



ORIGINAL ARTICLE

Mapping the trajectory of acute mild-stroke cognitive recovery using serial computerised cognitive assessment

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Abstract

Introduction: Cognitive impairment is common post-stroke. There is a need to understand patterns of early cognitive recovery post-stroke to guide both clinical and research practice. The aim of the study was to map the trajectory of cognitive recovery during the first week to 90-days post-stroke using serial computerised assessment.

Method: An observational cohort study recruited consecutive stroke patients admitted to a stroke unit within 48 hours of onset. Cognitive function was assessed using the computerised Cambridge Neuropsychological Test Automated Battery (CANTAB) daily for seven days, then 14, 30 and 90 days post-stroke. The CANTAB measured visual episodic memory and learning, information processing speed, visuo-spatial working memory, complex sustained attention and mental flexibility. Repeated measures MANOVA/ANOVA with Least Squares Difference post-hoc analyses were performed to ascertain significant change over time.

Result: Forty-eight participants, mean age 73, primarily mild, ischaemic stroke, completed all assessment timepoints. There was a trajectory of early, global cognitive improvement, indicative of a post-stroke delirium, that largely stabilised between 6 and 14-days post-stroke. Change over time was examined within each cognitive test, with one measure stabilising by day 6 (Reaction Time) and others detecting improving performances up to 14 days post-stroke.

Conclusions: Serial, computerised cognitive assessment can effectively map post-stroke cognitive recovery and revealed an early phase of global improvement over 14 days that is evidence for an acute post-stroke delirium. Resolution of post-stroke delirium in the second week following mild stroke indicates more extensive neuropsychological testing may be undertaken earlier than previously thought.

Keywords: Cognitive dysfunction; stroke; delirium; mild cognitive impairment; neuropsychological tests

Introduction

Stroke continues to be the second leading cause of death and disability globally (Krishnamurthi et al., 2020), with 30–40% of stroke-survivors experiencing persistent cognitive deficits (McDonald et al., 2019). Post-stroke cognitive impairment impacts individual quality of life (Barker-Collo et al., 2010; Nys et al., 2006) and function (Tatemichi et al., 1994) and increases burden on communities

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(Krishnamurthi *et al.*, 2020). There is a need to understand cognitive recovery patterns post-stroke to compare efficacy of therapeutic interventions against the rate of natural post-stroke improvement (Duncan *et al.*, 2000). A growing body of literature has described the long-term trajectory of post-stroke cognitive change (Levine *et al.*, 2015; Lo *et al.*, 2021; Mahon *et al.*, 2017; Zheng *et al.*, 2019) with general consensus that early cognitive deficits are complex and multifactorial due to processes of neuro-vascular injury and recovery, delirium, fatigue, fluctuating alertness and emotional distress (Lezak, 2012; McDonald *et al.*, 2019). However, there is limited information on the trajectory of cognitive recovery over the first week post-stroke, when cognition is impacted by the acute effects of stroke, despite the clinical requirement of early assessment to support critical decisions such as discharge disposition and referral to rehabilitation services (Australian Commission on Safety & Quality in Health Care, 2019; Lindsay *et al.*, 2014).

Cognitive screening post mild-stroke is essential as cognitive impairment is pervasive (Boulanger *et al.*, 2018; Lanctôt *et al.*, 2020; Pendlebury *et al.*, 2015; Stroke Foundation, 2022) and can result in reduced participation (Adamit *et al.*, 2014; Tellier & Rochette, 2015). With short length-of-stay in acute care, screening measures are conducted expeditiously post-stroke (Bertolin *et al.*, 2018; Verdelho *et al.*, 2021). Brief screening and more extensive neuropsychological testing are feasible early post-stroke (Nys *et al.*, 2005; van Zandvoort *et al.*, 2005), with screening tests more efficient and better tolerated by patients in acute care. However, there is no gold standard for cognitive screening (Hachinski *et al.*, 2006; Quinn *et al.*, 2018; Quinn *et al.*, 2021), with measures needing to cover a broad range of cognitive domains, be valid, feasible and sensitive for identification of impairments post-stroke (Chan *et al.*, 2017; Chan *et al.*, 2014; Stolwyk *et al.*, 2014). They also only provide a 'snapshot' at a single point in time and should be responsive to change for monitoring of cognitive recovery (Skirrow *et al.*, 2021), making it difficult for one tool to meet all requirements. Exploring new technologies could provide alternatives for measuring cognition in acute stroke.

Computerised cognitive assessments offer sensitive continuous measures that can be customised for select subtests and repeated to mark changes over short epochs of cognitive recovery (Aslam *et al.*, 2018; Pettigrew *et al.*, 2021; Zygouris & Tsolaki, 2015), such as the acute phase post-stroke (Bernhardt *et al.*, 2017). Computerised cognitive assessment platforms are feasible as research measures acutely post-stroke (Cumming *et al.*, 2012; Shopin *et al.*, 2013) and are designed for serial measurement of cognition over short time intervals (Cambridge Campos-Magdaleno *et al.*, 2021; Cognition, 2022; Skirrow *et al.*, 2021), but have not been used in both capacities in the acute post-stroke period. We aimed to map the trajectory of cognitive recovery during the first week post-stroke and up to 90-day follow-up using serial computerised cognitive assessment.

Materials and methods

Patients and setting

A prospective, single-centre, observational, cohort study was conducted in the Acute Stroke Unit of the Sunshine Coast University Hospital. Ethical approval was obtained from: The Prince Charles Hospital Human Research Ethics Committee, HREC/17/QPCH/163; the University of Queensland (#2017001149); and from University of the Sunshine Coast (S/17/1091). Data were collected from January to September 2018.

