ORIGINAL ARTICLE

Evaluating High-Functioning Young Stroke Survivors with Cognitive Complaints

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ABSTRACT: ***Background:*** The Montreal Cognitive Assessment (MoCA) is a commonly used cognitive outcome in stroke trials. However, it may be insufficiently sensitive to detect impairment in high-functioning stroke survivors. The National Institutes of Health (NIH) Toolbox Cognition Battery (NIHTB-CB), a 30-min comprehensive tablet-based cognitive assessment, may be a better choice to characterize cognitive issues in this cohort. ***Methods:*** We compared MoCA and NIHTB-CB performance in young stroke survivors (18–55 years) with excellent functional outcomes (modified Rankin Scale 0–1) reporting subjective cognitive complaints to that of age-matched healthy controls. We recruited 53 stroke survivors and 53 controls. We performed a sensitivity analysis in those participants with normal MoCA scores (≥26). ***Results:*** Median MoCA scores were not significantly different between stroke survivors (27.0 vs. 28.0) and healthy controls. Mean T scores for NIHTB-CB fluid (44.9 vs. 54.2), crystallized (53.8 vs. 60.0), and total cognition (49.1 vs. 58.4) components were significantly lower in stroke survivors compared to healthy controls ($p < 0.001$ for all). In participants scoring within normal range (≥26) on the MoCA, NIHTB-CB scores for all components remained significantly lower in stroke survivors. ***Conclusions:*** In young stroke survivors with excellent functional outcomes and subjective cognitive complaints, the NIHTB-CB, but not the MoCA, was able to detect differences in cognitive performance between stroke survivors and healthy controls. The NIHTB-CB may be a suitable outcome measure for cognition in clinical trials examining higher-functioning young stroke survivors.

RÉSUMÉ : Évaluer des jeunes survivants d'un AVC qui donnent à voir un haut niveau de fonctionnement mais qui font état de déficiences cognitives. ***Contexte*** **:** Le test cognitif de Montréal (ou MoCA) est un outil couramment utilisé à la suite d'AVC. Il peut cependant s'avérer insuffisamment sensible pour détecter les déficiences qui affectent les survivants d'un AVC qui donnent à voir un haut niveau de fonctionnement. À cet effet, il est possible que le *NIH Toolbox Cognition Battery* (NIHTB-CB), une évaluation cognitive complète de 30 minutes effectuée sur une tablette, soit plus indiqué pour caractériser les déficiences cognitives présentes chez ces patients. ***Méthodes*** **:** Nous avons ainsi comparé les performances au MoCA et au NIHTB-CB de jeunes survivants d'un AVC qui étaient âgés de 18 à 55 ans et qui donnaient à voir d'excellents résultats en matière de fonctionnement à l'échelle modifiée de Rankin (0-1) tout en faisant état de déficiences cognitives par rapport à des témoins en santé appariés en fonction de l'âge. Pour ce faire, nous avons recruté 53 survivants d'un AVC et 53 témoins. Nous avons aussi effectué une analyse de sensibilité chez les participants dont les scores au MoCA étaient normaux (≥ 26). ***Résultats*** **:** Les scores médians au MoCA ne se sont pas révélés notablement différents entre les survivants d'un AVC (27,0) et les témoins en santé (28,0). Les scores T moyens au NIHTB-CB pour les habiletés fluides (44,9 contre 54,2), les habiletés cristallisées (53,8 contre 60,0) et la cognition totale (49,1 contre 58,4) se sont par ailleurs avérés significativement plus faibles chez les survivants d'un AVC par rapport aux témoins en santé ($p < 0{,}001$ pour tous ces volets évalués). Chez les participants dont les scores au MoCA étaient situés dans la fourchette normale (≥ 26), les scores au NIHTB-CB pour tous les volets évalués sont demeurés significativement plus bas chez les survivants d'un AVC. ***Conclusions*** **:** Chez des jeunes survivants d'un AVC donnant à voir un haut niveau de fonctionnement et se plaignant néanmoins de déficiences cognitives, le NIHTB-CB, et non le test MoCA, a permis de détecter des différences de performance cognitive entre les survivants d'un AVC et des témoins en santé. Le NIHTB-CB peut ainsi être un outil d'évaluation approprié de la cognition dans le cadre d'études cliniques portant sur des jeunes survivants d'un AVC qui donnent à voir un haut niveau de fonctionnement.

