ARTICLE

Association of Depression and Anxiety With Cognitive Impairment 6 Months After Stroke

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Abstract

Objective

To investigate the associations between general cognitive impairment and domain-specific cognitive impairment with depression and anxiety at 6 months poststroke.

Methods

Participants were patients with confirmed acute stroke from the OCS-Care Study who were recruited on stroke wards in a multisite study and followed up at a 6-month poststroke assessment. Depression and anxiety symptoms were assessed by the Hospital Anxiety and Depression Scale subscales, with scores greater than 7 indicating possible mood disorders. General cognitive impairment at follow-up was assessed using the Montreal Cognitive Assessment (MoCA); stroke-specific cognitive domain impairments were assessed using the Oxford Cognitive Screen (OCS). Linear regression was used to examine the associations between cognition and depression/anxiety symptoms at 6 months, controlling for acute stroke severity and activities of daily living impairment, age, sex, education, and co-occurring poststroke depression/anxiety.

Results

A total of 437 participants (mean age, 69.28 years [SD 12.17], 226 male [51.72%]) were included in analyses. Six-month poststroke depression (n = 115, 26%) was associated with 6-month impairment on the MoCA (β = 0.96, standard error [SE] 0.31, p = 0.006) and all individual domains assessed by the OCS: spatial attention (β = 0.67, SE 0.33, p = 0.041), executive function (β = 1.37, SE 0.47, p = 0.004), language processing (β = 0.87, SE 0.38, p = 0.028), memory (β = 0.76, SE 0.37, p = 0.040), number processing (β = 1.13, SE 0.40, p = 0.005), and praxis (β = 1.16, SE 0.49, p = 0.028). Poststroke anxiety (n = 133, 30%) was associated with impairment on the MoCA (β = 1.47, SE 0.42, p = 0.001) and spatial attention (β = 1.25, SE 0.45, p = 0.006); these associations did not remain significant after controlling for co-occurring poststroke depression.

Conclusion

Domain-general and domain-specific poststroke cognitive impairment was found to be highly related to depressive symptomatology but not anxiety symptomatology.

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Glossary

ADL = Barthel Index of Activities of Daily Living; **CI** = confidence interval; **FDR** = false discovery rate; **HADS** = Hospital Anxiety and Depression Scale; **MoCA** = Montreal Cognitive Assessment; **NIHSS** = NIH Stroke Scale; **OCS** = Oxford Cognitive Screen; **OR** = odds ratio; **WMS-R** = Wechsler Memory Scale–Revised.

Mood disorders are common after stroke, occurring at higher rates than in the general population.[1,2] Poststroke depression and anxiety can have a negative effect on long-term recovery.[3] Cognitive status is an important predictor of poststroke depression.[4] However, research has provided inconsistent evidence of domain-specific associations between cognition and poststroke mood.

One of the most consistently reported risk factors for poststroke depression is cognitive impairment.[4] However, research into the effect of domain-specific cognitive impairment has yielded inconsistent findings. Acute impairments in language, visual memory, visuospatial neglect, executive functioning, and working memory have been associated with depressive symptoms at 3 months[5] and 6 months poststroke.[6] In comparison to poststroke depression, the association of poststroke anxiety with cognition has received very little attention. One study reported associations between poststroke anxiety and impaired processing speed but not executive function or verbal memory.[7] Anxiety at 1 year poststroke has been associated with overall cognition.[8]

The majority of studies have only measured acute/subacute cognitive impairment[5–7] and it remains unclear how persistent cognitive impairment (>6 months poststroke) is associated with mood disorders after 6 months poststroke. Furthermore, despite their high comorbidity,[7] depression and anxiety are rarely studied together[7,8] and models examining cognition–mood associations seldom control for co-occurrence of depression and anxiety. The aim of this study was to examine domain-specific relationships between lasting cognitive impairment and risk of poststroke depression and anxiety at 6 months poststroke while controlling for counterpart mood symptoms to examine whether cognitive impairment is associated with depression independent of anxiety and vice versa.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The information used in this study was collected from the OCS-Care Study (ISRCTN50857950; registered on March 27, 2014) with the approval of the local ethics committee (West Midlands: Coventry and Warwickshire National Research Ethical Committee, REC reference 12/WM/00,335). All participants provided written informed consent. All procedures were in accordance with the Declaration of Helsinki. No recognizable persons in photographs, videos, or other information are included.