Participant screening included all patients diagnosed with stroke by senior medical consultants. Eligible patients were aged 18 years or older and within 48 hours of stroke onset. Patients were excluded if they: were palliative in treatment intent; previously had diagnoses of dementia or extensive mental illness; were blind or were anticipated to be unavailable for follow-up. The Principal Investigator provided study information to all consecutive eligible patients and invited them to participate. Signed consent was obtained from participants or substitute decision-makers.

Data collection tools

Demographic information - age, gender, premorbid function, education, occupation and comorbid medical conditions - were gathered from medical records and participant interview. Admission medical entries and imaging (Computerised Tomography, CT and Magnetic Resonance Imaging, MRI) provided stroke-specific information: National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989) for stroke severity (Adams et al., 1999), stroke type, hemisphere, symptoms and reperfusion therapies.

Participants were screened for cognitive confounders: the Depression, Anxiety and Stress Scale-21 assessed for clinical symptoms of anxiety and depression (Ng et al., 2007) and was provided to the patient to read while questions were read through with the primary investigator; the Wechsler Test for Adult Reading (WTAR) estimated pre-stroke intellectual capacity (Full Scale intelligence Quotient, FSIQ) (Steward et al., 2016) and the 4-A's Test screened for delirium (4-AT) (Lees et al., 2013).

Data were collected from Version 7.1 of the Montreal Cognitive Assessment (MoCA); routinely used by local clinicians to screen cognitive function for assessment of rehabilitation needs post-stroke. The MoCA screens cognitive domains of Executive Function, Naming, Attention, Language, Abstraction, Delayed Recall and Orientation (Nasreddine et al., 2005). It has been shown to predict long-term cognitive and functional outcomes, and is valid and feasible in the acute phase post-stroke (Abzhandadze et al., 2019; Chiti & Pantoni, 2014; Koski, 2013; Zietemann et al., 2018).

Cambridge neuropsychological test automated battery (CANTAB)

The CANTAB (Connect version) was the primary cognitive outcome measure. The CANTAB is a computerised, portable (tablet-based), cognitive assessment battery that presents parallel versions and randomised stimuli to minimise practice effects for extensive serial assessment (Cambridge Cognition, 2021). Automated scoring and instruction remove human error, reduce variance in administration and allow non-specialist staff to administer tests. Additionally, on reaction time-based measures, time to move is partitioned from cognitive processing time to decide and react, enabling the separation of cognitive speed from impaired motor functions post-stroke. The subtests primarily utilise visual stimuli, reducing language dependent effects and allowing those with language impairment to participate in testing (Cacciamani et al., 2018; Crivelli et al., 2021). Additionally, the CANTAB platform uses embedded practice sessions to ensure participants can successfully perform the task before proceeding to the assessment phase of the test.

The CANTAB features 23 modular subtests, with studies on subtest properties and availability of normative data confined to a limited set (Aslam et al., 2018). Subtest selection was determined by domains of post-stroke cognitive impairment identified in previous research (Cumming et al., 2013; Mole & Demeyere, 2020) and limited by overall time to perform the customised battery, accommodating for participants' reduced tolerance early post-stroke. Verbal measures were not selected, for inclusivity of people with aphasia and as aphasia is routinely screened separately. The selected CANTAB measures are outlined in Table 1, in order of presentation for testing.

Procedure

Following enrolment, participant demographic and stroke-specific information were collected. CANTAB assessment was performed daily for 7 days, with follow-up at 14, 30 and 90-days post-stroke (+3 days for 30 and 90-day follow-up) in hospital and subsequent community settings post-discharge. The MoCA, version 7.1 was administered within the first week as per standard clinical practice. The 4-AT was conducted from the date of enrolment, and the DASS-21 and WTAR were administered in the first four days with DASS-21 repeated at 14 days. For

Table 1. CANTAB Subtests and Key Measures

Subtest	Key Measures
<p>Paired Associates Learning (PAL) A measure of visual episodic memory and learning. Patterns are revealed in boxes on the screen (adjusting to different levels of up to 8 patterns to avoid ceiling effects) and participants must remember where each pattern was located.</p>	<p><i>PAL Total Errors Adjusted (PALTEA)</i> Raw score total number of errors adjusted for incomplete trials. The greater the number of errors the worse the memory performance. This measure allows comparison on performance to be made across all participants regardless of those that were unable to complete the final stage of the task.</p>
<p>Five-Choice Reaction Time (RTI) A measure of information processing speed and attention. Participants hold their finger on a graphic 'button' until one of five circles flashes yellow. As swiftly as possible, the participant must touch the circle which flashed and then return their finger to the button.</p>	<p><i>RTI Mean 5-Choice Reaction Time (RTIFMRT)</i> Average reaction time (msec) on the 5 choice RTI task excluding time taken to move to the target. Mean RT is a relatively pure measure of attentional speed and resources. <i>RTI Mean 5-Choice Movement Time (RTIFMMT)</i> Average movement time (msec) in responding to the 5 choice RTI tasks. This is a measure of motor response speed independent of attentional resources.</p>
<p>Spatial Working Memory (SWM) A measure of visual working memory capacity. A task where participants try to locate a yellow square concealed in an array of red boxes but must recall where they have previously located a yellow square and avoid those boxes.</p>	<p><i>SWM Total Errors (SWMTE)</i> Raw score total number of errors adjusted for incomplete trials. Greater the number of errors the worse the working memory capacity. <i>SWM Strategy (SWMS)</i> Raw strategy score assessing strategy use by participant across trials. This measure uses a composite score of various forms of errors made in performing the task.</p>
<p>Rapid Visual Processing (RVP) A measure of signal detection sensitivity and sustained attention. Participants are required to rapidly process a string of target sequences with digits presented at a rate of 100 digits/minute.</p>	<p><i>Rapid Visual Processing 'A' Prime (RVP A')</i> Calculates detection of the target sequence and is a precise measure of attentional processing capacity. RVP A' is a ratio score, with higher scores indicating improved attentional capacity.</p>
<p>Multi-tasking Test (MTT) A measure of executive function through mental flexibility tasks involving random rule shifts, as well as congruency with symbol meaning vs physical location.</p>	<p><i>MTT Incongruent Trial Mean Latency (MTTLNOM)</i> Calculates the mean latency in decision time (msec) on the conflictual incongruent trial.</p>

participants exhibiting symptoms of delirium (scoring ≥ 4), the 4-AT was repeated, and the number of days with clinically recognised delirium was recorded.

