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Right-left asymmetry in corticospinal tract microstructure and dexterity are uncoupled in late adulthood

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ABSTRACT

Ageing leads to a decline in white matter microstructure and dexterous function of the hand. In adolescents, it has previously been shown that the degree of right-left asymmetry in the corticospinal tract (CST) is linearly related with right-left asymmetry in dexterity. Here, we tested whether this association is also expressed in older adults. Participants completed a simple circle drawing task with their right and left hand as a measure of dexterity and underwent whole-brain diffusion weighted imaging at 3 Tesla (n = 199; aged 60–72 years). Fractional anisotropy and mean diffusivity of right and left CST were extracted from a manually defined region-of-interest. Linear regression analyses were computed to replicate the analyses in adolescents. Frequentist analyses were complemented with a Bayesian analytical framework. Outcome measures were compared with those previously reported in adolescents (aged 11–16 years). Asymmetries in white matter microstructure of the CST were evident and comparable to the degree of lateralisation observed in adolescence. Similarly, asymmetries in dexterity were evident, but to a lesser degree than in adolescents. Unlike in adolescents, we found no evidence of a linear relationship between asymmetries in CST microstructure and dexterity. Complementary Bayesian regression analysis provided moderate evidence in favour of the null hypothesis, pointing towards a lack of association between the structural and functional measures of right-left asymmetry. Our findings are compatible with the notion that, by late adulthood, a diverging impact of age on white matter structure and dexterous hand function dilutes the structure-function relationship between CST microstructure and manual proficiency that has been reported in adolescents.

1. Introduction

The motor function of the hand declines with age, impairing one's ability to perform skilled manual actions (Bowden and McNulty, 2013; Ward, 2006). Reduced dexterity affects activities of daily living such as dressing, eating, hygiene maintenance and medication use. Since these motor skills determine maintenance of functional independence, older adults with impaired dexterity are more likely to require social care and to live in supported housing (Ostwald et al., 1989). Further, from banking to vaccine appointments, a wide range of services are increasingly reliant on the dexterous handling of computers and mobile phones. While recent developments of age-friendly technologies have been promising Marston and Samuels (2019), these only remedy a symptom. To address the cause, we must better understand dexterity within the context of ageing.

The ability to independently move and jointly control individual fingers in order to produce stable and automatic movement patterns with the hand is at the backbone of dexterity and enables the skillful manipulation of tools (e.g., pencil, spoon). This requires a fast flow of information from the motor cortex to the spinal motor neurons supplying

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the hand muscles, via the corticospinal tract (CST) (Andersen and Siebner, 2018; Lemon, 2019; Lemon, 2008). The CST shows a significant degree of lateralisation. Previous work from our group used diffusion weighted magnetic resonance imaging (DWI) of the brain to study the microstructure of the CST in typically developing right-handed adolescents. Mean fractional anisotropy (FA) was found to be higher in the left CST than in the right CST (Angstmann et al., 2016). The degree of right-left microstructural asymmetry in the corticospinal tract was linearly related with right-left asymmetry in a measure of dexterity: The larger the right-to-left asymmetry in CST FA, the larger the relative right-hand advantage in terms of fluent circle drawing (Angstmann et al., 2016). We do not yet know, however, whether this structure-function relationship, observed in adolescents, is preserved in old age. Examining the relationship between these asymmetries in CST microstructure and circle drawing ability may provide valuable insight into the ageing brain.

Aging may weaken or strengthen the relationship between CST microstructure and dexterous hand use. On the one hand, it is possible that this brain-function association weakens with age because both, the microstructure of the corticospinal tract and dexterity, are susceptible to age-related changes. For instance, FA in the CST peaks relatively late and is believed to reach maturity in the 30s (Lebel et al., 2012). Manual dexterity, based on the performance on the Purdue Pegboard task, has been shown to significantly decline in the 60s Bowden and McNulty (2013). The diverging rates of development may result in a weaker link between the CST and dexterity in older individuals. From a more theoretical perspective, predictions can be made based on models borrowed from the neighbouring field of cognitive neuroscience. For instance, it has been suggested that ageing is accompanied by a reduction in hemispheric asymmetry of brain activations associated with cognitive functions Cabeza (2002). Support for the HAROLD model (Hemispheric Asymmetry Reduction in OLDer adults) comes from a body of functional neuroimaging studies, particularly of memory and executive functions (for review, see (Eyler et al., 2011)). If extrapolating beyond cognition, this would predict a decrease in hemispheric asymmetry in corticospinal tract microstructure in older adults in relation to manual motor function. On the other hand, decades-worth of practicing dexterous skills in the dominant hand, but not the other, may drive experience-driven plasticity in the CST. Decades of asymmetry in dexterous activities may, therefore, strengthen the asymmetry in CST microstructure. This would, in turn, suggest that the association between asymmetries in these two domains is preserved in ageing individuals.

In this study, we aimed to test whether the findings reported by Angstmann and colleagues (2016), namely that right-left asymmetry in dexterity scaled proportionally with the right-left asymmetry of fractional anisotropy (FA) and mean diffusivity (MD) between the left and right CST, could be extended to late adulthood (60+ years of age). Further, given the lack of characterisation of manual dexterity in older adults, we also tested the effects of age and sex on dexterity.

