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The Oxford cognitive screen (OCS) as an acute predictor of long-term functional outcome in a prospective sample of stroke patients

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ABSTRACT

The Oxford Cognitive Screen (OCS) was developed to measure cognitive impairment in stroke. Here, we test if the OCS administered acutely in stroke patients provides useful information in predicting long-term functional outcome. A group of first-time stroke patients ($n = 74$) underwent an acute behavioral assessment comprising the OCS and the NIHSS within one-week post-stroke. Functional outcome was evaluated using the Stroke Impact Scale 3.0 (SIS 3.0) and the Geriatric Depression Scale (GDS) at 6 and 12-months post-stroke. We compared the predictive ability of the OCS and NIHSS, separately or in combination, to predict different domains of behavioral impairment at a chronic evaluation. The OCS accounted for 61% of variance of SIS physical domain, 61% of memory domain, 79% of language domain, 70% of participation domain and 70% of recovery domain. The OCS accounted for a greater percentage of outcome variance than demographics and NIHSS. The most informative predictive model included the combination of demographics, OCS and NIHSS data. The OCS, performed early after stroke, is a strong independent predictor of long-term functional outcome and significantly improves the prediction of outcome when considered alongside the NIHSS and demographics.

Abbreviations: OCS, Oxford Cognitive Screen; NIHSS, National Institute of Health Stroke Scale; SIS, Stroke Impact Scale; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

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1. Introduction

Stroke prognosis can be determined by predictors such as age, acute severity, gender, education level, and pre-existing comorbidities[1,2,3]. Among these features, acute severity is considered the most important factor affecting long-term outcome[4,5,6]. In clinical practice, stroke severity is typically assessed with the National Institutes of Health Stroke Scale (NIHSS), a stroke-specific version of the neurological examination, including subtests covering different functional domains (i.e. visual field, motor, sensory, attention and language deficits). This scale has gained broad acceptance in clinical practice since it provides strong prognostic value and applicability, however it has been criticized for emphasizing the physical domain, neglecting the assessment of cognitive deficits that affect the great majority of stroke survivors (de Haan et al., 2006; Jaillard et al., 2009). To assess this issue, several authors have developed stroke-specific and clinically applicable cognitive screening tools (Veerbeek et al., 2011). Among such tools, the Oxford Cognitive Screen (OCS) has gained acceptance for the assessment of cognitive impairments with robust validity and reliability (Demeyere et al., 2015). The OCS is a neurobehavioral battery that allows a rapid assessment of several cognitive domains (i.e., language, memory, attention, calculation and praxis). The main advantage of this evaluation, in addition to its bedside design, is its high sensitivity for stroke-specific cognitive deficits, especially aphasia and neglect[9,10]. Although these tools have shown promising results in the acute setting, their prognostic value for long term functional outcome in comparison to well-known clinical features (e.g., age, education, and acute impairment) remains uncertain. As a result, while several studies have shown that cognitive deficits represent powerful predictors of recovery and quality of life (Fahey et al., 2018; Harvey, 2015), they remain cursorily assessed in the acute clinical setting, and in commonly employed measures of outcome (i.e. the mRS and Barthel Index). (Weimar, König, Kraywinkel, Ziegler, & Diener, 2004).

To address this issue, we investigated the predictive power of acute cognitive deficits on long term functional outcome with two main objectives. The first aim was to test whether the OCS, administered early after stroke, is an independent predictor of long-term functional outcome at 6–12 months as measured by the Stroke Impact Scale (SIS) (Weimar et al., 2004) and the Geriatric Depression Scale (GDS). These behavioral batteries provide an outcome evaluation beyond the physical sequelae of stroke, assessing health related quality-of-life features that are not evaluated in commonly used outcome measures (i.e. Rankin scale and Barthel Index) including emotion, communication, memory and thinking, and social role function (Adams et al., 1999). The second aim was to compare the predictive ability of known prognostic variables (i.e. age, demographics, NIHSS) with the OCS to select the best set of clinical variables for long-term functional outcome prediction.

2. Methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. No part of the study procedures or analysis plans was preregistered prior to the research being conducted.

2.1. Study sample

Patients were prospectively recruited during a period of 11 months (from January 2018 to November 2018), from the Neurology Clinic and Stroke Unit of the Padova Hospital and the Stroke Unit of the S. Antonio Hospital of Padova. Patients with a first-symptomatic stroke, either ischemic or hemorrhagic, were selected according to the following inclusion and exclusion criteria.

Inclusion criteria: (1) Age 18 or greater. No upper age limit; (2) First symptomatic stroke, ischemic or hemorrhagic; (3) Up to two ischemic lacunes, clinically silent, less than 15 mm in size on CT scan; (4) Time of enrollment: <2 weeks from stroke onset; (5) Awake, alert and capable of participating in research.

Exclusion criteria: (1) Previous stroke based on clinical imaging; (2) Multifocal strokes; (3) Inability to maintain wakefulness in the course of testing; (4) more than two asymptomatic lesions on CT scan; (5) Presence of central nervous system Neoplasms; (6) Presence of neurodegenerative diseases; (7) Previous central nervous system surgeries; (8) Presence of schizophrenia, bipolar disorder, major depression, or other severe psychiatric conditions; (9) Presence of other medical conditions that preclude active participation in research and/or may alter the interpretation of the behavioral/imaging studies (10) Absence of the patients' consent.

