Association between brain structure and fine motor function: findings from the population-based Rhineland Study

Xingwang Yang,[a] Weiyi Zeng,[a] Santiago Estrada,[a,b] Monique M. B. Breteler,[a,c] and N. Ahmad Aziz[a,d,*]

[a]Population Health Sciences, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
[b]AI in Medical Imaging, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
[c]Institute for Medical Biometry, Informatics and Epidemiology (IMBIE), Faculty of Medicine, University of Bonn, Bonn, Germany
[d]Department of Neurology, Faculty of Medicine, University of Bonn, Bonn, Germany

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Summary

Background Although an association between brain atrophy and decreased fine motor function has been reported, results from previous studies are inconsistent. We aimed to investigate whether decreased fine motor function is reflected in age- and sex-associated changes in brain structure across the adult lifespan in a large community dwelling cohort study.

Methods The Rhineland Study is an on-going population-based prospective cohort study in Bonn, Germany. We used cross-sectional data from the first 8318 participants of the Rhineland Study (age range: 30–95 years), who underwent baseline assessments between March 2016 and November 2022. A digital spiral drawing test was utilised to evaluate fine motor skills: tracing precision (deviation area), tracing velocity, and frequency of tremor. Brain volumetric and cortical thickness measures were obtained from 3T T1 MRI scans. The relationship between brain structure and fine motor function was examined with multivariable regression, while adjusting for age, sex, education, smoking status and grip strength.

Findings Smaller volumes and/or thinner cortices in several brain regions were associated with decreased tracing precision (higher tracing deviation area) and higher tremor frequency, including total brain volume (tracing area: $\beta = -0.108$, 95% CI = −0.180 to −0.037; tremor frequency: $\beta = -0.077$, 95% CI = −0.164 to −0.011), hippocampal volume (tracing area: $\beta = -0.052$, 95% CI = −0.089 to −0.015), and cortical thickness of the precentral gyrus (tracing area: $\beta = -0.052$, 95% CI = −0.082 to −0.023). Smaller total cerebellar volume ($\beta = 0.061$, 95% CI = 0.022–0.100) and total cerebellar grey matter volume ($\beta = 0.060$, 95% CI = 0.022–0.099) were both associated with lower tracing velocity. Women performed significantly better on all three dimensions of fine motor function, but age-associated changes in fine motor function did not differ between sexes.

Interpretation Our findings indicate that fine motor function is worse in older adults, and is better in women. Moreover, changes in total brain volume and the thickness of several key motor cortices are robustly related to fine motor function, with the strongest effect for tracing precision.

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Introduction

In ageing populations, one of the major healthcare challenges facing society is maintaining the fitness and mobility of individuals into old age in order to preserve their functional independence and quality of life.[1] Motor function has been demonstrated to be a key determinant of both fitness and mobility.[2,3] Fine motor function involves the coordinated use of a large number of (relatively small) arm and hand muscles and is indispensable for performing daily activities like using small utensils

*Corresponding author. Population Health Sciences, German Center for Neurodegenerative Diseases (DZNE), Venusberg-Campus 1/99, 53127, Bonn, Germany.
E-mail address: Ahmad.Aziz@dzne.de (N.A. Aziz).

Research in context

Evidence before this study

We conducted a comprehensive search of PubMed for articles pertaining to the human fine motor function in relation to age, sex, and brain structure (from inception to May 01, 2025). Search terms included "fine motor function", "spiral drawing", or "Archimedes spiral", in combination with "brain structure", "brain volume", "cortical thickness" or "atrophy". Previously, several small-scaled studies provided preliminary and inconsistent estimates of age and sex effects on fine motor function in adult (up to 220 cases) and paediatrics populations (up to 525 cases). Additionally, a population-based study reported an association between brain structure (acquired through 1.5T MRI) and fine motor performance (up to 1912 cases). Although these previous studies suggest a relationship between several brain regions and fine motor function, the current evidence is inconclusive and inconsistent, likely due to relatively small sample sizes and heterogeneous and suboptimal methods, especially low MRI spatial resolution and a lack of objective measures for fine motor function assessment. It was particularly unclear whether a simple quantitative fine motor function task could reflect age-associated changes in brain structure.

Added value of this study

This large population-based study, including about 8000 individuals, provides insights into the determinants of fine motor function across the adult lifespan. We found that fine motor function is worse in older adults, and is better in women. Importantly, our findings reveal an age-dependent association between key brain structures and fine motor function, including total brain volume, hippocampal volume, and the thickness of critical motor regions such as the precentral and paracentral gyri. These associations became particularly pronounced in older age groups, suggesting that fine motor function may serve as a sensitive indicator of age-related structural brain changes. By leveraging digital spiral drawing tasks, a scalable and objective assessment tool, this study advances our understanding of the neuroanatomical basis of fine motor control and its decline.

Implications of all the available evidence

We present evidence supporting the utility of digital spiral drawing tasks as a promising tool for assessing fine motor function in the general population. Furthermore, our results indicate that changes in fine motor function performance could be used as a sensitive marker of subtle alterations in brain structure. These results have important implications for early detection of age-related neurological decline and could inform the development of targeted interventions to preserve motor function in ageing populations. Additionally, our study bridges a critical gap in the literature by providing robust evidence on sex- and age-related differences in fine motor function, offering a foundation for future research into the underlying mechanisms. Collectively, this work contributes to the growing body of evidence supporting the integration of digital motor assessments into clinical and research settings for monitoring brain health and ageing.

and devices such as pens/pencils, cutlery, phones and computers, as well as buttoning, lacing and opening and closing of small boxes. The Archimedes' spiral drawing test (SDT) is widely used in the clinic to assess fine motor skills, particularly in patients with movement disorders like essential tremor (ET), Parkinson's disease (PD), and multiple sclerosis (MS).[4–7] Digital versions of the SDT enable objective assessment of fine motor control through quantification of parameters such as velocity, radial distance, and tremor frequency.[8]

Fine motor function deteriorates with age and has been associated with cognitive decline and neurodegenerative diseases.[9,10] For example, dexterity was found to decrease with age and was associated with worse executive performance.[3] Interestingly, fine hand movements were found to be more symmetrical in women, whereas men performed more asymmetrically, although sex effects were relatively modest compared to age effects.[11] Nevertheless, currently available estimates of age and sex effects on fine motor function are mostly derived from small-scaled and heterogenous studies, warranting larger population-based investigations for delineating the complex associations of age and sex with fine motor function across the adult lifespan.

Changes in brain structure may account for the worsening of fine motor function with age. Previous studies on ageing populations have indeed found an association between cerebral and cerebellar atrophy and decreased fine motor skills required for a coordinated and smooth execution of voluntary movements.[12,13] However, thus far results have been inconsistent, with other studies reporting no association between volumes of some brain structures (e.g., cerebellar volume) and fine motor skills.[14] These discrepancies could be due to the large heterogeneity of the different study cohorts with regard to age, sex, socio-economic background, as well as lifestyle factors including alcohol consumption and smoking.

In this study, we aimed to examine differences in fine motor function across the adult lifespan, as quantitatively assessed through a digital SDT, and to evaluate whether these differences are sex-dependent. Secondly, we investigated which components of fine motor function (including speed, precision, and tremor) are most strongly associated with age and sex. Lastly, we assessed the association between brain structure (especially measures of structural integrity of motor regions including the cerebellum, basal ganglia, and motor

cortex due to their important role in initiating and regulating body movements) and components of fine motor function.