2. Methods

2.1. Study sample

The sample was drawn from the LIve active Successful Ageing (LISA) study, a randomised controlled trial of a one-year resistance-training intervention, which is described in detail elsewhere (Eriksen et al., 2016). LISA participants were 451 community-dwelling adults aged between 62–70 years. Participants underwent a battery of tests before (baseline) and after (year 1) a year-long intervention and will continue to be followed-up for up to 10 years. The LISA study inclusion criteria included independent living and performing less than 1hr/week of strenuous exercise. Individuals were excluded if diagnosed with a current severe unstable medical disease (e.g., active cancer), musculoskeletal diseases that could inhibit training, or current use of medication that could influence the effects of training (e.g., androgens). For our present analysis, we further excluded participants who were left-handed, reported a diagnosis of a neurological disorder, or displayed significant artifacts on their MRI scans, resulting in a final sample size of $n = 199$. In the present analysis, we included the first time-point at which participants completed the circle drawing task. The circle drawing task was introduced as an additional measure after data collection had started. As a result, 55.3% of included participants completed this measure at baseline, while 44.7% only did so at the first follow-up (year 1).

The LISA study received ethical approval from the Ethical Committees of the Capital Region of Denmark (No. H-3-2014-017) and the Danish Data Protection Agency. It complied with the declaration of Helsinki and was registered on clinicaltrials.gov (NCT02123641).

2.2. Measurements

2.2.1. Circle drawing

Participants performed a circle drawing task with their right and left hands. Participants were instructed to continuously draw concentric superimposed circles at a constant speed, while keeping the ulnar part of the hand resting on the table. Circles were first drawn with the right hand in a clockwise direction for 10 s, and then with the left hand in a counterclockwise direction for 10 s. A pressure sensitive digitising tablet (WACOM Intuos4 large PTK-840, Wacom Technology Corporation, Vancouver, WA, USA) recorded the writing trace that was produced by the tip of the pen at a sample rate of 200 Hz (Fig. 1). Using CS-Win software (v10.05; MedCom, Germany), these traces were then automatically segmented into consecutive up-and-down strokes, from which the kinematics of the movement was derived. This method employs a non-parametric kernel estimation to calculate movement derivates, including velocity and frequency of the drawing strokes Marquardt and Mai (1994). Further, the coefficient of variance for peak drawing velocity was calculated to denote variability of movement (CV = standard deviation/mean). Lower CV values for peak drawing velocity are indicative of less variability in circle drawings and, accordingly, of more proficient circle drawing movements.

As a measure of asymmetry, the laterality indices for CV (LI_{cv}) and frequency (LI_{freq}) were calculated:

$$LI_{freq} = \left(\frac{Frequency_{Right-Hand} - Frequency_{Left-Hand}}{Frequency_{Right-Hand} + Frequency_{Left-Hand}} \right) x\ 100$$

Negative LI values are indicative of higher proficiency of movement in the left hand, while positive values suggest a higher proficiency with the right hand.

2.3. Magnetic Resonance imaging

2.3.1. MRI acquisition

Whole-brain MRI scans were acquired at the Danish Research Centre for Magnetic Resonance (DRCMR) on a 3T TX Philips Achieva Scanner MRI scanner (Philips Healthcare) using a 32-channel head coil. 3D T1-weighted images were acquired over 244 slices with isotropic voxels of 0.85 mm^3 (TR = 9.3, TE = 2.7 ms, 288 × 288 matrix, and flip angle = 8°). DWI scans were also acquired (EPI with SENSE factor 2, TR/TE = 9265/85 ms, 112 × 112 matrix, 66 slices, isotropic voxel size $2 \times 2 \times 2$ mm^3, 62 uniformly distributed directions at $b = 1000$ s/mm^2 and 1 at $b = 0$ s/mm^2). Two additional volumes were collected at $b = 0$ with reverse phase-encoding directions used to correct for susceptibility artefacts.

2.3.2. MRI data processing

MRI data were pre-processed using tools from the FMRIB Software Library (FSL v6.0.1; (Woolrich et al., 2009)). DWI images were corrected for susceptibility artefacts using the 'topup' tool and reverse phase-encoded images as reference (Smith et al., 2004) and for subject motion and eddy currents using 'eddy' Andersson and Sotiropoulos (2016). Voxel-wise statistical analysis of the DTI data was carried out using Tract-Based Spatial Statistics (TBSS; Smith et al (2006)). First,

