand dynamometer (Hydraulic Hand Dynamometer, Model: SH5001, Saehan Corporation, Korea). Participants were instructed to sit upright, feet positioned flat on the ground, shoulder in a neutral position, elbow in a 90° flexion, the forearm in a neutral position and the wrist in 0°–30° of extension. Data were collected alternately for the right and left hand with a break of 30 s between measurements. Participants were asked to keep the force stable for 4 s for each trial. Three trials per hand were executed. If the third measurement was the highest, data collection continued until performance dropped below that of a previous measurement. In

Table 1
Correlation between age and motor measures. Abbreviations: R: right hand, L: left hand, Pegtime: pegboard completion time, Tap: # taps, VMC: visual motor control task, Errdur: error duration, Errperc: error percentage, GF: grip force.

Correlations	Age	PegTime_R	PegTime_L	Tap_R	Tap_L	VMC_duration	VMC_errdur	GF_Max_R	GF_Max_L
Age	1								
p value	<0.001								
Number of subjects	191								
PegTime_R	.354**	1							
p value	<0.001								
Number of subjects	190	190							
PegTime_L	.334**	.675**	1						
p value	<0.001	<0.001							
Number of subjects	189	189	189						
Tap_R	−.254**	−.251**	−.203**	1					
p value	<0.001	<0.001	0.005						
Number of subjects	187	187	187	188					
Tap_L	−.134	−.246**	−.291**	.718**	1				
p value	0.066	0.001	<0.001	<0.001					
Number of subjects	188	187	187	188	188				
VMC_duration	.279**	.200**	.252**	−.268**	−.261**	1			
p value	<0.001	0.007	<0.001	<0.001	<0.001				
Number of subjects	178	177	177	178	178	178			
VMC_errdur	.145	.175*	.188*	−.295**	−.270**	.531**	1		
p value	0.054	0.02	0.012	<0.001	<0.001	<0.001			
Number of subjects	178	177	177	178	178	178	178		
GF_Max_R	−.196**	−.128	−.07	.337**	.323**	−.446**	−.339**	1	
p value	0.008	0.086	0.353	<0.001	<0.001	<0.001	<0.001		
Number of subjects	182	181	180	180	180	170	170	182	
GF_Max_L	−.217**	−0.118	−0.092	.335**	.334**	−.442**	−.344**	.953**	1
p value	0.003	0.113	0.218	<0.001	<0.001	<0.001	<0.001	<0.001	
Number of subjects	181	180	180	180	180	170	170	181	181

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

this study grip force refers to the highest performance measured for the right hand (maximum grip force). Motor tapping was measured using the tapping test from the motor performance series (MLS, Vienna Test System). Participants were asked to tap with a pen-like device as many times as possible on a 4 × 4 cm square during 32 s. In this study motor tapping refers to the number of taps in 32 s executed with the right hand. Behavioral measures were excluded from analysis if values exceeded 3 standard deviations from the mean.

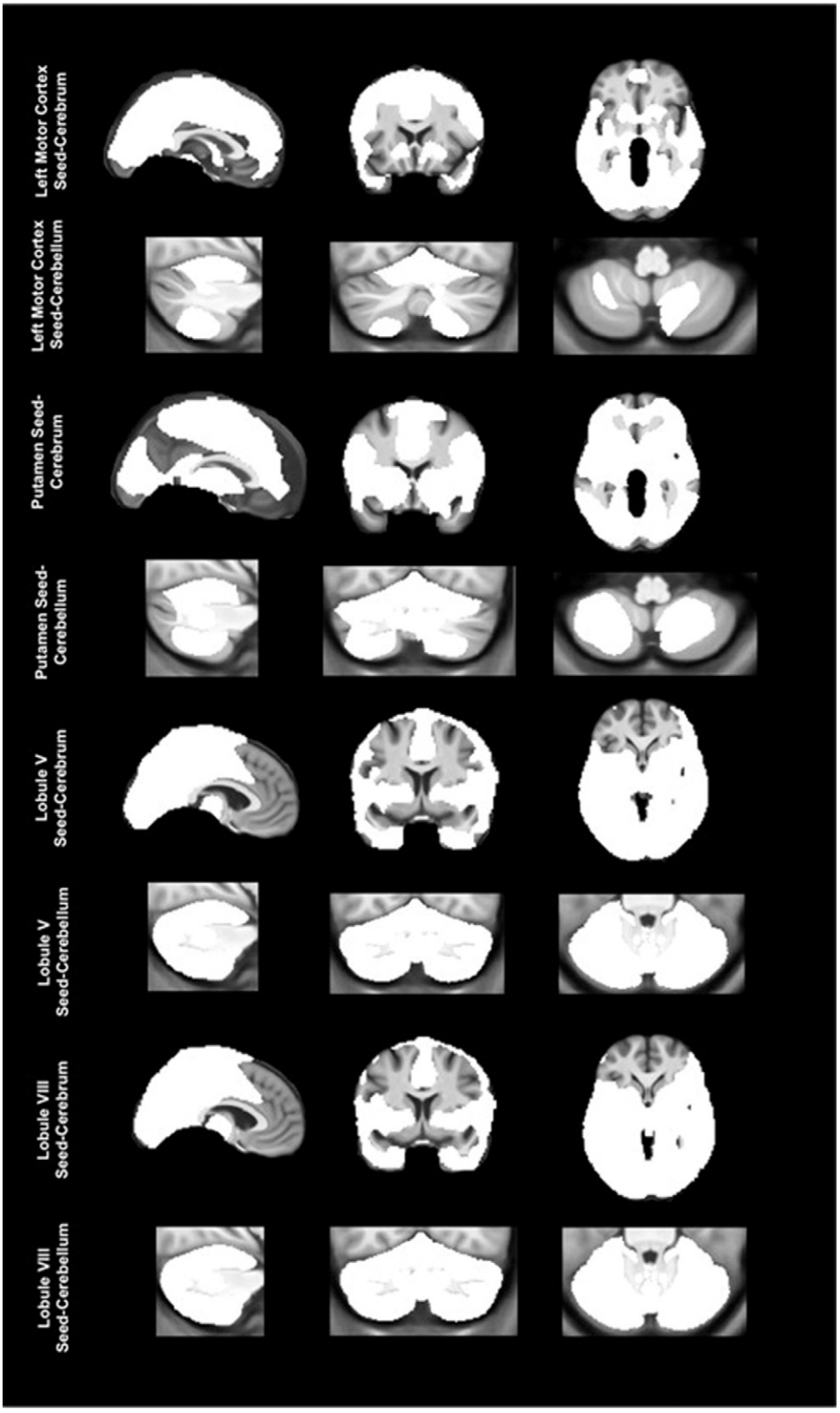

Fig. 1. The statistical threshold for all the seed connectivity masks was set to $p < 0.01^{-16}$ (uncorrected). Each row shows connectivity patterns for the seed regions listed on the left. For example, the top row illustrates cortical regions that were correlated with the time course of activity in the left motor cortex seed; the second row illustrates cerebellar regions that were correlated with the time course of activity in the left motor cortex seed. Left in the images corresponds to the left hemisphere.

fMRI data acquisition

Functional MRI data were collected with a 3 T Philips Ingenia scanner at the University Hospital Zurich. T2*-weighted BOLD image parameters were: TR = 2 s, TE = 21 ms, flip angle = 76°, FOV = 220 × 220 mm, voxel size = 3.43 × 3.43 × 3.5 mm, 43 axial slices, 7.39 min. A visual fixation cross was presented to the subject using a head coil with front facing mirror system. Participants were instructed to look at the cross and not to think about anything in particular.