Methods

Study design

We used cross-sectional data from the first 8318 participants of the Rhineland Study (age range: 30–95 years), who underwent baseline assessments between March 2016 and November 2022. The Rhineland Study is an on-going population-based prospective cohort study in Bonn, Germany. The study recruits residents aged 30 years and above from two geographically defined areas in Bonn, Germany. The only other inclusion criterion was sufficient command of the German language to provide written informed consent. The initial analysis for age and sex effects was based on 7985 out of the first 8318 participants of the Rhineland Study. Participants with bilateral amputations or blindness (N = 8) were excluded. In addition, 313 participants failed to complete the spiral drawing task study due to: refusal to perform the task (N = 33), technical/acquisition failure (N = 196) or incomplete/erroneous data (N = 84). Reasons for incomplete/erroneous data included failure to exert sufficient pressure with the tip of the pen on the tablet while drawing the spiral, leading to incomplete data collection, and multiple drawing attempts compromising the post-processing procedure. Furthermore, we flagged tremor frequencies over 12 Hz as likely erroneous values and excluded as outliers (N = 12). The second analytical set, used for the subsequent analysis of the role of potential risk factors, consisted of 6210 participants with complete covariates data, excluding 1775 participants due to missing covariates. Finally, for the third analytical sample, which was used for estimating the association of brain-imaging measures and fine motor function, participants without MRI data (N = 2625), with missing covariates (N = 234), or with extreme intracranial volume values (N = 2) were excluded, resulting in 5124 participants (Fig. 1).

Fine motor function measurements

The participants' fine motor skills were assessed using the SDT test, which consisted of clockwise tracing of the outline of a clockwise Archimedes spiral template (diameter: 8.5 cm) on a digital tablet (Samsung Galaxy Note 10.1, model: SM-P600). During the SDT procedure, participants were instructed to position the pen (Samsung S-Pen, model: ET-PP600SWEGWW) tip at the centre of the spiral.[4] To ensure the validity of the assessment, participants were told not to rest their hand or arm on the desk, and to trace the spiral using their dominant hand, with an emphasis on achieving both accuracy and speed. Pen tip's cartesian coordinates (x, y) on the tablet were recorded by a touch screen (monitor refresh rate: 60 Hz). Automatic quantitative analyses were performed using custom-made software written in R (version 4.2.3, The R Foundation). Tracing area, tracing velocity, and tremor frequency were calculated to assess participants' fine motor function performance. The tracing area was defined as the space between the provided template spiral and the participants' drawn spiral (Fig. 2). The distance between two adjacent points was determined based on their coordinates, and the speed between each pair of points was subsequently calculated. The average tracing speed and its standard deviation were computed over the entire drawing period. To facilitate better comparisons of speed differences between individuals, standardised tracing velocity was calculated as the ratio of average tracing speed and the standard deviation of tracing speed. The frequency of tremor was defined as the dominant frequency of the tracing signal as obtained through a Fast Fourier Transform (FFT),[15,16] which decomposed the signal into its respective frequency domain representations. During data post-processing, we set a cutoff value of 4 Hz to distinguish between random jitter/technical artefacts and slight tremor.

Brain MRI

MRI scans were obtained using a 3T Siemens MAGNETOM Prisma system (Siemens Healthcare, Erlangen, Germany). The system is equipped with an 80 mT/m gradient and a 64-channel head-neck coil. T1-weighted images were acquired utilising a multi echo Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence with an isotropic spatial resolution of 0.8 mm.[17] The acquisition parameters were as follows: acquisition time (TA) of 6.5 min, repetition time (TR) of 2560 ms, inversion time (TI) of 1100 ms, a flip angle of 7°, and a field-of-view measuring 256 × 256 mm, comprising 224 sagittal slices. For data post-processing, the standard FreeSurfer stream (v.6.0) was used to extract brain structure volumes and cortical thickness.[18] FreeSurfer divides the brain segmentation into cortical (aparc) and subcortical (aseg) structures. Parcellation of the cortical structures was set to FreeSurfers's "Desikan-Killiany-Tourville" atlas. Segmentation quality was visually evaluated in a subset (n = 2661, 46.7%) based on criteria like incidental findings, examination annotations, age-corrected extreme volumetric values, and a random selection. In addition, we utilised the within cohort volumetric age dependency to identify participants outside of two standard deviations of the expected population volume. This section provides a summary of the MRI acquisition and processing protocols used in the Rhineland Study as the detailed MRI protocol has been described previously.[17]

Additionally, we conducted exploratory analyses of brain morphometry changes using two well-validated techniques. Vertex-based surface analysis (SBM) was applied to investigate the association between local

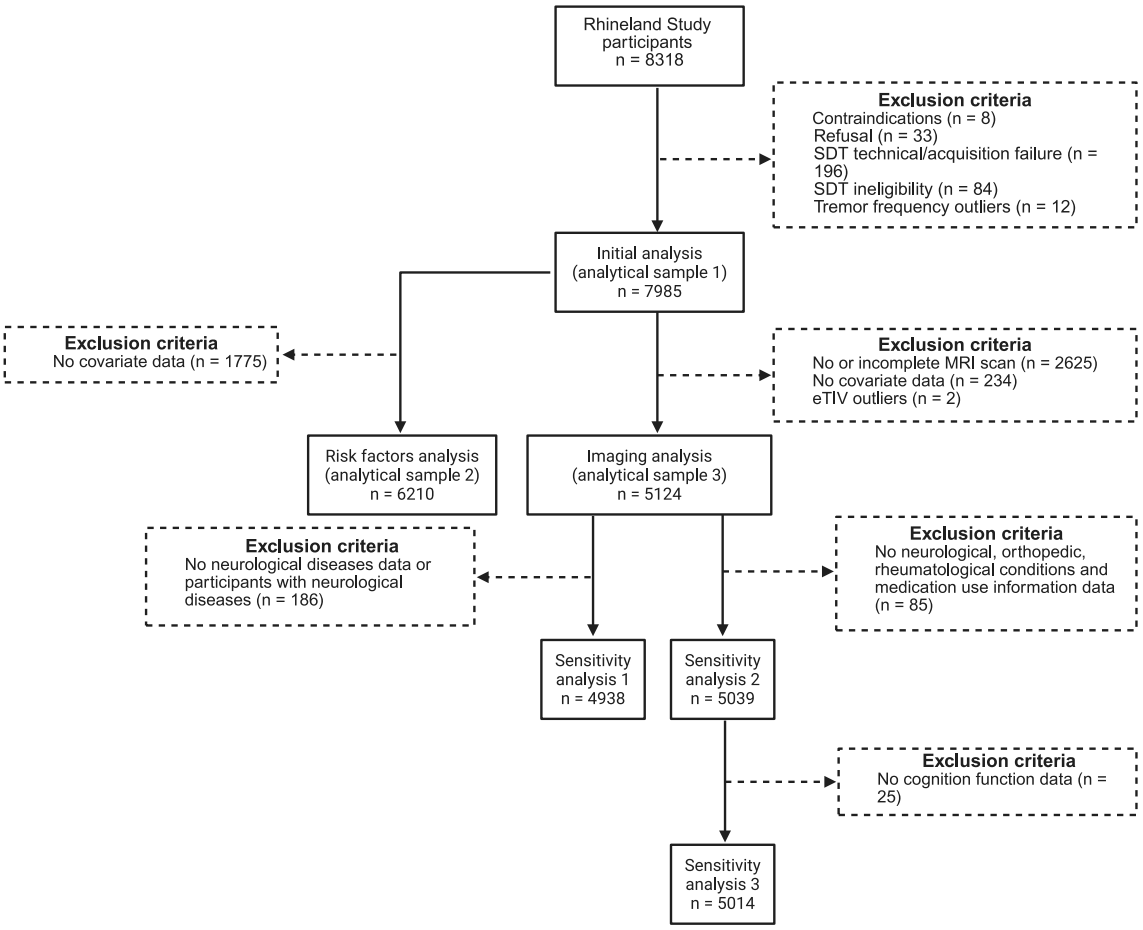

Fig. 1: **Participant flowchart**. Of the 8318 participants initially enrolled in the Rhineland Study, 333 were excluded due to contraindications (bilateral amputations or blindness), refusal, technical failure, ineligibility for the SDT, or tremor frequency outliers, resulting in an initial analytical sample (analytical sample 1) of 7985 participants. A separate risk factor analysis excluded 1775 participants with missing covariates, yielding a risk factors analysis sample (analytical sample 2) of 6210. For imaging analysis (analytical sample 3), participants without MRI data, with missing covariates, or extreme intracranial volume values were excluded, resulting in 5124 participants. Abbreviations: SDT = spiral drawing test; eTIV = estimated total intracranial volume.

cortical thickness and fine motor function. Individual thickness maps were registered to a group-averaged surface and smoothed with a 10-mm full-width-half-maximum (FWHM) kernel using FreeSurfer. Moreover, voxel-based morphometry analysis (VBM) was applied to investigate the association between grey matter volume and fine motor function. T1-weighted images were segmented into grey matter, white matter and CSF images using Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, UCL).[19] Grey matter images were normalised into the MNI space and further modulated and smoothed with an isotropic Gaussian kernel of 8 mm FWHM.