From January 2019 to May 2019, all patients previously selected whose stroke occurred either 6 or 12 months before ($N = 114$) were administered a telephonic assessment by means of the Stroke Impact Scale 3.0 (SIS 3.0) to evaluate long-term functional outcome.

For 40 out of 114 patients we were not able to collect functional outcome data at follow-up. The great majority of them did not answer the phone-calls, others had a second stroke, died, or did not give their consent to participate (see Supplementary Figure 1_Enrollment flowchart). The final sample included $n = 74$ patients.

2.2. Behavioral assessment

All recruited patients were assessed within the first week post-stroke after symptoms onset with an acute neurobehavioral battery that included the NIHSS and OCS (see Supplementary Figure 2_ Study design). The NIHSS is a battery of 15 subtests: level of consciousness, gaze and visual field deficits, facial palsy, upper and lower motor deficits (right and left side), limb ataxia, sensory impairment, inattention, dysarthria and language deficits. The total score was used as a measure of initial stroke severity. The OCS is structured in ten subtests covering five cognitive domains: language (picture naming, pointing and sentence reading subtests), praxis (meaningless gestures test), number processing (number writing and calculation subtests), attention (broken heart test to measure sustained attention and egocentric/allocentric

neglect) and memory (orientation, recall and recognition, and episodic memory subtests).

Several additional clinical data were collected for each patient based on detailed history: demographics (age at enrollment, gender, education, handedness and profession), stroke etiology (hemorrhagic or ischemic), the presence of stroke risk factors and relevant comorbidities (i.e., smoke, neurological history, psychological history, cardiac history, diabetes mellitus, vision history), stroke familiarity, clinical presentation, and home therapy.

Outcome was measured either at six ($n = 38$) or twelve months ($n = 36$) using the SIS 3.0 during a telephone interview. The SIS 3.0 is a stroke-specific outcome measure that consists of items measuring eight domains of function (strength, hand function, activities of daily living/instrumental activities of daily living, mobility, communication, emotion, memory and thinking, and participation). (Duncan et al., 2003).

Furthermore, since depression is a common sequela following stroke (Medeiros et al., 2020) and it is considered a possible confound for the evaluation of stroke functional recovery (Robinson & Jorge, 2016; van de Weg et al., 1999), we also evaluated depression using the Geriatric Depression Scale (GDS) (Saposnik et al., 2011). The GDS is a robust tool for the assessment of mood disorders, specifically developed for the elderly population. Importantly, both SIS 3.0 and GDS telephone administration (Kwon et al., 2006) have been validated on the Italian population (Vellone et al.; Galeoto et al., 2018).

When patients were not available to undergo the telephonic interview on their own (for incapability of using the phone, aphasia, or poor general health conditions; $n = 6$), we administered the SIS 3.0 to their relatives or other proxies living with them using a validated SIS proxy version (Duncan et al., 2002).

Conversely, patients for which was not possible to obtain a GDS score for different reasons (i.e., proxy respondents' interview, lack of compliance in completing the test, tiredness; $n = 10$), the GDS was not administered to their relatives since a proxy version of this tool has not been validated.

2.3. *Data preprocessing*

Demographics and acute behavioral data were collected as mentioned above and used as potential outcome predictors. Acute behavioral data consisted of OCS subtests scores and NIHSS total score. We chose to use the NIHSS total score instead of its sub-scores since we were more interested in understanding whether the degree of stroke severity, rather than specific physical deficits, was a reliable predictor of post-stroke functional outcome.

All OCS sub-scores were transformed such that larger values corresponded to more severe deficits. Then, non-informative variables (i.e., showing a SD close to zero), and variables showing a significant floor effect (i.e, ≥90% of patients scoring 0) were excluded. Considering these two criteria, two OCS subtests were removed from the analysis, i.e., Orientation and Semantics.

We then checked whether there were significant differences in SIS sub scores between patients tested at 6 ($N = 38$) or 12 ($N = 36$) months. To this end, we built a logistic regression model that showed that none of the SIS sub scores significantly differed between the 6- and 12-months population; this result suggests that functional outcome at 6 months after stroke was comparable to that obtained at 12 months (See Supplementary Figure 3_Comparison of SIS scores distributions). This is in line with several studies showing that the great majority of functional recovery occurs within the first 6 months (Lee et al., 2015; Meyer et al., 2015). For these reasons, the two populations were merged in a single larger population for the statistical analyses.

Finally, since SIS is a self-report questionnaire, the answers could be affected by the individual level of depression. To rule out the impact of depression on individual responses, the GDS score was included as covariate in the subsequent analysis. In the cases of patients for which a GDS score was not available, we estimated it from the SIS item 3 "Mood and emotions" since literature reports high correlation (i.e., $r = .77$[23]) among these indices, as confirmed also in our sample (Pearson's $r = .78$, $p < .001$).

