Poststroke Executive Function in Relation to White Matter Damage on Clinically Acquired CT Brain Imaging

Georgina Hobden, MS, Margaret Jane Moore, DPhil,*† Grant Mair, MD,‡ Sarah T. Pendlebury, FRCP, DPhil,§‖ and Nele Demeyere, PhD*§*

Downloaded from http://journals.lww.com/cogbehavneurol by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 10/09/2023

Background: Executive function (EF) impairments are prevalent post stroke and are associated with white matter (WM) damage on MRI. However, less is known about the relationship between poststroke EF and WM damage on CT imaging.

Objective: To investigate the relationship between poststroke EF and WM damage associated with stroke lesions and WM hypointensities (WMHs) on clinically acquired CT imaging.

Method: This study analyzed data from the Oxford Cognitive Screening Program, which recruited individuals aged ≥18 years with a confirmed stroke from an acute stroke unit. The individuals completed a follow-up assessment 6 months post stroke. We included individuals with a CT scan showing a visible stroke who completed follow-up EF assessment using the Oxford Cognitive Screen–Plus rule-finding task. We manually delineated stroke lesions and quantified then dichotomized WM damage caused by the stroke using the HCP-842 atlas. We visually rated then dichotomized WMHs using the Age-Related White Matter Changes Scale.

Results: Among 87 stroke survivors (M_{age} = 73.60 ± 11.75; 41 female; 61 ischemic stroke), multivariable linear regression showed that stroke damage to the medial lemniscus (B = –8.86, P < 0.001) and the presence of WMHs (B = –5.42, P = 0.005) were associated with poorer EF 6 months post stroke after adjusting for covariates including age and education.

Conclusion: Poorer EF was associated with WM damage caused by stroke lesions and WMHs on CT. These results confirm the importance of WM integrity for EF post stroke and demonstrate the prognostic utility of CT-derived imaging markers for poststroke cognitive outcomes.

Key Words: stroke, executive function, CT, white matter hyperintensities

(*Cogn Behav Neurol* 2023;00:000–000)

EF = executive function. **OCS** = Oxford Cognitive Screen. **ROI** = region of interest. **WM** = white matter. **WMH** = white matter hyperintensity.

Stroke is the third greatest cause of disability burden worldwide (Feigin et al., 2014; Lozano et al., 2012). Although stroke mortality rates have decreased due to improved acute care (Seminog et al., 2019), there is a higher prevalence of chronic stroke survivors (GBD 2016 Stroke Collaborators, 2019) and, thus, a higher prevalence of poststroke cognitive impairment (Pendlebury et al., 2019). In particular, executive dysfunction is estimated to affect 19–75% of chronic stroke survivors (Hurford et al., 2013). Previous research has linked poststroke executive function (EF) impairment with reduced quality of life (Pohjasvaara et al., 2002), disability in activities of daily living (Mole and Demeyere, 2020), and increased mortality (Melkas et al., 2010).

Research using MRI has shown associations between poststroke executive dysfunction and both focal lesions affecting white matter (WM) pathways (Muir et al., 2015) and WM hyperintensities (WMHs) of presumed vascular origin (Veldsman et al., 2020), which affect 64–86% of stroke survivors and are a key feature of vascular dementia (Fu et al., 2005). Although these published studies provide valuable insight into the neural mechanisms underpinning poststroke executive dysfunction, they yield comparatively ungeneralizable results due to their reliance on MRI, which is not always suitable for a

Received for publication October 6, 2022; accepted April 21, 2023.

From the *Department of Experimental Psychology, University of Oxford, Oxford, England; †Queensland Brain Institute, University of Queensland, Queensland, Australia; ‡Centre for Clinical Brain Sciences, University of Edinburgh, and Neuroradiology, Department of Clinical Neurosciences, National Health Service Lothian, Edinburgh, Scotland; §Wolfson Centre for Prevention of Stroke and Dementia, Wolfson Building, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, England; and ‖National Institute for Health Research Oxford Biomedical Research Centre and Departments of General (Internal) Medicine and Geratology, John Radcliffe Hospital, Oxford, England.

Supported in part by the National Institute for Health Research (NIHR) Clinical Research Network, a priority program grant (SA PPA 18/100032) from the Stroke Association, an Economic and Social Research Council grant (ES/P000649/1) to G.H., and an advanced fellowship (NIHR302224) from the NIHR to N.D. G.M. is the Stroke Association Edith Murphy Foundation Senior Clinical Lecturer (SA L-SMP 18\1000).

N.D. is a developer of the Oxford Cognitive Screen–Plus but does not receive any remuneration from its use. The remaining authors declare no conflicts of interest.

A previous version of this manuscript was posted to medRxiv as doi:10.1101/2021.11.12.21266247

Correspondence: Georgina Hobden, MS, Department of Experimental Psychology, Anna Watts Building, Woodstock Road, Oxford, OX2 6GG, United Kingdom (email: georgina.hobden@psy.ox.ac.uk).

Supplemental digital content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.cogbehavneurol.com.

Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2023 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/cogbehavneurol by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 10/09/2023

significant, nonrandom portion of the stroke population, such as individuals with implanted paramagnetic devices (Singer et al., 2004).

CT is the most used imaging modality in acute stroke settings, and CT is often the *only* imaging modality available in underserved global regions (Frija et al., 2021). Therefore, it is critical to determine CT's prognostic utility for poststroke outcomes. Although previous studies have investigated the role of stroke-specific WM damage or WMHs in isolation (e.g. Veldsman et al., 2020), no study to our knowledge has investigated how these conditions interact in the same patient sample.

We used CT imaging that had been acquired during routine clinical care to investigate the association between poststroke EF and both stroke lesion-related WM damage and WMHs. Using routinely acquired CT imaging, we investigated these associations in a relatively representative patient sample. We developed the following hypotheses:

- EF that is assessed using the Oxford Cognitive Screen Plus (OCS–Plus; Demeyere et al., 2021) rule-finding task would be negatively associated with the disconnection of WM tracts that have been previously implicated in EF (e.g., inferior longitudinal fasciculus) (Santiago et al., 2015). That is, poorer performance on an EF task would be predicted by increased levels of WM tract disconnection.
- EF that is assessed using the OCS–Plus rule-finding task would be negatively associated with WMHs that are measured using the Age-Related White Matter Changes Scale (Wahlund et al., 2001). That is, poorer performance on an EF task would be predicted by increased levels of WMHs.