Covariates

Participants' demographic data such as age and sex were based on self-reports. Based on the American Society of Hand Therapists and Southampton Prototype Handbook, handgrip strength was measured with a handheld Jamar Plus Digital Dynamometer (Patterson Medical, Patterson, MD, USA).[20] Additionally, smoking status was categorised into current, former, or nonsmoker, based on a self-administered question. Participants' alcohol consumption was defined as average amount of pure alcohol, quantified in mass (g) consumed per day, and was reported as part of a self-administered semi-quantitative food frequency questionnaire (FFQ). Educational level was categorised using the criteria set by the International Standard Classification of Education (ISCE) 2011. Accordingly, the highest attained education level of participants was defined as low (encompassing lower secondary education or its equivalent), middle (spanning from upper secondary education to undergraduate university level), and high

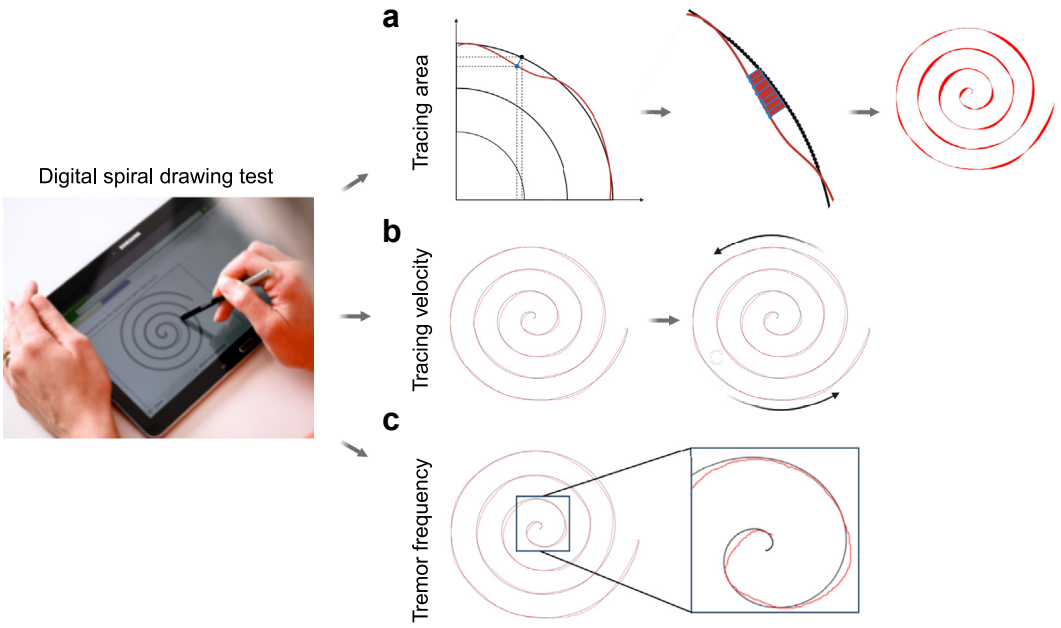

Fig. 2: **Digital spiral drawing test. a)** Tracing area: For each point on the traced spiral, the nearest point on the spiral template was identified and the Euclidean distance between the traced and this nearest point on the template was calculated (left). For each pair of adjacent points on the traced spiral and the corresponding points on the template, the area enclosed by the corresponding quadrilateral was estimated (middle). The tracing area (highlighted in red) was derived as the cumulative sum of all these subareas (right). **b)** Tracing velocity: The standardised tracing velocity was defined as the ratio of average tracing speed and the standard deviation of tracing speed. **c)** Tremor frequency: the dominant frequency of the tracing signal as obtained through a Fast Fourier Transform.

(pertaining to postgraduate university studies). Furthermore, participants' medical histories, encompassing neurological (e.g., Parkinson disease, multiple sclerosis, stroke, and intracranial haemorrhage) were obtained through self-reports and categorised as 'yes', 'no', or 'unknown'. These medical histories were subsequently converted into binary variables, indicating either presence or absence of each condition. Given that participants with worse visual acuity tended to perform worse on the SDT, best corrected visual acuity of both eyes was also included as a covariate. Briefly, the global cognitive score was obtained by averaging the domain scores for working memory (Corsi Block-Tapping Test and Digit Span Test), episodic verbal memory (Auditory Verbal Learning and Memory Test (AVLT)), processing speed (Trail-Making Test A and Pro-Saccade Task), and executive function (Word Fluency Task, Trail-Making Test B, and Anti-Saccade Task). Further detailed information on the cognitive test battery used in the Rhineland Study can be found in a previous publication.[21]

Ethics

The protocol of Rhineland Study was approved by the ethics committee of the University of Bonn Medical Faculty (Ref: 338/15). The study is conducted according to the International Conference on Harmonization Good Clinical Practice standards (ICH-GCP), with written informed consent from all participants obtained in accordance with the Declaration of Helsinki.

Statistics

To assess the association of age, sex and other covariates with SDT measurements (dependent variable), we used separate multivariable regression models. SDT measurements, including tracing area, standardised tracing velocity, and tremor frequency were right-skewed and were therefore log transformed. In the first model we included age and sex as predictor variables. Next, we added a quadratic term for age to evaluate potential nonlinear relationships between age and SDT measurements. In a subsequent model, we additionally adjusted for education level, best corrected visual acuity, smoking status, alcohol consumption, and handgrip strength to assess potential confounding by these variables. Finally, we included an age × sex interaction term to evaluate whether the association between age and SDT measurements was modified by sex.

To assess the relationship between brain structure and SDT measurements, and whether it might be confounded by other factors, we fitted several multivariable regression models. In the first model we included brain structure (independent variable), and age and sex as covariates. In subsequent models, we employed the same analytical strategy as described

above. Finally, we included an age × brain structure interaction term to evaluate whether the association between brain structure and SDT measurements was modified by age. Furthermore, we divided the sample into three equal-size age groups (age 30–49 years, 50–60 years and 61–95 years) to explore whether the association is more pronounced in older age groups. Considering the possible effect of head size on brain volumes, estimated total intracranial volume (eTIV) was included as a covariate in all volumetric analyses. Given that tremor frequency was not normally distributed even after logarithmic transformation, the 95% confidence intervals (CIs) around the regression coefficients (βs) in models with tremor frequency as the outcome were based on bias-corrected accelerated bootstrapping with 8000 re-samplings. Furthermore, we tested whether the association between brain structure and SDT measurements was altered after excluding participants with neurological disorders in an additional sensitivity analysis (sensitivity analysis #1). Additionally, we conducted another sensitivity analysis (sensitivity analysis #2) to examine whether the association between brain structure and SDT measurements was altered after adjusting for participants' neurological, orthopaedic, and rheumatological conditions, as well as medication use that may affect motor function. In a subsequent sensitivity analysis (#3), we added a global cognitive score to examine whether the association between brain structure and SDT measurements changed after adjusting for participants' global cognitive performance, and neurological, orthopaedic, and rheumatological conditions, as well as medication use that may affect motor function.