Participants

This is a secondary analysis of data acquired from a subsample of the OCS-Care Study, a multicenter sample of patients with stroke recruited consecutively between July 2014 and July 2016 from 37 sites in England.[9] Originally, participants were included if they met the following criteria: (1) acute stroke (within 10 weeks of confirmed stroke); (2) adult (≤90 years of age); (3) able to concentrate sufficiently for 1 hour as judged by the multidisciplinary care team in the hospital; (4) sufficient language comprehension to pass the first orienting tests (the Oxford Cognitive Screen [OCS] Picture Naming and Semantics tasks); and (5) willing and able to give informed consent. Further to this, participants were only included in the present analyses if they had complete data including stroke severity and activities of daily living during the acute stage and had completed cognition and mood assessments at 6 months follow-up. This was necessary to allow for comparison between statistical models for different cognitive domains as casewise exclusion based on missing data may lead to slightly different samples being included in different models.

Mood Assessment

Depression and anxiety symptomatology were assessed using the Hospital Anxiety and Depression Scale (HADS).[10] The HADS consists of 7 items each for depression and anxiety with answers rated 0–3 for each question, providing 2 subscales with a range of 0–21 for depression (HADS-D) and anxiety (HADS-A). Scores above 7 indicate possible cases while scores above 11 indicate probable cases of depression/anxiety. Since its introduction, the HADS has been used extensively in clinical practice and research and has been found to have high sensitivity and reliability.[11] The HADS was administered to participants during a 6-month face-to-face follow-up assessment. While we used the cutoff scores to describe the prevalence of depressive and anxious symptoms, the HADS subscales were entered into analyses as continuous variables.

Cognitive Assessment

General cognitive status and domain-specific cognitive impairments were assessed by trained research nurses or occupational therapists in all participating research centers. Although the research was completed before Montreal Cognitive Assessment (MoCA) administration certification was available, all research staff completed an induction by the

study team in which they were trained to administer both OCS and MoCA.

Cognitive status was assessed using the MoCA.[12] The MoCA consists of a single A4 page and can be administered in approximately 15 minutes. While it contains assessments of several cognitive functions, there are no separable norm data to determine cutoffs in subsections. Instead, a total score out of 30 is calculated, with scores <26 considered indicative of cognitive impairment.[12] Although originally developed for mild cognitive impairment and dementia, the MoCA is commonly used to screen for cognitive impairment in patients with stroke and has been shown to have good sensitivity to cognitive impairment after stroke.[13]

Domain-specific impairments were assessed using the OCS.[14] The OCS is a cognitive screening tool designed specifically to assess common cognitive impairments in patients with stroke. With a typical administration time of 15–20 minutes, the OCS consists of 10 subtests that can be categorized into 6 cognitive domains: spatial attention (object and spatial neglect), executive function (trails switching accuracy), language (picture naming, semantic understanding, sentence reading), episodic memory (orientation, verbal recall, verbal recognition), number processing (number writing, calculation), and praxis (hand gesture imitation). Subtests are binarized into impaired/unimpaired based on normative scores for each subtest. Each cognitive domain is treated as impaired if at least one subtest in the domain is classed as impaired. A detailed description of the tests alongside normative data and validation have been published previously.[14,15]

Acute Stroke Severity Assessment

Baseline assessment of stroke severity was assessed via the NIH Stroke Scale (NIHSS).[16] The NIHSS is a brief 11-item observation scale that addresses cognitive and motor problems after stroke. Baseline stroke impact on daily life functioning was assessed via the Barthel Index of Activities of Daily Living (ADL). The Barthel Index consists of 10 items that measure a person's daily functioning, specifically activities of daily living and mobility.

Statistical Analysis

All analyses were carried out in R (version 3.6.3). Preliminary analyses to examine group differences in demographics, clinical stroke features, and cognitive impairment between participants included in the analysis and those excluded for missing data were conducted using univariate analyses (*t* tests for continuous variables, χ^2 test for categorical data). For the core analyses, pirate plots and univariate linear regression models were used to assess associations between cognitive metrics and HADS subscale scores.