2.4. *Statistical analysis*

Age, gender, education level, comorbidities, NIHSS and OCS scores were included as predictors of long-term functional outcome in a series of nested linear regression models. We built each model by progressively adding predictors to a null model including only the intercept (see Table I, Nested prediction models). Then, we compared baseline demographic models with models including clinical data (NIHSS) and a cognitive screen (OCS). Specifically, we tested three models including demographic variables (M1 to M3), one model included also pre-stroke disability features (M4—Demographics&Disability), one model considered acute stroke severity measures by means of the NIHSS as in the everyday clinical practice (M5—Clinical); one model added the OCS scores, thus including a cognitive evaluation (M6—Clinical&Cognitive). We also built two models including only OCS variables and NIHSS score, respectively (see Table I, M_{OCS} and M_{NIHSS}).

All models included GDS score as covariate to account for mood-related potential biases in the responses to the SIS questionnaire. The presence of pre-stroke comorbidities was also evaluated and included as predictor as it was crucial to control for possible concomitant diseases affecting functional abilities.

Table 1 – Nested prediction models.

Models	Predictors of interest
$\mathbf{M_0}$	Intercept only
$\mathbf{M_{1\_Demographics1}}$	Age
$\mathbf{M_{2\_Demographics2}}$	Age + Gender
$\mathbf{M_{3\_Demographics3}}$	Age + Gender + Education
$\mathbf{M_{4\_Demographics\&Disability}}$	Age + Gender + Education + Comorbidities
$\mathbf{M_{5\_Clinical}}$	Age + Gender + Education + Comorbidities + NIHSS
$\mathbf{M_{6\_Clinical\&Cognitive}}$	Age + Gender + Education + Comorbidities + NIHSS + OCS
$\mathbf{M_{OCS}}$	OCS scores
$\mathbf{M_{NIHSS}}$	NIHSS score

The whole set of multiple linear regression models was then built to predict each functional outcome domain (i.e., SIS score). All models were compared in terms of R^2 to highlight the best model.

Finally, the best model was used to predict SIS scores with a leave-one-out (LOO) procedure: in each step the model was built on N-1 observations and tested with the left-out observation. This procedure was repeated for N iterations and the accuracy of the prediction was assessed by correlating actual and predicted SIS scores (Pearson's *r*).

All patients included in the present study gave their written consent, and the study conforms with World Medical Association Declaration of Helsinki.

Table I. *Nested Prediction Models. Notably, all models included the GDS score as a covariate to account for mood-related potential biases in the responses to the SIS questionnaire.*

3. Results

A sample of patients ($n = 114$) with a first symptomatic stroke, either ischemic or hemorrhagic, were prospectively recruited from two neurology units of the Azienda Ospedale Universita' of Padua according to the inclusion criteria. Patients were tested with an acute neurobehavioral battery at 5 ± 3.6 days post stroke. Approximately half of the patients ($n = 58$) were contacted by phone at 6 months (187 ± 20 days) after the first neurobehavioral assessment, of which $n = 38$ underwent the follow-up assessment. The remaining patients ($n = 56$) were contacted at 12 months post stroke (378 ± 15 days), with $n = 36$ undergoing the follow-up assessment.

The recruited patients that did not undertake the follow-up assessment ($n = 40$) did not differ significantly from our clinical sample in terms of stroke severity (mean NIHSS 3.8 *vs* 2.7; $p = .11$). Patients with SIS score obtained by proxy respondents ($n = 6$) did not show significantly stroke higher severity as compared to our study population at the acute timepoint (mean NIHSS 3.9 *vs* 2.5; $p = .19$). At the follow-up evaluation proxy responders performed significantly worse in the SIS Communication and Understanding subdomain (proxy responders mean SIS score 55.7 *vs* non-proxy responders 83.5; p .009, while no significant differences emerged in the other subdomains. While this result is in line with previous studies (Duncan et al., 2002) and may partially depend on the nature of certain lesions that selectively cause a certain degree of anosognosia, larger samples of patients ($n = 6$ proxy respondents in our sample) are needed to assess this issue in depth.

3.1. Clinical representativeness of the study sample

The study sample was composed of all Caucasian participants with a mean age of 67 years old. Most patients were male (59%) with a mean age of 65 years old. Female participants were 41% of the sample with a mean age of 69 years old. Most participants completed Middle school (52%), 8 years in the Italian educational system. The most frequently identified risk factors were hypertension (65% of patients), smoking (37%), diabetes mellitus (16%), atrial fibrillation (12%), and coronary artery disease (4%).

The mean NIHSS on admission was 6.9 ± 6.4 and 2.6 ± 2.9 at the time of testing. At the time of admission, 59% of the cases were mild (score 0–6), 30% moderate (score 7–15), and 11% severe (score 16–42). Motor deficits were most frequently observed (90% of patients), while aphasia (38%) and neglect (22%) were identified less frequently. Lesions equally involved the right hemisphere and the left hemisphere (45% and 42%, respectively). Only 3% involved the cerebellum or brain stem. The great majority of strokes were ischemic (90%), with 10% hemorrhagic (See Supplementary Table 1 for Study sample characteristics).

