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RESEARCH ARTICLE

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Structural brain networks correlating with poststroke cognition

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Abstract

Cognitive deficits are a common and debilitating consequence of stroke, yet our understanding of the structural neurobiological biomarkers predicting recovery of cognition after stroke remains limited. In this longitudinal observational study, we set out to investigate the effect of both focal lesions and structural connectivity on post-stroke cognition. Sixty-two patients with stroke underwent advanced brain imaging and cognitive assessment, utilizing the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE), at 3-month and 12-month poststroke. We first evaluated the relationship between lesions and cognition at 3 months using voxel-based lesion-symptom mapping. Next, a novel correlational tractography approach, using multi-shell diffusion-weighted magnetic resonance imaging (MRI) data collected at both time points, was used to evaluate the relationship between the white matter connectome and cognition cross-sectionally at 3 months, and longitudinally (12 minus 3 months). Lesion-symptom mapping did not yield significant findings. In turn, correlational tractography analyses revealed positive associations between both MoCA and MMSE scores and bilateral cingulum and the corpus callosum, both cross-sectionally at the 3-month stage, and longitudinally. These results demonstrate that rather than focal neural structures, a consistent structural connectome underpins the performance of two frequently used cognitive screening tools, the MoCA and the MMSE, in people after stroke. This finding should encourage clinicians and researchers to not only suspect cognitive decline when lesions affect these tracts, but also to refine their investigation of novel approaches to differentially diagnosing pathology associated with cognitive decline, regardless of the aetiology.

KEYWORDS
cognition, connectometry, MMSE, MoCA, stroke, white matter

Abbreviations: dMRI, diffusion-weighted magnetic resonance imaging; FA, fractional anisotropy; FDR, false discovery rate; QA, quantitative anisotropy; WM, white matter.

1 | INTRODUCTION

Cognitive impairments are a common and debilitating consequence of stroke, impacting between 8% and 71% of stroke survivors (Eskes et al., 2015; Jokinen et al., 2015). With an expected 27% increase in the number of people living with stroke by 2047 (Wafa et al., 2020), reliable predictors of cognitive recovery and prognoses are needed to ensure that resources supporting those with residual cognitive impairment are targeted and equitable. It is well accepted that the presence of a cognitive impairment dramatically impacts recovery after stroke (Ginex et al., 2022; Lugtmeijer et al., 2021), and yet our understanding of neurobiological biomarkers to predict recovery of cognitive impairments remains limited (Boyd et al., 2017; Tahmi et al., 2022).

To understand the recovery of cognitive processes after stroke, the contribution of the different structural neural networks supporting these functions must be clarified. Given the limited use of functional imaging in clinical practice, proposed predictors must be germane to neuroanatomical information available with standard clinical imaging. Many studies have demonstrated that white matter integrity predicts poststroke recovery including global cognitive scores (Kliper et al., 2014), and across multiple cognitive and motor domains (Ramsey et al., 2017; Salvalaggio et al., 2020). Moreover, white matter integrity of the contralesional hemisphere has also been associated with cognitive recovery after stroke (Dacosta-Aguayo, Graña, Fernández-Andújar, et al., 2014). These findings underline the relevance of structural network connections supporting cognitive processes in the brain and how perturbations in white matter connectivity can give rise to cognitive impairment (Reijmer et al., 2016; Siegel et al., 2022).

In terms of the structural neural networks supporting cognition, studies have typically highlighted the contribution of white matter structures to discrete cognitive functions after stroke, such as spatial neglect (Karnath et al., 2011), language (Sihvonen et al., 2023) and executive functioning and memory (Bubb et al., 2018), rather than global measures of cognition. Global measures of cognition, such as the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), are commonly used in clinical practice to screen for global and specific mental functions (Saa et al., 2019). Given that disparate brain regions are likely involved in underpinning global measures of cognition, rather than singular focal neural structures, lesion-symptom mapping approaches alone are unlikely to advance our understanding of the necessary cortical networks. A network approach will likely be essential to advancing our understanding of the neural networks involved, and utilizing this to inform predictors of recovery (Siegel et al., 2022).

Diffusion magnetic resonance imaging (dMRI) studies utilizing global measures of cognition have evaluated whole-brain connectivity measures and shown that they correlate with poststroke cognitive impairments (Aben et al., 2021; Kern et al., 2022). However, studies are lacking that utilize whole-brain structural connectivity data, while evaluating individual white matter tracts and their contribution to poststroke cognitive outcomes. A clearer understanding of the structural networks underlying cognition, and the recovery of cognition, would help clinicians to provide reliable prognoses of cognitive impairment and recovery. Correlational tractography utilizing connectometry is an analysis approach that uses quantitative anisotropy (QA)-based permutation testing to identify white matter tracts associated with a variable of interest. This approach, compared to more conventional approaches utilizing fractional anisotropy (FA)-based measures, has been shown to be more sensitive due to there being less susceptibility to the partial volume effects of free water, crossing fibres and non-diffusive materials (Jin et al., 2019; Yeh et al., 2013). Although we have recently demonstrated this in one aspect of cognitive processing, namely language after stroke (Sihvonen et al., 2023), no studies have utilized whole-brain connectometry to investigate the structural connectome underpinning poststroke cognition beyond language (Sihvonen et al., 2023), nor how this impacts the recovery of function after stroke. Of note, when using this approach in the language domain, the corpus collosum, a white matter structure not typically considered in the context of language, was shown to be integral to the structural connectome supporting language function. This contribution likely reflected the interhemispheric neural communication required for functional language tasks in the presence of a lesion (Sihvonen et al., 2023). In addition, given there was a differential pattern of network associations demonstrated within the single cognitive domain of language function, it is likely that more general, global measures of cognition, as obtained using the MoCA (Nasreddine et al., 2005) and the MMSE (Folstein et al., 1975), are also likely to reflect the integrity of a broader neural network, involving intra- and inter-hemispheric communication, rather than be reliant upon a single structure–function relationship.

