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Disrupted cortico-cerebellar connectivity in older adults

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ABSTRACT

Healthy aging is marked by declines in a variety of cognitive and motor abilities. A better understanding of the aging brain may aid in elucidating the neural substrates of these behavioral effects. Investigations of resting state functional brain connectivity have provided insights into pathology, and to some degree, healthy aging. Given the role of the cerebellum in both motor and cognitive behaviors, as well as its known volumetric declines with age, investigating cerebellar networks may shed light on the neural bases of age-related functional declines. We mapped the resting state networks of the lobules of the right hemisphere and the vermis of the cerebellum in a group of healthy older adults and compared them to those of young adults. We report disrupted cortico-cerebellar resting state network connectivity in older adults. These results remain even when controlling for cerebellar volume, signal-to-noise ratio, and signal-to-fluctuation noise ratio. Specifically, there was consistent disruption of cerebellar connectivity with both the striatum and the medial temporal lobe. Associations between connectivity strength and both sensorimotor and cognitive task performances indicate that cerebellar engagement with the default mode network and striatal pathways is associated with better performance for older adults. These results extend our understanding of the resting state networks of the aging brain to include cortico-cerebellar networks, and indicate that age differences in network connectivity strength are important for behavior.

Introduction

Aging is associated with cognitive and motor declines (Park and Reuter-Lorenz, 2009; Seidler et al., 2010). Older adults show declines in cognitive function (Park et al., 2001), and also have deficits in motor learning (Anguera et al., 2011; Bo et al., 2009). Neuroimaging research has demonstrated that older adults show more bilateral patterns of brain activation during both cognitive (Reuter-Lorenz et al., 2000) and motor tasks (Mattay et al., 2002; Naccarato et al., 2006). Furthermore, there are age differences in resting state functional brain networks (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Langan et al., 2010; Wiggins et al., 2011, 2012; Wu et al., 2007), along with differences in brain volume (Raz et al., 2005). Investigations of the neural substrates of performance declines with age have focused heavily on the cerebral cortex, despite known age differences in cerebellar volume, and contributions of this structure to both motor and cognitive behaviors (Bernard and Seidler, in press; Hoogendam et al., in press; Raz et al., 1998, 2001; Stoodley et al., 2012). Given the diverse behavioral functions of the cerebellum, along with its known structural differences in young and older adults, further investigation in aging, particularly with respect to resting state networks, is warranted.

Resting state functional connectivity MRI analyses have provided insight into the networks of the aging brain. The default mode network (DMN) has been especially well studied (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008). Connectivity within the DMN is decreased in older adults and is related to performance on cognitive tasks (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008). There are also age differences in functional motor cortical connectivity, which are associated with motor performance (Langan et al., 2010; Wu et al., 2007). While these studies indicate that there are age differences in cortical resting state brain networks, none has investigated cerebellar connectivity. Investigating resting state cortico-cerebellar networks may provide key insight into both the motor and cognitive declines associated with healthy aging.

The cerebellum plays a role in a wide variety of motor and cognitive behaviors, and the structure contains a well-defined functional topography (Stoodley and Schmahmann, 2009; Stoodley et al., 2012). Anterior

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lobules and lobules VIIIa and VIIIb are associated with motor functions, whereas the remaining posterior lobules are associated with cognitive functions. Furthermore, there are connections between anterior regions of the cerebellum (specifically, lobules IV and V) as well as lobule VIII in the posterior cerebellum with the motor cortex, and separate loops connecting the lateral and posterior cerebellum (particularly Crus I and Crus II) and the prefrontal cortex (Middleton and Strick, 2001; Kelly and Strick, 2003; for a review see Strick et al., 2009). Converging evidence for dissociable structural connections has also been found in the human brain (Salmi et al., 2009). Resting state cortico-cerebellar networks have been extensively mapped in young adults (Bernard et al., 2012, in press; Buckner et al., 2011; Habas et al., 2009; Krienen & Buckner, 2010; O'Reilly et al., 2010). However, a gap in the literature exists with respect to age differences in cortico-cerebellar network connectivity. Quantifying these age differences may provide key insights into age declines in motor and cognitive function. Given the functional topography within the cerebellum, and its roles in both motor and cognitive task performances, it is a potentially important target of investigation in aging.

In the current study we used resting state functional connectivity magnetic resonance imaging to map large-scale cortico-cerebellar networks in older adults. We compared these results with maps previously reported for young adults (Bernard et al., 2012), while controlling for the potentially confounding influences of signal-to-noise ratio (D'Esposito et al., 2003) and cerebellar volume. Given the indication of decreased resting state connectivity in older adults' cortical networks (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Wu et al., 2007), we hypothesized that cortico-cerebellar connectivity would also be decreased in older adults. A subset of older adult participants completed a sensorimotor and cognitive test battery, allowing us to investigate the relationships between cortico-cerebellar network connectivity strength and behavior. We predicted that connectivity strength of lobules in the anterior cerebellum would be associated with sensorimotor task performance, while connectivity strength of posterior lobules (excluding lobules VIIIa and VIIIb which are associated with motor functions), particularly Crus I and Crus II would be associated with cognitive behaviors.