We present 2 sets of analyses where the effects of cognition on depression or anxiety were examined separately. Multivariable linear regression was applied using the lm function in R to assess the association between cognition and HADS-D/HADS-A scores while controlling for confounding variables. Cognitive predictors included MoCA cognitive impairment (score < 26), OCS total number of impaired domains (categorized as 0, 1, or 2 or more domains impaired, due to a skewed distribution), and impairment on each individual cognitive domain separately. Two sequential models were applied for each cognitive measure as predictor variables with HADS-D/HADS-A score as the dependent variable. Model 1 controlled for age at stroke, sex, education (years), NIHSS, and Barthel score. To assess whether cognition is associated with depression independently of anxiety and vice versa, model 2 additionally controlled for HADS-A in the models predicting HADS-D and HADS-D in the models predicting HADS-A. Several covariates were binarized due to skewed or limited range distributions and were classed as impaired vs spared based on clinical cutoffs. Stroke severity was classified as minor stroke vs major stroke with NIHSS scores >3 indicating major stroke.[17] The Barthel score was classified as impaired vs unimpaired daily functioning, with a score <95 indicating impairment.[18] Age at stroke and years of education were mean centered. The increased risk of type I error due to multiple comparisons was corrected for by applying the false discovery rate (FDR) procedure as implemented using the p.adjust function in R.

Logistic regression was applied as secondary analysis. Models with symptom group membership as the dependent variable were based on HADS subscale cutoffs of 8 of more to be considered depressive or anxious cases. Only cognitive variables that were found to be associated with HADS subscales in model 2 were analyzed. This was because there was a large proportion of participants who were both depressive and anxious. Thus, linear models were necessary first to interrogate the associations of interest while controlling for co-occurring mood symptoms. Covariates again included age at stroke, sex, education, NIHSS score, and Barthel score. Years of education was binarized into high (those with more than 11 years of education) and low (those who left school before age 16) due to the violation of the assumption of linearity between the logit of the outcome and each predictor variable.

Data Availability

Anonymized data and code have been made available at http://osf.io/SBMPR.

Results

In the original OCS-Care Study, 467 participants completed assessments and questionnaires during the acute stage post-stroke and at a 6-month follow-up.[9] Thirty of these participants had missing data for at least one variable of interest and were therefore excluded from all subsequent analysis in order for statistical models to be compared across the exact same sample. Table S1 (osf.io/sbmpr/) shows that there were no significant differences in demographics or clinical stroke features between the subsample and the 30 excluded individuals. However, a greater proportion of the excluded participants did have an impairment in the language domain (33.3%) compared to the subsample with complete data (17.9%), $\chi^2 = 3.886$, $p = 0.0487$, suggesting aphasia symptoms may have

contributed to increased missingness of questionnaire data in particular. In total, 437 participants were included in all analyses.

The mean age of the sample included in analyses was 69.28 years (SD 12.17), 226 were male (51.72%), and the average number of years of education was 11.82 (SD 2.89). The average follow-up interval between acute assessment and 6-month assessment was 208.88 days (SD 29.26) (6.74 months). Of these participants, 149 (34.10%) were considered to have had a major stroke (NIHSS >3) and 252 (57.67%) were considered to be disabled in some ADLs (Barthel ADL score <95). Cognitive impairment assessed by the MoCA (score <26) was present in 232 (53.10%) participants at 6-month follow-up. For OCS outcomes, 128 (29.29%) were impaired in one cognitive domain and 105 (24.03%) were impaired on multiple cognitive domains.

Table 1 shows the number of possible and probable cases for depression and anxiety in the sample at the 6-month poststroke assessment (based on HADS cutoffs). Of the participants who were noncases, 266 (60.8% of whole group) did not have depression or anxiety symptoms. Of the possible and probable cases, 77 (17.6% of whole group) participants had both depression and anxiety symptoms.

Depression

Being impaired in the MoCA or having 1, 2, or more impairments in the OCS was associated with higher HADS-D scores compared to no impairments (figure 1). Supplementary figure S1 (available at osf.io/SBMPR/) shows pirate plots comparing HADS-D for individual cognitive domains on the OCS; all 6 domains showed significantly higher HADS-D scores in the impaired groups compared to not impaired groups ($p < 0.01$).