Statistical analysis

Analyses were performed using IBM SPSS for Windows (version 27.0). Participants with missing data for all CANTAB subtests in a single assessment timepoint were removed from analysis (incomplete data). Participants with missing data for some (not all) CANTAB subtests within a timepoint or over multiple timepoints were retained.

Independent samples t-test and Chi-Square were used to compare participants who completed all timepoints with those who did not across key demographic variables. Variables from similar cognitive domains were entered into a repeated measures MANOVA to control for study-wide type I error rate. Significant multivariate tests were followed by repeated measures ANOVAs for each of the variables corrected for family-wise error, to determine significant change over time.

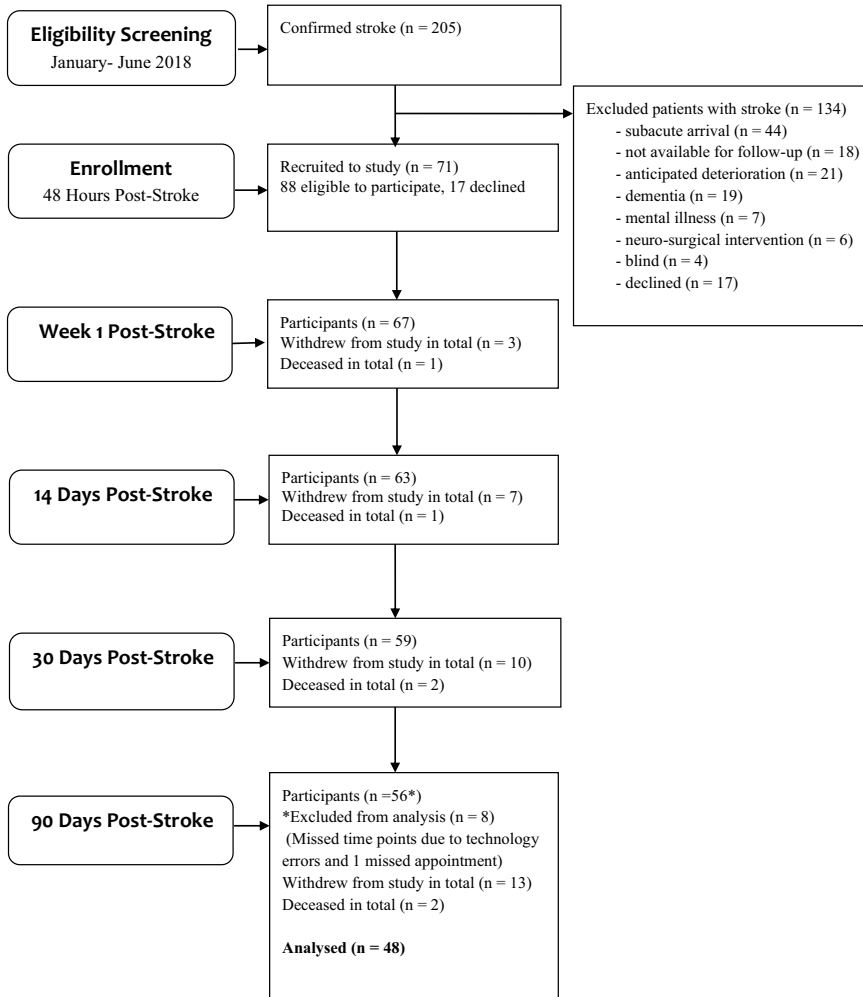


Figure 1. Participant flow diagram.

Unrelated variables were analysed using independent repeated measures ANOVAs. Post-hoc analyses of change over time were examined by Least Square Differences comparison ($p < .05$).

Results

Participant information

Of the 88 patients determined eligible to participate, 17 declined and 71 participants were recruited. Thirteen of the 71 participants withdrew prior to 90-day follow-up: four were not accessible for follow-up, two had ongoing medical issues, and 7 declined to participate further. Two participants died, seven missed an entire assessment time point due to technology errors and one failed to attend an appointment. A final sample of 48 participants was available for trajectory analysis (Fig. 1).

Demographic data

The 48 participants were equally distributed for gender and stroke hemisphere, with a mean age of 73 years, and the majority sustained a mild, ischaemic stroke (NIHSS <6). Average length of stay

in acute care approached 5 days with 25% of participants exhibiting symptoms of delirium. More than 40% exhibited symptoms of depression the first week, dropping to 30% by day 14. As per usual clinical practice, participants with functional language deficits were screened using the Western Aphasia Battery. Three participants had moderate and three mild aphasia, with one omitted from analysis due to technology error. Three of these participants could perform the WTAR at 14 days. One was also unable to complete DASS-21 or MoCA the first week but could participate at day 14. All could perform the CANTAB. MoCA mean score was 22.7 with over half scoring at or above 23 (Table 2).