3.2. Functional outcome assessment

We collected SIS scores by telephonically administering the questionnaire at 6 or 12 months after stroke onset. Since we did not find significant differences in SIS scores between patients tested at 6 *vs*. 12 months, the data from both samples were pooled. Supplementary Figure 3 shows the distribution of scores in each domain (i.e., physical, memory and thinking, mood and emotion; communication and understanding; participation; and recovery) for the whole group of patients.

Fig. 1 shows the distribution of SIS scores across each subtest with higher scores indicating better performance. Supplementary Figure 4 shows the cumulative distribution of OCS scores with higher scores indicating better performance.

To evaluate the relation between SIS sub scores, OCS sub scores, GDS, and NIHSS scores, we computed a correlation matrix (see Fig. 2; red: positive correlation; blue: negative correlation**)**. We found a strong positive correlation between SIS subdomain scores (mean Pearson's r = .62, SD = .148), with the highest correlation between participation and recovery ($r = .87$). We also observed a moderate correlation within the OCS scores (mean r = .38, SD = .22), with the highest correlation between episodic memory and number writing ($r = .78$), and between these scores and the SIS scores (mean $r = .27$, SD = .12). Importantly, the GDS scores (i.e., high scores indicate higher levels of depression) showed a strong negative correlation with all SIS scores (mean $r = -.64$, SD = .12), confirming the expected important negative impact of depression on functional outcome as measured by a questionnaire. Finally, initial stroke severity captured by the acute NIHSS scores (i.e., high scores indicate worse performance) showed a negative relationship with both long-term outcome (SIS; mean $r = -.52$, SD = .12) and OCS scores (mean $r = -.39$, SD = .17).

3.3. Prediction of long-term post stroke impairment

Besides describing the correlation between acute and follow-up measures, we aimed to formally quantify and compare the accuracy of acute measurements (i.e., NIHSS, OCS) in predicting long-term functional outcome. To this end, we built a series of linear regression models to select the best predictors for long-term outcome. The models are described in the Methods section and Table I. In summary, the models included baseline demographic information (M1 to M3), comorbidity (M4), clinical (M5) and clinical+cognitive (M6) information collected in acute. In addition, two models were built including only OCS and NIHSS scores, respectively (M_{OCS} M_{NIHSS}). Importantly, all models included GDS scores as