METHOD

Participants

Our project is a retrospective analysis of data from the Oxford Cognitive Screening Program (Demeyere et al., 2015), which recruited a consecutive sample of stroke survivors from the acute stroke unit at Oxford University Hospital and conducted a follow-up neuropsychological assessment at 6 months.

The Oxford Cognitive Screening Program recruited all individuals with a confirmed stroke diagnosis who were aged ≥18 years, able to remain alert for 20 minutes, and able to provide informed consent. Our investigation included those individuals who had both completed a follow-up assessment using the OCS–Plus 6 months post stroke (between November 2016 through March 2020) and had a usable CT scan from the acute stage post stroke (i.e., within 0–14 days post stroke) showing a visible stroke lesion. We excluded individuals if their CT scan showed evidence of additional nonstroke pathology, such as a brain tumor, or multiple temporally distinct strokes, or if the OCS–Plus rule-finding task was not completed.

The Oxford Cognitive Screening Program received regional National Health Service ethics approval (OCS-Tablet and OCS-Recovery studies, NHS RECs 14/LO/0648 and 18/SC/0550). All of the individuals provided written or witnessed informed consent at both study recruitment and follow-up.

Assessments

The individuals completed the EF assessment in their homes 6 months post stroke using the OCS–Plus, which is a tablet-based cognitive screen that is designed to provide fine-grained measures of memory and EF (Demeyere et al., 2021; Webb et al., 2022). This screen has been validated against standardized pen-and-paper neuropsychological assessments in a large (N = 320) normative aging sample (Demeyere et al., 2021). The OCS–Plus contains 10 tasks and takes an average of 24 minutes to complete. OCS–Plus tasks assess specific cognitive domains with minimal interference from impairments within other cognitive domains, such as language and memory (Humphreys et al., 2017).

The OCS–Plus contains four tasks that are designed to assess EF: rule-finding, trails, selection, and figure copy. Each task places different demands on the EF subdomains: updating, shifting, and inhibition (Miyake et al., 2000). The tasks also vary in the extent to which they rely on other skills, such as visuospatial attention and motor abilities.

For the present study, we used the OCS–Plus rule-finding task to assess EF. This task is broadly analogous to the Brixton Spatial Anticipation Test (Burgess and Shallice, 1996), but it can be administered more quickly and places lower demands on numerical processing and visuospatial attention (i.e., patterns follow top-to-bottom rather than left-to-right rules, which reduces potential confounds from visuospatial neglect). The task, which is completed on a computer tablet, presents three columns of squares and triangles on the tablet. These shapes vary regularly in luminosity (Figure 1).

There is a red dot within one of the shapes, and this dot moves throughout the array according to a specific but changing spatial rule. Individuals must learn the rule guiding the movement of the dot in order to predict where the dot will appear next. Individuals are prompted to tap the shape where they think the dot will appear next. The task scores performance accuracy automatically based on the number of correct location predictions that are made (range = 0–43). Further details about the administration and scoring of the OCS–Plus rule-finding task are provided in Demeyere et al., (2021) and Webb et al., (2022).

We based our decision to use the OCS–Plus rule-finding task to assess EF on several considerations. First, the rule-finding task provides a relatively comprehensive measure of EF because it taps all three EF subdomains (i.e., updating, shifting, and inhibition) by requiring individuals to update their working memory representation of the spatial pattern (updating), apply new spatial rules to make predictions once a new rule has been learned (shifting), and inhibit obsolete rules (inhibition). Second, we considered calculating a composite score based on all four OCS–Plus EF tasks, but the meaningfulness of a

Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2023 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/cogbehavneurol by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 10/09/2023

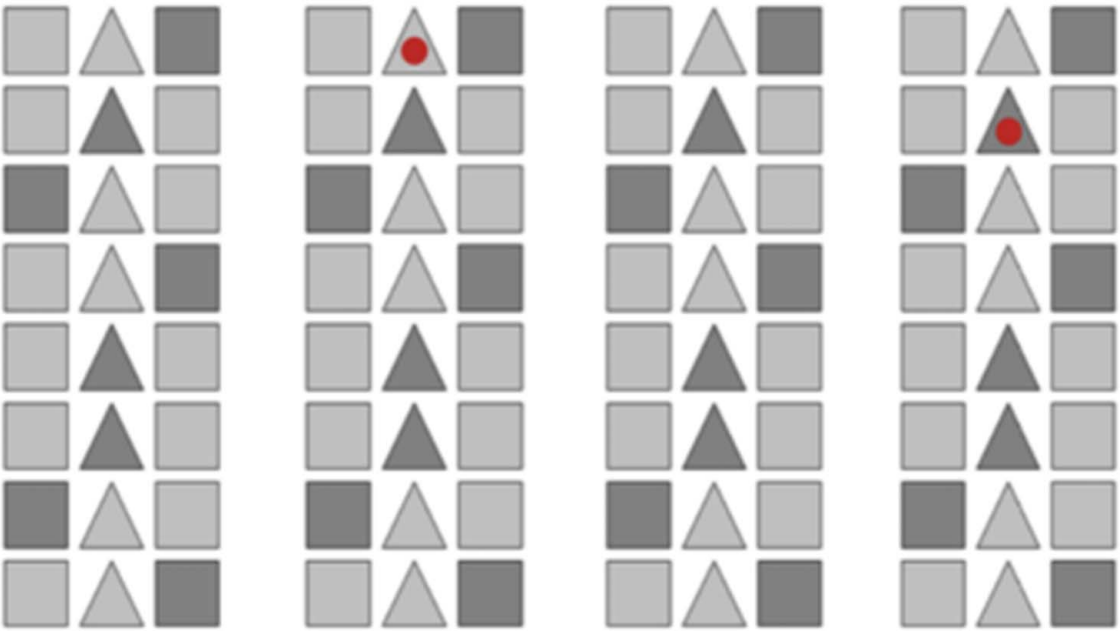

FIGURE 1. A schematic diagram of the OCS–Plus rule-finding task. The task shows three columns of alternating geometric shapes (squares-triangles-squares), rows of alternating luminosity (dark–light), and a red dot that moves around the pattern following changing spatial rules. The task involves learning the spatial rules to predict where the dot will go next based on previous moves. **OCS** = Oxford Cognitive Screen.

composite score would not be clear. In addition, normative data exist for individual tasks only, and no standard format for a composite score on the OCS–Plus is currently available (Demeyere et al., 2021). Nevertheless, we note that the Brixton Spatial Anticipation Test, and by corollary, the OCS–Plus rule-finding task, may lack specific sensitivity to frontal lobe dysfunction (Mole et al., 2020), although see also Burgess and Shallice (1996), Primativo et al (2017), and Reverberi et al (2005).

