Multidomain cognitive dysfunction after minor stroke suggests generalized disruption of cognitive networks

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Abstract
Objective: Although small strokes typically result in “good” functional outcomes, significant cognitive impairment can occur. This longitudinal study examined a cohort of patients with minor stroke to determine the pattern of deficits, evolution over time, and factors associated with outcome.

Methods: Patients admitted to the hospital with their first clinical minor stroke (NIH Stroke Scale [NIHSS] ≤ 10, absence of severe hemiparesis, aphasia, or neglect) were assessed at 1 month post-infarct, and a subset were followed over time (with 6- and 12-month evaluations). Composite scores at each time point were generated for global cognition, verbal memory, spatial memory, motor speed, processing speed, and executive function. Paired t-tests evaluated change in scores over time. Regression models identified factors associated with initial performance and better recovery.

Results: Eighty patients were enrolled, evaluated at 1 month, and prospectively followed. The average age of the participants was 62.3 years, and mean education was 13.5 years. The average stroke volume was 6.6 cc; mean NIHSS score was 2.8. At 1 month, cognitive scores were below the normative range and > 1 standard deviation below the patient’s peak (“recovery”) score for every cognitive domain, strongly suggesting that they were well below patients’ prestroke baselines. Forty-eight patients followed up at 6 months, and 39 at 12 months. Nearly all (98%) patients significantly improved in global cognition (averaged across domains) between 1 and 6 months. Between 6 and 12 months, recovery was variable. Higher education, occupational class, and Caucasian race were associated with higher recovery scores for most domains.

Conclusions: Cognitive impairment across multiple domains is common following minor stroke regardless of infarct location, suggesting a global process such as network dysfunction that improves over 6 months. Degree of recovery can be predicted using baseline factors.
INTRODUCTION

Despite declining from the third to fourth leading cause of death in the United States in 2011 (Towfighi & Saver, 2011), stroke remains prevalent and often debilitating. It is a leading cause of long-term disability worldwide (Feigin et al., 2017), and results in billions of dollars in healthcare expenditures and lost wages annually (Go et al., 2013). Advances in detection and treatment, including use of intravenous tissue plasminogen activator (IV tPA) and mechanical thrombectomy, have converted what would have been large hemispheric lesions into smaller infarcts with better overall long-term outcomes (Berkhemer et al., 2015; Campbell et al., 2015; Demchuk et al., 2015; Saver et al., 2015; The National Institute of Neurological Disorders And Stroke rt-PA Stroke Study Group, 1995). However, patients presenting with so-called “minor stroke” can be left with significant symptoms that may be more difficult to appreciate but are nonetheless disabling (Shi et al., 2015; Winward et al., 2009). Although individuals with low NIH Stroke Scale scores often lack a dense hemiparesis or aphasia, many report at least some degree of cognitive impairment, mood disorder, or fatigue. These symptoms slow their functional recovery and delay return to their normal home and workplace activities (Marsh et al., 2018).

Post-stroke dementia and progressive vascular cognitive impairment are well described in the literature (Henon et al., 2001; Leys et al., 2005; O’Brien et al., 2003; Pendlebury & Rothwell, 2009; Pohjasvaara et al., 1998). The Secondary Prevention of Small Subcortical Strokes (SPS3) trial found that in the early months after stroke, mild cognitive impairment (MCI) was present in nearly half of patients presenting with a single lacunar infarct despite minimal or no physical disability (Jacova et al., 2012). In another cohort, Pendlebury et al. (2011) reported an initial cognitive decline in individuals with TIA and minor stroke that improves but may be associated with long-term dysfunction.

The domain-specific pattern of cognitive deficits and recovery trajectory for patients after minor stroke is not as well characterized, and neither are the patient characteristics and stroke factors associated with a better outcome. In this study, we build off the work of SPS3 by longitudinally examining cognition in patients presenting with minor stroke to determine the typical pattern of deficits, recovery curve, and factors that influence improvement.