To this end, we specifically assessed the relationship between poststroke cognitive abilities, as measured by two popular screening assessments of poststroke cognition (the MoCA and MMSE), and neuroanatomical structural integrity. Integrity was investigated in terms of both localized structure–function relationships, and the broader neural networks' relationship to function. The MoCA and MMSE were specifically chosen due to their clinical and research (Saa et al., 2019) popularity and use, given that predictors of recovery of cognition are likely to be implemented into clinical practice more readily if both the neuroimaging techniques and the cognitive measures employed are routinely used in clinical and research practice. Moreover, little is known about the neural architecture underpinning performance on either tool, or the extent to which their tasks tap into the same structure–function relationship. Although there has been shown to be a strong relationship between behaviour assessed by these two assessments in acute stroke ($R^2 = .78$; $p < .0001$) (Shen et al., 2016; Suda et al., 2020), little is known about this relationship beyond this early stage, and once neural damage has stabilized. As such, elucidating the whole-brain structural networks underpinning cognition after stroke, as measured by both tools, will contribute to our understanding of the neural structures being used to support the same cognitive functions being assessed in a global screen of cognitive abilities.

We utilized both a voxel-based lesion symptom mapping approach (Dronkers et al., 2004) and whole brain connectometry (Yeh, Badre, et al., 2016) based correlational tractography on multi-shell dMRI data, acquired at the late subacute stage after stroke. For a

subset, we were also able to use 12-month follow-up data to investigate how this relationship changed from the subacute (3 months) to the chronic (12 months) stage. Based on the previous dMRI evidence (Sihvonen et al., 2023), we hypothesized: (i) global measures of cognitive function will be associated with distributed neuroanatomical structural networks, 'connectomes', rather than discrete neuroanatomical regions; (ii) similar structural connectomes will be associated with both the MoCA and MMSE, due to their largely overlapping functional foci; and that (iii) intra- and inter-hemispheric structural connections, including the corpus callosum, would be involved in the structural connectome underpinning overall measures of cognitive performance.

2 | MATERIALS AND METHODS

2.1 | Participants and study design

This longitudinal cohort study is a part of the 'STroke imAging pRevention and Treatment (START)' study approved by Human Research Ethics Committees (HREC 2009.79 and H2010/03588; and for future analysis HREC17Austin281). All participants gave informed written consent in accordance with the Declaration of Helsinki. Inclusion criteria were: presenting with acute ischemic stroke, aged ≥18 years. Exclusion criteria were: contraindication to imaging with MRI; pre-stroke modified Rankin Score (mRS) score of ≥2 (indicating previous disability); any terminal illness such that the patient would not be expected to survive more than 1 year; clinically evident pregnancy; and non-English speaking. Sixty-two participants with a mean lesion volume of 77.8 mL (SD 10.4) were recruited from five hospital sites in Victoria, Australia 2010–2013 (PrePARE substudy; Carey et al., 2015).

2.2 | Cognitive assessment

Global cognitive impairment was screened using the MoCA (Nasreddine et al., 2005) and the MMSE (Folstein et al., 1975). Assessments were carried out by an occupational therapist trained in administration of the tools at two time points, 3 months (mean = 95.8 days, SD = 1.7 days) and 12 months (mean = 370.0 days, SD = 1.4 days), after stroke.

2.3 | MRI data acquisition and reconstruction

All neuroimaging data was acquired on a 3-Tesla Siemens Trio MRI scanner (Siemens, Erlangen, Germany) with a 32-channel head coil. MRI data was acquired at 3 months (mean = 95.8 days, SD = 1.8 days), and 12 months (mean = 370.0 days, SD = 1.3 days.) For each participant, a high-resolution structural 3D T1-weighted image (MP-RAGE; TR = 1900 ms; TE = 2.55 ms; 256 × 256 matrix, 160 slices, 216 mm FOV; voxel size = 1 mm^3) and dMRI data with 13 non-diffusion weighted volumes and 85 diffusion weighted volumes (25 volumes with $b = 1000$ s/mm^2 and 60 volumes with $b = 3000$ s/mm^2) covering the whole brain and brainstem were acquired (TE = 110 ms, TR = 8500 ms, 2.5 × 2.5 × 2.5 mm^3 resolution). T1-weighted images were collected for the whole sample ($n = 62$) at 3-month stage. Multi-shell dMRI data were collected at 3-month poststroke for a sample of 31 participants, 24 of which also had dMRI data collected at the 12-month follow-up.

Structural T1-weighted images were preprocessed and normalized using the Statistical Parametric Mapping software (SPM12; www.fil.ion.ucl.ac.uk/spm/) under MATLAB R2018b. Stroke lesions were manually delineated to the individual T1 images slice-by-slice (by A.J.S) using the MRIcron software package (http://people.cas.sc.edu/rorden/mricron/index.html). Individual T1-weighted images and lesion images were then reoriented according to the anterior commissure and segmented using Unified Segmentation (Ashburner & Friston, 2005) with medium regularization. During the preprocessing, individual lesion images were used to apply cost function masking to achieve optimal normalization of the lesioned brain tissue, with no post-registration lesion shrinkage or out-of-brain distortions (Brett et al., 2001; Ripollés et al., 2012). The segmented grey and white matter tissue probability maps were modulated and normalized to the Montreal Neurological Institute (MNI) space. In addition, the lesion masks defined in native space were also registered to MNI space using the normalization parameters obtained during the segmentation process. Finally, the tissue probability maps and lesion images were smoothed with an 8-mm full width at the half maximum kernel.