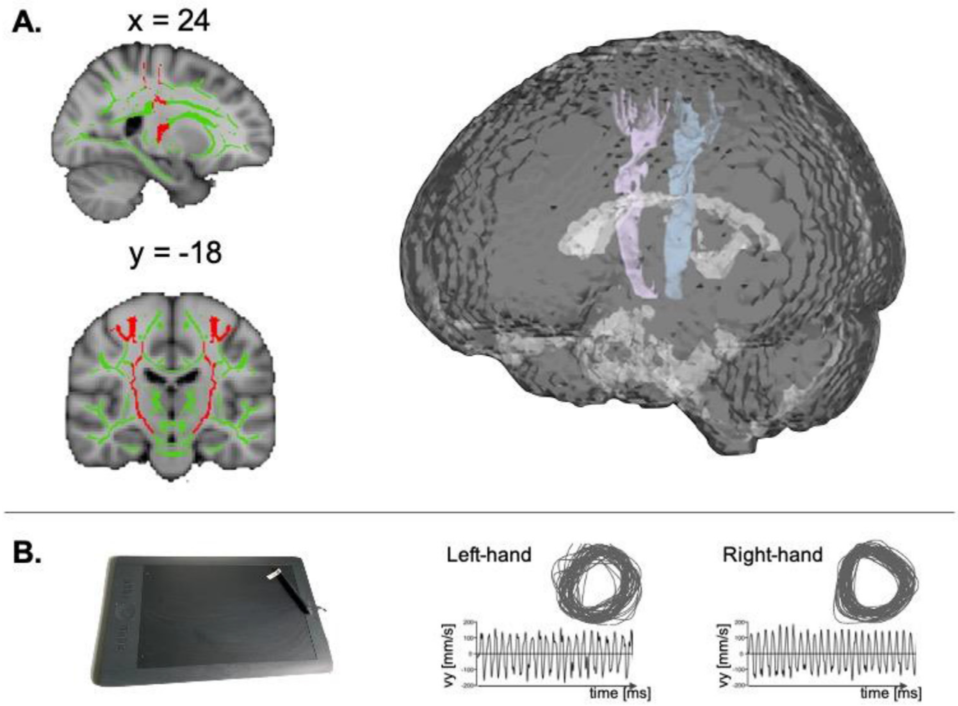

Fig. 1. Panel (a) depicts the ROIs of the corticospinal tract. On the left, the ROIs are overlaid on the mean FA skeleton and the corresponding sagittal and coronal slices of the standard MNI-152 template. On the right, a smoothed 3D visualisation of the left and right ROIs within a rendering of the MNI-152 template. Panel (b) illustrates the digitizing tablet used to collect the circle drawing data, as well as an example of left- and right-handed circle-drawings and the up-and-down strokes calculated from their respective hand traces.

FA images were created by fitting a tensor model to the raw diffusion data using the linear method with DTIFIT. All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT (Andersson et al., 2007), which uses a b-spline representation of the registration warp field. Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. The mean FA skeleton was thresholded at FA > 0.25. In order to test for asymmetries in the diffusion metrics, a symmetric FA skeleton was derived by restricting the original skeleton to the areas that are sufficiently close to being symmetric (tbss_sym). Each subject's aligned FA data was projected onto this skeleton. The nonlinear warps and skeleton projection stages were then applied to the mean diffusivity (MD) images.

The CST was manually traced on the symmetric skeleton, following the methods outlined in Angstmann et al 2016 (Fig. 1). Briefly, ROIs were drawn to include the white matter underlying the hand knob and the corresponding sensorimotor cortex. Below the level of the corpus callosum, the ROI was guided by probabilistic information from the JHU white matter tractography atlas available in FSLview (Hua et al., 2008). Voxels inferior to MNI slice z = -14 were excluded. Each ROI contained 1848 voxels. The MD values of three participants were high, exceeding 0.0008 mm^2/s, suggesting that CSF or lesions may have contributed to the MD measure due to partial volume effects (Koo et al., 2009). Upon inspection, these three participants presented significant structural lesions in areas overlapping the ROI and were therefore excluded from the study (Fig. 2).

2.3.3. Sample characteristics and covariates

Age, sex and years of full-time education were recorded for all participants at the time of assessment. Handedness was established by asking participants to state their dominant hand.

2.4. Statistical analyses

Statistical analyses were performed in RStudio version 1.3.1056 (RStudio Team, 2020), running on R version 4.0.2 (R Core Team, 2020), with the psych Revelle (2018), BayesFactor (Morey and Rouder (2018) and ggplot2 (Wickham and Sievert, 2016) packages.

Mean and standard deviations of all outcome measure are reported for descriptive purposes. Two-tailed paired t-tests were performed to test whether the difference between right and left metrics significantly differed from zero. QQPlots were visually inspected to test for deviations from a normal distribution. Linear models were applied to examine the relationship between age, sex, dexterity and DTI metrics (FA and MD). Laterality in the circle drawing performance and ROI measures was examined using multiple linear regression models. To replicate the analyses reported by Angstmann and colleagues (2016), linear regression were conducted with the laterality indices from the circle drawing task as dependent variables and the laterality indices from the CST as predictors. Models were then repeated to include age, sex and whole hemisphere white matter asymmetry as covariates. The statistical threshold for significance was set at 0.025, to accommodate a Bonferroni correction for testing two different DTI outcomes.

In post-hoc analyses, we applied a Bayesian framework to complement our interpretation of the relationship between asymmetries in circle drawing and DTI metrics of the CST. Using default priors and 1000 iterations, four univariate Bayesian regressions were conducted, one for each combination of circle drawing and DTI metrics ($LI_{CV\ or\ Freq} \sim LI$ of $CST_{FA\ or\ MD}$). In line with evidence categories proposed by Wetzels and colleagues (2011), Bayes Factors (BF_{01}) above 3 were interpreted as moderate evidence for the null hypothesis (H_0): that the laterality index of circle drawing measures (LI_{freq} and LI_{CV}) does not vary as a function of asymmetry in the CST.

In an exploratory analysis, we tested whether the asymmetry in circle drawing performance was associated with asymmetry elsewhere in the white-matter skeleton using a voxel-based analysis. We examined associations between the asymmetry indices from the circle drawing task, LI_{cv} and LI_{freq}, and the left-right skeletons of FA and MD acquired from tbss_sym. For this, a generalised linear model was applied using randomise (5000 permutations), a tool for permutation-based nonparametric testing (Winkler et al., 2014), with age and sex as covariates. Thresholding was carried out using TFCE (threshold-free cluster enhancement)(Smith and Nichols, 2009) and clusters were assessed for significance at $p < 0.05$, corrected for multiple comparisons across space.