SUBJECTS AND METHODS

STUDY POPULATION

We enrolled a prospectively collected cohort of adults presenting to our Comprehensive Stroke Center with their first-ever clinical ischemic stroke who subsequently followed up in our outpatient stroke clinic. All strokes were mild in severity, as defined by an initial NIH Stroke Scale (NIHSS) (Brott et al., 1989) score of 10 or less (higher than some definitions in order to allow for deep lacunes with hemiparesis alone). To meet inclusion criteria, hospitalized inpatients with acute ischemic infarcts were also required to have good baseline function (pre-stroke modified Rankin Score [mRS] ≤ 2; Rankin, 1957) and no evidence of large vessel occlusion (e.g., M1 or M2 proximal vessel involvement). Evidence of ischemia and absence of intracerebral hemorrhage were confirmed with brain magnetic resonance imaging (MRI). Non-native English speakers, those with history of prior clinical stroke, previously documented dementia, untreated psychiatric illness, uncorrected hearing or visual loss, or evidence of aphasia or neglect were excluded. Participants who gave written informed consent were enrolled and underwent an expanded cognitive evaluation at their first follow-up visit approximately 6–8 weeks post-stroke. A subset then returned for reassessment 6 and 12 months post-infarct.

2.2 Standard protocol approvals, registrations, and patient consents

The study’s protocols and ethical standards were reviewed and approved by the Johns Hopkins Institutional Review Board. All participants provided written informed consent prior to participating.

2.3 Clinical and cognitive assessment

At each clinic visit, participants completed several patient-reported outcome measures including the Stroke Impact Scale (Duncan et al., 1999), Barthel Index for Activities of Daily Living (Wade & Collin, 1988) (overall function), Patient Health Questionnaire (PHQ-9) (Williams et al., 2005) (depression), and Functional Assessment of Chronic Illness Therapy (FACIT) (Webster et al., 2003) (fatigue). They were also administered a battery of cognitive tests by a member of the study team blinded to study results or prior assessments. The neurocognitive assessment was developed to be brief, amenable to repeated administrations, and to cover five domains: verbal memory, spatial memory, motor speed, processing speed, and executive function. The battery consisted of an initial screen for global cognition using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) (given its use in many prior studies), followed by more in-depth assessment with the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001) Fluency and Trail Making Tests; Hopkins Verbal Learning Test (HVLT) (Benedict et al., 1998); Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict et al., 1996); Symbol Digit Modalities Test (SDMT) (Sheridan et al., 2006); and Grooved Pegboard Test (GPT) (Ashendorf...
et al., 2009). When possible, alternative testing versions were used at follow-up visits.

Raw scores for all tests were converted to T-scores according to age-specific normative data from respective test manuals. The following T-scores were averaged for composite domain scores: Verbal Memory: HVLT total learning, HVLT delayed recall; Spatial Memory: BVMT-R total learning, BVMT-R delayed recall; Motor Processing Speed: D-KEFS Trail Making trial 5, GPT dominant hand, GPT nondominant hand; Processing Speed: SDMT written trial, SDMT oral trial, D-KEFS Trail Making trial 1; Executive Function: D-KEFS letter fluency, D-KEFS category fluency, D-KEFS Trails Making trials 2, 3, and 4. Cognitive measures were classified into cognitive domains based on consensus of two neuropsychologists. A Global Composite Score was generated by averaging all tests across domains.

2.4 | Moderating variables (Table 1)

Additional information regarding: patient demographics (age, sex, self-identified race, handedness, education, occupation level [ranging from unskilled to professional]), social support (living with someone at home), functional baseline (pre-stroke mRS), medical history (history of dementia, depression, hypertension, hyperlipidemia, diabetes, smoking), stroke characteristics (stroke severity [NIHSS score on admission and discharge]), stroke volume, affected hemisphere, stroke location (cortical vs. subcortical), amount of white matter disease (CHS score; Manolio et al., 1994), etiology (The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment Investigators, 1998), and type of rehabilitation post-discharge (inpatient, home, outpatient, and none) were collected as potential moderating variables.

2.5 | Statistical analysis

Data were analyzed using Stata version 14 (College Station, TX). To determine the degree of impairment due to stroke (providing evidence initial performance was not a patient’s cognitive baseline), as well as the degree of improvement over time for each patient, a “recovery score” was generated for each patient for each cognitive test. The recovery score was determined by using the highest of the patient’s follow-up scores (from either the 6- or 12-month evaluation). The patient’s score at 1-month was subtracted from his/her recovery score to determine maximal degree of improvement over time. We also evaluated the degree of improvement between 1 to 6 months, and 6 and 12 months to determine differences in improvement rate over time using paired t-tests. Linear regression was used to determine the factors associated with: (1) initial cognitive performance at 1 month, (2) higher composite recovery scores for each cognitive domain, and (3) degree of change between the score at 1-month and the recovery score. The factors significant in univariate analysis (p < .05; age, race, sex, education, occupation, and admission NIHSS) for peak/recovery score were used in multivariable regression models. In secondary analyses, differences were explored based on stroke location: left versus right hemisphere, and pure subcortical lacunes versus those with cortical involvement. Patients failing to return for reassessment were censored at the time that they were lost to follow-up and group characteristics were compared for those who returned versus were lost to determine potential bias.

