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Aging associated changes in the motor control of ankle movements in the brain

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Abstract

Although age-related gait changes have been well characterized, little is known regarding potential functional changes in central motor control of distal lower limb movements with age. We hypothesized that there are age-related changes in brain activity associated with the control of repetitive ankle movements, an element of gait feasible for study with functional magnetic resonance imaging (fMRI). We analyzed standardized functional magnetic resonance imaging data from 102 right-foot dominant healthy participants aged 20–83 years for age-associated effects using FSL and a meta-analysis using coordinate-based activation likelihood estimation. For the first time, we have confirmed age-related changes in brain activity with this gait-related movement of the lower limb in a large population. Increasing age correlated strongly with increased movement-associated activity in the cerebellum and precuneus. Given that task performance did not vary with age, we interpret these changes as potentially compensatory for other age-related changes in the sensorimotor network responsible for control of limb function.

Keywords

age; aging; gait; foot movements; motor control

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Disclosure statement

The authors have no actual or potential conflicts of interest to disclose.

1 Introduction

With aging, individuals increasingly display impaired motor performance across a variety of tasks and ability domains (Seidler et al., 2010). Functional magnetic resonance imaging (fMRI) studies suggested preceding functional changes of movement representations with older age (Carp et al., 2011) or age-related white matter changes (Linortner et al., 2012). Advanced age might thus induce compensatory neuroplastic processes in subcortical motor networks, in response to changes in the neurobiology of motor control systems (Ward, 2006). Consistent with this view, older compared to younger adults show stronger activation in the ipsilateral motor cortex (Mattay et al., 2002; Ward and Frackowiak, 2003) and higher levels of neural activity in subcortical (cerebellar) motor areas.

However, these conclusions are largely based on studies of simple, unilateral movements of the upper limb (Noble et al., 2011). Few similar studies focusing on lower limb movements have been reported (Zwergal et al., 2012), despite the high frequency and clinical relevance of gait problems with aging (Callisaya et al., 2013; Kreisel et al., 2013). Existing studies suggested an increase of multisensory cortical control of motor functions with age (Zwergal et al., 2012) and an age-related shift from automated to more controlled movement processing, associated with increased cognitive monitoring involving executive areas (Heuninckx et al., 2005; Heuninckx et al., 2008). Together, these findings appear to indicate a more conscious locomotor and postural strategy in older adults (Zwergal et al., 2012). However, a direct test for age-effects on cerebral activation during ankle movements, previously used as a probe for gait in clinical and rehabilitation studies (Enzinger et al., 2008; Enzinger et al., 2009) has not been performed in larger samples yet.

Given the possible relevance of such findings for the correct interpretation of studies using fMRI lower-limb movements across various cohorts, we reanalyzed data from a large cohort of 102 healthy participants to investigate age-related effects on brain activity associated with unilateral ankle movements. Thereby, we compared findings obtained by 2 different analysis approaches: (1) Standard FSL FEAT cluster-based analysis and (2) a meta-analysis using coordinate-based activation likelihood estimation (GingerALE) to detect quantitative interstudy consistencies in activation by generating maps of activation likelihood estimates.

2 Methods

2.1 Participants

fMRI data sets of 102 healthy people ($M = 48.7 \pm 18.8$ years, age range 20-83 years) who had served as control participants in previous fMRI studies at our institutes using identical paradigms were combined for analysis. All participants met the criteria of right-handedness and sensu lato right-footedness (preference for kicking a ball with the right foot), as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Inclusion criteria were absent history of neuropsychiatric diseases or other severe medical conditions, a morphologically normal magnetic resonance imaging (MRI) scan of the brain on T1-weighted images and normal or corrected to normal vision (Enzinger et al., 2009; Katschnig et al., 2011; Linortner et al., 2012; Loitfelder et al., 2011 and Schwingenschuh et al., 2013). From the original data set of 111 participants, 9 participants had to be excluded from further analysis cause of

missing T1-weighted structural scans (4 people), significant deviations from the scanning protocol (2 people), premature termination of the study resulting in an insufficient number of functional volumes (135 instead of 180, 1 person), absent right foot movement fMRI data (1 person) and left handedness (1 person). This resulted in a final cohort of 102 participants (Table 1).

2.2 Data acquisition

All study participants underwent MRI examinations at 3 Tesla systems of the same manufacturer (Siemens Healthcare, Erlangen, Germany; Tim Trio at Graz: $N = 75$ (4 studies) and Varian INOVA MRI system at Oxford: $N = 27$ (1 study)).

2.2.1 Magnetic resonance imaging—Structural imaging included a T₁-weighted 3D MPRAGE sequence with 1mm isotropic resolution (repetition time [TR]/echo time [TE]/inversion time/ fractional anisotropy = 1900 ms/2.19 ms/900 ms/9°) and a matrix size of 256 x 256 in all participants. A fast FLAIR sequence was obtained in a subset of 41 individuals (TR/TE/inversion time = 10 ms/70 ms/2500 ms, in plane resolution = 0.9 x 0.9 mm², slice thickness = 4 mm and field of view = 220 mm).