Table 1 Scores on Hospital Anxiety and Depression Scale (HADS) Subscales for Depression and Anxiety at 6 Months Poststroke by Mood Status, Clinical Status, and Cognitive Status

	HADS-D subscale	HADS-A subscale
Whole group	5.28 (4.06)	5.76 (4.28)
Noncases	3.33 (2.22)	4.42 (3.26)
Possible cases	8.71 (0.75)	8.33 (4.11)
Probable cases	13.21 (2.57)	10.94 (4.7)
Minor stroke	4.59 (3.65)	5.4 (4.14)
Major stroke	6.62 (4.47)	6.46 (4.47)
ADL unimpaired	4.42 (3.8)	5.38 (4.43)
ADL impaired	5.91 (4.14)	6.04 (4.14)
MoCA unimpaired	4.32 (3.53)	5.11 (3.75)
MoCA impaired	6.13 (4.31)	6.34 (4.62)
OCS unimpaired	4.21 (3.57)	5.25 (3.95)
OCS 1 impairment	5.62 (3.8)	5.63 (4.37)
OCS 2 or more impairments	6.96 (4.62)	6.9 (4.59)

Abbreviations: ADL = Barthel Index of Activities of Daily Living; MoCA = Montreal Cognitive Assessment; OCS = Oxford Cognitive Screen.
Values are mean (SD).

All cognitive metrics were positively associated with HADS-D after FDR correction for multiple comparisons. Having 2 or more domain impairments on the OCS was the predictor variable with the largest β value, suggesting that the accumulative effects of impairment on multiple domains is an important risk factor of depressive symptoms. Overall, the β values were slightly attenuated in model 2, which additionally controlled for anxiety symptoms using the HADS-A subscale (table 2).

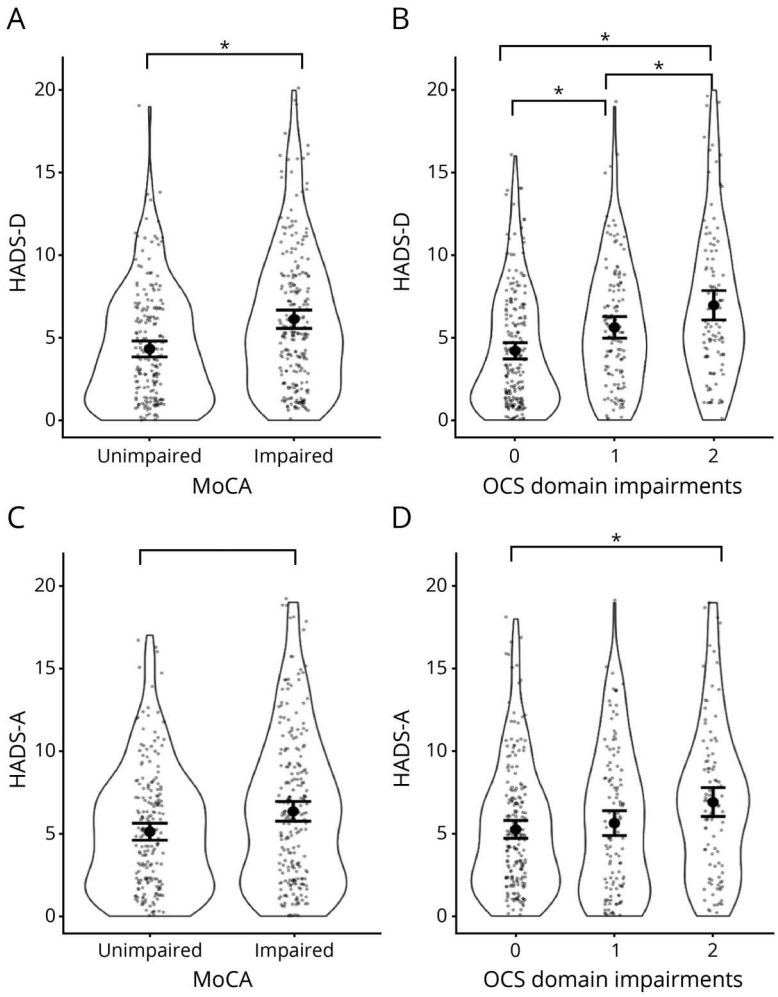
Results from the logistic regression carried out in secondary analyses are presented in figure 2. There was an increased risk of possible depression in individuals with an impairment on the MoCA (odds ratio [OR] 3.04, 95% confidence interval [CI] 1.84–5.14), 1 cognitive domain impairment on the OCS (OR 2.19, CI 1.25–3.87), 2 or more cognitive domain impairments on the OCS (OR 3.37, CI 1.85–6.23), impaired spatial attention (OR 1.83, CI 1.10–3.03), impaired language (OR 1.80, CI 1.02–3.16), impaired number processing (OR 2.46, CI 1.37–4.43), and impaired praxis (OR 2.40, CI 1.16–4.95). Only impairment on executive function (OR 1.82, CI 0.88–3.7) and memory (OR 1.75, CI 0.99–3.05) were not associated with increased risk of depression. Groupwise comparisons of the depressed vs not depressed groups for logistic regression are shown in Supplementary Table S2 (osf.io/SBMPR/).