Keywords: Stroke, Cognition, Cognitive impairment, MoCA, Young adults, Rehabilitation

doi:10.1017/cjn.2021.137 Can J Neurol Sci. 2022; 49: 368–372

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Received April 23, 2021. Final Revisions Submitted June 7, 2021. Date of Acceptance June 10, 2021.

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Introduction

Stroke in younger adults is becoming increasingly common.[1] Compared with older counterparts, young stroke survivors are likelier to remain functionally independent,[2,3] but still face a significant burden of 'invisible' complications, including issues with pain, mood, fatigue, and cognition, affecting day-to-day function and quality of life.[4–8]

The Montreal Cognitive Assessment (MoCA) is commonly used to measure cognitive outcomes in clinical trials and is a guideline-recommended screening tool for post-stroke cognitive impairment.[9] The MoCA's potential ceiling effect, however, may make it insufficiently sensitive to characterize more subtle cognitive impairments following nondisabling stroke.

The NIH Toolbox Cognition Battery (NIHTB-CB) is a 30-min tablet-based standardized assessment for measuring cognitive impairment across neurological conditions, including stroke.[10] It provides a more detailed neurocognitive assessment than the MoCA, which may make it better suited for evaluation of subtle cognitive deficits, but is briefer than detailed multidomain cognitive assessments that have been used to characterize post-stroke cognitive impairment in the research setting.[5,11,12] Unlike the MoCA, NIHTB-CB scores are normalized to age, sex, education, and race ethnicity.[13]

We compared performance on the MoCA and the NIHTB-CB in a cohort of young stroke survivors with excellent functional outcomes and at least one subjective cognitive complaint, and age-matched healthy controls. We also performed a sensitivity analysis examining differences in NIHTB-CB performance in participants with normal MoCA performance. The findings of our study are intended to guide stroke trialists in considering an appropriate brief cognitive assessment in higher-functioning young survivors.

Methods

Design

We performed a case–control study. Sample sizes were determined a priori to detect differences between two independent group means, assuming 80% power ($\alpha = 0.05$, two-tail) and published estimates of NIHTB-CB and MoCA performance in stroke patients.[10,14]

Participants were 18–55 years old. Additional inclusion criteria for stroke survivors included documented clinical diagnosis of transient ischemic attack, ischemic, or hemorrhagic stroke within the last 3 years; discharge from acute care, modified Rankin Scale (mRS) 0–1, and at least one subjective cognitive complaint using the checklist for cognitive and emotional consequences following stroke (CLCE-24). We included patients with self-reported cognitive deficits as our study's objective was to characterize cognitive issues in young, high-functioning stroke survivors reporting subtle, yet persistent and bothersome cognitive deficits. As we were specifically interested in comparing cognitive test performance as opposed to the effects of stroke type or lesion location, we were inclusive of ischemic and hemorrhagic stroke survivors with any lesion location. Exclusion criteria for all participants were limited English proficiency, aphasia, history of concurrent neurological or psychiatric condition, substance use disorder, limited use of one's dominant hand, and exposure to the NIHTB-CB within the past year. Stroke survivors and healthy controls were recruited from stroke clinics, advertisements at a local academic hospital, and the health authority institute website.

The experimental protocol was approved by the local clinical research ethics board and conformed to the Declaration of Helsinki. All participants provided informed consent.

Outcome Measures

Demographic data were collected with a questionnaire and clinical data were extracted from electronic medical records. Stroke type was classified as ischemic or hemorrhagic and etiologies were classified by Trial of Org 10172 in Acute Stroke Treatment (TOAST) or structural vascular, medication, amyloid angiopathy, systemic disease, hypertension, undetermined (SMASH-U) classifications, respectively.[15,16] Subjective cognitive complaints were assessed using the CLCE-24, a validated instrument for assessing post-stroke cognitive and emotional complaints.[17] Depressive symptoms were measured with the Patient Health Questionnaire (PHQ-9)[18] and quality of life was measured with the EuroQol five dimensions (EQ-5D).