For each subject two T1-weighted Ultrafast Gradient Echo 3D (TFE; turbo field echo) images were acquired with the following scan parameters: TR = 8.18 ms, TE = 3.799 ms, flip angle = 8°, FOV = 240 × 240 mm, slice thickness = 1.0 mm, 160 sagittal slices; matrix = 256 × 256. In addition, for each subject we collected a T2-weighted multi slice Turbo Spin Echo image with the following scan parameters: TR = 3000 ms, TE = 80 ms, flip angle = 90°, FOV = 230 × 182.87 mm, voxel size = 0.45 × 0.45 × 1.0, slice thickness = 5.0 mm, 28 axial slices, matrix = 488 × 390.

fMRI data preprocessing

First, the rs-fcMRI data were corrected for slice timing using sinc interpolation to the median reference slice and realigned for head motion correction using statistical parametric mapping software (SPM8, Welcome Department of Imaging Neuroscience, Institute of Neurology, London, United Kingdom). Whole brain rs-fcMRI images were normalized to MNI52 space using a multi-step approach. First, the T1 images were averaged using Anatomical Average from the FMRIB Software Library (FSL) toolbox. The averaged T1 images were corrected for field homogeneities using N4ITK (Tustison et al., 2010)

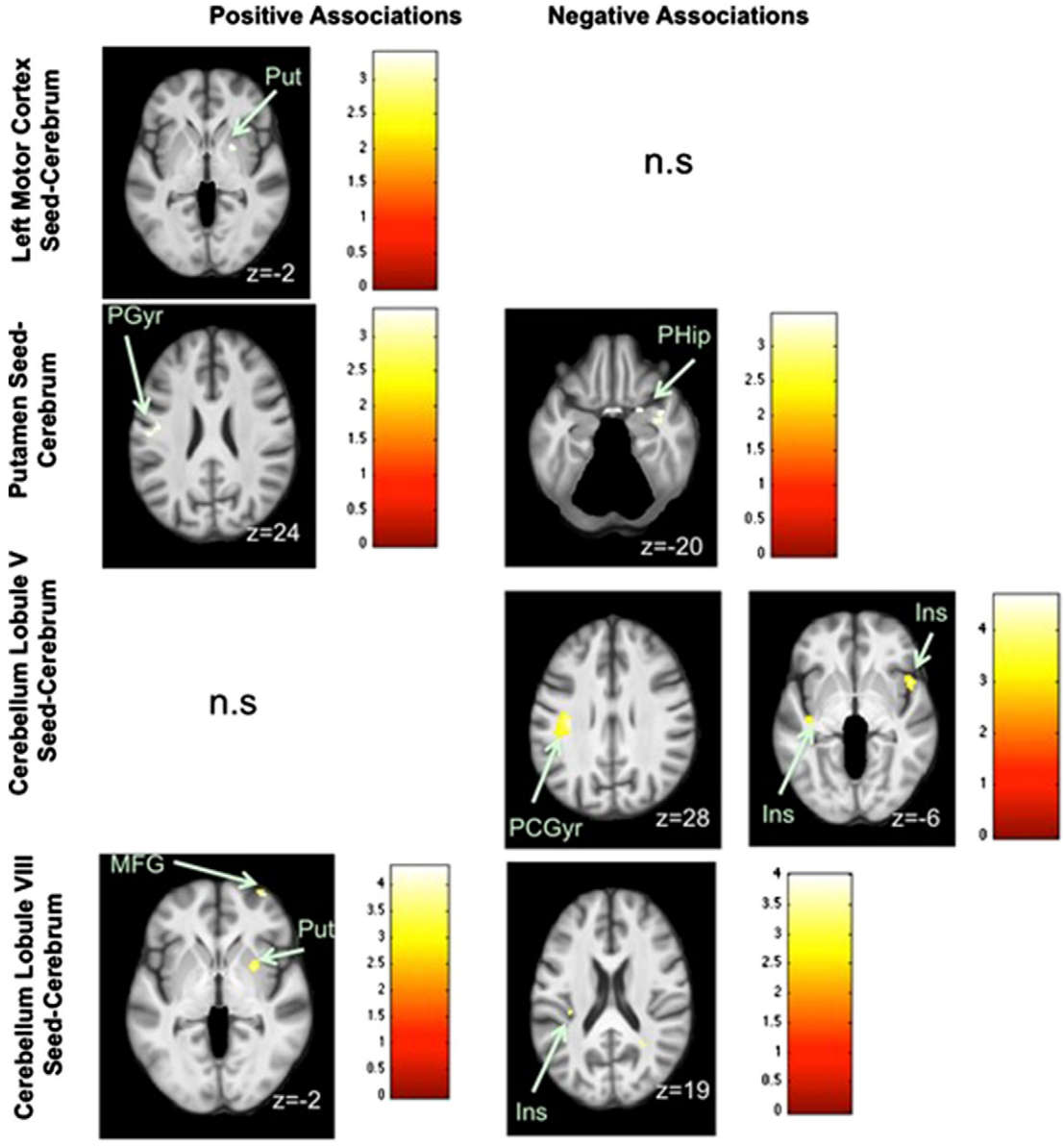

Fig. 2. Seed regions are depicted on the left side of the figure. Axial slices are presented. Significant increases in correlations with age are depicted as positive associations (left column of images) whereas decreases in correlations with age are depicted as negative associations (right column of images). MFG: middle frontal gyrus; Ins: insula; Put: putamen; CGyr: cingulate cyrus; IFGyr: inferior frontal gyrus; PGyr: pre-central gyrus; PCGyr: postcentral gyrus; WM: white matter; MOFG: medial orbito frontal gyrus; PHip: parahippocampal gyrus. Left in the images corresponds to the left hemisphere.

within an intracranial mask that was obtained using FSL's brain extraction tool (BET). The bias field corrected averaged image was skull stripped using FSL's BET and smoothed with a Gaussian kernel of 0.9 mm. SPM8 was used to coregister the smoothed skull stripped T1 average image to the mean rs-fcMRI echo planar image (EPI). The co-registered images were normalized to MNI152 common space using affine registration using Advanced Normalization Tools (ANTS; http://picsl.upenn.edu/software/ants/). The resulting warp parameters were applied to the 4D EPI images that were subsequently smoothed with a Gaussian kernel of 4 mm.