To allow comparison of effect sizes between different models and outcomes, all continuous independent and dependent variables were z-standardised. Model fits and normality of residuals were confirmed through visual inspection. For each predictor, p-values were calculated using the two-sided regression coefficient t-statistic. False discovery rate (FDR) correction was applied to adjust for multiple comparisons (including 29 comparisons for volumetric and 19 comparisons for cortical thickness measures) with FDR $q < 0.05$ considered statistically significant. Effect estimates are presented with the corresponding two-sided 95% CIs. All statistical analyses were performed in R (version 4.2.3, The R Foundation).

For the exploratory analyses of the relation between fine motor function and brain morphometry, general linear models were applied with age, age^2, sex, education level, best corrected visual acuity, smoking status and eTIV (only for VBM) as covariates. For VBM, p-values were calculated using the two-sided regression coefficient t-statistic and statistical inference was made at $p < 0.001$ after family-wise error correction for multiple comparisons. For SBM, p-values for clusters were computed based on permutation and clusters were considered significant with a cluster-forming threshold of $p < 0.05$ and 1000 iterations.[22,23]

Role of funders
The funders played no roles in the study design, data collection, data analysis, interpretation, or the writing of the manuscript.

Results

Characteristics of the study population
The characteristics of the study population are presented in Table 1. A comparison of demographic characteristics between male and female participants is presented in Supplementary Table S1. Participants were aged 30–94 years (56.5% female), and had a relatively high level of education, and good visual acuity. Given the relatively high proportion of missing brain MRI imaging data, a comparison between participants with and without brain MRI imaging data is provided in Supplementary Table S2. Participants with brain MRI data were younger and had a higher level of education.

Age effects and sex differences
The associations of age and sex with each SDT measure are presented in Fig. 3, and Supplementary Tables S3–S5. After adjustment for education level, best corrected visual acuity, smoking status, alcohol consumption, and handgrip strength, increasing age was significantly associated with a lower standardised tracing velocity (β = –0.166, 95% CI = –0.196 to –0.136), and larger tracing area (β = 0.242, 95% CI = 0.212–0.272) and higher tremor frequency (β = 0.099, 95% CI = 0.069–0.130). Age showed an exponential association with both tracing velocity and tremor frequency. Women performed better than men on all three SDT measures. After controlling for the effects of age, women had a significantly lower tracing area (β = –0.129, 95% CI = –0.051 to –0.207), lower frequency of tremor (β = –0.130, 95% CI = –0.055 to –0.212), and higher tracing velocity (β = 0.205, 95% CI = 0.285–0.125) (multivariable linear regression t-statistic, false discovery rate corrected $p < 0.05$). Further analysis revealed no significant interactions between age and sex in any of the SDT outcomes.

Covariates and risk factors
Smoking status was significantly associated with tracing area (former vs. current smoker: β = –0.166 [95% CI, –0.246 to –0.087]; never vs. current smoker: β = –0.239 [95% CI, –0.319 to –0.160]), while no association was found with tracing velocity (former vs. current smoker: β = 0.068 [95% CI, –0.013 to 0.150]; never vs. current smoker: β = 0.009 [95% CI, –0.072 to 0.090]) or tremor frequency (former vs. current smoker: β = –0.062 [95% CI, –0.153 to 0.018]; never vs. current smoker: β = –0.063 [95% CI, –0.150 to 0.016]). No significant associations were observed between alcohol

consumption and any of the SDT measures. Additionally, education level (middle level vs. high level: β = –0.130 [95% CI, 0.080–0.179]) was significantly associated with tracing area, while grip strength (β = 0.051 [95% CI, 0.010–0.092]) and best corrected visual acuity (β = –0.040 [95% CI, –0.067 to –0.013]) were significantly associated with tracing velocity (multivariable linear regression t-statistic, false discovery rate corrected $p < 0.05$). Therefore, smoking status, grip strength, education level and best corrected visual acuity were included as covariates in subsequent analyses (Supplementary Tables S3–S5).

Associations between predefined brain regions and fine motor function

After adjustment for age, sex, education level, best corrected visual acuity, smoking status, handgrip strength and eTIV, we found that smaller total brain volume (β = –0.108, 95% CI = –0.180 to –0.037), as well as smaller total (β = –0.118, 95% CI = –0.184 to –0.052), cortical (β = –0.088, 95% CI = –0.147 to –0.029), subcortical (β = –0.059, 95% CI = –0.109 to –0.009), supratentorial (β = –0.100, 95% CI = –0.163 to –0.037), and occipital grey matter volumes (β = –0.056, 95% CI = –0.092 to –0.020) were significantly associated with larger tracing area. Similarly, smaller volumes of the ventral diencephalon (β = –0.083, 95% CI = –0.125 to –0.042) and the hippocampus (β = –0.052, 95% CI = –0.089 to –0.015) were significantly associated with larger tracing area. Both smaller total cerebellar volume (β = 0.061, 95% CI = 0.022–0.100) and total cerebellar grey matter volume (β = 0.060, 95% CI = 0.022–0.099) were significantly associated with lower tracing velocity (multivariable linear regression t-statistic, false discovery rate corrected $p < 0.05$) (Fig. 4a, Supplementary Table S6). In contrast, lower volumes of total brain (β = –0.077, 95% CI = –0.164 to –0.011), ventral diencephalon (β = –0.038, 95% CI = –0.077 to –0.002), pallidum (β = –0.054, 95% CI = –0.094 to –0.022), total white matter (β = –0.057, 95% CI = –0.119 to –0.006), subcortical grey matter (β = –0.052, 95% CI = –0.098 to –0.005), supratentorial (β = –0.073, 95% CI = –0.153 to –0.011) and temporal white matter (β = –0.080, 95% CI = –0.144 to –0.030), frontal white matter (β = –0.057, 95% CI = –0.116 to –0.006), insular white matter (β = –0.049, 95% CI = –0.096 to –0.007), and temporal grey matter (β = –0.056, 95% CI = –0.108 to –0.011) were significantly associated with higher tremor frequency. However, larger occipital grey matter volume was significantly associated with a higher frequency of tremor (β = 0.054, 95% CI = 0.018–0.097) (multivariable linear regression CIs estimated using bias-corrected accelerated bootstrapping with 8000 re-samplings) (Fig. 4a, Supplementary Table S7).

Next, we examined whether the associations between brain volumetric measures and fine motor function performance varied by age. For tracing area and