The only significant demographic differences between participants analysed and those excluded from analysis was acute care length of stay which was nearly twice as long for those excluded. There was a trend toward greater rates of delirium in excluded participants, however mean MoCA scores were similar between groups suggesting attention difficulties associated with delirium were not severe enough to adversely impact a cognitive screening measure. Three participants in the excluded group had delirium for >10 days. For included participants, delirium clinically resolved an average of 4 days post-stroke. Lastly, a significantly higher proportion of participants with moderate to severe stroke had incomplete data (74%) compared to mild stroke (26%) (Table 2).

Trajectory data

Raw mean scores are summarised in Table 3. Standard scores were available for PALTEA and RVP A', which indicate that participants' average scores were trending below a healthy adult population at all time-points for these subtests.

As missing values occurred at random intervals in the data, they were replaced by the sample mean for that subtest at that timepoint so as not to impact on the overall mean and standard deviation of the sample at that timepoint. Sixteen participants had missing subtest values replaced: seven at day 2; four at day 3; four at day 4; one at day 5; two at day 6; two at day 7; five at day 8; one at day 14; two at day 30; zero at day 90 – representing 1.9% of all values. Out of 2400 subtests administered, 32 subtests were not completed due to participant factors (i.e. fatigue, nausea, difficulties sustaining attention) and 17 were completed but not recorded due to technology errors.

All CANTAB measures correlated with age and DASS-21 scores at $r < 0.40$; thus, age and depression were not meaningful covariates for any variable. Subtest key measures within the same cognitive test (i.e. RTI and SWM subtests) were significantly correlated with each other, and repeated measures MANOVA was performed for within subtest key measures to control for family-wise error.

Multi-tasking Test

For MTT mean latency on the incongruent trial (MTTLNOM), a significant change over time was found ($F_{(9,423)} = 5.557$, $p < 0.001$, $\eta^2_p = 0.106$, power = 1.00) (Fig. 2). Post-hoc Least Square Differences comparison of timepoints identified 22 differences ($p < 0.05$) with performances slower to demonstrate improvements initially, but then readily improving from day 5 until day 8 post-stroke when performances stabilised (Table 4).

Paired associates learning

Repeated measures ANOVA was conducted for total errors adjusted on the Paired Associates Learning task (PALTEA) (Fig. 2) identifying a significant change over time ($F_{(9,39)} = 4.656$, $p < 0.001$, $\eta^2_p = 0.518$, power = 0.994). Post-hoc Least Square Differences comparison of timepoints identified 18 differences ($p < 0.05$) with performances improving significantly from day 2 to 3 with ongoing improvements until day 14 post-stroke, after which performances stabilised

Table 2. Demographic and Clinical Characteristics of Participants with Data for All Timepoints vs Participants with Missing Data in One or More Timepoints Post-stroke ($n = 71$)

<i>n (%) or mean (+SD)</i>	Participants with no missing time points	Participants with missing time points	Comparison of participant groups
	($n = 48$)	($n = 23$)	$P < 0.05^{††}$ (95% CI)
Sex (Female)	23 (48%)	7 (30%)	.163
Age (years) [§]			
Mean (SD)	72.7 (10.4)	78.2 (11.8)	.353
Median	72.5	80.5	
Range	51–91	44–96	
Education (years)			
Mean (SD)	11.3 (2.6)	12 (3.3)	.195
Median	10.5	12	
Range	7–19	4–18	
Stroke type			
Ischaemic	45 (94%)	22 (96%)	—
Haemorrhagic	3 (6%)	1 (4%)	—
Hemisphere			
L	23 (48%)	8 (35%)	—
R	21 (44%)	13 (56%)	—
Bilateral	4 (8%)	2 (9%)	—
Severity			
Mild	46 (96%)	17 (74%)	.005*
Mod	2 (4%)	5 (22%)	
Severe	0	1 (4%)	
Aphasia on admission	5 (10%)	1 (4%)	—
LOS acute (days)			
Mean (SD)	4.8 (2.4)	9.9 (8.4)	.009*
Median	4.5	8	
Range	1–11	2–34	
MoCA			
Completed	46 (96%)	16 (70%)	—
Mean (SD)	22.7 (4.3)	22.6 (3.5)	.888
Range	12–30	18–29	
Score ≥ 23	27 (56%)	8 (35%)	.546
Participants with delirium	12 (25%)	10 (44%)	.087
Days of delirium			
Mean (SD)	0.7 (1.4)	4.2 (8.7)	.064
Median	0	0	
Range	0–5	0–34	

(Continued)

Table 2. (Continued)

<i>n</i> (%) or mean (+SD)	Participants with no missing time points		Participants with missing time points		Comparison of participant groups
WTAR (Estimated FSIQ)					
Mean (SD)	103.26 (8.4)		106.1 (7.5)		.514
Median	101		106.1		
Range	84–117		91–118		
Depression	<i>Day 4</i>	<i>Day 14</i>	<i>Day 4</i>	<i>Day 14</i>	
	<i>n</i> = 48	<i>n</i> = 48	<i>n</i> = 21	<i>n</i> = 16	
Normal	27 (56%)	33 (69%)	13 (62%)	12 (75%)	0.417 <i>Day 4</i>
Mild	6 (13%)	4 (8%)	1 (5%)	0 (0%)	
Moderate	10 (21%)	7 (15%)	2 (10%)	1 (6%)	
Severe	+ 4 (8%)	4 (8%)	2 (10%)	1 (6%)	
Unable	1 (2%)	0 (0%)	2 (10%)	2 (13%)	
Anxiety					
Normal	31 (65%)	31 (65%)	15 (71%)	11 (69%)	0.262 <i>Day 4</i>
Mild	5 (10%)	5 (10%)	1 (5%)	2 (13%)	
Moderate	6 (13%)	4 (8%)	1 (5%)	1 (6%)	
Severe	+ 5 (10%)	8 (17%)	1 (5%)	0 (0%)	
Unable	1 (2%)	0 (0%)	2 (10%)	2 (13%)	
Stress					
Normal	34 (71%)	36 (75%)	14 (67%)	10 (63%)	—
Mild	6 (13%)	1 (2%)	1 (5%)	3 (19%)	
Moderate	6 (13%)	7 (15%)	2 (10%)	0 (0%)	
Severe	+ 1 (2%)	3 (6%)	1 (5%)	1 (6%)	
Unable	1 (2%)	0 (0%)	2 (10%)	2 (13%)	

[†]Data *p* values determined by Chi-square for categorical variables (Gender, Delirium, Stroke Hemisphere, Stroke Severity, Stroke Type, Depression, Anxiety, Stress) and Independent-Samples *t*-tests, for the remainder of the comparisons.