2.2.2 Functional magnetic resonance imaging—Functional data were acquired using a single shot gradient echo-planar imaging sequence TR = 3000 ms, TE = 30 ms, spin angle 90°, matrix size 64x64, with 180 volumes per functional run (scanning time 9 minutes). Voxel dimensions were 3 x 3 x 3 mm for the Tim Trio system and 4 x 4 x 6 mm for the Varian INOVA MRI system.

2.3 fMRI paradigm

The fMRI paradigm was identical for all participants. Participants had to perform active right and left ankle movements in separate runs using a purpose-built wooden apparatus, allowing a maximum displacement of 30°. Blocks of active foot movement (30 seconds), visually paced at a fixed rate (1 Hz for dorsi- and plantarflexion), alternated with interspersed periods of absolute rest (21 seconds). Proper adherence to the paradigm was monitored by an observer and traced using a potentiometer. Before entering the scanner, participants practiced the paradigm using the same device in a quiet separate room. In an attempt to reduce stimulus-correlated motion, participants' heads were secured with Velcro straps in a foam-cushioned holder and their knees were flexed to approximately 135° using a soft roll placed beneath the knees (Enzinger et al., 2009; Enzinger et al., 2008).

2.4 Data analysis

2.4.1 Magnetic resonance imaging—Structural MRI data were reviewed by an experienced observer (Christian Enzinger) to exclude morphologic abnormalities.

2.4.2 Functional magnetic resonance imaging—fMRI data were analyzed using FMRI Expert Analysis Tool (FEAT, version 5.92, part of FSL, www.fmrib.ox.ac.uk/fsl). The following prestatistical processing was applied: motion correction using MCFLIRT; non-brain removal using BET; spatial smoothing using a Gaussian kernel of FWHM 5 mm; mean intensity normalization by a single multiplicative factor; high-pass temporal filtering

(Gaussian-weighted least squares straight line fitting, with $\sigma = 54.0$ seconds). Time series statistical analysis was carried out using FILM with local autocorrelation correction. Registration to high resolution structural and/or standard space images was carried out using FLIRT and registration results were checked visually. No participant had to be excluded because of artifacts, slice dropouts, or excessive head motion (as defined by > 3 mm in any direction). In first level analyses, contrasts for active movements versus rest were computed for each individual, including head motion parameters as covariates.

2.4.2.1 Mean group activation analyses – FSL FEAT versus GingerALE:

FSL FEAT: Mixed effects analysis (FLAME 1+2) was performed to generate second-level contrasts at the group level (initial cluster forming threshold $Z > 3.1$, [corrected] cluster extent significance threshold of $p = 0.01$), using the first level analysis results. To control for possible confounding effects, the factors “study” or “scanner” independently were included as a regressor in mean group- and higher level analyses, and possible differences regarding the effect of these 2 covariates on activation were tested by higher-level contrasts.

GINGER ALE: To further confirm these findings, mean group activation also was calculated performing coordinate-based activation likelihood estimation (ALE) meta-analysis (GingerALE software; www.brainmap.org). ALE allows the detection of quantitative interstudy consistencies in activation by generating maps of activation likelihood estimates. In this approach, the peak maxima of the mean activation maps of respective study populations serve as input for the analyses. Activation foci are modeled as probability distributions centered at the respective coordinates and then the overlap between studies is assessed (Eickhoff et al., 2009; Turkeltaub et al., 2012). We first generated separate group statistics for each study, for right and left foot movement, respectively (Table 1). All 5 studies with $N = 102$ participants and $n = 28$ foci contributed to the ALE meta-analysis (both conditions). ALE values were weighted by the sample size of each contributing study. Results were thresholded using the false discovery rate method (corrected p -values of $p < 0.05$), an FWHM median value of 9.28 and a minimum cluster size of 100 mm^3 (Eickhoff et al., 2009; Turkeltaub et al., 2012; Turkeltaub et al., 2002).

2.4.2.2 Higher-level age correlation analysis: FSL FEAT higher-level correlation analysis (demeaning of age) on first level whole brain imaging data (mixed effects analysis, FLAME 1+2, $Z > 3.1$, cluster $p = 0.01$; controlling for study as potential source of variance) served to explore a possible age effect. Based on the significant results of the correlation analyses, regional brain masks were defined for subsequent region of interest (ROI) analyses. Using FEATQUERY, the median signal changes within the ROIs were computed for each individual and for dominant right- and nondominant left ankle movement.

2.4.3 General statistical analyses—SPSS (Statistical Package of Social Sciences, Chicago, Illinois, version 16.0) was used for general statistical analyses. For FSL FEAT correlation analysis (including age as a continuous variable) we applied z-transformation. Reprocessing and illustration of the results of the ROI analysis was done using SPSS. To identify which of the 10 ROIs exhibit the strongest relation to age, a forward stepwise linear regression analysis including all these ROIs was used to statistically assess whether the correlations were different in magnitude across ROIs.

3 Results

3.1 Mean group activation associated with right (RF) and left foot (LF) movement versus rest

Using FSL FEAT analysis, contrasts of unilateral active foot movements versus rest showed significant activations in expected spatial location and distribution for movements with both feet (Enzinger et al., 2008). Regions of activation included the primary motor cortex (MI) and supplementary motor area (both bilateral with a contralateral activation peak), the primary (SI) and secondary (SII) somatosensory cortices and the basal ganglia (contralateral), the cerebellum (ipsilateral), and the occipital gyri (contralateral/bilateral). Analyses of left foot movement versus rest revealed additional ipsilateral secondary somatosensory cortex activation and basal ganglia recruitment. For both feet, the cerebellar activation extended to the brainstem (Figure 1A and Table 2).