	All participants	Subset with covariates available	Subset with MRI available	p-value[a]
N (n, %)	7985	6210	5124	
Age (years, SD)	55.46 (13.65)	54.85 (13.35)	54.30 (13.30)	<0.01
Sex (n, %)				
Male	3476 (43.50)	2711 (43.70)	2223 (43.40)	0.96
Female	4509 (56.50)	3499 (56.30)	2901 (56.60)	
Grip strength [kg, SD]	36.66 (11.31)	36.60 (11.24)	36.64 (11.27)	0.95[b]
Education level (n, %)				
High	4197 (53.10)	3382 (54.50)	2866 (55.90)	<0.01[b]
Low	147 (1.90)	93 (1.50)	67 (1.30)	
Middle	3559 (45.00)	2735 (44.00)	2191 (42.80)	
Best corrected visual acuity	1.12 (0.21)	1.13 (0.20)	1.13 (0.20)	0.09[b]
Alcohol consumption [g/d, SD]	19.76 (30.16)	19.29 (27.78)	19.34 (29.67)	0.60[b]
Smoking status (n, %)				
Current	939 (12.20)	717 (11.80)	619 (12.30)	0.18[b]
Former	3142 (40.80)	2478 (40.80)	1958 (38.90)	
Never	3618 (47.00)	2882 (47.40)	2459 (48.80)	
Hand dominance				
Both	230 (3.0)	195 (3.1)	151 (2.9)	0.954[b]
Right	7033 (91.7)	5693 (91.7)	4712 (92.0)	
Left	405 (5.3)	321 (5.2)	260 (5.1)	
Standardised spiral tracing velocity	2.60 (0.39)	2.61 (0.39)	2.61 (0.39)	0.16[b]
Spiral tracing area [cm^2] (SD)	4.97 (2.25)	4.94 (2.22)	4.90 (2.21)	0.22[b]
Spiral tremor frequency [Hz] (SD)	4.10 (0.44)	4.10 (0.43)	4.10 (0.43)	0.77[b]
Self-report medical conditions, n (%)				
Rheumatism				
Unknown	16 (0.2)	10 (0.2)	5 (0.1)	0.055
No	7612 (96.1)	5978 (96.8)	4940 (96.9)	
Yes	292 (3.7)	186 (3.0)	151 (3.0)	
Arthrosis				
Unknown	42 (0.5)	31 (0.5)	29 (0.6)	<0.001
No	5765 (72.8)	4635 (75.1)	3877 (76.1)	
Yes	2115 (26.7)	1509 (24.4)	1191 (23.4)	
Osteoporosis				
Unknown	13 (0.2)	10 (0.2)	9 (0.2)	0.243
No	7536 (95.0)	5911 (95.7)	4889 (95.8)	
Yes	380 (4.8)	258 (4.2)	205 (4.0)	
Gout				
Unknown	38 (0.5)	23 (0.4)	22 (0.4)	0.151
No	7273 (91.6)	5699 (92.2)	4739 (92.8)	
Yes	626 (7.9)	462 (7.5)	345 (6.8)	
Parkinson's disease				
No	7951 (99.7)	6187 (99.7)	5111 (99.8)	0.443
Yes	25 (0.3)	17 (0.3)	10 (0.2)	
Dementia				
Unknown	3 (0.0)	1 (0.0)	2 (0.0)	0.893
No	7966 (99.9)	6199 (99.9)	5116 (99.9)	
Yes	7 (0.1)	4 (0.1)	3 (0.1)	
Multiple sclerosis				
Unknown	2 (0.0)	2 (0.0)	2 (0.0)	0.864
No	7925 (99.4)	6158 (99.3)	5080 (99.2)	
Yes	49 (0.6)	44 (0.7)	39 (0.8)	
Intracranial haemorrhage				
Unknown	24 (0.3)	21 (0.3)	14 (0.3)	0.420
No	7879 (98.8)	6131 (98.9)	5076 (99.2)	
Yes	68 (0.9)	48 (0.8)	29 (0.6)	

(Table 1 continues on next page)

	All participants	Subset with covariates available	Subset with MRI available	p-value[a]
(Continued from previous page)				
Stroke				
Unknown	7 (0.1)	6 (0.1)	4 (0.1)	0.822
No	7851 (98.5)	6111 (98.6)	5056 (98.8)	
Yes	111 (1.4)	82 (1.3)	59 (1.2)	
Medication use, n (%)				
Diazepam				
No	7872 (100.0)	6137 (100.0)	5065 (100.0)	
Yes	0	0	0	
Phenobarbital				
No	7871 (100.0)	6136 (100.0)	5064 (100.0)	0.952
Yes	1 (0.0)	1 (0.0)	1 (0.0)	
Diphenhydramine				
No	7866 (99.9)	6134 (100.0)	5063 (100.0)	0.656
Yes	6 (0.1)	3 (0.0)	2 (0.0)	
Haloperidol				
No	7871 (100.0)	6137 (100.0)	5065 (100.0)	
Yes	0	0	0	
Chlorpromazine				
No	7871 (100.0)	6137 (100.0)	5065 (100.0)	
Yes	0	0	0	
Olanzapine				
No	7867 (99.9)	6135 (100.0)	5063 (100.0)	0.868
Yes	4 (0.1)	2 (0.0)	2 (0.0)	
Risperidone				
No	7867 (99.9)	6136 (100.0)	5062 (99.9)	0.479
Yes	4 (0.1)	1 (0.0)	3 (0.1)	
Amitriptyline				
No	7812 (99.2)	6100 (99.4)	5034 (99.4)	0.433
Yes	60 (0.8)	37 (0.6)	31 (0.6)	
Fluoxetine				
No	7841 (99.6)	6111 (99.6)	5047 (99.6)	0.865
Yes	33 (0.4)	27 (0.4)	19 (0.4)	
Carbamazepine				
No	7861 (99.9)	6129 (99.9)	5059 (99.9)	0.948
Yes	11 (0.1)	8 (0.1)	6 (0.1)	
Mephenytoin				
No	7872 (100.0)	6137 (100.0)	5065 (100.0)	
Yes	0	0	0	
Levodopa				
No	7844 (99.6)	6118 (99.7)	5049 (99.7)	0.825
Yes	31 (0.4)	21 (0.3)	17 (0.3)	
Propranolol				
No	7854 (99.8)	6120 (99.8)	5052 (99.7)	0.796
Yes	16 (0.2)	15 (0.2)	13 (0.3)	

[a]Comparison of demographic variables among all participants and the two subsets: Welch's Two Sample t-test (continuous variables); Pearson's Chi-squared test (categorical variables). [b]Additionally adjusted for age and sex.

Table 1: **Demographic characteristics.**

frequency, we found that with older age, the association between many brain volumetric measures (including total brain, total grey matter, occipital grey matter, ventral diencephalon, hippocampal, supratentorial total and grey matter volumes) and larger tracing area became more pronounced, specifically in the group aged over 60 years. However, the associations between brain volumetric measures and tracing velocity were only statistically significant in the middle-aged group (age 50–60 years) (Supplementary Figure S1a).

After accounting for age, sex, and other covariates we found that thinner mean cortical thickness of the total brain (β = –0.044, 95% CI = –0.075 to –0.013), and middle temporal (β = –0.039, 95% CI = –0.069 to –0.008), paracentral (β = –0.060, 95% CI = –0.088 to –0.033), parahippocampal (β = –0.030, 95% CI = –0.057 to –0.004), pars opercularis (β = –0.038, 95% CI = –0.067 to –0.009), precentral (β = –0.052, 95% CI = –0.082 to –0.023), posterior cingulate (β = –0.035, 95% CI = –0.063 to –0.007), superior frontal (β = –0.032, 95% CI = –0.061 to –0.004), superior parietal (β = –0.040, 95% CI = –0.068 to –0.011), superior temporal (β = –0.040, 95% CI = –0.071 to –0.008), and supramarginal gyri (β = –0.044, 95% CI = –0.076 to –0.012) was significantly associated with larger tracing area (i.e., lower precision) (Figs. 4b and 5, and Supplementary Table S8). Additionally, a thicker paracentral cortex (β = 0.047, 95% CI = 0.019–0.076) was significantly associated with higher tracing velocity (multivariable linear regression t-statistic, false discovery rate corrected $p < 0.05$). For frequency of tremor, we found that thinner mean cortical thickness of the total brain (β = –0.037, 95% CI = –0.074 to –0.001), and middle temporal (β = –0.039, 95% CI = –0.071 to –0.007), postcentral (β = –0.035, 95% CI = –0.071 to –0.001), praecuneus (β = –0.034, 95% CI = –0.070 to –0.001), superior temporal (β = –0.044, 95% CI = –0.081 to –0.011), and supramarginal gyri (β = –0.046, 95% CI = –0.086 to –0.008) was significantly associated with higher tremor frequency (multivariable linear regression CIs estimated using bias-corrected accelerated bootstrapping with 8000 re-samplings) (Figs. 4b and 5, and Supplementary Table S9). Furthermore, we found that the associations between mean cortical thickness of the total brain, middle temporal, superior parietal, superior temporal, supramarginal gyri and tracing area were age-dependent, with stronger associations in older participants. Conversely, the associations between several brain cortical thickness measures, such as precentral (β = –0.055, 95% CI = –0.120 to –0.004), postcentral (β = –0.064, 95% CI = –0.136 to –0.016) and superior parietal (β = –0.060, 95% CI = –0.130 to –0.021) regions, and tracing frequency were significantly more pronounced in the middle-aged groups (Supplementary Figure S1b).