Finally, post-hoc analyses using general linear models were conducted to compare the obtained outcomes with those from a sample of

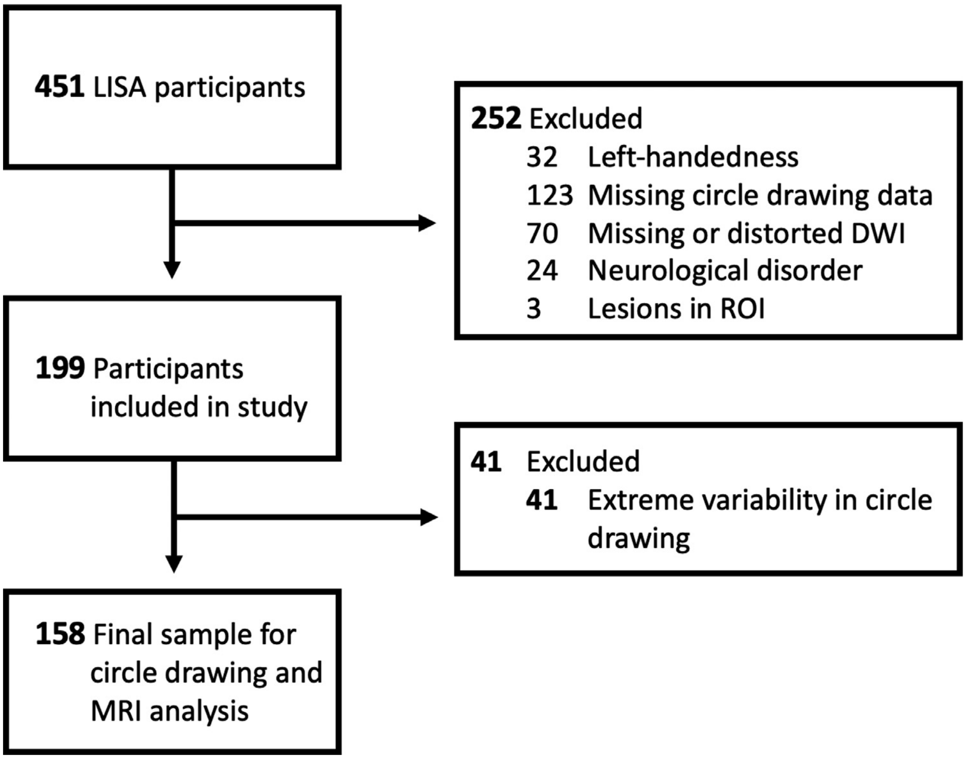

Fig. 2. Flow chart of sample selection.

adolescents that had completed the same circle drawing task. For this, the previously published data from 52 participants (age range: 11–16 years) were obtained (Angstmann et al., 2016).

3. Results

The 199 participants included in our analyses had a mean age of 66.9 ± 2.5 years. The sample was predominantly female (60.3%) and, on average, had 14.6 ± 2.0 years of full-time education. Fig. 3 summarises the distribution of DTI and kinematic data in histograms. The DTI data provided evidence for an asymmetry of CST microstructure. Within the CST ROI, 3 out of 4 participants showed a negative right-left laterality index for FA (74.3% of sample) and 9 out of 10 participants showed a positive laterality index for MD (89.9% of sample). These findings are compatible with higher FA and lower MD values in the left CST relative to the right CST. Most participants also showed a right-hand advantage in the circle drawing task. The majority of participants showed a lower CV of peak drawing velocity (LI_{CV}: 69.8% of sample) and a higher stroke frequency (LI_{freq}: 80.4% of sample) for right-hand circle drawing.

At the group level, the variability of peak drawing velocity showed an asymmetric distribution with a rightward tail of the distribution for both, right-hand and left-hand circle drawing (Fig. 3). Forty-one participants had a CV above 0.5 during circle drawing with the right or left hand, indicating extreme variability of peak drawing velocity during circle drawing. We excluded the circle drawing data from these participants with highly variable drawing performance from the presented linear models. Paired t-tests confirmed that the mean difference between right and left DTI and circle drawing metrics all significantly differed from 0 (all $p < 0.001$; Appendix 1). In an post-hoc analysis, we examined group differences between excluded participants and the remaining sample. The excluded sub-sample did not differ from included participants in terms of age or years of education, but had a smaller proportion of female participants (see Appendix 2).

The laterality indices of microstructural DTI and circle drawing metrics did not vary with age within the age range covered by the sample (all $p > 0.05$; Fig. 4). Only the laterality index of FA differed between sexes. Female participants showed a larger difference between right and left mean FA of the CST than male participants ($b = -0.36, p = 0.013$). Associations between contralateral pairs of CST microstructure and circle drawing (e.g., FA of left CST and CV of right-hand circle drawing) were not significant (Appendix 3). This remained the case when including age and sex as covariates.

3.1. Association between asymmetry in dexterity and CST microstructure

Asymmetries in FA and MD did not significantly predict the laterality index of either outcome from the circle drawing task (Table 1). This was also the case for female- and male-only sub-groups (Appendix 4).