We also evaluated performance on a non-EF control task to determine whether any associations between WM damage and OCS–Plus rule-finding task performance were specific to EF. The OCS praxis task, which is part of the OCS (Demeyere et al., 2015), was selected as a control task because this task does not rely heavily on updating, shifting, and inhibition, but rather requires individuals to coordinate motor responses in order to copy a series of actions. Individuals completed the OCS praxis task on the same day they completed the OCS–Plus rule-finding task, ~6 months post stroke.

Lesion Analyses

We collected acute whole-brain nonenhanced CT scans (slice thickness 5 mm) from the acute stage post stroke (i.e., within 14 days post stroke) for each individual. Two experienced researchers (G.H. and M.M.) manually delineated the stroke lesions on native space scans using the MRIcron software package (McCausland Center for Brain Imaging) and following a standardized processing procedure (Moore, 2022) while blinded to the behavioral and clinical data. A consultant neuroradiologist with >13 years of experience (G.M.) evaluated the resultant lesion masks for accuracy and advised on minor adjustments to the lesion masks. Following G.M.'s evaluation, we smoothed the lesion masks at 5 mm full width at half maximum in the z direction and binarized them using a threshold of 0.5. We used SPM 12 and Clinical Toolbox (Rorden et al., 2012) to reorient the scans and lesion masks to the anterior commissure and warp them into 1 × 1 × 1 mm stereotaxic space.

We used binarized lesion masks to calculate stroke volume and WM disconnection severity statistics. The Lesion Quantification Toolkit (Griffis et al., 2021) quantified WM tract disconnection severities based on the stroke lesion delineation for 70 canonical WM tracts, as defined by the HCP-842 streamline tractography atlas (Yeh et al., 2018) with the corpus callosum divided into five segments. The toolkit works on the CT by embedding the lesion into the HCP-842 as a region of interest (ROI) and iteratively loading the streamline trajectories for each of the tracts. The toolkit then filters the files to retain only those streamlines that intersect the volume occupied by the lesion.

For each tract, we calculated disconnection severity by converting the number of disconnected streamlines into a percentage of the total number of streamlines that were assigned to that tract. We calculated separate metrics for each hemisphere, then averaged across hemispheres to produce a single measure per individual for each ROI. Each ROI was then binarized as disconnected (≥10% disconnection) or not disconnected (< 10% disconnection) (Griffis et al., 2021). We also calculated a measure of WM disconnection to reflect the extent of stroke lesion-related disconnection across the brain by summing the number of disconnected ROIs for each individual (range = 0–40).

Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2023 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/cogbehavneurol by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 10/09/2023

WMH Ratings

We used the Age-Related White Matter Changes visual rating scale to evaluate WMHs on CT imaging. G.H. assigned visual ratings while blinded to the behavioral and clinical data. G.H. assigned visual ratings for WMHs in five regions within each hemisphere (10 regions total): frontal, parieto-occipital, temporal, infratentorial, and basal ganglia. Visual ratings for WMHs ranged from 0 to 3 for each region, according to the criteria provided in Table 1. G.M. independently evaluated the WMHs in order to increase the robustness of the evaluations. G.H. and G.M. revisited and discussed cases where their evaluations differed in order to reach a final consensus before statistical analysis. When a brain region in one hemisphere was affected by stroke damage to the extent that WMHs could not be evaluated, this region was assigned the same score as the same region in the opposite hemisphere.

To measure the severity of the WMHs across the brain, we summed the assigned scores across all 10 regions (range = 0–30). To account for the ordinal nature of the data and in line with previous research (e.g., Simoni et al., 2012), we used this total score to categorize WMHs as absent (0), mild (1–5), moderate (6–10), or severe (>10). Category thresholds provided in parentheses were chosen based on previous research (Simoni et al., 2012). Very few stroke survivors in our sample were categorized as having moderate or severe WMHs, so we dichotomized the WMHs as *present* (i.e., mild, moderate, or severe) or *absent* for all subsequent statistical analyses in order to ensure two sufficiently large groups for statistical comparison.

Statistical Analysis

We performed all of the statistical analyses using the computer software R-Studio (V.4.0.2) after cleaning the behavioral and clinical data. We imputed missing values for individual age (n = 7) and education (n = 30) using mean substitution.

We used multivariable linear regression analyses to evaluate poststroke EF in relation to (a) stroke damage to WM ROIs across the brain, (b) stroke damage to individual WM ROIs, and (c) WMHs. Then, we used a multivariable linear regression analysis to evaluate the relative contributions of stroke lesion-related WM damage and WMHs to poststroke EF, including as predictor variables any significant predictors of EF that were identified in the original analyses. In all of the analyses, the outcome measure was the OCS–Plus rule-finding task accuracy score.

All of the analyses included age, sex, years of education, stroke type (ischemic, haemorrhagic), stroke lateralization (left, right, bilateral), stroke territory (anterior cerebral artery, middle cerebral artery, posterior cerebral artery, vertebrobasilar, intraventricular, multiple territories), and stroke volume as covariates. We conducted further analyses without stroke territory as a covariate. We also performed the above analyses using performance on a non-EF control task (OCS praxis task) as the dependent variable.

We visually inspected all of the residual plots to test the assumptions of linearity, normality of residuals, and homogeneity of residuals variance. We applied Bonferroni correction to correct for inflated false positive rates due to multiple comparisons.