Diffusion images were denoised using Marchenko-Pastur PCA method (Veraart et al., 2016) implemented in the MRTrix3 software (Tournier et al., 2019). Next, Gibbs ringing artefact correction was performed with a method based on local subvoxel-shifts (Kellner et al., 2016). After this, the dMRI data were reconstructed in the MNI space using q-space diffeomorphic reconstruction (Yeh & Tseng, 2011) that allows the construction of spin distribution functions (Yeh et al., 2010) in DSI Studio (http://dsi-studio.labsolver.org, version April 7 2021), and corrected for motion. The b-table was checked by an automatic quality control routine to ensure its accuracy (Schilling et al., 2019). Normalization was carried out using the anisotropy map of each participant and a diffusion sampling length ratio of 1.25. Quality of the normalization was inspected using the R^2 values denoting goodness-of-fit between the participant's anisotropy map and template. Each participant's forceps major and minor were inspected and used as an anatomical benchmark to confirm the normalization quality (Hula et al., 2020). The restricted diffusion was quantified using restricted diffusion imaging (Yeh et al., 2017) and quantitative anisotropy (QA) was extracted as the local connectome fingerprint (Yeh, Vettel, et al., 2016) and used in the connectometry analysis.

2.4 | Voxel-based lesion-symptom mapping

Voxel-based lesion-symptom mapping (VLSM) relations were evaluated using NiiStat (https://www.nitrc.org/projects/niistat/). Two

separate analyses were carried out to identify lesions associated with lower MoCA and MMSE scores. Only voxels lesioned in at least six patients (~10% of the sample) were included in the analyses. Analyses were adjusted for lesion volume and voxelwise analysis, with corresponding voxelwise p values corrected for multiple comparisons using false discovery rate (FDR) thresholding with the alpha level set to $p < .05$.

2.5 | Correlational tractography analysis

Diffusion MRI connectometry (Yeh, Badre, et al., 2016) analysis was carried out using correlational tractography under DSI Studio (available at: http://dsi-studio.labsolver.org/). Correlational tractography utilizing connectometry works by identifying associations between study variables and local white matter connectomes (Yeh, Badre, et al., 2016). Unlike FA-based structural connectome analyses, which identify differences in the mean values for the whole white matter tract or using voxel-based FA values, connectometry uses QA, a diffusion orientation distribution function based measure, to track only the segment of the fibre bundle that exhibits significant association with the study variable. To do this, dMRI data are reconstructed into a standard template space (MNI) to map a local connectome matrix from the studied sample. Study-relevant variables, here MoCA and MMSE scores, are then associated with this local connectome matrix to identify local connectomes expressing significant associations with the variable of interest. These local connectomes are then tracked along the core pathway of a fibre bundle (based on Human Connectome Project 1065 template data) using a fibre tracking algorithm and compared with a null distribution of coherent associations using permutation statistics. In total, four multiple regression models were calculated: two models were used to identify the local connectomes associated with MoCA and MMSE scores at the late subacute stage after stroke. Two further regression models were used to identify the longitudinal local connectome changes associated with longitudinal change (12 months >3 months) in MoCA and MMSE scores. All analyses were adjusted for age and lesion volume. Local connectomes with T-scores exceeding 3 were selected (Hula et al., 2020) and tracked using a deterministic fibre tracking algorithm (Yeh et al., 2013) to obtain correlational tractography. The tracks were filtered by topology-informed pruning (Yeh et al., 2019) with eight iterations, and a length threshold of 30 voxel distance was used to identify significant tracts. QA values were normalized to homogenize the data. Bootstrapping resampling with 1000 randomized permutations was used to obtain the null distribution of the track length and estimate the FDR. Alpha level was set to $p < .05$.

2.6 | Data availability

Anonymized analysed data reported in this manuscript are available from the corresponding author upon reasonable request and subject to approval by the appropriate regulatory committees and officials.

3 | RESULTS

3.1 | Clinical and demographic details

Participant details and demographics are reported in Table 1.

3.2 | Behavioural analysis

A Pearson's correlation showed that performance on the MoCA and MMSE (see Table 2) were significantly correlated ($r = .484$, $p < .001$).

3.3 | Voxel-based lesion-symptom mapping ($n = 62$)

To identify lesion areas associated with global cognitive performance, we conducted VLSM analyses for the MoCA total scores and MMSE total scores at the 3-month stage. Neither MoCA nor MMSE scores were significantly associated with any brain areas that were lesioned at the 3-month stage.

3.4 | Correlational tractography analysis

3.4.1 | Cross-sectional analyses ($n = 31$)

At the 3-month stage, both MoCA and MMSE scores were positively associated (i.e., higher QA associated with greater MoCA or MMSE

TABLE 1 Patient characteristics/demographics in both the late subacute stage after stroke, and those with longitudinal follow-up.