To maximize cerebellar normalization accuracy, we isolated the cerebellum using the SUIT toolbox (Diedrichsen, 2006) and registered the isolated cerebellum to the SUIT template that we previously warped to MNI152 space. The normalization steps for the cerebellum were identical to the ones for the whole brain described above.

Gray matter and intracranial volume

Controlling functional connectivity maps for gray matter (GM) volume (Damoiseaux et al., 2008) and total brain volume (Brodtmann et al., 2009) can increase the reliability of rs-fcMRI studies and can indicate whether changes in functional connectivity maps are associated with brain atrophy. Therefore, we included relative GM volume (GM/intracranial volume (ICV)) as an additional covariate in the connectivity analyses (O'Brien et al., 2006). Probabilistic GM, white matter (WM) and cerebrospinal fluid (CSF) maps were obtained by segmenting the bias field corrected T1 average images using the 'new segment' module under SPM8. ICV was obtained using a multistep approach that started with summing the GM, WM, and CSF maps. The resulting image was thresholded at 0.1, binarized, and holes that did not touch the edge of the field of view were filled. This image was then masked by the 'inskull' mask that was created by feeding the bias field corrected averaged T1 image and the T2 image that was adjusted for bias field inhomogeneity in the same way as the T1 image, into FSL's BET2. To obtain GM and ICV in ml, we multiplied the number of voxels in this final mask by the volume in ml per voxel.

Functional Connectivity Analysis

To generate functional connectivity maps we first extracted the time course of activity from four seed regions: primary motor cortex, striatum, and two in the cerebellum. 4 mm ROI seeds were placed in the left (dominant) brain hemisphere and the right (dominant) cerebellum. The primary motor cortex seed (MNI, Left hemisphere: −38, −26, 50) was taken from a meta-analysis of finger tapping studies by Witt et al. (2008) whereas the putamen seed (MNI Left hemisphere: −28, 2, 4) was taken from a study by Di Martino et al., (Di Martino et al., 2008). We also used cerebellar lobule V and Lobule VIII (MNI, Right Lobule V: 16, −52, −22 MNI, Right Lobule VIII: 20, −57, −53) as seeds because previous reports have identified their activation during finger movements (Wiestler et al., 2011). The Data Processing Assistant for Resting-State fMRI (DPARSF) software package (Chao-Gan and Yu-Feng, 2010) and the Resting-State fMRI Data Analysis Toolkit (REST, http://www.restfmri.net) (Song et al., 2011) were used for calculation of the functional connectivity maps. After normalization and preprocessing (see above) the functional images were spatially smoothed using a Gaussian kernel of 4 mm full width at half-maximum. Linear drift was removed by using DPARSF detrend, and a temporal filter (0.01–0.08 Hz) was applied to reduce low-frequency drifts and physiological high-frequency noise. Six head motion realignment parameters (3 rotations and 3 translations) in addition to signals from the WM and CSF were regressed out during the calculation of functional connectivity maps (cf. Jo et al. 2013). For whole brain analysis WM and CSF signals were extracted based on the mask provided by the REST

Table 2
MNI coordinates of the local maxima of the cortical regions showing functional connectivity with motor cortex, putamen, cerebellum Lobule V and Lobule VIII seed regions that vary with age. All results are $p < .001$ and cluster threshold was set to 10 voxels. *L*, *left*; *R*, *right*.

Seed region correlations in the cerebrum	Type of association	Region	MNI Coordinates			T-value	cluster size
			X	Y	Z		
L motor cortex (N = 191)	Positive	R putamen	22	6	−2	3.43	16
L putamen (N = 191)	Positive	L precentral gyrus	−46	−8	24	3.39	21
	Negative	R superior temporal gyrus	40	2	−20	3.46	42
		R parahippocampal gyrus	22	6	−20	3.36	12
R lobule V (N = 191)	Negative	L post central gyrus	−36	−20	28	4.67	211
		R superior temporal gyrus	48	12	−10	4.19	136
		L superior temporal gyrus	−48	4	−10	3.84	19
		R Cuneus	12	−78	16	3.83	444
		R calcarine sulcus	36	−48	14	3.8	138
		L calcarine sulcus	−24	−60	14	3.68	97
		Precuneus	0	−84	48	3.66	68
		L insula	−40	−18	−6	3.58	25
		L superior temporal gyrus	−42	−42	14	3.49	72
		L temporal lobe, white matter	−36	−58	10	3.41	30
		L middle temporal gyrus	−40	−74	16	3.34	18
R lobule VIII (N = 191)	Positive	R middle frontal gyrus	34	58	−6	4.34	169
		R putamen	28	10	6	4.01	99
		R thalamus	12	0	12	3.68	70
		L white matter cluster encompassing pallidum	−10	2	4	3.57	43
		L middle frontal cortex	−34	46	20	3.44	16
		L thalamus	−16	−10	12	3.27	14
		R inferior frontal gyrus	52	34	4	3.23	10
	Negative	L insula	−38	−26	26	3.98	74
		R parahippocampal gyrus	20	−34	−18	3.97	61
Seed region correlations in the cerebellum							
L motor cortex						n.s.	
L putamen						n.s.	
R lobule V						n.s.	
R lobule VIII						n.s.	

toolkit. For the cerebellum analysis, cerebellar WM and CSF signals were extracted based on 5 mm spherical ROIs. The connectivity maps were converted to z-scores using Fisher's r-to-z transformation. The individual z-values were then entered into a random effect, one-sample *t*-test in a voxel-wise manner to determine the regions with significant positive and negative connectivity with the specific seeds. After calculating voxel-wise connectivity maps for each seed region, we used each connectivity map as an explicit mask for calculating age, motor tapping and grip force related functional connectivity maps. Because of the relatively large number of subjects in our analysis, we chose a rather conservative statistical threshold, ($p < 0.01^{-16}$, uncorrected) for the initial voxel-wise connectivity maps and we evaluated the correlations with age and motor performance within these masks (see, Fig. 1).

We tested the association between age and rs-fcMRI using a general linear model including the main variable of interest as age, and GM as percentage of ICV, diastolic blood pressure, and smoker status as covariates of no interest. We chose to use diastolic blood pressure rather than systolic because of a previous paper documenting an association between diastolic but not systolic blood pressure and brain volume in a sample of 500 participants (Ikram et al., 2008). Moreover, in our sample, systolic and diastolic blood pressure are relatively well correlated (r ~ .60) and the variance of the two metrics is also similar.