GingerALE meta-analysis also was performed to confirm localizations of consistent responses across all studies and experiments. For both, LF and RF movements, significance adjusted activation clusters were found in the primary sensorimotor cortex (MI and SI, contralateral) and the cerebellum (anterior part/lobule VIII; both ipsilateral). Additional activations were identified for movement of the RF in the medial frontal gyrus (BA 6, contralateral) and for movement of the LF activation in the superior temporal gyrus (BA 22, ipsilateral). See Figure 1B and Table 3.

3.2 Correlational analyses – age and movements of the right and left feet

Significant age effects on the neural correlates of foot movement were found both for the right and left foot. Correlation analysis identified increased cerebellar (RF and LF, bilateral), occipital (RF and LF, contralateral) and precuneal activation (RF, contralateral and LF, ipsilateral), as well as basal ganglia (RF, bilateral) and frontal activation (LF, bilateral) with increasing age. The opposite correlation (increased activation with younger age) did not show significant results. All these analyses were calculated including the covariate “study” and the reported findings did not change when using “scanner” as a covariate instead.

To examine whether the positive correlational effects were driven by activation or deactivation, ROI analyses were performed for the respective regions and their median signal change was plotted (see Figure 2 and Table 2).

The scatter plots revealed that the positive correlation in the cerebellum was driven most distinctively by variation in strength of activation (RF and LF; Table 4 for a listing of local maxima), with similar findings for the basal ganglia (RF) and the frontal cortex (LF). The positive correlation in the occipital gyrus and precuneus was driven by relatively stronger deactivations in participants with younger ages (RF and LF).

To draw any conclusions about differences in magnitude across the ROIs, subsequently a stepwise linear regression analysis was performed. All 10 ROIs were included serving as predictor variables; with age as a criterion variable. Three variables significantly predicted age, accounting for 37% of the variation: one cluster each in the cerebellum for left and right foot movements and one cluster in the precuneus with left foot movement ($R^2 = 0.37$, $p <$

0.015). Each of these 3 variables contributed independently to the model (standard coefficients [significance] of 0.31 [0.002], 0.24 [0.008] and 0.23 [0.015]). Non-significant predictors in this type of analysis were, for the right foot: the bilateral basal ganglia, right occipital cortex and right precuneus; and for the left foot: the right and left frontal cortex and left occipital cortex.

4 Discussion

Analyzing a large fMRI data set from 102 healthy adults, we here characterized the functional representations of unilateral dominant and nondominant ankle movements, focusing on the aspect of age. For the first time in a large population, we identified several brain areas with robustly increased activity with aging in clinically asymptomatic healthy participants.

Our study provides evidence of age-related increases in brain activity in the cerebellum, precuneus and occipital cortex, as well as basal ganglia (dominant RF only) and precuneal (nondominant LF only) during simple repetitive separate right and left ankle dorsiflexion movements. We also performed ROI analyses for these areas and created scatter plots of age versus median signal change within these clusters (Figure 2) to distinguish activation from deactivation. In general, clusters showed a similar pattern with higher activation with increasing age. Exceptions were most clear in the precuneus and occipital gyrus, which appeared to be deactivated relative to rest with younger and activated with older age. Stepwise regression analyses revealed that activation in 3 regions significantly predicted age, accounting for 37% of the variation: 1 cluster each in the cerebellum for left and right foot movements and 1 cluster in the precuneus for left foot movement.

The increased cerebellar activation with age is of particular interest as the cerebellum represented the structure with the highest correlation coefficient and an independent prediction of age was also confirmed by formal statistics analyzing the differences among the ROIs. It is widely accepted that the cerebellum acquires and stores internal models of the motor apparatus that are critical for feed forward control and complex coordinated movements (Ebner and Pasalar, 2008). The cerebellum also is involved in the amplification and refinement of motor commands initiated and regulated by the complementary basal ganglia after descending from the motor cortex (Tunik et al., 2009). It also contributes to a great extent to postural and equilibrium control (Ioffe et al., 2007) and plays a key role in motor skill learning (Matsumura et al., 2004; Timmann et al., 2010). The cerebellum demonstrates clear somatotopic organization and distinct loci of activation have been defined in the anterior lobe for distal and proximal segments of the upper limb (elbow and hand; Grodd et al., 2001) and different segments of the leg (toes, ankle, and knee; Kapreli et al., 2007), suggesting 4 different “homuncular” control regions (Mottollese et al., 2013). In our study, lobules IV-VI, VIII-IX and crus I were activated with dominant foot movement and higher age, while nondominant foot movement activated lobules III, VI and crus I. The lobules IV-V are believed to be connected with the sensorimotor cortices. In contrast, crus I has demonstrated functional connectivity with prefrontal and posterior-parietal cortices, possibly relating to the additional frontal activity observed with higher age for LF movements (Mottollese et al., 2013). It is therefore not directly involved in motor or sensory

processing but instead appears engaged in cognitive functions (O'Reilly et al., 2010). It is thus tempting to interpret the higher cerebellar activity as a compensatory response to covert age-related declines in sensorimotor network functions for the control of lower limb movement that lead to a higher cognitive demand for nondominant ankle movements with increasing age.