[‡]Where cell is blank, insufficient *n* for analysis.

[§]21 year-old outlier removed.

^{||}Academic professor with multiple PhD's removed as outlier.

[¶]Ischaemic includes stroke w/ haemorrhagic transformation.

*Significant at *p* < 0.05, two-tailed.

(Table 4). For z-score analysis, one-way repeated measures ANOVA was significant, $F_{(9,423)} = 6.104$, $p < 0.001$, $\eta^2_p = 0.115$, power = 1.0). With results otherwise identical to raw score analysis.

Five-choice reaction time

Across both five-choice RTI measures (movement time and reaction time), repeated measures MANOVA returned a significant effect of time ($F_{(18,30)} = 2.656$, $p = 0.009$, $\eta^2_p = 0.614$, power = 0.964). Follow-up repeated measures ANOVAs for each of the subtests, corrected for family-wise error, were performed. For RTI five-choice movement time (RTIFMMT), a significant change over time was found ($F_{(9,423)} = 1.883$, $p = 0.053$, $\eta^2_p = 0.039$, power = 0.828) (Fig. 2). For

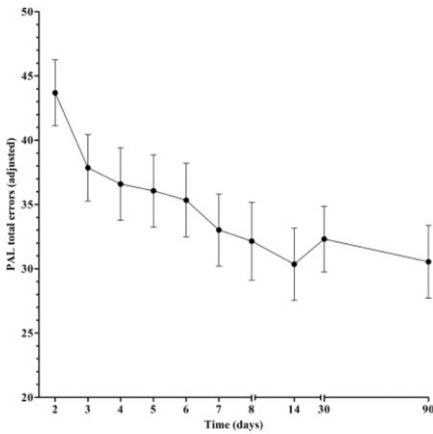
Table 3. CANTAB Subtest Mean Scores by Day Post-stroke

CANTAB Subtests [†]	PALTEA Visual episodic memory and learning total errors adjusted				RTIFMRT Reaction time (mS)		RTIFMMT Movement time (mS)		SWMTE Spatial working memory total errors		SWMS Spatial working memory-strategy use		RVP A' Visual sustained attention sensitivity to target sequence			MTTLNOM Multitasking test mean latency of response (mS) mental flexibility		
	<i>n</i>	\bar{x} (SE) Range	<i>z</i> -Score \bar{x} (SE) Range	%ile Score \bar{x}	<i>n</i>	\bar{x} (SE) Range	<i>n</i>	\bar{x} (SE) Range	<i>n</i>	\bar{x} (SE) Range	<i>n</i>	\bar{x} (SE) Range	<i>n</i>	\bar{x} (SE) Range	<i>z</i> -Score \bar{x} (SE) Range	%ile Score \bar{x}	<i>n</i>	\bar{x} (SE) Range
Day 2	48	43.7(2.6) 7.0-68.0	-1.23(0.13) -2.3 to 0.44	19	45	525.7(22.0) 362-1309	45	415.8(21.1) 201-820	45	21.2(1.1) 0.00-39.00	45	9.24(0.3) 2.0-12.0	42	0.82(0.01) 0.68-0.92	-1.14(.08) -2.3-0.03	17	41	1001.0(16.5) 748-1216
Day 3	48	37.9*(2.6) 8.0-69.0	-0.94(0.13) -2.3 to 0.64	25	48	516.9(18.9) 348-1048	48	409.8(26.8) 202-1215	48	21.0(1.4) 0.00-47.00	48	9.40(0.3) 3.0-13.0	45	0.83(0.01) 0.67-0.94	-0.98(.10) -2.3-0.58	21	44	998.8(21.3) 724-1356
Day 4	47	36.6(2.8) 5.0-67.0	-0.84(0.14) -2.3 to 0.99	28	47	486.4(18.2) 333-1162	47	400.7(31.0) 195-1578	47	20.1(1.5) 0.00-57.00	47	8.98(0.4) 2.0-13.0	45	0.84*(0.01) 0.62-0.97	-0.89(.12) -2.3-0.99	25	47	989.7(21.3) 688-1337
Day 5	48	36.1(2.8) 4.0-67.0	-0.82(0.14) -2.3 to 1.17	29	48	485.8*(15.1) 327-849	48	387.4(20.2) 198-890	48	20.4(1.5) 0.00-45.00	48	8.73(0.4) 2.0-12.0	47	0.86*(0.01) 0.68-0.99	-0.63(.13) -2.3-2.05	31	48	1005.1(24.7) 660-1399
Day 6	48	35.3(2.9) 4.0-63.0	-0.77(0.14) -2.3 to 0.88	30	48	471.9*(13.3) 323-754	48	384.2(21.6) 198-1067	48	18.6(1.2) 0.00-36.00	48	8.90(0.4) 2.0-12.0	46	0.86(0.01) 0.60-1.0	-0.59(.15) -2.3-2.33	32	47	971.9(20.9) 693-1318
Day 7	48	33.0*(2.8) 3.0- 63.0	-0.66(0.15) -2.3 to 0.99	33	48	489.4(17.5) 325-1001	48	394.1(26.9) 175-1294	48	19.0(1.6) 0.00-51.00	48	8.81(0.4) 2.0-12.0	47	0.87*(0.01) 0.72-1.0	-0.48(.13) -2.3-2.05	35	47	971.2(23.4) 597-1309
Day 8	48	32.2(3.0) 4.0-67.0	-0.59(0.15) -2.3 to 0.99	36	48	488.2(21.1) 316-1270	48	373.9*(18.2) 202-892	48	19.6(1.7) 0.00-65.00	48	9.23(0.3) 2.0-12.0	45	0.87(0.01) 0.70-0.99	-0.45(.13) -2.3-1.75	36	46	939.8*(24.9) 624-1311
Day 14	48	30.4*(2.8) 5.0-67.0	-0.51(0.14) -2.3 to 0.88	37	48	463.5(16.0) 306-974	48	367.8(16.4) 201-807	48	16.9*(1.3) 0.00-43.00	48	8.58(0.3) 2.0-12.0	47	0.89*(0.01) 0.66-0.99	-0.20(.15) -2.3-2.05	45	48	924.5*(26.2) 596-1245
Day 30	48	32.3(2.6) 8.0-68.0	-0.64(0.13) -2.3 to 0.84	33	48	461.7(15.1) 317-983	48	367.9(20.0) 198-1093	48	17.4 (1.2) 0.00-30.00	48	8.88(0.4) 2.0-13.0	46	0.89(0.01) 0.71-1.0	-0.18(.16) -2.3-2.33	45	48	943.8(24.4) 650-1261
Day 90	48	30.5(2.8) 4.0-68.0	-0.47(0.15) -2.3 to 0.99	37	48	488.9(27.8) 341-1637	48	369.4(18.0) 161-718	48	19.7 (1.3) 0.00-39.00	48	8.77(0.4) 2.0-13.0	48	0.89(0.01) 0.74-0.99	-0.15(.15) -2.3-1.75	46	48	951.2(24.2) 625-1351