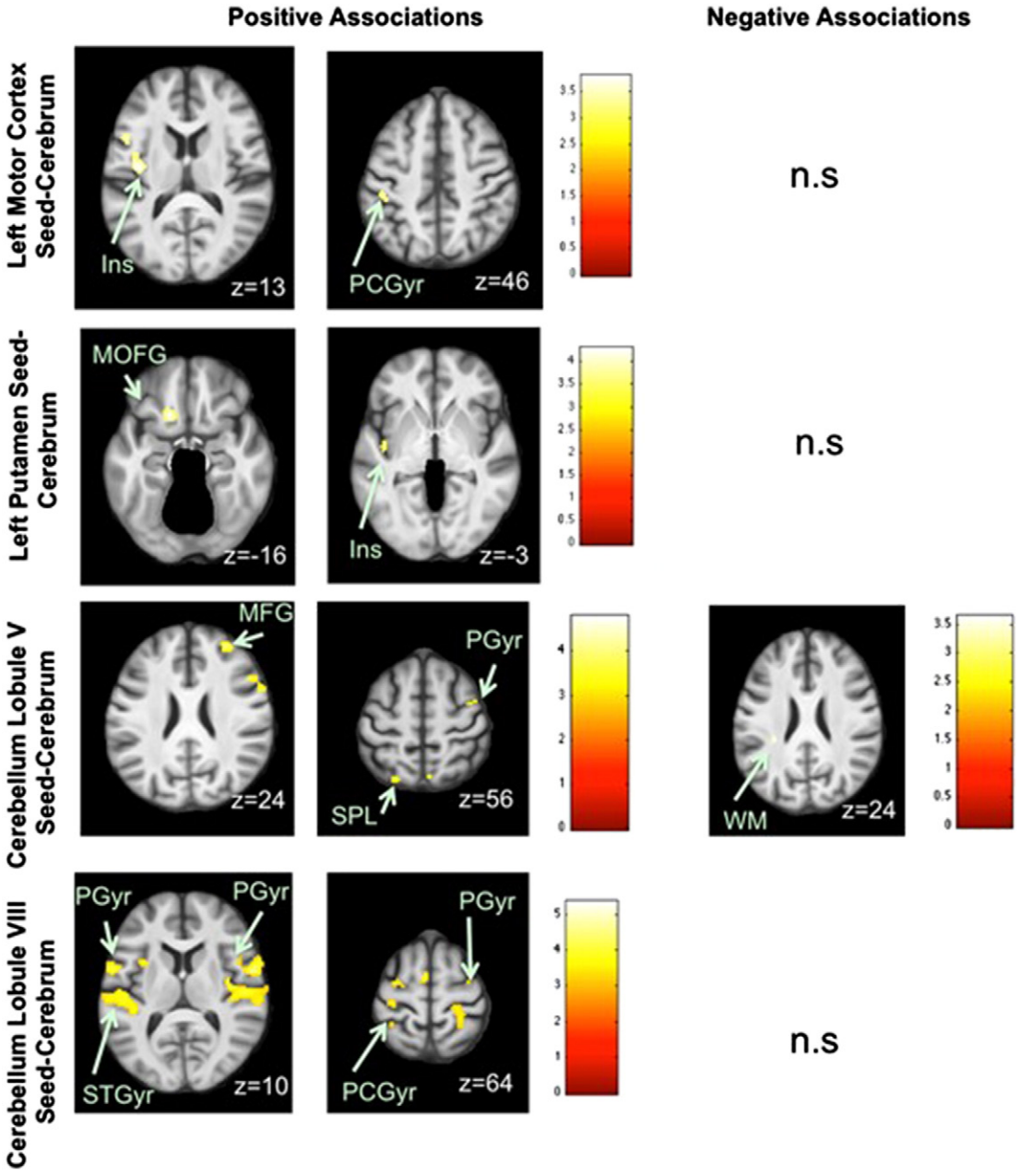

Fig. 3. Areas exhibiting positive and negative connectivity with motor tapping performance. Seed regions are depicted on the left side of the figure. Axial slices are presented. Significant increase in correlations between the seed region and age is depicted as positive associations on the left side of the figure whereas decrease in correlations is depicted as negative associations on the right side. MFG: middle frontal gyrus; Ins: insula; Put: putamen; CGyr: cingulate cyrus; lFGyr: inferior frontal gyrus; PGyr: pre-central gyrus; STGyr: superior temporal gyrus; SPL: superior parietal lobule; PCGyr: postcentral gyrus; WM: white matter; MOFG: medial orbito frontal gyrus. Left in the images corresponds to the left hemisphere.

To explore the association between motor tapping and maximum grip force we used the same general linear model, with either motor tapping speed or maximum grip force as covariates of interest. Consistent with similar studies (Langan et al., 2010), we evaluated these maps using an uncorrected $p < 0.001$ (unless otherwise indicated) with a minimum cluster threshold of 10 voxels.

Results

Behavioral results

After calculating descriptive statistics (mean motor tapping = 189.8 taps/32 s, sd = 21.6; mean maximum grip force strength = 34.1 kg. sd = 10.7), we identified one outlier for the motor tapping task and excluded the participant from further analysis. We therefore retained 187 participants for the motor tapping task and 182 participants for the grip force task. Age was significantly negatively correlated with motor tapping ($r = -0.25$ $p < .001$, $N = 187$) and grip force ($r = -0.20$, $p = .004$, $N = 182$).

Gray Matter Volume Results

We found a significant negative correlation between age and GM volume as percentage of ICV ($r = -0.23$ $p = 0.001$, $N = 191$).

Functional connectivity results

Associations between age and rs-fcMRI

Connectivity between the left motor cortex seed and the right putamen increased in association with age (see Fig. 2); cerebellar lobule VIII and putamen connectivity also increased with age. Moreover, there was lower connectivity strength with greater age between the cerebellar lobule V and VIII seeds with the sensorimotor portion of the insular cortex. Right cerebellar lobule VIII also showed decreased connectivity with the insula and the parahippocampal gyrus with higher age. Additionally, lobule VIII showed increased connectivity with the middle and inferior frontal gyri and the putamen with age. Fig. 2 depicts the areas exhibiting enhanced and decreased connectivity in association with greater age between the seed regions and the rest of

Table 3
MNI coordinates of the local maxima of the cortical regions showing functional connectivity with motor cortex, putamen, cerebellum Lobule V and Lobule VIII seed regions that are associated with motor tapping performance. *L*, *left*; *R*, *right*.