2.6 | Data availability

This study is registered with ClinicalTrials.gov (NCT04188522), where data are available for review. Additional data will be made available by the PI upon request.

3 | RESULTS

Between November 2016 and July 2020, 80 patients meeting inclusion criteria were enrolled in the study. The demographic and clinical characteristics of the cohort at each time point are shown in Table 1. Participants’ initial study visit was an average of 42.2 (SD = 21.4) days after stroke. Forty-eight patients returned for reassessment at 6 months (M = 207.3 days, SD = 30.7) after stroke, and of those 39 returned for their 12-month reassessment (M = 396.0 days, SD = 71.1). Due to the COVID-19 pandemic, we experienced a higher than expected rate of nonreturn. However, there were no major differences between those who came for their 12-month visit and those who did not (see Table S1). The average patient age of the entire cohort was 62.3 (SD = 14.1) years. Forty-five percent (n = 36) were male and 28% were African American. The average level of education was 13.5 years, and there was a broad range of occupations from unskilled to professional. Importantly, the average pre-stroke modified Rankin score was 0 for the majority of individuals. The average admission NIHSS score was 2.8 with a stroke volume of 6.6 cc. The majority of strokes were due to small vessel occlusions and were split fairly evenly between left and right hemispheres. Minor differences in demographic and clinical factors by stroke hemisphere and location (cortical vs. subcortical) are presented in the Supplementary material (Tables 2 and 3).