	3 months	12 months
Participants (*n*)	62	24
Age (mean ± SD years)	63.03 ± 12.98	60.26 ± 12.59
Males	18	8
Education (years) (mean ± SD years)	11.62 ± 3.34	11.97 ± 3.26
Days poststroke to MRI (mean ± SD days)	95.46 ± 10.33	369.81 ± 12.12

Abbreviations: MRI, magnetic resonance imaging; n, number of participants; SD, standard deviation.

TABLE 2 Mean (range) and standard deviation (SD) of patient behavioural scores on the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE), at 3 and 12 months after stroke.

	3 months	12 months
MoCA	26.72 (15–30)	26.49 (14–30)
	SD = 2.87	SD = 3.39
MMSE	27.44 (20–30)	27.62 (14–30)
	SD = 2.10	SD + 2.09

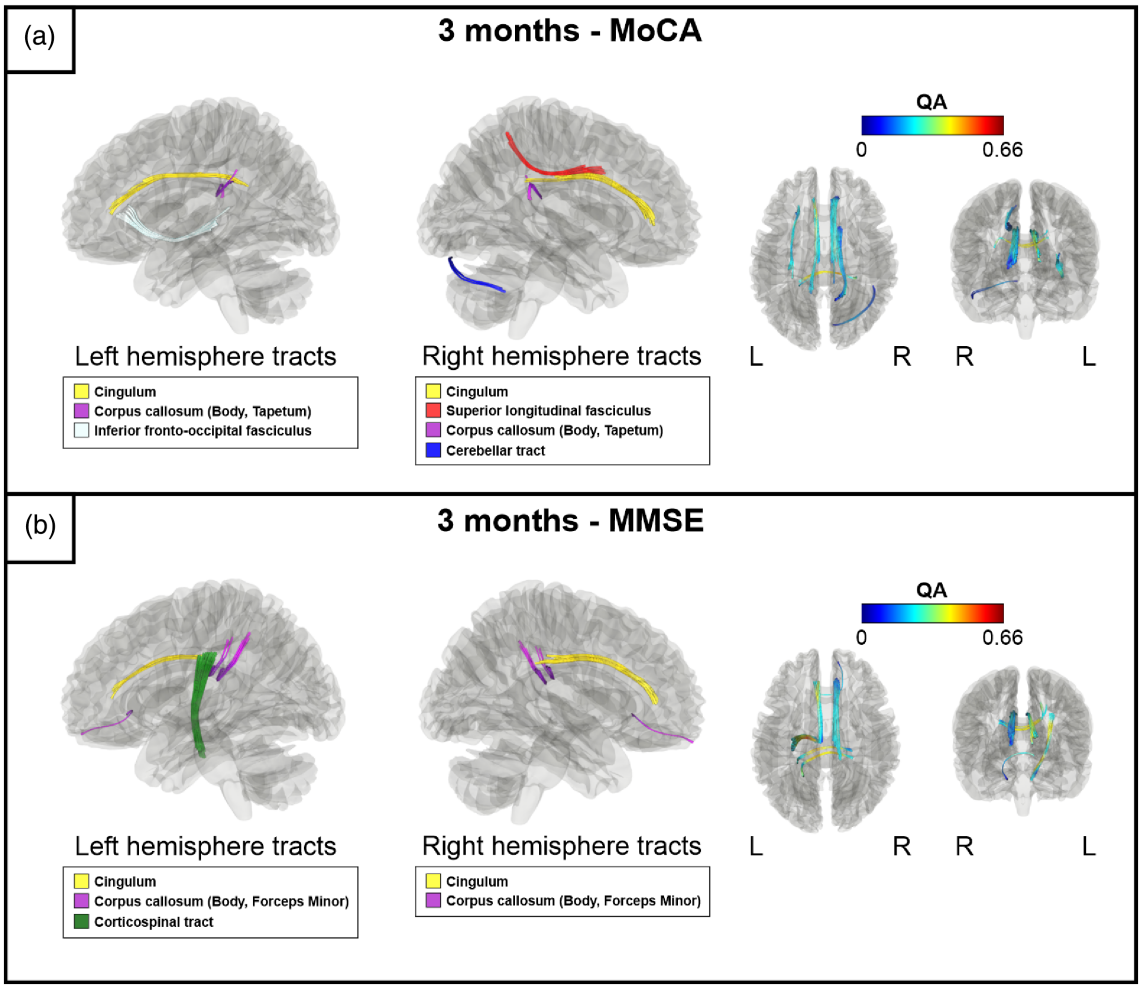

FIGURE 1 Cross-sectional findings at 3 months poststroke showing tracts positively associated with MoCA and MMSE scores. (a) Tracts positively associated with MoCA score at the 3-month stage ($N = 31$). (b) Tracts positively associated with MMSE score at the 3-month stage ($N = 31$). All results are thresholded at p_{FDR} <0.05. FDR, false discovery rate; L, left; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; R, right.

score) with segments of the bilateral cingulum and corpus callosum, $p_{FDR} < .05$ (Figure 1a,b). In addition, greater MoCA scores were associated with higher QA in the left inferior fronto-occipital fasciculus, the right superior longitudinal fasciculus and cerebellar tracts, $p_{FDR} < .05$ (Figure 1a). In contrast, greater MMSE scores were associated with higher QA in the left corticospinal tract, $p_{FDR} < .05$ (Figure 1b). Exact p_{FDR} values, segment volumes and mean QA values for each significant segment have been reported in Table 3. Negative associations were not observed.