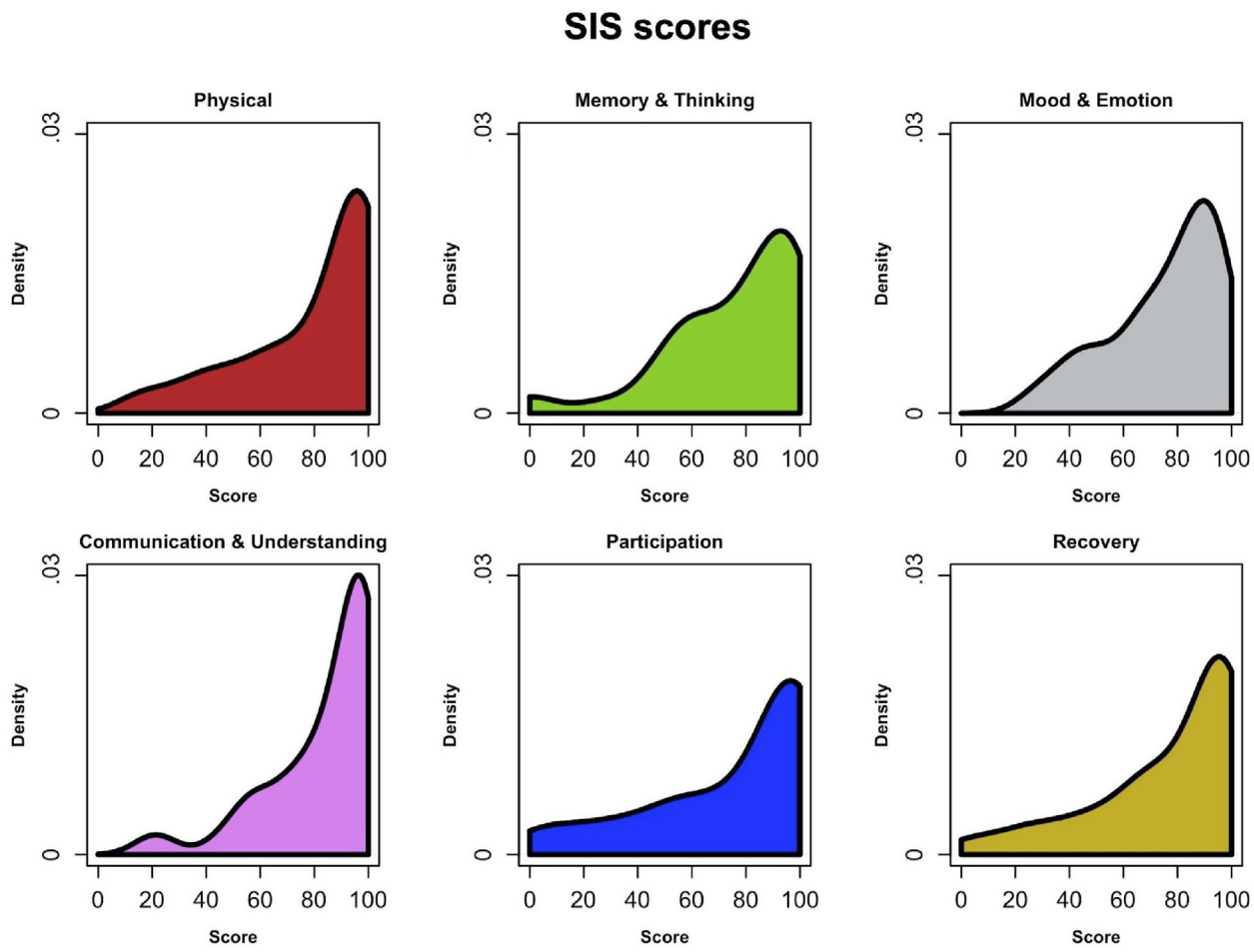

Fig. 1 – Distribution of weighted-SIS scores. A score of 100 represents no disability; a score of 0 represents the highest degree of disability. Notably, "Physical" is composed of "Physical problems", "Mobility", "Daily activities", "Hand function" SIS domains (right).

covariate to account for the influence of depression on SIS scores. For each model we computed the percentage of explained variance of the corresponding SIS score in terms of R^2, computed as in (Jaeger et al., 2017).

Then, for each SIS score we ran a series of pairwise non-parametric comparisons (across 2000 permutations) on the difference of R^2, to decide the best model explaining SIS data (see Fig. 3). All models were significant but showed markedly different levels of R^2 across SIS scores (range: .21—.83; see Fig. 3), with the highest performance reached by model M_6 for Mood and Emotions, and the lowest being related to model M_0 for Communication and Understanding.

On average the inclusion of demographic data (age and gender) to the null model significantly improved the percentage of explained variance (M1-M2). The further inclusion of education and comorbidities (M3-M4) did not substantially increase the level of R^2. The most informative models included acute stroke severity data (i.e., NIHSS; M5) and clinical and cognitive impairment (i.e., NIHSS+OCS; M6). In particular, the addition of cognitive deficits substantially improved the prediction of outcome in all subdomains of function. Indeed, M6 explained the highest percentage of variance in Physical ($R^2 = .68$), Memory and thinking ($R^2 = .66$), Mood and emotions ($R^2 = .83$), Communications and understanding ($R^2 = .44$), Participation ($R^2 = .73$) and Recovery ($R^2 = .73$). Notably, the level of acute cognitive impairment alone (M_{OCS}) also performed well. In fact, M_{OCS} was more predictive of SIS domains as compared to M_{NIHSS} (see Supplementary Table 2 for R2 values for each model in each SIS subdomain).

Taken together, these results show that M6 – a combination of demographics, NIHSS and OCS—outperformed all the other models and accounted for the great majority of outcome variance for all SIS domains (mean explained variance across SIS scores = 67%, range: 44%–83%). Interestingly, the second most predictive model included only on OCS scores (M_{OCS}; mean explained variance = 64%, range: 40%–79%). The SIS domain less accurately described by the set of models was Communication and Understanding (30% on average).

Since model M6 explained the greatest percentage of behavioral variance in all SIS scores, as compared to the other models, we tested its ability to predict SIS domains in a Leave-One-Out (LOO) design. Specifically, the model was iteratively built on N-1 observations and tested on the remaining observation, and the prediction accuracy was evaluated by correlating actual and predicted SIS values (Fig. 4). The model