The MoCA is a simple screening test for mild cognitive impairment (MCI). The MoCA assesses multiple cognitive domains (i.e. visuospatial, executive function, naming, memory, attention, language, abstraction, delayed recall, and orientation) to produce a composite score from 0–30, where higher values indicate better cognitive function; a score of <26 suggests MCI.[19] The MoCA crudely corrects for level of education, where one point is added to the total score for individuals with ≤12 years of formal education; scores are not otherwise adjusted for demographic differences.[19] The NIHTB-CB is a tablet-based assessment comprising seven instruments that are classified as measures of crystallized cognition (i.e. picture vocabulary and oral reading recognition) or fluid cognition (i.e. picture sequence memory, pattern comparison processing speed, list sorting working memory, Flanker inhibitory control and attention, and dimensional change card sort).[20] NIHTB-CB scoring adjusts for demographic factors including age, sex, education, ethnicity, and race. We report fully corrected T scores (mean = 50, SD = 10).[13]

The NIHTB-CB was administered on a 9.7″ iPad Pro (Apple, California, USA). All assessments were administered by trained research personnel in a quiet, distraction-free room.

The entire assessment including the informed consent process took approximately 90 min to complete.

Statistical Analysis

Demographic data were separated by group. Each dependent variable was assessed for skewness. Mean and standard deviations were reported for normally distributed data, and median and interquartile ranges (IQRs) were reported for skewed data. Group comparisons were made with Student's *t*-tests for parametric data, Mann–Whitney U test for nonparametric data and chi-square test for categorical data. Cohen's *d* effect sizes were calculated for between-group comparisons. For nonparametric data, Eta-squared effect sizes were calculated and then converted into Cohen's *d*.[21] Significance was set at $p = 0.05$. A sensitivity analysis was performed for individuals with normal MoCA performances (score ≥ 26). All group comparisons were repeated for the sensitivity analysis.

https://doi.org/10.1017/cjn.2021.137 Published online by Cambridge University Press

Table 1: Baseline characteristics of all participants and those with MoCA ≥ 26 only

	Control Group ($n = 53$)	Stroke Group ($n = 52$)	Significance (p)
All Participants			
Sex (n, % female)	27 (50.9)	19 (36.5)	0.14
Age (years; median, IQR)	44.0 (36.5–49.0)	47.0 (38.5–51.0)	0.12
Education Years (mean, SD)	15.9 (2.1)	15.2 (2.2)	0.09
EQ-5D (median, IQR)	0.91 (0.90–0.95)	0.84 (0.75–0.91)	<0.001
PHQ-9 (median, IQR)	2.0 (1.0–4.0)	5.0 (2.0–8.0)	<0.001
Time (days) post-stroke (median, IQR)		90.0 (59.0–179.8)	
mRS 0 (n, %)		14 (26.9)	
mRS 1 (n, %)		38 (73.1)	
CLCE-24 (mean, SD)		7.7 (4.3)	
MoCA ≥ 26			
Sex (n, % female)	21 (47.7)	9 (27.3)	0.07
Age (years; median, IQR)	45.0 (27.0–49.8)	47.0 (40.0–50.5)	0.28
Education Years (mean, SD)	16.0 (2.2)	15.3 (2.2)	0.17
EQ-5D (median, IQR)	0.95 (0.90–0.95)	0.84 (0.76–0.95)	0.005
PHQ-9 (median, IQR)	2.0 (1.0–4.8)	5.0 (2.0–8.0)	<0.001
Time (days) post-stroke (median, IQR)		79 (62.0–113.5)	
mRS 0 (n, %)		9 (27.3)	
mRS 1 (n, %)		24 (72.7)	
CLCE-24 (median, IQR)		7.5 (7.0)	

CLCE-24 = checklist for cognitive and emotional consequences following stroke; EQ-5D = EuroQol five dimensions; IQR = interquartile range; MoCA = Montreal Cognitive Assessment; mRS = modified Rankin Scale; PHQ-9 = Patient Health Questionnaire; SD = standard deviation.