3.1 | Functional outcomes

At the time of their first study visit, the majority of patients had recovered well physically. Their average Barthel Index was 97.7 (SD = 8.6), NIH Stroke Scale score was .8 (SD = 1.6), and modified Rankin scale score was 1.1 (SD = 1.0), suggesting patients were almost back to normal in terms of physical recovery. However, using a Likert scale of 0–7, they reported an average of only 5.4 (SD = 1.7) when asked about degree of symptom resolution (0 = no resolution, 7 = complete resolution). They reported low scores (M = 37.7, SD = 11.3) on the FAICT, indicating significant fatigue, and on the PHQ-9 (M = 4.5, SD = 5.4), indicating mild depressive symptoms. Their scores on the Stroke Impact Scale were consistently in the high 80s to low 90s out of a possible 100 across domains indicative of good, but imperfect recovery. These outcomes improved over time (see Table 2).
| Population characteristics | 1 month, N = 80 | 6 months, N = 48 | 12 months, N = 39 |
|----------------------------|----------------|----------------|------------------|
| Age, mean years (SD)       | 62.3 (14.1)    | 60.6 (14.8)    | 60.0 (14.8)      |
| Race, n black (%)          | 22 (27.5)      | 13 (27.1)      | 12 (30.8)        |
| Sex, n male (%)            | 36 (45.0)      | 24 (50.0)      | 19 (48.7)        |
| Handedness, n right (%)    | 64 (85.3)      | 40 (87.0)      | 31 (83.8)        |
| Education, mean years (SD) | 13.5 (2.5)     | 13.9 (2.6)     | 13.6 (2.7)       |
| IQ, mean (SD)              | 107.6 (11.6)   | 107.8 (11.5)   | 106.1 (11.6)     |
| Social Support (%)         | 70 (90.9)      | 41 (89.1)      | 32 (84.2)        |
| Occupation Class Code      |                |                |                  |
| 1—professional, n (%)      | 10 (14.1)      | 7 (15.6)       | 5 (13.2)         |
| 2—intermediate, n (%)      | 12 (16.9)      | 9 (20.0)       | 8 (21.1)         |
| 3—skilled, n (%)           | 16 (22.5)      | 10 (31.1)      | 7 (18.4)         |
| 4—semiskilled, n (%)       | 24 (33.8)      | 14 (31.1)      | 12 (31.6)        |
| 5—unskilled, n (%)         | 9 (12.7)       | 5 (11.1)       | 6 (15.8)         |
| Prestroke mRS              |                |                |                  |
| 0, n (%)                   | 71 (93.4)      | 44 (93.6)      | 35 (89.7)        |
| 1, n (%)                   | 5 (6.6)        | 3 (6.4)        | 4 (10.3)         |
| Charlson comorbidity index, mean (SD) | 2.0 (1.4) | 2.0 (1.4) | 2.0 (1.5) |
| Depression, n (%)          | 14 (17.9)      | 10 (20.8)      | 7 (17.9)         |
| Hypertension, n (%)        | 63 (78.8)      | 38 (79.2)      | 31 (79.5)        |
| Hyperlipidemia, n (%)      | 54 (67.5)      | 37 (77.1)      | 27 (69.2)        |
| Diabetes, n (%)            | 30 (37.5)      | 16 (33.3)      | 16 (41.0)        |
| Smoking, n (%)             | 16 (20.0)      | 7 (14.6)       | 8 (20.5)         |
| Admission NIHSS (SD)       | 2.8 (2.4)      | 2.8 (2.3)      | 2.5 (2.4)        |
| Discharge NIHSS (SD)       | 1.7 (2.2)      | 1.6 (1.6)      | 1.4 (1.7)        |
| Stroke volume, mean cc (SD)| 6.6 (13.5)     | 7.9 (16.2)     | 7.8 (15.1)       |
| Hemisphere, n left (%)     | 39 (48.8)      | 25 (52.1)      | 20 (51.3)        |
| Subcortical only, n (%)    | 44 (55.0)      | 27 (56.3)      | 19 (48.7)        |
| Cortical only, n (%)       | 9 (11.3)       | 6 (12.5)       | 5 (12.8)         |
| Etiology                   |                |                |                  |
| Large artery atherosclerosis, n (%) | 21 (26.3) | 13 (27.1) | 11 (28.2) |
| Cardioembolism, n (%)      | 11 (13.8)      | 6 (12.5)       | 6 (15.4)         |
| Small vessel occlusion, n (%) | 34 (42.5) | 21 (43.8) | 16 (41.0) |
| Other determined etiology, n (%) | 7 (8.8) | 5 (10.4) | 2 (5.1) |
| Undetermined etiology, n (%) | 7 (8.8) | 3 (6.3) | 4 (10.3) |
| White matter grade (CHS Score) |             |                |                  |
| 0, n (%)                   | 1 (1.3)        | 0 (0)          | 0 (0)            |
| 1, n (%)                   | 2 (2.6)        | 1 (2.1)        | 0 (0)            |
| 2, n (%)                   | 39 (50.7)      | 23 (48.9)      | 21 (56.8)        |
| 3, n (%)                   | 22 (28.6)      | 14 (29.8)      | 10 (27.0)        |
| 4, n (%)                   | 9 (11.7)       | 5 (10.6)       | 3 (8.1)          |
| 5, n (%)                   | 2 (2.6)        | 2 (4.3)        | 2 (5.4)          |
| 6, n (%)                   | 2 (2.6)        | 2 (4.3)        | 1 (2.7)          |

(Continues)
**TABLE 1** (Continued)

| Population characteristics | 1 month, N = 80 | 6 months, N = 48 | 12 months, N = 39 |
|----------------------------|-----------------|-----------------|------------------|
| Rehabilitation             |                 |                 |                  |
| None, n (%)                | 18 (24.7)       | 6 (13.6)        | 6 (16.2)         |
| Inpatient, n (%)           | 17 (23.3)       | 10 (22.7)       | 6 (16.2)         |
| Home, n (%)                | 19 (26.0)       | 12 (27.7)       | 11 (29.7)        |
| Outpatient, n (%)          | 19 (26.0)       | 16 (36.4)       | 14 (37.8)        |