RESULTS

Participants

We collected data from 122 stroke survivors from the acute stroke unit at Oxford University Hospital who had both completed a follow-up assessment using the OCS–Plus 6 months post stroke and had a usable CT scan from the acute stage post stroke showing a visible stroke lesion. Of these, three patients were excluded because their CT scan showed evidence of additional nonstroke pathology, 20 were excluded because their CT scan showed multiple temporally distinct strokes, and 12 were excluded because they did not complete the OCS–Plus rule-finding task. The demographic and clinical details of the resultant sample of 87 stroke survivors, obtained from relevant medical records, are presented in Table 2.

The present study included 87 stroke survivors (41 female; 46 male). The mean age of the individuals was 73.60 years (SD = 11.75). The individuals had on average 12.74 years of education (SD = 3.67). Fifty-eight participants were right handed, four were left handed, and the handedness of 25 was unknown. All of the individuals had sustained either an ischemic stroke (n = 61) or a hemorrhagic stroke (n = 26). There was a roughly equal distribution of right hemisphere strokes (n = 43) and left hemisphere strokes (n = 41); three individuals had a bilateral stroke. CT imaging was acquired on average 0.94 days after the stroke (SD = 2.31, range = 0–13).

TABLE 1. Visual Rating Criteria for the Age-related White Matter Changes Scale

	0	1	2	3
Frontal Parieto-occipital Temporal Infratentorial	No lesions (including symmetrical, well-defined caps or bands)	Focal lesions	Beginning confluence of lesions	Diffuse involvement of the entire region, with or without U-fibres
Basal ganglia	No lesions	Single focal lesion	≥2 focal lesions	Confluent lesions

White matter hyperintensities on CT were defined as hypodense areas of ≥5 mm.

Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2023 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/cogbehavneurol by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 10/09/2023

TABLE 2. Patient Demographic and Clinical Information

Characteristic	Statistic
Age, M (SD)	73.60 (11.75)
Education, M (SD)	12.74 (3.67)
Sex, n (%)	Female: 41 (47.13) Male: 46 (52.87)
Handedness, n (%)	Right: 58 (66.67) Left: 4 (4.60) Unknown: 25 (28.74)
Stroke type, n (%)	Ischemic: 61 (70.11) Hemorrhagic: 26 (29.89)
Stroke lateralization, n (%)	Unilateral right hemisphere: 43 (49.43) Unilateral left hemisphere: 41 (47.13) Bilateral:† 3 (3.45)
Stroke location, n (%)	Anterior cerebral artery: 3 (3.45) Middle cerebral artery: 61 (70.11) Posterior cerebral artery: 8 (9.20) Basilar artery: 7 (8.05) Intraventricular: 3 (3.45) Multiple territories: 5 (5.75)
Stroke volume (cm^3), MED (IQR)	10.82 (3.13–45.00)
Days between stroke and scan, M (SD)	0.94 (2.31)

†Bilateral stroke is defined as a single stroke crossing the midline.
IQR = interquartile range. **MED** = median.

The mean score for the OCS–Plus rule-finding task was 18.29 (SD = 8.29, range = 2–37). Figure 2 presents a lesion overlay of the sample. The median stroke volume across the individuals was 10.82 cm^3. Table 3 shows the prevalence and extent of ROI disconnection for the sample. Overall, there was a good level of lesion coverage across the ROIs that were considered in the present investigation. A mean of 9.79 (SD = 8.97, range = 0–34) ROIs were disconnected by at least 10%. WMHs were categorized as absent, mild, moderate, or severe for 32, 31, 15, and 9 individuals, respectively. To ensure two sufficiently large groups for statistical comparison, we binarized the WMHs as absent (n = 32) or present (n = 55) for all of the subsequent statistical analyses.

The multivariable linear regression evaluating poststroke EF in relation to stroke lesion-related WM damage using the overall WM tract disconnection score (i.e., number of ROIs disconnected by at least 10%) showed that EF was not significantly associated with the overall stroke lesion-related WM disconnection measure, although age and stroke volume were significant negative predictors of poststroke EF. Table S1 in the supplementary digital content (SDC; http://links.lww.com/CBN/A131) provides full model statistics.

The multivariable linear regressions evaluating poststroke EF in relation to individual ROI-level tract disconnection severity showed that poststroke EF was significantly associated with damage to the medial lemniscus (B = –7.75, P = 0.001, 95% CI [–12.35 –3.17]) (Figure 3A). In addition, age and stroke volume were again significantly negatively associated with poststroke EF. SDC Table S1 (http://links.lww.com/CBN/A131) provides full model statistics.

When stroke territory was not included as a covariate, the medial lemniscus remained significantly associated with poststroke EF (B = –6.09, P = 0.008, 95% CI [–10.52 –1.67]), although this did not reach the Bonferonni correction threshold ($\alpha < 0.00125$). When the medial lemniscus was included as a predictor variable, but stroke territory was not included as a covariate, the regression model explained 35.07% of the variance in poststroke EF.