The precuneus has been implicated in higher-order cognitive processes such as episodic memory, motor imagery and spatial aspects of motor behavior control (Cavanna and Trimble, 2006; Grefkes et al., 2004). Precuneus activation has often been reported in functional imaging studies involving the execution (Kawashima et al., 1995) or preparation (Astafiev et al., 2003) of spatially guided behaviors such as goal-directed hand movements like pointing or reaching. Wenderoth et al. (2005) observed precuneus activation with execution of spatially complex bimanual coordination tasks compared with unimanual subtasks. Reaction time studies suggested involvement in movement control with reference to buffered memory (precuneus activation with reaction time reduction; Oishi et al., 2005). Another interesting point relates to the fact that the precuneus and occipital gyri belong to structures that become increasingly activated primarily with higher age, but are deactivated relative to rest at younger ages. This suggests that simple ankle dorsiflexion movements demand additional compensatory activation of cortico-cerebellar areas with aging, just as is found for more complex and cognitive demanding manual tasks and fine motor skills. Further, the precuneus and surrounding posteromedial areas are among the brain structures displaying the highest resting metabolic rates, with its tonic activity decreasing transiently during engagement in non-self-referential goal-directed actions (Cavanna and Trimble, 2006). These new findings of age effects for ankle movements generally appear to be in line with findings from other functional imaging studies that have shown that older compared with younger adults activate widespread additional brain networks during performance of (simple) motor tasks (Bernard and Seidler, 2012; Van Impe et al., 2009; Ward, 2006). The increase in the spatial extent of activation with age may reflect decreased distinctiveness of motor representations at older age, or, alternatively, indicate a compensation for age-related subtle declines in cognitive or sensory function (Carp et al., 2011; Heuninckx et al., 2008; Noble et al., 2011; Park and Reuter-Lorenz, 2009). In contrast, neural activation following varying task complexity or body side seems to be independent of age (Van Impe et al., 2009).

To further confirm the robustness of our findings we applied 2 different analytical approaches (FSL FEAT and GingerALE). For both feet, the FSL FEAT analysis showed expected activation in the primary and secondary motor cortices (bilateral with contralateral peak), the bilateral supplementary motor area and basal ganglia, the ipsilateral cerebellum and the contralateral occipital cortex. This pattern is in line with previous studies and emphasizes more bilateral activity (with a lateralized activation peak in most brain regions) associated with lower ankle dorsiflexion compared with the more asymmetrical, lateralized upper limb movements, (Enzinger et al., 2009; Huda et al., 2008; Kapreli et al., 2006; Luft et al., 2002; MacIntosh et al., 2004; Zheng et al., 2007). The fact that the cerebellar activation associated with lower limb movement extended to the brainstem (pedunculopontine nucleus) further supports the idea that brain activity related to simple foot movements overlaps with the locomotor network. The GingerALE analysis also identified significant adjusted

activation clusters in the primary sensorimotor cortex (contralateral peak) and the cerebellum (anterior part / lobule VIII, both ipsilateral), for both dominant right- and nondominant left foot movements. In addition, movement of the dominant foot activated the medial frontal gyrus; movement of the nondominant foot SII and the superior temporal gyrus. Generally, ALE meta-analysis facilitates the estimation of consistency across multiple published brain imaging findings, thus presenting a way of assessing spatial reproducibility (Eickhoff et al., 2009; Turkeltaub et al., 2012). Such data pooling allows usage of already existing but statistically frequently underpowered neuroimaging studies to reduce small sample size effects, the variability in the labeling of brain regions, and possible center specific effects such as bias of scanner, image acquisition and time point (Costafreda, 2009). Following this approach, each activation focus of our 5 studies was modeled as the peak of a 3D Gaussian probability distribution. The weighted average then allowed estimation of the true effect size as opposed to a less precise effect size derived from a single study under a given single set of assumptions and conditions. Using FSL FEAT for fMRI data analysis (including the factor “study” or “scanner” as regressor of no interest), for active movement of both feet, larger activation of primary and secondary motor cortices was found than for the basal ganglia and the cerebellum. However, the reverse was seen using ALE meta-analysis, that is, clusters were more prominent for the cerebellum and basal ganglia than for cortical motor areas.

Although this study provides the hitherto largest analysis of participants following the same experimental fMRI protocol for ankle movements, it has also limitations. Foot dominance was assessed as a subcategory of the Edinburgh Handedness Inventory (Oldfield, 1971) while more elaborated inventories on leg dominance are available (Chapman et al., 1986, Schneiders et al., 2010) and discrepancies between hand and foot dominance have been reported (Spry et al., 1993). We thus refrained from a thorough discussion of the laterality aspect in our study. Also, a more refined assessment of particular “foot abilities” (such as dancing, playing football, etc.) would have enabled more detailed analyses. Future work might also wish to examine possible age effects in left-footed participants (Rocca and Filippi, 2010). Further, as this was not the primary goal of our study, we did not subject participants to refined walking testing which might have revealed subtle preclinical behavioral changes and would have allowed for correlation analyses of variation in these parameters with functional cerebral activation. In addition, while we excluded participants with severe neurologic or other severe medical conditions, we did not assess age-related medical conditions like well-treated arterial hypertension, obesity, and controlled diabetes. We thus also could not assess the potential effect of these factors on brain functional changes. Importantly, when comparing the findings obtained by the 2 analytical approaches, it needs to be considered that the meta-analytical approach showed relatively lower confidence, most likely because of the overall comparatively small number of individual studies (5) used and their heterogeneity. Finally, there is evidence that White Matter Hyperintensities (WMH) severity and extent increase with age (Enzinger et al., 2007) and own previous work suggested WMH-severity to have an effect on functional activation associated with foot movements (Linortner et al., 2012). However, the aims of the different studies from which the fMRI data have been aggregated were different and scanning protocols therefore did not all include T2-weighted and / or fluid-attenuated inversion