Anxiety

Being impaired in the MoCA or having 2 or more impairments in the OCS was associated with higher HADS-A scores compared to no impairments (figure 1). When comparing HADS-A for individual cognitive domains on the OCS, only impairments in spatial attention ($p = 0.009$), language ($p = 0.042$), and number processing ($p = 0.026$) showed higher HADS-A scores compared to individuals not impaired in those domains (additional pirate plots for separate cognitive domains are provided in Supplementary figure S1, osf.io/SBMPR/).

In model 1 (controlling for age at stroke, sex, education, NIHSS score, and Barthel score), general cognitive impairment on the MoCA, having 2 or more cognitive domain impairments on the OCS, and impaired spatial attention were positively associated with HADS-A scores after FDR correction for multiple comparisons. Language impairment, number impairment, and praxis impairment were positively associated but did not survive FDR multiple comparison correction. See table 3 for multivariable regression values with HADS-A scores as the dependent variable.

Figure 1 Pirate Plots Describing the Distributions of Depression and Anxiety Scores



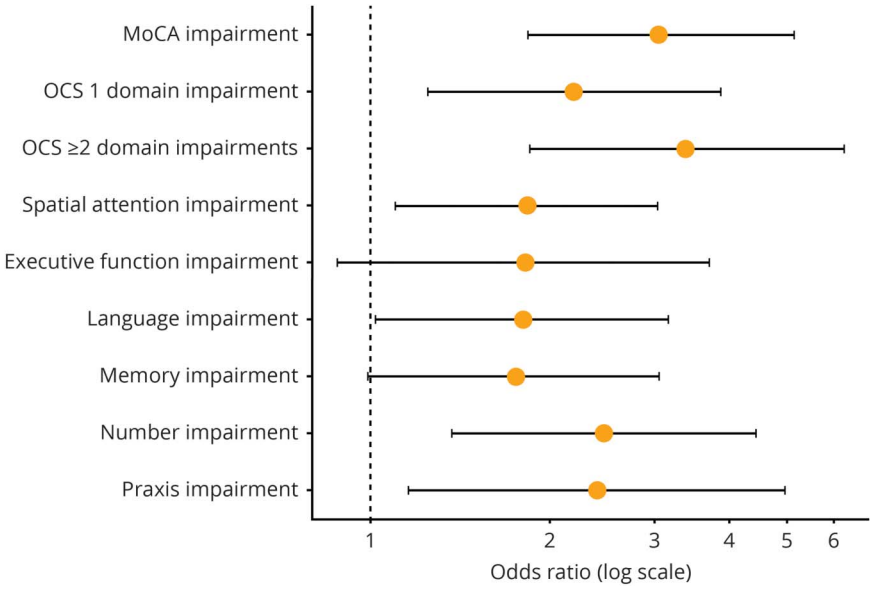
(A) Hospital Anxiety and Depression Scale–depression (HADS-D) scores compared between unimpaired and impaired participants on the Montreal Cognitive Assessment (MoCA). (B) HADS-D scores compared between participants with no cognitive domains impaired (0), 1 domain impairment (1), and 2 or more cognitive domain impairments (≥2). (C) Hospital Anxiety and Depression Scale–anxiety (HADS-A) scores compared between unimpaired and impaired participants on the MoCA. (D) HADS-A scores compared between participants with no impairment, 1 impairment, and 2 or more impairments. Small dots indicate raw data, large dots indicate means with 95% confidence intervals; full data distributions are shown with the smoothed density curves. *$p < 0.05$. MoCA = Montreal Cognitive Assessment; OCS = Oxford Cognitive Screen.