Association between regional grey matter density and fine motor function

For the VBM analysis, higher grey matter density in temporal lobe (left superior: t_{Max} = –5.18, cluster size = 27,787 voxels; left inferior: t_{Max} = –4.15, cluster size = 7431 voxels; right inferior: t_{Max} = –4.38, cluster size = 15,015 voxels), thalamus (t_{Max} = –4.96, cluster size = 53,954 voxels), and cuneus

***Fig. 3:* Associations between age, sex and fine motor performance.** The number of participants in this analysis was 7985. **a)** Scatterplots showing age-related changes in tracing area in male (turquoise) and female (red). **b)** Scatterplots showing age-related changes in tracing velocity in male (turquoise) and female (red). **c)** Scatterplots showing age-related change in tremor frequency in male (turquoise) and female (red). Note: A lower tracing precision (larger tracing deviation area), slower tracing velocity, and higher frequency of tremor correspond to worse fine motor performance.

(left: $t_{Max} = -4.25$, cluster size = 6356 voxels) was significantly associated with smaller tracing area (t-statistic $p < 0.001$, corrected for family-wise error rate). Higher grey matter density in the left cerebellum was also significantly associated with faster tracing velocity ($t_{Max} = 4.46$, cluster size = 15,165 voxels, t-statistic $p < 0.001$, corrected for family-wise error rate, Fig. 6, Supplementary Table S10). No significant association was found between grey matter density and tremor frequency (t-statistic $p > 0.9$, corrected for family-wise error rate).

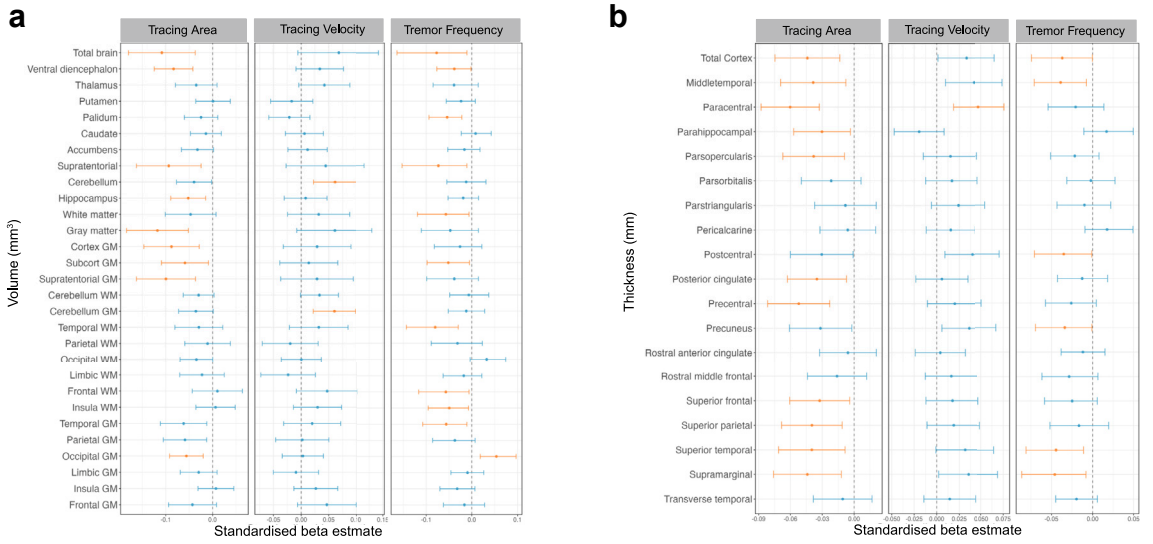

***Fig. 4:* Associations between brain structure and fine motor performance.** The number of participants in this analysis was 5124. Results that remained statistically significant after correction for multiple comparisons (false discovery rate $p < 0.05$, multivariable linear regression t-statistic) are indicated in orange. The x-axis indicates the SD change of fine motor function per SD change of brain volumetric measures or cortical thickness measures, and the corresponding 95% confidence intervals. **a)** Forest plots showing associations between brain volumetric measures and fine motor performance after adjustment for education level, best corrected visual acuity, smoking status, and handgrip strength and total intracranial volume (Model 3). **b**) Forest plots depicting associations between cortical thickness and fine motor performance after adjustment for education level, best corrected visual acuity, smoking status, and handgrip strength (Model 3). Abbreviations: GM = grey matter, SD = standard deviation, WM = white matter.

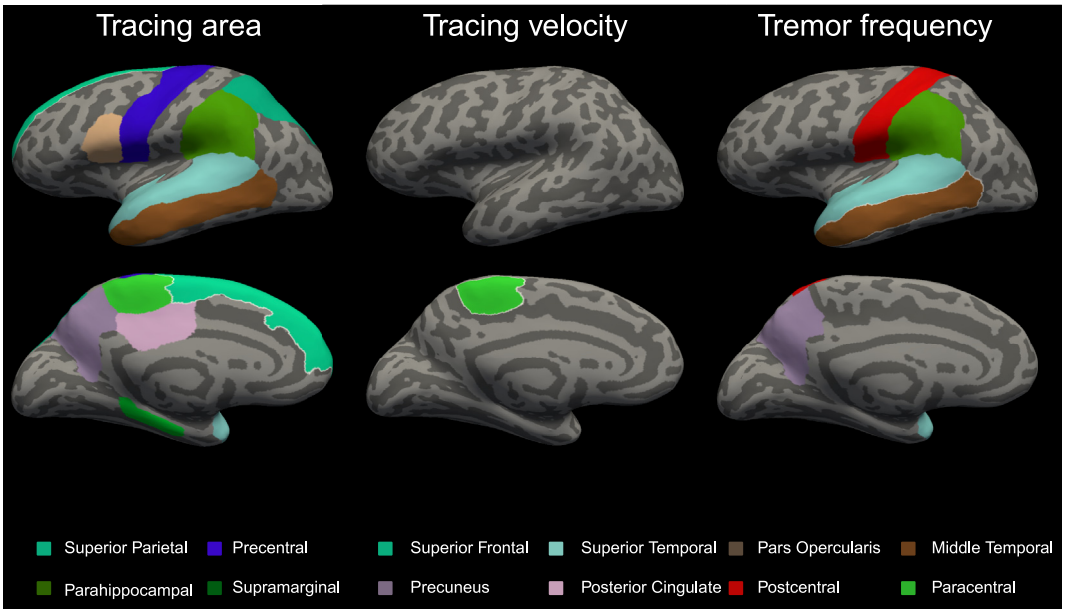

***Fig. 5:* Schematic illustration of the association of cortical thickness with fine motor function performance.** Cortical thickness was associated with tracing area (left), tracing velocity (middle), and tremor frequency (right). The associations are displayed on a template brain (sagittal view). The number of participants in this analysis was 5124. Only cortical areas are displayed, which exhibited a significant association with fine motor function at a false discovery rate corrected $p < 0.05$ (multivariable linear regression t-statistic).