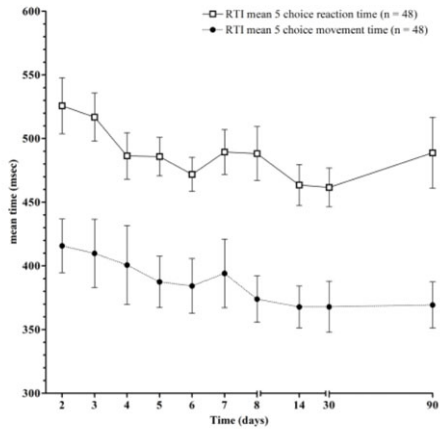
[†]In *n* and mean (standard error).

*Indicates significant point of change starting from day 2, with subsequent asterisks in same column indicating a significant point of change from the previous significant point of change.

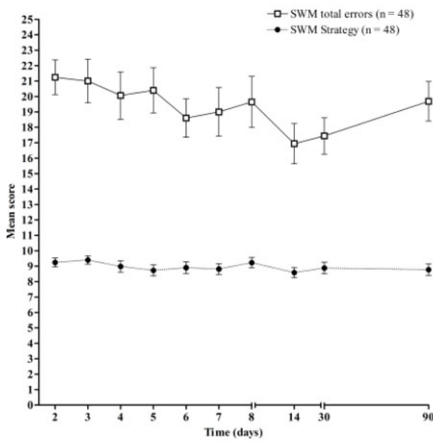
(a) PAL – Visual episodic memory and learning



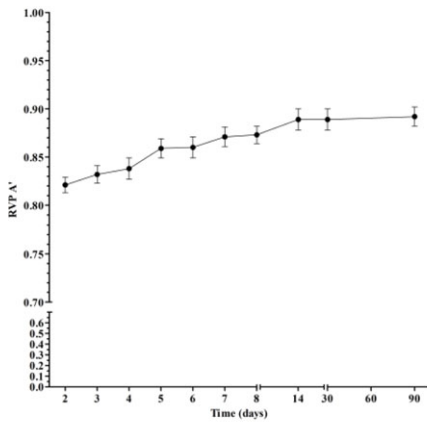
(b) RTI – Reaction time and movement time



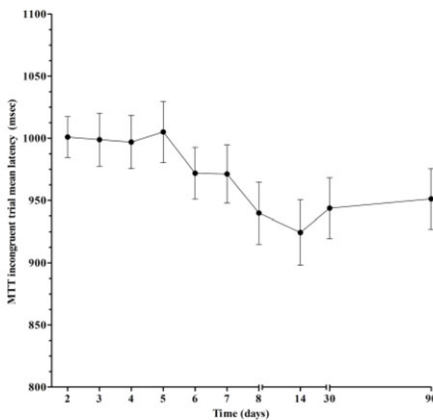
(c) SWM – Spatial working memory total errors and strategy



(d) RVP A' – Visual sustained attention



(e) MTT – Multitasking and mental flexibility test



^aFor all graphs, except the RVP A', a downward trajectory indicates improved performance in time or number of errors.

Figure 2. The trajectories of estimated marginal mean scores for CANTAB key measures plotted on graphs over ten timepoints from 2 to 90 days post-stroke, where all graphs show a significant trend towards improvement that stabilises from 6-14 days post-stroke, apart from the Spatial Working Memory Strategy subtest which does not show significant change.^a

$p. = 0.167$, $\eta^2_p = 0.030$, power = 0.693), while for SWMTE a significant change over time was found ($F_{(9,423)} = 2.452$, $p. = 0.010$, $\eta^2_p = 0.050$, power = 0.928) (Fig. 2). Post-hoc Least Square Differences comparison of timepoints identified 10 differences in SWMTE ($p < 0.05$) with performances improving until day 14 post-stroke, after which performances stabilised (Table 4).