3.5 | Longitudinal analyses ($n = 24$)

Longitudinal (12-month >3-month poststroke) change in both MoCA and MMSE scores were positively associated with longitudinal (12-month >3-month poststroke stage) QA changes in the corpus callosum and segments of the bilateral cingulum, left corticospinal tract, and left inferior fronto-occipital fasciculus, $p_{FDR} < .05$ (Figure 2a,b). In addition, MMSE change scores were positively associated with longitudinal change in QA segments of the left inferior longitudinal fasciculus and right thalamic radiation ($p_{FDR} < .05$) (Figure 2b). Exact p_{FDR} values, segment volumes and mean QA values for each significant segment have been reported in Table 3. Negative associations were not observed.

4 | DISCUSSION

Using VLSM and QA-based whole-brain correlational tractography analyses, we provide novel evidence that global cognitive outcomes after stroke may not be associated with singular focal grey matter structures, but rather with widespread structural neural circuits, in particular involving the cingulum and the corpus callosum. The consistency of the findings across two widely used clinical screens of cognitive abilities suggests that the same neural architectures underpin the functional behaviours assessed using these two screening tools in a

TABLE 3 Significant tract segments associated with performance on the MoCA, MMSE at both 3-month poststroke and longitudinally (12-month >3-month poststroke).

	p_{FDR} value	Segment volume	Segment QA_{Mean}
MoCA—3 months			
Left cingulum	.003	760 mm^3	0.28
Right cingulum	.003	1291 mm^3	0.24
Corpus callosum	.003	229 mm^3	0.39
Left IFOF	.003	470 mm^3	0.24
Right SLF	.003	547 mm^3	0.19
Right cerebellar tracts	.003	227 mm^3	0.12
MMSE—3 months			
Left cingulum	.002	487 mm^3	0.28
Right cingulum	.002	1225 mm^3	0.25
Corpus callosum	.002	482 mm^3	0.35
Forceps minor	.002	72 mm^3	0.20
Left corticospinal tract	.002	1028 mm^3	0.36
MoCA—longitudinal			
Left cingulum	.001	579 mm^3	0.28
Right cingulum	.001	1580 mm^3	0.24
Corpus callosum	.001	3340 mm^3	0.35
Forceps minor	.001	3580 mm^3	0.28
Left corticospinal tract	.001	3556 mm^3	0.37
Left IFOF	.001	112 mm^3	0.28
MMSE—longitudinal			
Left cingulum	.002	1267 mm^3	0.24
Right cingulum	.002	542 mm^3	0.24
Corpus callosum	.002	1422 mm^3	0.35
Forceps minor	.002	1228 mm^3	0.29
Tapetum	.002	97 mm^3	0.37
Left corticospinal tract	.002	244 mm^3	0.37
Left IFOF	.002	612 mm^3	0.25
Left ILF	.002	665 mm^3	0.24
Right thalamic radiation	.002	188 mm^3	0.20

Note: For each significant segment, p_{FDR} values with respect to length of the finding, segment volumes and mean QA.

Abbreviations: IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; QA_{Mean}, mean quantitative anisotropy value; SLF, superior longitudinal fasciculus.

poststroke population. In particular, we have demonstrated that the cingulum and the corpus collosum are both integral to global cognitive function after stroke. Our findings provide novel evidence that the structural integrity of white matter networks underpinning performance on these cognitive screening tools may be useful in capturing a continuum of cognitive performance, from healthy functioning to impaired functioning, and possibly the differential diagnosis of a range of pathological processes impacting cognition. Future research, utilizing neuropsychological measures that capture a range of performance in healthy brains, as well as clinical presentations, would be an important future direction to build on this differentiation. This is the first longitudinal study evaluating the contribution of individual white matter pathways to poststroke measures of global cognitive outcomes.

A positive relationship was observed between performance on both the MoCA and MMSE and QA within bilateral cingulum at the 3-month stage. This relationship persisted when considering longitudinal change scores (12-month >3-month poststroke stage) within the whole-brain white matter connectome. Unsurprisingly, given its anatomical connections to cortical nodes within cognitive control networks, this frontal association tract has been shown to influence performance on cognitive tasks in other populations (healthy controls and mild cognitive impairments) (Metzler-Baddeley et al., 2012), specifically the dorsal/anterior parts of the cingulum bundle, appear to mediate performance on tasks requiring cognitive control, attention and executive function (for review see Bubb et al., 2018). Adjacent to the cingulum, and receiving projections from it, lies the dorsal anterior