*IQ estimated using the Wide Range Achievement Test (WRAT).*

**TABLE 2** Functional and cognitive outcomes

| Functional Outcome               | 1 month  | 6 month  | 12 month  | Recovery score* |
|----------------------------------|----------|----------|-----------|-----------------|
|                                  | (n = 80) | (n = 48) | (n = 39)  |                 |
| Barthel index-ADLs, mean (SD)    | 97.7 (8.6) | 100.0 (0.0) | 98.0 (10.2) |                 |
| FACIT-fatigue, mean (SD)         | 37.7 (11.3) | 39.7 (10.8) | 41.2 (9.1)   |                 |
| PHQ-9-depression, mean (SD)      | 4.5 (5.4)  | 3.7 (4.3)  | 2.6 (3.0)   |                 |
| NIHSS- severity, mean (SD)       | .8 (1.6)   | .2 (0.4)   | .2 (0.7)    |                 |
| mRS, mean (SD)                   | 1.1 (1.0)  | .5 (0.5)   | .7 (1.0)    |                 |
| Symptoms, mean (SD)              | 5.4 (1.7)  | 5.7 (1.6)  | 6.4 (1.9)   |                 |
| Quality of life, mean (SD)       | 5.2 (1.9)  | 5.5 (1.6)  | 6.2 (1.3)   |                 |
| Stroke impact scale              |          |          |           |                 |
| 1—UE, mean (SD)                  | 79.4 (24.6) | 84.2 (19.1) | 85.1 (19.3) |                 |
| 2—thinking, mean (SD)            | 88.2 (15.8) | 88.8 (12.8) | 90.3 (11.5) |                 |
| 3—mood, mean (SD)                | 85.9 (17.7) | 85.5 (13.2) | 87.1 (11.4) |                 |
| 4—communication, mean (SD)       | 91.8 (17.2) | 93.9 (10.2) | 96.5 (8.3)  |                 |
| 5—ADLs, mean (SD)                | 91.1 (20.2) | 99.2 (10.5) | 96.2 (10.7) |                 |
| 6—mobility, mean (SD)            | 86.5 (19.1) | 93.9 (8.0)  | 91.6 (13.3) |                 |
| 7—fine motor, mean (SD)          | 86.3 (22.9) | 92.7 (12.7) | 92.4 (11.2) |                 |
| 8—socialization, mean (SD)       | 81.1 (20.8) | 89.6 (16.5) | 88.4 (19.5) |                 |
| MoCA, mean (SD)                  | 24.6 (3.4)  | 25.8 (3.5)  | 24.6 (4.2)  |                 |
| Composite cognition scores       |          |          |           |                 |
| Verbal memory, mean (SD)         | 30.7 (8.8)  | 35.4 (9.9)  | 35.8 (11.5) | 38.2 (11.3)     |
| Spatial memory, mean (SD)        | 21.5 (7.7)  | 47.9 (12.8) | 49.3 (14.5) | 49.8 (14.1)     |
| Motor speed, mean (SD)           | 34.1 (9.2)  | 37.7 (11.1) | 40.4 (12.2) | 40.8 (11.1)     |
| Processing speed, mean (SD)      | 36.6 (9.0)  | 45.3 (9.1)  | 48.0 (9.6)  | 47.5 (9.7)      |
| Executive function, mean (SD)    | 45.4 (10.0) | 48.7 (9.8)  | 50.1 (10.7) | 50.8 (9.9)      |
| Global cognition, mean (SD)      | 36.0 (6.8)  | 43.3 (8.8)  | 45.0 (9.4)  | 44.5 (9.3)      |

*Recovery Score—highest score at EITHER 6 or 12 months indicating peak performance/highest level of recovery.

3.2 Initial cognitive performance

Cognitive impairment was common, particularly in the first few months of stroke recovery. The mean MoCA score at the 1-month visit was 24.6 (SD = 3.4); 49.4% of individuals scored below 26, a threshold commonly used to identify mild cognitive impairment (Nasreddine et al., 2005), and 6.3% scored below 19, consistent with severe impairment (Trzepacz et al., 2015). Composite T-scores for each cognitive domain are reported in Table 2, while scores for individual tasks can be found in the Supplementary Information (Table 4). At 1-month post-stroke T-scores were below 50 (the normative mean) for every domain, and consistently at least one standard deviation below the recovery score. This suggests that initial performance was likely well below that of the patient’s pre-stroke baseline and improved over time (Figure 1). The lowest initial scores were seen in spatial memory. There were no major differences in
performance between those with left versus right hemisphere lesions, with the exception verbal memory, which was more impaired among those with right hemisphere lesions. There were no differences in performance between those with only subcortical strokes and those with cortical involvement.