Seed region correlations in the cerebrum for motor tapping contrast	Type of association	Region	MNI coordinates			T-value	Cluster size
			X	Y	Z		
L motor cortex (N = 187)	Positive	L insula	−40	−10	12	3.82	335
		R post central gyrus	54	−18	20	3.62	71
		L post central gyrus	−44	−42	24	3.51	409
		R mid cingulum	6	4	34	3.51	58
		L post central gyrus	−28	−42	52	3.44	32
L putamen (N = 187)	Positive	L middle orbitofrontal gyrus	−16	20	−16	4.31	83
		L insula	−50	10	48	3.66	32
		L middle frontal gyrus	−44	−10	−4	3.51	33
R lobule V (N = 187)	Positive	R infrontal frontal gyrus	16	26	−28	4.79	124
		R superior frontal gyrus	28	54	−12	4.32	110
		R infrontal frontal gyrus	50	36	14	3.93	26
		R middle frontal gyrus	32	50	24	3.87	103
		R middle frontal gyrus	36	−6	62	3.79	70
		R precentral gyrus	54	10	40	3.76	188
		R precuneus	6	−68	60	3.49	46
		R precuneus	2	−78	44	3.49	46
		L superior parietal lobule	−24	−72	56	3.48	26
		R post central gyrus	58	−30	50	3.34	12
	Negative	L parahippocampal cortex	−16	−26	−20	3.64	15
		L white matter	−30	−34	24	3.61	18
R lobule VIII (N = 187)	Positive	L putamen	−22	10	−4	5.37	399
		R precentral gyrus	52	−16	4	4.51	2535
		L superior temporal gyrus	−58	6	6	4.27	303
		L superior temporal gyrus	−52	−42	20	4.21	762
		L superior frontal gyrus	−6	−2	66	3.96	106
		R post central gyrus	26	−28	70	3.8	206
		R middle frontal gyrus	34	−8	60	3.74	39
		L post central	−50	−16	44	3.65	102
		L middle frontal gyrus	−28	−8	64	3.64	39
		L anterior cingulate	−8	26	28	3.58	10
		L post central gyrus	−24	−36	70	3.54	112
		R cingulate cortex	6	20	28	3.51	28
		L precentral gyrus	−32	−24	64	3.51	37
		R middle frontal gyrus	32	44	24	3.46	11
		R inferior parietal lobule	52	−30	46	3.45	56
		L supramarginal gyrus	−62	−52	28	3.36	17
		L cingulate gyrus	−8	−36	40	3.31	13
		R precuneus	8	−74	34	3.28	13
		R cingulate gyrus	6	−18	38	3.26	10
		R cingulate gyrus	10	8	36	3.25	16
Seed region Correlations in the cerebellum							
L motor cortex						n.s.	
L putamen						n.s.	
R lobule V						n.s.	
R lobule VIII	Negative	L cerebellum crus II	−33	−86	−37	3.13	23

the cerebrum. The specific connectivity maps for each seed region are presented in Table 2.

Associations between motor performance and rs-fcMRI

We found that connectivity strength between the seed ROIs (motor cortex, the putamen, and cerebellar lobule VIII) and insula/temporal cortex was stronger in individuals who produced a greater number of taps (see Fig. 3, Table 3). In addition, cerebellar lobule V showed enhanced correlation with the primary and secondary motor areas and frontal regions with higher motor tapping (see Fig. 3).

We also observed decreased connectivity strength in association with a greater number of taps between cerebellar lobule VIII and Crus II (Table 3).

With respect to grip force we found that resting state connectivity strength between the motor cortex seed and the bilateral sensorimotor cortex and supplementary motor area was greater in better performing individuals (see Fig. 4). We found stronger connectivity between the putamen seed region and the medial frontal cortex and precuneus with greater grip strength as well, whereas the cerebellar seeds showed mainly stronger connectivity with the frontal cortex and temporal regions with greater grip force (see Fig. 4). For a full list of significant associations see Table 4.

Cerebellar Lobule V also showed increased connectivity with lobules VIIIa and VIIIb in association with greater grip force (see Fig. 5).

Discussion

The goal of this study was to determine whether and how age and motor performance are associated with rs-fcMRI in a large sample of healthy older adults. Consistent with the existing literature, we found

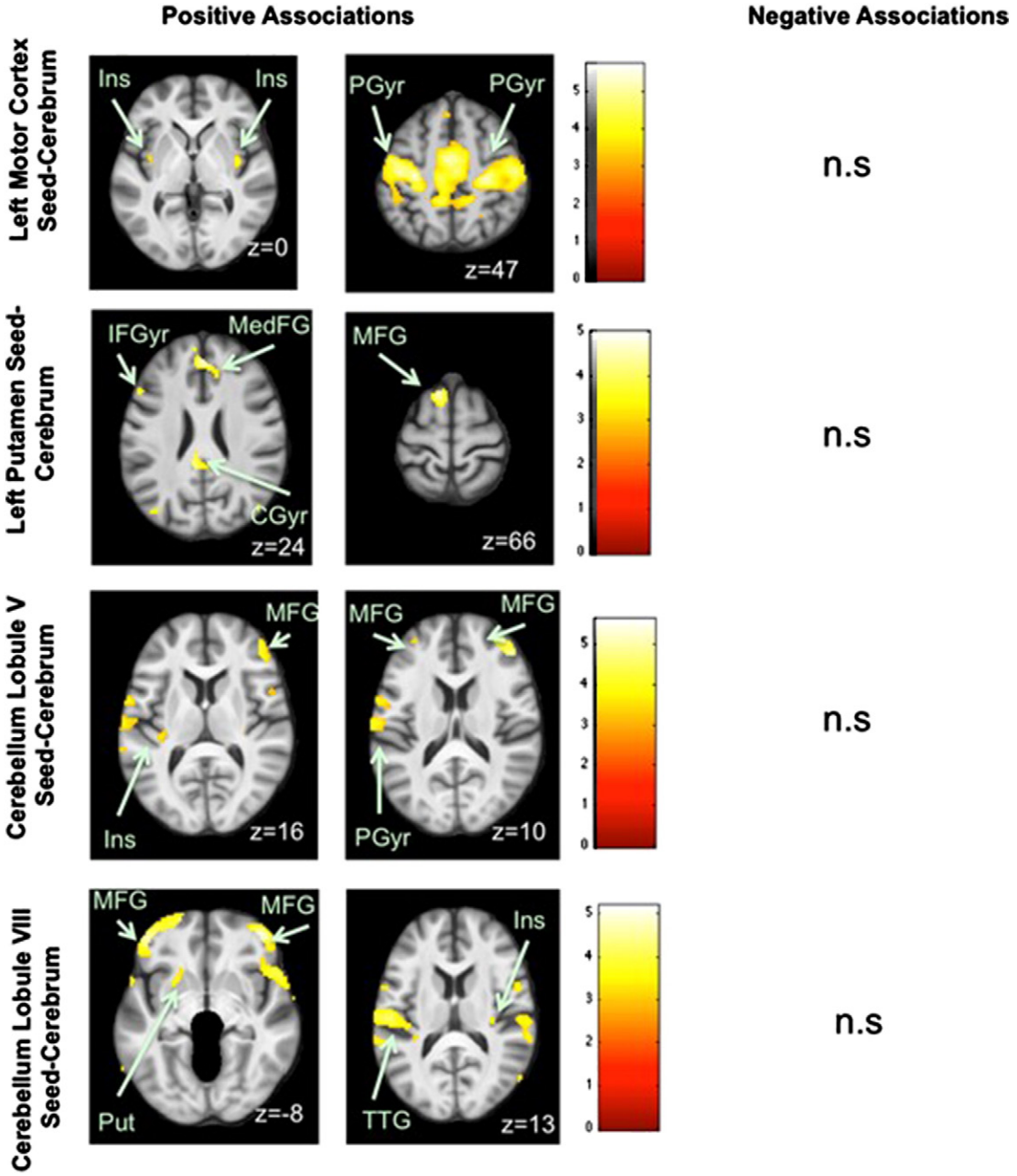

Fig. 4. Areas exhibiting positive and negative connectivity with grip force. Seed regions are depicted on the left side of the figure. Axial slices are presented. Significant increase in correlations between the seed region and grip force strength is depicted as positive associations on the left side of the figure whereas decrease in correlations is depicted as negative associations on the right side. MFG: middle frontal gyrus, MedFG: medial frontal gyrus; Ins: insula; Put: putamen; CGyr: cingulate cyrus; IFGyr: inferior frontal gyrus; PGyr: pre-central gyrus; TTG: transverse temporal gyrus. Left in the images corresponds to the left hemisphere.