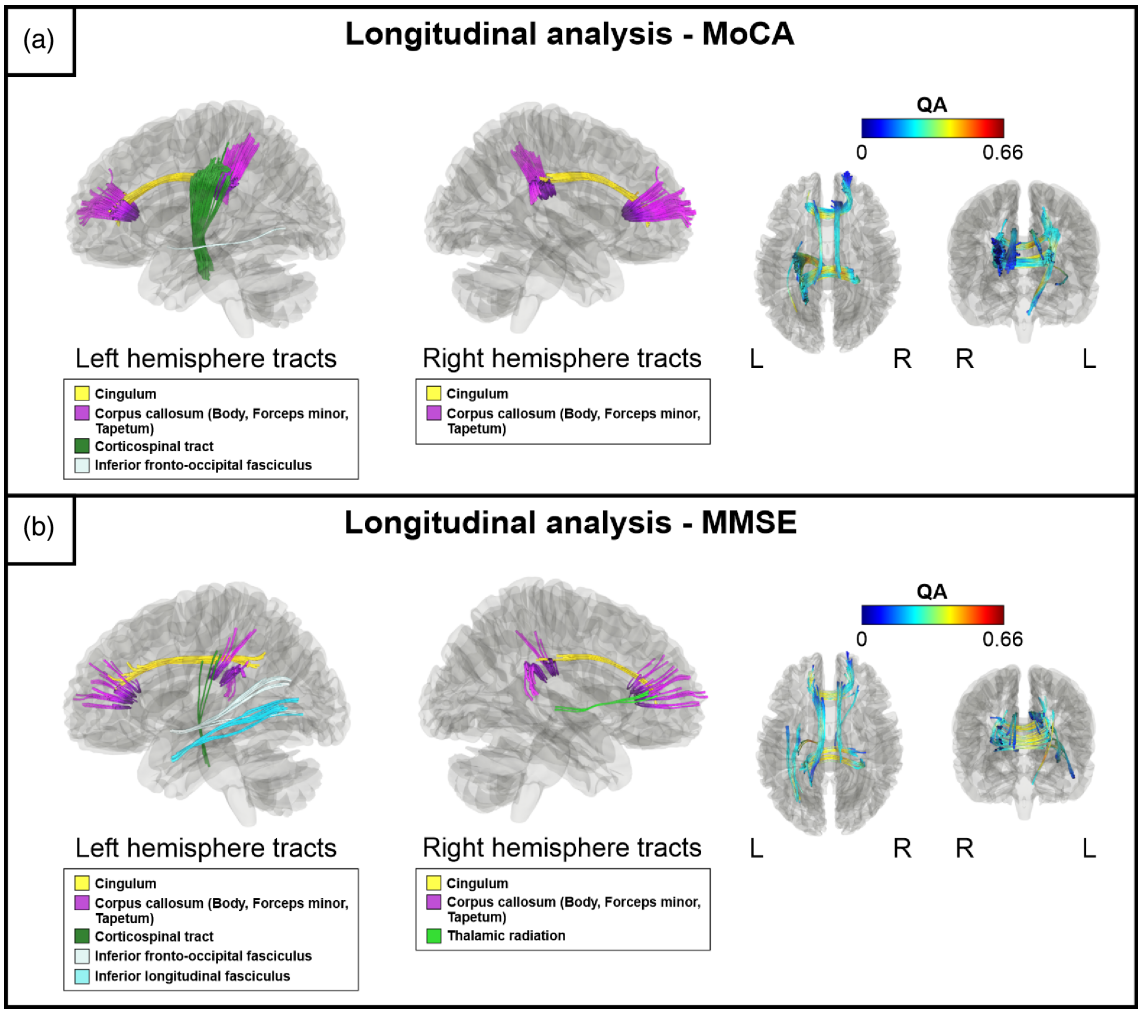

FIGURE 2 Longitudinal findings (12 months minus 3 months poststroke) showing positively associated tracts with MoCA and MMSE change score. (a) Positively associated tracts (longitudinal QA change) with MoCA change score ($N = 24$). (b) Positively associated tracts (longitudinal QA change) with MMSE change score ($N = 24$). All results are thresholded at p_{FDR} <0.05. FDR, false discovery rate; L, left; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; QA, quantitative anisotropy; R, right.

cingulate cortex (dACC), a key node within the saliency network (Seeley et al., 2007) involved in the control of goal-directed behaviour in healthy participants (Sliwinska et al., 2017), and chronic stroke (Brownsett et al., 2014; Rushworth et al., 2003). The integrity of the cingulum microstructure is essential to ensuring rapid communication between the dACC and other networks (Metzler-Baddeley et al., 2012). Further, the cingulum contains connections to the medial parietal and temporal lobes, implicated in the functional neural networks involved in task-specific behaviour. The importance of this structure in measures of global cognition, such as used in this study, is unsurprising given that structural disruption of the cingulum has been associated with cognitive decline in performance on these tools in pathologies, such as Alzheimer's disease (Bozzali et al., 2012; Braak & Braak, 1995), and mild cognitive impairment (Bozzali et al., 2012; Bubb et al., 2018). In Alzheimer's disease, although the progressive pathology is initially localized to the entorhinal cortex and hippocampus, as the disease progresses, it extends to cognition-dependent neocortical regions (Bozzali et al., 2012; Braak & Braak, 1995). In addition to progressive pathologies, our results suggest that the segments of the cingulum connecting to these neocortical regions are also important for performance on global measures of cognition after a stroke, both within the initial 3-month stage of recovery, when imaging sequences are typically acquired, and well into the chronic (12-month) stage of recovery, when spontaneous recovery is considered minimal (Bernhardt et al., 2019).

In addition to the cingulum, at the 3-month stage, as well as longitudinally, performance on both the MoCA and MMSE was also associated with QA within the corpus callosum (Figure 1a). A body of work by Davis and Cabeza (2015) has demonstrated that cross-hemispheric communication, associated with the successful performance of complex perceptual and semantic matching tasks, is constrained by white matter integrity. They also found a robust relationship between behavioural performance, cross-hemispheric functional connectivity and structural measures of callosal integrity in older adults (Davis et al., 2012). It is not clear if the role that the corpus callosum takes in integrating information from both hemispheres is inhibitory,

preventing contributions from the contralateral hemisphere during lateralized function, or excitatory (Hellige et al., 1989). In previous work by our group (Sihvonen et al., 2023), we suggest that the specificity of involvement of the corpus callosum, highlighted through the use of more complex language measures, necessitating the involvement of both domain-specific and domain-general neural networks, provides evidence that while some right hemisphere white matter pathways may make a maladaptive contribution to the recovery of language, other pathways support the recovery of language, especially language comprehension abilities. In the same way, the multiple components of cognition, evaluated by the MoCA and MMSE, likely necessitate bilateral neural contributions from task-specific networks, but also domain-general networks, especially when utilizing metrics of global measures of cognition in the presence of a lesion.