Table 2: NIHTB-CB performance (fluid, crystallized, and total cognition) in healthy controls and stroke survivors for all participants and in those with MoCA ≥ 26

All Participants ($n = 105$)	Control Group ($n = 53$)	Stroke Group ($n = 52$)	Significance (p)	Effect Size (Cohen's d)
Fluid Cognition (n, %)	54.2 (9.6)	44.9 (10.8)	<0.001*	0.9
Crystallized Cognition (n, %)	60.0 (7.5)	53.8 (7.9)	<0.001*	0.8
Total Cognition (n, %)	58.4 (7.5)	49.1 (8.4)	<0.001*	1.2
MoCA ≥ 26 ($n = 77$)	**Control Group ($n = 44$)**	**Stroke Group ($n = 33$)**	**Significance (p)**	**Effect Size (Cohen's d)**
Fluid Cognition (n, %)	55.1 (8.4)	49.2 (7.5)	0.002*	0.7
Crystallized Cognition (n, %)	60.4 (7.8)	55.7 (6.9)	0.007*	0.6
Total Cognition (n, %)	59.1 (6.8)	52.8 (6.0)	<0.001*	1.0

MoCA = Montreal Cognitive Assessment; NIHTB-CB = NIH Toolbox Cognition Battery.
*$p < 0.05$.

Results

We recruited 53 stroke survivors and 53 healthy controls. One participant in the stroke group had no clinical documentation to confirm their diagnosis in retrospect, and was excluded from the analysis. Nearly two-thirds (33/52; 63%) of stroke survivors and four-fifths (44/53; 83%) of controls had an MoCA score ≥ 26. Demographics were similar between stroke survivors and controls. EQ-5D scores were lower, and PHQ-9 scores were higher in stroke survivors (Table 1). CLCE-24 data are reported in the Data Supplement (Supplemental Table S1). When comparing stroke survivors and controls with MoCA ≥ 26, there were no significant demographic differences between groups. Detailed characteristics on stroke type, mechanism, and location are reported in Data Supplement (Supplemental Table S2).

There was no significant difference between MoCA performance in healthy controls (median = 28.0, IQR = 26.0–29.0) and stroke survivors (median = 27.0, IQR = 24.0–28.0) $p = 0.05$; Cohen's d effect size was 0.4. NIHTB-CB scores significantly differed for each composite outcome between groups, both overall and when limited to those with MoCA ≥ 26 (Table 2, Figure 1).

https://doi.org/10.1017/cjn.2021.137 Published online by Cambridge University Press

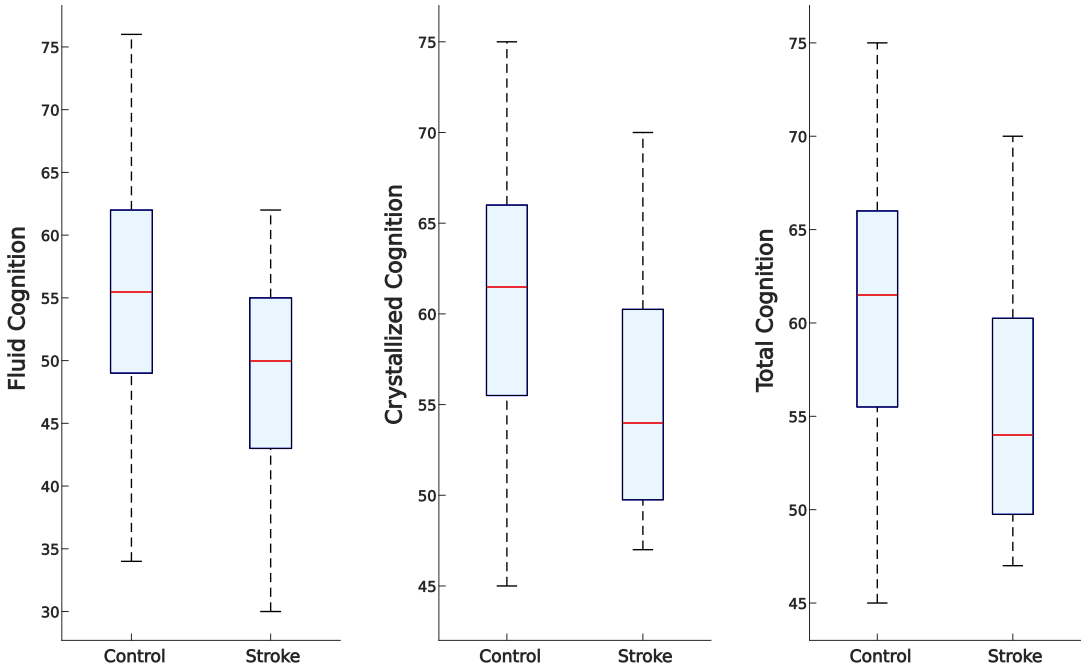

Figure 1: Boxplot of NIHTB-CB (fluid, crystallized, and total cognition) performance between healthy controls and stroke survivors with MoCA ≥ 26. Red lines indicate median, boxes interquartile range, and whiskers range of data. Asterisks indicate statistically significant at $p < 0.05$.