Association between regional cortical thickness and fine motor function

Significant associations between vertex-wise cortical thickness and fine motor function are illustrated in Fig. 7. Thicker precentral (left: $t_{Max} = -4.51$, cluster size = 2367.52 mm^2; right: $t_{Max} = -5.21$, cluster size = 4777.63 mm^2) and lateral-occipital cortices (left: $t_{Max} = -4.99$, cluster size = 1576.86 mm^2) were associated with smaller tracing area, and thicker superior-temporal cortex was significantly associated with lower

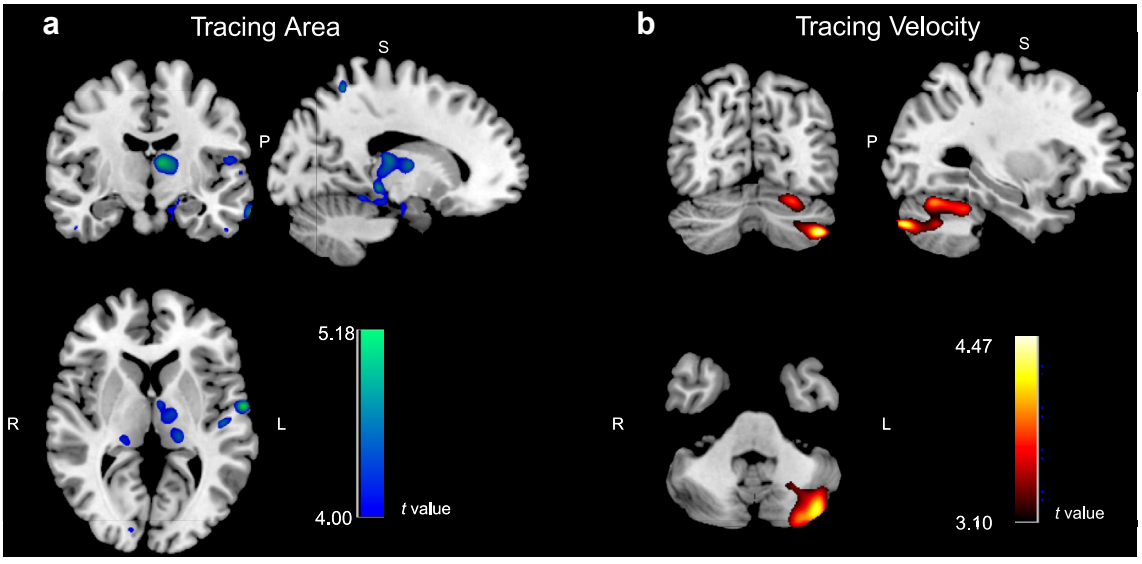

***Fig. 6:* Statistical maps showing voxel-wise associations between grey matter density and fine motor function.** For both **a)** tracing area and **b)** tracing velocity, panels show results derived from the voxel-based morphometry analyses using multivariable linear regression models in SPM12 (N = 5124). Maps have been rendered on the standard brain image (MNI152) using MRIcron, and were thresholded at $p < 0.001$ (multivariable linear regression t-statistic) and corrected for family-wise error. Multivariable regression coefficient t-statistics of grey matter change are coded as indicated by the colour bar. Positive associations are depicted in red and negative associations in blue. Abbreviations: P = posterior, S = superior, R = right, L = left.

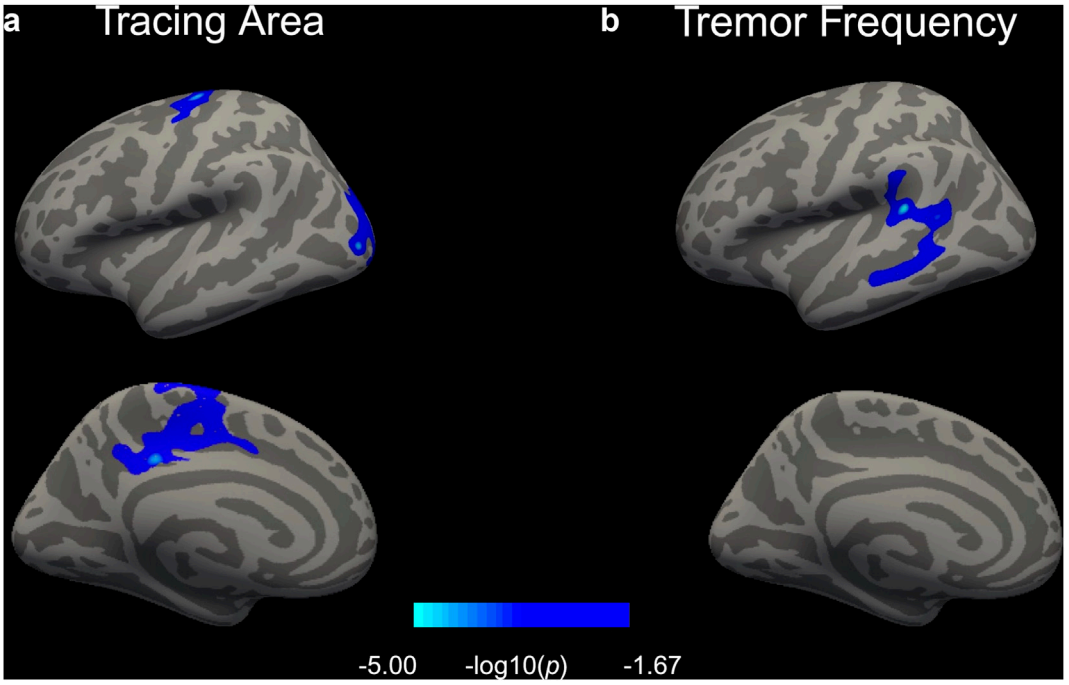

Fig. 7: **Statistical maps showing vertex-wise associations between cortical thickness and fine motor function.** For **a)** tracing area and **b)** tremor frequency, panels show results derived from the vertex-based morphometry analyses using generalised linear regression models in FreeSurfer (N = 5124). Maps have been rendered on the fsaverage template using FreeSurfer and were threshold at $p < 0.05$ (multivariate linear regression and permutation-based cluster-forming threshold) and 1000 iterations. Negative associations are depicted in blue.

tracing frequency (permutation-based cluster $p < 0.05$, with 1000 iterations). Thicker temporal and occipital cortices were also weakly associated with faster tracing velocity; however, this association did not survive multiple comparisons correction.

Sensitivity analysis

Our results did not change materially after exclusion of participants with known neurological diseases (Supplementary Figure S2). Similarly, adjusting for participants' global cognitive performance, and neurological, orthopaedic, and rheumatological conditions, as well as medication use did not materially change the magnitude or the statistical significance of our findings (Supplementary Figures S3 and S4, Supplementary Tables S11–S14).

Discussion

In this large, population-based study of adults 30 years and older, we combined high-resolution structural brain imaging with a continuous quantitative approach to evaluate fine motor function performance across adult lifespan. We found that fine motor function, as assessed through SDT (measuring tracing precision, tracing velocity, and tremor frequency) markedly changed with advancing age. Importantly, this association was independent of other established risk factors for fine motor dysfunction, including education level, handgrip strength, visual acuity, alcohol consumption, and smoking. Compared to men, women performed better on all three dimensions of fine motor function. We also found an age-dependent association between many brain structures and fine motor function, which became particularly pronounced in older age groups, including the volumes of total brain and hippocampus, as well as the thickness of several critical motor regions such as the para- and precentral gyri. In addition, we performed comprehensive SBM and VBM analyses of multiple brain structural features, and identified significant associations of cortical thickness and grey matter intensity with fine motor function.

In line with some previous studies employing simpler fine motor tasks such as the Purdue Pegboard test and finger tapping tasks, we also observed age-related change of fine motor function as measured by quantitative SDT.[24,25] Using standardised quantitative scores enabled us to identify motor outcome measures most sensitive to age effects. Specifically, we observed that tracing area, a measure of motor precision, exhibited the strongest association with age, and was the only variable among the three outcomes that showed a linear association with age. In contrast, another population-based study in 1912 community-dwelling

adults reported that deviation from the template remained stable up to 75 years of age, with steep worsening afterwards.[14] This discrepancy may be attributed to the wider age range and larger sample size of our study. In addition to motor precision, we also observed an exponential association of tracing velocity and tremor frequency with advancing age. Interestingly, the observed tremor frequency in this population-based cohort ranged from 4 to 12 Hz, spanning the range of tremor frequencies associated with the most common movement disorders, including Parkinson's disease (4–6 Hz), essential tremor (4–8 Hz), as well as enhanced physiological tremor (6–12 Hz).[26] Higher frequency tremors, such as orthostatic tremor (>13 Hz) are exceedingly rare, and if present, mainly affect the lower limbs,[26] aligning with their low prevalence in our cohort. Although our study was conducted in a general population rather than a clinical cohort, these findings raise the possibility that tremor detected through the spiral drawing test may serve as a potential biomarker for tremor-related movement disorders. However, as our study is cross-sectional, future longitudinal research is needed for establishing whether increased tremor during the spiral drawing test is linked to a higher risk of developing movement disorders, such as essential tremor and Parkinson's disease. Sex differences were observed in all three SDT outcomes, parallelling previous findings of superior fine motor function in women.[27] Although recently it was suggested that differences in fine motor precision between sexes may be attributed to test conditions and age,[11] our study demonstrates that sex differences in fine motor performance are independent of age and likely depend on other factors that still remain to be elucidated.