3.3 Improvement over time

At 6 months, MoCA performance had improved for many individuals (M = 25.8, SD = 3.5), with only 35.4% scoring below 26 and 6.3% below 19. Changes in composite T scores are displayed in Figure 2. Differences between the 1-month and recovery scores were significant for every cognitive domain. Ninety-seven percent of patients improved between the 1- and 6-month visit. The degree of change was statistically significant between 1 and 6 months for all domains, and consistently greater than that seen between 6 and 12 months, where differences were not significant. Between 6 and 12 months, some patients improved but others (31%) failed to improve or demonstrated lower scores in global cognition at the 12-month visit. These same changes were seen on the MoCA, with the mean score falling to 24.6 (SD = 4.2) at the 12-month visit. Forty-six percent of individuals achieved a score below 26; 10.3% obtained scores lower than 19.

3.4 Predictors of improvement

Factors associated with greater peak/recovery scores in global cognition, verbal memory, spatial memory, processing speed, and executive function include higher levels of education and occupational grade, Caucasian race, and lower stroke severity (Figure 3). Higher scores in motor speed were associated with younger age and lower stroke severity. Similar factors were associated with initial cognitive performance at 1 month. In contrast, these factors were typically not associated with absolute difference in score between 1 and 6 months, suggesting that patients improved by the same amount over time and those who performed better at 6 months had also performed better at 1 month, likely indicating a better premorbid baseline. In multivariable regression, race remained significantly associated with peak/recovery score for global function, verbal and spatial memory, and executive function (Table S5).

4 DISCUSSION

Despite their small size and varied locations, minor strokes producing low NIHSS scores can result in significant cognitive dysfunction and functional impairment that dramatically affects quality of life. This dysfunction was seen almost uniformly across cognitive domains, although most notably in verbal memory, spatial memory, and processing speed initially after infarct and is associated with poor patient-reported outcomes. While the deficits may at first appear rather small and possibly inconsequential, the recovery experienced by patients when comparing their 1-month scores to their best (“recovery”) score indicates that performance 1 month after stroke is far from their premorbid baseline.

Post-stroke dementia has an established basis in the literature and is prevalent, particularly in those over the age of 60 (Del Ser et al., 2005; Henon et al., 2001; Leys et al., 2005; Pendlebury & Rothwell, 2009; Pendlebury et al., 2011; Pendlebury et al., 2010). However, patients with smaller strokes often experience a distinct syndrome in the subacute phase of stroke recovery that is characterized by difficulty with executive function, focus, concentration, and other aspects of attention (Marsh et al., 2020; Sharma et al., 2020). Although these deficits can be hard for friends and family to appreciate, especially in previously high-functioning active individuals, they can be debilitating. These deficits may lead to difficulty in the workplace, particularly for those with cognitively demanding jobs, as well as interpersonal difficulty, which may result in social isolation or depression (Edwards et al., 2006). Understanding that many of these difficulties may be short-lived, and being able to better predict what recovery may look like, can help to better counsel patients and families, and more successfully reintegrate individuals with tremendous potential back to their prior home and workplace environments.

In our patients with minor stroke, we found deficits bridging all major cognitive domains. Interestingly, spatial memory was most significantly impaired at 1-month, but then showed the greatest recovery at the 6-month time point, while verbal memory remained well below average at both time points. Processing speed and executive function, areas where patients subjectively noted significant difficulty, were relatively less affected, although scores were still consistently below the expected norms. Similar to patterns of recovery for hemiparesis or aphasia, for all cognitive domains with the exception of motor speed, the highest rate of improvement was seen between 1 and 6 months, with average scores plateauing between 6 and 12 months. This is likely the result not only of a larger positive change in score for patients, but also the fact that recovery was variable over the later time period, with nearly a third of patients failing to improve further or actually declining. Further studies are underway to better understand the variability over this time period and to determine whether we can predict and modify those with a negative trajectory.
FIGURE 2 There were significant differences between 1-month and recovery scores for all cognitive domains, as well as between 1 and 6 months, but not 6–12 months.

Somewhat surprisingly, there did not appear to be major differences in patterns of dysfunction for those with right versus left hemisphere lesions, despite prior studies suggesting hemispheric differences associated with multiple modalities (Su et al., 2015). The one exception was verbal memory, which has been reported more commonly with left hemisphere lesions. In our study, patients with right hemisphere lesions had more significant verbal memory deficits; this may also have been due to the small, but significant difference in level of education between groups. Similarly, a consistent pattern was seen between those with lacunes involving only subcortical locations compared to small strokes with cortical involvement. Both types resulted in the same picture of “multi-modality dysfunction.” One explanation, supported by our previous work and a publication by Lopes et al. (2021) in Neurology, is that a subcortical lacune in any location undercut the cortex and disrupts the entire cognitive network (Marsh et al., 2020).