Table 2 Effects of Cognitive Impairment on Depressive Symptoms at 6 Months Poststroke

	Model 1			Model 2		
	β (SE)	*t* Value	*p* Value	β (SE)	*t* Value	*p* Value
MoCA < 26	1.820 (0.391)	4.652	<0.001[a]	0.96 (0.308)	3.12	0.002[a]
OCS 1 impairment	1.351 (0.436)	3.097	0.002[a]	1.037 (0.338)	3.063	0.002[a]
OCS 2 or more impairments	2.556 (0.479)	5.335	<0.001[a]	1.473 (0.377)	3.909	<0.001[a]
Spatial attention impairment	1.418 (0.423)	3.356	0.001[a]	0.672 (0.329)	2.045	0.041[a]
Executive impairment	1.991 (0.615)	3.237	0.001[a]	1.373 (0.473)	2.902	0.004[a]
Language impairment	1.507 (0.493)	3.055	0.002[a]	0.874 (0.381)	2.296	0.022[a]
Memory impairment	1.182 (0.483)	2.445	0.015[a]	0.764 (0.371)	2.059	0.040[a]
Number impairment	1.792 (0.519)	3.452	0.001[a]	1.126 (0.401)	2.811	0.005[a]
Praxis impairment	2.016 (0.634)	3.178	0.002[a]	1.157 (0.49)	2.36	0.019[a]

Abbreviations: MoCA = Montreal Cognitive Assessment; OCS = Oxford Cognitive Screen.
Results from models 1 and 2. MoCA coded as unimpaired vs impaired (<26).
[a] Significant after false discovery rate correction for multiple comparisons.

Figure 2 Odds Ratios for Risk of Possible Depression (HADS-D > 7) for Each Cognitive Metric Assessed



Bars indicate confidence intervals. Model is corrected for age, sex, education, NIH Stroke Scale score, and Barthel score. MoCA = Montreal Cognitive Assessment; OCS = Oxford Cognitive Screen.

As no cognitive metrics were associated with HADS-A independent of depression, no logistic regression models were carried out for anxiety.

Discussion

In a large sample of patients with stroke who were followed up at 6 months poststroke, we found that a general measure of cognitive impairment (MoCA score standard cutoff) as well as impairment in multiple domains, as measured by the OCS, was associated with elevated levels of poststroke depressive symptomatology independent of stroke severity, ADL impairment, age at stroke, sex, education, and co-occurring anxiety symptomatology. Poststroke anxiety showed limited associations with cognition and these were lost when controlling for co-occurring poststroke depressive symptomatology. These results suggest that while overall severity of cognitive impairment shows similar associated risk for poststroke depression or anxiety, there are different patterns of associations between specific cognitive impairments and risk of poststroke depression compared to poststroke anxiety and that observed associations between poststroke cognitive

Table 3 Effects of Cognitive Impairment on Anxious Symptoms at 6 Months Poststroke

	Model 1			Model 2		
	β (SE)	*t* Value	*p* Value	β (SE)	*t* Value	*p* Value
MoCA < 26	1.465 (0.421)	3.477	0.001[a]	0.225 (0.335)	0.671	0.502
OCS 1 impairment	0.539 (0.473)	1.138	0.256	−0.39 (0.371)	−1.051	0.294
OCS 2 or more impairments	1.858 (0.520)	3.571	<0.000[a]	0.101 (0.416)	0.242	0.809
Spatial attention impairment	1.251 (0.452)	2.767	0.006[a]	0.284 (0.353)	0.803	0.422
Executive impairment	1.034 (0.662)	1.563	0.119	−0.342 (0.513)	−0.667	0.505
Language impairment	1.058 (0.529)	2.001	0.046	0.023 (0.411)	0.055	0.956
Memory impairment	0.695 (0.517)	1.343	0.180	−0.119 (0.399)	−0.298	0.766
Number impairment	1.116 (0.558)	2.000	0.046	−0.119 (0.435)	−0.273	0.785
Praxis impairment	1.438 (0.68)	2.114	0.035	0.054 (0.529)	0.102	0.919

Abbreviations: MoCA = Montreal Cognitive Assessment; OCS = Oxford Cognitive Screen.
Results from models 1 and 2.
[a] Significant after false discovery rate correction for multiple comparisons.

impairment and anxiety may in fact be due to co-occurring depression. The finding that these associations were found to be independent of stroke severity and initial disability has important implications for targeted therapy of poststroke cognitive impairment and mood disorders. It is common for patients with cognitive impairment to present with multiple neuropsychiatric symptoms,[19] and indeed, this was the case in the present study. Thus, neuropsychiatric treatments should still target all present mood disorders. However, based on these results, it may be expected that interventions targeting cognitive recovery or depressive mood may have a positive impact on both cognition and mood.