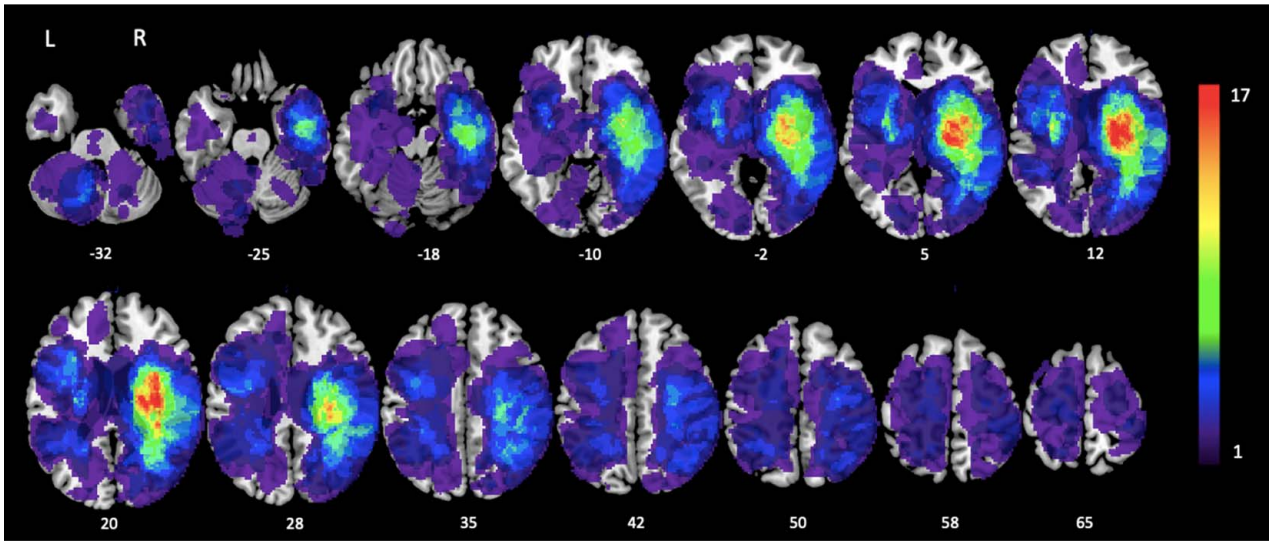

FIGURE 2. A lesion overlay map of the study sample (N = 87) presented in neurologic convention. Color indicates the number of individuals with lesions in each area. MNI coordinates of each transverse section (*z*-axis) are provided. **MNI** = Montreal Neurological Institute.

Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2023 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/cogbehavneurol by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 10/09/2023

TABLE 3. Descriptive Statistics for Each White Matter ROI From the HCP-842 Analyzed in the Present Investigation

ROI	Patients With any ROI Disconnection n (%)	Patients With >10% ROI Disconnection n (%)	Average Percentage Disconnection M (SD)
Anterior commissure	41 (47.13)	31 (35.63)	25.66 (38.81)
Arcuate fasciculus	45 (51.72)	37 (42.53)	17.62 (22.09)
Acoustic radiation	38 (43.68)	30 (34.48)	14.90 (20.97)
Cerebellum	14 (16.09)	5 (5.75)	1.49 (4.75)
Corpus callosum (anterior)	34 (39.08)	14 (16.09)	6.03 (13.24)
Corpus callosum (mid-anterior)	41 (47.13)	24 (27.59)	11.83 (24.49)
Corpus callosum (central)	31 (35.63)	22 (25.29)	14.56 (29.95)
Corpus callosum (mid-posterior)	44 (50.57)	21 (24.14)	16.36 (32.81)
Corpus callosum (posterior)	61 (70.11)	28 (32.18)	21.22 (33.48)
Corticospinal tract	57 (65.52)	40 (45.98)	18.80 (21.66)
Corticostriatal tract	72 (82.76)	33 (37.93)	11.01 (13.41)
Central tegmental tract	8 (9.20)	7 (8.05)	5.30 (18.88)
Corticothalamic pathway	77 (88.51)	40 (45.98)	13.79 (16.30)
Cingulum	28 (32.18)	15 (17.24)	5.38 (12.41)
Dorsal longitudinal fasciculus	7 (8.05)	7 (8.05)	6.18 (22.06)
Extreme capsule	47 (54.02)	40 (45.98)	19.68 (22.01)
Frontal aslant tract	30 (34.48)	25 (28.74)	7.14 (23.15)
Frontopontine tract	52 (59.77)	37 (42.53)	16.81 (20.48)
Fornix	17 (19.54)	16 (18.39)	9.02 (22.41)
Inferior cerebellar penducle	8 (9.20)	8 (9.20)	3.18 (11.19)
Inferior fronto-occipital fasciculus	53 (60.92)	37 (42.53)	17.80 (22.67)
Inferior longitudinal fasciculus	33 (37.93)	22 (25.29)	10.03 (18.49)
Lateral lemniscus	4 (4.60)	4 (4.60)	1.86 (9.14)
Middle cerebellar peduncle	19 (21.84)	5 (5.75)	1.65 (6.96)
Medial longitudinal fasciculus	6 (6.90)	5 (5.75)	4.16 (17.64)
Medial lemniscus	22 (25.29)	20 (22.99)	9.58 (18.16)
Middle longitudinal fasciculus	35 (40.23)	29 (33.33)	15.49 (22.17)
Occipitopontine tract	43 (49.43)	32 (36.78)	16.89 (22.45)
Optic radiation	36 (41.38)	25 (28.74)	12.41 (21.18)
Posterior commissure	16 (18.39)	7 (8.05)	7.09 (25.09)
Parietopontine tract	51 (58.62)	38 (43.68)	17.60 (21.28)
Reticulospinal tract	6 (6.90)	6 (6.90)	2.61 (10.38)
Superior cerebellar peduncle	27 (31.03)	14 (16.09)	8.21 (18.62)
Superior longitudinal fasciculus	37 (42.53)	23 (26.44)	9.72 (16.30)
Spinothalamic tract	25 (28.74)	21 (24.14)	9.07 (17.08)
Temporopontine tract	36 (41.38)	28 (32.18)	15.15 (21.73)
Uncinate fasciculus	26 (29.89)	16 (18.39)	7.75 (16.58)
U-fibres	61 (70.11)	23 (26.44)	7.68 (10.95)
Vermis	9 (10.34)	7 (8.05)	6.26 (22.60)
Vertical occipital fasciculus	16 (18.39)	10 (11.49)	4.40 (12.16)

ROI = region of interest.

The multivariable linear regression evaluating poststroke EF in relation to the presence of WMHs showed that poststroke EF was significantly poorer in individuals with WMHs compared with individuals without WMHs ($B = –4.17$, $P = 0.042$, 95% CI [–8.18 –0.15]) (Figure 3B). Additionally, age and stroke volume were significantly negatively associated with poststroke EF. No other covariates were significant. SDC Table S1 (http://links.lww.com/CBN/A131) provides full model statistics.

In the multivariable linear regression evaluating poststroke EF in relation to both stroke lesion-related WM damage and WMHs, medial lemniscus damage (absent vs present) and WMHs (absent vs present) were included as predictor variables of interest. This model was significant ($F_{18, 68} = 3.86$, $R^2 = 0.51$, $R^2_{\text{adjusted}} = 0.37$, $P < 0.001$): Poststroke EF was associated with both stroke damage to the medial lemniscus ($B = –8.86$, $P < 0.018$, 95% CI [–13.29 –4.43]) and the presence of WMHs ($B = –5.42$, $P = 0.023$, 95% CI [–9.12 –1.72]), although there was no significant interaction between these factors.