Discussion

Cognition is one of the most important outcomes affecting quality of life in functionally independent stroke survivors and is increasingly used as an outcome in stroke trials.[9,22,23] Although the MoCA is a commonly used measure of cognition, we found that MoCA scores were similar between our cohort of functionally independent young stroke survivors and healthy controls. Differences were seen, however, between groups on the NIHTB-CB, both overall and when restricted to individuals with normal MoCA scores. Our findings suggest that more sensitive cognitive batteries may be required to better ascertain the burden of post-stroke cognitive deficits in high-functioning young survivors who have normal cognitive screens but persistent cognitive complaints.

Previous work has demonstrated cognitive deficits in young stroke survivors compared to age-matched healthy controls. A large recent study examining 277 young stroke survivors (68% with an mRS 0–1, mean age = 40 years) and 146 healthy controls found similar mini-mental status exam scores (mean = 26.3, SD = 2.6 vs. 27.2, SD = 1.9) but more marked differences in performance on a detailed cognitive battery that included 10 tests measuring processing speed, visuoconstruction, working, immediate and delayed memory, attention, and executive functioning.[5] Compared to a more extensive neuropsychological battery, the NIHTB-CB is comparatively brief while still maintaining sufficient sensitivity to relative differences in cognitive performance between stroke survivors with subtle cognitive issues versus healthy controls. Thus, in clinical trials focused on cognitive outcomes in higher-functioning young survivors, the NIHTB-CB may serve as a means to assess cognitive performance where the MoCA may not be sufficiently sensitive to detect differences between groups. The shorter assessment times as compared to a more extensive cognitive battery may also be more suitable in resource-limited settings. Furthermore, a shorter battery may be welcome in a patient group prone to post-stroke fatigue.

There are limitations to our study. We have not adjusted for the potential confounding effects of depression, fatigue, pain, or other post-stroke sequelae on cognitive performance. However, we note that, similar to what has been reported previously, the group of young stroke survivors reported more depressive symptoms on the PHQ-9 and lower quality of life on the EQ-5D compared to controls, and acknowledge that these factors may have impacted performance. Still, this does not detract from our finding that differences were seen on NIHTB-CB performance that were not detected on the MoCA. Our work warrants further confirmation in a larger study focused solely on individuals with normal MoCA performances, and corrected for the potential confounding effects of post-stroke complications. Finally, though one might not expect nearly 20% of young controls to have MoCA scores under 26, this is in keeping with previous studies examining young healthy individuals.[24,25]

Conclusion

In young stroke survivors with excellent functional outcomes and subjective cognitive complaints, the NIHTB-CB, but not the MoCA, was able to detect differences in cognitive performance between stroke survivors and healthy controls. The NIHTB-CB may be a suitable outcome measure for cognition in clinical trials examining higher-functioning young stroke survivors.

Acknowledgements

We thank Zoe O'Neill and Michelle Yuan for their assistance with data collection. Formal permission to use the MoCA in this study was obtained from Dr. Nasreddine.

https://doi.org/10.1017/cjn.2021.137 Published online by Cambridge University Press

Conflict of Interest

Dr. TSF receives in-kind study medication from Bayer Canada. The other authors report no conflicts. This study was supported by the Canadian Institutes of Health Research. Dr. TSF is supported by the Vancouver Coastal Health Research Institute, the Michael Smith Foundation for Health Research, and the Heart and Stroke Foundation of Canada.

Statement of Authorship

Dr. ADR, Ms. LEK, and Dr. TSF all made substantial contributions to study conception and design, acquisition of data, and analysis and interpretation of data. Ms. HMD made substantial contributions to data acquisition. Dr. ADR, Ms. LEK, Dr. NDS, and Dr. TSF have been involved in drafting the manuscript and revising it for important intellectual content. All authors read and approved the final manuscript.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.137.

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