For regression models predicting LI_{freq}, the Bayes factors indicated the data was more likely to occur under the null hypothesis than in the models with LI_{FA} ($BF_{01} = 5.49$) or LI_{MD} ($BF_{01} = 5.38$) as predictors. With LI_{CV} as the dependent variable, univariate regressions with LI_{FA} ($BF_{01} = 5.48$) or LI_{MD} ($BF_{01} = 5.48$) as predictors resulted in Bayes Factors that suggest that the data are approximately 5 times more likely to occur under the null hypothesis. Overall, across outcome measures, the Bayes factors indicated moderate evidence in favour of the null hypothesis.

3.2. Voxelwise analysis of the entire white matter skeleton

Voxelwise analysis were applied to test whether asymmetries elsewhere in the white matter skeleton were associated with asymmetries in the circle drawing task. No significant clusters were observed.

3.3. Comparison with sample of adolescents

In a post-hoc analysis, we obtained the data from the Angstmann et al. (2016) paper in order to compare the performance between the younger (HUBU, age range: 11–16 years) and older (LISA, age range: 60-72 years) cohorts. The HUBU sample consisted of 52 right-handed adolescents, with 18 male and 34 female participants. On average, the relation between MD and FA values in the right and left

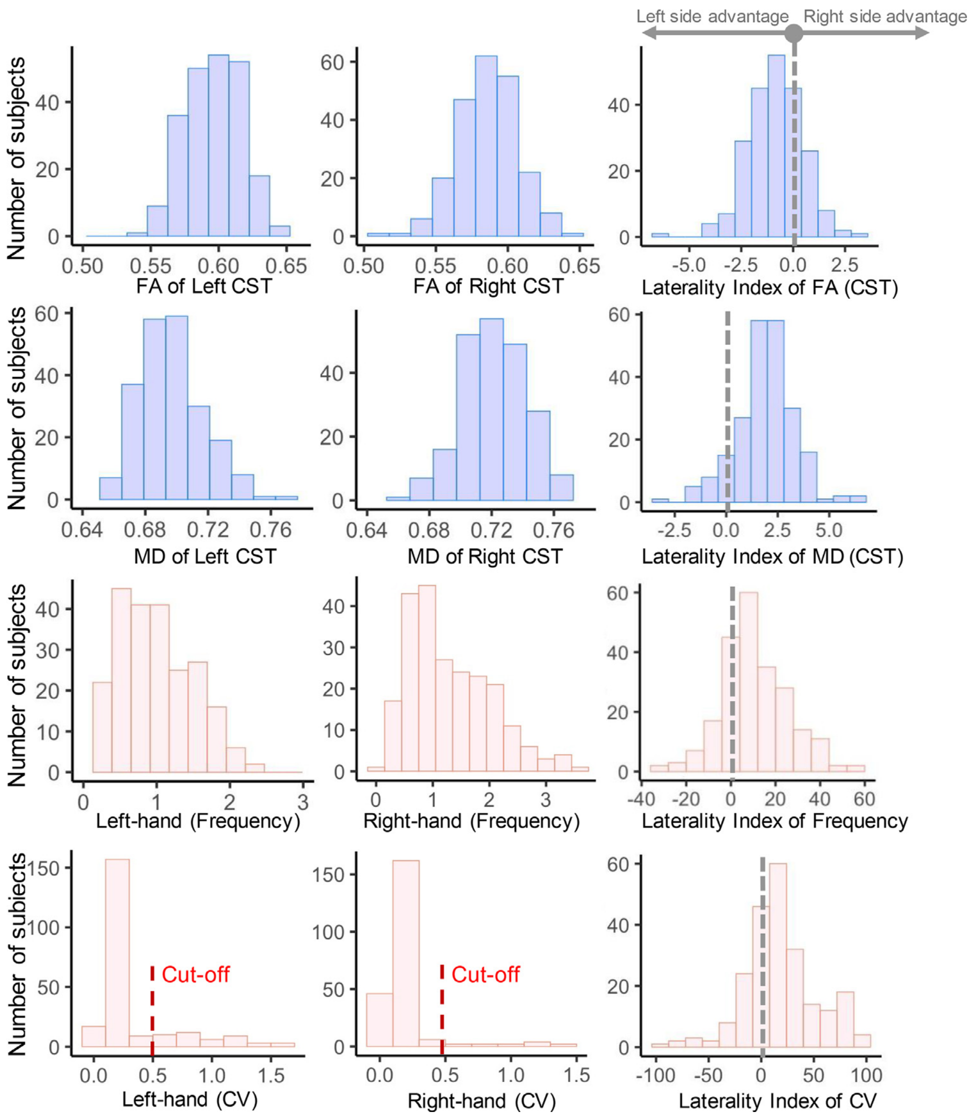

Fig. 3. Distribution of laterality indices observed in the corticospinal tract (CST) fractional anisotropy (FA) and mean diffusivity (MD) and circle drawing metrics. MD values are scaled (x1000).

Table 1
Linear regression models predicting laterality in the circle drawing task (LI_{freq} and LI_{CV}) with right–left asymmetry of fractional anisotropy (FA) and mean diffusivity (MD) in the corticospinal tract (CST).