Performance on the OCS praxis task was not predicted by the overall stroke lesion-related WM disconnection measure, individual ROI-level tract disconnection severity, or the presence of WMHs. SDC Table S2 (http://links.lww.com/CBN/A131) provides full model statistics.

Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2023 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/cogbehavneurol by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 10/09/2023

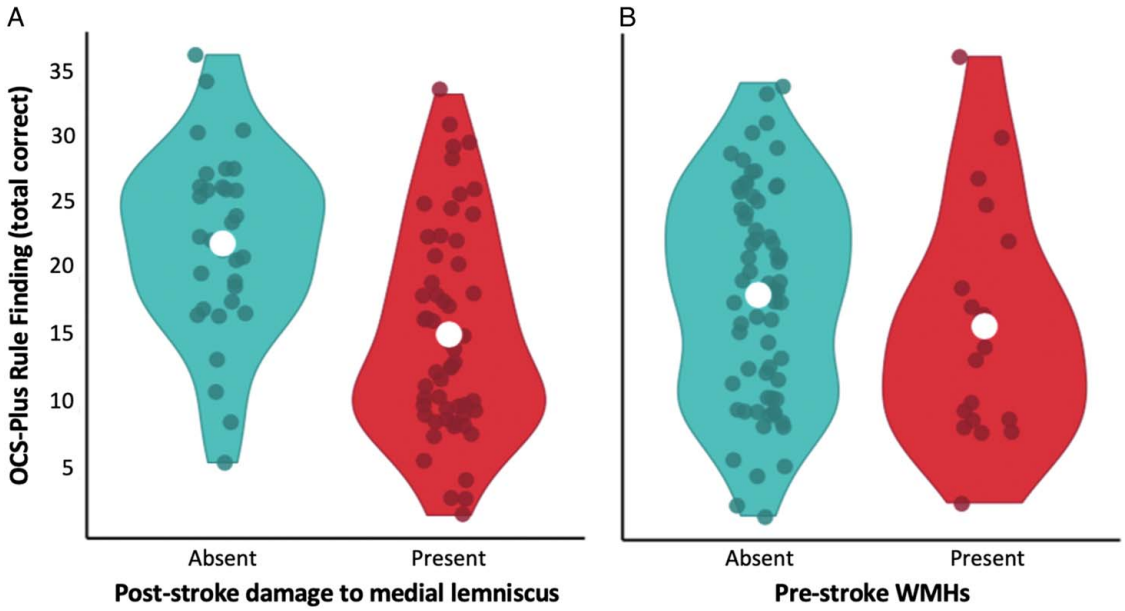

FIGURE 3. The relationship between poststroke executive function and **A.** stroke damage to the medial lemniscus and **B.** WMHs. Means are plotted (in white) along with individual patient scores (points). **OCS** = Oxford Cognitive Screen. **WMH** = white matter hyperintensity.

DISCUSSION

We found poorer EF 6 months post stroke in individuals with stroke damage affecting the medial lemniscus and individuals with WMHs on clinically acquired CT imaging. These findings highlight the impact of both stroke lesion-related WM damage and WMHs, potentially stemming from small vessel disease, on poststroke cognitive outcomes. Furthermore, our results highlight the prognostic utility of CT-derived imaging measures for investigating poststroke cognitive outcomes.

Stroke Damage

Stroke lesion-related WM damage to the medial lemniscus was associated with significantly poorer EF 6 months post stroke. This result was somewhat unexpected, as previous research has suggested that the medial lemniscus plays a key role in proprioception (Gardner and Johnson, 2013), but its involvement in EF is less well evidenced. Indeed, current evidence supports mainly a correlational association between EF and medial lemniscus integrity (Cho and Jang, 2021; Subramaniam et al., 2018). For example, Subramaniam et al (2018) found that greater WM microstructural integrity within the medial lemnisci, as determined by fractional anisotropy analyses of MRI data, predicted improved EF after cognitive training in individuals with schizophrenia.

Although it remains a possibility that the medial lemniscus plays a direct role in EF, the current study and previous research (e.g., Cho and Jang, 2021; Subramaniam et al., 2018) demonstrate only a correlational association, and further research is required to demonstrate a direct link between medial lemniscus damage and executive dysfunction. Furthermore, when stroke territory was not included as a covariate of interest, and after correction for multiple comparisons, the medial lemniscus did not remain a significant predictor of EF, which suggests that the general location of stroke damage explains variance alongside the specific tract that is affected.

Although we found an association between medial lemniscus damage and EF, we did not find significant associations between poststroke EF and stroke damage to any other WM pathways that have been implicated in EF, such as the inferior longitudinal fasciculus (Santiago et al., 2015). Again, this was somewhat unexpected, but these null results may be explained by our conservative approach to multiple comparison correction, lack of statistical power in analyses of some tracts that were damaged only rarely, and differences in our patient sample compared with that in previous studies. For example, previous MRI studies have generally included younger individuals without contraindications to MRI (Kantarci et al., 2011); in contrast, our study used a largely unselected and therefore more clinically representative cohort of stroke survivors.

WM Hyperintensities

The presence of WMHs on routinely acquired CT imaging was also associated with significantly poorer EF 6 months post stroke. This finding is critically important because it suggests that poststroke executive dysfunction may not be caused exclusively by patterns of stroke lesion-related damage, but may also be linked to large-scale network integrity issues that are potentially caused by cerebral small vessel disease. Our study adds to previous studies that have reported an association between WMHs and poststroke cognitive outcomes (Ball et al., 2022; Pendlebury and Rothwell, 2009; Pendlebury et al., 2019)

Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2023 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/cogbehavneurol by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 10/09/2023

by demonstrating that WMHs remain a key predictor of poststroke EF, even when stroke lesion-related WM damage is taken into account.

Clinical Implications

Our results highlight the potential value of routinely acquired CT imaging for use in clinical research and clinical practice. Although MRI has traditionally been the favored modality in clinical research, due to its higher spatial resolution and improved soft tissue contrast compared with CT (Wippold, 2007), the present study demonstrates that CT detects levels of WM damage that correlate meaningfully with poststroke cognitive outcome, even after adjusting for important covariates (e.g., age, education). This finding is important given that CT is commonly acquired in clinical practice and is often the only imaging modality available in underserved and under-resourced global regions (Frija et al., 2021). Future studies should assess the prognostic utility of CT-derived imaging measures for predicting other clinical, cognitive, and functional outcomes post stroke (Pendlebury et al., 2022).