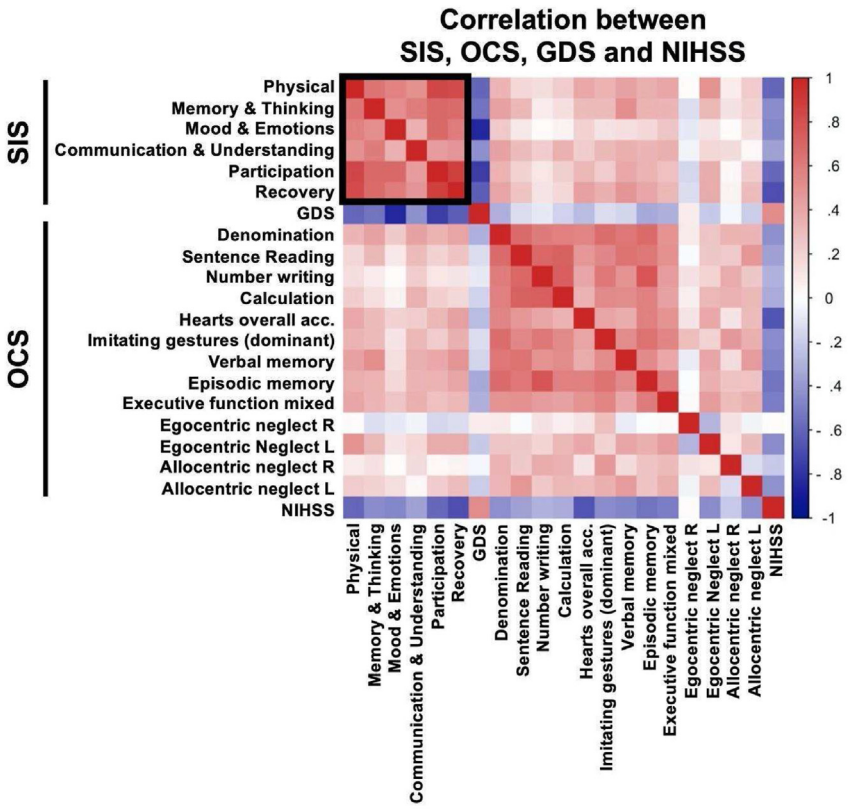

Fig. 2 – Correlation matrix showing the degree of correlation (Pearson's r) between SIS, OCS, GDS and NIHSS scores. Red = positive correlation; Blue = negative correlation; White = no correlation.

M6 showed a good predictive performance in 5 out of 6 SIS domains (all Pearson's r > .44). Specifically, the model predicted Physical ($r = .70$, $p < .001$), Memory and thinking ($r = .44$, $p < .001$), Mood and emotions ($r = .82$, $p < .001$), Participation ($r = .65$, $p < .001$), and Recovery ($r = .68$, $p < .001$) domains (Fig. 4). Conversely, the correlation was not significant for the Communication and understanding score ($r = .10$, $p = .42$).

4. Discussion

We investigated whether the Oxford Cognitive Screen (OCS) can be considered an acute predictor of long-term functional outcome. Furthermore, we studied the combination of predictors that better explain long-term functional impairment. We aimed to define the role of the OCS compared to other clinically relevant predictors in the definition of post stroke prognosis.

4.1. *The OCS as an independent predictor of functional outcome*

The OCS administered early after stroke is a relevant predictor of long-term functional outcome. Specifically, the OCS relates to long-term performance (assessed with the SIS 3.0) in cognitive and physical functional domains. Acute OCS scores (MOCS) significantly predicted memory, mood and emotions, language ability, social participation, physical status (including physical impairments, mobility, ADL/IADL, and Hand function) and global recovery (Fig. 3 and Supplementary Table 2).

"Memory and thinking" scores were well predicted by the OCS. This result is in line with recent studies that have shown a high sensitivity of the OCS in detecting post-stroke cognitive deficits. Acute impairment in the memory domain has been consistently associated with long-term negative outcome (Demeyere, Robotham, & Oestergaard Riis, 2019; Mancuso et al., 2018). Only the OCS was able to significantly improve outcome prediction in this domain in comparison to all other factors (from R^2 ~.4 *vs* to .6).

OCS subtests showed a general good prediction ability of post stroke mood. In this domain, established predictors are stroke severity, age, level of disability and gender (Murata et al., 2000; Vojtikiv-Samoilovska & Arsovska, 2018). Even though a few studies found no correlation between acute cognitive deficits and post-stroke depression (Hackett & Anderson, 2005), others have reported a strong association (Murata et al., 2000; Vojtikiv-Samoilovska & Arsovska, 2018). Our results suggest that acute cognitive impairment should be considered a definite risk factor for post-stroke depression. At the chronic timepoint we found a strong negative correlation between chronic GDS scores and all SIS subdomains (see Fig. 2 correlation matrix). While this confirms that mood disorders have a negative effect on outcome, the direction whether cognitive impairment leads to depression or whether post-stroke depression leads to impairment is still being debated