Although our findings across the cingulum and the corpus callosum were noticeably consistent for both screening tools, a few differences were evident in the relationships observed with each of the tools. First, while in the 3-month stage, the left inferior fronto-occipital fasciculus was only associated with performance on the MoCA, it was positively associated with longitudinal changes across both assessments. The left inferior fronto-occipital fasciculus has been associated with language processing, as well as goal-oriented behaviour, and visual switching tasks (Almairac et al., 2015; Herbet et al., 2019), connecting the occipital cortex to the temporal, frontal and parietal regions including language regions such as Broca's areas and Wernicke's areas, and cortical regions associated with multiple demand networks (dorsal lateral prefrontal and parietal cortices) (Aboitiz et al., 1992; Passarotti et al., 2002; Stephan et al., 2007). This high degree of connectivity supports rapid communication within and between networks that underpin the array of cognitive functioning required to complete the tasks across both assessment tools. It is expected that as the brain recovers over time, it adapts to be able to recruit existing networks that underpin cognition, that were perhaps either directly damaged, or suboptimally recruited in the earlier stages, or that alternative networks are recruited to support performance and/or compensation for impairments (Brownsett et al., 2014; Hartwigsen & Saur, 2019; Kümmerer et al., 2013). It could be that the subtle differences across screening tools make the MoCA performance more reliant on this structure during the subacute phase, but when considering changes over time, both tools are reliant on this structure to support the widespread connectivity essential for global cognitive functioning.

Second, our results demonstrated that the right superior longitudinal fasciculus was positively associated with 3-month MoCA scores only, and not change scores on the MoCA, nor the MMSE either cross-sectionally or longitudinally. The superior longitudinal fasciculus is the largest association tract in the brain. It connects perisylvian regions, and is largely asymmetrical, with the left being implicated in language processes (Janelle et al., 2022), and the right with executive tasks with visuospatial processing (De Schotten et al., 2011; Ribeiro et al., 2023). Similar to the inferior fronto-occipital fasciculus, the three divisions of the superior longitudinal fasciculus connect almost all lobes within that hemisphere, and as such are involved in multiple cognitive skills. Although both assessments likely involve multiple skills requiring this tract, our results suggest that the executive functioning demands and visuospatial processing load within each assessment may differ, such that the MoCA may tap into these skills to a greater extent than the MMSE. The fact that this relationship does not hold when considering longitudinal change scores, could reflect an upregulation, or greater reliance of these skills during the earlier phases of recovery.

Third, in our data, although there was no association with either screening tool at the 3-month stage, change scores on the MMSE only were associated with QA in the left inferior longitudinal fasciculus. The inferior longitudinal fasciculus is a bidirectional long-range tract that connects the occipital, and temporal-occipital regions of the brain and processes visual information. Left lateralized lesions to this tract are associated with visual processing cognitive deficits, such as visual agnosia and alexia (Herbet et al., 2017). Bilateral anterior portions are also associated with semantic processing, with unilateral damage presenting with milder impairments than when bilateral damage is observed (Lambon Ralph et al., 2016; Patterson et al., 2007; Patterson et al., 2015). Although both assessments involve visual processing skills and semantic skills, a positive association between change in MMSE scores and longitudinal change in QA recovery, could be mediated by differences in the visual processing and semantic skills demanded by this screening tool.

Finally, greater MMSE scores were associated with higher QA in the left corticospinal tract at the 3-month stage, and longitudinal change in both MoCA and MMSE scores. The cortical control of both cognitive and motor behaviours is mediated through the corticostriatal–thalamic–cortical circuits, and so whereas longitudinal change appears to be associated with the task demands of both screening tools, at the 3-month stage, the MMSE may utilize the cortical connections underpinned by these tracts to a greater extent, suggesting that there may be differences between the cognitive aspects of each of the assessments, and/or the motor-based behaviours demanded by the assessments.

We not only provide evidence that behavioural performance on both tools is significantly correlated ($r = .484$, $p < .001$) in people with poststroke cognitive deficits, but our data also highlights that both assessments are underpinned by similar white matter connections, namely the cingulum and the corpus callosum, reflecting the overlap between widespread cognitive networks recruited due to the overlapping tasks demands associated with both screening tools. This overlap highlights that global cognitive processing, or more precisely a surrogate measure of global cognition, regardless of the tool used to assess it, is underpinned by domain-specific and domain-general functional neural networks, reliant on cortical and white matter structures.

Much of our knowledge of the neuroanatomical distribution of the many domain-specific neural networks underpinning different cognitive functions has emerged from studies that have employed functional imaging methodologies (Dosenbach et al., 2007; Dosenbach et al., 2008; Raichle, 2015). In the presence of stroke, the interaction of both domain-specific and domain-general networks is also likely to influence cognitive performance and recovery, with

multiple functional neural networks interacting to support, modulate and alter cognitive performance (Brownsett et al., 2014; Eriksson et al., 2023). For example, altered resting-state connectivity within the default mode network, including the dorsal medial prefrontal cortex, posterior cingulate cortex and the angular gyrus (Menon, 2011), typically active during passive, task-free states, has been shown to correlate with cognitive performance after stroke (Dacosta-Aguayo et al., 2015; Dacosta-Aguayo, Graña, Savio, et al., 2014; Tuladhar et al., 2013).