Once the prognostic utility of clinically acquired CT imaging has been established more firmly, data from routinely acquired CTs can be incorporated into clinical risk prediction algorithms for poststroke outcome, particularly should automated quantitative assessment methods become widely available for CT. Such algorithms would facilitate the identification of individuals who are at risk of poor cognitive and functional outcomes post stroke in circumstances when only CT is available, which may be particularly beneficial in underserved countries.

Study Limitations

Several limitations are present within this study.

- Our assessment of poststroke WM damage and WMHs may have been complicated by the presence of cerebral edema, which is a common sequela of stroke. Nevertheless, edema typically peaks 3–5 days post stroke (Dostovic et al., 2016), and only six CTs in our investigation were acquired during or after this period. We ran the analyses excluding these six individuals and found largely similar results, although the association between WMHs and EF was slightly reduced, potentially due to the reduced power of the smaller overall sample (SDC Table S3; http://links.lww.com/CBN/A131).
- We used a different measurement approach to assess stroke-related WM damage and WMHs: We assessed the former using a semi-automated tract disconnection measure and the latter using a visual rating approach. This was necessitated by the current lack of openly available automated or semi-automated quantitative tools to assess WMHs on CT, despite the availability of such tools for MRI (Griffanti et al., 2016).
- The limited sample size left us underpowered to investigate any dose-responsive effect of poststroke WM damage and WMHs. Nevertheless, we found significant results for both stroke lesion-related WM damage and WMHs after dichotomizing these variables, suggesting that our approach was sufficiently sensitive with regard to the cognitive data.
- MRI sequences are more sensitive than noncontrast CT to acute ischemia (for review, see Brazzelli et al., 2009). Using CT imaging in the present study led to the exclusion of a large number of stroke survivors whose ischemic lesions were not visible on acute imaging, but we justify our approach by noting the widespread use of CT in clinical practice and therefore larger numbers overall than would be available with routine clinical MR imaging.
- The relatively small sample size may have caused overfitting in the multivariable linear regression models.
- Although we aimed to include a clinically representative sample by recruiting consecutively from a regional stroke unit, the need for informed consent and 6-month follow-up likely resulted in some selection bias.

CONCLUSION

Our study confirms that poststroke EF is associated with both stroke lesion-related WM damage and WMHs in a clinically representative patient sample using routine clinically acquired CT imaging. Our results demonstrate the influence of both stroke damage and WM damage, potentially linked to cerebral small vessel disease, on poststroke cognitive outcomes. Furthermore, our results have implications for clinical research and clinical practice by demonstrating the prognostic utility of CT-derived imaging measures for predicting poststroke cognitive outcomes. However, future prognostic studies are required to confirm this finding given the limitations of our study.

ACKNOWLEDGMENTS

The authors thank the individuals who took part in the Oxford Cognitive Screening study and all of the research staff who contributed toward data collection. In particular, the authors acknowledge the contributions to data collection and curation for the Oxford Cognitive Screening data made by Ellie Slavkova, MS, Grace Chiu, MS, and Romina Basting, MS, of the Department of Experimental Psychology at the University of Oxford.

REFERENCES

Ball EL, Sutherland R, Squires C, et al. 2022. Predicting post-stroke cognitive impairment using acute CT neuroimaging: a systematic review and meta-analysis. *Int J Stroke*. 17:618–627. doi:10.1177/17474930211045836

Brazzelli M, Sandercock PA, Chappell FM, et al. 2009. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. *Cochrane Database Syst Rev*. 4:CD007424. doi:10.1002/14651858.CD007424.pub2

Burgess PW, Shallice T. 1996. Bizarre responses, rule detection and frontal lobe lesions. *Cortex*. 32:241–259. doi:10.1016/S0010-9452(96)80049-9

Cho MJ, Jang SH. 2021. Relationship between post-traumatic amnesia and white matter integrity in traumatic brain injury using tract-based spatial statistics. *Sci Rep*. 11:6898. doi:10.1038/s41598-021-86439-0

Demeyere N, Riddoch MJ, Slavkova ED, et al. 2015. The Oxford Cognitive Screen (OCS): validation of a stroke-specific short cognitive screening tool. *Psychol Assess*. 27:883–894. doi:10.1037/pas0000082

Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2023 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/cogbehavneurol by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 10/09/2023

Demeyere N, Haupt M, Webb SS, et al. 2021. Introducing the tablet-based Oxford Cognitive Screen–Plus (OCS–Plus) as an assessment tool for subtle cognitive impairments. *Sci Rep*. 11:8000. doi:10.1038/s41598-021-87287-8

Dostovic Z, Dostovic E, Smajlovic D, et al. 2016. Brain edema after ischaemic stroke. *Med Arch*. 70:339–341. doi:10.5455/med-arh.2016.70.339-341

Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. 2014. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 383:245–254. doi:10.1016/S0140-6736(13)61953-4

Frija G, Blažić I, Frush DP, et al. 2021. How to improve access to medical imaging in low- and middle-income countries? *E Clinical Medicine*. 38:101034. doi:10.1016/j.eclinm.2021.101034

Fu JH, Lu CZ, Hong Z, et al. 2005. Extent of white matter lesions is related to acute subcortical infarcts and predicts further stroke risk in patients with first ever ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 76:793–796. doi:10.1136/jnnp.2003.032771

Gardner E, Johnson K. 2013. The somatosensory system: receptors and central pathways. In: Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ, Mack S, eds. *Principles of Neural Science*, 5th ed. McGraw-Hill; 473–497.