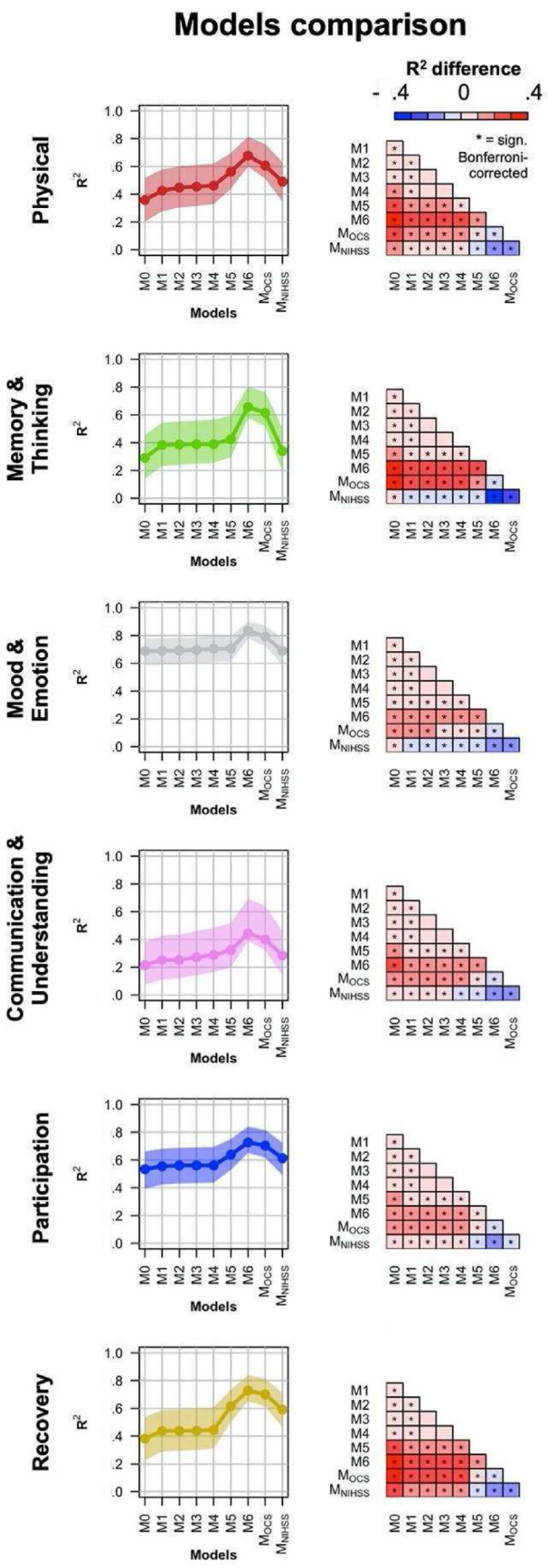

Fig. 3 – Comparison of model predictions for individual SIS subdomains. For each SIS score, a comparison between different models (x axis) in terms of explained variance (R^2;y axis) is presented. The shaded area indicates the 95% Confidence Interval. For all variables a peak of R^2 corresponded to model M_6 (i.e., in which OCS scores were added to a model including demographics and NIHSS score). The set of matrices shows the pairwise comparison of models' R2. Each square depicts the difference between two models ($MODEL_{row}$—$MODEL_{column}$) and the color indicates magnitude and sign of such difference. Red indicates higher values (i.e., $MODEL_{row}$'s R2 > $MODEL_{column}$'s R2) and blue indicating lower values (i.e., $MODEL_{row}$'s R2 < $MODEL_{column}$'s R2).

(Godefroy et al., 2018; Hackett & Anderson, 2005) and further analysis (i.e., a moderation analysis) need to be performed to better characterize this complex relationship.

OCS significantly predicted perceived language impairments even though it explained a relatively low percentage of variance in comparison to other considered domains. As the "communication and understanding" SIS domain does not only evaluate the patient's aphasia but includes tasks that assess executive functions and social involvement (i.e., questions regarding: "how difficult was it to call another person on the telephone, selecting the correct phone number and dialing?"), we expected to predict a greater amount of variance for this comprehensive domain. On the other hand, as for the 'Memory and Thinking' domain, the OCS was the only variable that significantly increased the amount of explained behavioral variance.

A high percentage of variance of "Participation" and "Recovery" domains were accounted for by acute OCS scores. Specifically, executive functions impairments were strongly associated with long-term social participation. This result is consistent with studies that identify these deficits as reliable predictors of long-term participation (Skidmore et al., 2010; Viscogliosi et al., 2011). Social restriction is common after stroke and strongly influences the quality of life and the perceived health status of these patients (Mayo et al., 2002; Saposnik et al., 2011). The identification of the most relevant predictors of participation and recovery is becoming imperative as patients at risk of social restriction would benefit from targeted rehabilitation interventions (Obembe & Eng, 2016).

Finally, it is worth noting that we found that the model including cognitive data showed comparable results with the model including the NIHSS score for the physical/motor outcome domain. On one hand, this is in line with recent studies showing that the presence of cognitive impairments significantly correlates with a greater dependence and motor inactivity (Paker et al., 2010; Oros et al.). On the other hand, we show that a purely cognitive screening, performed at patient's bedside, can be as informative as the NIHSS, a mainly physical evaluation, even about motor outcome function. Besides its important practical implications, this result is in line with the high correlation values we found among SIS patient scores at different timepoints: within SIS functional domains (chronic) and between NIHSS and OCS subtests (acute) (see Fig. 2 Correlation Matrix). NIHSS scores were highly anti-correlated with OCS cognitive scores. In previous work, we have shown this correlation can be explained by the low dimensional

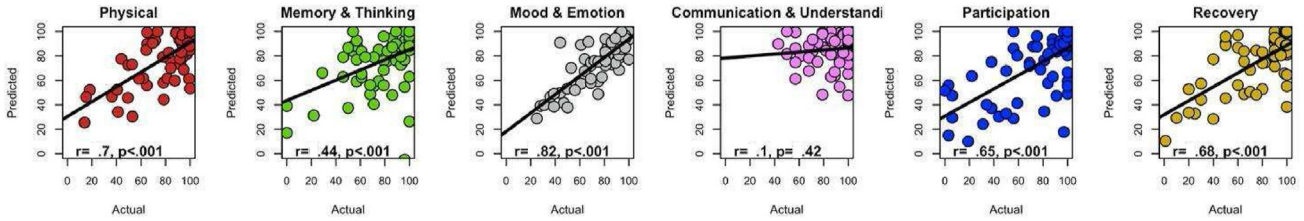

Fig. 4 – Prediction of SIS scores from model M6. Each scatterplot shows the correlation (Pearson's r) between actual SIS scores and values predicted by model $M_{6\ Clinical\&Cognitive}$ with a Leave-One-Out (LOO) design.