recovery sequences needed for WMH analyses in all occasions. We therefore were not able to test the effect of WMH. This limitation of our study should be specifically addressed in future studies.

In summary, our study highlights increased BOLD-response associated with lower limb movements with increasing age and suggests a brain compensatory response to age-related deficits in sensorimotor control of the distal lower limb. Defining the underlying age-related deficits should contribute to a better understanding of factors contributing to impairments of gait with aging. This evidence for a role for compensatory responses provides a framework for understanding pathologic gait changes with diffuse brain vascular or degenerative changes and specific functional systems to target with novel gait and balance training interventions.

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References

- Astafiev SV, Shulman GL, Stanley CM, Snyder AZ, Van Essen DC, Corbetta M. Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. *J Neurosci*. 2003; 23:4689–4699. [PubMed: 12805308]
- Bernard J, Seidler R. Evidence for motor cortex dedifferentiation in older adults. *Neurobiol Aging*. 2012; 33:1890–1899. [PubMed: 21813213]
- Callisaya ML, Beare R, Phan TG, Blizzard L, Thrift AG, Chen J, Srikanth VK. Brain structural change and gait decline: a longitudinal population-based study. *J Am Geriatr Soc*. 2013; 61:1074–1079. [PubMed: 23796055]
- Carp J, Park J, Hebrank A, Park DC, Polk TA. Age-related neural dedifferentiation in the motor system. *PLoS One*. 2011; 6:e2941. doi: 10.1371/journal.pone.0029411
- Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*. 2006; 129:564–583. [PubMed: 16399806]
- Chapman JP, Chapman LJ, Allen JJ. The measurement of foot preference. *Neuropsychologia*. 1987; 15:579–584.
- Costafreda SG. Pooling fmri data: meta-analysis, mega-analysis and multi-center studies. *Front Neuroinformatics*. 2009; 3:33. doi: 10.3389/neuro.11.033.2009
- Ebner TJ, Pasalar S. Cerebellum predicts the future of motor state. *Cerebellum*. 2008; 7:583–588. [PubMed: 18850258]
- Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp*. 2009; 30:2907–2926. [PubMed: 19172646]
- Enzinger C, Fazekas F, Ropele S, Schmidt R. Progression of cerebral white matter lesions – clinical and radiological considerations. *J Neurol Sci*. 2007; 257:5–10. [PubMed: 17321549]
- Enzinger C, Johansen-Berg H, Dawes H, Bogdanovic M, Collett J, Guy C, Ropele S, Kischka U, Wade D, Fazekas F, Matthews PM. Functional MRI correlates of lower limb function in stroke victims with gait impairment. *Stroke*. 2008; 39:1507–1513. [PubMed: 18340092]
- Enzinger C, Dawes H, Johansen-Berg H, Wade D, Bogdanovic M, Collett J, Guy C, Kischka U, Ropele S, Fazekas F, Matthews PM. Brain activity changes associated with treadmill training after stroke. *Stroke*. 2009; 40:2460–2467. [PubMed: 19461018]
- Grefkes C, Ritz A, Zilles K, Fink GR. Human medial intraparietal cortex subserves visuomotor coordinate transformation. *Neuroimage*. 2004; 23:1494–506. [PubMed: 15589113]