Similarly, task-positive resting state networks have also been associated with both cognitive performance and behavioural recovery of cognitive functions. For example, the salience network, involving the dorsal anterior cingulate and the anterior insula (Seeley et al., 2007), has been shown to be involved in a range of cognitive skills in healthy and clinical populations, including set maintenance (Dosenbach et al., 2007; Seeley et al., 2007), language (Brownsett et al., 2014; Geranmayeh et al., 2014; Sliwinska et al., 2017), conflict monitoring (Elton & Gao, 2014; Ham et al., 2013) and task switching (Jilka et al., 2014). In addition, the frontal–parietal network (FPN), involving the dorsolateral prefrontal cortex and the posterior parietal regions, has been associated with sustained attention, cognitive flexibility and working memory (Eriksson et al., 2015; Lugtmeijer et al., 2021; Murphy et al., 2020). Multiple functional networks are likely essential to the effective completion of the tasks employed within assessments of post-stroke global cognitive function. For example, during completion of the paper folding task in the MMSE (requiring comprehension of verbal instructions to fold a piece of paper, and then subsequently placing the folded paper on the knee), in addition to the language and motor networks required to understand and complete the task, the saliency network is likely upregulated to support cognitive task switching, and the FPN, associated with sustained attention, cognitive flexibility and working memory (Eriksson et al., 2015; Lugtmeijer et al., 2021; Murphy et al., 2020), will also support the attention and memory demands of the task. Although disentangling these anatomical contributions is not necessary to determining clinical functioning, understanding which neural networks may have been damaged by a stroke, and therefore may function sub-optimally, could support the development of more reliable predictors of outcome after stroke.

Although the cingulum and the corpus collosum were important for both assessments reflecting the network basis of global cognitive function, it was not clear why the inferior fronto-occipital and superior longitudinal fasciculi were associated with the MoCA, but not the MMSE, and the inferior longitudinal fasiculus was associated with the MMSE and not the MoCA. The inferior fronto-occipital and superior longitudinal fasciculi, and to a certain extent, the inferior longitudinal fasciculus, have been consistently associated with language production (Catani et al., 2007; Forkel & Catani, 2018; Hillis et al., 2018; Saur et al., 2010). Both the MoCA and the MMSE require a combination of spoken comprehension and responses, and to our knowledge, no studies have specifically compared the language load across these two tests. However, the MMSE does require sentence-level production, repetition, and comprehension, in addition to the task directions, and so the additional linguistic burden associated with these components may have confounded performance on this assessment, and therefore its association with these tracts. Perhaps a relationship exists when the tasks are not reliant on a heavy language load, but when additional linguistic complexities are evident, alternative networks are needed to support the language-heavy components of the screening test. Nevertheless, the language load within both the MMSE and MoCA is problematic in poststroke cohorts, given the large prevalence of aphasia within a typical stroke population (Sinanović et al., 2011; Wall et al., 2015).

By adopting a connectometry approach, this represents the first study to directly compare the white matter structures underpinning both MMSE and MoCA, using a whole-brain connectometry approach. However, it must be acknowledged that as our sample size is relatively modest, particularly in the longitudinal dataset ($n = 24$), and while this work contributes to our understanding of the relationship between behaviour and structure, out-of-sample analyses are required to translate these findings into predictors of outcome, that are able to be implemented into clinical practice. To this end, future larger-scale longitudinal studies are needed to assess the out-of-sample validity of the current results.

In addition, although this study deliberately set out to look at the consistency of the connectome underpinning global measures of cognition, more sensitive assessment of cognitive impairments is needed to inform meaningful prognoses for those living with impairments. Our results suggest that the approach of using global measures of cognition may be useful in detecting structural breakdowns that may contribute to a broad global cognitive impairment. While this may be useful for differentiating and identifying pathological processes, it cannot identify areas of impairment, or indeed targets of possible behavioural interventions.

5 | CONCLUSION

In summary, we have demonstrated that rather than singular focal neural structures, a consistent structural connectome, including the cingulum and the corpus collosum, underpins the tasks used to obtain global cognitive measures from two frequently used, cognitive screening tools, the MoCA and the MMSE, in people after stroke. By illustrating that this connectome is crucial to cognitive functioning after stroke, we build on evidence that has demonstrated the importance of these tracts to cognition in degenerative processes, such as Alzheimer's disease and MCI (Bozzali et al., 2012; Dong et al., 2014), and with possible deterioration after stroke (Brodtmann et al., 2020). This consistency allows clinicians and researchers to not only suspect cognitive decline when lesions affect these tracts, but also to refine their investigation of novel approaches to differentially diagnosing pathology associated with cognitive decline, regardless of the aetiology. Such refinements, or subsequent investigations, might include the identification of structures that may lead to changes in behaviour, in particular, if there is a lesion compromising the corpus callosum or the cingulum, this may lead to cognitive issues. Importantly, investigating

relationships using participants with a variety of lesion aetiologies (i.e., stroke versus tumour) and localization (i.e., infarction of the anterior versus middle cerebral artery), could provide an avenue for investigating more focal damage, and so allow us to understand the individual contribution of tracts. Although the popular clinical tests evaluated in this study prohibit a comparison to healthy populations due to ceiling effects and limited psychometric validity in our clinical population, more detailed neuropsychological assessments could be used to demonstrate a continuum across healthy and different pathological populations.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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