Although prior studies have shown cognitive impairment following minor stroke (Jacova et al., 2012; Pendlebury et al., 2011), many of them studied patients at a single time point and described a post-stroke dementia rather than the transient phenomenon we found in our population. In addition, in our cohort we were able to further evaluate both the pattern of deficits based on lesion location, and factors associated with recovery. Compared to patients in the SPS3 trial, we found a similar high rate of MCI, but with impairment spread more consistently across all cognitive domains, regardless of lesion location. While this can be explained by assuming that minor disruption of the cognitive networks at any location has the ability to result in a pattern of global dysfunction (which would be consistent with recent studies using functional imaging) (Lopes et al., 2021; Marsh et al., 2020), an alternative explanation may be the longitudinal nature of the study and the sampling pattern. Although major differences were not found with respect to stroke location at the time points we evaluated, the varied nature in overall recovery seen, particularly between 6 and 12 months, suggests that if cognition were more frequently sampled, small additional differences in recovery pattern may be found. Stroke volume was also not associated with cognitive performance. This is likely due to the fact that all strokes were small (mean volume ~6 cc). The choice to include only small strokes in areas not traditionally associated with cognitive deficits (i.e., subcortical) was intentional to illustrate that a lesion in any location is capable of resulting in a picture of global dysfunction.

The factors associated with better peak/recovery scores varied for cognitive domains. Ultimate performance in motor speed was negatively associated with age and stroke severity, while factors typically associated with better scores in the other domains included potential indicators of cognitive reserve such as education and occupation. Although non-modifiable post-stroke, their significance emphasizes the importance of pre-stroke baseline cerebrovascular health and function on overall prognosis, as well as the level to which a patient may return following recovery, which is consistent with prior literature (Jacquin et al., 2014; Sachdev et al., 2006). The concept of cognitive reserve suggests that there are individual differences in susceptibility to brain changes that may include stroke, white matter disease, or Alzheimer’s pathology that can either be due to actual differences in the brain itself (perhaps the overall health, degree of white matter disease, or amount of atrophy) or in the way individual tasks are performed (where factors like education or IQ may play a role) (Stern, 2012). McHutchinson et al. (2019) followed patients with minor stroke for 3 years and noted fluctuations in estimated IQ using the NART and cognitive ability. Increases in NART score were associated with a higher level of education (McHutchison et al., 2019). Given this variability in measurement, we chose to obtain a “pre-morbid IQ” assessment only at 12 months post-infarct to allow for the longest recovery period to
There is a difference in the patterns between motor performance and other domains. p-Values for univariate analyses were labeled as positive or negative based on the direction of the association and then log transformed so that a value of 1.3 corresponds to a p-value of .05. Significant p-values are designated by an asterisk.

Similar factors were associated with degree of impairment at 1 month; however, fewer factors were associated with the degree of an individual’s change in T score for each domain. This suggests that there is a fairly consistent degree of recovery in cognition following stroke that is relatively constant, independent of other factors such as rehabilitation. In other words, an infarct results in the initial level of impairment that is predictable based on variables such as stroke severity, age, and cognitive reserve. Each domain then improves predictably to a peak level of function. A similar concept has been proposed for motor recovery, independent of factors such as rehabilitation (Prabhakaran et al., 2008). What is worth noting is that some individuals subsequently go on to decline after initially improving. Further studies are needed to determine if interventions apart from the modes of
traditional rehabilitation implemented in this study may be more important in influencing the degree of improvement. In addition, the factors associated with longer term trajectories that appear to vary across individuals, and determination of whether a patient’s curve is modifiable, warrant further study. Alternative explanations for the lack of factors associated with degree of change in recovery include that our sample size was inadequate at later time points given our attrition rate to fully evaluate potential variables, or that the variables most important in influencing the degree of change in performance were not evaluated.