GBD 2016 Stroke Collaborators. 2019. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 18:439–458. doi:10.1016/S1474-4422(19)30034-1

Griffanti L, Zamboni G, Khan A, et al. 2016. BIANCA (Brain Intensity AbNormality Classification Algorithm): a new tool for automated segmentation of white matter hyperintensities. *Neuroimage*. 141:191–205. doi:10.1016/j.neuroimage.2016.07.018

Griffis JC, Metcalf NV, Corbetta M, et al. 2021. Lesion Quantification Toolkit: a MATLAB software tool for estimating grey matter damage and white matter disconnections in patients with focal brain lesions. *Neuroimage Clin*. 30:102639. doi:10.1016/j.nicl.2021.102639

Humphreys GW, Duta MD, Montana L, et al. 2017. Cognitive function in low-income and low-literacy settings: validation of the tablet-based Oxford Cognitive Screen in the health and aging in Africa: a longitudinal study of an INDEPTH community in South Africa (HAALSI. *J Gerontol B Psychol Sci Soc Sci*. 72:38–50. doi:10.1093/geronb/gbw139

Hurford R, Charidimou A, Fox Z, et al. 2013. Domain-specific trends in cognitive impairment after acute ischaemic stroke. *J Neurol*. 260:237–241. doi:10.1007/s00415-012-6625-0

Kantarci K, Senjem ML, Avula R, et al. 2011. Diffusion tensor imaging and cognitive function in older adults with no dementia. *Neurology*. 77:26–34. doi:10.1212/WNL.0b013e31822313dc

Lozano R, Naghavi M, Foreman K, et al. 2012. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 380:2095–2128. doi:10.1016/S0140-6736(12)61728-0

Melkas S, Vataja R, Oksala NKJ, et al. 2010. Depression–executive dysfunction syndrome relates to poor poststroke survival. *Am J Geriatr Psychiatry*. 18:1007–1016. doi:10.1097/JGP.0b013e3181d695d7

Miyake A, Friedman NP, Emerson MJ, et al. 2000. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cogn Psychol*. 41:49–100. doi:10.1006/cogp.1999.0734

Mole JA, Demeyere N. 2020. The relationship between early post-stroke cognition and longer term activities and participation: a systematic review. *Neuropsychol Rehabil*. 30:346–370. doi:10.1080/09602011.2018.1464934

Mole J, Foddai E, Chan E, et al. 2020. Is the Brixton Spatial Anticipation Test sensitive to frontal dysfunction? Evidence from patients with frontal and posterior lesions. *J Clin Exp Neuropsychol*. 42:531–543. doi:10.1080/13803395.2020.1776223

Moore M. 2022. *A practical guide to lesion symptom mapping*. *PsyArXiv*. Preprint posted online January 12, 2022. doi:10.31234/osf.io/2jxr9

Muir RT, Lam B, Honjo K, et al. 2015. Trail Making Test elucidates neural substrates of specific poststroke executive dysfunctions. *Stroke*. 46:2755–2761. doi:10.1161/STROKEAHA.115.009936

Pendlebury ST, Rothwell PM. 2009. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol*. 8:1006–1018. doi:10.1016/S1474-4422(09)70236-4

Pendlebury ST, Rothwell PM, Oxford Vascular Study. 2019. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. *Lancet Neurol*. 18:248–258. doi:10.1016/S1474-4422(18)30442-3

Pendlebury ST, Thomson RJ, Welch SJV, et al. 2022. Utility of white matter disease and atrophy on routinely acquired brain imaging for prediction of long-term delirium risk: population-based cohort study. *Age Ageing*. 51:afab200. doi:10.1093/ageing/afab200

Pohjasvaara T, Leskelä M, Vataja R, et al. 2002. Post-stroke depression, executive dysfunction and functional outcome. *Eur J Neurol*. 9:269–275. doi:10.1046/j.1468-1331.2002.00396.x

Primativo S, Clark C, Yong KXX, et al. 2017. Eyetracking metrics reveal impaired spatial anticipation in behavioural variant frontotemporal dementia. *Neuropsychologia*. 106:328–340. doi:10.1016/j.neuropsychologia.2017.10.014

Reverberi C, Lavaroni A, Gigli GL, et al. 2005. Specific impairments of rule induction in different frontal lobe subgroups. *Neuropsychologia*. 43:460–472. doi:10.1016/j.neuropsychologia.2004.06.008

Rorden C, Bonilha L, Fridriksson J, et al. 2012. Age-specific CT and MRI templates for spatial normalization. *Neuroimage*. 61:957–965. doi:10.1016/j.neuroimage.2012.03.020

Santiago C, Herrmann N, Swardfager W, et al. 2015. White matter microstructural integrity is associated with executive function and processing speed in older adults with coronary artery disease. *Am J Geriatr Psychiatry*. 23:754–763. doi:10.1016/j.jagp.2014.09.008

Seminog OO, Scarborough P, Wright FL, et al. 2019. Determinants of the decline in mortality from acute stroke in England: linked national database study of 795 869 adults. *BMJ*. 365:l1778. doi:10.1136/bmj.l1778

Simoni M, Li L, Paul NLM, et al. 2012. Age- and sex-specific rates of leukoaraiosis in TIA and stroke patients: population-based study. *Neurology*. 79:1215–1222. doi:10.1212/WNL.0b013e31826b951e

Singer OC, Sitzer M, du Mesnil de Rochemont R, et al. 2004. Practical limitations of acute stroke MRI due to patient-related problems. *Neurology*. 62:1848–1849. doi:10.1212/01.WNL.0000125320.53244.FA

Subramaniam K, Gill J, Fisher M, et al. 2018. White matter microstructure predicts cognitive training-induced improvements in attention and executive functioning in schizophrenia. *Schizophr Res*. 193:276–283. doi:10.1016/j.schres.2017.06.062

Veldsman M, Werden E, Egorova N, et al. 2020. Microstructural degeneration and cerebrovascular risk burden underlying executive dysfunction after stroke. *Sci Rep*. 10:17911. doi:10.1038/s41598-020-75074-w

Wahlund LO, Barkhof F, Fazekas F, et al. 2001. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 32:1318–1322. doi:10.1161/01.STR.32.6.1318

Webb SS, Hobden G, Roberts R, et al. 2022. Validation of the UK English Oxford cognitive screen-plus in sub-acute and chronic stroke survivors. *Eur Stroke J*. 7:476–486. doi:10.1177/23969873221119940

Wippold FJ. 2007. Head and neck imaging: the role of CT and MRI. *J Magn Reson Imaging*. 25:453–465. doi:10.1002/jmri.20838

Yeh FC, Panesar S, Fernandes D, et al. 2018. Population-averaged atlas of the macroscale human structural connectome and its network topology. *Neuroimage*. 178:57–68. doi:10.1016/j.neuroimage.2018.05.027

Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2023 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.