Table 4
MNI coordinates of the local maxima of the cortical and cerebellar regions showing functional connectivity with motor cortex, putamen, cerebellum Lobule V and Lobule VIII seed regions that are associated with the maximum grip force strength of the participant. *L*, *left*; *R*, *right*.

Seed region correlations in the cerebrum for grip force contrast	Type of association	Region	MNI coordinates			T-value	Cluster size
			X	Y	Z		
L motor cortex (N = 182)	Positive	R precentral gyrus	30	−24	42	5.73	19576
		L superior frontal gyrus	−8	52	40	4.86	244
		R insula	36	−8	−4	4.58	106
		R cuneus	12	−76	30	3.89	146
		L middle frontal gyrus	−30	32	34	3.88	169
		R superior frontal gyrus	46	32	38	3.74	72
		Lsuperior Temporal Gyrus	−60	−40	18	3.67	84
		R middle frontal gyrus	54	36	18	3.52	22
		L precuneus	−18	−64	14	3.5	170
		L insula	−36	−4	0	3.5	43
		Frontal superior medial	−4	38	46	3.46	27
		L insula	−32	−20	16	3.44	46
		L frontal superior medial	−2	40	36	3.23	12
L Putamen (N = 182)	Positive	L precuneus	−4	−74	36	5.01	138
		L inferior frontal gyrus	−26	20	−14	4.63	98
		L superior frontal gyrus	−10	18	66	4.6	328
		R medial frontal gyrus	2	46	24	4.59	289
		R middle temporal gyrus	52	−76	20	4.59	115
		L inferior frontal gyrus	−54	24	14	4.48	209
		L middle temporal gyrus	−50	−62	18	4.43	328
		L cuneus	−2	−102	6	4.28	42
		L cingulate gyrus	−8	−34	26	4.26	336
		R middle frontal gyrus	34	12	40	4.13	164
		R cuneus	8	−102	6	3.93	39
		L middle temporal gyrus	−50	−12	−16	3.87	149
		R inferior orbito frontal cortex	40	24	−18	3.79	156
		L middle frontal gyrus	−40	56	0	3.59	66
		R superior temporal gyrus	58	−54	10	3.57	96
		L lentiform nucleus	−22	−12	−2	3.54	28
		L medial frontal gyrus	−16	56	−2	3.52	33
		R middle temporal gyrus	46	−38	0	3.51	79
		R posterior cingulate	16	−56	12	3.5	32
		L middle temporal gyrus	−56	−40	−4	3.48	41
		L middle temporal gyrus	−66	−52	0	3.4	18
		L white matter	−22	32	38	3.37	22
		R middle frontal gyrus	40	34	−2	3.43	19
		R inferior temporal gyrus	66	−54	−12	3.38	11
		L middle frontal gyrus	−42	4	50	3.32	22
R lobule V (N = 182)	Positive	R frontopolar cortex	38	58	−4	5.62	917
		L post central gyrus	−68	−16	14	4.14	190
		R cingulate gyrus	18	−26	40	3.97	48
		L precentral gyrus	−62	4	12	3.94	143
		L inferior temporal gyrus	−52	−20	−24	3.79	48
		L precuneus	−2	−58	66	3.7	217
		R cingulate gyrus	4	−12	38	3.67	251
		R occipital lobe	2	−102	4	3.59	20
		R middle temporal gyrus	64	−64	0	3.58	54
		L insula	−36	−26	10	3.56	46
		R claustrum	32	−20	2	3.56	57
		R parietal lobe	28	−30	42	3.53	22
		L middle frontal gyrus	−34	50	16	3.46	30
		L superior temporal gyrus	−66	−36	10	3.4	11
		L putamen	−24	14	−6	3.4	11
		R middle temporal gyrus	72	−42	2	3.34	12
		R superior frontal gyrus	22	−2	70	3.32	12
		L precuneus	−2	−70	56	3.31	22
		R precentral gyrus	54	10	12	3.28	17
R lobule VIII (N = 182)	Positive	R inferior frontal gyrus	44	50	−10	5.19	1975
		L middle frontal gyrus	−46	48	−8	4.68	556
		L superior temporal gyrus	−62	−20	2	4.62	843
		L inferior temporal gyrus	−60	−58	−22	4.35	115
		L superior temporal gyrus	−62	8	6	4.2	257
		R precentral gyrus	38	−10	0	3.8	242
		R middle temporal gyrus	62	−62	0	3.76	116
		L superior temporal gyrus	−66	−36	10	3.76	82
		L putamen	−24	16	−2	3.75	132
		R insula	32	18	8	3.56	19
		Precuneus	0	−68	20	3.56	42
		R insula	34	−18	22	3.48	47
		R Temporal_Inf_R	54	−2	−44	3.48	19
		R white matter	32	−34	34	3.47	15
		L Frontal_Inf_Orb_L	−26	26	−12	3.44	88

(continued on next page)

Table 4 (*continued*)

Seed region correlations in the cerebrum for grip force contrast	Type of association	Region	MNI coordinates			T-value	Cluster size
			X	Y	Z		
		L middle temporal gyrus	−64	−60	0	3.41	33
		R Temporal_Inf_R	58	−64	−20	3.41	13
		L transverse temporal gyrus	−34	−36	12	3.33	13
		R occipital lobe	56	−70	16	3.25	15
Seed region correlations in the cerebellum							
L motor cortex (N = 182)						n.s.	
L putamen (N = 182)						n.s.	
R lobule V (N = 182)	Positive	R lobules I–IV	17	−42	−25	3.89	285
		L lobule VIIIa	−31	−45	−58	3.75	358
		R lobule VIIIa	30	−40	−54	3.65	234
		R lobule VIIIb	14	−56	−64	3.57	22
		R lobule VI	29	−52	−22	3.51	145
		L crus II	−18	−90	−27	3.48	49
		L lobule VIIIa	−17	−68	−61	3.36	25
		R lobule VI	16	−56	−23	3.34	10
		L lobule V	−14	−49	−12	3.26	79
R lobule VIII (N = 182)	Positive	R lobule VIIIb	15	−57	−63	4.56	449
		L lobule VIIIb	−15	−66	−61	3.66	374

that age was associated with decreases in maximum grip force, the amount of taps produced in a set period of time, and gray matter volume (Seidler et al., 2010). We also observed complex relationships between rs-fcMRI with age; that is, connectivity increased within some portions of the sensorimotor networks with age but decreased within other portions. For the overwhelming majority of observed associations between connectivity and performance, greater connectivity was linked to better performance.