Rapid visual processing

Lastly, for RVP A', a repeated measures ANOVA identified a significant change over time ($F_{(9,423)} = 12.922$, $p. < 0.001$, $\eta^2_p = 0.749$, power = 1.00) (Fig. 2). Post-hoc Least Square Differences comparison of timepoints identified 37 differences ($p < 0.05$) with performances improving until day 6 where they slowed slightly but continued to improve until day 14 post-stroke, after which performances stabilised (Table 4). For z-score analysis, one-way repeated measures ANOVA was significant ($F_{(9,423)} = 26.015$, $p. < 0.001$, $\eta^2_p = 0.356$, power = 1.0). With results otherwise identical to raw score analysis.

In summary, post-hoc analyses of change over time for MTTLNOM, PALTEA, RTIFMRT, RTIFMMT, and RVP A' showed a significant change within the first week of measurement, to 8 days post-stroke (Table 3). The SWMTE post-hoc analysis did not identify significant change until day 14 post-stroke (Table 3). The SWMS measure did not show any significant change (Table 3). All measures had stabilised by day 14 post-stroke. Raw mean scores are available in Table 4. Standardised scores and percentile scores are available for PALTEA and RVP A' and reveal participant's mean scores fall below a healthy adult normative population

Discussion

Mapping the trajectory of cognitive recovery post-stroke

We found that cognitive recovery occurs steadily over the first 2 weeks post-stroke, a period we identify as post-stroke delirium, which has significant clinical implications for cognitive assessment in the acute stroke unit. Quality statements for acute stroke clinical care standards recommend that stroke survivors be assessed for rehabilitation needs, including cognitive status, within the first few days of admission to an acute stroke unit (Lindsay et al., 2014). Current practice in the acute stroke unit is screening cognition at a single time-point during a period of early, predictable global improvement (Quinn et al., 2018). Cognitive assessment results in this early phase, therefore, should be used as a marker for monitoring improvement and to direct acute clinical decisions, rather than an indicator of long-term impairment.

Monitoring cognitive improvement with pen and paper cognitive screening assessments poses a problem as alternate forms are largely not validated for serial testing over short time intervals or have few alternate versions (Costa et al., 2012; Nasreddine & Patel, 2016). In contrast, many computerised cognitive assessments, such as the CANTAB, are designed and validated for serial testing over short periods of time (Zygouris & Tsolaki, 2015); and, when used in conjunction with functional clinical assessment (Aslam et al., 2018), can be used to measure improvements during this period of acute recovery.

Our second finding is that early cognitive recovery largely stabilises by 6 to 14 days post mild stroke. Measures of visual episodic learning (PAL), impulse control and decision making (MTT), information processing speed (RTIFMRT), motor speed (RTIFMMT) and complex sustained attention (RVP) demonstrated steady significant change in the first week. Visual working memory (SWM) was slower to recover in the first week but showed significant change by day 14 when all measures stabilised. These results are consistent with a study that demonstrated generalised rather than domain specific cognitive improvement measured by traditional neuropsychological testing in the acute phase and followed up 12-24 months later (van Zandvoort et al., 2005). Additionally, differences in pace of recovery for cognitive processing speed (RTIFMRT), which significantly

increased to day 6, and motor speed (RTIFMMT), which demonstrated slightly slower recovery to day 8, confirms the importance of partitioning the two during early testing. Our results indicate that early cognitive recovery begins to stabilise from days 6 to 14 in mild ischaemic stroke survivors, suggesting that formal neuropsychological assessment may occur significantly earlier than previously considered to be clinically appropriate (De Haan *et al.*, 2006).

Domain-specific testing

Improved understanding of domain-specific patterns of recovery is clinically useful. Targeted cognitive assessment of a single domain (processing speed), found to be linked to long-term cognitive and functional impairment, has previously been suggested as time-efficient (Cumming *et al.*, 2012). Our results indicate that specific CANTAB subtests display high levels of sensitivity to early cognitive change following mild ischaemic stroke. The RVP A' measures complex sustained attention using a target sensitivity paradigm. Performances on RVP A' displayed steady, consistent improvement, showing significant daily change from very early post-stroke, day 4 through day 14, with flattening of the trajectory out to 30 and 90 days. The measure displayed narrow variance across all time-points indicating a high degree of reliability of measurement.

The only measure to demonstrate no change over time was the Spatial Working Memory Strategy (SWMS) task, which involves use of strategy to minimise working memory errors when attempting to recall and manipulate visuospatial information (Cambridge Cognition, 2022). A small study of 25 participants with amnesic mild cognitive impairment found a practice effect for the SWMS task when testing was separated by 6 months (Cacciamani *et al.*, 2018). However, our participants failed to demonstrate any significant change in score despite daily testing. Executive dysfunction is poorly predicted by stroke and is often present prior to stroke. (Heshmatollah *et al.*, 2021; Kliper *et al.*, 2014; Veldsman *et al.*, 2020). Possibly this measure reflects a high degree of stable pre-stroke executive dysfunction that did not change due to the chronic nature of the impairment. The non-significance observed on this measure suggests that SWMS is a less reliable method to detect early change following mild stroke.

Post-stroke delirium

We propose that this early improvement across a broad sample of cognitive domains is evidence of a distinct state of acute stroke-induced delirium that precedes a slower neuroplastic recovery process, consistent with clinical observations of this population. This acute recovery is expected to be due to secondary effects of the stroke resolving, rather than resolution of primary effects of neuronal death, which are not likely to demonstrate such quick restitution (Gottesman & Hillis, 2010; McDonald *et al.*, 2019).