We found that both volumes and grey matter density of many brain structures were associated with fine motor performance. Besides the previously reported association between smaller total brain volume, total grey matter volume and decreased tracing precision,[14] we found that smaller hippocampal volume was also related to lower tracing precision. Although the hippocampus is widely recognised for its role in memory processing,[28] it also engages in the regulation and planning of motor activities,[29] particularly during performance of motor sequences.[30] Furthermore, it is involved in generating theta waves,[31] which have been shown to improve motor performance.[32] Apart from the hippocampus, a study in infants during the first two postnatal years demonstrated that the volumetric development of the caudate and putamen is also associated with fine motor function, indicating that these structures may directly or indirectly influence the development and maturation of fine motor control.[33] This is supported by the association between smaller volumes of caudate nuclei and impaired fine motor coordination in patients with hippocampal atrophy aged between 9 and 25 years old.[34] However, this association was notably absent in our adult population, indicating that despite their important role in fine motor development, the caudate and putamen may not be the primary contributors to age-related changes in fine motor skills.

Another key finding of our study is that, despite accounting for best-corrected visual acuity, we observed a significant relationship between smaller occipital grey matter volume and decreased tracing precision, which may be due to impaired central visual feedback required for accurate visuomotor tracking movements.[35] Additionally, we found negative associations between subcortical and temporal grey matter volumes and tremor frequency, indicating that fine motor impairment may reflect grey matter loss across both the cerebrum and cerebellum. Unexpectedly, our study revealed that occipital grey matter volume was positively related to tremor frequency, which may indicate a higher rate of corrective movements. However, no significant association was observed between grey matter density and tremor frequency. Consequently, the exact role of the occipital lobe in hand-eye coordination and motor control remains to be explored further. In line with the well-established role of the cerebellum in sensorimotor function,[36,37] our study revealed an association between cerebellar grey matter volume, density and tracing velocity.

Our study underscores the complex relationship between the cerebral cortex and fine motor movements.[38,39] We observed an association between thinner cortical thickness in the precentral, paracentral, supramarginal, and superior parietal gyri and larger tracing area. Similarly, smaller cortical thickness in the praecuneus and postcentral gyri was associated with higher tremor frequency. While the frontoparietal network is involved in human fine motor tasks like pincer grasping, the ventral premotor cortex and the anterior and inferior parietal lobule operate synergistically with the primary motor cortex to enable coordinated movements.[40] Notably, we also found an association between the cortical thickness of the pars opercularis of the frontal gyrus, which contains Broca's area, and tracing precision. While traditionally regarded as a pivotal language area in the brain, the functions of Broca's area extend beyond language processing. Neuroimaging studies have demonstrated connections between the Broca's area and Brodmann's areas 6, 8 and 9 (including the (pre-)supplementary motor areas),[41] as well as the importance of this region for complex hand movements and motor sequence learning.[42,43] Furthermore, given the observed associations of cortical thickness of the superior temporal, middle temporal, and parahippocampal gyri (critical components of the memory circuit in the brain), and SDT measures, our findings also suggest that fine motor performance may be related to memory function in general.

Our study has both strengths and limitations. We utilised a digital SDT, which provides precise and

objective measurements of fine motor function, reducing the risk of subjective bias. Additionally, thanks to the implementation of our brain structure automatic segmentation pipeline, we were able to include a large number of participants and we accounted for a range of potential confounders, increasing the robustness of our findings. However, the analyses were based on cross-sectional data, which precluded assessment of longitudinal associations between changes in brain structure and fine motor function. Secondly, due to lack of more detailed information, we could not account for the size of the hand or the thickness of the fingers. Although these factor influence the outcomes of the Purdue Pegboard Test, it is still unknown whether they could also affect SDT performance.[44,45] Additionally, we were unable to incorporate pinch grip strength into our analysis as these data were not available in the Rhineland Study. Therefore, further investigations that also utilise measures of hand size and pinch grip are warranted to validate and extend our findings. Furthermore, as the SDT test was administered using a digital tablet and stylus pen, participants' familiarity with this technology might have influenced test performance, particularly among older individuals and those from lower socioeconomic backgrounds. Another potential limitation of our study could be that our assessment of fine motor function was restricted to the dominant hand. Additionally, the SDT was standardised to a clockwise direction for all participants. Finally, given that the diameter of the Archimedes spiral template used was 8.5 cm, an effect of wrist movements on SDT performance cannot be ruled out.

In conclusion, our findings indicate that older adults had worse fine motor performance, including precision and speed of targeted movements, highlighting the detrimental impact of ageing on motor control. Moreover, women outperformed men on all three dimensions of fine motor function, but exhibited similar age-dependent differences in fine motor function which may inform tailored interventions. Importantly, total brain volume, hippocampal volume, cerebellar grey matter volume and density, as well as thickness of several critical motor regions (including para- and precentral gyri) was strongly related to fine motor function. Among all measures of fine motor function, tracing precision was most strongly related to brain structure, and may therefore serve as a practicable and promising biomarker of early neurodegeneration.

Contributors

X.Y., W.Z. and S.E. contributed to the acquisition and analysis of data. A.A. and M.B. conceptualised and supervised the study. X.Y., A.A. and W.Z. drafted the manuscript. X.Y., W.Z., S.E., M.B. and A.A. accessed and verified the underlying data. All authors provided critical feedback and contributed to the writing and revision of the final version of the manuscript. All authors have read and approved the final version of the manuscript and confirm its accuracy and integrity.

Data sharing statement

The Rhineland Study dataset is not openly accessible due to data protection regulations. Access to data can be provided to scientists in accordance with the Rhineland Study's Data Use and Access Policy. For additional details or to request access to the Rhineland Study dataset, please contact RS-DUAC@dzne.de.

Declaration of interests

M.B. reports the following declarations of interests: Co-PI of the project: Cluster of Excellence, "ImmunoSensation2—the immune sensory system" from German Research Funding Foundation (DFG); Grant number: EXC 2151—390873048. Co-PI of the project: Collaborative Research Center 1454 "Metaflammation & Cellular Programming", German Research Funding Foundation (DFG); Grant number: 43232535. Co-PI of the project: Competence Cluster in Nutrition Research, "Diet—Body—Brain (DietBB2)", German Ministry for Science and Education (BMBF); Grant number: 01EA1809C. PI of the project: "PreBeDem–Mit Prävention und Behandlung gegen Demenz", German Ministry for Science and Education (BMBF); Grant number: 01KX2230. Collaborator of the project: "Perceived Stress, inflammation, and the risk of neurodegeneration", Alzheimer Forschung Initiative (AFI); Grant number: #22017. Co-PI of the project: "Early plasma biomarker signature of Alzheimer in the general population", Alzheimer Forschung Initiative (AFI); Grant number: #24054CB. She is a member of the Scientific Advisory Board of the Central Institute of Mental Health, Mannheim, Germany, a member of the Advisory Board of the Leibniz Institute on Aging–Fritz Lipmann Institute, and a member of the Executive Board of the Cluster of Excellence ImmunoSensation2.

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Other co-authors report no relevant declarations of interests for this article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2025.105771.

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