This study is not without limitations. We followed a relatively small number of individuals from a single institution. While this allowed us to control for quality, it lowered our statistical power and the generalizability of our results. In addition, in part due to the COVID-19 pandemic, not everyone completed testing at all three visits, although there were no major differences between those who returned and those who did not. Given the repeated administration of assessments, there is also the possibility of a practice effect leading to improvement over time rather than true recovery. However, some patients peaked at 6 rather than 12 months, arguing against an effect. It is also relatively common to administer neuropsychological testing for clinical purposes as frequently as every 6 months, and many tests such as the MoCA, have demonstrated good reliability when readministered as frequently as every 3 months (Julayanont et al., 2015). In addition, we did not account for supplementary rehabilitation or changes in physical activity or social situations following initial assessment and it is possible that these factors could have influenced long-term outcomes. Finally, despite being a relatively young, prospectively collected cohort of individuals with no history of dementia, the baseline cognitive status was unknown. To address, we used published T-scores to compare to a large normative population of similar age and evaluated a portion of patients over time (with each serving as his/her own control) to demonstrate improvement from their 1-month clinical performance.

The present study characterizes the nature of post-stroke cognitive deficits by evaluating recovery over time and identifying factors associated with recovery. By evaluating only individuals with minor stroke, we identified the effect of stroke on cognition and functional outcomes in a population with a huge potential for recovery. Independent of size and location, acute cognitive dysfunction is common after minor stroke and involves all cognitive domains, but especially visuospatial memory and processing speed. Most often, impairment significantly if not fully recovers, rather than persisting as with vascular dementia, although there are other similar features. We demonstrate that improvement is fairly consistent over the first 6 months. Baseline factors such as age, education, and occupation influence the final recovery score, although this is likely due to premorbid baseline, as degree of recovery is similar amongst individuals. Further studies are needed to determine if treatment may augment results or influence the more variable 6- to 12-month follow-up period and improve outcomes further. Better understanding the spectrum of post-stroke cognitive impairment will aid in diagnosis, treatment, and prognosis to improve morbidity.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

This study is registered with ClinicalTrials.gov (NCT04188522) where data are available for review. Additional data will be made available by the PI upon request.

PEER REVIEW

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REFERENCES

Ashendorf, L., Vanderslice-Barr, J. L., & McCaffrey, R. J. (2009). Motor tests and cognition in healthy older adults. Applied Neuropsychology, 16(3), 171–176. https://doi.org/10.1080/09084280903098562

Benedict, R. H., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins verbal learning test–revised: Normative data and analysis of inter-form and test-retest reliability. The Clinical Neuropsychologist, 12(1), 43–55. https://doi.org/10.1076/clin.12.1.43.1726

Benedict, R. H., Schretlen, D., Groninger, L., Dobraski, M., & Shpritz, B. (1996). Revision of the brief visuospatial memory test: Studies of normal performance, reliability, and validity. Psychological Assessment, 8(2), 145. https://doi.org/10.1037.1040-3590.8.2.145

Berkheme, O. A., Fransen, P. S. S., Beumer, D., Van Den Berg, L. A., Lingma, H. F., Yoo, A. J., Schonewille, W. J., Vos, J. A., Nederkoorn, P. J., Wermer, M. J. H., Van Walderveen, M. A. A., Staals, J., Hofmeijer, J., Van Oostayen, J. A., Lycklama À Nijeholt, G. J., Boiten, J., Brouwer, P. A., Emmer, B. J., De Bruijn, S. F., … Dippel, D. W. J. (2015). New England Journal of Medicine, 372(1), 11–20. https://doi.org/10.1056/NEJMoa1411587

Brott, T., Adams, H. P., Olinger, C. P., Marler, J. R., Barsan, W. G., Biller, J., Spilker, J., Hollerman, R., Eberle, R., & Heizberg, V. (1989). Measurements of acute cerebral infarction: A clinical examination scale. Stroke; A Journal of Cerebral Circulation, 20(7), 864–870. https://doi.org/10.1161/01.STR.20.7.864

Campbell, B. C. V., Mitchell, P. J., Kleinig, T. J., Dewey, H. M., Churilov, L., Yassi, N., Yan, B., Dowling, R. J., Parsons, M. W., Oxley, T. J., Wu, T. Y., Brooks, M., Simpson, M. A., Miteff, F., Levi, C. R., Krause, M., Harrington, T. J., Faulder, K. C., Steinfort, B. S., … Davis, S. M. (2015). Endovascular therapy for ischemic stroke with perfusion-imaging selection. New England Journal of Medicine, 372(11), 1009–1018. https://doi.org/10.1056/NEJMoa1414792

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). Delis–Kaplan Executive Function System (D-KEFS). Psychological Corporation.

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SUPPORTING INFORMATION

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