Circle drawing metric	DTI metric	CST LI		Age		Sex[a]		LI_{WH}		Adjusted R^2
		ß	*p*	*ß*	*p*	*b*	*p*	*ß*	*p*	
LI_{freq}	FA	0.029	0.717	–	–	–	–	–	–	-0.006
	FA[b]	0.011	0.897	-0.046	0.568	0.131	0.437	0.136	0.111	-0.005
	MD	-0.002	0.978	–	–	–	–	–	–	<0.001
	MD[b]	0.003	0.973	-0.035	0.654	0.080	0.628	-0.015	0.861	-0.021
LI_{CV}	FA	0.030	0.711	–	–	–	–	–	–	-0.006
	FA[b]	0.028	0.731	0.103	0.203	-0.082	0.630	-0.004	0.967	-0.013
	MD	0.032	0.714	–	–	–	–	–	–	-0.006
	MD[b]	0.020	0.835	0.106	0.198	-0.078	0.653	0.024	0.790	-0.013

LI_{WH}, Laterality index of FA or MD across whole hemisphere.
[a] Positive coefficient reflects higher values for females.
[b] Models included age, sex and LI_{WH} as covariates.

hemispheres were comparable between the younger and older cohorts (Fig. 5). Accordingly, the right-left asymmetry of CST microstructure did not significantly differ between the HUBU and LISA cohort.

In the circle drawing task, participants in the younger cohort performed the drawings at a higher frequency with both right- and left-hands (all $p < 0.001$). This was particularly evident for the right dominant hand for which stroke frequency showed a marked reduction in the older cohort. In contrast to the microstructural metrics, the asymmetry indices differed between groups. Adolescent participants in the HUBU sample displayed greater right-left hand advantage in frequency and CV than the LISA cohort, indicating reduced asymmetry in dexterity in older participants (Fig. 5).

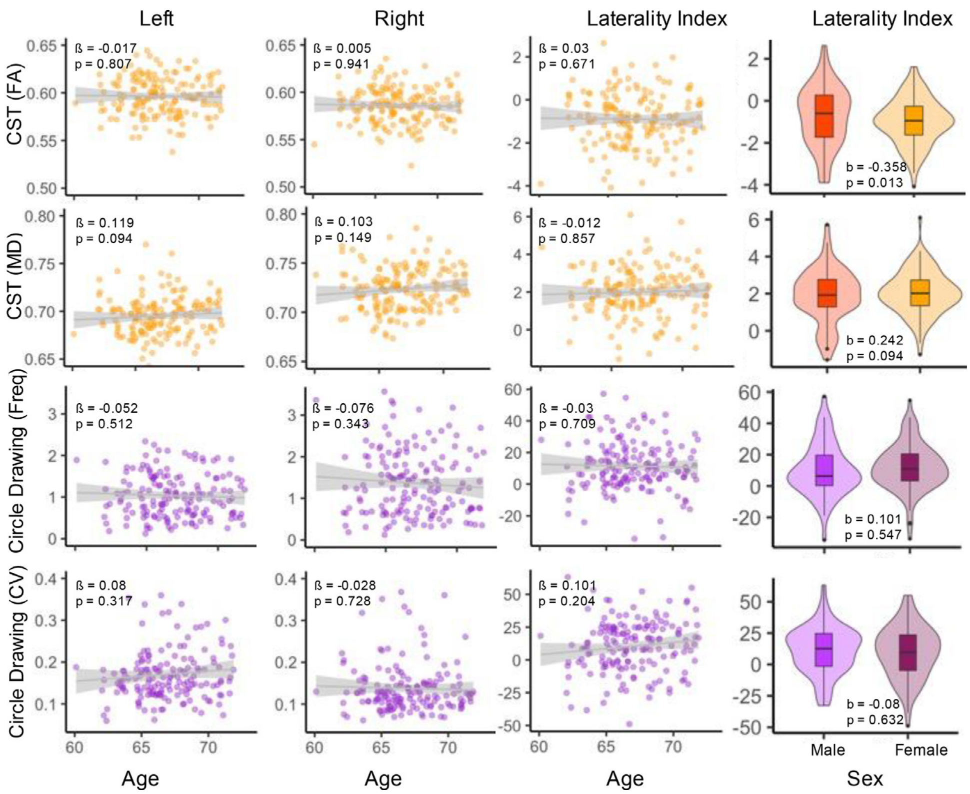

Fig. 4. Scatter plots of the linear relationships between unilateral corticospinal tract (CST) DTI (FA and MD) metrics and circle drawing (CV and Frequency) outcomes, their corresponding laterality indices, and age and sex. MD values are scaled (x1000). For each univariate linear regression, the corresponding standardised coefficient (ß) and *p*-value (p) is given. In the linear models with sex as a predictor, the unstandardised coefficient (b) is reported.