- Grodd W, Hulsmann E, Lotze M, Wildgruber D, Erb M. Sensorimotor mapping of the human cerebellum: fMRI evidence of somatotopic organization. *Hum Brain Mapp.* 2001; 13:55–73. [PubMed: 11346886]
- Heuninckx S, Wenderoth N, Debaere F, Peeters R, Swinnen SP. Neural basis of aging: the penetration of cognition into action control. *J Neurosci.* 2005; 25:6787–6796. [PubMed: 16033888]
- Heuninckx S, Wenderoth N, Swinnen S. Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. *J Neuroscience.* 2008; 28:91–99. [PubMed: 18171926]
- Huda S, Rodriguez R, Lastra L, Warren M, Lacourse MG, Cohen MJ, Cramer SC. Cortical activation during foot movements: II effect of movement rate and side. *Neuroreport.* 2008; 19:1573–1577. [PubMed: 18845938]
- Ioffe ME, Chernikova LA, Ustinova KI. Role of cerebellum in learning postural tasks. *Cerebellum.* 2007; 6:87–94. [PubMed: 17366270]
- Kapreli E, Athanasopoulos S, Papathanasiou M, Van Hecke P, Strimpakos N, Gouliamos A, Peeters R, Sunaert S. Lateralization of brain activity during lower limb joints movement. An fMRI study. *Neuroimage.* 2006; 32:1709–1721. [PubMed: 16859927]
- Kapreli E, Athanasopoulos S, Papathanasiou M, Van HP, Keleki D, Peeters R, Strimpakos N, Sunaert S. Lower limb sensorimotor network: issues of somatotopy and overlap. *Cortex.* 2007; 43:219–232. [PubMed: 17405668]
- Katschnig P, Schwingenschuh P, Jehna M, Švehlík M, Petrovic K, Ropele S, Zwick EB, Ott E, Fazekas F, Schmidt R, Enzinger C. Altered functional organization of the motor system related to ankle movements in Parkinson's disease: insights from functional MRI. *J Neural Transmission.* 2011:1–11.
- Kawashima R, Roland PE, O'Sullivan BT. Functional anatomy of reaching and visuomotor learning: a positron emission tomography study. *Cereb Cortex.* 1995; 5:111–122. [PubMed: 7620288]
- Kreisel SH, Blahak C, Baezner H, Inzitari D, Pantoni L, Poggesi A, Chabriot H, Erkinjuntii T, Fazekas F, Ferro JM, Langhorne P, et al. Deterioration of gait and balance over time: the effects of age-related white matter change – the LADIS study. *Cerebrovasc Dis.* 2013; 35:544–553. [PubMed: 23838682]
- Linortner P, Fazekas F, Schmidt R, Ropele S, Pendl B, Petrovic K, Loitfelder M, Neuper C, Enzinger C. White matter hyperintensities alter functional organization of the motor system. *Neurobiol Aging.* 2012; 33:197.e1–9. DOI: 10.1016/j.neurobiolaging.2010.06.005
- Loitfelder M, Fazekas F, Petrovic K, Fuchs S, Ropele S, Wallner-Blazek M, Jehna M, Aspeck E, Khalil M, Schmidt R, Neuper C, et al. Reorganization in cognitive networks with progression of multiple sclerosis: insights from fMRI. *Neurology.* 2011; 76:526–533. [PubMed: 21300967]
- Luft AR, Smith GV, Forrester L, Whittall J, Macko RF, Hauser TK, Goldberg AP, Hanley DF. Comparing brain activation associated with isolated upper and lower limb movement across corresponding joints. *Hum Brain Mapp.* 2002; 17:131–140. [PubMed: 12353246]
- MacIntosh BJ, Mraz R, Baker N, Tam F, Staines WR, Graham SJ. Optimizing the experimental design for ankle dorsiflexion fMRI. *Neuroimage.* 2004; 22:1619–1627. [PubMed: 15275918]
- Matsumura M, Sadato N, Kochiyama T, Nakamura S, Naito E, Matsunami K, Kawashima R, Fukuda H, Yonekura Y. Role of the cerebellum in implicit motor skill learning: a PET study. *Brain Res Bull.* 2004; 63:471–483. [PubMed: 15249112]
- Mattay VS, Fera F, Tessitore A, Hariri AR, Das S, Callicott JH, Weinberger DR. Neurophysiological correlates of age-related changes in human motor function. *Neurology.* 2002; 58:630–635. [PubMed: 11865144]
- Mottolese C, Richard N, Harquel S, Szathmari A, Sirigu A, Desmurget M. Mapping motor representations in the human cerebellum. *Brain.* 2013; 136:330–342. DOI: 10.1093/brain/aws186 [PubMed: 22945964]
- Noble JW, Eng JJ, Kokotilo KJ, Boyd LA. Aging effects on the cortical control of grip force magnitude: an fMRI study. *Exp Gerontol.* 2011; 46:453–461. [PubMed: 21296649]
- Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia.* 1971; 9:97–113. [PubMed: 5146491]