Functional connectivity and age

In a sample of healthy older adults ranging from 65 to 87 years, we found several regions of increased sensorimotor network connectivity with age. For example, left motor cortex and right putamen connectivity was positively associated with age, as was connectivity between right cerebellar lobule VIII with the bilateral inferior frontal gyri and the thalamus. Interestingly, connectivity between the right cerebellar lobule V and the left postcentral gyrus, the bilateral calcarine fissures, and several regions in the temporal lobe was negatively associated with age, as was connectivity between right lobule VIII with the left insula and the right parahippocampal gyrus. The only other study that we are aware of which has examined age effects on cerebellar connectivity is a paper recently published by our group (Bernard et al., 2013). In that study we evaluated fewer subjects (35 young versus 38 older adults) and evaluated age differences with cross sectional group comparisons. We found that, based on the cerebellar seed regions investigated, older adults exhibited both reduced and enhanced connectivity relative to young adults. It is also interesting that lobules VIII and V exhibit differing connectivity patterns with age. We chose to investigate connectivity with cerebellar lobules V and VIII given recent interest in cerebellar organization. Both of these structures are known to have motor functions and exhibit resting state functional connectivity with the primary motor cortex (Bernard et al., 2013). However, they appear to have differential functions. For example, lobules IV, V, and VI contribute to visuomotor and force field adaptation tasks, while lobules VIIIa and VIIIb do not (Bernard et al., 2013; Donchin et al., 2012; Burciu et al., 2014). Moreover, lobule V exhibits consistent somatotopic digit representations while the orientation differs across subjects in lobule VIII (van der Zwaag et al., 2013).

We also observed age-related decreases in connectivity between cerebellar seed regions and the bilateral insula. Two voxel-based morphometry (VBM) studies have reported notable declines in gray matter density in the insula with age (Good et al., 2001; Sowell et al., 2003). It is notable that even after correcting for percentage of gray matter we observed significant decreases in connectivity with this region. One possible explanation comes from a recent study by Roski et al. (2013), which reported an age-related reduction in posterior insular connectivity with the supplementary motor area and other sensorimotor regions. The authors suggested that these connectivity declines result due to decreases in sensory processing that occur with aging.

A highly consistent finding in the aging literature is decreasing default network connectivity with increasing age (Andrews-Hanna et al., 2007; Bluhm et al., 2008; Damoiseaux et al., 2008). While research on aging and sensorimotor connectivity is scant by comparison, a few emerging studies have reported *increasing* connectivity in motor networks with age (cf. Langan et al., 2010; Ystad et al., 2011; Fling et al., 2012; Song et al., 2014). Furthermore, Mathys et al. (2014) have reported increasing connectivity with age between the subthalamic nucleus with the sensorimotor cortex and putamen, but decreasing connectivity with the caudate nucleus, thalamus, and insula. In several cases, increasing sensorimotor connectivity with age has been suggested to be compensatory (cf. Mathys et al., 2014; Song et al., 2014). Our current findings of greater connectivity strength linked to better manual motor function support this notion. We have however also documented that increased interhemispheric motor connectivity with age is associated with reductions in interhemispheric inhibition (Fling et al., 2012; Fling and Seidler, 2012) suggesting that it may emerge from age-related declines in inhibitory neurotransmitters.

One hypothesis that has been put forth to explain reductions in functional connectivity with age is the notion that it may arise from decreased dopamine levels (Ferreira and Busatto, 2013). However, this hypothesis might suggest then that patients with Parkinson's disease should exhibit even greater hypoconnectivity than older adults, but in fact the opposite has been reported with Parkinson's patients who are off medication (Kwak et al., 2010; Yu et al., 2013). Clearly more work is needed to understand the effects of age on functional connectivity.

Another potential contributing factor to negative associations between connectivity and age could be age related declines in gray matter volume. However, in the current study and others (Bernard et al., 2013; Damoiseaux et al., 2008; Onoda et al., 2012) older adults still exhibit decreased resting state functional connectivity even after adjusting for gray matter volume. Thus the factor(s) underlying connectivity reductions in older adults remain as yet to be determined.

Post-hoc effect size calculations for the current study and two previous studies (Bernard et al., 2013; Langan et al., 2010) showed large effect sizes (Cohen's $d > 0.7$) for the association between age and

connectivity. Therefore, we do not think that differences between the current study and others are due to over powering in the current sample. To address the functional significance of resting state sensorimotor connectivity, we examined how connectivity relates to motor performance in older adults, as elaborated below.

Motor measures and functional connectivity

In general, we found that both grip strength and the ability to rapidly produce taps were positively associated with sensorimotor network connectivity. For example, individuals with greater resting state connectivity between the left motor cortex and the bilateral postcentral gyrus and the left insula exhibited greater grip strength and produced a greater number of taps in 32 s. Similarly, those with greater connectivity between cerebellar lobule V with the pre- and postcentral gyri and several prefrontal cortical regions exhibited better motor performance than their peers. Lobule VIII connectivity with bilateral pre- and postcental gyri and middle frontal gyri was positively associated with motor tapping performance. These associations between connectivity strength and task performance echo what is known about the neural bases of finger tapping and force production. For example, tapping speed has been linked primarily to the motor cortex and cerebellum (Lutz et al., 2005), and we found that regions exhibiting greater connectivity with the motor cortex, cerebellar lobule V, and putamen were linked to faster tapping speed. Additionally, control of grip force has been linked to these regions as well as the supplementary motor cortex and basal ganglia nuclei (cf. Spraker et al., 2007). Here, we found that connectivity between the motor cortex with the bilateral sensorimotor cortex and the supplementary motor area was associated with greater grip force. In general, these findings suggest that older adults who maintain stronger sensorimotor connectivity outperform their peers on measures of manual motor function.