The results from the fully adjusted model 2 for depression confirm previous reports that general cognitive impairment after stroke is associated with depression at 6 months poststroke.[6,20] By using the stroke-specific OCS assessment, this study extended these findings to show that having an impairment in one or more cognitive domains increases depressive symptomatology, suggesting that there is an additive effect of domain-specific cognitive impairments on the risk of depressive symptomatology, with those having more than 2 cognitive domain impairments at greater risk of poststroke depression. Furthermore, we were able to assess associations between impairment in specific domains and depressive symptomatology. We found positive associations between depressive symptomatology and impairments in all domains assessed, including spatial attention, executive function, language processing, memory, number processing, and praxis. While spatial attention (including neglect), executive functioning, language processing, and memory have been more commonly studied and found to be related to poststroke depression,[5,6,21] number processing and praxis have not received the same level of investigation. Here we show that these domains are important contributors in the profile of cognitive impairment related to poststroke depression as they each have the highest ORs of the 6 individual domains assessed by binary logistic regression in the secondary analyses. Furthermore, impairments in these 2 domains are common among stroke survivors.[22]

Episodic memory as assessed by the OCS was significantly associated with poststroke depressive symptomatology. This is in contrast with an earlier report from Hosking et al.[23] that episodic verbal memory as assessed by the Verbal Paired Associates subtest of the Wechsler Memory Scale–Revised (WMS-R)[24] was not associated with poststroke depression. As the OCS was designed specifically for patients with stroke and allows for nonverbal responses when oral communication is impaired, it is possible that it provides a more accurate description of memory impairment compared to the WMS-R subtests in patients with stroke, and that may explain the discrepancy in our current findings. While Nys et al.[6] reported significant associations between visual memory and 3-month poststroke depression symptomatology, they did not find any association with verbal memory impairment, again suggesting that relying on verbal abilities in patients with acute stroke may cloud associations between episodic memory and poststroke depression. Hommel et al.[5] did find significant associations between acute impairments in verbal episodic memory and 3-month poststroke depression, but the association was lost when they controlled for demographics and clinical stroke features.

Our finding that executive function was associated with poststroke depressive symptomatology in linear regression models but was not associated with poststroke depression in the logistic regression was surprising. In similar logistic regression analyses, positive associations between poststroke depression symptoms and impairments in various aspects of executive function have been consistently reported.[5,6,23] Executive function in the OCS is assessed using a trails task, which involves set shifting and inhibiting previously learned responses. However, a limitation of the OCS assessment of executive function is that it remains a single screening subtest and as such does not address other important components of the executive domain including abstraction, multitasking, and problem solving. Other studies use tasks that examine these executive function traits and have found associations with depression.[5,6] Performance on the Hanoi Tower[25] was associated with poststroke depression independently of demographics and clinical stroke features.[5] This is a complex task that measures multiple facets of executive function and may be more sensitive to deficits than the OCS trails task. Nys et al.[6] administered a comprehensive battery of executive function tests that were shown to be associated with poststroke depression. However, the models did not control for stoke severity or other clinical features.[6]

For poststroke anxiety, we found that general cognitive impairment and severity as measured by number of domains impaired on the OCS were related to increased anxiety symptoms. This is supported by a previous finding of a cross-sectional relationship between poststroke anxiety and general cognition at 1 year poststroke.[8] However, others have reported no associations between anxiety and cognition.[26] When individual components of cognition were analyzed, only impairment on the praxis task was significantly associated with anxiety symptoms, independently of other important risk factors. To our knowledge, this is the first time that apraxia has been found to be associated with poststroke anxiety. The fact that no other domain tested was associated with poststroke anxiety is similar to previously reported findings that executive function and verbal memory were not related to anxiety at 3 months poststroke.[7] However, when depressive symptoms were added in model 2, there were no significant associations between anxiety symptoms and any of the cognitive measures used. Very few studies have investigated poststroke depression and anxiety together. Barker-Collo[7] had previously reported that performance on cognitive tests explained more variance in poststroke depressive symptomatology that it did in anxiety symptomatology but the study did not control for co-occurrence. As poststroke depression and anxiety are highly correlated,[8] it is important to control for depressive

symptoms when investigating independent associations between cognitive impairment and poststroke anxiety. Lee et al.[8] found that while acute impairment on the MMSE was associated with anxiety in the first 2 weeks after stroke, this effect was lost once controlling for depressive symptoms. At 1-year poststroke follow-up they found that MMSE scores were associated with anxiety independently of depressive symptoms present during the acute stage but did not control for co-occurring poststroke depression at the 1-year assessment. With 58% of participants who tested positive for possible/probable anxiety also testing positive for depression in this sample at 6 months, we saw that controlling for depressive symptoms removed significant associations between cognitive impairment and anxiety. Therefore, it is possible that observed associations between poststroke cognitive impairment and anxiety were actually being driven by associations with depression.