- Oishi K, Toma K, Bagarinao ET, Matsuo K, Nakai T, Chihara K, Fukuyama H. Activation of the precuneus is related to reduced reaction time in serial reaction time tasks. *Neurosci Res.* 2005; 52:37–45. [PubMed: 15811551]
- O'Reilly JX, Beckmann CF, Tomassini V, Ramnani N, Johansen-Berg H. Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. *Cereb Cortex.* 2010; 20:953–965. [PubMed: 19684249]
- Park DC, Reuter-Lorenz P. The adaptive brain: Aging and neurocognitive scaffolding. *Annu Rev of Psychol.* 2009; 60:173–196. [PubMed: 19035823]
- Rocca MA, Filippi M. FMRI correlates of execution and observation of foot movements in left-handers. *J Neurol Sci.* 2010; 288:34–41. [PubMed: 19896144]
- Schneiders AG, Sullivan SJ, O'Malley KJ, Clarke SV, Knappstein SA, Taylos LJ. A valid and reliable clinical determination of footedness. *PM R.* 2010; 2:835–841. [PubMed: 20869683]
- Schwingschuh P, Katschnig P, Jehna M, Kögl-Wallner M, Seiler S, Wenzel K, Ropele S, Langkammer C, Gatteringer T, Ott E, Fazekas F, et al. Levodopa changes brain motor network function during ankle movements in Parkinson's disease patients. *J Neural Transm.* 2013; 120:423–433. DOI: 10.1007/s00702-012-0896-6 [PubMed: 22990677]
- Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, Kwak Y, Lipps DB. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav Rev.* 2010; 34:721–733. [PubMed: 19850077]
- Spry, S., Zebas, C., Visser, M. What is Leg Dominance?. In: Hamill, J., editor. *Biomechanics in Sport XI. Proceeding of the XI Symposium of ISBS*; MA: Amherst. 1993.
- Timmann D, Drepper J, Frings M, Maschke M, Richter S, Gerwig M, Kolb FP. The human cerebellum contributes to motor, emotional and cognitive associative learning. A review *Cortex.* 2010; 46:845–857. [PubMed: 19665115]
- Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *Neuroimage.* 2002; 16:765–780. [PubMed: 12169260]
- Turkeltaub PE, Eickhoff SB, Laird AR, Fox M, Wiener M, Fox P. Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. *Hum Brain Mapping.* 2012; 33:1–13.
- Tunik E, Houk JC, Grafton ST. Basal ganglia contribution to the initiation of corrective submovements. *Neuroimage.* 2009; 47:1757–1766. [PubMed: 19422921]
- Van Impe A, Coxon JP, Goble DJ, Wenderoth N, Swinnen SP. Ipsilateral coordination at preferred rate: effects of age, body side and task complexity. *Neuroimage.* 2009; 47:1854–1862. [PubMed: 19539766]
- Ward NS, Frackowiak RS. Age-related changes in the neural correlates of motor performance. *Brain.* 2003; 126:873–888. [PubMed: 12615645]
- Ward S. Compensatory mechanisms in the aging motor system. *Ageing Res Rev.* 2006; 5:239–254. [PubMed: 16905372]
- Wenderoth N, Debaere F, Sunaert S, Swinnen SP. The role of anterior cingulate cortex and precuneus in the coordination of motor behaviour. *Eur J Neurosci.* 2005; 22:235–246. [PubMed: 16029213]
- Zheng L, Chen H, Ouyang L, Yao D, Gao JH. Quantitative analysis of asymmetrical cortical activity in motor areas during sequential finger movement. *Magn Reson Imaging.* 2007; 25:1370–1375. [PubMed: 17482410]
- Zwergal A, Linn J, Xiong G, Brandt T, Strupp M, Jahn K. Aging of human supraspinal locomotor and postural control in fMRI. *Neurobiol Aging.* 2012; 33:1073–1084. DOI: 10.1016/j.neurobiolaging.2010.09.022 [PubMed: 21051105]

Figure 1.

Comparison of FSL FEAT (FSL) and GingerALE (G. Ale) meta-analysis results for network activation associated with ankle movement versus rest in 102 healthy participants for the dominant right (upper 2 rows) and non-dominant left (lower 2 rows) foot. Selected slices of activation maps (FSL FEAT, z-coordinates, $Z > 3.1$, $p = 0.01$) or cluster peaks (ALE analysis, cluster peak extremes, $p < 0.05$) are shown in radiological convention, where the left side represents the right side of the brain (and vice versa) (where 2 z-values are displayed, the 1 one represents FSL FEAT results). Abbreviations: ALE, activation likelihood estimation; FEAT, fMRI expert analysis tool.

Figure 2.

Results of ROI analyses for clusters with significant age correlation with dominant right foot (RF) and nondominant left foot (LF) movements, plotting percentage median signal change along the y-axis and age (in years) along the x-axis. Note that these graphs are not intended to provide statistical inferences, which has already been established for these significant clusters. The scatter plots are presented to allow for visualization of whether the established positive correlation is driven by positive activation or negative deactivation across the age range. Results are displayed separately for all significant regions (left column RF and right

column LF; insets illustrate location of the ROI). Also plotted are the regression line, zero-axis, median (md) and correlation value (r). Figures are ranked according to strength of activation from top to bottom, with activated structures on top and partially deactivated structures on bottom. The green frames highlight those regions that exhibited the strongest relation to age by linear stepwise regression analysis. Abbreviation: ROI, region of interest.

Table 1

Description of the pooled study cohort regarding data source and number, scanner, mean age, age range, and gender of respective participants.

Data source	Number of participants (% of total pool)	Scanner (Siemens, Erlangen, Germany)	Age [years]		Gender, m/f, N (%)	
			<i>M</i> ± <i>SD</i>	Min – Max		
Loitfelder et al. (2011)	34 (33.3)	3.0-T Tim Trio	30.6 ± 8.8	20 – 52	16/18 (47/53)	
Enzinger et al. (2009)	27 (26.5) ^a	3.0-T Varian INOVA	52.7 ± 17.1	26 – 80	10/17 (37/63)	
Katschnig et al. (2011)	19 (18.6)	3.0-T Tim Trio	61.5 ± 6.8	48 – 75	10/9 (53/47)	
Linortner et al. (2012)	17 (16.7)	3.0-T Tim Trio	69.7 ± 6.6	60 – 83	4/13 (24/76)	
Schwingsenschuh et al. (2013)	5 (4.9)	3.0-T Tim Trio	30.0 ± 5.4	25 – 38	2/3 (40/60)	
Total	102 (100)	---	48.7 ± 18.8	20 – 83	42/60 (41/59)	

Key: f, female; m, male; *M*, mean; *N*, number; *SD*, standard deviation

^aIncludes unpublished data.