structure of acute impairment that follows stroke. In other words, a few factors of correlated deficits, both physical and cognitive, can explain the majority of behavioral variance of stroke survivors (Corbetta et al., 2015, Bisogno et al., 2021). In this work, we confirm this result and show this relationship persists at a chronic stage even when considering a functional outcome measure (i.e., SIS). Namely, the SIS subdomain scores were strongly related (i.e., especially participation and recovery), suggesting physical and cognitive outcome tend to be positively correlated, thus explaining the high percentage of variance accounted for by our cognitive evaluation across all behavioral domains.

4.2. *The integration of the OCS in acute stroke clinical assessment*

If the OCS is a strong prognostic factor for functional outcome, how does it perform compared to other known features? Can it lead to a significant improvement in post stroke prognosis prediction if applied in the everyday clinical practice? To test this hypothesis, we compared different nested prediction models based on classical clinical features with the addition of an acute post-stroke cognitive evaluation. Specifically, we considered age, stroke severity (NIHSS), gender, education level, and previous comorbidities as further predictors for our analysis. The M6 model (see Table 1), comprising demographics, stroke severity (NIHSS) and cognitive status (OCS), explained the highest percentage of long-term behavioral variance in all SIS domains (Fig. 3). Furthermore, this model significantly predicted, with moderate to high correlation coefficients, all functional domains except for the 'Communication and Understanding' scores (Fig. 4). These findings substantially show the integration of a short bedside cognitive assessment and the NIHSS significantly improved the prediction of long-term functional outcome in stroke patients. This integration was possible in approximately 90% of our sample, showing very high levels of applicability in the clinical population. Finally, and most importantly, previous studies have shown it can be considered a sensitive measure of the main axes of behavioral impairment in a prospective sample of first-time stroke patients. Specifically, while previous studies on the factor structure of the sole NIH stroke scale (Lyden et al., 2004) have identified two factors explaining the majority of post stroke behavioral variance, we show in previous work the NIHSS/OCS combination replicates the 3-factor structure previously identified in Corbetta et al., 2015 through a comprehensive 2-h long neurobehavioral battery covering multiple domains (i.e., motor, language attention, memory). Overall, these results demonstrate the robust applicability, sensitivity, and prognostic value of the OCS, thus suggesting its integration in clinical practice for acute stroke management.

5. Limitations

Regarding the present study's limitations, it is important to note that the final sample included $n = 74$ patients. This represents a small-medium population and replication studies in larger independent datasets are necessary to confirm our results. Nevertheless, our results showed reliable statistical significance and general agreement with the known literature. Another limitation relates to the evaluation of the patients' pre-stroke status. Specifically, quantitative information on the amount of WMC (i.e. leukoaraiosis) were not available for all patients since not all of them had undergone an MRI scan. No other pre-event standardized cognitive evaluations (i.e, MMSE or MoCA) or depression screening tools (GDS/BDI) were available. As these variables have been identified as solid predictors of functional outcome (Luijten et al., 2021) further studies should consider them as potential confound.

6. Conclusion

The high prevalence of cognitive deficits following stroke and their impact on patients' recovery strongly suggests the importance of a cognitive evaluation early after stroke. In this study we show that a prompt detection of cognitive deficits is a strong predictor of post stroke functional outcome. Most importantly, we demonstrate that the integration of a short, bedside cognitive screening tool with common clinical features significantly improves the clinicians' ability to predict patients' prognosis and can therefore allow early interventions as well as tailored rehabilitation programs.

CRediT author statement

Antonio Luigi Bisogno: Conceptualization, Data curation, Writing – original draft, preparation. Luca Franco Novelletto: Data curation, Writing – original draft, preparation. Andrea Zangrossi: Methodology, Writing – original draft, preparation. Serena De Pellegrin: Investigation. Silvia Facchini: Investigation; Anna Maria Basile: Supervision; Claudio Baracchini: Supervision. Maurizio Corbetta: Conceptualization, Writing – review & editing

Data availability

The data that support the findings of this study are available from the corresponding author. The conditions of our ethics approval do not permit public archiving of anonymised study data. Readers seeking access to the data should contact the lead author ALB or the local ethics committee at the Department of Neuroscience, University of Padova. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Requestors do not have pre-specified conditions to fulfill. No specific analysis code was used in this study. All behavioral assessments including the NIHSS (https://www.ninds.nih.gov/search?search_api_fulltext=sites+default+files+NIH+Stroke+Scale+Booklet.pdf), OCS (https://www.ocs-test.org) and SIS 3.0 (https://strokengine.ca/en/assessments/stroke-impact-scale-sis/#Seethemeasure) are freely publicly available. No part of the study procedures or analysis was pre-registered prior to the research being conducted.

Declaration of competing interest

The authors report no conflicts of interest. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

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Supplementary data

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