It is interesting that connectivity strength between motor regions and more traditional "cognitive" regions in the prefrontal cortex is associated with motor function. Several previous studies have suggested that motor control becomes more cognitively demanding with age (Seidler et al., 2010), and indeed recruitment of prefrontal regions during performance of a motor task is associated with better

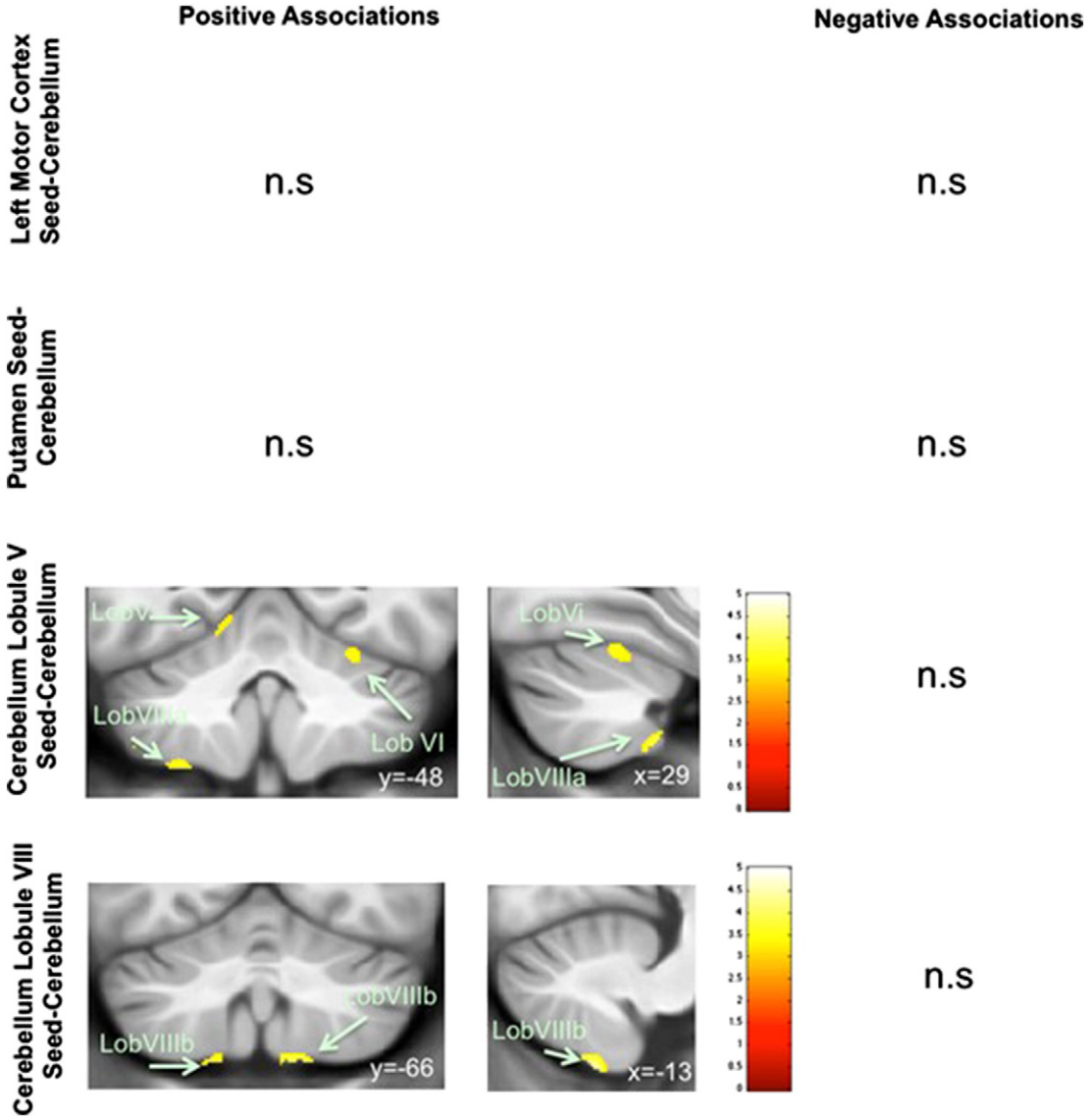

Fig. 5. Areas exhibiting positive and negative connectivity with the maximum strength during the grip force task in the cerebellum. Seed regions are depicted on the left side of the figure. Axial slices are presented. Significant increase in correlations between the seed region and age is depicted as positive associations on the left side of the figure whereas decrease in correlations is depicted negative associations. Abbreviation, Lob: lobule. Left in the images corresponds to the left hemisphere.

performance for older adults (Heuninckx et al., 2008). Our findings suggest that the extent to which motor and prefrontal interactions take place at rest might be an indication of motor performance (measured outside of the scanner) in healthy older adults. It would be of interest to determine whether motor-prefrontal resting state connectivity also predicts the extent to which prefrontal regions are recruited during the performance of a motor task. A substantial body of work suggests that over-activation in the prefrontal cortex seen in older adults serves a compensatory role; that is, it is associated with better task performance (Park and Reuter-Lorenz, 2009).

Some studies have reported that activation of the ipsilateral motor cortex is associated with better task performance for older adults (Mattay et al., 2002) while we have previously observed the opposite association (Langan et al., 2010). Here, we found that stronger resting state connectivity of the left motor cortex and cerebellar lobules V and VIII with both the left and the right pre- and postcentral gyri is associated with better performance. It has been reported that older adults place greater reliance on the ipsilateral primary sensorimotor cortex when compared to young adults during a grip force task (Ward et al., 2008). Moreover, we also found an effect of increased connectivity with increases in grip force strength within the cerebellum. Previous work has reported increased bilateral activation in the cerebellum of older participants during motor task performance (Ward and Frackowiak, 2003).

We also observed that greater connectivity between the motor cortex and the posterior insula was associated with better motor tapping and grip force production. Moreover, a recent resting state functional connectivity study also found that the posterior insula resting state signal is correlated with those of the premotor, sensorimotor, and supplementary motor regions (Cauda et al., 2011). Previous studies have reported that the posterior insula plays a significant role in sensorimotor integration (Rizzolatti and Wolpert, 2005).

It is interesting that resting state functional connectivity was correlated with performance measured "off line", outside of the scanner. Resting state connectivity can be viewed as providing a potential pre-task activation or connectivity level, which could be beneficial for task performance or not optimal. Indeed several studies have shown that resting state functional connectivity is predictive of brain activation levels during subsequent task performance (cf. Langan et al., 2010) and that it is related to underlying structural connectivity metrics (Fling et al., 2012; Hermundstad et al., 2013). Moreover, our finding of increased resting state connectivity associated with better motor performance in older adults is compatible with what has been reported in young adults. For example, greater connectivity in hippocampal networks is associated with better memory task performance (Wang et al., 2010) and greater caudate network connectivity predicts better motor sequence learning (Stillman et al., 2013).

One potential limitation is that the current approach investigates age in a cross-sectional rather than longitudinal fashion; however, we are currently following this cohort of individuals and acquiring data each year. It will be of interest to determine whether time point one measures are predictive of future function and / or can serve as indicators of potential future declines. Moreover, although we reported results with an uncorrected p value of $<.001$, it is notable that we observed relationships even after controlling for age, gray matter volume, and other potential confounding health variables. It is also to be expected that our effect sizes might be smaller than much of the previous literature which examines the effects of age over a large range, typically spanning both young and older adults.

Conclusions

In conclusion, we found both positive and negative associations between sensorimotor network connectivity strength and age, even after adjusting for potential confounding variables. Motor performance was generally linked to stronger connectivity within these networks in healthy older adults. It remains to be seen whether this holds for longitudinal measurements. It would also be important to examine in the future whether and how various interventions – such as exercise, motor coordination, diet, etc. – affect functional connectivity patterns in older adults.

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