Table 2

Mean activation results for dominant right foot (RF) and nondominant left foot (LF) ankle dorsiflexion movements, using FSL FEAT analysis. Coordinates (in MNI standard space) and activation significance (Z statistics) for cluster-based statistical contrasts (all $Z > 3.1$, $p = 0.01$).

Condition	Anatomic region	Hemisphere (L/R)	Number of voxels ^a	Max Z score	MNI coordinates of maximum Z score		
Mean right foot movements vs. rest (RF)	Paracentral lobule	L	3574	7.53	-4	-32	64
	Cerebellum IV-V	R	1526	8.25	16	-38	-26
	Superior temporal gyrus	L	1444	6.07	-52	-32	18
	Middle occipital gyrus	L	326	4.69	-40	-68	0
	Rolandic operculum	R	271	4.61	50	-28	20
Mean left foot movements vs. rest (LF)	Paracentral lobule	R	3770	8.03	2	-26	64
	Cerebellum IV-V	L	1218	7.21	-18	-34	-32
	Superior temporal gyrus	R	1089	5.8	48	-30	18
	Inferior temporal gyrus	R	659	5.57	44	-68	-8
	Superior temporal gyrus	L	367	5.48	-48	-30	16
	Middle occipital gyrus	L	291	4.57	-40	-68	0
	Cerebellum VI	R	223	4.21	28	-60	-26
	Putamen	L	91	3.90	-28	-12	6

Key: L, left hemisphere; LF, left foot; R, right hemisphere; RF, right foot.

^aReported are clusters with 99 voxels.

Table 3

Mean activation results for dominant right foot (RF) and nondominant left foot (LF) ankle dorsiflexion movements, using ALE meta-analysis. Coordinates (in MNI space) and activation significance (ALE value $\times 10^3$) for voxel-based statistics (False Discovery Rate [FDR] thresholding, $p < 0.01$).

Condition	Anatomic region	Hemisphere (L/R)	Cluster size (mm ³) ^a	ALE ($\times 10^3$)	MNI coordinates for the weighted centre of each cluster		
Mean right foot movements vs. rest	Cerebellum, anterior lobe	R	1216	24.65	16	-36	-28
	Medial frontal gyrus, BA 6	L	208	10.61	-2	-18	62
	Paracentral lobule, BA 4	L	144	10.76	-2	-30	64
Mean left foot movements vs. rest	Cerebellum, anterior lobe	L	448	14.92	-20	-34	-32
	Paracentral lobule, BA 4	R	272	12.70	4	-32	66
	Superior temporal gyrus, BA 22	L	200	10.66	-50	4	-2
	Cerebellum, lobule VIII	L	136	9.85	-34	-56	-56
	Cerebellum, lobule VIII	L	101	9.29	-30	-58	-54

Key: ALE, Activation Likelihood Estimation value; BA, Brodmann area; L, left hemisphere; R, right hemisphere

^aReported are clusters with $> 100 \text{ mm}^3$

Table 4

Correlation analysis for age and dominant right foot / non-dominant left foot ankle dorsiflexion movements. Coordinates (in MNI standard space) and activation significance (Z statistics) for cluster-based statistical contrasts.

Condition	Anatomic region	Hemisphere (L/R)	Number of voxels ^a	Max Z score	MNI coordinates of maximum Z score		
					x	y	z
Positive Correlation: Age & RF active movement vs. rest Z>3.1, p = 0.01	Middle occipital gyrus	L	3245	7.51	-44	-76	-22
	Cerebellum, lobule VI	R		6.42	34	-44	-30
	Cerebellum, lobule IV-V	R	1481	6.24	6	-54	-22
	Cerebellar vermis, IV-V	L		5.89	-4	-52	-22
	Cerebellar vermis, IX	R		5.25	0	-54	-30
	Cerebellum, lobule VIII	R		5.18	8	-62	-30
	Cerebellum, crus I	R		4.89	28	-50	-38
	Precuneus	L	496	8.96	-2	-52	68
	Basal ganglia	R	311	5.06	14	-22	-10
	Basal ganglia	L	246	5.27	-28	-16	-6
	Inferior occipital gyrus	R	5322	5.84	4	-82	-16
	Cerebellum, crus I	R	2209	5.56	30	-56	-36
	Cerebellum, lobule III	R		5.53	4	-46	-20
Positive Correlation: Age & LF active movement vs. rest Z>3.1, p = 0.01	Cerebellum, crus I	L		5.38	-22	-66	-32
	Cerebellum, crus I	R		5.08	22	-64	-34
	Cerebellum, crus I	L		5.05	-12	-66	-30
	Cerebellum, lobule VI	L		4.82	-28	-54	-34
	Precuneus	L	840	6.29	-6	-50	76
	Middle frontal gyrus	L	176	5.73	-30	46	22
	Inferior frontal gyrus	R	172	4.54	48	24	-14
	Inferior occipital gyrus	R		5.84	4	-82	-16
	Cerebellum, crus I	R		5.56	30	-56	-36
	Cerebellum, lobule III	R		5.53	4	-46	-20

Key: L, left hemisphere; LF, left foot; LF-F, flipped left foot; R, right hemisphere; RF, right foot.

^aReported are clusters with 99 voxel.