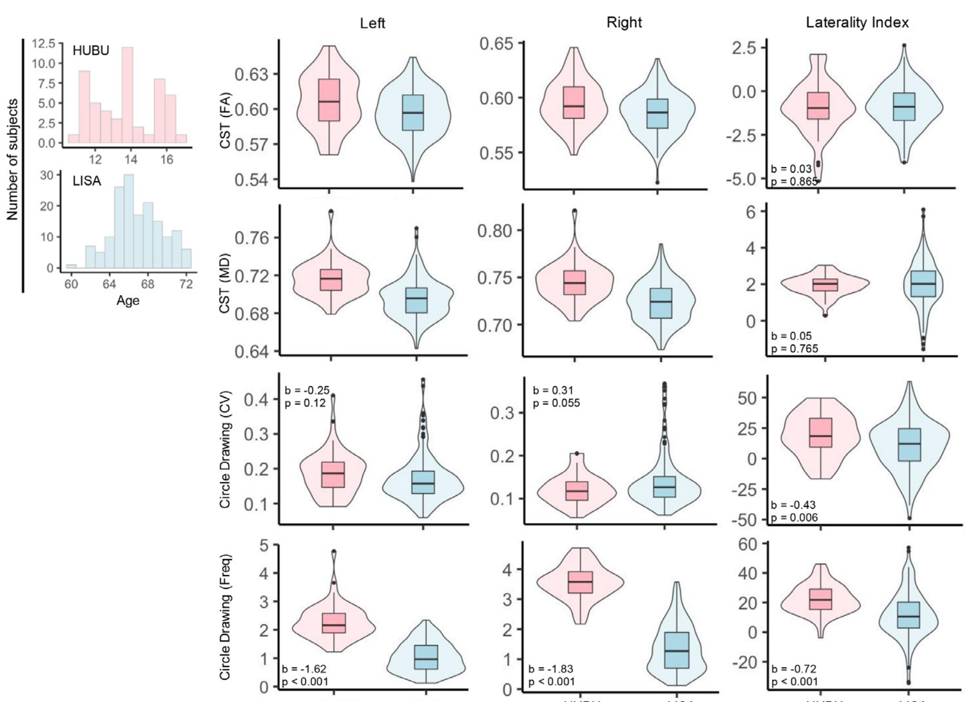

Fig. 5. On the left-hand side, histograms illustrate the age range for the HUBU and LISA cohorts. DTI (FA and MD) and circle drawing (frequency and CV) measures from both cohorts are presented in violin plots, both unilaterally and their corresponding laterality indices. For each univariate linear model, the corresponding unstandardised coefficient (b) and *p*-value (p) is given. Between-group comparisons of absolute FA and MD values were not conducted due to between-study differences in MRI scanners and sequence parameters. MD values are scaled (x1000).

4. Discussion

We tested whether the relationship between asymmetry in CST microstructure and fluent circle drawing, previously observed in adolescents (Angstmann et al., 2016), was preserved in older adults. Using well-established DTI-based metrics, we found no evidence for an association between asymmetries of microstructure in the CST and asymmetries in dexterity. Further, while the aim to replicate Angstmann et al. (2016)'s analysis prescribed a frequentist method, we complemented our findings with a Bayesian approach. Overall, we found moderate evidence in favour of the null hypothesis, namely that right-left asymmetries in CST microstructure did not predict right > left advantage in a simple circle drawing task. In the following sections, we first discuss the microstructural and behavioural findings separately and then, comment on the absence of a relationship between CST microstructure and circle drawing ability in our older sample.

The degree of asymmetry in CST microstructure did not significantly differ between the younger (aged 11 to 16 years) and older (aged 62 to 70 years) samples, suggesting that age effects on CST microstructure are similarly expressed in left and right CST. This is in contrast to predictions made based on the HAROLD model, borrowed from the field of cognitive neuroscience, which suggests a reduction of hemispheric asymmetry in relation to (cognitive) behaviour (Cabeza, 2002). In terms of sex differences in the older sample, we observed that female participants showed greater FA asymmetry in the CST, with a LI indicative of a stronger left side advantage. This effect was driven by a small difference in the right hemisphere: On average, men had higher FA in the right CST than women (Appendix 5). This pattern of results adds to an unclear body of literature regarding sex differenes in CST microstructure, as previous studies have reported no sex differences in DTI metrics of the CST (Inano et al., 2011), as well as higher FA in both right and left CSTs of males (Ritchie et al., 2018). Given the differing age ranges of the studied samples (e.g. 44–77 years in Ritchie et al. (2018) and 25–85 years in Inano et al. (2011)), it is possible that sex-related right-left differences in CST microstructure may be expressed differently in females and males across the lifespan.

The circle drawing task is suited to probe age associated reduction in dexterity, because the task requires a high level of skill and automation. Further, the task's short duration and simple instructions makes it suitable for samples of varying ages and health statuses. The pencil has to be pressed onto the drawing board and moved in a fast and stereotyped fashion, requiring an efficient synchronisation of the fingers holding the pencil. In comparison to the younger sample, the older sample showed a marked decrease in stroke frequency in the circle drawing task, particularly in the dominant right hand. These findings extend previous work on age-related decline in manual proficiency (Bowden and McNulty, 2013; Martin et al., 2015), suggesting that dexterous drawing skill is already less efficient during late adulthood. While the time to complete a circle was prolonged, the variability of drawing velocity did not differ consistently between the two samples. This suggests that the older cohort was slower than the adolescent cohort, but the stability of the motor innervation pattern from circle to circle was still relatively stable with the notable exception of a subgroup in whom velocity profiles were highly variable, as indexed by a high CV. Of note, we found no significant effect of age on dexterity within the cohort of older adults. This can be attributed to the relatively narrow age range of our sample (60–72 years). Given the large inter-individual variability in task performance, a wider age range would be needed to detect significant age-related differences (e.g., 20–88 in Bowden and McNulty, 2013).

While the degree of asymmetry in CST microstructure did not significantly differ between the younger (aged 11 to 16 years) and older (aged 60 to 72 years) samples, older participants showed a diluted right-hand advantage in the circle drawing task compared to the younger sample. A weaker right-hand advantage at the group level was found for both kinematic metrics, stroke frequency and variability of peak velocity. The right-left laterality indices for stroke frequency and variability also spanned a larger range in the older sample. This indicates a higher degree of inter-individual variability regarding the right-hand advantage for circle drawing during late adulthood. Together, the findings suggest that dexterous drawing movements with the preferred right hand are more sensitive to decline with age, because the level of skilled performance is higher for the preferred hand at young age.