The results of this study should be considered in light of several limitations. While the results suggest that persistent cognitive impairment is associated with greater chance of patients with stroke having symptoms of poststroke depression and to some extent also anxiety, the cross-sectional design does not allow for inference of causality. It may be the case that altered mood hinders the recovery of cognitive functioning or results in poorer performance on cognitive tasks. Support for the first idea comes from evidence that antidepressants have improved cognition after stroke.[27] However, Nys et al.[6] found that cognitive impairment during the acute stroke stage was associated with depressive symptomatology after 6 months poststroke and more recent evidence has suggested that general cognitive impairment at 6 months poststroke is associated with increased risk of depression 5 years poststroke.[28] It is possible that there is a bidirectional relationship between depression/anxiety and cognitive impairment in individuals poststroke. Future longitudinal studies with multiple assessments of both cognition and mood would allow for a more advanced understanding of these relationships through, for example, random-intercept cross-lagged panel modeling.[29,30] It should be noted that there is some evidence that lesion location may be related to depression, with left hemisphere lesions conferring higher risk of poststroke depression, which fits with reports of language impairments relating to higher rates of depression post stroke.[21] There was a large amount of missing data regarding the location of the stroke lesion in this sample, though the findings of in particular apraxia, number, and language impairments associations with poststroke depression fit with this. We suggest that the relationship with lesion location is likely being driven by the cognitive impairments, rather than any particular neuroanatomical reason for depressive symptomatology being related to the left hemisphere. As a result of the large amount of missing data, lesion location could not be included in our multivariable analyses. Prestroke depression has also been shown to be an important predictor of poststroke depression.[28] Such data were not available for the current dataset. Future work examining cognition–mood associations should examine interactions with prestroke depression and anxiety.

Another important limitation of the present analyses is the lack of information about premorbid intelligence, prestroke cognitive decline, or measures of cognitive reserve. These are important variables that have recently been shown to be associated with cognitive impairment and capacity for recovery from stroke.[31] However, education, which has been shown to be related to premorbid intelligence[32] and is often included in proxy measures of cognitive reserve, was included as a covariate in the present analyses. Lastly, the OCS and HADS are screening tools and the present findings need to be expanded upon using more comprehensive neuropsychological testing and in-depth psychological mood assessments. The HADS as a screening tool for depression and anxiety is also limited and there is evidence that it is more a measure of global distress than clinical mood disorders.[33] Thus, while we were measuring mood symptoms in the present study as detected with this questionnaire, this potentially is distinct from clinical diagnoses of depression and anxiety and future research employing clinical diagnoses of poststroke mood disorders is required to impact on clinical recommendations.

A key strength of this study is the use of the OCS to assess impairment in individual cognitive domains that are commonly affected in stroke and how they are associated with poststroke depression and anxiety. The advantages of the OCS are that it was designed specifically to assess for common domain-specific cognitive impairments poststroke, such as aphasia, apraxia, and neglect, while allowing for participants to complete assessments even when motor or language impairments are present.[15] This means that some of the more severely impaired participants could continue to participate. However, it is clear from comparisons with the 30 participants who were excluded that some with severe language impairments were still not able to complete all the necessary assessments to be included in the present analyses. Therefore, it is possible that by excluding some of the most severely aphasic patients, we are still underestimating the impact of poststroke language impairment on depression/anxiety; despite this, a large sample of patients with stroke contributed to this study, providing substantial statistical power for analyses.

This is one of few studies that have examined poststroke depression and anxiety alongside wide-ranging cognitive screening in the same cohort. We found different profiles of associations with domain-specific cognitive impairment and depressive vs anxiety symptomatology at 6 months poststroke. While poststroke depression was associated with impairments in all cognitive domains tested, anxiety was not found to be associated with cognitive impairment independently of depressive symptoms. Future work should focus on longitudinal experiments in order to elucidate the temporal relationships between domain-specific cognitive impairment and mood disorders in stroke survivors as these associations may have important implications for therapeutic applications.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix Authors

Name	Location	Contribution
Owen A. Williams, PhD	University of Oxford, UK	Conceptualized the study, analyzed the data, interpreted the data, drafted the manuscript
Nele Demeyere, PhD	University of Oxford, UK	Provided the data, conceptualized the study, interpreted the data, revised the manuscript, provided final approval, supervised the study

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