In keeping with a delirium state, the effect of post-stroke delirium appears to be generalised across cognitive domains rather than domain specific. All CANTAB measures (Fig. 2) demonstrated pronounced cognitive improvement, with the notable exception of SWMS which did not show significant change. Other studies have revealed that when detailed neuropsychological testing is performed early post-stroke, the cognitive profile remains similar 6-24 months later, with the same constellation of impaired versus unimpaired domains (Nys *et al.*, 2005; Wolf & Rognstad, 2013; van Zandvoort *et al.*, 2005). Two of these studies assessed cognition 4-20 days post-stroke, and found generalised improvements, and the third study by Wolf & Rognstad (2013) assessed cognition at 3 weeks and found a stable cognitive profile. This generalised global recovery was captured when testing occurred at <3 weeks post-stroke, which is consistent with our findings. However, our findings suggest an earlier stabilisation of post-stroke delirium between 6 and 14 days post mild stroke.

Other studies have suggested that acute stroke causes a delirium-state (Maldonado, 2018; McManus *et al.*, 2009; Stockholm *et al.*, 2019), but acknowledged difficulty in distinguishing which

factors were associated with delirium. Stroke severity is a known predictor of delirium (Oldenbeuving et al., 2011; Qu et al., 2018a), which supports the premise that stroke induces a delirium state in the acute phase. A systematic review of delirium assessment tools used in stroke and variations in reported delirium, suggested that acute stroke may cause delirium-like symptoms (Stokholm et al., 2019). A comparison of two delirium screening tools concluded that delirium detected within four days of stroke was precipitated by the stroke as no other cause was evident (Caeiro et al., 2004). Another found higher incidence of delirium in an acute stroke population when compared to acute coronary patients and concluded that delirium was likely caused by stroke (Mc Manus et al., 2009). However, these studies did not directly demonstrate early, global cognitive recovery separate from clinically recognised delirium.

One quarter of our participants had observable symptoms of delirium, captured on the 4-AT, which is validated for use in acute stroke (Lees et al., 2013; Qu et al., 2018b). This proportion is consistent with prior research reporting delirium to be present in 13-48% of stroke survivors (Oldenbeuving et al., 2007). However, using the 4-AT, most participants with symptomatic delirium appeared to resolve by day four post-stroke. When testing with a highly sensitive, computerised cognitive battery, the steady recovery we were able to measure implies ongoing resolution of this delirium state, beyond the days captured by the 4-AT. Sub-syndromal delirium has been described in the acute stroke population (Pasinska et al., 2018), which suggests that post-stroke delirium is on a continuum of severity made apparent by the more sensitive computerised testing used in our study. For mild post-stroke delirium, fluctuations in attention, a feature used in the clinical diagnosis of delirium (American Psychiatric & American Psychiatric Association, 2013), may be less apparent and therefore not captured by the delirium screening. These results illustrate that cognitive impairment is pervasive acutely post-stroke.

Strengths

Serial computerised cognitive assessment was sensitive enough to capture detailed information on domain-specific cognitive impairment and demonstrate significant recovery in a predominantly mild, ischaemic stroke cohort. These computerised assessments are highly reproducible and protect against practice effect ensuring the findings are likely to be reliable. We were also able to include stroke patients with aphasia who are often excluded in cognitive research (Wall et al., 2015). Further, we compared sensitive cognitive testing with a validated delirium screen to highlight limitations of delirium screening in a mild stroke cohort. Lastly, we gathered data up to 90 days to ensure we captured the period of greatest change post-stroke.

Limitations

Participants were classified as predominantly mild stroke and results less generalisable to a severe stroke cohort. Our selected subtests do not include assessment of language and Verbal Paired Associates could be added to address this commonly impaired domain. As well, this is a single-centre study in a dedicated acute stroke unit and results may differ in alternate settings. Lastly, our cohort of 48 participants was small and additional research with larger numbers will be required to verify these results.

Suggestions for further research

Further research is recommended to confirm the stability of domain-specific patterns of post-stroke cognitive impairment which would assist early, targeted cognitive interventions. Large studies of computerised testing could define more sensitive thresholds for identifying delirium than current screening tools. Further, exploring a broader range of computerised measures may reveal tests optimal for both screening and identification of specific clinically relevant deficits.

Some studies have found that cognition continues to recover months to years post-stroke (Hofgren *et al.*, 2007; Hurford *et al.*, 2012), while others demonstrate a decline in cognitive function (Jokinen *et al.*, 2015; Levine *et al.*, 2015). Hochstenbach *et al.* (2003) found that most stroke survivors showed no change in cognitive performance over a 2-year period, while some declined and others improved. The stroke survivors that improved accounted for the general upward trend of cognitive function. Further research may reveal different patterns of acute post-stroke recovery, which may be useful in predicting individual cognitive trajectories.

Conclusion

Serial computerised cognitive assessment is able to illustrate early generalised recovery over 14 days that is evidence for a distinct post-stroke delirium state. Post-stroke delirium appears to be far more common than is currently appreciated, and can be measured, even in mild stroke. Computerised cognitive assessment may be a more sensitive tool to identify delirium than current clinical screening tools. We have identified stabilisation of this acute cognitive recovery between 6 and 14 days for mild-stroke, indicating that more detailed neuropsychological testing may be performed earlier than previously understood. Further exploration of serial cognitive performance in delirium states could help us better understand this common and costly complication.

Data availability statement. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Ethics approval. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethical approval was obtained from The Prince Charles Hospital Human Research Ethics Committee, HREC/17/QPCH/163; the University of Queensland (#2017001149) and from University of the Sunshine Coast (S/17/1091).

Consent to participate. Informed consent was obtained from individual participants and/or substitute decision-makers for all participants included in the study.

Consent for publication. Participants or their substitute decision-makers signed informed consent regarding publishing their data.

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