Method

Participants

We recruited 35 older (age ± stdev; 64.55 ± 6 years, 13 females) and 38 young adults (22.76 ± 2.95 years, 17 females) from the University of Michigan and greater Ann Arbor community as part of a larger study. All participants were healthy, with no history of neurological or psychiatric disorder, and had no contraindications for fMRI scanning. Participants signed a consent form approved by the University of Michigan Medical Institutional Review Board. Three young adult participants were excluded from analyses due to motion artifacts, and two young adult participants were excluded due to technical problems during data collection, leaving a total of 33 (15 female) young adult participants. Data from the young adults have been previously reported (Bernard et al., 2012) and serve as an age comparison group for the older adults in this study.

fMRI data acquisition

Functional MRI data were collected with a 3T GE Signa scanner at the University of Michigan. A single-shot gradient-echo reverse spiral pulse sequence (Glover and Law, 2001) was used to collect either 300 (all older adults and n = 12 young adult participants) or 240 (n = 18 young adult participants) T2*-weighted BOLD images (TR = 2 s, TE = 30 msec, flip angle = 90°, FOV = 220 mm × 220 mm, voxel size = 3.4 mm × 3.4 mm × 3.2 mm, 40 axial slices). For the structural images, a 3D T1 axial overlay (TR = 8.9 msec, TE = 1.8 msec, flip angle = 15°, FOV = 260 mm, slice thickness = 1.4 mm, 124 slices; matrix = 256 × 160) was acquired for anatomical localization. To facilitate normalization, a 110-slice (sagittal) inversion-prepped T1-weighted anatomical image using spoiled gradient-recalled acquisition in steady state (SPGR) imaging (flip angle = 15°, FOV = 260 mm, 1.4 mm slice thickness) was acquired. A visual fixation cross was presented to the subject using a rear projection visual display. Participants were instructed to look at the cross and not to think about anything in particular. A pressure belt was placed on the abdomen of each subject to monitor the respiratory signal. A pulse oximeter was placed on the subject's finger to monitor the cardiac signal. The respiratory, cardiac, and fMRI data collection were synchronized such that the onset of the resting state scan was time-locked with the onset of collection of both the cardiac and respiratory signals.

fMRI data analysis

The functional MRI data were preprocessed as part of the standard processing stream at the University of Michigan. First, K-space outliers in the raw data greater than two standard deviations from their mean were replaced with the average of their temporal neighbors. Second, images were reconstructed using field map correction to remove distortions from magnetic field inhomogeneity. Third, physiological variations in the data from the cardiac and respiratory rhythms were removed via regression (Glover et al., 2000). This removed the effects of the first and second order harmonics of the externally collected physiological waveforms. Fourth, slice-timing differences were corrected using local sinc interpolation (Oppenheim et al., 1999). Lastly, we used MCFLIRT in the fMRIB Software Library (Jenkinson et al., 2002) to perform motion correction (using the 10th image volume as the reference). For all participants, head motion was less than 0.1 mm in the x, y, or z direction (young adult average = 0.09, 0.03, and 0.02 mm and older adult average = .006, .004, and .003 mm, in the x, y, and z directions, respectively). Structural images were skull-stripped using FSL and we then registered the 3D T1 SPGR to the functional images using Advanced Normalization Tools (ANTS; Avants et al., 2008; Penn Image Computing & Science Lab, http://www.picsl.upenn.edu/ANTS/). The data were then normalized to MNI space using ANTS. Additionally, because of the potential for distortions when normalizing the cerebellum to standard space (Diedrichsen et al., 2009), the cerebellum was normalized separately to a spatially unbiased atlas template (SUIT; Diedrichsen, 2006; Diedrichsen et al., 2009) also using ANTS. This resulted in normalized whole-brain structural and functional images, and separately normalized cerebellar structural and functional images.

Functional connectivity analysis

Because of the variable duration of the resting state scans, only the *first* 8 min of functional data were used in our analyses. Additionally, the first five volumes were discarded to all for scanner equilibration. The following procedures were used to generate functional connectivity maps (low frequency timecourse correlation maps). The data were first filtered using a second order dual-pass band-pass filter to examine the band of interest (0–0.08 Hz) and to exclude higher frequency sources of noise such as heart rate and respiration (Biswal et al., 1995; Peltier et al., 2003).

Second, the timecourse of BOLD activity was extracted from each of the 10 lobules within the right cerebellar hemisphere and 8 lobules within the vermis using masks created with the SUIT atlas (Diedrichsen et al., 2009). The SUIT atlas and normalization method was developed to more accurately investigate the cerebellum, and used anatomical landmarks to validate the normalization and lobular regions (Diedrichsen, 2006; Diedrichsen et al., 2009). These 18 lobules were used as the seed regions in our resting state analysis. Because very little is known about the cerebellum in aging, we chose to investigate all of these lobules, though we limited our investigation to the dominant (right) hemisphere.