Unlike in the younger sample (Angstmann et al., 2016), our findings show no linear relationship between right-left asymmetries in CST microstructure and circle drawing in late adulthood. This lack of association may reflect age-related changes in both brain structure and dexterous hand function, which are believed to occur at different rates. Further, increased inter-individual variability is a common feature of ageing. Older adults show increased heterogeneity in measures of brain structure (Nyberg et al., 2012) and cognitive function (Ardila, 2007; Buczylowska & Petermann, 2016). The age-related increase in variability noted in late adulthood is presumed to reflect increased differentiation and the accumulation of confounding factors over the life course Nelson and Dannefer (1992). For instance, increased variability due to age-related factors such as white matter lesions, global cortical atrophy and joint stiffness may influence and weaken the CST-dexterity relationship. Since we also found no linear relation between contralateral pairs of CST microstructure and circle drawing (e.g., FA of left CST and CV of right-hand circle drawing), we argue that normal variations in microstructural properties of the CST may not be of major importance in determining velocity and automation of fluent circle drawing during late adulthood. Other components of the motor system such as cortico-basal ganglia-thalamic and cortico-cerebello-thalamic sensorimotor loops may be more relevant in securing motor proficiency.

This study has some limitations. This study focused on one aspect of dexterity, the fast and automatic ability to produce coordinated movements with one hand to grasp and control a tool. This dexterous skill was probed using a unimanual circle drawing task. While this task was undeniably a test of manual proficiency, the observed lack of coupling between CST structure and function may not generalise to other manual tasks probing other aspects of unimanual or bimanual motor control. Further studies using different measures of manual proficiency would be needed to clarify whether a structure-function relationship between CST microstructure and dexterity may still be expressed during late adulthood for other aspects of manual proficiency. Further, only right-handed adults were included in the present analysis. This reduced the confounding effects of handedness. As previously argued Andersen and Siebner (2018), and also observed in our distribution of laterality indices, a strong habitual preference for one hand (handedness) does not translate to strong asymemtry in manual proficiency (dexterity). On the other hand, the focus on consistently right-handed individuals reduced the generalisability of our findings to left-handed individuals. The study therefore provides no insight into how handedness may impact on the relationship between dexterity and CST. A combination of TBSS and ROI approaches was selected in order to directly replicate the methods from Angstmann and colleagues (2016). It is worth noting, however, that other available methods, such as three-dimentional reconstructions, could provide even more detailed information on the tract of interest (Steventon et al., 2016). Given that DTI is sensitive to both micro- and macrostructure, it is not possible to disentangle the influence of axon trajectory architecture from their microstructure on our FA measures. Other methods, such as microscopic fractional anisotropy mapping, may help resolve this issue (Andersen et al., 2020). While the comparisons between cohorts provide an informative snapshot of differences between adolescents and older adults, they must be interpreted with caution. The DTI metrics from the two datasets have been collected using two different MRI scanners (3T Philips Achieva vs. 3T Siemens Trio) and acquisition parameters which might have led to systematic differences in the DTI metrics. For this reason, we did not test the between-cohort differences in absolute MD and FA values. In contrast, the dexterity measures were obtained using the same task, tablet and movement derivatives, enabling a direct comparison between the two studies. Further, cross-sectional analyses comparing the young and old are not sufficient for the understanding of ageing. As Raz and Lindenberger (2011) argued, "only time will tell" – in other words, to study the passing of time (ageing) we need to allow time to pass (in a longitudinal design). Accordingly, LISA participants will continue to be followed-up for up-to 10 years. Once this data is collected, it will be of interest to examine the trajectories of change in dexterity and its relationship with white matter microstructure over a 10-year period.

5. Conclusions

With increasingly dexterous demands to our increasing ageing population, we must better understand the relationship between brain structure and dexterity in late adulthood. The current study aimed to test whether the association between the asymmetries in the corticospinal tract and dexterity, previously shown in adolescents, could be replicated in older adults. Asymmetries in white matter microstructure of the CST were evident and comparable to the degree of lateralisation observed in adolescence. Asymmetries in dexterity, as measured by a circle drawing task, were evident, but to a lesser degree than in adolescents. Importantly, unlike in adolescence, the degree of lateralisation in manual proficiency and CST microstructure were not associated.

Declaration of Competing Interest

Hartwig R. Siebner has received honoraria as speaker from Sanofi Genzyme, Denmark and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark, Lophora ApS, Denmark, and Lundbeck A/S, Denmark, and as editor-in-chief (Neuroimage Clinical) and senior editor (NeuroImage) from Elsevier Publishers, Amsterdam, The Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany and from Gyldendal Publishers, Copenhagen, Denmark.

Credit authorship contribution statement

Naiara Demnitz: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Kathrine Skak Madsen:** Methodology, Formal analysis, Writing – review & editing. **Line K. Johnsen:** Data curation, Writing – review & editing. **Michael Kjaer:** Resources, Funding acquisition, Writing – review & editing, Supervision. **Carl-Johan Boraxbekk:** Conceptualization, Methodology, Writing – review & editing, Resources, Supervision. **Hartwig R. Siebner:** Conceptualization, Methodology, Resources, Funding acquisition, Writing – review & editing, Supervision.

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Statement on data and code availability

The LISA dataset is currently not openly available due to restrictions imposed by GDPR and Danish regulations on the protection of personal information (data are not fully anonymized).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118405.

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